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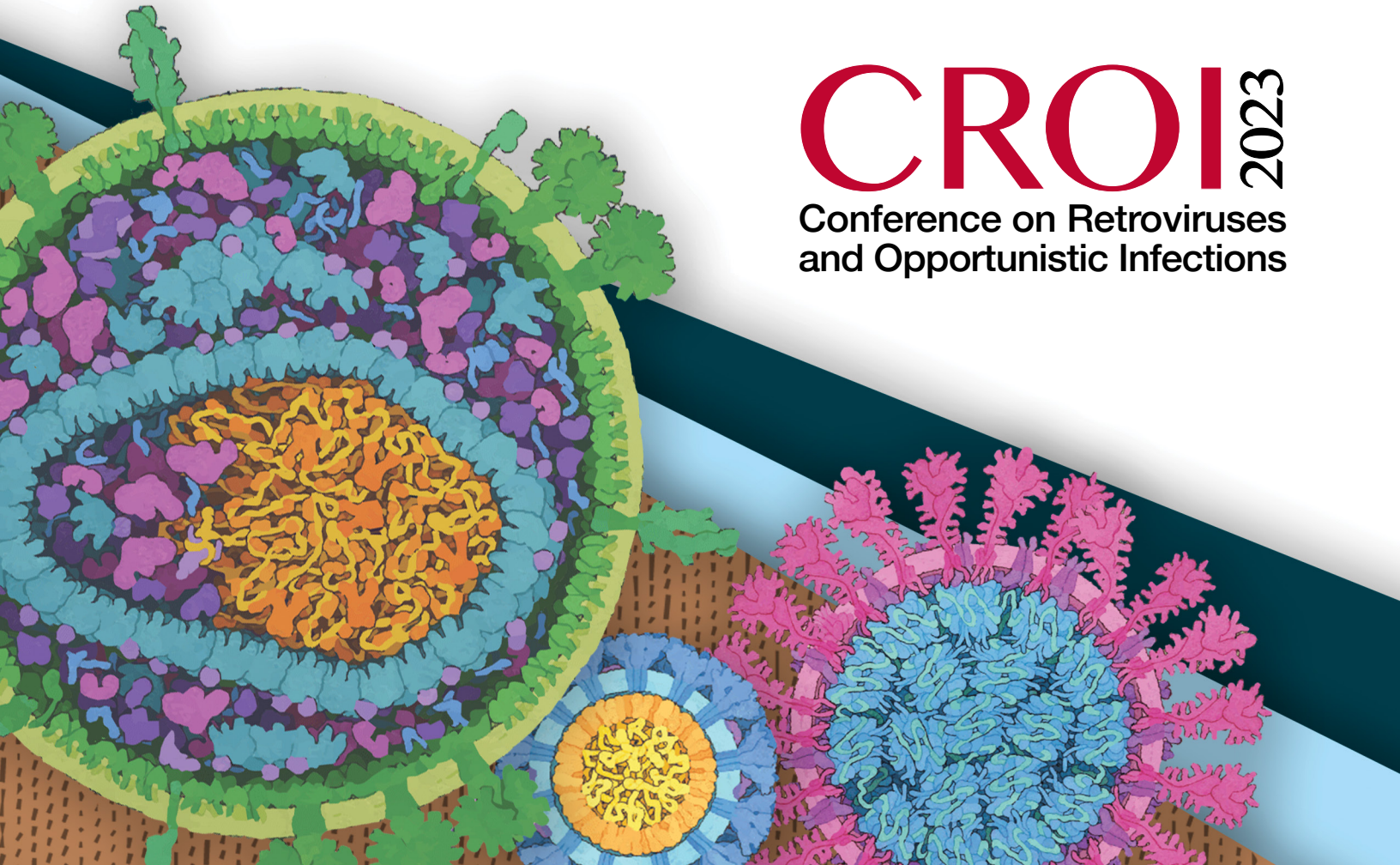
Topics in Antiviral Medicine™

A publication of the IAS–USA

Special Issue: Abstracts From the 2023 Conference on Retroviruses and Opportunistic Infections

Announcements



Topics in Antiviral Medicine™

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About This Issue

This issue of *Topics in Antiviral Medicine* is a special issue that includes the abstracts from the 2023 Conference on Retroviruses and Opportunistic Infections (CROI). This issue is funded and supported by IAS–USA.

Information on citing presentations from CROI 2023 is available on the Resources page at CROIconference.org.

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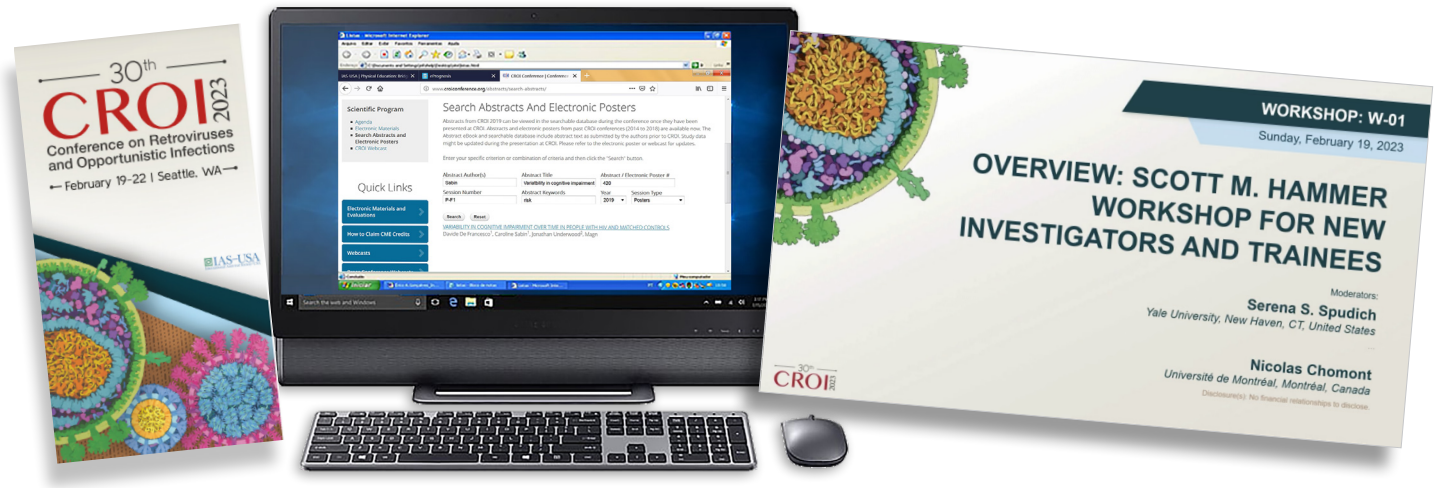
CROI 2023 Resources

Resources from CROI 2023 can be found at www.CROIconference.org. The CROI 2023 Resources page includes the following resources and more.



The CROI Program and Information Guide includes information about sessions, speakers, and other details about CROI 2023. In addition to the Special Issue of *Topics in Antiviral Medicine*™, abstracts from CROI 2023 can be viewed in the Abstract eBook and searchable database. Beginning March 22, 2023, plenaries, interactive sessions, oral abstract presentations, and poster abstract presentations will be available as webcasts. Archived webcasts from CROI 2014 to 2022 are also available. Visit the resources page of www.CROIconference.org for more details.

ABSTRACTS

Note: The data in these abstracts were current at the time they were submitted, which may have been months before the start of CROI. For the most up-to-date data, please view the posters and oral abstract presentations.

To search for specific keywords, presenters, or authors on this document, hold the "Ctrl" and press the "F" keys on your keyboard (or "Command" and "F" keys for some Apple devices) to prompt a word search.

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INVITED SESSION PRESENTATION SUMMARIES

1 OVERVIEW: SCOTT M. HAMMER WORKSHOP FOR NEW INVESTIGATORS AND TRAINEES

Nicolas Chomont[1], **Serena S. Spudich**[2]
[1]*Université de Montréal, Montréal, Canada,* [2]*Yale University, New Haven, CT, USA*

Over the past four decades, remarkable progress has been made in understanding HIV epidemiology, pathogenesis, treatment, and prevention from the combined efforts of community members, clinicians, investigators, and funding agencies worldwide. Yet more work and new approaches are needed to achieve the ambitious goal of ending the epidemic and ensuring optimal quality of life for those living with HIV. To encourage and stimulate the next generation of investigators, the CROI Program Committee organizes an annual Workshop for New Investigators and Trainees comprised of expert and comprehensible talks to cover current knowledge and controversies in basic, clinical, and public health investigation into HIV and related infections, and to highlight relevant work to be presented over the ensuing days at CROI. This year, the program will begin with a presentation by Dr Stuart Neil on novel aspects of the molecular virology of HIV-1 and SARS-CoV-2. Following this, Dr Guido Silvestri will cover the immune responses against HIV and SARS-CoV-2. Ms Dawn Averitt, an HIV treatment policy advocate and activist will provide a community perspective on the power of community engagement in research. In the following presentation, Dr Monica Gandhi will review novel therapeutic strategies for HIV. Dr Raphael Landovitz will address advances in different strategies for preventing HIV transmission. Dr John Mellors will review advances in preclinical and clinical approaches for functional or sterilizing HIV-1 cure. The workshop will end with an intervention by Dr Rochelle Walensky, who will discuss career opportunities in research and public health. By completing the workshop, attendees will have achieved a head start toward maximizing the knowledge gained and research ideas arising from CROI 2022.

2 SINGLE-CELL ANALYSIS OF THE RNA, PROTEIN, AND GLYCAN FEATURES OF HIV-INFECTED CELLS

Nadia R. Roan
Gladstone Institutes, San Francisco, CA, USA

High-parameter single-cell analysis tools such as CyTOF and scRNAseq have enabled deep examination of HIV-infected cells at an unprecedented level of resolution, and have advanced our understanding of HIV transmission, pathogenesis, and persistence. CyTOF, which enables quantitation of ~40 surface and intracellular proteins on hundreds of thousands of cells at the single-cell level, has revealed insights into the phenotypic features of HIV-infected cells from blood and multiple tissue compartments. CyTOF-Lec, an extension of CyTOF that simultaneously incorporates lanthanide-conjugated antibodies and lectins, has further revealed the glycan features of HIV-infected cells. One key advantage of high-parameter phenotyping of HIV-infected cells is that it enables computational approaches ¬– including one named Predicted Precursor as determined by SLIDE (PP-SLIDE) – to distinguish protein and glycan antigens remodeled by infection, from those preferentially expressed on HIV-susceptible cells. PP-SLIDE has further been expanded to predict the original phenotypic features reactivated latent cells prior to *ex vivo* stimulation, and enabled the identification of surface markers that can enrich for replication-competent reservoir cells from ART-suppressed people with HIV (PWH). The ability to enrich for unstimulated HIV reservoir cells, along with other technological developments enabling more efficient detection of HIV transcripts, has in turn enabled in-depth multiplexed transcriptomic and proteomic analysis of infected cells from virally-suppressed PWH by single-cell sequencing-based approaches. Together, these studies have revealed HIV-infected cells to be heterogeneous yet harboring distinct features, including gene expression signatures of cell survival, immune evasion, and cytolysis.

3 SINGLE-CELL MULTIOMIC ANALYSES OF THE HIV RESERVOIR

Michael R. Betts
University of Pennsylvania, Philadelphia, PA, USA

Recent single cell genomic methodology advances have enabled the measure of HIV DNA within infected cells to move beyond traditional bulk cell HIV DNA viral quantification, sequence intactness, and integration site analysis into the realm of in-depth single cell HIV reservoir studies. This talk will review the constellation of single cell genomic techniques for HIV reservoir characterization based on using the presence of integrated HIV DNA as a molecular tag to identify infected cells. Topics to be covered include a review of what the field has learned so far, remaining outstanding questions, and the practicality of implementing such strategies in the context of HIV cure and eradication studies.

4 SINGLE-CELL MULTIOMICS AND EXPANSION DYNAMICS OF HIV RESERVOIR OVER SPACE AND TIME

Ya-Chi Ho
Yale University, New Haven, CT, USA

Understanding how HIV persists over time in different anatomical locations is the key to deciphering mechanisms of HIV persistence, nominating biomarkers, and designing HIV cure strategies. Clinical samples are invaluable resources for understanding HIV persistence *in vivo*. However, HIV-infected cells are heterogeneous and rare *in vivo*. Advancement in single-cell technologies resolves the heterogeneity and rarity of HIV-infected cells. Advances in single-cell multi-omics methods profile HIV-infected cells (by HIV DNA and HIV RNA mapping) and respective epigenetic regulator, transcriptome, surface protein markers, and T cell clonality by combining ATAC-seq, RNA-seq, CITE-seq, and T cell receptor (TCR) sequencing within the same single cell. Standard practices such as doublet removal, integration (batch effect correction), cell type annotation, and determining sensitivity and specificity of HIV mapping are required to generate high dimensional single-cell profiles that are reproducible and biologically meaningful. By tracking cells having the same T cell receptor sequences, the immune phenotype of different T cells within the same T cell clone (responding to the same antigen) can be tracked over different time points, at different anatomical locations, and before and after antigen stimulation. By examining the transcriptome of frozen tissues *in situ* without making cellular suspensions, called spatial transcriptomics, cell-cell interactions in tissue microenvironments can be examined at 55 µm resolution down to 10 µm and even single-cell resolution. Expanding from spatial transcriptomics, spatial ATAC-seq and spatial protein phenotyping provide additional understanding of cellular states *in situ*. The main challenge of using these advanced methods in HIV reservoir profiling remains to be the rarity of HIV-infected cells. Overall, advanced single cell technologies, with careful bioinformatic analysis and biological validations, revolutionized our understanding of HIV-infected cells down to the single cell level over space and time.

5 NOVEL APPROACHES TO CHARACTERIZING IMMUNE RECOGNITION

Michael Birnbaum
Massachusetts Institute of Technology, Cambridge, MA, USA

The adaptive immune system is breathtakingly complex. B and T cells both rely upon somatically recombined antigen receptors with theoretical diversity of 10^{15} possible combinations to recognize the host of possible pathogens or transformed cells that may be encountered. While this complexity is key to proper immune function, it also complicates its study. A comprehensive understanding of T and B cell recognition can aid in understanding how immune responses succeed or fail, how to generate better predictive computational models, and how to design the next generation of therapies. In this presentation, I will introduce adaptive immune recognition, and provide an overview of both established and emerging technologies to interrogate what the immune system sees.

6 FULMINANT HEPATITIS IN CHILDREN

Luz Helena Gutierrez Sanchez
University of Alabama at Birmingham, Birmingham, AL, USA

Fulminant hepatitis in children is a dynamic and life-threatening condition with a broad differential diagnosis. Diagnosis is age dependent and therefore evaluation of patients presenting with hepatitis should be tailored to age. There was an increased number of hepatitis of unknown etiology seen globally late 2021 and in 2022. Early reports show a pattern of fulminant hepatitis in children (majority of them bellow 5 years in age) with high frequency of human adenovirus viremia, more specifically human adenovirus type 41. Further investigations have shown presence of adeno-associated virus 2. Pathophysiology of etiology is unclear, as tissue samples have not shown direct viral cytopathology. Possible etiology for the increased number in cases of fulminant hepatitis remains unclear at this time.

7 HBV PREVENTION: NEWER VACCINES AND THE BOUNDARIES OF HBV PROTECTION

H. Nina Kim
University of Washington, Seattle, WA, USA

After participating in this session, attendees will be able to

- Describe the newer options for hepatitis B immunization and their seroprotective efficacy in key subpopulations.
- Summarize our current understanding of the role of antiviral therapy in HBV prevention.
- Identify the current gaps in knowledge related to HBV immunity in the patient with HIV and an isolated hepatitis B core antibody profile.

8 HEPATITIS DELTA INFECTION AMONG PERSONS LIVING WITH HIV

Charles Béguelin
University of Bern, Bern, Switzerland

Approximately 5-10% of individuals with hepatitis B surface antigen (HBsAg) are coinfected with the hepatitis delta virus (HDV), totaling 15-60 million people worldwide. The prevalence of HDV-coinfection varies considerably across clinical settings, geographic areas, and the constellation of risk factors within study populations. Injection drug use is a well-known route of transmission for HDV and probably the main one in high-income countries, whereas other routes of transmission remain less clear, with high-risk sexual behaviors being suggested as one. Epidemiological data on HDV infection among persons living with HIV (PLWH) remain limited as the uptake of routine testing is generally suboptimal due to the lack of awareness, issues with standardizing diagnostic techniques and limited treatment options. Hepatitis delta is the most severe form of viral hepatitis: a faster progression to liver cirrhosis, hepatic decompensation and hepatocellular carcinoma (HCC) has been described in populations with and without HIV. The magnitude of HDV replication seems to be an important driver of morbidity.

In This work-shop we will discuss testing recommendations for Hepatitis B and delta, the natural history of HBV/HDV coinfection, new treatment of hepatitis delta and how to monitor treatment success, as well as screening indications for HCC.

9 ADAPTIVE PLATFORM TRIALS: EXPERIENCE FROM THE COVID-19 PANDEMIC

Michael D. Hughes
Harvard T.H. Chan School of Public Health, Boston, MA, USA

Adaptive platform trials are randomized clinical trial designs that enable the evaluation of multiple interventions in a single, highly standardized trial framework undertaken using a master protocol. Fundamental to these designs is allowance for interventions to be added during the course of the study, sharing of a control group in evaluating multiple interventions in parallel, and decision criteria for dropping interventions for futility or efficacy based on interim analyses. Other more complex adaptations may also be incorporated, such as changing allocation ratios across randomized arms in response to interim results, seamless phase II to III transitions, and sample size re-estimation. A large number of platform trials were initiated in response to the COVID-19 pandemic. I will review some key features of platform trial designs with illustrations from the COVID-19 arena, and discuss advantages and challenges of using them in comparison to traditional randomized trials.

10 UNPACKING MODELING STUDIES

Viviane D. Lima
British Columbia Centre for Excellence in HIV/AIDS, Vancouver, BC, Canada

There is increasing recognition of the usefulness of mathematical models in informing public health intervention strategies and policymakers on how to address different epidemics. Over the years, we have seen many models testing different interventions to prevent the spread of HIV. Lately, mathematical models have been used to assess interventions focused on controlling the spread of COVID-19 and, more recently, of Mpox. However, as we will show in this presentation, we saw considerable pressure to fast produce mathematical models for COVID-19 to inform on different policies to control the spread of this disease. Consequently, we saw that several of these models missed the mark, and others, although not perfect, were useful in making predictions based on different interventions. In this presentation, I will describe how mathematical models have informed public health Interventions. We will provide an overview of the use of mathematical models to prevent HIV, COVID-19 and Mpox. I will propose a list of criteria to evaluate and write publications involving mathematical models. Finally, I will discuss some of the lessons learned for properly using mathematical models and interpreting results and propose a pathway moving forward.

11 SOCIAL AND BEHAVIORAL SCIENCE: THE MISSING INGREDIENT TO SUCCESSFUL CLINICAL TRIALS

Heidi van Rooyen
Human Sciences Research Council, Cape Town, South Africa

This talk considers the role of social and behavioral science at every stage of the clinical trial process from design to enrolment, participation, retention and outcomes. Based on a review of the literature and three decades' experience as a social scientist conducting leading HIV and COVID studies, it argues that understanding human behavior and decision-making alongside the context in which these decisions are made are key to effective, efficient and quality clinical trials.

12 MODELING THE DYNAMICS OF HIV INFECTION: ESTABLISHING PARADIGMS FOR TREATMENT AND CURE

Alan S. Perelson
Los Alamos National Laboratory, Los Alamos, NM, USA

Although mathematics and physics are commonly thought of as being abstract and not of much practical use particularly in medicine, theoretical ideas expressed mathematically changed the way we think about HIV infection and its treatment. I will show how this approach when used to analyze clinical data led to fundamental insights about HIV and its successful control with drug therapy. The challenge now is to cure HIV. I will discuss current mathematical and experimental approaches that suggest the immune system can be manipulated for this task.

13 HIV AND GLOBAL HEALTH IN A PANDEMIC ERA

Kevin M. De Cock
Centers for Disease Control and Prevention (former), Nairobi, Nairobi Area, Kenya

Four broad themes run through this year's N'Galy-Mann lecture: clinical medicine, HIV, health security, and global health. Three patterns of disease characterized medicine in East Africa at the time that AIDS was first described in the United States: diseases of poverty, mainly infectious; non-communicable diseases with differing international epidemiology; and classic tropical diseases restricted in distribution by ecologic needs of parasites and vectors. Limited resources did not prevent the practice of good medicine under adverse circumstances, nor application of basic principles of research.

The recognition of a second AIDS virus (HIV-2) in West Africa in the mid-late 1980s required applied research to assess implications and potential global impact of this novel infection. CDC established a second collaborative research site in sub-Saharan Africa, Projet RETRO-CI, in Abidjan, Cote d'Ivoire (the first was Projet SIDA in the Democratic Republic of Congo, where N'Galy and Mann made seminal contributions). Controversy around HIV-2 diagnosis, transmission, and pathogenicity was slowly resolved through West African research showing HIV-2 was an AIDS-causing pathogen, slower than HIV-1 in its progression, and less transmissible until late in the course of infection. Mother-to-child transmission was exceptionally rare. Claims that HIV-2 protected against HIV-1 were not substantiated. Projet RETRO-CI clarified the spectrum of HIV-associated disease and the dominant role of tuberculosis. Placebo-controlled trials demonstrated efficacy of short-course zidovudine for prevention of perinatal transmission of HIV-1, and of cotrimoxazole prophylaxis in reducing hospitalization and mortality in persons with HIV. Global health today is dominated by discourse around health security. The West African and Congolese Ebola epidemics since 2014 aroused strong declarations, yet the world was poorly prepared to address the pandemic of COVID-19. Health in the world has changed substantially since AIDS emerged. As 2030, the year for delivery on the Sustainable Development Goals, approaches, development assistance for health remains essential to address traditional, unfinished commitments yet does not match today's global burden of disease. CROI attendees are encouraged to remember colleagues lost to COVID-19 and other challenges; to assess priorities in today's global health, including relating to HIV; and to reflect on what issues N'Galy and Mann would focus on today.

14 COMMUNITY AND ADVOCATES ARE EQUAL PARTNERS IN RESEARCH AND DEVELOPMENT

Yvette A. Raphael
Advocacy for Prevention of HIV and AIDS, Midrand, Gauteng, South Africa

Yvette Raphael will take the audience on a journey, sharing how cisgender women, and their allies, organized in Africa and across the world, to go beyond simply being study participants to being research leaders in the fight for a future free of new infections. Community leadership is not nice to have, and it is not performative. It is an imperative, and advocates must be equal partners in the effort. Vulnerable communities and populations must always be centered as we work collaboratively, transparently, and equally side-by-side with governmental agencies, researchers, product developers, policymakers, and funders, among others. The only way we end the epidemic is with leadership coming from communities, including Black Women in Africa and around the world.

15 20 YEARS OF PEPFAR: LOOKING BACK, STRIDING FORWARD

John Nkengasong
US Department of State, Washington, DC, USA

We are closer to ending HIV/AIDS as a public health threat. During its first 20 years, PEPFAR has worked with partner-country governments and other stakeholders, including the Global Fund to Fight AIDS, Tuberculosis and Malaria, UNAIDS, communities, and other partners to end HIV/AIDS as a public health threat by 2030. Thanks to global and local HIV stakeholders, according to UNAIDS, AIDS-related deaths have been cut by 64% since their peak in 2004 and new infections have been reduced by 42% through the delivery of essential prevention and treatment services. Globally, 73% of people living with HIV are accessing antiretroviral therapy (ART) and 20 million of them are supported by PEPFAR worldwide.

PEPFAR has helped prevent HIV infection in men and boys, including by supporting 30 million voluntary medical male circumcisions in east and Southern Africa. Since 2015, new HIV diagnoses among adolescent girls and young women have declined in all geographic areas implementing the PEPFAR-led DREAMS (Determined, Resilient, Empowered, AIDS-free, Mentored, and Safe) public-private partnership. In this past year, the program provided critical care and support for 7 million orphans, vulnerable children, and their caregivers so they can survive and thrive, HIV testing for over 64 million people and over a million received PrEP.

Through PMTCT and comprehensive programming, PEPFAR enabled 5.5 million babies to be born HIV-free to mothers living with HIV.

Finally, PEPFAR's investments also strengthen the systems that drive effective, efficient, and sustainable health care. PEPFAR has helped train 340,000 health care workers to deliver and improve HIV care and other health services, creating a lasting health system for partner countries to confront other current and future health challenges.

16 THE PATH TO HEPATITIS B CURE

Anna S. Lok
University of Michigan, Ann Arbor, MI, USA

HBV infection remains a major global health burden, with 1.5 million new infections, 296 million chronically infected persons, and 820,000 HBV-related deaths in 2019. Current treatment with pegylated interferon alfa (pegIFNα) or nucleos(t)ide analogues (NAs) can suppress HBV DNA replication, decrease liver inflammation, reverse liver fibrosis and decrease risk of cirrhosis, hepatocellular carcinoma and liver-related deaths. However, HBsAg loss rarely occurs. It is generally accepted that sterilizing cure is not feasible, thus, the goal is to achieve functional cure defined as sustained clearance of HBsAg and HBV DNA after completing a finite course of treatment. Functional cure will require silencing of cccDNA and integrated HBV DNA and restoration of immune response to HBV. Combination therapy of direct-acting antiviral drugs and immune modulatory therapies will be necessary to completely suppress HBV replication, decrease HBsAg production to very low levels, and activate or remove blockade of HBV-specific immune response. Suppression of HBV replication may involve combinations of NA, capsid assembly modulators (CAMs), and entry inhibitors, though translation inhibitors such as small interfering RNAs (siRNA) and antisense oligonucleotides (ASO) may contribute. Decrease in HBsAg production may involve combinations of entry inhibitors, translation inhibitors - siRNA/ASO, and drugs that block release of HBV or viral proteins such as nucleic acid polymers (NAP). Combination of CAMs and NAs result in deeper suppression of HBV DNA replication but has minimal effect on HBeAg or HBsAg production and withdrawal of therapy leads to near universal viral relapse. siRNA/ASO with or without NAs lead to marked decrease in HBsAg production but rates of HBsAg loss remain low with strategies tested so far. To date, clinical trials of immune modulatory therapies have met with limited success. New approaches including combination of therapeutic vaccines and check point inhibitors, and HBV antibodies aimed to neutralize HBV and to enhance antigen presentation. So far, few of the new therapies have resulted in HBsAg loss at the end of treatment

and even fewer have resulted in off-treatment HBsAg loss. In addition to new drugs, development of standardized assays of new HBV markers to confirm target engagement, assess cccDNA transcription, and to confirm "cure" need to occur in parallel. Availability of assays to measure recovery of HBV-specific immune response would help identify which patients need additional immune modulatory therapies. Platform trials should be deployed to improve efficiency. Safety remains a high priority given the excellent safety profile of NAs. While the goal of achieving functional HBV cure in a high proportion of patients remains remote, the efforts invested in the last 5 years have provided important tools and insights towards achieving that goal.

17 ORIGINS OF HIV-1 AND SARS-CoV-2

Michael Worobey
University of Arizona, Tucson, AZ, USA

Dr. Worobey will discuss the scientific evidence for when, where and how both the HIV/AIDS pandemic and the COVID-19 pandemic originated, and what we can learn from this knowledge to prevent or mitigate future pandemics. In both cases, cross-species transmission into humans via wildlife consumption, versus via laboratory accident, were plausible hypotheses of origin. And in both cases, there is now overwhelming evidence in favor of the "natural" zoonosis route. Indeed, in the case of COVID-19, we have insights into the genesis of the pandemic that are in many ways unparalleled in the history of investigating pandemic origins.

18 FROM PROMISE TO REALIZATION: SEQUENCING AND SURVEILLANCE FROM HIV-1 TO SARS-CoV-2

Emma B. Hodcroft
University of Bern, Basel, Basel-Stadt, Switzerland

The advent of cheaper viral sequencing and opportunity to offer customized treatment through identification of resistance mutations in patients with HIV-1, also offered the first large-scale opportunity to use sequencing to generate insights into a global infectious disease pandemic. Using HIV-1 sequences, scientists were able to track mutations globally and within countries and use them to gain groundbreaking understanding of virus transmission and the evolution of resistance. Though invaluable in contributing to our knowledge of virus dynamics, much of what was feasible with HIV-1 was difficult to extend to other viruses due to the challenges and expense of full-genome sequences and the difficulty of obtaining samples from acute infections. More recent advances have made next-generation sequencing (NGS) possible and affordable, and growing realization of the insights sequencing can contribute has increased interest in generating sequences for an increasing variety of viruses. Against this backdrop of an advent of a new age of genomics in viral research, the SARS-CoV-2 pandemic has thrown sequencing and phylogenetics into the limelight, allowing the collection and sequencing of more samples than could even be conceived prior to 2020. It's a opportune time to consider not only where we've come from, but how the promise of 14 million sequences has been realized, and what the future holds for sequence-enabled pathogen research.

19 ANTIBODY-DRIVEN EVOLUTION OF HIV-1 AND SARS-CoV-2

Paul D. Bieniasz
Rockefeller University, New York, NY, USA

In this presentation, Dr Paul Bieniasz will discuss antibody-driven evolution of HIV-1 and SARS-CoV-2.

20 THE LANDSCAPE OF ADHERENCE TESTING

Peter L. Anderson
University of Colorado Anschutz Medical Campus, Aurora, CO, USA

Inadequate adherence to modern ART is commonly defined as <80% of doses taken, and that for daily PrEP depends on route of exposure; <4 doses per week on average for men and <6-7 doses per week on average for women. Inadequate ART adherence is common, estimated at ~40% in the USA and that for daily PrEP is as high as 30%-90% depending on the population and study. This underscores the need for accurate and precise adherence measurement tools to help interpret study results and manage patient care. This presentation will review the current landscape of objective adherence measurement tools with a focus on drug concentrations in blood, urine, and hair. Additionally, important considerations for using adherence measurements will be reviewed including the importance of aligning adherence measurements with intentional versus unintentional nonadherence. Finally, the application of adherence measurements to understand pharmacokinetic forgiveness, clinical trial efficacy, and adherence-response relationships will be discussed.

21 DIGITAL TECHNOLOGIES FOR SUPPORTING ADHERENCE

Lisa Hightow-Weidman
Florida State University, Tallahassee, FL, USA

It is estimated that adherence to chronic medications is approximately 50%, resulting in an annual cost of at least 500 billion dollars in the United States (US) alone (e.g., ~16% of the total US health care expenditures). Further, medication nonadherence can affect overall healthcare utilization, quality and length of life, and health outcomes. To date, there is no "gold standard" measure of adherence. Thus, adherence measurements that are easy to operationalize, provide valid and complete data and are not cost prohibitive are greatly needed. Digital technologies can provide both direct and indirect measures of adherence and have the potential to allow for both adherence monitoring and intervention delivery through provision of "real-time" information and through direct connections to providers. Video observed therapy (VOT) has been conditionally recommended by the WHO as an alternative to directly observed therapy (DOT) and can be delivered both synchronously and asynchronously. Ingestible biosensors (e.g., digital pills) have been shown to be both feasible and acceptable across multiple disease states, though additional research is needed prior to broad-scale deployment. Tools that leverage automation, artificial intelligence (AI) and machine learning can aid in the prediction of nonadherence and provide timely prompts and tailored reminders, thus offering the potential for delivery of personalized medicine. A brief review on how digital technologies can be utilized to support adherence, through both measurement and intervention will be provided. The advantages and limitations of currently available digital technologies for measuring adherence will be discussed, highlighting the unique characteristics and performance of these tools in the context of intervention trials to improve adherence outcomes. Practical strategies, best practices, challenges, and future opportunities will be presented.

22 CONSIDERATIONS FOR MEASURING ADHERENCE WITH LA/ED THERAPIES IN LOW- AND MIDDLE-INCOME

Catherine Orrell
Desmond Tutu Health Foundation, Cape Town, South Africa

Newer long acting (LA) and extended duration formulations are becoming available for the treatment of HIV; removing the need for daily tablet taking. Most data currently available are for those already suppressed on oral daily ART (switch studies). As resource limited settings move towards registration of the first of these LA preparations, we explore who living with HIV might be the best fit for the use of LA/ED preparations in a RLS; and discuss health system considerations in monitoring adherence during the roll out these undoubtedly useful products, which might require more clinic visits and staff skill.

23 FROM EFFICACY TO EFFECTIVENESS: CATALYZING ROLLOUT OF LONG ACTING PrEP

Nyaradzo M. Mgodi
University of Zimbabwe, Harare, Zimbabwe

Translating data from clinical trials into policy and clinical practice. Barriers and facilitators for implementation. Lessons learnt from oral PrEP rollout. Challenges unique to LMIC.

24 INEVITABLE INEQUALITIES: WHY ME KEEP MAKING THE SAME MISTAKES AND HOW WE CAN STOP IT

Laron E. Nelson
Yale University, New Haven, CT, USA

The discovery of the effectiveness of long-acting injectable agents for HIV pre-exposure prophylaxis holds great promise for accelerating an end to the epidemic in the United States and Getting to Zero new HIV infections globally. Nonetheless, inequities that currently persist despite the introduction of daily oral PrEP agents offer important lessons about the potential of new innovations to widen racial, ethnic and gender disparities in HIV incidence. This presentation will discuss the pre-existing interlocking social, structural and policy impediments that threaten to undermine equity in the prevention impact of long-acting injectable agents for PrEP as well as discuss approaches to optimize progress towards achieving global HIV prevention targets by avoiding the repeat of past mistakes.

25 LA PrEP: WHAT WE KNOW AND WHAT WE STILL NEED TO KNOW

Sunil S. Solomon
The Johns Hopkins University School of Medicine, Baltimore, MD, USA

The findings of the two Phase 3 long acting cabotegravir pre-risk exposure prophylaxis trials (HPTN 083 and 084) have heralded a new era of HIV prevention. But demonstration of efficacy in select populations is only the first step. To truly capitalize upon the potential of LA PrEP, it is imperative that these Phase 3 trials are translated to real-world settings to ensure access to all populations vulnerable to HIV infection. However, we do not necessarily know the best ways to deliver LA PrEP in populations that might benefit the most. This presentation will provide an overview of gaps in data ranging from efficacy to acceptability at the individual-, provider- and structural-levels that may be required to usher in a new era of HIV prevention - one that includes LA cabotegravir for PrEP.

26 HIV RESERVOIRS: OBSTACLES TO A CURE

Janet M. Siliciano
The Johns Hopkins University School of Medicine, Baltimore, MD, USA

The major barrier to curing HIV infection is a latent reservoir in resting CD4+ T cells that was initially demonstrated with a quantitative viral outgrowth assay (QVOA) in which T cell activation is used to reverse latency and allow exponential viral outgrowth. In persons living with HIV (PLWH) who are on suppressive antiretroviral therapy (ART), decay of this reservoir is so slow ($t_{1/2}$ = 44 mo) that lifetime persistence is guaranteed. Recent studies of HIV integration sites suggest that selection against inducible proviruses gradually transforms the reservoir to a non-inducible state of deep latency. However, our recent QVOA studies of PLWH on ART for 20 years show no decrease in inducible, replication-competent proviruses. This finding was confirmed with the intact proviral DNA assay (IPDA), a digital droplet PCR assay that excludes most of the defective proviruses that complicate reservoir measurements. Defective proviruses can be excluded by the QVOA, the IPDA, and by sequencing based assays. However, the latter are non-quantitative due to inefficiencies of the long-distance PCRs involved. The reason that the reservoir of inducible, replication-competent proviruses does not continue to decay is that latently infected cells can proliferate following encounter with antigen. Activation of CD4+ T cells through the antigen receptor can reverse latency, exposing cells to viral cytopathic effects and immune clearance. However, cells can also proliferate without latency reversal, allowing generation of large clones of infected cells that still retain the potential to produce virus following a subsequent stimulation. Rebound upon treatment interruption can come from large clones or minor variants representing less than 1% of the reservoir. Thus, preventing rebound requires reduction of the reservoir by many logs, a daunting proposition given that no clear reductions have been proven in clinical trials. A critical factor in rebound is whether the viruses that are induced are resistant to autologous neutralizing antibodies which effectively prevent rebound from a substantial but variable fraction of reservoir viruses. Inducing immune responses to the subset of reservoir variants that are not effectively controlled by the immune response may provide a more feasible approach to cure than non-specific interventions that requiring multi-log reductions to produce a significant delay in viral rebound following treatment interruption.

27 RESTRICTIONS ON REPRODUCTIVE RIGHTS AND THEIR IMPACT ON PEOPLE LIVING WITH HIV

Denise J. Jamieson
Emory University, Decatur, GA, USA

This presentation will review how recent legislative actions in the United States have restricted the reproductive rights of people living with HIV. Specifically, we will use the Dobbs v. Jackson Supreme court decision and subsequent state restrictions as a U.S. case study utilizing specific clinical scenarios and conclude with larger global considerations based on the US example of how abortion restrictions may impact health.

28 APPROACHES TO PEDIATRIC CURE

Philip J.R. Goulder
University of Oxford, Oxford, England, United Kingdom

Major differences exist between HIV infection in children and adults which impact both on cure potential and on the approach to achieving cure. The tolerogenic, highly regulated, early-life immune environment is associated with weak antiviral immunity and rapid HIV disease progression in cART-naive children, but the benefits of low-level immune activation may outweigh the disadvantages in increasing cure potential among early-cART treated children. The combination of early-life immunity and very early initiation of cART in children results in small, low-diversity viral reservoirs that diminish rapidly to undetectable levels. The second major difference between paediatric and adult infection is viral transmission from the mother. In mother-to-child transmission, the transmitted virus has relatively low replicative capacity, which is associated with low reservoir size in the recipient. There are also striking immune sex differences in early life that increase female fetal susceptibility to MTCT and that also appear to decrease cure potential among females, at least in infancy. This presentation will discuss the factors that are currently believed increase cure potential among children and, based on this, the strategies being adopted now and that may be adopted in the future to facilitate paediatric cure.

29 NONHUMAN PRIMATE STUDIES OF PEDIATRIC CURE INTERVENTIONS

Ann Chahroudi
Emory University School of Medicine/Children's Healthcare of Atlanta, Atlanta, GA, USA

Interventions to reduce HIV reservoirs and prevent viral rebound in the absence of ART would be highly beneficial for the 1.7 million children living with HIV. Pediatric nonhuman primate models have informed our understanding of viral persistence following perinatal infection as well as the safety and efficacy of cure strategies. Infant rhesus macaques can be infected with SIV or SHIV strains by experimental infection of dams during pregnancy, inoculation of amniotic fluid, or, more commonly, through oral exposure in the first days of life to simulate intrapartum swallowed blood and/or vaginal secretions or later in infancy to model breast milk transmission. Antiretroviral therapy (ART), most commonly in the form of a single subcutaneous injection of two reverse transcriptase inhibitors and one integrase inhibitor given daily, can then be used to suppress viral replication. Approaches to prevent reservoir establishment, reverse viral latency, clear infected cells, and enhance immune control of virus replication have been tested and results of these studies will be reviewed. Specific cure approaches evaluated in infant nonhuman primate models include polyfunctional antibodies, including those with broadly neutralizing capacity, therapeutic vaccines, Toll-Like Receptor (TLR) agonists, and a non-canonical NF-kB pathway activator. This body of work has highlighted important distinctions in responses to interventions in pediatric vs. adult systems, highlighting the importance of targeted studies at different ages. Finally, ideas for future research in infant nonhuman primates designed to inform cure-directed clinical trials for children living with HIV will be discussed.

30 PROGRESS IN CLINICAL TRIALS OF PEDIATRIC HIV CURE

Roger L. Shapiro
Harvard University, Boston, MA, USA

Children living with HIV are ideal candidates for strategies that may lead to post-treatment control following antiretroviral treatment (ART), and those treated from very early life may have unique features that are especially favorable for cure research. With early effective ART, the latent intact HIV reservoir is drastically reduced as the immune system matures through early life. Such children may have the potential for post-treatment control through the outright elimination of intact virus, its elimination from encoding regions of the genome, or immune control mechanisms. This talk will focus on approaches to pediatric cure that include early ART, the use of broadly neutralizing monoclonal antibodies (bNAbs), and the potential for vaccine-based therapies that may promote post-treatment viral control. The talk will review key studies and recent clinical trials, and opportunities for novel approaches. New data for reservoir dynamics and reservoir markers specific to the pediatric population will be discussed, and the talk will address some of the challenges of performing pediatric cure research (including the need for analytic treatment interruption studies and access to new agents) as well as the unique opportunities to understand avenues to cure offered by pediatric trials.

31 FUTURE DIRECTIONS IN OUTPATIENT THERAPY FOR MILD TO MODERATE COVID-19

Kara W. Chew
University of California Los Angeles, Los Angeles, CA, USA

Robust efforts to rapidly develop outpatient therapies for acute COVID-19 leveraged existing platforms and small molecule antivirals originally developed for other viral infections to rapidly identify multiple effective therapies that reduce risk for hospitalization and death in persons at increased risk for severe COVID-19 and have been authorized for this use. These have included single and combination anti-SARS-CoV-2 monoclonal antibodies (mAbs),

remdesivir, nirmatrelvir/ritonavir, molnupiravir, and convalescent plasma in select populations. However, the limitations of mAbs became evident early, and none are currently authorized for use in the U.S. The remaining available therapies each have limitations, such as drug-drug interactions, challenges with administration, or uncertain and potentially lower efficacy. In this presentation, we will discuss the evidence for antiviral therapy for mild-to-moderate COVID-19 – who should be treated? – in today's context of vaccinations, prior infections, and lower hospitalization and death rates. We will also discuss selection of therapy for immunocompromised persons and touch on the COVID-19 therapeutics pipeline and current challenges in outpatient COVID-19 clinical trial design.

32 VIRAL REBOUND DURING AND AFTER SARS-CoV-2 TREATMENT

Jonathan Z. Li
Harvard Medical School, Cambridge, MA, USA

SARS-CoV-2 viral rebound after treatment with nirmatrelvir-ritonavir is an area of ongoing concern for both patients and providers. However, viral rebound has been described both during and after treatment with other antiviral therapies as well. It also appears that viral and symptom rebound can occur in the absence of antiviral therapy, especially in the immunosuppressed patient population. In this presentation, we will review the pathogenesis and risk factors for viral rebound during and after SARS-CoV-2 treatment. We will also explore the clinical and transmission risk of viral rebound and potential management strategies.

33 WHAT WE KNOW NOW ABOUT LONG COVID SYNDROMES

Michael J. Peluso
University of California San Francisco, San Francisco, CA, USA

It is now widely accepted that SARS-CoV-2 infection can affect long-term health and quality of life. Long COVID, a type of post-acute sequelae of SARS-CoV-2 infection (PASC) characterized by persistent unexplained symptoms, has a major impact on the health of many COVID-19 survivors. Although many individuals (up to 30%) experience some limited symptoms in the weeks and months following COVID-19, the prevalence of severe disabling Long COVID is less common (perhaps <5%). Long COVID syndromes are variable and include general (e.g., fatigue) and organ-system specific symptoms (e.g., shortness of breath, palpitations, neurocognitive symptoms), as well as symptoms resembling other medically unexplained syndromes (e.g., myalgic encephalomyelitis/chronic fatigue syndrome, dysautonomia, post-exertional malaise). For reasons not yet understood, female sex is a strong predictor of Long COVID, as is the presence of certain comorbidities, particularly obesity. Mechanisms that might plausibly contribute to Long COVID include irreversible tissue damage associated with acute infection, persistence of SARS-CoV-2 antigen or possibly a viral reservoir, residual or ongoing immune activation and inflammation, reactivation of other latent human viruses, microvascular dysregulation and thrombotic events, microbial translocation, dysbiosis, and autoimmune phenomena. These mechanisms may act in isolation or in combination to drive Long COVID syndromes. Notably, many if not all of these pathways have been implicated as possible mechanisms for the excess rate of cardiovascular disease and other comorbidities in people living with HIV. Industry engagement in Long COVID research is growing, and NIH funding for clinical trials is emerging through programs such as the RECOVER Initiative. As a result, we are entering an era of experimental medicine, in which potential interventions will be used as tools to probe the biology of the disease. This presentation will provide an overview of the proposed biological mechanisms contributing to Long COVID, with a focus on the current state of evidence, human and animal models, and the emerging therapeutic agenda.

34 IMPLEMENTING THE PrEP AND PEP TOOLKIT

Colleen Kelley
Emory University, Atlanta, GA, USA

Since FDA approval of daily, oral FTC/TDF for HIV pre-exposure prophylaxis (PrEP) in 2012, the HIV prevention field has been diligently working on the development of more options for biomedical interventions to empower users with choice of prevention products. While the metaphorical HIV prevention 'toolkit' remains sparsely filled, some people can now benefit from the use of on-demand oral FTC/TDF or injectable, long-acting cabotegravir for HIV prevention in addition to daily, oral FTC/TDF or FTC/TAF. However, stark racial, gender, and global disparities in PrEP use and significant implementation challenges are hindering the true potential of PrEP to reduce HIV incidence for all populations and achieve the US Ending the HIV Epidemic initiative goals. For clinical providers of PrEP, access to post-exposure prophylaxis (PEP) services, supporting persistence on PrEP, implementing new PrEP follow-up care guidelines, and providing holistic sexual health services are evolving components of cutting-edge PrEP care delivery. In this talk, we will review the current landscape of PrEP and PEP options, identify challenges to wide-spread uptake, summarize current best practices for implementing the PrEP and PEP toolkit, and identify outstanding questions for future research.

35 PREVENTION OF STIs IN ADULTS AND ADOLESCENTS A SEXUAL REPRODUCTIVE HEALTH PERSPECTIVE

James Kiarie
World Health Organization, Geneva, Switzerland

Sustained scale up of STI prevention requires an approach that comprehensively addresses the reproductive health, sexual health and wellbeing of affected and at-risk adults and adolescents. Beyond upcoming interventions such doxyPEP and vaccines that this presentation will focus on, they will be discussed in the context of the entire prevention armamentarium including socio behavior change, condoms, screening and treatment.

The impact of STI prevention interventions will be determined not only by their efficacy but also by a cascade of need, demand, uptake and adherence as seen in other sexual reproductive health areas such a contraception, antenatal care and HIV PrEP. Programs to prevent STIs will need to draw on lessons from these areas for rights-based approaches to address each level of this cascade in the context of client choice. It will be important to consider socio, economic and health system contexts for sustainability and scale up of the prevention of STIs. In this session we will also discuss what is still unknown and where STI prevention needs to go. This will include concerns regarding antimicrobial resistance, the state of evidence and research, appropriateness of the interventions for different populations and STIs, systematic screening, and controversies in the field.

36 MPOX PREVENTION

Jade Ghosn
University of Paris Cité, Paris, France

Since May 2022, dozens of countries worldwide have reported cases of mpox in individuals with no link with endemic countries in Africa. This 2022 multi-country outbreak has mostly affected MSM. On January 5, 2023, a cumulative total of 83 943 confirmed cases have been reported to WHO from 110 countries in all 6 WHO regions, 96.6% being young men. To contain the spread of this outbreak, several countries have recommended vaccination with the 3rd generation live Modified Vaccinia Ankara (MVA), first as a post-exposure vaccination of exposed individuals, and rapidly after as a preventive pre-exposure strategy in at-risk individuals (multiple-partner MSM). In addition, WHO and the United States CDC issued specific risk-reduction guidelines targeted towards the MSM key population (including, but not limited to abstaining from risk exposure until two weeks after the second dose of the vaccine, avoiding kissing, limiting the number of sexual partners). As of January 2, 2023, only 8 of the 110 affected countries have reported an increase in the weekly number of cases, and 79/110 have not reported new cases for over 21 days, the maximum incubation period of the disease. The extent of contribution of vaccination and/or behavioral exposure mitigation strategies in this waning epidemic is unknown. Globally, vaccines are available in North America and Europe, whereas Africa remains without access to vaccines. Thus, even if some countries in Europe and North America can control and eliminate mpox, other countries in Africa will remain affected, which will be inequitable in addition to being also a threat to future outbreaks worldwide. For mpox, stigma, discrimination and racism have been particularly directed against MSM, trans people, gender diverse communities and people from previously affected regions. This may prolong the disease outbreak by refraining people from coming forward for information or seeking testing or care, subsequently undermining public health efforts. Specific interventions addressing misconceptions and stigma are needed. Also, of particular interest are congregated settings (prisons, dormitories, schools), as well as sexual networks of heterosexual individuals. In this talk, we will present current literature on the efficacy of MVA on mpox prevention and we will try to decipher to which extent vaccination roll-out and community engagement did play a role in the control of the 2022 outbreak. Also, we will address the role and how much does asymptomatic infection contribute to spread of the infection.

37 HOW THE HUSH COMPLEX PROTECTS YOUR GENOME FROM RNA-DERIVED RETROELEMENTS

Paul J. Lehner
Cambridge University, Cambridge, United Kingdom

Since the discovery of reverse transcriptase, retrotransposition, the reverse transcriptase-mediated conversion of RNA to cDNA and its subsequent genome integration is now recognized as the predominant route by which our genome acquires new genetic material. Indeed retroelements (retroviruses/retrotransposons) make up >40% of the human genome. This acquisition of new genetic material may be beneficial, increasing genome diversity and resilience, or potentially catastrophic as seen in HIV infection, exposing the genome to invasion from foreign, RNA-derived DNA. Retrotransposition is therefore tolerated, but needs to be closely regulated. My group discovered and characterised 'HUSH' (Human Silencing Hub), an epigenetic transcriptional repressor complex which silences invading DNA. HUSH defends the genome from retroelement attack from outside the cell i.e. retroviruses (including HIV) and from within the cell (LINE1 retrotransposons). HUSH is therefore a unique RNA-dependent genome surveillance system linking transcription to epigenetic gene silencing.

HUSH's ability to immediately identify and silence invading transgenes led to the question: What does HUSH recognize in the genome? We found that HUSH discriminates 'self' from 'non-self' genomic DNA by recognizing 'intronless' DNA, the essential hallmark of reverse transcription. Retroelements (retroviruses/retrotransposons) are RNA-derived and therefore lack non-coding introns. Intronless cDNA provides the 'pathogen-associated molecular pattern', which allows HUSH to distinguish invading retroelements from host genes. This discovery provides an elegant solution to how the host genome silences retroelement-derived invaders, provides the basis for genome immune-surveillance and defines a novel function for introns: to distinguish 'self' from 'non-self' DNA. The identification of an immune-surveillance system to protect the genome from 'reverse genetic flow' (from RNA to DNA) was unanticipated and reveals a new aspect of innate immunity - immunosurveillance of the genome, a compartment not thought to be accessible to the immune system. HUSH is not only of fundamental biological importance - HUSH inhibition also has major therapeutic potential. As HUSH represses long cellular cDNAs >1.5kb, strategies over the last 50 years to express genes for a wide range of purposes have, somewhat unwittingly, been a battle against HUSH. HUSH inhibition therefore has the potential to dramatically improve gene expression, and to release neo-antigens for cytotoxic T-lymphocyte recognition for immunotherapy.

38 THE SCIENCE OF AGING: LESSONS FOR HIV AT THE INTERFACE OF COMMONALITY AND HETEROGENEITY

George A. Kuchel
University of Connecticut, Farmington, CT, USA

In this presentation, Dr George Kuchel will discuss the science of aging and potential lessons for HIV. He will describe our evolving understanding of the biology of aging and how heterogeneity involving these mechanisms may affect multi-morbidity, functional status, and frailty, as well as evidence for how HIV or its treatment may exacerbate these problems. The presentation will also outline opportunities for interventions on these pathways and considerations for trials testing interventions targeting biological aging that may affect multiple discrete disease outcomes and/or functional status.

39 STAGE THE SETTING: THE EPIDEMIOLOGY OF THE MPOX VIRUS

John Brooks
Centers for Disease Control and Prevention, Atlanta, GA, USA

This presentation with provide an epidemiologic snapshot of the multicountry clade IIb 2022 mpox outbreak.

40 MOLECULAR PATHOGENESIS AND THERAPEUTIC TARGETS FOR MPOX VIRUS

Stuart N. Isaacs
University of Pennsylvania, Philadelphia, PA, USA

The 2022 global outbreak of mpox was unprecedented. It was remarkable in that there have been over 80,000 cases in locations that have not historically reported mpox disease. Also, rather than an initial zoonotic exposure, the outbreak has been driven by sustained human-to-human transmissions. The outbreak has tested our preparedness for a smallpox event and there is much we can learn about mpox and the effectiveness of the available countermeasures. Orthopoxviruses are large DNA viruses with genomes of ~200,000 base pairs and replication occurs in the cytoplasm of infected cells. During an infection, two forms of infectious virus are generated that have important roles in transmission and spread within a host. The outbreak has revealed the existence of a previously unidentified subclade (clade IIb) that likely has different properties than the other clades (clade I and IIa). Given the complex lifecycle requiring multiple viral enzymes and proteins involved in immune evasion, there are many therapeutic targets. Use of combination therapies in immunocompromised patients with mpox as well development of additional therapeutics are likely warranted to combat future outbreaks. To successfully contain the current outbreak, continued testing of patient populations with sexually transmitted infections will likely be needed. To prevent future global outbreaks, resources are needed in less wealthy countries.

41 IMMUNOLOGY AND VACCINOLOGY PERSPECTIVES FOR MPOX VIRUS

Sharon Frey
Saint Louis University, St Louis, MO, USA

This 20-minute presentation will include a brief history of mpox and the Modified Vaccinia Ankara (MVA) vaccination (JYNNEOS) approved for use against mpox in the US.

42 EFFECT OF NEW VIRAL VARIANTS ON NEUTRALIZING ANTIBODY POTENCY AND BREADTH

Penny L. Moore
University of the Witwatersrand, Johannesburg, South Africa

South Africa has experienced several waves of SARS-CoV-2 infection following a slow vaccine roll-out. This resulted in extremely high population infection, with >98% of South Africans seropositive, and multiple cases of reinfection with diverse variants, which has shaped the quality and titers of antibody responses. South Africa also bears the brunt of the HIV pandemic, with 7.5 million PLWH. Of these, 2 million people do not access antiretroviral therapy, with implications for their ability to mount effective humoral responses, and to clear SARS-CoV-2 infection. Here, Moore will describe population-level vaccine-induced and hybrid humoral immunity in PLWH and HIV-uninfected individuals.

43 MEMORY B CELL RESPONSES TO NEW VIRUS VARIANTS: RELEVANCE TO THE CONCEPT OF ORIGINAL A

Marion Pepper
University of Washington, Seattle, WA, USA

In this presentation, Dr Marion Pepper will discuss Memory B cell responses to COVID-1

44 EPITOPE MASKING DURING A RECALL RESPONSE: IMPLICATIONS FOR COVID AND HIV VACCINES

Facundo Batista
Harvard University, Cambridge, MA, USA

Some of the first immunological experiments of the 20th century—on antibody feedback inhibition—demonstrated that past exposure does not merely expedite the humoral response to secondary challenges but, rather, alters the nature of that response. Despite this history, the mechanisms underpinning these classic observations and their relationship to modern vaccine design remain obscure. Circulating antibodies produced during a primary challenge can have enhancing or, conversely, inhibitory effects on later humoral responses. Using preclinical vaccine models, we dissected this apparent contradiction to find that the interaction between serum antibodies and the entry of cognate naïve B cell lineages to germinal centers was determined by the interplay of breadth, affinity, and titer. Epitope-focused vaccine designs for HIV-1 elicit circulating antibodies capable of entirely obstructing their cognate naive B cells, with important implications for the ongoing design of boost-phase immunogens. Conversely, SARS-CoV receptor binding domain (RBD) immunization elicits a polyclonal serum response that enhances the proportion of high-affinity cognate B cells in germinal centers, providing a partial explanation for the effectiveness of current boost protocols but also presaging diminishing returns unless new epitopes are introduced. The resolution of these surface-level contradictions points toward a unified interactive model and emphasizes that, to move vaccinology forward, the basic biology of the humoral immune system cannot remain a black box.

45 CASE PRESENTATIONS, DISCUSSION, AND ANSWERS TO AUDIENCE QUESTIONS

Georg Behrens[1], Vidya Mave[2], Judith S. Currier[3], Jennifer Jao[4], Peter Reiss[5], Pam S. Douglas[6], Ntobeko Ntsui[7], Donal O'Shea[8], Giada Sebastiani[9]
[1]Medizinische Hochschule Hannover, Hannover, Germany, [2]Center for Infectious Diseases, Pune, India, [3]University of California Los Angeles, Los Angeles, CA, USA, [4]Northwestern University, Chicago, IL, USA, [5]University of Amsterdam, Amsterdam, Netherlands, [6]Duke University School of Medicine, Durham, NC, USA, [7]University of Cape Town, Cape Town, South Africa, [8]University College Dublin, Dublin, Ireland, [9]McGill University, Montreal, QC, Canada

This case-based and interactive session will provide an up-to-date overview of the pathogenesis, prevention, and treatment of cardiovascular disease and heart failure in HIV medicine. Experts will discuss the state-of-the-art management of non-alcoholic fatty liver disease (NAFLD), including its clinical indicators in people living with HIV. The case presentations and panel discussions will reveal the emerging science on the tight regulation of adult body weight and how obesity affects the immune system in a way that is not dissimilar to the impact of HIV. We will provide insights into new treatments transforming the obesity landscape. After attending this session, the delegates will have an advanced understanding of the development, prevention, and treatment of the most important cardio-metabolic complications in HIV medicine and the consequences for clinical management.

46 COUNTERING VACCINE AND HEALTH MIS AND DISINFORMATION: AN EVIDENCE-BASED APPROACH

Scott C. Ratzan
City University of New York, Princeton, NJ, USA

COVID-19 was the first pandemic that unfolded in an information environment transformed by the ubiquitous mass and social media. Sensational misinformation and deliberate disinformation proliferated capturing hearts and minds. Traditional medical and public health organization's voices were well-intentioned and informed to communicate about the threat of SARS-CoV-2 infection and appropriate countermeasures (for example, masking and vaccines) but were overwhelmed. This new reality on communicating health and science was called out by the World Health Organization in 2020 as an Infodemic. In 2021, the U.S. Surgeon General issued his first report entitled "Confronting Health Misinformation: The U.S. Surgeon General's Advisory on Building a Healthy Information Environment" urging at scale investment to tackle misinformation.

Yet, while warnings were issued, mis- and disinformation proliferated with a palpable casualty emerging with waning vaccine confidence and uptake globally. This fundamental tenet of public health—vaccination—is at risk as a credible defense against disease and illness. This is not due to the microbial vectors but instead the societal response gathering momentum during the COVID "infodemic".

This "endemic" challenge on how we communicate health and science will be described with an evidence-based perspective vetted in the field of communication with conceptual, scientific and theoretical grounding. This presentation will offer approaches to help build scientific, health and vaccine literacy, counter mis- and dis-information and foster strategic health communication capabilities at all levels of society.

47 WHAT CAN I DO? THE CHALLENGE OF HEALTH MISINFORMATION ONLINE

Emily Vraga
University of Minnesota, Minneapolis, MN, USA

Concerns about misinformation are not new, but the rise of social media has supercharged the risks of misinformation to the populace, especially when that misinformation deals with vaccination and communicable disease. Studies have documented the prevalence of online misinformation on a range of topics and platforms. Social media features like fierce competition for audience attention, the potential for online echo chambers, and the prominent role of influencers explain the success of online misinformation. Journalism and health organizations contribute to the problem when they do not follow best practices for communicating scientific consensus and addressing uncertainty in health recommendations. However, understanding the impact of such misinformation is further complicated by recognizing that prevalence of misinformation does not equate to exposure.

As a result, scholars and practioners have turned their attention to identifying best practices for addressing misinformation and reducing its spread. Three strategies for responding to the challenge of misinformation hold the most promise. First, prebunking misinformation involves giving people the tools to build resilience against misinformation before it spreads. This can happen by inoculating people against common misinformation strategies, educating the public with news and health literacy skills, and rebuilding trust in expert institutions tasked with conveying accurate information to the public. Second, debunking misinformation requires directly responding to and offering corrective information to concrete cases of viral misinformation. Third, promoting high quality information ensures that the public can easily find and identify the information they need, filling potential information voids and avoiding overload. Such high quality information must come from a variety of trusted sources to ensure its success in reaching the diverse audiences.

Given the scope and speed with which misinformation can spread on social media, no one strategy will be sufficient to mitigate its potential harms to the public. Instead, we must build layers of resilience to misinformation by promoting high quality information, prebunking misinformation when it is likely to spread, and debunking misinformation after it has gone viral. This response requires concerted efforts from experts, journalists, platforms, and users alike, and each has a role to play.

48 WHAT'S FUELING THE SPREAD OF MISINFORMATION: LOOKING BEYOND FAKE FACTS

Heidi J. Larson
London School of Hygiene & Tropical Medicine, Brussels, Belgium

Misinformation is a systemic issue that breeds on distrust. The solution lies in not only informational debunking, but trust building to counter the fertile ground factors that fuels the spread of viral misinformation. This presentation, "What's fueling the spread of misinformation: Looking beyond fake facts" will focus on the historic and current triggers and fertile group factors that fuel the contagion of mis- and disinformation with impacts of human health and risk disruption to clinical trials and health interventions. Multiple examples and approaches to mitigate the spread of misinformation will be presented.

ORAL ABSTRACTS

100 LENACAPAVIR INHIBITS VIRION MATURATION BY BLOCKING FORMATION OF CAPSID PENTAMERS

Szu-Wei Huang, Lorenzo Briganti, Guochao Wei, Arun Annamalai, Stephanie Bester, Nikoloz Shkriabai, **Mamuka Kvaratskhelia**
University of Colorado, Aurora, CO, USA

Background: HIV-1 capsid contains ~1,500 capsid proteins (CA) arranged into ~250 hexamers and exactly 12 pentamers, which introduce curvatures to allow assembly of a closed, conical structure during virion maturation. Because CA contributes to different aspects of the viral replication cycle, small molecules that target this protein have the potential to exert their effects in both early and late stages of the virus life cycle. Lenacapavir (LEN) is a first-in-class, long-acting, and ultra-potent HIV-1 CA inhibitor. We and others have previously elucidated a multi-modal mechanism of action of LEN during early steps of infection. LEN also potently inhibits late steps of HIV-1 replication. However, the underlying mechanism for this antiviral activity is unclear. In clinical trials resistance mutations to LEN emerged in 8 participants (6 with M66I). However, the underlying mechanism for this major drug resistant substitution is unclear.
Methods: We used transmission electron microscopy to monitor LEN effects on assembly of capsomers *in vitro*, high-resolution X-ray crystallography to investigate effects of the M66I change on LEN and CPSF6 binding to CA hexamers, and virology assays to delineate LEN effects during late steps of HIV-1 replication.
Results: Unexpectedly, we found that during assembly of capsid like particles *in vitro*, LEN specifically blocked formation of CA pentamers but not hexamers. Consequently, unlike cellular cofactor IP6, which promotes formation of conical, closed mature structures comprised of both hexamers and pentamers, LEN treatments yielded open-ended tubular assemblies, which contained exclusively hexamers. Consistent with these observations, our virology assays revealed opposing effects of IP6 and LEN during virion maturation. Additionally, we have elucidated the structural basis for M66I mediated viral resistance to LEN. Remarkably, the beta-side change of Ilu66 introduced steric hindrance specifically with respect to LEN, whereas the M66I change had no effects on IP6 mediated assembly of correctly matured virions or capsid binding to CPSF6, which engages the same hydrophobic CA pocket as LEN.
Conclusion: Our studies have revealed the previously undescribed antiviral mechanism of action of and viral resistance to LEN. These findings provide means for developing second generation CA inhibitors with a higher barrier to resistance.

101 INHIBITION OF NEUTRAL SPHINGOMYELINASE 2 BLOCKS HIV-1 MATURATION

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Background: Sphingomyelinases (SMases) are key enzymes that hydrolyze sphingomyelin (SM) to generate phosphorylcholine and ceramide. Ceramides at the plasma membrane (PM) are critical for a variety of biological functions, including the formation and stabilization of lipid rafts that are assembly sites for HIV. Neutral sphingomyelinase 2 (nSMase2) is the major sphingomyelinase in mammalian cells that generates ceramide at the PM. Previous studies identified phenyl(R)-(1-(3-(3,4-dimethoxyphenyl)-2,6-dimethylimidazo[1,2-b] pyridazin-8-yl)pyrrolidin-3-yl)carbamate (PDDC) as a potent and selective inhibitor of nSMase2. Because of its key role in ceramide biosynthesis, we hypothesized that nSMase2 might be required for HIV-1 assembly, release, or maturation.
Methods: To investigate the role of nSMase2 in HIV-1 replication, we either knocked down nSMase2 with shRNA or treated virus-producing cells with PDDC and monitored virus assembly, release, maturation, and infectivity by using a variety of techniques. *In vitro* selection experiments were performed to obtain PDDC-resistant virus. The impact of PDDC on virus release and morphology of other retroviruses was also analyzed.
Results: We found that the nSMase2 inhibitor PDDC, or shRNA-mediated depletion of nSMase2, impairs HIV-1 Gag and GagPol processing, resulting in a profound impairment in particle maturation and infectivity. The defect in Gag and GagPol processing is not due to direct inhibition of HIV-1 protease activity or reduced incorporation of GagPol into virions. Analysis by thin section transmission electron microscopy and cryo-electron tomography shows that disrupting nSMase2 in virus-producer cells alters the morphology of HIV-1 particles and prevents particle maturation. We found that disruption of nSMase2 blocks the maturation of HIV-1, SIVmac, HIV-2, and equine infectious anemia virus but not that of murine leukemia virus or feline immunodeficiency virus. Using a sub-optimal dose of PDDC in HIV-1-infected human T cells we were able to select and identify mutations in Gag that confer partial resistance to PDDC.
Conclusion: These studies demonstrate a role for nSMase2 in lentiviral morphogenesis and maturation and suggest that specific alterations in the lipid composition of assembling virus particles profoundly impact late stages of the lentiviral replication cycle.

102 INVESTIGATING THE ROLE OF CAPSID STABILITY IN INNATE IMMUNE SENSING OF HIV-1 CORES

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Background: The emergence of antiretroviral drug resistance has hindered progress toward combatting the ongoing HIV/AIDS epidemic. A promising drug target, HIV-1 capsid (CA) is a genetically fragile protein that plays essential roles throughout the viral replication cycle. We recently demonstrated that destabilization of the CA lattice increases the propensity to form aberrant virus particles. In these particles, the genomic RNA (gRNA) and enzymes are localized between the CA lattice and viral envelope. We showed that the lack of protection by the CA lattice results in premature loss of gRNA and integrase (IN) in a proteasome-independent manner. Recent studies have implicated that CA may shield viral nucleic acids from the host sensor proteins that initiate antiviral responses. Here, we directly tested whether tampering with the stability of the HIV-1 CA lattice results in premature exposure and innate sensing of viral nucleic acids in infected cells.
Methods: To this end, we examined the expression levels of interferon stimulated genes (ISGs) upon infection of monocyte-like THP-1 cells with WT and mutant viruses bearing cores with altered stability. THP-1 cells were infected with equivalent numbers of VSV-G pseudotyped viruses with CA stabilizing or destabilizing mutations. ISG induction was assessed by qRT-PCR at 24 and 48 hours post-infection. We applied one-way or two-way ANOVAs to continuous variables and assessed statistical significance at the 0.05 level.
Results: The WT virus and viruses with destabilizing mutations induced low to moderate levels of ISG expression in a reverse transcription-dependent manner. Contrary to our predictions, we found that stabilization of the capsid lattice through the E45A substitution induced a more potent innate immune response. Sensing of viruses bearing hyperstable capsids was also dependent on reverse transcription and the cGAS-STING pathway. Interestingly, we found a differential requirement for TREX1 exonuclease for sensing of WT versus CA E45A HIV-1 and no involvement of the recently reported CA-binding protein PQBP1 in innate sensing.
Conclusion: Taken together, our study provides novel insight into yet another proposed role of CA in the evasion of innate immune sensing and suggests that viral nucleic acids remain accessible to innate sensing despite capsid stabilization.

103 MUTATIONS OUTSIDE INTEGRASE LEAD TO HIGH-LEVEL RESISTANCE TO DOLUTEGRAVIR

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Background: We reported that mutations in the envelope glycoprotein (Env) can broadly reduce HIV-1 susceptibility to ARVs. The aim of the current study was to examine the pathway(s) by which HIV-1 develops high-level resistance to the integrase (IN) strand transfer inhibitor (InSTI) dolutegravir (DTG).

Methods: Long-term passaging of lab-adapted and primary viral isolates using the SupT1 T-cell line was performed over nearly one year with an escalating concentration (0.1 – 2,000 nM) of DTG. Viral sequence analysis was performed longitudinally. Identified mutations were introduced into WT HIV-1 molecular clones and the replication kinetics and viral infection through cell-cell contact were examined in the presence and absence of drug. To measure the multiplicity of infection (MOI), we monitored viral replication by co-infection with eGFP- and mRuby-expressing reporter viruses harboring the Env mutations.
Results: In a manner independent of viral isolate and coreceptor usage, HIV-1 became resistant to DTG by sequentially acquiring mutations in Env and Gag-nucleocapsid (NC) in the absence of resistance mutations in IN. The selected NC mutations clustered in the zinc-finger domain and conferred modest (3-5 fold) resistance to InSTIs. An Env mutant, 7XEnv, containing seven substitutions (V85A, S162K, R298K, Q363R, A541V, V693I and G825E) exhibited faster-than-WT replication and resistance to multiple classes of ARVs, with the fold resistance being markedly higher for InSTIs. Viral transmission of 7XEnv through cell-cell contact is 15-fold more efficient than WT, resulting in a higher MOI and reduced sensitivity to DTG. Viral infection using VSV-G-pseudotyped viruses over a range of MOIs revealed that InSTIs are more readily overwhelmed by high MOI compared to RT inhibitors. Co-infection experiments using fluorescently tagged reporter viruses demonstrated that 7XEnv infection leads to a higher number of cells expressing multiple proviruses compared to WT.
Conclusion: These findings demonstrate that a combination of mutations in Env and NC can confer high-level resistance to InSTIs in the absence of IN mutations. The Env mutations overcome inhibition by InSTIs through increased MOI mediated by highly efficient cell-cell transfer. These results advance the understanding of how HIV-1 can evolve resistance to ARVs in the absence of mutations in drug-target genes and provide new insights into the contribution of cell-cell transfer to viral replication and drug resistance.

104 MX2 ANTIVIRAL SPECIFICITY IS AFFECTED BY GTPase ACTIVITY AND CAPSID-CypA INTERACTIONS

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Background: Mx2 (myxovirus resistance 2), an antiviral protein whose expression is strongly upregulated by type 1 interferon, localizes to the nuclear pore complex (NPC) and inhibits HIV-1 infection by preventing nuclear import of the viral preintegration complex. The HIV-1 capsid (CA) is the major viral determinant for sensitivity to Mx2, and complex interactions between Mx2, CA, nucleoporins (Nups), cyclophilin A (CypA), and other cellular proteins influence the outcome of viral infection. Like Mx1, Mx2 is comprised of a GTPase domain connected to a carboxy-terminal stalk domain via a tripartite bundle-signaling element (BSE), however while GTPase function and higher order oligomerization are generally required for the antiviral activity of Mx1, they are dispensable for the anti-lentiviral activity of Mx2.
Methods: To explore the interactions between Mx2, the viral CA, and CypA, we utilized a CRISPR/AAV approach to generate CypA knock-out cell lines as well as cells that express CypA from its endogenous locus, but with specific point mutations that would abrogate CA binding but should not affect enzymatic activity or cellular function.
Results: We found that antiviral activity of Mx2 was altered in CypA mutant cell lines in a virus-specific manner, as elimination of CA-CypA interactions reduced the antiviral activity of Mx2 against HIV-1 but not HIV-2. We additionally found that infection of CypA knock-out and point mutant cell lines with wild-type HIV-1 and CA mutants recapitulated the phenotypes observed upon cyclosporine A (CsA) addition, indicating that effects of CsA treatment are the direct result of blocking CA-CypA interactions and are therefore independent from potential interactions between CypA and Mx2 or other cellular proteins. Interestingly, abrogation of GTP hydrolysis by Mx2 conferred enhanced antiviral activity when CA-CypA interactions were abolished. Elimination of GTPase activity also altered the Nup requirements for Mx2 localization and activity against wild-type HIV-1 and the G89V CA mutant which does not bind CypA.
Conclusion: Our data demonstrate that the antiviral activity of Mx2 is affected by CypA-CA interactions in a virus-specific and GTPase activity-dependent manner. These findings further highlight the importance of the GTPase domain of Mx2 in regulation of substrate specificity and interaction with nucleocytoplasmic trafficking pathways.

105 HOST CELL GLYCOSYLATION DIFFERENTIALLY AFFECTS CCR5- AND CXCR4-TROPIC HIV-1 INFECTION

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Background: HIV-1 infection typically involves a selection bottleneck that leads to successful transmission of one or a few HIV variants, which are nearly always CCR5-tropic (R5). While the preferential transmission of R5 over CXCR4-tropic (X4) viruses is well known, the viral or host properties that drive this selection remain a longstanding question in the field. We recently performed CRISPR knockout screens in primary CD4+ T cells to enrich for HIV restriction factors and identified SLC35A2 as a candidate inhibitory factor of a X4 virus but not an R5 variant. SLC35A2 is a human UDP-galactose transporter whose inactivation causes truncated glycans. We therefore hypothesized that normal host cell glycosylation impairs X4 infection, which may contribute to R5 selection during transmission.
Methods: For screen validation, we inactivated SLC35A2 in CD4+ T cells from two donors and infected with the full-length R5 (Q23.BG505) and X4 (LAI) strains used in the screen as well as four more R5 (Q23, SF162, BaL, 93MW965) and X4 (NL4-3, 92UG021, 92UG029, 92UG024) viruses. Glycan features were assessed via lectin staining. Finally, we analyzed a published RNA-seq dataset to compare *SLC35A2* expression in CD4+ T cells from matched blood and female genital tract samples.
Results: SLC35A2 edited CD4+ T cells enhanced X4 infection, whereas R5 infection was notably lower than wildtype cells. This phenotype was consistent across eight additional strains: SLC35A2 editing increased X4 infection 5-28 fold and reduced R5 levels 36-96 fold. Lectin staining detected a higher prevalence of terminal b-GlcNAc on N-glycans (5.31% GS-II+) and terminal a-GalNAc on O-glycans (4.61% VVA+) in SLC35A2 inactivated cells whereas these populations were negligible (< 1%) in wildtype cells, indicating altered, truncated glycosylation with SLC35A2 knockout. Examination of *SLC35A2* expression patterns revealed that SLC35A2 expression is elevated in CD4+ T cells in the important transmission site of the lower female genital tract as compared to the blood.
Conclusion: Our study uncovered an underappreciated role for host cell glycans on HIV infection; namely, that wildtype glycosylation promotes R5 infection while hindering that of X4. This differing phenotype may be even more pronounced in the genital tract due to elevated levels of *SLC35A2*, a gene required for normal glycosylation. The differential impact of host cell glycosylation on X4 and R5 viruses may therefore largely drive R5 selection during HIV transmission.

106 THE FRACTION OF CELLS WITH UNSPLICED HIV RNA IS NOT ASSOCIATED WITH PLASMA VIREMIA

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Background: Untreated viremic controllers (VC) have low levels of plasma HIV RNA compared to untreated non-controllers (NC). We asked if the different levels of viremia between VC and NC were better explained by the fraction of infected PBMC containing unspliced HIV RNA (usRNA) or by the number of copies of usRNA in single infected cells.
Methods: PBMC were obtained from donors with chronic HIV infection who were untreated VC (n=8; plasma HIV RNA 60-2,000 copies/mL), untreated NC (n=7; plasma HIV RNA 5,700-275,000 copies/mL), or NC on ART (n=5; plasma HIV RNA < 50 copies/mL). We applied cell-associated HIV RNA and DNA single-genome sequencing (CARD-SGS) to estimate the total number of infected cells/million PBMC, the fraction of infected cells containing usRNA, and the levels of usRNA in single infected cells (N=9,557).
Results: The number of infected cells was significantly lower in VC (median 32 HIV DNA/million) compared to NC (1,092/million) ($p < 0.01$) and donors on ART (117/million) ($p < 0.01$). The number of cells with HIV usRNA/million PBMC was also significantly lower in VC (median 2.3 HIV usRNA/million) compared to NC (89.4/million) ($p < 0.01$) and donors on ART (45.8/million) ($p < 0.01$). Both were positively correlated with the level of viremia in the untreated donors

(Spearman=0.77; p=0.001). By contrast, the fraction of infected cells with usRNA did not differ across the 3 groups (median 9% in VC, 7% in NC, and 18% in those on ART; p=0.46; Figure 1A) and was not associated with detectable plasma viremia (Spearman= -0.32, p=0.18). Single infected cells with >20 molecules of usRNA were detected in 6/7 donors in the NC group, 2/9 donors in the VC group (p=0.04, Fisher's exact test), and were not detected in ART-treated group (0/5 donors; Figure 1B).

Conclusion: These data reveal that levels of plasma viremia are determined by the total number of infected cells and the number of rare cells with high levels of HIV usRNA but not by differences in the fraction of infected cells with HIV usRNA. The finding that ~80-95% of infected cells in individuals with chronic HIV infection do not contain HIV usRNA, independent of levels of plasma viremia or ART status, implies that viremic control is not from a block to proviral expression, but rather by a block of viral spread to other cells.

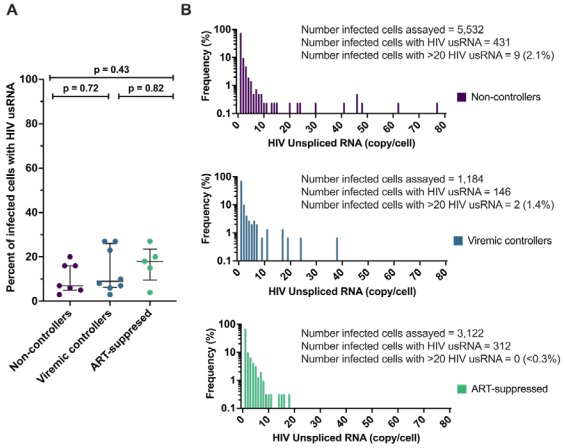

Figure 1. Difference in the fraction of infected cells with HIV usRNA in Non-controllers, Viremic controllers, and donors on ART. (A) The fraction of infected cells with HIV usRNA measured by CARD-SGS (ordinary one-way ANOVA with Tukey's multiple comparison test). (B) Distribution of the number of HIV usRNA copies per cell in each group.

107 HUMAN ANTI-ACE2 MONOCLONAL ANTIBODIES AS PAN-SARBECOVIRUS PROPHYLACTIC AGENTS

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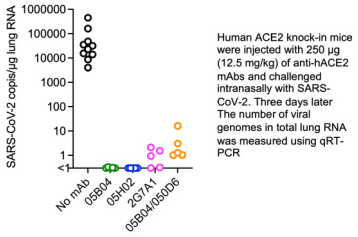
Background: Human monoclonal antibodies from convalescent individuals that target the SARS-CoV-2 spike protein have been deployed as therapeutics against SARS-CoV-2. However, nearly all of these antibodies have been rendered obsolete by SARS-CoV-2 variants that evolved to resist similar, naturally occurring antibodies. Moreover, Most SARS-CoV-2 specific antibodies are inactive against divergent sarbecoviruses

Methods: By immunizing mice that carry human immunoglobulin variable gene segments we generated a suite of fully human monoclonal antibodies that bind the human ACE2 receptor (hACE2) rather than the viral spike protein and were engineered to lack effector functions such as ADCC.

Results: These ACE2 binding antibodies block infection by all hACE2 binding sarbecoviruses, including emergent SARS-CoV-2 variants, with a potency that of the most potent spike binding therapeutic antibodies. Structural and biochemical analyses revealed that the antibodies target an hACE2 epitope that engages SARS-CoV-2 spike. Importantly, the antibodies do not inhibit hACE2 enzymatic activity, nor do they induce ACE depletion from cell surfaces. The antibodies exhibit favorable pharmacology in human ACE2 knock in mice and provide near complete protection of hACE2 knock-in mice against SARS-CoV-2 infection.

Conclusion: ACE2 binding antibodies should be useful prophylactic and treatment agents against any current and future SARS-CoV-2 variants, as well as hACE2-binding sarbecoviruses that might emerge as future pandemic threats.



108 SARS-CoV-2 VARIANTS EVOLVED CONVERGENT STRATEGIES TO REMODEL THE HOST RESPONSE

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Background: Five variants of concern (VOCs) have dominated COVID-19 disease etiology since 2020—Alpha, Beta, Gamma, Delta, and Omicron—possessing over 150 defining genomic alterations. Here, we used global proteomic and genomic approaches to study the host responses and selective forces driving VOC evolution.

Methods: We infected Calu-3 human lung epithelial cells with 5 VOCs and 2 wave 1 (W1) controls and performed mass spectrometry abundance proteomics, phosphoproteomics, and mRNA sequencing at 10 and 24 hours post infection. We additionally performed affinity purification mass spectrometry (APMS) by individually expressing all VOC mutant viral proteins (52) and corresponding W1 forms in human cells to quantify differential virus-host protein-protein interactions. Data was integrated using network modeling and bioinformatics to pinpoint VOC-specific differences. Four novel mutant viruses were developed using reverse genetics technology to validate the impact of specific genomic alterations.

Results: We discovered VOCs evolved convergent molecular strategies to remodel the host response by modulating viral RNA and protein levels (most notably of N, Orf9b, and Orf6), altering nucleocapsid phosphorylation, and rewiring virus-host protein complexes. Integrative systems analyses revealed that Alpha, Beta, Gamma, and Delta ultimately converged in the suppression of interferon stimulated genes (ISGs) relative to W1 viruses, but Omicron BA.1 did not, and Delta induced more pro-inflammatory genes compared to other VOCs. Altered regulation of ISGs correlated with the expression of viral innate immune antagonist proteins, including Orf6, N, and Orf9b; for example, Omicron BA.1 depicted a 2-fold decrease in Orf6 expression. We identified mutations that alter expression of Orf9b (N D3L and N -3A del) and the novel VOC protein N* (N R203K/G204R), and confirmed Orf6 innate immune antagonism using recombinant virus technology. Remarkably, Omicron BA.4 and BA.5 regained strengthened innate immune antagonism compared to BA.1, which again correlated with enhanced Orf6 expression, though dampened in BA.4 by a mutation (D61L) that we discovered disrupts the Orf6-nuclear pore interaction.

Conclusion: Collectively, our findings suggest SARS-CoV-2 convergent evolution overcomes human innate immune barriers, laying the groundwork to understand future coronavirus evolution associated with immune escape and enhanced human-to-human transmission.

109 SimpliciTB RESULTS AND HEPATIC SAFETY OF PRETOMANID REGIMENS +/- PYRAZINAMIDE

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Background: Pre-clinical and early-phase studies of a bedaquiline-pretomanid-moxifloxacin-pyrazinamide (B-Pa-M-Z) regimen show significant treatment-shortening potential for TB. Pa has been studied clinically in various

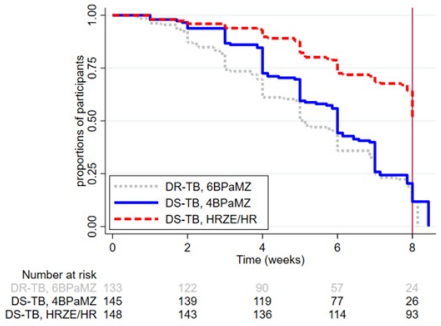
combinations, with and without Z. Safety has been carefully monitored in these studies.

Methods: SimpliciTB study was an open-label safety and efficacy study in 303 DS-TB patients randomized 1:1 to 4-months BPaMZ vs 6-months HRZE, and 6-months BPaMZ in 152 DR-TB patients. Primary efficacy endpoint was time to culture negative status through 8 weeks; a key secondary endpoint was relapse-free cure at week 52. In a separate analysis, 3 groups representing PaZ-containing regimens (PaZX, n=841), BPaL (n=290), and HRZE (n=340) were aggregated across all 6 TB Alliance studies of ≥8 weeks. Liver safety (max treatment-emergent [TE] ALT elevations) was analyzed through 8 weeks.

Results: In the SimpliciTB MITT population, 47% and 84% of DS-TB participants (and 86% of DR-TB participants) were culture-negative by week 8 in HRZE and 4BPaMZ arms respectively, meeting superiority of 4BPaMZ over HRZE; HR 2.9 (95% CI 2.2 – 4.0) (figure 1). At week 52, 7%, 17%, and 17% of participants had unfavourable outcomes in the HRZE, 4BPaMZ and 6BPaMZ arms, respectively (TB-MITT population); 4-month BPaMZ did not meet non-inferiority (12% margin) vs HRZE. The higher proportion of BPaMZ unfavourable outcomes was driven primarily by hepatotoxicity-related treatment discontinuations: HRZE (0%), 4BPaMZ (7%) and 6BPaMZ (6%). In the PP population (treatment discontinuations excluded), 4BPaMZ was non-inferior to HRZE: risk difference 1.8% (95% CI: -2.9%-6.5%). The multistudy analysis showed incidences (95% CI) of TE ALT elevations >3xULN of 10.8% (8.8-13.1), 8.6% (5.7-12.5), and 5.6% (3.4-8.6), respectively, in those receiving PaZX, BPaL, and HRZE. Severe (grade 4) TE ALT elevations >8xULN occurred in 4.6% (3.3-6.3), 1.0% (0.2-3.0), and 2.7% (1.2-5.0), with median increases of 20x, 10x, and 10x, respectively, for PaZX, BPaL, and HRZE.

Conclusion: SimpliciTB results validate observations from pre-clinical relapsing mouse model experiments which identified BPaMZ as a regimen with high efficacy and treatment shortening potential, but hepatic toxicity precluded treatment completion in ~6-7% of patients. The multistudy analysis showed that Pa-Z-containing regimens were associated with a hepatic safety profile distinct from BPaL, with a higher incidence and degree of grade 4 ALT elevations.

SimpliciTB Primary efficacy analysis Time to culture negative status by 8 weeks (MITT)



110 STANDARD VS DOUBLE DOSE DOLUTEGRAVIR IN HIV-ASSOCIATED TUBERCULOSIS: WEEK 48 RESULTS

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Background: Rifampicin induces genes important in the metabolism and transport of dolutegravir. The resulting drug-drug interaction can be overcome by doubling the daily dose of dolutegravir, but this increases costs and risk of stockouts in high burden settings. We recently presented week 24 findings from the RADIANT-TB trial that showed adequate virological suppression with both standard and double dose dolutegravir in participants on rifampicin-based antituberculosis therapy. Here we present week 48 outcomes in order to detect later emergence of dolutegravir resistance.

Methods: RADIANT-TB was a phase 2b, non-comparative, randomized, double-blind, placebo-controlled trial of standard versus double dose dolutegravir among adults with tuberculosis on rifampicin-based therapy conducted in Khayelitsha, Cape Town, South Africa. Participants were randomized to receive tenofovir/lamivudine/dolutegravir and either supplemental dolutegravir or placebo continued for two weeks after stopping antituberculosis therapy. Key outcomes at week 48 were proportion with HIV-RNA < 50 copies/mL (by FDA snapshot algorithm modified intention-to-treat and per protocol), treatment emergent dolutegravir resistance, and adherence assessed by tenofovir-diphosphate (TFV-DP) on dried blood spots (DBS).

Results: 108 participants were enrolled: 38% female, median baseline CD4 cell count 184 cells/mm^3 (IQR 145 to 316) and HIV-RNA 5.2 log$_{10}$ copies/mL (IQR 4.6 to 5.7). Proportions with virologic suppression at weeks 24 and 48 were similar between arms (Table 1), but lower at week 48 than at week 24. One participant in the supplemental dolutegravir arm and 3 in the placebo arm were lost to follow-up by week 48 and deemed not suppressed in the modified intention-to-treat analysis. None of the 19 participants with study defined virological failure developed treatment emergent resistance to dolutegravir. TFV-DP DBS concentrations indicating poor adherence (< 350 fmol/punch) were found in a higher proportion of participants at week 48 than at week 24 (12/93 versus 4/103; P-value = 0.02). Grade 3 and 4 adverse events occurred at similar rates between arms at week 48.

Conclusion: Virologic suppression was lower at 48 than at 24 weeks for both arms, likely due to declining adherence assessed by TFV-DP DBS. Our findings suggest that standard dose dolutegravir with rifampicin-based antituberculosis therapy might be adequate.

Proportions with HIV-RNA <50 copies/mL by arm at weeks 48 and 24

	TLD + 50mg DTG (n=53)	TLD + Placebo (n=55)
Week 48		
mITT, n (% [95% CI])	34/49 (69% [55-82%])	35/52 (67% [53-80%])
PP, n (% [95% CI])	34/47 (72% [57-84%])	35/46 (76% [61-87%])
Week 24		
mITT, n (% [95% CI])	43/52 (83% [70-92%])	44/53 (83% [70-92%])
PP, n (% [95% CI])	43/51 (84% [71-93%])	44/52 (85% [72-93%])

TLD = tenofovir/lamivudine/dolutegravir, mITT = modified intention-to-treat, PP = per protocol

111 INCREASED TB PREVENTIVE THERAPY COVERAGE WITH INTEGRATED COMMUNITY-BASED IPT AND ART

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DO ART Study Team

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Background: Tuberculosis (TB) is a leading cause of mortality among people living with HIV and is prevented by isoniazid preventive therapy (IPT). Uptake is low despite guidelines that recommend IPT for all people with HIV (PWH) in high TB prevalence settings, in part due to limited integration into ART services. We tested the efficacy of integrated community-based ART and IPT services on IPT initiation and continuation.

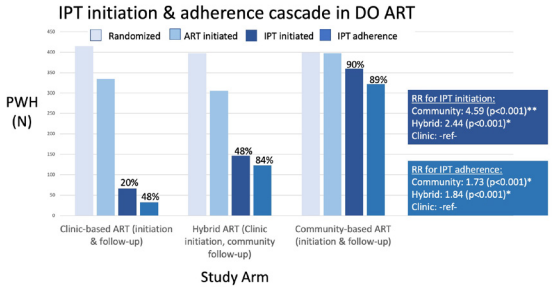
Methods: The DO ART Study tested integrated IPT and community-based ART in KwaZulu-Natal, South Africa. PWH were randomized 1:1:1 to 1) clinic-based services including standard-of-care IPT; 2) community-based ART and IPT initiation, delivery, quarterly refills, and decentralized monitoring; or 3) hybrid services with clinic ART and IPT initiation and community follow-up. In intervention groups, participants were screened by lay health workers for TB symptoms and contraindications to IPT, and if eligible, were offered IPT 1 month after ART initiation. Quarterly IPT refills were synchronized with ART dispensing. IPT initiation and adherence were assessed through chart review, medication dispensing logs, and quarterly self-report. IPT continuation was defined as refill receipt. A subset of participants had urine tested for isoniazid metabolites at community IPT refill visits to assess concordance with self-reported adherence.

Results: Between 2/2017-3/2019, 1,212 PLWH, including 540 (45%) men, were randomized. Of 1,039 (441, 42% men) who initiated ART, 573 (55%) initiated IPT during 12-months follow-up. Compared to clinic-based IPT uptake of 20%, IPT initiation was 90% in the community-based delivery group (RR=4.59, 95% CI 3.69-5.71), and 48% in the hybrid group (RR=2.44, 95% CI 1.91-3.12). Among participants initiating IPT, continuation was similar in the hybrid (84%) (RR=1.84 95% CI 1.43-2.37) and community-based delivery (89%) groups (RR=1.73, 95% CI 1.33-2.34); compared to 48% continuation in the clinic-based group. Gender was not associated with IPT use. Isoniazid metabolites were present in 164/259 (63%) of participants who reported taking IPT.

Conclusion: Community-based delivery of IPT with ART was associated with more than four-fold higher rate of IPT initiation and two-fold higher

continuation than standard clinic-based care in South Africa. High levels of IPT uptake and continuation were achieved through integration into community-based ART delivery, and demonstrated feasibility, adherence, and acceptability. Urine testing can complement self-reported adherence measures.

IPT initiation and adherence cascade in DO ART



112 RCT OF ECONOMIC INCENTIVES FOR REDUCED ALCOHOL USE AND INH ADHERENCE AMONG PWH

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Background: Alcohol use is common among persons with HIV (PWH) and is a risk factor for TB disease, non-adherence to INH preventive therapy (IPT) and antiretroviral therapy (ART), and hepatotoxicity during IPT. Interventions are urgently needed to reduce hazardous alcohol use and improve IPT adherence among PWH.

Methods: We conducted a 2x2 factorial randomized controlled trial among PWH (≥18 years) on ART, with latent TB infection (PPD≥5mm) and hazardous alcohol use in Uganda. We randomized 680 participants (1:1:1:1) initiating 6-months of IPT to: no incentives (Arm 1 control) or incentives contingent on no recent alcohol use (Arm 2), recent INH adherence (Arm 3), or both (awarded independently, Arm 4). The escalating financial incentives were contingent on monthly point-of-care (POC) urine tests that were negative for ethyl glucuronide, a biomarker of recent alcohol use (Arms 2 & 4), or positive on IsoScreen, a biomarker of recent INH use (Arms 3 & 4). The primary alcohol use outcome was non-hazardous use by self-report (Alcohol Use Disorder Identifier Test-Consumption [AUDIT-C< 3 women, < 4 men], prior 3 months) and phosphatidylethanol (PEth, past month alcohol biomarker) < 35 ng/mL at 3- and 6-months post-enrollment. The primary INH adherence outcome was >90% MEMS cap bottle opening of days INH prescribed. Secondary outcomes included PEth and MEMS cap openings as continuous measures.

Results: At baseline (N=680), median age was 39 (IQR: 32-47), 470 (69%) were male, 598/663 (90%) had HIV viral load < 40 c/mL, median AUDIT-C was 6 (IQR: 4-8) and median PEth was 252 ng/mL (IQR: 87-579). Non-hazardous alcohol use was more likely in the arms with the alcohol intervention (Arms 2+4) than those with no alcohol intervention (Arms 1+3): 17.6% vs. 9.9%, respectively, with adjusted risk difference of 7.6% (95% CI: 2.7%-12.5%, p=0.003). Incentives for INH adherence did not increase INH adherence vs control, with MEMS adherence of 72.8% and 72.9% in the INH incentive (Arms 3+4) and no INH incentive arms (Arms 1+2): adjusted risk difference -0.2%; 95% CI 7.0%-6.5%, p=0.944). Secondary outcomes are shown in **Table**.

Conclusion: Escalating financial incentives contingent on reduced alcohol use and/or INH adherence by monthly POC testing led to significant reductions in biomarker-confirmed alcohol use, but no change in INH adherence among PWH with latent TB infection and hazardous alcohol use receiving IPT. This trial is among the first to show efficacy of incentives in reducing alcohol use in sub-Saharan Africa.

Primary and secondary endpoints in a randomized controlled trial of economic incentives for reduced alcohol use and increased INH adherence among PWH with latent TB infection and hazardous alcohol use in Uganda.

	Alcohol Reduction			INH Adherence		
	Intervention (Arms 2+4)	Control (Arms 1+3)	p value*	Intervention (Arms 3+4)	Control (Arms 1+2)	p value*
Main outcome: Non-hazardous alcohol use (PEth <35 ng/mL **and** non-hazardous AUDIT-C) at 3- **and** 6-months (%, 95%CI)	17.6% (13.8-22.2)	9.9% (7.0-13.8)	0.003	N/A	N/A	-
Main outcome: INH adherence (>90% bottle opening by MEMS cap of days INH prescribed (%, 95% CI)	N/A	N/A	-	72.8% (67.8-77.4)	72.9% (67.7-77.5)	0.944
PEth level (ng/mL) at 6 months (median, 95% CI)	134.0 (106.2-174.8)	170.5 (152.0-226.8)	0.084	N/A	N/A	-
Proportion MEMS cap openings of prescribed days (median, 95% CI)	N/A	N/A	-	96.7% (95.6-97.2)	96.7% (95.6-97.2)	0.152

*p-values based on multivariable models controlling for sex, site, and other intervention arm. The continuous PEth model additionally controlled for baseline PEth level.

113 EFFICACY AND SAFETY OF 8-WK TUBERCULOSIS TREATMENT REGIMENS IN THE TRUNCATE-TB TRIAL

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The TRUNCATE-TB trial team

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Background: The TRUNCATE-TB trial (NCT03474198) found that the TRUNCATE strategy – initial treatment for 8 weeks (with BDQ/LZD regimen; extended up to 12 weeks for unsatisfactory clinical response); post-treatment follow-up; prompt retreatment (standard regimen) for relapse – was non-inferior to the standard treatment strategy at 96 weeks. Here we analyse efficacy and safety of the trial *regimens* (distinct from the efficacy and safety of the overall TRUNCATE *strategy* in which they were deployed).

Methods: Participants with rifampicin-susceptible pulmonary TB at 18 Asian/African sites were randomised (adaptive design) to receive the standard regimen for 24 weeks or one of four novel 5-drug regimens for 8-weeks (up to 12 weeks; table). We assessed regimen efficacy using *unfavorable outcome* (UFO; composite including treatment failure; relapse; death; non-attendance at week 96, without evidence of prior disease clearance); and estimated Bayesian probability that UFO risk difference vs standard treatment was < 12%. Safety was assessed by adverse events of grade ≥3 (AE≥3) during/within 30 days of stopping the initial regimen.

Results: Of the 674 randomised participants (male 62%, smear positive 73%, lung cavitation 54%), 4 withdrew/were lost to follow-up by week 96; overall, 80% assigned novel regimens stopped after exactly 8 weeks, 9% extended up to 10 weeks; 3% extended up to 12 weeks. Three arms (standard, hRIF/LZD, BDQ/LZD) enrolled to full sample size; two (hRIF/CFZ, RPT/LZD) ceased enrollment early for pragmatic reasons (not efficacy/safety; n in table). Proportions with UFO were 3.9%, 25.0% and 13.8% in the standard, hRIF/LZD and BDQ/LZD arms respectively; probability that risk difference vs standard arm was < 12% was 0.01 in hRIF/LZD and 0.81 in BDQ/LZD arm; the risk difference vs standard arm was reduced in subgroups with lower disease burden. Proportions with AE≥3 were 13.8%, 10.9%, and 11.1% in the standard, hRIF/LZD and BDQ/LZD arms respectively; 2 (1.1%) acquired BDQ resistance in the BDQ/LZD arm, none acquired resistance in other arms.

Conclusion: Unfavourable outcome was more frequent with 8-week regimens than the 24-week regimen, as expected. However, with the BDQ/LZD regimen the excess was modest and likely can be reduced further by adjusting criteria for treatment extension by subgroup; the regimen was safe. An 8-week initial treatment duration appears to be a feasible target for most people with TB, with the excess of unfavourable outcomes manageable within the TRUNCATE strategy.

Table: Randomised drug regimens

Arm (n randomised)	Drugs in regimen				
Standard regimen, 24w (n=181)	Rifampicin 10mg/kg	Isoniazid	Pyrazinamide	Ethambutol	-
High-dose rifampicin and linezolid, 8w (n=184) (hRIF/LZD)	Rifampicin 35mg/kg	Isoniazid	Pyrazinamide	Ethambutol	Linezolid 600mg
High-dose rifampicin and clofazimine, 8w (n=78) (hRIF/CFZ)	Rifampicin 35mg/kg	Isoniazid	Pyrazinamide	Ethambutol	Clofazimine 200mg
Rifapentine and linezolid, 8w (n=42) (RPT/LZD)	Rifapentine 1200mg	Isoniazid	Pyrazinamide	Levofloxacin 1000mg	Linezolid 600mg
Bedaquiline and linezolid, 8w (n=189) (BDQ/LZD)	Bedaquiline 400mg daily, 2w; 200mg 3/w, 6w	Isoniazid	Pyrazinamide	Ethambutol	Linezolid 600mg

114 PanACEA SUDOCU COMBINATION DOSE-FINDING TRIAL SHOWS SUTEZOLID IS A SAFE OXAZOLIDINONE

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Background: Linezolid is a critical component of current MDR-TB treatment, but is too toxic for wider use. Sutezolid is a novel oxazolidinone, with a hypothesized improved safety profile. Sutezolid was previously only clinically tested in a 14-day monotherapy study.

Methods: The PanACEA Sutezolid Dose-Finding and Combination Evaluation (SUDOCU) study was a novel approach at defining the exposure-response relationship of a drug in a combination that would be usable in DS-and MDR-TB, allowing the assessment of late toxicities. Participants with drug-sensitive pulmonary TB were randomized to sutezolid 0mg, 600mg OD, 1200mg OD, 600mg BD or 800mg BD, in addition to bedaquiline, delamanid and moxifloxacin at standard doses, for 12 weeks. The primary efficacy endpoint was the slope of decline of bacterial load, measured by MGIT TTP, weekly for 12 weeks. Safety outcome included oxazolidinone class toxicities myelosuppression and neuropathy.

Results: 75 participants were enrolled in four sites in Tanzania and South Africa. 59 (75%) were male, 2 (3%) were people living with HIV and the median weight was 53.0kg. TTP increased over 12 weeks in all arms; there was no evidence for a difference in slope between arms. No clinical neuropathy occurred during 12 weeks of treatment. One potential event of myelosuppression was noted: an HIV-coinfected patient on ARVs developed neutropenia < 500/µl with a possible etiology of benign ethnic neutropenia. No anemia or thrombocytopenia developed. One participant experienced hepatotoxicity, but no other patients had treatment stopped due to abnormal liver enzymes. 4 patients experienced a prolongation of their QTcF interval of more than 60ms over baseline, but none of them had an absolute QTcF >500ms.

Conclusion: In PanACEA SUDOCU, sutezolid given over 12 weeks at various doses showed no neuropathy nor myelosuppression, except one case of neutropenia with a possible alternative cause. The drug is a safe combination partner within the four-drug combination tested. We were not able to demonstrate a dose-effect on slope of TTP over time for sutezolid, when added to a potent three drug combination; which may have been a limitation to our study design.

115 cccDNA SILENCING AND LIMITED DECAY OF INFECTED CELLS IN HIV-HBV (HBeAG-) DURING NUCs

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Background: Hepatitis B e antigen (HBeAg)-negative chronic hepatitis B (CHB) is characterized by lower serum HBV DNA levels than HBeAg-positive CHB. Nucleos(t)ide analogues (NUC), the mainstay of treatment for CHB, effectively suppress HBV replication and are associated with decreased covalently closed circular DNA (cccDNA) transcription in HBeAg-positive disease. However, the effects of NUCs on the intrahepatic burden of infection and on cccDNA transcription in HBeAg-negative disease are poorly understood.

Methods: We studied paired liver biopsies (separated by a mean of 3.5 years) from five HBeAg-negative HIV-HBV coinfected men (one was a HBeAg seroconverter (SC)) during NUCs. We performed single-cell laser capture microdissection to isolate 200-300 cells from each biopsy and droplet digital PCR to quantify 3 viral targets from each hepatocyte: total HBV DNA, cccDNA, and pre-genomic RNA (pgRNA). We defined an infected cell as positive for any target and a transcriptionally silent cell as cccDNA positive and pgRNA negative. Wilcoxon signed-rank tests were used to compare between groups.

Results: The men were 41 to 57 years at biopsy 1 (Bx 1) and they received tenofovir with emtricitabine as part of HBV-active antiretroviral therapy (ART). The HBeAg SC (HB11) started ART one month prior to Bx 1 with loss of detectable HBeAg 7 months later. His HBV DNA was 6.63 $\log_{10}$ IU/ml at Bx 1. The other four men (HB8, 9, 10, 12) were on ART for ≥5.5 years and had HBV DNA < 29 IU/ml at Bx 1. A high proportion of cells were infected at both biopsies but declined significantly between biopsies in all except HB12 ($p< 0.05$) (Table). Extrapolating these values demonstrates that eradicating HBV from the liver assuming constant NUC adherence is not achievable within these individuals' lifetimes. We observed that 10-57% of infected cells were transcriptionally inactive for HB 8, 9, 10, 12; these proportions only declined significantly between biopsies in HB8 ($p< .001$). Notably, infected cells that were transcriptionally inactive increased in the HBeAg SC: 0.4% to 5%.

Conclusion: Long-term NUCs effectively reduce infected hepatocytes in HBeAg-negative HIV-HBV coinfected individuals. However, infection still persists, with >10% infected cells being transcriptionally inactive. Though this data supports the ability of NUCs to reduce infection, these results underscore the limitations in eradicating HBV with NUCs alone. Future strategies to irreversibly silence cccDNA transcription may result in a functional cure.

Change in intracellular HBV markers and transcriptional activity between biopsies

Participant ID	HB8		HB9		HB10		HB12		HB11 (seroconverter)	
Biopsy no. (no. of hepatocytes studied)	1 (249)	2 (257)	1 (268)	2 (176)	1 (248)	2 (270)	1 (226)	2 (262)	1 (267)	2 (271)
Plasma HBV DNA (log_{10}IU/mL)	UD	UD	UD	UD	UD	UD	UD	UD	6.63	UD
Intracellular markers										
Hepatocytes infected %[A,B]	17.7 (12.9, 22.4)	9.3 (5.8, 12.9)	11.6 (7.7, 15.4)	5.7 (2.3, 9.1)	10.5 (6.7, 14.3)	4.1 (1.7, 6.4)	6.2 (3.1, 9.3)	9.9 (6.3, 13.5)	97.4 (95.5, 99.3)	81.9 (77.3, 86.5)
Transcriptionally inactive[A,C] % all cells	10.0 (6.3, 13.8)	1.2 (0, 2.5)	4.9 (2.3, 7.4)	0.6 (0, 1.7)	2.4 (0.5, 4.3)	0.7 (0, 1.8)	1.8 (0.1, 3.5)	3.1 (1.0, 5.1)	0.4 (0, 1.1)	4.1 (1.7, 6.4)
Transcriptionally inactive[A,C] % infected cells	56.8 (42.2, 71.5)	12.5 (0, 25.7)	41.9 (24.6, 59.3)	10.0 (0, 28.6)	23.1 (6.9, 39.3)	18.2 (0, 41.0)	28.6 (4.9, 52.2)	30.8 (13.0, 48.5)	0.4 (0, 1.1)	5.0 (2.1, 7.8)

[A]A hepatocyte was defined as infected if any of the 3 viral targets (total HBV DNA, cccDNA, or pgRNA) was detectable in the cell. [B]Percent of cells (95% Confidence Interval
[C]Transcriptional inactivity was defined in cells in which cccDNA was detectable, but pgRNA was not detectable.

116 PREDICTORS OF HEPATITIS B TREATMENT RESPONSE IN PEOPLE WITH HIV/HBV COINFECTION

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Background: Response to hepatitis B treatment in people with HIV-1/HBV varies by baseline (BL) HBV DNA level and HBeAg status. Here we present a subanalysis of 48W outcomes from a phase 3 study (ALLIANCE) comparing bictegravir/emtricitabine/tenofovir alafenamide (B/F/TAF) vs dolutegravir + emtricitabine/tenofovir disoproxil fumarate (DTG+F/TDF) in participants initiating treatment for HIV-1 and HBV to examine HBV DNA suppression and predictors of HBs/eAg loss in this coinfected population.

Methods: Adults with HIV-1/HBV were randomized 1:1 to initiate blinded treatment with B/F/TAF or DTG+F/TDF (with corresponding placebo). Coprimary endpoints were proportion with HIV-1 RNA < 50 copies/mL (Snapshot) and HBV DNA < 29 IU/mL (missing=failure) at W48: B/F/TAF was noninferior to DTG+F/TDF at achieving HIV-1 RNA < 50 copies/mL and superior at achieving HBV DNA < 29 IU/mL (Avihingsanon et al., AIDS 2022). Subgroup analyses determined the proportion with HBV DNA < 29 IU/mL stratified by BL HBV DNA < or ≥ 8 $\log_{10}$ IU/mL and HBeAg status (-/+ at BL). A multivariate analysis (MVA) was conducted to evaluate predictors of HBV DNA < 29 IU/mL and HBs/eAg loss.

Results: 243 participants were randomized/treated (121 B/F/TAF, 122 DTG+F/TDF) from 46 sites globally. HBV DNA < 29 IU/mL was achieved by 53% (63%

B/F/TAF, 43% DTG+F/TDF), HBsAg loss by 9% (13% B/F/TAF, 6% DTG+F/TDF) and HBeAg loss by 20% (26% B/F/TAF, 14% DTG+F/TDF). Among those with BL HBV DNA < 8 log_{10} IU/mL (116/241), B/F/TAF-treated participants achieved significantly higher rates of HBV DNA < 29 IU/mL compared to DTG+F/TDF (87% vs 68%, p=0.008); for those with HBV DNA ≥8 log_{10} IU/mL at BL (125/241), B/F/TAF was also numerically higher (39% vs 23%, p=0.073). Among those who were HBeAg+ at BL (187/241), B/F/TAF-treated participants achieved significantly higher rates of HBV DNA < 29 IU/mL compared to DTG+F/TDF (51% vs 31%, p=0.0065); in those who were HBeAg- (54/241), response was also numerically higher (100% vs 92%, p=0.055). Baseline predictors of HBV DNA < 29 IU/mL from a MVA were: HBeAg-, HBV DNA < 8 log_{10} IU/mL, ALT >ULN and treatment with B/F/TAF; BL predictors of HBs/eAg loss included BL ALT >ULN and BL CD4 ≥200 cells/μL (Table 1).

Conclusion: In adults with HIV-1/HBV coinfection initiating therapy, B/F/TAF resulted in superior HBV DNA suppression compared to DTG+F/TDF. In MVA, B/F/TAF treatment was an independent predictor of HBV DNA suppression.

Multivariate Logistic Regression Analysis

Table 1. Multivariate Logistic Regression Analysis

	Predictor	Contrast	Odds Ratio	95% CI	p-value
HBV DNA <29 IU/mL	HBeAg	Negative vs Positive	17.1	(3.84, 76.22)	0.0002
	HBV DNA (log10)	<8 vs ≥8	5.22	(2.63, 10.33)	<0.0001
	ALT (AASLD ULN)	>ULN vs ≤ULN	2.29	(1.19, 4.42)	0.0137
	Treatment	B/F/TAF vs DTG+F/TDF	2.44	(1.29, 4.61)	0.006
HBsAg Loss	ALT (AASLD ULN)	>ULN vs ≤ULN	5.31	(1.70, 16.62)	0.0041
	CD4 (cells/μl)	≥200 vs <200	13.32	(1.74, 102.28)	0.0128
	Treatment	B/F/TAF vs DTG+F/TDF	1.97	(0.73, 5.29)	0.1775
HBeAg Loss	ALT (AASLD ULN)	>ULN vs ≤ULN	2.83	(1.31, 6.13)	0.0083
	CD4 (cells/μl)	≥200 vs <200	2.98	(1.21, 7.36)	0.0178
	Treatment	B/F/TAF vs DTG+F/TDF	1.72	(0.79, 3.72)	0.1685

117 PAGE-B SCORE TO ESTIMATE THE HEPATOCELLULAR CARCINOMA RISK IN PEOPLE WITH HIV AND HBV

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Swiss HIV Cohort Study, EuroSIDA, ATHENA and Aquitaine

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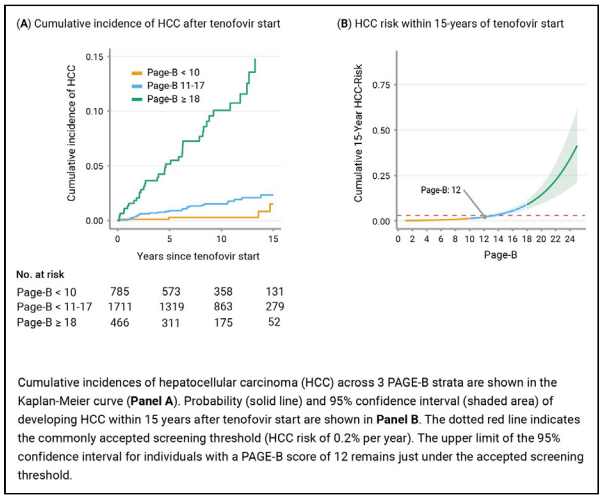
Background: Hepatitis B virus (HBV) coinfection is common among people with HIV (PWH) and the most important cause of hepatocellular carcinoma (HCC) worldwide. Whereas the PAGE-B risk score, based on age, sex and platelets, is recommended for the prediction of HCC among individuals with HBV monoinfection, it has not been evaluated in PWH. We performed an external validation of PAGE-B in people with HIV/HBV coinfection in Europe.

Methods: Using data from four European cohorts (Swiss HIV Cohort Study, EuroSIDA, ATHENA and Aquitaine), we included PWH with a positive HBsAg and without HCC before starting tenofovir. We estimated the predictive performance of the PAGE-B score on the occurrence of HCC within 15 years after tenofovir start. Model discrimination was assessed after multiple imputation using Cox regression with the prognostic index as covariate, and by calculating Harrell's c-index. Model calibration was assessed by comparing cumulative incidence estimates using the Kaplan-Meier method with the original PAGE-B derivation study.

Results: In total, 2,963 individuals with HIV/HBV coinfection were included. The median age was 41 years (IQR 35–47), 466 (16%) were women, 2,023 (68%) were Caucasian, and 314 (11%) had evidence of liver cirrhosis. PAGE-B was < 10 in 26.5%, between 10 and 17 in 57.7%, and ≥ 18 in 15.7% of patients. Within a median follow-up of 9.6 years, 68 individuals developed HCC (2.58/1000 person-years, 95% CI 2.03–3.27). The regression slope of the prognostic index for developing HCC within 15 years was 0.93 (95% CI 0.61–1.25), and the pooled c-index was 0.77 (range 0.73–0.80), both indicating good model discrimination comparable to the original model derivation study. The cumulative incidence of HCC over five years was 5.6% in individuals with a PAGE-B score ≥18 in our study (Fig. **A**) compared to 17% in the derivation study, indicating differences in model calibration. A PAGE-B cut-off of < 10 had a negative predictive value of 99.4% for HCC within 5 years, and the HCC risk of a score < 12 remained below the commonly accepted screening threshold (Fig. **B**)

Conclusion: For individuals with HIV/HBV coinfection, PAGE-B provides a valid and accurate tool to estimate the risk of developing HCC. Individuals with a PAGE-B score < 10 are at very low risk for developing HCC. Accurate risk prediction has the potential to increase surveillance uptake in high-risk individuals, as well as reducing healthcare cost by avoiding screening of individuals with a very low HCC risk.

Cumulative incidence of hepatocellular carcinoma



Cumulative incidences of hepatocellular carcinoma (HCC) across 3 PAGE-B strata are shown in the Kaplan-Meier curve (**Panel A**). Probability (solid line) and 95% confidence interval (shaded area) of developing HCC within 15 years after tenofovir start are shown in **Panel B**. The dotted red line indicates the commonly accepted screening threshold (HCC risk of 0.2% per year). The upper limit of the 95% confidence interval for individuals with a PAGE-B score of 12 remains just under the accepted screening threshold.

118 MUCOSAL PHARMACOLOGY OF DOXYCYCLINE FOR BACTERIAL STI PREVENTION IN MEN AND WOMEN

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Background: Oral doxycycline (DOX) prophylaxis is a promising strategy to prevent bacterial sexually transmitted infections (STIs). Clinical trials demonstrated a 200 mg oral DOX dose taken by men who have sex with men (MSM) after sexual exposure can provide protection against STIs. However, mucosal pharmacokinetic data at the site of STI exposure and DOX activity are lacking. We examined mucosal DOX concentrations in men and women to better understand DOX efficacy and inform dose optimization for STI prevention.

Methods: Eleven male and 9 female participants provided blood and mucosal swabs up to 7 days after receiving a 200 mg oral DOX dose. Rectal, vaginal and cervical biopsies as well as urethral swabs were collected 24 hours after dosing. DOX was measured by liquid chromatography-mass spectrometry with a lower limit of quantification of 10 ng/mL for plasma and 2.5 ng/sample for swabs and biopsies. Secretion concentrations were estimated using swab weight. Concentrations are reported as geometric mean and 95% confidence interval. Time above the 90% minimum inhibitory concentration (MIC_{90}) was assessed for susceptible *Neisseria gonorrhoeae* (NG), *Treponema pallidum* (TP) and *Chlamydia trachomatis* (CT).

Results: Rectal secretion DOX concentrations peaked at 48 hours, 8 hours in vaginal secretions, and 4 hours in plasma. Rectal and vaginal DOX exposure up to 96 hours were 2- and 3-times that of plasma, respectively. Rectal and vaginal secretion DOX concentrations remained above the MIC_{90} for 48, 72 and 96 hours, longer than in plasma, for NG, TP and CT, respectively. DOX concentrations in rectal (616 ng/g; 495 – 766 ng/g), vaginal (261 ng/g; 98 – 696 ng/g) and cervical tissue (410 ng/g; 193 – 870 ng/g) were only 1- to 2-times the MIC_{90} for NG, but at least 2- and 4-times greater than the MIC_{90} for TP and CT, respectively. Urethral secretion DOX was estimated to be at least 4-times the MIC_{90} for NG, TP and CT, and greater than plasma or mucosal concentrations.

Conclusion: DOX efficiently distributes to mucosal sites and maintains inhibitory concentrations against TP and CT for 3-4 days after dosing, but only 2 days for NG which may impact level of protection. This study provides the first pharmacologic data on mucosal DOX exposures associated with STI protection among MSM, predicts high vaginal efficacy, and informs a rational DOX dose optimization for STI prevention in men and women.

119 ANRS 174 DOXYVAC: AN OPEN-LABEL RANDOMIZED TRIAL TO PREVENT STIs IN MSM ON PrEP

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Background: Increased rates of sexually transmitted infections (STI) are reported among men who have sex with men (MSM), in particular those using pre-exposure prophylaxis for HIV (PrEP). Interventions to reduce STI incidence are needed.

Methods: MSM on PrEP with a history of STI in the past year, were randomized in an open-label factorial design trial to receive doxycycline post-exposure prophylaxis (Doxy PEP: 200 mg within 72h of condomless sex) or no PEP (2:1); and 2 shots of meningococcal B vaccine (Bexsero®) or no vaccine (1:1). Participants were tested centrally at baseline, every 3 months and when symptomatic for *N. gonorrhoeae* (GC) and *C. trachomatis* (CT) by PCR in throat, anus and urine. Serologic tests for syphilis were performed every 3 months. A committee adjudicated STI blinded to study arms. The co-primary endpoints were: the incidence of first episode of CT or syphilis for Doxy PEP and the incidence of a first episode of GC, 1 month after the second injection, for the vaccine intervention, using an intent-to-treat analysis. We used Cox proportional hazard models to compare incidence between Doxy PEP and no PEP adjusted for vaccine intervention and vice versa. Following external evidence, a single interim analysis occurred in September 2022 at the request of the DSMB who recommended to stop the trial for efficacy. Results for data collected up to July 15, 2022 are presented.

Results: Between January 19, 2021, and July 15, 2022, 546 MSM were randomized and 502 were analyzed. Median age: 39 years, median of 10 sexual partners in past 3 months. Median follow-up: 9 months. There was no interaction between the two prevention strategies for the primary endpoints. The incidence of a first episode of CT or syphilis was 5.6 and 35.4 per 100 PY in the Doxy PEP and no PEP arms, respectively (aHR: 0.16; 95%CI: 0.08-0.30). The incidence of a first episode of GC was 20.5 and 41.3 per 100 PY in the Doxy PEP and no PEP arms, respectively (aHR: 0.49; 95%CI: 0.32-0.76). The incidence of a first episode of GC was 9.8 and 19.7 per 100 PY in the meningococcal B vaccine and no vaccine arms, respectively (aHR: 0.49; 95%CI: 0.27-0.88). No drug-related SAE was reported.

Conclusion: Among MSM on HIV PrEP, doxycycline PEP significantly reduced the incidence of CT and syphilis and also had a significant impact on the incidence of GC. Meningococcal B vaccine also reduced the incidence of GC.

120 DOXYPEP & ANTIMICROBIAL RESISTANCE IN N. GONORRHOEAE, COMMENSAL NEISSERIA & S. AUREUS

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Background: Doxycycline post-exposure prophylaxis (doxy-PEP) is highly effective in reducing *N. gonorrhoeae* (GC), *C. trachomatis* (CT), and syphilis among men who have sex with men (MSM) and transgender women (TGW). Understanding the effect of doxy-PEP use on antimicrobial resistance (AMR) in N.gonorrhoeae and bacteria which can cause disease (*S.aureus*) or transmit resistance (*Neisseria spp*) is unknown.

Methods: DoxyPEP is a randomized open-label trial among MSM/TGW living with HIV or on PrEP with GC, CT, or early syphilis in the past year; participants were randomized 2:1 to 200 mg doxycycline within 72 hours of condomless sex or no doxycycline (SOC). At months 0 (M0) and 12 (M12), nasal/oropharyngeal swabs were cultured for *S. aureus* (SA) with doxycycline resistance (doxy-R) defined as MIC ≥16 µg/ml by E-test and oropharyngeal swabs cultured for commensal *Neisseria* (doxy-R: MIC ≥2 µg/ml by E-test). Participants with a positive GC test were instructed to return for swabs for GC culture through the CDC SURRG program (TCN-R: MIC≥2.0 µg/ml by agar dilution). Overall proportion with growth or AMR at M12 were compared by Fisher's exact test.

Results: Of 501 participants as of May 2022, *S.aureus* was cultured at M0 in 44.2% and doxy-R SA in 6.3% (Table). At M12, S.aureus was cultured from 29.2% in the doxy-PEP arm and 45.2% in the SOC arm (p=0.036), with doxy-R SA present in 11.7% and 4.8% (p= 0.19), respectively. At M0, methicillin-resistant-SA (MRSA) was cultured from 5.9%, and at M12, 1.5% in the doxy-PEP arm and 6.5% in SOC arm (p=0.077). At M0, *Neisseria spp* were cultured from 86.8% with doxy-R *Neisseria* in 61.8%. At M12, *Neisseria spp* were cultured from 85.2% in the doxy-PEP arm and 89.3% in the SOC arm (p = 0.64), and doxy-R was 69.7% and 44.6%, respectively (p=0.017). Among GC diagnoses, 17% (44/256) had phenotypic susceptibility results; M0 TCN-R was 28.4% (4/15), and after enrollment, 38.5% (5/13) in the doxy-PEP arm and 12.5% (2/16) in the SOC arm.

Conclusion: Doxy-PEP reduced *S.aureus* colonization by 16% without a significant increase in doxy-R SA. A majority had doxy-R commensal *Neisseria* at baseline, with an unexpected decrease in doxy-R *Neisseria spp* in the SOC arm. These modest changes in doxy-R S.aureus and *Neisseria spp* are unlikely to have clinical significance and must be considered in context of >60% STI reduction with doxy-PEP. Doxy-PEP may be less protective against incident TCN-R GC; surveillance for the impact of TCN-R GC on doxy-PEP efficacy and doxy-PEP on GC resistance is needed.

S.aureus, *Neisseria spp*, and *N. gonorrhoeae*: Bacterial isolation and phenotypic resistance to the tetracycline antibiotic class at enrollment and during DoxyPEP study

	Month 0		Month 12	
S. aureus	*Staph (+)*	*Doxy-resistance*	*Staph (+)*	*Doxy-resistance*
All *S. aureus*				
Doxy-PEP	42.2% (141/334)	3.6% (12/334)	29.2% (40/137)	11.7% (16/137)
Standard of care	48.4% (78/161)	11.8% (19/161)	45.2% (28/62)	4.8% (3/62)
			p=0.036	p=0.19
MRSA				
Doxy-PEP	6.0% (20/334)	0.3% (1/334)	1.5% (2/137)	0.0% (0/137)
Standard of care	5.6% (9/161)	2.5% (4/161)	6.5% (4/62)	1.6% (1/62)
			p=0.077	p=0.31

	Month 0		Month 12	
Commensal *Neisseria*	*Neisseria (+)*	*Doxy-resistance*	*Neisseria (+)*	*Doxy-resistance*
Doxy-PEP	88.1% (266/302)	62.6% (189/302)	85.2% (104/122)	69.7% (85/122)
Standard of care	84.3% (129/153)	60.1% (92/153)	89.3% (50/56)	44.6% (25/56)
			p=0.64	p=0.0017

	Month 0		On Study	
N. gonorrhoeae	*Gonorrhea diagnoses*	*TCN-resistance testing available* (n=15)*	*Gonorrhea diagnoses*	*TCN-resistance testing available* (n=29)*
Doxy-PEP	65	28.6% (2/7)	79	38.5% (5/13)
Standard of care	34	25.0% (2/8)	78	12.5% (2/16)

**N.gonorrhoeae* phenotypic TCN-resistance testing was not available in 83% (212/256) gonorrhea diagnoses for following reasons: culture not collected, due to gonorrhea treatment before culture or other reason (57%, 120/212), the culture failed to grow (39%, 82/212), or resistance testing on cultured isolate was not available due to contamination and viability issues (5%, 10/212)

121 DOXYCYCLINE POSTEXPOSURE PROPHYLAXIS FOR PREVENTION OF STIs AMONG CISGENDER WOMEN

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Background: Bacterial sexually transmitted infections (STIs) are repsonsible for significant and disproportionate morbidity and mortality in cisgender women, among whom STI incidence has been rising globally. Doxycycline taken as postexposure prophylaxis (PEP) was efficacious at preventing STIs among cisgender men who have sex with men and transgender women, but no trials among cisgender women have been done.

Methods: We conducted an open-label randomized trial of doxycycline PEP (doxycycline hyclate 200mg taken within 72 hours of sex) compared with standard of care (e.g., quarterly screening and treating STIs) among women aged 18-30 years in Kisumu, Kenya. Participants were required to already be taking daily oral HIV preexposure prophylaxis (PrEP). Contraception was not required, and doxycycline was stopped during pregnancy. Weekly SMS surveys z

Results: We enrolled 449 cisgender women; women completed 97% of expected follow-up visits. Median age was 24 years (IQR 21-27), 36.7% reported transactional sex at enrollment, and baseline STI prevalence was 17.9% (14.1% C. trachomatis, 3.8% N. gonorrhoeae, 0.4% T. pallidum). Incident STI events were detected at 109 follow up visits (85 C. trachomatis, 31 N. gonorrhoeae,

including 8 with both; 1 T. pallidum): 50 among those assigned to doxycycline PEP and 59 among those assigned STI screening and treatment alone (RR 0.88, 95% CI 0.60-1.29, p=0.51). Analysis with follow-up time censored once participants became pregnant (n=80), analysis of each STI separately, and subgroup analyses (including by age, contraceptive use, transactional sex, and STI detected at baseline) found similar results. There were no serious adverse events determined to be related to use of doxycycline. No incident HIV infections were detected. Weekly SMS surveys had an overall 81% response rate, and women assigned to PEP reported taking doxycycline PEP at least as many days they had sex in 78% of surveys.

Conclusion: Among young cisgender women with high prevalence and incidence of STIs, the use of doxycycline PEP following sex did not reduce incident STIs.

122 POTENTIAL IMPACT AND EFFICIENCY OF DOXY-PEP AMONG PEOPLE WITH OR AT RISK OF HIV

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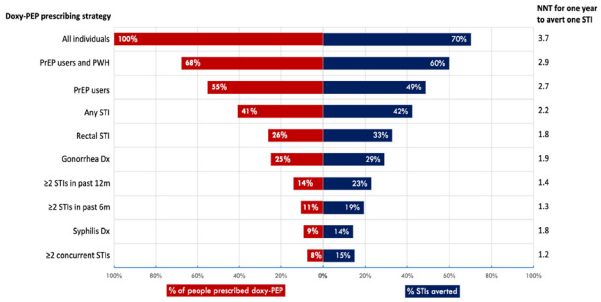
Background: Doxycycline post-exposure prophylaxis (doxy-PEP) reduces bacterial sexually transmitted infection (STI) risk in people with HIV (PWH) or using HIV preexposure prophylaxis (PrEP). However, ongoing decision-making about federal and local guidance for doxy-PEP prescribing is complicated by concerns about potential harms of widespread use. We sought to identify doxy-PEP prescribing strategies that would minimize overall doxy-PEP use while maximizing impact on STIs.

Methods: We used electronic health record data on gay and bisexual men (GBM), transgender women, and non-binary people assigned male at birth with ≥2 STI tests (chlamydia, gonorrhea, or syphilis) at Fenway Health, a Boston clinic focused on LGBT health, during 2015-2020. Patients were followed from first STI test until last test or end of 2020. We defined 10 potential doxy-PEP prescribing strategies: prescribed to (1) all individuals, (2) PrEP users, (3) PrEP users/PWH; and prescribed after (4) any STI, (5) rectal STI, (6) ≥2 STIs in 12m, (7) ≥2 STIs in 6m, (8) ≥2 concurrent STIs, (9) syphilis or (10) gonorrhea Dx. We also explored strategies 4–10 restricted to PrEP users/PWH. We evaluated counterfactual scenarios in which patients who met each criterion were prescribed doxy-PEP indefinitely (strategies 1–3) or for 12m (strategies 4–10). We assumed STI incidence during doxy-PEP use would have been reduced by clinical trial efficacy estimates. For each strategy, we estimated the proportion prescribed doxy-PEP, overall STIs averted, and number needed to treat with doxy-PEP per year to avert 1 STI (NNT).

Results: Among 10,562 patients (94% GBM; 54% PrEP users; 14% PWH), incidence of any STI was 39.8/100py. Across strategies, NNT ranged from 1.0–3.8 (median=1.7) and proportion of STIs averted ranged from 8%–70% (median=20%). Prescribing doxy-PEP to all patients averted 70% of STIs (NNT=3.7); prescribing to PrEP users/PWH (68% of patients) averted 60% of STIs (NNT=2.9; Figure). Prescribing doxy-PEP after any STI reduced the proportion of patients on doxy-PEP to 41% and averted 42% of STIs (NNT=2.9). Prescribing after concurrent or repeated STIs was most efficient (lowest NNTs). Restricting strategies 4–10 to PrEP users/PWH had minimal effect on NNT and reduced impact on STIs.

Conclusion: Prescribing doxy-PEP to individuals with STIs, particularly concurrent or repeated STIs, could avert a substantial proportion of subsequent STIs. The most efficient prescribing strategies are based on STI history rather than HIV status or PrEP use.

Proportion of individuals prescribed doxy-PEP (red), proportion of STIs averted (blue), and number needed to treat (NNT) with doxy-PEP for one year to avert one STI (right) for each doxy-PEP prescribing strategy.



123 CLUSTER RANDOMISED TRIAL OF RISK-DIFFERENTIATED CARE FOR FEMALE SEX WORKERS: AMETHIST

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Background: Strengthening outreach and community mobilisation are promising approaches for reducing HIV transmission attributable to sex work.

Methods: We allocated 22 clusters using restricted random allocation (1:1) to usual care or *AMETHIST* interventions. A cluster was the female sex worker (FSW) population around a clinic providing the services listed below.

Usual care: FSW-friendly services, HIV testing, PrEP / referral to government ART services, contraception, condoms, STI syndromic management, health education and legal advice; all supported by peer educators.

AMETHIST: usual care plus peer-led microplanning (outreach tailored to address individual vulnerability) and participatory self-help groups to support risk-differentiated HIV prevention, testing, ART/PrEP and adherence.

1o outcome: proportion of all FSW at risk of HIV transmission (HIV-positive, not virally suppressed and not consistently using condom) or HIV acquisition (HIV-negative and not protected by condoms or PrEP).

Outcomes were determined in a respondent driven sampling (RDS) endline survey in all 22 clusters after 28 months of intervention delivery. Analyses were pre-specified, RDS-weighted and age-adjusted.

Results: AMETHIST was implemented June 2019-October 2021. During this period there were more clinic registrations, HIV tests and PrEP/ ART initiations at AMETHIST compared to Usual care sites.

4444 FSW aged 18+ were enrolled in the endline survey, providing questionnaire data, biospecimens (n=4443) including dried blood spot (HIVAb, HIV viral load), plasma (TDF levels) and self-taken vaginal swabs for STI and Y-chromosome testing (to validate condom use reports). 46.2% were living with HIV of whom 1790/1973 (90.7%) were virologically supressed. 586/2334 (25.1%) of the HIV negative women reported currently taking PrEP, but only 2 had plasma TDF levels >700fmol/punch.

There was no impact on the primary endpoint of population level risk of HIV transmission/acquisition. The proportion of HIV positive FSW with a viral load >1000copies/uL was low in both arms, and significantly reduced in the AMETHIST intervention arm. There was no impact of AMETHIST on risk of HIV acquisition.

See Table 1 AMETHIST.

Conclusion: Risk of HIV transmission in HIV positive women was low (95:95:95 achieved) and further improved by the AMETHIST Intervention. Risk of HIV acquisition was high and unchanged. Sustaining testing and treatment and strengthening HIV prevention including through long-acting PrEP is critical.

Table 1 AMETHIST

	AMETHIST	Usual Care	
Program data	**Number (%)**		**p**
Clinic registration	8443	3824	
HIV tests	11882	6808	
New HIV diagnoses	667	533	
ART linkage	622 (93%)	456 (86%)	<0.0001
PrEP initiations	3377	1610	
Trial Outcomes: RDS survey data	**n/N mean RDS adj %**		**Age-adj risk diff (95% CI)**
1° Risk of transmission/acquisition	1156/2131; 55.3%	1104/2137; 52.7%	-0.9% (-5.7%, 3.9%)
2° Transmission risk HIV +ve	63/931; 5.8%	103/1041; 10.4%	-5.5% (-8.2%, -2.9%)
2° Acquisition risk HIV -ve	1093/1200;92.1%	1001/1096; 92.2%	-0.6% (-4.6%, 3.4%)
2° % HIV +ve with VL>1000c/ul	68/931; 6.5%	115/1041; 11.2%	-5.8% (-8.8%, -2.7%)

124 RANDOMIZED TRIAL OF COMMUNITY HEALTH WORKER DELIVERED DYNAMIC CHOICE HIV PREVENTION

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Background: Maximizing HIV prevention coverage requires community entry points and structured models for delivering patient-centered choices over time. We hypothesized that a dynamic choice prevention (DCP) intervention, including flexibility to move between PrEP and PEP and delivered by community health workers (CHW), would increase HIV biomedical prevention coverage among persons at risk in rural Sub-Saharan Africa.
Methods: We conducted a cluster randomized trial among persons (≥15 years) with current or anticipated risk of HIV in Uganda and Kenya (SEARCH; NCT04810650). Intervention villages received DCP delivered by CHW with clinician support. DCP included: 1) product choice (daily oral PrEP [TDF/XTC] or post-exposure prophylaxis [PEP]) with the option to switch over time, 2) service location choice, 3) HIV self-testing option, 4) 24/7 phone access to clinician, and 5) CHW & provider training on client-centered care. Control villages received standard of care prevention referrals. The primary outcome was biomedical prevention coverage: proportion of 48-week follow-up with self-reported PrEP/PEP use. Coverage during self-reported HIV risk periods was a secondary outcome. Arms were compared using TMLE, accounting for clustering.
Results: From May-July 2021, we enrolled 429 people (212 intervention; 217 control) in 16 villages; 57% were women and 35% aged 15-24 years. 58% of intervention participants chose PrEP and 58% chose PEP at least once over 48 weeks. Choice of self-testing increased from 52% at baseline to 71% at week 48. Choice of out-of-facility (vs. clinic) delivery was ≥98% throughout. Among 413 (96%) participants with primary outcome ascertained, average biomedical prevention coverage was 28% in intervention vs. 0.5% in control (27.5% absolute increase; 95%CI: 23.0-31.9%, p < 0.001). Effect sizes were similar in men and women. Coverage during periods of HIV risk was 36.6% in intervention vs. 0.9% in control (35.7% absolute increase; 95%CI: 27.5-43.9%, p< 0.001).
Conclusion: In this cluster randomized trial, existing community health workers successfully delivered a dynamic choice prevention strategy (product/location/test), allowing persons to switch between modalities including PEP. The intervention increased biomedical coverage by 28%; however, substantial time at risk of HIV remained uncovered by biomedical prevention, highlighting the need for additional interventions.

125 CLUSTER RANDOMIZED TRIAL OF INTEGRATED HIV AND SEXUAL & REPRODUCTIVE HEALTH SERVICES

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Background: Youth living with HIV (YLWH) have disproportionately poor virological outcomes. We hypothesized that a community-based intervention incorporating the whole HIV cascade (testing, treatment, adherence support) integrated with sexual & reproductive health (SRH) services, would improve HIV outcomes among youth. Integrating SRH may increase engagement in a hard-to-reach group with limited access to health services.
Methods: A cluster randomized trial (CHIEDZA) was conducted across 3 provinces in Zimbabwe, each randomized 4:4 to control (existing services) or to intervention clusters (total 24 clusters). A cluster was a geographically demarcated area with a community center, from where weekly integrated HIV & SRH services were delivered to intervention cluster residents aged 16-24 years. The primary outcome was virological suppression (VS) (< 1000copies/ml) among YLWH after 30 months, ascertained through a population-based survey of 700 18-24 year olds/cluster (total 16,800). Secondary outcomes assessed each step of the HIV cascade.
Results: 36,991 youths accessed the CHIEDZA intervention (estimated 95% of eligible population in intervention clusters), of whom 84% had ≥1 HIV test. Of the 1539 YLWH CHIEDZA intervention attendees (24% newly diagnosed), 1445 (94%) were linked to HIV care of whom 1409 (97%) were taking ART; of 815 on whom VL was available, 80% had VS.
The population-based survey enrolled 17682 (95% of those eligible), 60.7% female; 47.7% aged 21-24 years. In the intervention arm, 29% reported accessing CHIEDZA. HIV prevalence was 5.9% and 7.5% in intervention and control arms respectively. A higher proportion in the intervention than control arm reported having an HIV test (71.1% vs 66.1%, p=0.016) and knowledge of HIV status (68.5% vs 63.1%, p=0.057). There was no difference by arm in the primary outcome (40% vs 37.8%, RR 1.05 (95% CI 0.86-1.28), or in secondary outcomes. Among older YLWH taking ART, VS was higher in the intervention than the control arm (interaction p=0.017) (Table 1).
Conclusion: Despite high levels of HIV testing and treatment achieved by CHIEDZA, there was no population level impact on VS. While the intervention did increase knowledge of HIV status among youth at population level, those at highest HIV risk were not identified, which likely explains lack of intervention effect. Mobility explains the 29% reported coverage at endline (despite 95% eligible population served). Nearly 50% of YLWH remain undiagnosed; strategies to address this are urgently needed.

Table 1: Primary and secondary outcomes stratified by age and sex

Outcome		Cluster-level geometric mean prevalence		Risk Ratio (95% CI)	p-value
		Control	Intervention		
Primary outcome stratified by sex and age (years)					
VS (*in YLWH*)	Male	36.5%	38.5%	1.05 (0.69-1.62)	0.80
	Female	39.1%	40.8%	1.04 (0.85-1.27)	0.67
	18-20	32.3%	27.6%	0.87 (0.58-1.31)	0.49
	21-24	38.8%	45.4%	1.16 (0.93-1.44)	0.18
Secondary outcomes by sex (aligned to UNAIDS 90-90-90 targets)					
Know HIV diagnosis (*in YLWH*)	Male	49.6%	53.8%	1.08 (0.75-1.57)	0.66
	Female	59.2%	58.3%	0.99 (0..79-1.23)	0.90
Taking ART (*in YLWH)**	Male	96.9%	90.2%	0.93 (0.84-1.03)	0.18
	Female	98.2%	94.5%	0.96 (0.93-1.00)	0.049
VS (*in those taking ART*)	Male	80.3%	81.2%	1.01 (0.68-1.51)	0.94
	Female	67.8%	74.7%	1.10 (0.97-1.25)	0.13
Secondary outcomes by age in years (aligned to UNAIDS 90-90-90 targets)					
Know HIV diagnosis (*in YLHW*)	18-20	49.4%	52.4%	1.06 (0.79-1.43)	0.68
	21-24	57.3%	59.3%	1.03 (0.82-1.31)	0.77
Taking ART (in YLHW*)	18-20	96.8%	91.0%	0.94 (0.86-1.03)	0.19
	21-24	97.9%	94.2%	0.96 (0.90-1.03)	0.22
VS (*in those taking ART*)	18-20	70.7%	56.4%	0.80 (0.57-1.11)	0.17
	21-24	69.0%	81.3%	1.18 (1.06-1.31)	0.005

**YLWH who know their diagnosis*

126 RECENT HIV INFECTION SURVEILLANCE IN BREASTFEEDING WOMEN IN MALAWI: JUL 2019-JUL 2022

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Background: HIV infections can be characterized as recent (acquired within the previous 12 months) using a rapid test for recent infection (RTRI) and a viral load (VL) ≥1,000 copies/mL as part of a recent infection testing algorithm (RITA). Recent HIV infection surveillance (RIS) aims to identify geographic areas and subpopulations where potential transmission is occurring in order to guide public health response. To better understand recent infections among breastfeeding women (BFW) accessing HIV testing services (HTS), we reviewed data from Malawi's RIS system.
Methods: We analyzed RIS data from July 2019 to July 2022, among individuals ≥13 years with an HIV-positive result, from 27 districts in Malawi. Proportions of RITA-recent infections were calculated by dividing RITA-recents by the total

valid RTRI results. Proportions were calculated by demographic characteristics and statistically significant differences were identified using chi-square tests ($p \leq 0.05$).

Results: Among 55,347 newly diagnosed HIV-positive clients with a RITA result, 666 (1.2%) were BFW. The median age of BFW was 25 (IQR: 22-30). Fifty-three BFW (8.0%) had a RITA-recent infection compared to 2.0%, 3.6%, and 3.4%, ($p \leq 0.00$) of males, non-pregnant females, and pregnant females, respectively. By age group, the proportion RITA-recent among BFW was 8.9%, 7.1%, 8.1%, and 0.0% among 15-24yo, 25-34yo, 35-44yo, and 45-54yo, respectively. Regarding HTS entry points, the maternal and child health/under 5, maternity, and post-natal entry points accounted for 32.1% of RITA-recent BFW, whereas voluntary testing and counseling accounted for 45.3%. Among RITA-recent BFW, 47 (88.7%) self-reported their last HIV test result as negative and 3 (5.7%) as inconclusive. Among RITA-recent BFW with a previous negative result, 93.6% received their last HIV test within the past year and 61.7% within the past 6 months.

Conclusion: RIS in Malawi identified about one recent infection out of every eight newly diagnosed HIV+ breastfeeding women, although BFW contribute < 2% of new diagnoses at HTS. The majority of RITA-recent BFW tested negative within the past 6 months. This suggests that while antenatal testing programs have high coverage, risk of HIV acquisition persists throughout pregnancy and breastfeeding, therefore prevention strategies could be enhanced for this group. Future analyses that investigate risk factors and geographic variation could inform counseling messages, partner engagement, and prevention options.

127 DELIVER: A SAFETY STUDY OF A DAPIVIRINE VAGINAL RING AND ORAL PrEP DURING PREGNANCY

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Background: Pregnancy represents a high-risk period for HIV acquisition. The monthly dapivirine vaginal ring (DVR) has been clinically shown to reduce HIV risk with no safety concerns in nonpregnant reproductive-aged cisgender women; however, data during pregnancy are limited. Here we report safety data from the first two cohorts of pregnant participants in MTN-042/DELIVER, a phase 3b, randomized, open-label safety trial of DVR and oral tenofovir disoproxil fumarate/emtricitabine (TDF/FTC) (MTN-042/DELIVER, NCT03965923.)

Methods: Eligible pregnant individuals aged 18 to 40 in Malawi, South Africa, Uganda, and Zimbabwe were randomized 2:1 to monthly DVR or daily TDF/FTC. Participants in cohort 1 initiated product use between 36 0/7-37 6/7 weeks gestation; in cohort 2 product use was started at 30 0/7- 35 6/7 weeks gestation. All participants continued product use until delivery or 41 6/7 weeks gestation. Pregnancy outcomes and complications reported at the time of delivery were assessed and summarized using descriptive statistics and compared to local background rates obtained through a systematic chart review (MTN-042B).

Results: One-hundred and fifty participants were enrolled into cohort 1 with 101 randomized to DVR and 49 to TDF/FTC. One-hundred and fifty-seven participants were enrolled into cohort 2 with 106 randomized to DVR and 51 to TDF/FTC. Demographic and clinical characteristics were similar by study arm for each cohort. In cohort 1, one stillbirth and one neonatal death occurred, both in the TDF/FTC arm. One stillbirth and one neonatal death occurred in cohort 2, both in the DVR arm. The prevalence of preterm delivery was 2% in cohort 1 and 6% in cohort 2. In both cohorts, pregnancy complications were rare, with hypertensive disorders being the most commonly reported, and generally similar to local background rates (Table 1). There were no cases of fever of unclear etiology or preterm premature rupture of membranes reported. In cohort 2, there was 1 (1%) case of chorioamnionitis in the DVR arm and 1 (1%) of endometritis in the TDF/FTC arm, and 2 (4%) of puerperal sepsis in the TDF/FTC arm.

Conclusion: In this first study of a long-acting HIV prevention agent in pregnancy, adverse pregnancy outcomes and complications were uncommon when DVR and TDF/FTC were used in the third trimester of pregnancy and were similar to rates observed in the communities where the study is being conducted. These data support plans for subsequent investigation of DVR safety earlier in pregnancy.

Maternal pregnancy complications by study arm

Pregnancy Complication	Cohort 1		Cohort 2		Local background frequencies in MTN-042B[1]
	Dapivirine (n=99) n (%)	TDF/FTC (n=49) n (%)	Dapivirine (n=106) n (%)	TDF/FTC (n=51) n (%)	
Any hypertensive disorder of pregnancy	3 (3%)	4 (8%)	9 (8%)	5 (10%)	10.5% (10.0,11.3)
Gestational hypertension	3 (3%)	2 (4%)	6 (6%)	5 (10%)	4.4% (4.0,4.8)
Pre-eclampsia without severe features	0 (0%)	1 (2%)	1 (1%)	0 (0%)	2.2% (1.9,2.5)
Pre-eclampsia with severe features	0 (0%)	1 (2%)	2 (2%)	0 (0%)	2.1% (1.9,2.4)
Eclampsia	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0.6% (0.5,0.8)
Peripartum/Antepartum hemorrhage	0 (0%)	1 (2%)	2 (2%)	2 (4%)	N/A[2]
Postpartum hemorrhage	2 (2%)	1 (2%)	2 (2%)	0 (0%)	3.2% (2.9,3.6)

[1]Balkus JE, Neradilek M, Fairlie L, et al. Assessing pregnancy and neonatal outcomes in Malawi, South Africa, Uganda, and Zimbabwe: Results from a systematic chart review. PLoS One. 2021;16(3):e0248423. doi:10.1371/journal.pone.0248423

[2]N/A=not assessed

128 RANDOMIZED TRIAL OF DYNAMIC CHOICE HIV PREVENTION IN ANTE/POSTNATAL CARE CLINICS

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Background: Women seen for ante and postnatal care (ANC) remain at risk for HIV in rural sub-Saharan Africa, despite routine access to PrEP. Patient-centered prevention delivery models that offer structured choices in product, testing and visit location may increase coverage. Few studies evaluate actual prevention choices made by clients, nor the impacts of a dynamic choice delivery model on biomedical prevention coverage.

Methods: We conducted an individually randomized trial (SEARCH; NCT04810650) among women (≥15 years) with current or anticipated risk of HIV infection seen at ANC clinics in rural Kenya and Uganda to evaluate the effect of a dynamic choice prevention (DCP) model (intervention) versus standard-of-care (control). DCP included: 1) product choice (daily oral PrEP [TDF/XTC] or post-exposure prophylaxis [PEP]) with option to switch over time; 2) service location choice; 3) HIV self-testing option; 4) 24/7 phone access to clinician; and, 5) provider training on patient-centered care. The primary outcome was biomedical prevention coverage over 48 weeks (proportion of months with self-reported PreP or PEP use); self-reported use during months a client retrospectively reported HIV risk was a secondary outcome.

Results: We enrolled 400 women between April and July 2021 (203 intervention, 197 control); 38% were pregnant; 94% reported no PrEP or PEP use for prior 6 months; 52% were aged 15-24y. Among 384/400 (96%) of women with outcome ascertained, the intervention increased biomedical prevention coverage by 40.2% (95%CI: 33.8%-46.7%; $p < 0.001$); mean coverage was 70% in intervention vs. 29% in control. Similar effect sizes were seen across age and baseline pregnancy status. The intervention also increased coverage during months at risk of HIV: 81% in intervention vs. 43% in control (38.1% absolute increase; 95%CI: 31.2%-45.0%; $p < 0.001$). Among intervention participants, 100% chose PrEP and 11% chose PEP at least once during 48 weeks. Choice of off-site visits increased over time (61% selected out-of-facility delivery at week-48 vs. 22% at baseline), as did choice of HIV self-testing (59% selected self-testing at week-48 vs. 34% at baseline).

Conclusion: In this randomized study, a patient-centered dynamic choice intervention that provided flexibility in product modality, testing and service location more than doubled biomedical HIV prevention coverage in a high-risk population already routinely offered access to biomedical prevention options.

129 MATERNAL POINT-OF-CARE VIRAL LOAD AT DELIVERY IMPACTS INFANT ARV PROPHYLAXIS REGIMEN

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Background: Despite tremendous achievement in reducing HIV mother-to-child-transmission (MTCT), 150,000 children were newly infected in 2020 globally. High maternal viral load (VL) at delivery is among the strongest risk factors for MTCT. Currently, the choice of postnatal antiretroviral prophylaxis (PNP) for HIV-exposed infants is based on WHO high-risk (HR) criteria. We aimed to estimate the contribution of point-of-care (PoC) maternal VL testing at delivery in profiling the risk of MTCT and its impact on standard PNP or enhanced PNP (ePNP) for HIV-exposed infants.
Methods: The cluster-randomized LIFE trial was conducted at 28 health facilities in Tanzania and Mozambique. At delivery, the intervention arm A provided PoC maternal VL to aid MTCT HR assessment in addition to clinical criteria and antenatal care information as available in the control arm B only. In Tanzania both arms initiated ePNP based on maternal risk factors, including VL for arm A, while in Mozambique, ePNP was provided universally. We used mixed effects logistic regression models to estimate the effect of our intervention on the proportion of infants 1) identified as HR (Tanzania and Mozambique) and 2) HR infants receiving ePNP (Tanzania only). Standard errors were clustered to account for health facility and multiple births.
Results: A total of 6512 mothers living with HIV were enrolled: 72% were diagnosed before the 2nd trimester, 99% were on ART, and 78% were virally suppressed at delivery. Of 6568 newborns, 781 (12%) were classified as HR (636 (19.5%) vs. 145 (4.4%) in arms A and B, respectively; p< 0.0001). In arm A, 512 (80.5%) HR infants were classified only based on maternal PoC VL at delivery. In arm B, overall 609 (18.4%) additional infants would have been identified as HR if their mothers would have received PoC VL assessment. In Tanzania, HR infants in arm A were significantly more likely to receive ePNP, with 67/112 (59.8%) vs. 16/51 (31.4%) receiving ePNP in arms A and B, respectively (OR 4.49, 95% CI: 1.23, 16.36). However, 40.2% in arm A and 68.6% in arm B did not receive ePNP despite available information for HR classification at delivery.
Conclusion: PoC maternal VL testing at delivery significantly increased the proportion of infants identified as HR. Further, HR infants with maternal PoC VL at delivery were more often initiated on ePNP. However, linkage of HR infants to appropriate antiretroviral prophylaxis remains suboptimal, warranting consideration of universal ePNP irrespective of transmission risk.

130 MULTICOMPONENT INTERVENTION IMPROVES VIRAL SUPPRESSION FOR PREGNANT/POSTPARTUM WOMEN

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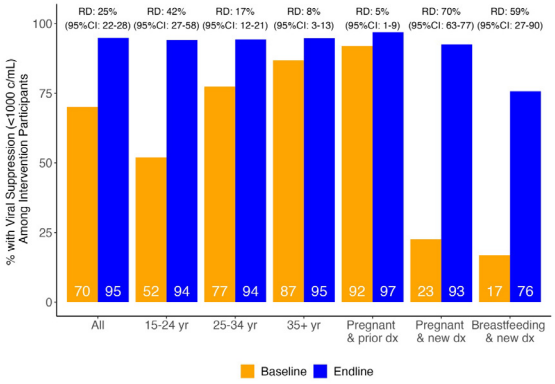
Background: Achieving viral suppression among pregnant and breastfeeding women is essential to eliminate vertical transmission of HIV in Sub-Saharan Africa. We hypothesized that an enhanced viral load counseling and standardized peer-mother support (ENHANCED-SPS) intervention would increase viral suppression among pregnant and breastfeeding women in rural Uganda.
Methods: This was a cluster randomized trial evaluating the effect of the ENHANCED-SPS intervention among pregnant and post-partum women receiving HIV care at 14 facilities in rural Southwestern Uganda (NCT04122144). Intervention participants received point-of-care viral load testing and enhanced viral load counseling during clinic visits along with bi- weekly phone counseling from a trained peer-mother over a period of 12 months. Within the intervention arm, we compared the proportion with viral suppression (HIV RNA< 1000 c/mL) at baseline and 12 months, accounting for clustering and missing measures. Endpoint data were not available in the control arm, preventing a by-arm comparison.
Results: We enrolled 505 pregnant and post-partum women at the 7 intervention clinics from September 2019 to October 2020. Participants' median age was 28 years, 157/505 (31%) were newly diagnosed with HIV, 77% (388/505) were on an EFV-based regimen and 70% [95%CI: 66-74%)] were virally suppressed. After 12 months of the ENHANCED-SPS intervention, viral suppression was 95% (95%CI:93%,97%), corresponding to a 25% (95%CI:22-28%; p< 0.001) absolute increase from the baseline measurement. The intervention increased suppression within subgroups of age, ART regimens, and enrollment group, with the greatest increase among those newly diagnosed: 70% increase (95%CI:63-77%) among pregnant women and 59% increase (95%CI:27-90%) among breastfeeding women.
Conclusion: The multi-component, peer-led intervention significantly increased virologic suppression within 1 year of implementation. Despite the observed increase following the intervention, viral suppression among breastfeeding women remains far below the target rates, highlighting the need for additional interventions during the postpartum period.

Viral suppression (<1000 c/mL) among the intervention particpants



131 IMPROVED STRATEGY TO PREVENT HIV POSTNATAL TRANSMISSION: A RANDOMIZED TRIAL

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Background: HIV transmission through breastfeeding remains a bottleneck to eliminate pediatric HIV infections in Africa. We aimed to assess the efficacy of a combined intervention including maternal viral load (VL) point of care (POC) testing and extended infant postnatal prophylaxis (PNP) to prevent postnatal transmission at 12 months in Lusaka (Zambia), Ouagadougou and Bobo-Dioulasso (Burkina Faso).
Methods: Breastfed HIV-exposed infants were enrolled at the 2nd infant immunization visit (EPI-2, 6-8 weeks). A POC HIV DNA was done at EPI-2, and HIV-infected infants were promptly initiated on ART. HIV-exposed uninfected infants (HEU) infants and their mothers were then randomized to two arms. In the intervention arm, mothers had a POC VL testing during EPI-2 and M6 visits. Infants whose mothers had a VL >1000 cp/mL were initiated on lamivudine (3TC) until M12 or until 8 weeks after cessation of breastfeeding. The control group implemented PMTCT activities as per local WHO-derived guidelines. The primary outcome was infant HIV transmission at M12. Secondary outcomes were safety and the period at high risk of transmission defined as no PNP and a maternal VL >1000 cp/mL while breastfeeding.
Results: From Dec 2019 to Sep 2021, 1526 HIV-exposed infants were enrolled and had HIV diagnosis at EPI-2. Among them, 20 infants were newly diagnosed with HIV, started prompt ART, and 1506 HEU infants (1342 from Zambia and 164 from Burkina Faso) were randomized (753 in each arm). Baseline characteristics were similar between arms. The mothers had a median age of 30.6 years (IQR:26.0-35.0), and 98.4% were on ART. In the intervention arm, the POC VL prompted 3TC initiation for 102 infants (85 at EPI-2 and 17 at M6). The period at high risk for transmission was 0.47/100 person-days (95%CI: 0.44-0.50) in the intervention arm vs. 6.58/100 person-days (95%CI: 6.47-6.70) in the

control arm. Within 12 months of follow-up, 1 HIV transmission occurred in the intervention arm vs. 6 in the control arm, yielding transmission rates of 0.19/100 person-years (95%CI:0.005-1.05) and 1.17/100person-years (95%CI:0.43-2.55), respectively. The rate of SAE was similar in both arms.

Conclusion: Our randomized controlled trial showed that an intervention nested in EPI and combining POC measurement of maternal viral load and, when unsuppressed, same-day infant single PNP initiation was safe and reduced the period at high risk of more than 90%, which resulted in a sharp reduction (though not significant) of HIV transmission at 12 months.

132 BIRTH POINT-OF-CARE TEST & TREAT REDUCES EARLY MORTALITY AMONG HIV INFECTED INFANTS

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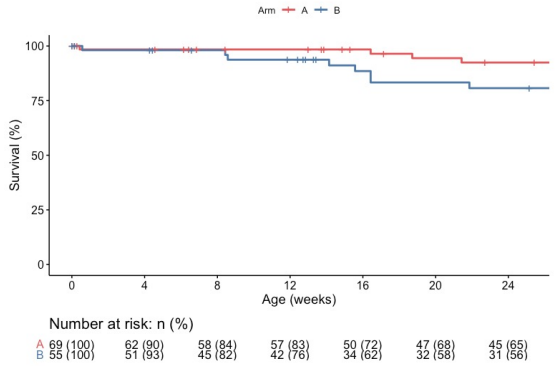
Background: Early mortality among infants with HIV is high and peaks at 2-3 months of age. Late diagnosis delays access to antiretroviral treatment (ART), often past the mortality peak. We assessed the impact of a point-of-care (PoC) HIV early infant diagnosis (EID) test & treat strategy at birth on viral suppression and mortality up to 24 weeks of age among HIV-infected infants in Mozambique and Tanzania.

Methods: We conducted a cluster-randomized trial at 28 public health facilities. Intervention arm A sites (n=14) provided PoC EID and immediate nurse-directed, physician-supported ART initiation for positive infants at birth, while control arm B sites (n=14) offered PoC EID and linkage to ART from 4-6 weeks of age. Infant ART at birth included nevirapine-based regimens, and by 4-6 weeks infants were switched or started on lopinavir/r granule-based regimens. Study visits were conducted at birth, 4-6 weeks, 12 weeks and 24 weeks. The Kaplan-Meier method was used to compare survival between arms. Mixed-effects Cox proportional-hazards models adjusted for time of HIV infection with standard errors clustered at the health facility level were used to estimate hazard ratios (aHR). Proportions of infants virally suppressed (< 1000 copies/ml) at 24 weeks of age between arms are reported.

Results: Among 6606 infants enrolled, 3298 in arm A and 3308 in arm B, 124 were diagnosed HIV-infected by 12 weeks of age (transmission rate 1.88%; 95% CI: 1.56, 2.23). HIV infection was detected at birth, 6 weeks and 12 weeks in 64 (51.6%), 40 (32.3%), and 20 (16.1%) infants, respectively. Overall, ART was initiated in 116 (93.5%) infants within 2 days of diagnosis, including 35/38 (92.1%) infants diagnosed at birth. Proportions of infants virally suppressed at 24 weeks of age did not differ between arms, and were 7/30 (23.3%) in arm A and 6/22 (27.3%) in arm B with available viral load. After a median follow-up time of 23.9 weeks (IQR: 12.9, 26.3), 4 (5.8%) infants in arm A died at median 17.6 weeks, significantly lower than 8 (14.5%) in arm B at median 14.9 weeks (aHR 0.27; 95% CI: 0.08, 0.90; Figure 1).

Conclusion: PoC test & treat at birth was feasible in resource-limited settings and resulted in a relative reduction of 73% in early mortality among HIV-infected infants. The combination of PoC EID at birth with dolutegravir-based infant ART might improve the poor viral suppression observed with LPV/r granules, potentially further enhancing the beneficial impact of birth test & treat on infant mortality.

Figure 1: Survival over time according to intervention group (A: PoC EID and ART initiation from birth; B: PoC EID and linkage to ART initiation at 4-6 weeks of age), with follow-up duration of 24 weeks of age (total n=124). Censored values (+) indicate last known follow-up time for infants still at risk.



133 POSTMORTEM CHARACTERIZATION OF HIV-ASSOCIATED UNDER-5 DEATHS IN FOUR CHAMPS SITES

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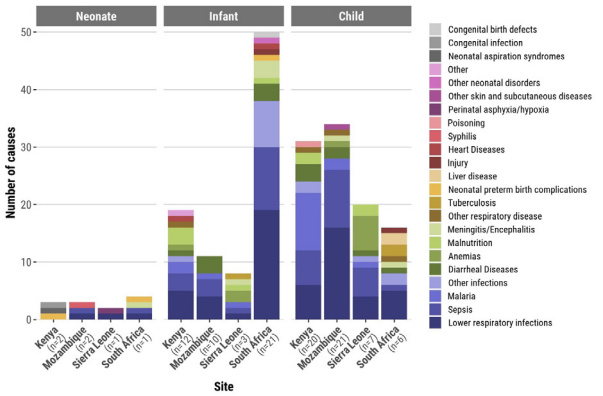
Background: The Child Health and Mortality Prevention Surveillance (CHAMPS) Network conducts mortality surveillance in children using advanced postmortem techniques, providing a unique opportunity to investigate in depth causes of death (COD) in children in Africa and South Asia. Here we present CHAMPS COD findings in children who died from HIV (CDHIV) in four HIV high-burden countries

Methods: CHAMPS collects comprehensive data on <5 years deaths in seven countries using minimally invasive tissue sampling (MITS), comprehensive pathogen screening using molecular methods, clinical record abstraction and verbal autopsy. Immediate, underlying, and comorbid COD are determined by a panel of multidisciplinary specialists using ICD-10 codes, after reviewing all available data. All 2016-2021 cases from Kenya, Mozambique, Sierra Leone and South Africa were included. Adjusted cause-specific mortality fractions (aCSMF) were calculated for HIV identified anywhere in the causal chain leading to death; aCSMF was defined as the proportion of deaths attributed to HIV among all cases completing expert review, adjusted using variables identified a priori from the literature and clinical expertise, including age, sex, location of death, season of death, and verbal autopsy cause of death

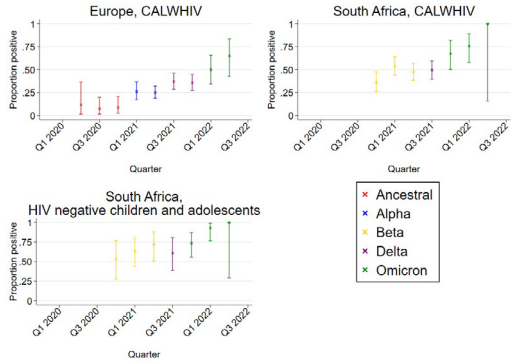
Results: Investigation of 1992 deaths from the four countries using MITS identified 106 (5.3%) with a confirmed HIV diagnosis in the causal chain; of which 6 (5.7%) were neonatal deaths, 46 (43.4%) were infant deaths, and 54 (50.9%) were in child (12-59 months) deaths. HIV aCSMFs were highest in Mozambique (9.68 [90% Bayesian CrI: 8.09–11.50]) and Kenya (9.02 [90% Bayesian CrI: 6.60–12.03]), and lowest in Sierra Leone (4.14 [90% Bayesian CrI: 2.68-6.13]) and South Africa (3.90 [90% Bayesian CrI: 2.87-5.19). Among the 106 CDHIV, 63 (56.7%) also had lower respiratory infections, 42 (37.8%) had sepsis, 17 (15.3%) had malaria, 14 (12.6%) had diarrheal diseases, and 14 (12.6%) had other infections as COD (Figure 1). Kenya had higher prevalence of malaria in infants CDHIV than South Africa or Mozambique, while South Africa had more meningitis and liver disease than other sites.

Conclusion: HIV remains a major cause of child death in sub-Saharan Africa despite high coverage of prevention of mother-to-child-transmission (PMTCT) services. The most common other causes of death in HIV-infected children yield insight into interventions beyond pediatric ART that could have the greatest impact in reducing child deaths.

Other causes of death anywhere in the causal chain for N children who died from HIV in CHAMPs sites, by site and age group



Seroprevalence of SARS-CoV-2 antibodies in Europe and South Africa, by HIV status and calendar quarter of sampling. Colours indicate dominant variant based on GISAID data for adults and children.



134 SARS-CoV-2 IN CHILDREN & ADOLESCENTS LIVING WITH HIV IN EUROPE & SOUTH AFRICA

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Background: Adults living with HIV may have higher risk of SARS-CoV-2 infection than HIV negative adults. There are no published data on seroprevalence of SARS-CoV-2 in children and adolescents living with HIV (CALWHIV).

Methods: We did a repeat SARS-CoV-2 seroprevalence study in 7 paediatric HIV observational cohorts in 5 countries in the European Pregnancy & Paediatric Infections Cohort Collaboration (EPPICC; Belgium, Greece, Spain, Ukraine, United Kingdom (UK)) and also the Cape Town Adolescent Antiretroviral Cohort (CTAAC), South Africa (SA) (CALWHIV and HIV negative adolescents). Participants gave 2 blood samples for SARS-CoV-2 antibody testing ~6 months apart during routine visits between May 2020 and July 2022, and completed questionnaires on SARS-CoV-2 exposure/infection and vaccine status. Clinical and demographic data were extracted from clinic records.

Results: Of 906 participants, 53%(477) were female, 89%(803) CALWHIV, median [IQR] age at first visit 17[15-19] years. Most were enrolled in SA (45%, 410/906), UK (23%, 205/906) or Ukraine (18%, 160/906). 85%(767/906) had 2 blood samples and the rest a single sample. For CALWHIV, at time of first sample, 99%(761/765) were on antiretroviral therapy, median CD4 count was 666[478-858] cells/mL, 70%(535/764) had HIV-1 viral load < 50c/mL. Of those with known SARS-CoV-2 vaccine status, 23%(181/773) CALWHIV and 22% (22/100) HIV negative participants received ≥1 vaccine dose. 6%(43/762) of CALWHIV had a documented prior SARS-CoV-2 positive PCR (including 2 hospitalised for COVID, neither severe), and 16%(124/762) self-reported previous positive test and/or COVID-19 symptoms, giving a total of 17%(128/762) with any previous infection. Based on serum testing, 63%(562/898) of participants overall were seropositive on at least one sample (55% (269/488) Europe, 67% (205/307) SA CALWHIV, 85% (88/103) SA HIV negative group), and among the unvaccinated subgroup, 53%(408/765) were seropositive (41% (167/412) Europe, 64% (168/263) SA CALWHIV, 81% (73/90) SA HIV negative). Among samples taken prior to or in absence of vaccination, the proportion testing antibody positive increased over time (Figure). Of unvaccinated CALWHIV with ≥1 positive result, 17%(52/299) reported any previous SARS-CoV-2 infection.

Conclusion: Most CALWHIV were SARS-CoV-2 seropositive by mid-2022 despite low vaccine coverage. Fewer had documented or self-reported COVID-19 infection or disease, suggesting most infections were mild or asymptomatic.

135 SINGLE-CELL PROTEOGENOMIC PROFILING OF HIV-1 RESERVOIR CELLS

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Background: HIV-1 reservoir cells persist lifelong despite ART but may be vulnerable to host immune responses that could be exploited for HIV-1 cure strategies. Here, we used a novel single-cell, next-generation sequencing approach for the direct *ex vivo* phenotypic profiling of individual HIV-1 infected memory CD4 (mCD4) T cells from peripheral blood (PB) and lymph nodes (LN) of people living with HIV-1.

Methods: mCD4 T cells derived from PB and LN of 8 participants were analyzed by a novel single-cell proteogenomic profiling assay. Cells were labeled with oligomer-tagged antibodies directed against n=53 surface markers and encapsulated into single cells. Multiplex PCR was conducted to amplify small fragments of genomic HIV-1 DNA (n=18) and the viral-host chromosomal junctions of large clones, coupled with amplification of antibody-bound oligomer tags. DNA and protein libraries were sequenced and biocomputationally deconvoluted.

Results: We analyzed n=530,143 individual mCD4 T cells from PB of 5 participants with around 10 years of suppressed viremia: n=2,859 represented HIV-infected cells; n=193 cells harbored genome-intact HIV-1; n=125 included clonally-expanded reservoir cells. Cells encoding for intact HIV or being part of large clones displayed more mature, effector memory phenotypic features and frequently expressed ensemble signatures of surface markers conferring increased resistance to immune-mediated killing (such as PVR and HVEM), paired with elevated expression of immune checkpoint markers (such as PD1 and KLRG1) likely to limit proviral gene transcription. A total of n=396,628 mCD4 T cells from LN were assayed from 3 participants who received ART for around 10-15 years: n=3,888 were HIV-1 infected cells, and n=111 cells harbored genome-intact HIV-1. Cells encoding for intact proviruses were equally distributed between T follicular helper cell (TFH) and resident memory (TRM) CD4 cells and expressed higher levels of CD44, the IL-21 receptor (CD360), and the IL-7 receptor (CD127), all of which are associated with cell survival.

Conclusion: Cells encoding intact proviruses display distinct phenotypic features in PB and LN and upregulate markers associated with proviral transcriptional repression, resistance to immune-mediated killing, and cell survival. We propose that these phenotypic changes result from immune selection processes, implying that only small subsets of infected cells with optimal adaptation to their anatomical immune microenvironment can survive during long-term ART.

136 THE IMPACT OF 3BNC117, 10-1074, AND LEFITOLIMOD ON HIV-1 PERSISTENCE: THE TITAN TRIAL

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Background: Toll-like receptor 9 (TLR9) agonists stimulate innate antiviral immunity, prime adaptive immune responses and reverse latency in people with HIV-1 infection (PWH). Further, broadly neutralizing anti-HIV-1 antibodies (bNAbs) can boost HIV-specific immunity and enhance killing of infected cells through Fc-dependent mechanisms. Here, we evaluated the impact of the TLR9 agonist Lefitolimod and dual bNAb treatment on ART-free virological control.

Methods: In a phase IIa multicenter, randomized placebo-controlled, double-blinded trial (TITAN study; NCT03837756), consenting PWH on suppressive ART were pre-screened for bNAb sensitivity and randomized into one of four groups: A) placebo /placebo; B) lefitolimod (LEFI) /placebo; C) placebo /bNAbs; or D) LEFI /bNAbs. LEFI (120 mg) or placebo were given subcutaneously (SC) weekly from week 1 through week 8. 3BNC117 at 30 mg/kg and 10-1074 at 20 mg/kg or placebo were given intravenously (IV) at week 3 and at week 6. Analytical treatment interruption (ATI) of antiretroviral therapy went from week 3 to 26, or viral rebound, whichever came first. The primary endpoint was time to loss of virological control (plasma HIV-RNA >1,000 c/mL for 4 weeks or confirmed >100,000 c/mL). Secondary endpoints were safety and rebound viral kinetics. bNAb sensitivity was assessed by PhenoSense and HIV envelope sequencing.

Results: 46 participants were randomized to either placebo/placebo (n=11), LEFI/placebo (n=11), placebo/bNAbs (n=12), or LEFI/bNAbs (n=12). The median time to loss of virological control was 32 days (interquartile range [IQR]:21-77) in group A, 35 days (IQR:28-42) in group B, 119 days (IQR:77-175) in group C, and 98 days (IQR:70-119) in group D. The groups receiving bNAbs had significant longer time to loss of virological control compared to placebo (log-rank, P< 0.0005). Six individuals did not meet ART restart criteria during the 24-week ATI (1 in B; 4 in C; 1 in D). The combination of LEFI and bNAbs vs. bNAbs alone did not result in improved virological control (log-rank, P=0.42). More mild adverse events were reported in group D. Two severe adverse events were reported (one vasovagal reaction [unrelated] and one infusion related reaction [considered related to 3BNC117]).

Conclusion: In a double-blinded trial among PWH on suppressive ART, harbouring virus sensitive to study bNAbs, the dual bNAb treatment led to a significant delay in viral rebound during ATI, but there was no added effect on virological control of the TLR9 agonist, lefitolimod.

137 VIRAL AND HOST MEDIATORS OF PERSISTENT LOW-LEVEL VIREMIA

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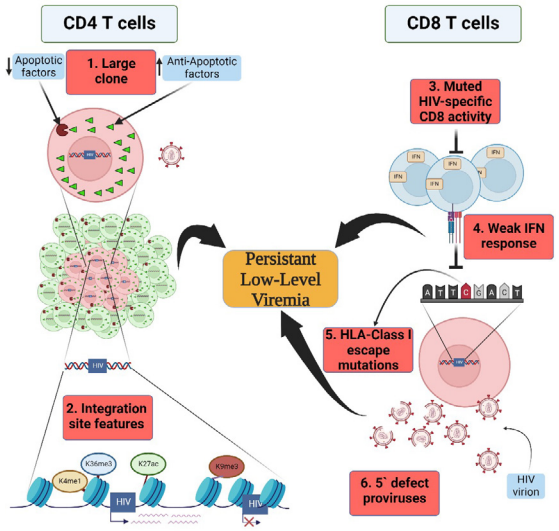
Background: Persistent low-level HIV-1 viremia (pLLV) can occur in people with HIV despite high adherence to antiretroviral therapy (ART), without significant drug resistance, and due to unclear mechanisms.

Methods: We enrolled 8 ART-treated participants with ≥3 HIV-1 RNA levels between 40-1000 copies/mL over 24 months. Near-full length sequencing of the proviruses and pol-env sequencing of plasma HIV were performed. Matched integration site assay was used to identify the host chromosomal integration sites and ChIP-seq data from primary total CD4+ T cells was incorporated through the ROADMAP database. CD4+ T cell transcriptomic profiling and HIV-specific CD8+ T cell reactivity were compared to ART-suppressed comparators. Those intact proviruses contributing to plasma viremia were defined as "producers", and those that did not contribute to viremia as "non-producers".

Results: Participants had median age of 61 years, ART duration of 17 years and pLLV of 32 months. Median (range) of tenofovir in dried blood spots was 3702 (2771-6684) fmol/punch, consistent with high cumulative adherence. Plasma pLLV sequences were comprised primarily of large clones without evidence of viral evolution over time. In 38% of participants, producers harbored 5'-deletions in the packaging site. Compared to 10 ART-suppressed comparators, pLLV participants had a significantly larger intact reservoir in peripheral blood (p=0.001). Compared to non-producers, producer host integration sites were enriched in chromosome 19 and were in closer proximity to histone marks H3K9me3 and H3K36me3. Compared to ART-suppressed comparators, pLLV demonstrated significant upregulation of anti-apoptotic genes in CD4+ cells, with downregulation of pro-apoptotic pathways and type I/II interferon-related genes. There was no significant difference in HIV-specific CD8+ T cell reactivity between pLLV and ART-suppressed comparators. Producers harbored more HLA escape mutations compared to non-producers (p=0.04), and this difference was most prominent in nef genes. Nef escape mutations and HIV-specific CD8+ T cell responses were strongly correlated (r=0.9, p=0.008).

Conclusion: These results demonstrate that non-suppressible HIV viremia is driven by the critical intersection of factors at the viral genetic, epigenetic and cellular level (Figure). This study represents the most comprehensive assessment of persistent low-level viremia to date and provide insight into ART-independent factors necessary for HIV clearance.

Figure: Schematic diagram of viral, epigenetic and immune factors associated with persistent low-level viremia



138 PROVIRUSES IN SELF-REACTIVE CD4+ T CELLS ARE A COMMON SOURCE OF RESIDUAL HIV VIREMIA

Fengting Wu[1], Milica Moskovljevic[1], Hao Zhang[2], Angelica Camilo-Contreras[1], Filippo Dragoni[1], Nathan L. Board[1], Anushka Singhal[1], Jun Lai[1], Luis J. Montaner[3], Janet M. Siliciano[1], Robert F. Siliciano[1], Francesco R. Simonetti[1]

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Background: Despite adherence to ART, some individuals experience persistent nonsuppressible HIV viremia (NSV, VL >20 cps/mL) due to clones of infected CD4+ T cells producing virus. However, mechanisms driving constant expression of these proviruses are not understood. We hypothesized that infected clones cross-reactive to ubiquitous self-antigens could produce residual viremia.

Methods: We characterized residual viremia from 8 donors on ART with NSV. In a fully autologous system, monocyte-derived dendritic cells (DC) were pulsed with protein lysates from sorted PBMCs or viral antigens (HIV, CMV), and co-cultured with CD4+ T cells for 7 days with antiretrovirals. Viral particle production was measured by ultrasensitive quantification and single genome sequencing. We also studied 5 ART-treated individuals with undetectable VL.

Results: Study participants had NSV for a median of 5 years (range 3-10), caused by a single or multiple plasma clones (mean 4, range 1-10). In all participants, stimulation of CD4+ T cells with lysate-pulsed DCs led to the production of virus identical to the variants contributing to HIV RNA in plasma. Virus was released in response to lysates from one or more PBMC fractions (either B, T, or myeloid cells), suggesting reactivity to a ubiquitously presented antigens. In some donors, we also detected virus production upon stimulation

with Gag p55. Addition of anti-MHC class II antibody significantly reduced or prevented virus release, confirming that induction of HIV expression was dependent on interaction between peptide:MHCII–TCR. Without stimulation, CD4+ T cells didn't lead to virus production. Conversely, non-specific activation with anti-CD3/CD28, when compared with autologous lysates, resulted in significantly higher virus production (HIV copies/mL, AUC 68,986 vs 2,352, p-value 0.0006) from multiple variants (average 5.71, range 1-12, versus 1-2 variants, respectively). Finally, in 3 of 5 participants with suppressed VL, stimulation with autologous lysates caused release of virus that matches QVOA isolates, suggesting this phenomenon is common among PLWH on ART, not just in those with NSV.

Conclusion: Our results show that recognition of self-antigens *ex vivo* can induce latency reversal and production of virus identical to infectious predominant plasma clones. This work provides a new understanding of spontaneous reservoir activity, explaining why only a rare subset of proviruses can cause persistent residual viremia and potentially viral rebound upon ART interruption.

139 *EX VIVO* HIV DNA INTEGRATION IN STAT3 DRIVES T CELL PERSISTENCE AND OVERGROWTH

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Background: Defective HIV proviruses within a few specific genes have been associated with T cell clonal expansion and persistence during ART, likely due to LTR-driven overexpression of the host gene via insertional mutagenesis. We have previously linked insertional mutagenesis of *STAT3* to clonal expansion in T cells infected *ex vivo* with an HIV vector. Additionally, proviruses integrated in *STAT3* and *LCK* have been implicated in insertional mutagenesis driving rare cases of AIDS-associated T cell lymphoma. We hypothesize that *STAT3* integrations can lead to persistent HIV+ primary T cells infected *ex vivo*, which can model HIV-driven T-, and possibly B-, cell lymphoma.

Methods: Primary Human CD4+ T cells from three different donors were obtained from STEMCELL Technologies and infected with replication incompetent NL43dEnv with a gfp reporter. T cells were cultured in RPMI 1640 with IL-2 and stimulated with anti-CD3/CD28 beads. T cells from donors with persistent cells were taken for qPCR, Integration Site Analysis, and RNA-seq. T cells with persistent populations were later cultured with a Tat inhibitor (triptolide) to identify what role Tat and proviral LTRs plays in cell persistence. Flow cytometry was used to assess cell viability and gfp and STAT3 expression.

Results: After day 126 post infection, three of the six replicates from one donor contained resurgent HIV (gfp) positive cell populations, with two of the three consisting of greater than 50% gfp+ cells. Integration site analysis identified the persistent HIV+ replicates all shared clonal integrations within Intron 1 of *STAT3*. RNA-seq identified overexpression of *STAT3* and its downstream targets. These signatures were similar to HIV-driven T cell lymphomas described by *Mellors et al*, which shared similar *STAT3* related expression patterns. The role of Tat in cell persistence needs to be further investigated but triptolide leads to a decrease in STAT3 expression and cell persistence.

Conclusion: ¬We have confirmed that proviral integrations within *STAT3* provide a selective advantage to primary CD4+ T cells infected with replication-incompetent HIV *ex vivo*. Additionally, these persistent HIV+ cells show similar overexpression patterns to HIV-driven T cell lymphomas thus providing a model for studying HIV-driven mutagenesis in T cells. We are exploring how Tat inhibition can reduce the selective advantage of proviral insertional mutagenesis, thus providing a potential therapeutic approach and prevention strategy for HIV-driven T cell lymphomas.

140 THERAPEUTIC VACCINATION OF SHIV-INFECTED, ART-SUPPRESSED INFANT RHESUS MACAQUES

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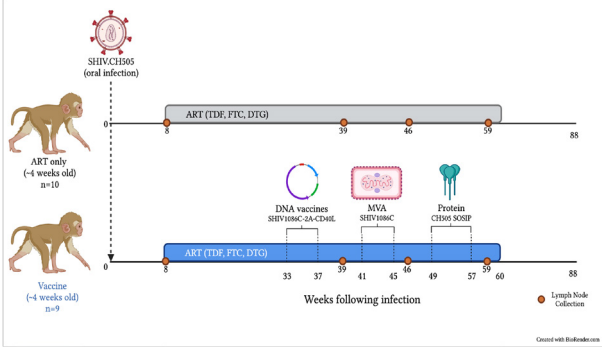
Background: Breastfeeding based HIV transmission accounts for the majority of new pediatric HIV infections. Antiretroviral therapy (ART) fails to eradicate HIV reservoirs, which lead to rapid viral rebound following ART interruption. Therapeutic interventions effective in eliminating viral reservoirs and thereby delaying or preventing viral rebound in the absence of ART would be highly valuable for children living with HIV, who otherwise must be on ART for their lifetime. The objective of this study was to evaluate the immunological and virological impact of DNA/MVA/Protein-based therapeutic vaccination in a pediatric model of oral SHIV-infected ART-suppressed infant rhesus macaques (RMs).

Methods: A total of 19 infant RMs of ~4 wks of age were orally infected with SHIV.C.CH505.375H.dCT and placed on daily ART at 8 wpi. After complete viral suppression, a group of 9 animals was intramuscularly vaccinated with two doses each of SHIV-DNA-rhCD40L, SHIV-MVA and CH505 SOSIP protein under ART. Ten RMs did not receive vaccinations and served as ART only controls. At 60 wpi, ART was interrupted (ATI) and all RMs were followed for 14 wks to study viral rebound kinetics. Peripheral blood (PB), lymph node (LN), and gut tissues were collected throughout the study for multiple virological and immunological analyses.

Results: DNA/MVA/Protein-based therapeutic vaccination was safe and highly effective in inducing highly functional SHIV-specific CD4+ and CD8+ T cell responses in PB and LN under ART. Vaccination also significantly expanded granzyme B- and perforin- expressing total and SHIV-specific CD8+ T cells in PB. HIV-Env specific binding and neutralizing antibody titers were increased significantly following vaccination and were significantly higher as compared to ART-only group. To our surprise, despite vaccine-induced robust immune activation, vaccination did not reduce viral reservoirs. Moreover, following ATI, no difference in terms of time to viral rebound or viral control were observed between the groups.

Conclusion: These data show that DNA/MVA/Protein-based therapeutic vaccination is safe and effective in mounting robust SHIV-specific humoral and cellular immune response in SHIV-infected ART-treated infant RMs. Notably, additional interventions such as latency reversal agents or immune checkpoint blockade may be required to reduce viral reservoirs and alter rebound dynamics post ART release in vaccinated RMs.

Fig. 1. Graphical schematics of the study design



141 VIRAL RESERVOIR LANDSCAPE OF CHILDREN WITH HIV IN BOTSWANA TREATED WITH DUAL bNAbs

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Background: To evaluate possible alternatives to ART among children living with HIV, the Tatelo clinical trial administered two broadly-neutralizing antibodies to children in Botswana with HIV clade C infection who had initiated ART at birth. Here we describe a high-resolution, cross-sectional and longitudinal analysis of the proviral reservoir landscape in Taleo participants.

Methods: Children were initially followed in the Early Infant Treatment (EIT) cohort, receiving continuous ART from birth; those entering Tatelo had HIV-1 RNA < 40 c/mL for ≥24 weeks prior to entry and were >96 wks of age. Tatelo participants received ART plus VRC01LS and 10-1074 (dosed every 4 wks) for at least 8 weeks, after which ART was stopped. Peripheral blood mononuclear cells were collected every 2-4 weeks. HIV-1 proviruses and chromosomal integration sites were analyzed using FLIP-seq and MIP-seq.

Results: Of 25 children treated with VRC01-LS and 10-1074 alone, eleven (44%) maintained HIV RNA < 400 c/mL through 24 weeks (controllers) and 14 (56%) had viral rebound >400 c/mL (rebounders). In total, 592 proviral genomes (216 intact, 376 defective) were obtained; 31 integration sites of intact proviruses and 29 integration sites of defective proviruses were identified. Frequencies of total, intact and defective proviruses at birth were lower in controllers than in rebounders. No significant changes in intact, defective and total proviral frequencies were observed in controllers before and after bNAb treatment. Rebounders demonstrated a significantly higher reservoir of intact proviruses immediately prior to or at virological rebound compared to Tatelo entry (p=0.004). Proviruses were preferentially integrated into genes, and evidence for clonal expansion of proviruses with identical integration sites was detected in multiple children. In two controllers with high frequencies of viral reservoir cells, and one rebounder with low HIV RNA rebound (742 copies/mL), intact proviruses were preferentially (67%) integrated in centromeric/satellite DNA, ZNF genes and non-genic DNA.
Conclusion: In children with early initiation of ART, very low viral reservoirs were observed in controllers, without detectable differences in proviral reservoir size before and after bNAb treatment. In contrast, intact and defective proviruses were more commonly identifiable among rebounders beginning at birth, and increased in frequency between bNab initiation and rebound.

142 SINGLE-CELL EPIGENETIC, TRANSCRIPTIONAL, AND PROTEIN STATES OF HIV RESERVOIR

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Background: The cellular program dictating productive HIV-1 infection versus latency remains unknown. Understanding the epigenetic regulators and transcriptional program of HIV-infected cells with undetectable HIV expression (HIV DNA+ RNA–) and active HIV expression (HIV RNA+) informs HIV eradication strategies.
Methods: We performed DOGMA-seq and TREK-seq to simultaneously capture 171 surface proteins, cellular transcriptome (RNA-seq), transcription factor (TF) activities (ATAC-seq), and T cell clonality (TCR sequencing) within the same single cells. We profiled paired memory CD4+ T cells during viremia and after suppressive ART from 6 HIV+ individuals from the Sabes cohort. Samples from 4 uninfected individuals served as controls.
Results: We captured 92,939 single cells (25,778 in viremia, 56,771 in viral suppression, and 10,660 in uninfected controls) each having protein expression, transcriptomic, and epigenomic profiles. We identified 233 HIV DNA+ RNA– cells and 256 HIV RNA+ cells (38 HIV DNA+ RNA+ cells and 218 HIV DNA– RNA+ cells) in viremia and 20 HIV DNA+ RNA– cells and 14 HIV RNA+ cells (3 HIV DNA+ RNA+ cells and 11 HIV DNA– RNA+ cells) in viral suppression. Both HIV DNA+ cells and HIV RNA+ cells were clonally expanded in cytotoxic Th1 in both viremia and viral suppression. Epigenetic profiling revealed distinct increase in AP-1 TF activity during viremia in HIV RNA+ cells ($q < 0.05$) but not in HIV DNA+ RNA– cells in comparison to uninfected memory CD4+ T cells. Comparing HIV+ Th1 T cell clones between viremia and viral suppression, we found increased AP-1 TF activity in viremia ($q < 0.05$) and increased KLF and ZNF TF activities in viral suppression ($q < 0.05$). Transcriptome profiling revealed positive regulation of IFNγ production in HIV DNA+ cells ($P < 0.005$) and cytotoxic T cell pyroptotic process in HIV RNA+ cells ($P < 0.005$) in viremia. Compared to uninfected memory CD4+ T cells, we found 113 and 94 differentially expressed genes in HIV DNA+ RNA– cells and HIV RNA+ cells, respectively. Among them, *IKZF3* and *GZMA* were significantly upregulated in both populations. *In vitro* validation showed that HIV-infected cells expressing IKZF3 had higher levels of cellular proliferation marker Ki67.
Conclusion: AP-1 transcription factor activity determines the high levels of HIV-1 expression in infected cells. IKZF3 may promote the proliferation of HIV-infected cells.

143 ANTI-IL-10/PD-1 IMMUNE MEDIATED CONTROL OF VIRAL REBOUND IN SIV INFECTED MACAQUES

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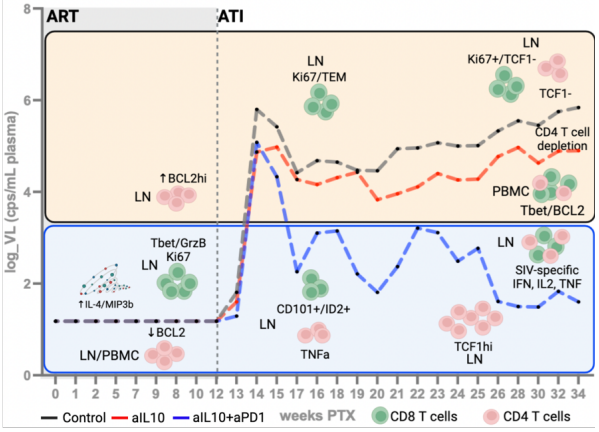
Background: IL10 and PD1 contribute to HIV reservoir persistence impeding HIV eradication. IL10 contributes to lack of effector function, antigen-presentation and promotes HIV reservoir survival. PD1 leads to T cell exhaustion and HIV latency. *We hypothesized that the dual blockade of IL10 and PD1 could synergize and lead to viral rebound control post-ATI (Analytical Treatment Interruption) by impeding on the survival of infected T cells and by rescuing T cell exhaustion and promoting memory and effector T-cell differentiation and function*.
Methods: 28 rhesus macaques (RMs) infected with SIVmac239 started antiretroviral therapy (ART) 42 days post-infection which was maintained for 14-months. Rhesusized aIL10 (n=10), aIL10/aPD1 (Combo therapy - n=10), or vehicle (n=8) was administered every 3-weeks starting 12 weeks pre-ATI and stopped 14-weeks post-ATI (week 26 PTX). Animals were followed longitudinally for biospecimen collections.
Results: Durable viral load control post-ATI (less than a 1000 cps/mL in 80% of the animals up to 6 months) in the combo treated RMs was associated with a biphasic immune response (Fig 1). I) pre-ATI poised immune response with i) significant induction of effector (GrzB+, Tbet+) and proliferating (Ki67+) CD8 T cells in LNs; ii) significant decay in the pro-survival protein BCL2 in CD4 T cells in LNs and PBMCs; we and others have shown that BCL2 levels are higher in infected cells and iii) elevated plasmatic pro-inflammatory environment (IL1b, IL18, IP10, MIP3b and MCPs). These pre-ATI features were associated with control of viremia 24 weeks post ATI (week 36 PTX) and highlights a poised state of T cell differentiation providing advantage to the combo treated RMs as compared to aIL10-treated and control RMs. ***II) Post-ATI (36 weeks PTX - 6 months on ATI)*** there was i) a significant expansion of SIV-specific CD4 and CD8 T cells in LNs associated with viral control; ii) preserved CD4 T counts and iii) contraction of effector T cells to cells with a stem-like phenotype (TCF1+).
Conclusion: The combo therapy set the stage for a poised immune effector state prior to ATI that enabled post-ATI differentiation and expansion of SIV specific CD4 and CD8 T cells leading to viral rebound control. A homeostatic environment, with preserved CD4 T cell counts and increased frequencies of cells expressing high levels of the stemness transcription factor TCF1, was uniquely observed in RMs that controlled the virus systemically and in tissues post-ATI.
Fig 1. Graphical abstract. Phases of the immune response induced by the combo therapy leading to viral rebound control post-ATI



144 EFFECTS OF EPLERENONE ON MYOCARDIAL PERFUSION AND FUNCTION: THE MIRACLE HIV STUDY

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Background: Subclinical cardiovascular disease (CVD) remains increased among persons with HIV(PWH). We have shown unique renin-angiotensin-aldosterone system (RAAS) physiology among PWH such that increased RAAS activation is associated with non-traditional CVD risk factors, including visceral adiposity, insulin resistance, inflammation, and altered natriuretic peptides. We sought to understand how RAAS blockade may improve CVD in HIV.

Methods: 40 PWH without known CVD on stable ART with HIV viral load< 100 c/mL were randomized to eplerenone 50mg (n=20) vs. placebo (n=20) BID in a 12-month double-blinded, placebo-controlled trial. Myocardial indices were assessed by coronary PET and cardiac MRI. Change was determined by T-test or Wilcoxon Rank Sums Test depending on normality of distribution.

Results: Treatment groups (eplerenone vs. placebo) were similar for age (53±7 vs. 56±6 yrs), male sex (75 vs. 75%), white race (55 vs. 55%), HIV duration (20±8 vs. 21±7 yrs), and CD4+ count (814[617,916] vs. 740[545,1122] cells/mL). Change in coronary flow reserve (CFR) on coronary PET was not significantly different(0.01±0.64 vs. -0.07±0.48, P=NS, eplerenone vs. placebo). In ITT analyses accounting for missing data, a higher proportion in the eplerenone vs. placebo group had improvements in CFR(75 vs. 40%, P=.02). In a subset analysis among those with impaired baseline CFR, eplerenone significantly improved CFR vs. placebo (0.28±0.27 vs. -0.05±0.36, P=.04). Eplerenone improved myocardial parameters on cardiac MRI including left ventricular end diastolic volume (-13±28 vs. 10±26mL, P=.03), global circumferential strain (-1[-3,1] vs. 2[0,4]s-1, P=.03), and stress myocardial blood flow (0.09±0.56 vs. -0.53±0.68 mL/min/g, P=.03). There was an increase in CD4+ count (127[-38,286] vs. -6[-168,53]cells/mL, P=.02) and a trend towards reductions in hsIL-6 (-0.8[-1.8, 0.4] vs. 0.2[-0.5, 2.2]pg/mL, P=.07) and hs-cTnT (0[-0.1, 0] vs. 0[0, 0.7]ng/L, P=.09) in the eplerenone vs. placebo-treated groups. Eplerenone was well-tolerated among PWH and lowered systolic blood pressure (-16±14 vs. -4±14 mmHg, P=.03) compared to placebo.

Conclusion: RAAS blockade with eplerenone improved key myocardial perfusion and diastolic dysfunction parameters among PWH. In addition, CFR improved significantly in a subset of PWH who had subclinical impairments in CFR at baseline. Moreover, eplerenone may have other novel properties to improve immune function in HIV, aside from its well-known mechanism of action related to BP and sodium regulation.

145 DEPRESSION AND ANXIETY ASSOCIATED WITH INCIDENT TYPE I AND II MI AMONG PWH

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Background: People with HIV (PWH) experience higher lifetime prevalence of major depression and anxiety than the general population. Depression and anxiety have been associated with increased risk of myocardial infarction (MI) in the general population and among PWH but with limited attention on the type of MI among PWH. We examined the association between depression and/or anxiety and incident Type 1 (T1MI) or Type 2 (T2MI) acute MI among PWH.

Methods: We examined data from 7 NA-ACCORD clinical cohorts (1997-2017) with adjudicated first MI, regardless of type; outcomes included T1MI (plaque rupture or cardiac intervention) or T2MI (demand ischemia). Baseline was when a participant entered observation for MI. We defined depression or anxiety as a time-varying ICD-coded diagnosis prior to an incident MI; we censored participants at death, loss to follow-up, or first MI (if it was not the outcome type of interest). We used Cox proportional hazard models to estimate the association between depression/anxiety and MI by type, adjusting for sex at birth, age, race/ethnicity, HIV acquisition group, substance use, and traditional and HIV-related risk factors for cardiovascular disease. We performed a test for interaction between depression and anxiety on the risk of MI.

Results: Of the 33,071 study participants followed for 168,846 person-years, 16,351 had a diagnosis of depression or anxiety (5,432 with both), and 16,720 never had a depression or anxiety diagnosis; 495 T1MIs and 374 T2MIs occurred. After adjusting for traditional and HIV-related risk factors, depression was a significant predictor of T1MI (aHR, 1.23 [95% CI, 1.02-1.49]) with a similar effect size and trend towards statistical significance for T2MI (aHR, 1.20 [95% CI, 0.96, 1.51]). Anxiety was not a significant predictor for T1MI (aHR, 0.92 [95% CI, 0.74-1.16]) but was significant for T2MI with a strong effect size (aHR, 1.42 [95% CI, 1.10-1.83]). We found no evidence for interaction between anxiety and depression. Ever smoking was a significant predictor for both T1MI and T2MI, while ever cocaine use and detectable viral load were significant predictors only for T2MI.

Conclusion: Diagnosed depression was a significant predictor of T1MI and suggestive for T2MI among PWH, whereas anxiety was associated only with T2MI. Further understanding of the role for mental health diagnosis and treatment to improve cardiovascular health among PWH is needed, including access to substance use disorder treatment and comorbidity management.

Table. Risk of incident Type 1 or Type 2 MI among people with HIV who have an existing diagnosis of depression or anxiety compared with people with HIV with no existing diagnosis of depression or anxiety.

	Type I MI*		Type II MI*	
	aHR	95% CI	aHR	95% CI
Demographics				
Male at birth	1.55	1.13, 2.14	0.98	0.72, 1.32
Age (scaled by 10 years)	1.50	1.35, 1.66	1.18	1.05, 1.33
Substance use				
Tobacco (ever/never)	1.88	1.45, 2.43	1.36	1.01, 1.84
Cocaine (ever/never)	0.97	0.71, 1.31	1.49	1.11, 1.99
Traditional CVD risk factors				
Hypertension	2.81	2.26, 3.49	2.50	1.93, 3.25
Diabetes Mellitus	1.33	1.05, 1.68	2.39	1.84, 3.11
Elevated total cholesterol or statin use	2.39	1.94, 2.96	1.02	0.80, 1.30
Chronic Kidney Disease (eGFR<60 mL/min)**	1.36	1.07, 1.74	3.05	2.37, 3.93
HIV-related risk factors				
History of protease inhibitor use (ever/never)	1.49	1.23, 1.81	1.07	0.85, 1.34
History of detectable viral load (ever/never)	1.13	0.85, 1.49	1.35	1.02, 1.79
Mental health comorbidities				
Anxiety	0.92	0.74, 1.16	1.42	1.10, 1.83
Depression	1.23	1.02, 1.49	1.20	0.96, 1.51

*Model is additionally adjusted for race/ethnicity, cohort, HIV transmission risk group, at-risk alcohol use, cannabis use, body mass index, history of AIDS, history of HCV co-infection, CD4 at ART initiation, and VL at ART initiation, and time-varying CD4.
**eGFR is calculated by the CKD-EPI equation.
Abbreviations: MI, myocardial infarction; aHR, adjusted Hazard Ratio; 95% CI, 95% confidence interval; CVD, cardiovascular disease; eGFR, estimated glomerular filtration rate.

146 WEIGHT AND METABOLIC CHANGES WITH CABOTEGRAVIR+RILPIVIRINE LONG-ACTING OR BICTEGRAVIR

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Background: Integrase strand transfer inhibitors (InSTIs) and tenofovir alafenamide–based regimens are potentially associated with weight gain and metabolic perturbations in people living with HIV (PLWH). Cabotegravir (CAB), an InSTI, plus rilpivirine (RPV), a non-nucleoside reverse transcriptase inhibitor, administered monthly or every 2 months (Q2M) is the first complete long-acting (LA) regimen recommended by treatment guidelines for the maintenance of HIV-1 virologic suppression. Modest body weight and lipid changes have been observed in participants receiving CAB+RPV LA therapy in Phase 3/3b studies. SOLAR (NCT04542070) is a Phase 3b noninferiority efficacy study, also evaluating weight and metabolic changes from baseline (BL) to Month (M)11/12 as additional endpoints, in PLWH switching to CAB+RPV LA Q2M vs. continuing on bictegravir/emtricitabine/tenofovir alafenamide (B/FTC/TAF).

Methods: Among 687 participants randomized (2:1; n=6 not dosed), 454 switched to CAB+RPV LA Q2M (175 elected for oral lead-in [OLI] and 279 elected for therapy without an OLI) and 227 continued on B/FTC/TAF. Changes from BL

in body weight, body mass index (BMI) category, waist and hip circumferences (WC, HC), waist-to-height ratio (WHtR), waist-to-hip ratio (WHR), muscle mass, total body fat, and proportion of participants with insulin resistance or metabolic syndrome were analyzed at M11 (LA without OLI)/M12 (LA with OLI and B/FTC/TAF).

Results: Median (interquartile range) change in body weight from BL was –0.40 kg (–2.95, 2.10) in the LA arm and +0.05 kg (–2.30, 1.95) in the B/FTC/TAF arm at M11/12 (Table). Mean (standard deviation) change in WC and HC was +0.19 cm (8.01) and +0.26 cm (7.81) in the LA arm, and +1.64 cm (9.19) and +0.51 cm (11.44) in the B/FTC/TAF arm at M11/12. There were no clinically relevant changes from BL to M11/12 in participants' WHtR, WHR, or the proportion of participants with metabolic syndrome, abdominal obesity, or insulin resistance in either arm.

Conclusion: This is the first randomized Phase 3b study to compare weight, anthropometric, and metabolic changes in a standardized manner among PLWH switching to CAB+RPV LA Q2M or continuing B/FTC/TAF. Changes in weight, BMI, and body composition measurements were minor and similar between treatment arms through M11/M12. There were no clinically relevant changes in the proportion of participants with metabolic syndrome, abdominal obesity, or insulin resistance between arms at M11/12.

Baseline Characteristics, Weight, and Metabolic Changes Through Month 11 or Month 12 From SOLAR

Safety population	CAB+RPV LA Q2M arm (n=454)	B/FTC/TAF (n=227)
Median age, years (range)*	37 (18, 74)	37 (18, 66)
≥50 years, n (%)	86 (19)	42 (19)
Female sex at birth, n (%)*	77/447 (17)	41/223 (18)
Race, n (%)*		
Black	95/447 (21)	49/223 (22)
White	307/447 (69)	156/223 (70)
Asian	23/447 (5)	11/223 (5)
Other†	22/447 (5)	7/223 (3)
BL median weight, kg (range)‡	81.3 (48.1, 199.7)	79.0 (43.3, 169.0)
Median weight change at M11/M12, kg (IQR)§	–0.40 (–2.95, 2.10)	0.05 (–2.30, 1.95)
5–<10% weight increase from BL‡ n (%)	47/408 (12)	23/213 (11)
≥10% weight increase from BL‡ n (%)‖	11/408 (3)	9/213 (4)
BL median BMI, kg/m^2 (range)‡	26.01 (16.63, 65.21)	25.28 (16.48, 52.16)
Median BMI change at M11/12, kg/m^2 (IQR)§	–0.13 (–0.95, 0.69)	0.01 (–0.73, 0.72)
BL BMI category, n (%)‖§		
Underweight (<18.5 kg/m^2)	8/454 (2)	3/227 (1)
Normal (18.5–<25 kg/m^2)	175/454 (39)	94/227 (41)
Overweight (25–<30 kg/m^2)	174/454 (38)	78/227 (34)
Obese (≥30 kg/m^2)	97/454 (21)	52/227 (23)
Participants changing BMI category at M11/M12, n (%)¶#		
Underweight -> normal	4/8 (50)	0/3 (0)
Normal -> overweight	13/175 (7)	12/94 (13)
Overweight -> obese [normal or underweight]	14/174 (8) [21/174 (12)]	7/78 (9) [10/78 (13)]
Obese -> overweight [normal or underweight]	8/97 (8) [1/97 (1)]	5/52 (10) [0]
BL mean HC, cm (mean change [SD] at M11/12)§	99.4 (0.26 [7.81])	98.9 (0.51 [11.44])
BL mean WC, cm (mean change [SD] at M11/12)§	92.4 (0.19 [8.01])	92.1 (1.64 [9.19])
BL median total body fat, % body fat (IQR)‡	23.0 (17.0, 31.0)	23.0 (18.0, 32.0)
Median total body fat change at M11/12, % (IQR)§	0.0 (–2.0, 3.0)	0.0 (–3.0, 1.0)
BL median muscle mass, kg (IQR)‡	59.05 (51.75, 65.85)	56.60 (49.0, 63.40)
Median muscle mass change at M11/12, kg (IQR)§	–0.20 (–2.70, 1.70)	0.10 (–1.30, 2.15)
Change in metabolic parameters†		
Proportion of participants with metabolic syndrome, n (%)**		
BL‡	75/454 (17)	38/227 (17)
M11/12	72/454 (16)	39/227 (17)
Proportion of participants with insulin resistance (HOMA-IR≥2), n (%)††		
BL‡	173/454 (38)	91/277 (40)
M11/12	169/454 (37)	82/277 (36)

*Described for the modified intention-to-treat exposed population (n=670; CAB+RPV LA Q2M arm, n=447; B/FTC/TAF arm, n=223). 11 participants were excluded from the ITT-E population (n=681), due to critical findings related to significant and persistent non-compliance to protocol requirements at one study site.
†Other race participants: American Indian or Alaska Native, n=14 (CAB+RPV LA Q2M) and n=2 (B/FTC/TAF); Native Hawaiian or other Pacific Islander, n=1 (B/FTC/TAF); multiple, n=8 (CAB+RPV LA Q2M) and n=4 (B/FTC/TAF).
‡Baseline is Day 1.
§Anthropometric assessments were considered non-evaluable (equal to missing) after initiation of lipid-modifying agent use by participants without any imputation. If participants took lipid-modifying agents within 12 weeks prior to the start of the study treatment, all the post-baseline values were deemed non-evaluable. Median weight and BMI (BL: CAB+RPV LA Q2M, n=409; B/FTC/TAF, n=203; mean change calculation: CAB+RPV LA Q2M, n=356; B/FTC/TAF, n=184), BL, HC, and WC (BL: CAB+RPV LA Q2M, n=408; B/FTC/TAF, n=198; mean change calculation: CAB+RPV LA Q2M, n=352; B/FTC/TAF, n=180), total body fat (BL: CAB+RPV LA Q2M, n=396; B/FTC/TAF, n=195; mean change calculation: CAB+RPV LA Q2M, n=331; B/FTC/TAF, n=168), muscle mass (BL: CAB+RPV LA Q2M, n=388; B/FTC/TAF, n=190; mean change calculation: CAB+RPV LA Q2M, n=323; B/FTC/TAF, n=164).
‖Changes in metabolic parameters and BMI category were analyzed in the safety population.
¶The denominators for the percentages are the total number of people in each BMI category at BL. Missing data at M11/12: CAB+RPV LA Q2M, n=46/454 (10%); B/FTC/TAF, n=14/227 (6%). No participants who were underweight at BL shifted to overweight or obese. No participants who were normal weight at BL shifted to obese.
**Metabolic syndrome is defined as having three abnormal findings out of the five risk factors (WC, triglycerides, HDL, BP, and fasting glucose).
††Insulin resistance was defined as a HOMA-IR score ≥2.
B/FTC/TAF, bictegravir/emtricitabine/tenofovir alafenamide; BL, baseline; BMI, body mass index; BP, blood pressure; CAB, cabotegravir; HC, hip circumference; HDL, high-density lipoprotein; HOMA-IR, Homeostatic Model Assessment-estimated Insulin Resistance; IQR, interquartile range; ITT-E, intention-to-treat exposed; LA, long-acting; M, month; Q2M, every 2 months; RPV, rilpivirine; SD, standard deviation; WC, waist circumference.

147 A LOSS OF ERα ATTENUATES DTG-MEDIATED DISRUPTION OF THERMOGENESIS IN BROWN ADIPOCYTES

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Background: Antiretroviral therapy (ART) containing integrase strand transfer inhibitors (InSTI) has been associated with weight gain in both ART-initiation and switch studies, especially in women, but the underlying mechanisms of sex-difference are unclear. Estrogen is recognized as a master regulator of the energy homeostasis and is a major determinant of sex differences in the control of energy homeostasis. Hence, we hypothesized that InSTIs may interrupt adipose function via estrogen receptor.

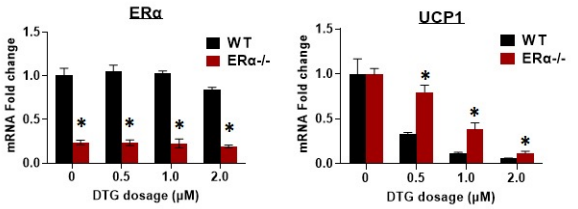
Methods: Estrogen receptor-mediated transcriptional activity was measured by luciferase reporter containing estrogen response element in the presence of dolutegravir (DTG), doravirine (DOR) and efavirenz (EFV). Estrogen receptor α (ERα) deficient cells were created from primary preadipocytes isolated from female mice (ERα$^{loxp/loxp}$) using a Cre/loxp system. Cells were treated with DTG for 8 days during differentiation into mature white or brown adipocytes. Mature adipocytes were analyzed for lipid accumulation by Oil Red O Staining, adipogenic markers by qRT-PCR and immunoblotting.

Results: We found that DTG treatment reduced estrogen-mediated ERE-reporter activity in a dose dependent manner and half of C_{max} value of DTG (2.5 uM) was sufficient to completely suppress reporter activity. However, DOR and EFV had no effect. We found that a genetic deletion of ERα by Ad-Cre alone did not affect overall adipogenesis as adipogenic markers (PPARγ, FABP4, and CEBPα/β) levels and lipid accumulation by Oil Red O staining were similar between ERα knockout (KO) and wild type (WT) adipocytes. However, a loss of ERα significantly attenuated DTG-mediated suppression of uncoupling protein 1 (UCP1), which is an essential for a thermogenic process in brown/beige adipocytes (Figure), and other brown adipogenesis markers (Dio2, CIDEA) in ERα KO compared to WT adipocytes. In addition, DTG-mediated suppression of mitochondrial respiratory chain, cytochrome oxidase complex IV (COX IV), lipid droplet associated protein 1 (perilipin1), hormone sensitive lipase (HSL) was blocked in ERα KO compared to WT adipocytes.

Conclusion: Our data showed that DTG inhibits estrogen signaling action modulated by ERα and a genetic deletion of ERα in adipocytes attenuates DTG-mediated suppression of thermogenesis. These findings suggest a novel

mechanism by which InSTIs may lead to weight gain potentially in a sex-dependent manner.

Figure. A loss of ERα attenuates DTG effect on UCP1 expression in brown adipocytes (n=6, *, P<0.05).



148 MICROBIOTA-DERIVED METABOLITES ARE POWERFUL BIOMARKERS FOR ANAL CANCER PREVENTION

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Background: The risk of anal cancer is markedly increased in PWH, especially in MSM, who exhibit specific microbiota signatures, possibly contributing to the greater HPV persistence and oncogenic potential. The low specificity of the current screening strategy for detecting high-grade squamous intraepithelial lesions (HSIL) hinders anal cancer prevention. We investigated in anal cytology samples microbiota derivatives associated with HSIL.

Methods: We recruited a discovery and a validation cohort in 4 clinical sites in Spain and Italy. Study participants were mostly MSM undergoing HSIL screening with high-resolution anoscopy and anal biopsies to confirm HSIL. We extracted the bacterial DNA, proteins, and metabolites from anal cytology samples, where we performed 16SrRNA gene sequencing,mass spectrometry, and targeted metabolite quantification.

Results: We included 213 participants, 167 in the discovery cohort (70 with confirmed HSIL), and 46 in the validation cohort (25 with confirmed HSIL). Patients with HSIL exhibited an increased abundance of *Prevotella copri*, while *Sneathia sanguinegens* were depleted. The microbiota associated with HSIL overexpressed proteins that converged in the production of succinyl-CoA and cobalamin, which levels were consistently increased in subjects with HSIL (**Figure 1A**).

The combination of succinyl-CoA and cobalamin overperformed the anal cytology, improving sensitivity from 91.2% to 96.6%, specificity from 34.1% to 81.8%, positive predictive value from 48.1% to 77.8%, and negative predictive value from 85.3% to 97.3% (**Figure 1B**). While the anal cytology correctly classified only 59.9% of individuals, the combination of both metabolites improved the classification to 87.7%. This test overcame internal (adjusted AUC 0.877) and external validation. From 98 false-positive cytologic results of succinyl-CoA and cobalamin levels reclassified to true negative results 49 (81.9%). Finally, we demonstrated a greater *in vitro* production of succinyl-CoA and cobalamin of *Prevotella copri* –enriched in participants with HSIL– vs. *Sneathia sanguinegens* –depleted in participants with HSIL–.

Conclusion: Cobalamin and succinyl-CoA are overexpressed in the anal microbiota of patients with HSIL and show an excellent diagnostic capacity. Their measurement overperforms anal cytology to screen for patients with HSIL. Hence, we discovered two powerful biomarkers, for which readily detection methods can be established, that could improve the current strategy for anal cancer screening.

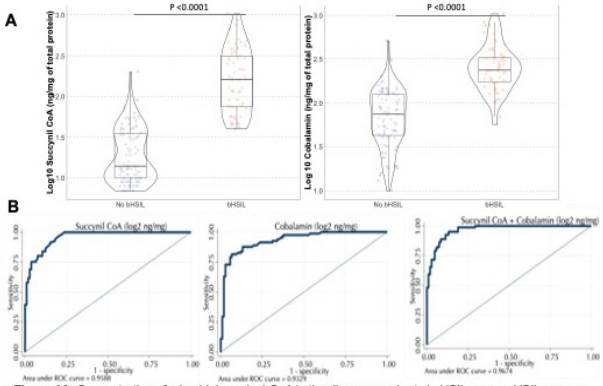

Figure 1A. Concentration of microbial succinyl-CoA in the discovery cohorts in HSIL vs. non-HSIL groups.
Figure 1B. Area under the receiver operating characteristic curve (AUC) estimates of the logistic regression models for the diagnosis of HSIL in the discovery cohort, including either the bacterial markers alone or in combination.

149 IMPACT OF INTEGRASE INHIBITORS ON CARDIOVASCULAR EVENTS IN PERSONS STARTING ART

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Swiss HIV Cohort Study

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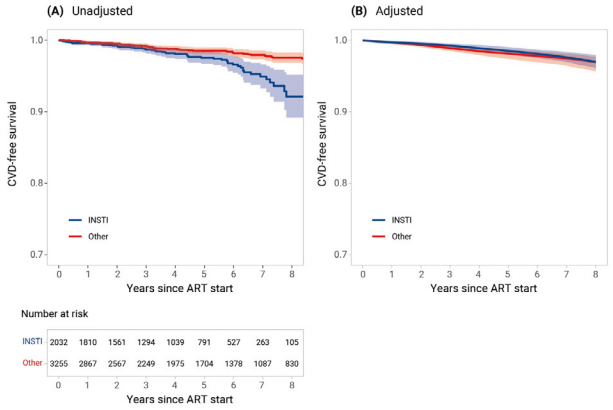
Background: Integrase strand transfer inhibitors (InSTI) have become essential components of antiretroviral therapy (ART). A recent study suggests that InSTI-based ART may lead to an increased risk for cardiovascular (CVD) events in the first two years compared to other ART combinations. However, analyzing treatment-naïve and treatment-experienced individuals together may have introduced bias. We estimated the impact of starting InSTI-based compared to other ART on cardiovascular events among treatment-naïve people with HIV (PWH) by emulating a target trial to minimize the risk of bias.

Methods: We included participants from the Swiss HIV Cohort Study who were treatment-naïve after May 2008, when the first InSTI became available in Switzerland. Baseline was defined as the date of the first treatment start (InSTI vs. other ART), and individuals were followed until the first CVD event (myocardial infarction, stroke, or intervention on arteries), loss to follow-up, death, or last cohort visit. Individuals who stopped the initial strategy (InSTI or other ART) were censored at that time. We estimated cardiovascular disease risk differences using pooled logistic regression with inverse probability of treatment and censoring weights, taking into account time-fixed and time-varying confounders (covariates listed in figure legend).

Results: Of 5287 treatment-naïve individuals, 2032 (38.4%) started InSTI-based ART, and 3255 (61.6%) started other ART combinations. Individuals who started InSTI were less likely to be women (16% vs. 26%), less likely to be of African origin (12% vs. 19%), and had a higher median CD4 nadir (346 vs. 281 cells/μL) compared to individuals starting other ART. Smoking status, history of cardiovascular disease, and use of antiplatelet agents were similar in both groups, but InSTI-starters were more likely to receive abacavir (26% vs. 11%). Within 25'567 person-years (PY), 113 CVD events occurred (incidence rate 4.42 per 1000 PY, 95% CI 3.68–5.31). Unadjusted incidence rates were 6.49 per 1000 PY (4.99–8.46) among InSTI starters and 3.39 per 1000 PY (2.62–4.39) among those who started other ART (**Panel A**). In adjusted analyses, risk differences between InSTI and other ART starters were -0.02% (-0.32% to 0.21%) after 1 year, -0.17% (-0.65% to 0.10%) after 2 years, and -0.38% (-1.29 to 0.52) after 5 years (**Panel B**).

Conclusion: In this target trial emulation, we found no evidence of a difference in CVD event risk with starting InSTI-based compared to other ART in treatment-naïve PWH.

Cardiovascular dosease events in people living with HIV starting ART



Cardiovascular disease events in people living with HIV starting ART
Panel A shows unadjusted Kaplan-Meier curves. **Panel B** shows survival curves adjusted for calendar year of ART start, sex, age, ethnicity, HIV transmission risk group, education level, nadir CD4, history of AIDS-defining disease, history of cardiovascular disease, family history of cardiovascular disease, hepatitis B and C virus coinfection, arterial hypertension, diabetes, renal function, and time-varying smoking status, use of abacavir, tenofovir alafenamide, antiplatelet and lipid-lowering drugs.
Shaded area = 95% confidence interval. **ART** = antiretroviral therapy, **CVD** = cardiovascular disease, **INSTI** = integrase inhibitors.

150 HIV-RELATED KAPOSI SARCOMA IN EAST AFRICA: CONTEMPORARY UPDATE ON STAGE AND SURVIVAL

Helen Byakwaga[1], Aggrey Semeere[2], Miriam Laker-Oketta[1], Megan Wenger[3], Elyne Rotich[4], Charles Kasozi[5], Winnie Muyindike[6], Philippa Kadama-Makanga[1], Sigrid Collier[7], Hilda Muwando[8], Toby Maurer[9], Esther Freeman[10], Samson Kiprono[11], Andrew Kambugu[8], Jeffrey Martin[3]
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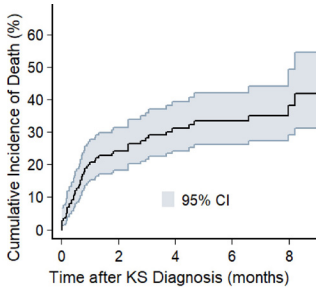
Background: Stage at time of diagnosis and survival after diagnosis are critical parameters regarding the control of any cancer in any geographical setting. Unlike in resource-rich settings where publicly funded cancer surveillance routinely monitors these parameters, these data are non-existent through routine means in resource-limited areas. This is particularly relevant for Kaposi sarcoma (KS) in East Africa, for which recent changes in HIV treatment and chemotherapy guidelines as well as the COVID-19 pandemic dictate an update regarding stage and survival.
Methods: From October 2021 to August 2022, we evaluated HIV-infected adults (age ≥ 18 years) with a new diagnosis of KS made in 4 different primary care facilities (or their associated inpatient units) in Kenya and Uganda using a process of rapid case ascertainment. KS diagnosis was confirmed by pathology. Participants were examined, at time of biopsy, to document the extent of lesions and subsequently monitored longitudinally for vital status.
Results: Among 180 HIV-infected adults identified with new onset KS, 31% were women, and the median (IQR) age was 35 (29-42) years. At time of KS diagnosis, 95% of the participants were taking ART, and the median (IQR) CD4+ T cell count was 197 (46-354) cells/mm^3; 46%, 20%, 11% and 23% had plasma HIV RNA of < 40, 40-1000, 1001-10,000 and >10,000 copies/ml, respectively. The median number of anatomic sites with KS lesions per participant was 7 (4-11); 26% of participants had oral KS lesions that interfered with either eating or speaking, 74% had KS-associated edema, and 86% had ACTG stage T1 (advanced KS). Over a median follow-up of 2.6 months (IQR: 0.75 to 5.5), 56 participants died, and only 3 lost to follow-up. Cumulative incidence of death (95% CI), via Kaplan-Meier estimation, at 2 months, 6 months and 8 months following KS diagnosis was 24% (18%-31%), 33% (26%-42%), and 38% (29-49%), respectively (Figure).
Conclusion: In a recently assembled community-based sample of adults with newly-diagnosed HIV-related KS in East Africa, the majority have advanced KS at the time of KS diagnosis, and survival is poor. The findings are stark in absolute terms for the "Treat-All" era and unchanged from parameters obtained in the 5 years prior, indicating no improvement in these aspects of the control of KS in the region. Along with primary prevention of KS (i.e., reducing its incidence), novel approaches are needed for earlier detection, more efficient linkage to oncologic care, and more potent therapy.

Survival Among Adults with HIV-Related Kaposi Sarcoma in East Africa



151 PHYLODYNAMICS OF HIV-1 VARIANT ACROSS POLAND AND UKRAINE

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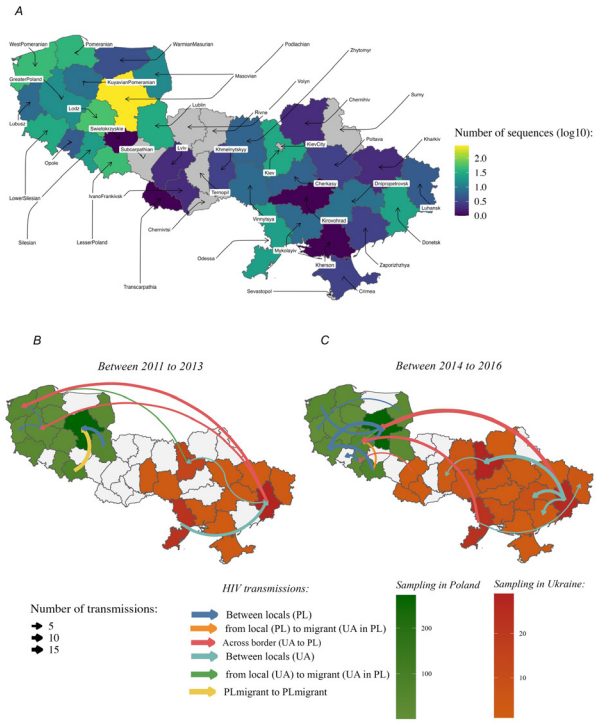
Background: In the countries of Eastern Europe (Russia, Belarus, Ukraine), where the HIV-1 epidemics are expanding, the A6 variant remains predominant. After the initiation of the war in Ukraine, Poland has become the principal refuge for Ukrainian citizens; however, migration from this country has been common over the last decade. Evolutionary analyses of viral sequences provide insights into migration events. The aim of this study was to explore the transmission dynamics of the HIV-1 A6 variant between Poland and Ukraine.
Methods: HIV A6 partial pol sequences from Poland (n=1185) and Ukraine (n=653) were combined with a background dataset of 7665 publicly available sequences from 37 other countries. We used maximum-likelihood phylogenetics and Bayesian inference to identify putative transmission clades. Clades were analyzed in an asymmetric discrete phylogeographic model to characterize HIV migration events (adjusted Bayes factor ≥3) between administrative regions of Poland and Ukraine.
Results: We identified 206 clades (n=1,362 sequences), of these, 63 were binational, containing both Polish and Ukrainian sequences. Migration events were almost exclusively unidirectional from Ukraine to Poland (99.4%). Multiple cross-border migrations were mainly from East and South Ukraine to Central and Western Poland. Donetsk and Odessa regions were the primary source (49.7% and 17.6%, respectively) of the variant dispersal. The most frequent destinations were in Masovian, the highest populated region where Warsaw, the largest city and also the capital of Poland, is located (67.3%); next in Lodz (18.2%); and West Pomerania (10.1%) states. Migration events started to increase in 2011 and remained stable until 2016, at the time of the initial war in the Donetsk region.
Conclusion: The most common HIV-1 A6 variant migration events to Poland were from Eastern Ukraine long time affected by the Russian-Ukrainian armed conflict. Geospatial A6 transmission networks are expanding in Poland, sustained by local viral dispersal and cross-border migration originating from Ukraine. More introductions are expected since the initiation of war in 2022, which may notably increase the burden of HIV in Central and Western European countries. There is an urgent need for expanded HIV diagnostics and antiretroviral treatment initiations among war-displaced populations to reduce the transmission networks.

Sampling density and phylodynamics of HIV A6 variant between Poland and Ukraine A. Sampling density of HIV-1 A6 variant. Regions with a lack of sequences were depicted in grey; Migration events between regions in Poland and Ukraine through time B. between 2011 and 2013; C. between 2014 and 2016. The thickness of the arrows corresponds to the average number of inferred migration events. Inward movements between a particular group and location are depicted in the same color. Regions are colored according to the number of sequences included in the clade. Phylogeographic inference was performed using the asymmetric discrete phylogeographic model implemented in the BEAST 1.10.5 software package



152 TIME TO KEY MILESTONES IN THE HIV INDEX TESTING/CONTACT TRACING PATHWAY IN INDIA

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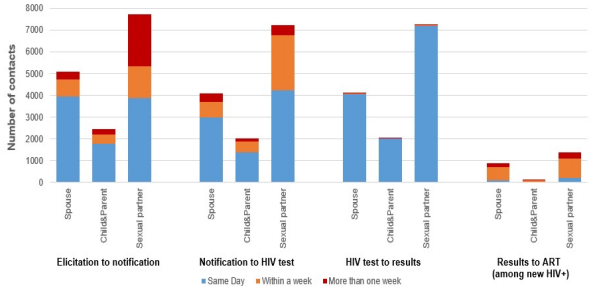
Background: Index testing, a WHO-endorsed form of contact tracing, is an evidence-based approach to enhance detection of people living with HIV (PLHIV). To optimize impact and efficiency, the process should rapidly identify contacts of newly diagnosed PLHIV and link them to immediate treatment. We estimate the time taken (in days) for each milestone along the index testing pathway from contact elicitation to linking HIV-positive contacts to treatment in one of the highest HIV burden states in India, Telangana.

Methods: As part of a PEPFAR-funded program, we implemented index testing in 50 testing and treatment facilities in five districts of Telangana. We analyzed program data from July 2020-January 2022. We calculated time (same day, within a week, > a week) between steps along the index testing continuum defined as the date when: 1) contact elicitation was started; 2) contact was notified; 3) contact was tested for HIV; 4) contact received results; and 5) HIV positive contact was linked to treatment. Associations between contact characteristics and time category were evaluated using chi-square tests.

Results: In total, 15,253 contacts were elicited and notified, 13,335 were tested and received results, 2,626 (20%) were diagnosed with HIV among whom 2,423 (92%) initiated on treatment. The median age of contacts was 32 years; 51% were non-spousal sexual partners, while 33% were spouses, and 16% biological children or parents. The time between each milestone varied significantly by age, gender, notification method, district and the type of contact ($p < 0.05$). Relative to spouses and children, sexual partners experienced delays at each of the first three steps, with the primary delay at the elicitation to notification step (31% took > a week vs. 7% of spousal contacts; Figure). Among sexual partners who took over a week for this initial step, the median delay was 41 days (interquartile range, 17-92) with 24% eventually testing HIV positive (compared to 15% positivity in spousal contacts who took > a week). Once HIV testing was complete, the experience of sexual partners was comparable to spousal contacts. Results were received the same day and most were linked to treatment within a week.

Conclusion: Overall, index testing was an efficient way to identify contacts and initiate newly diagnosed PLHIV on antiretroviral therapy. However, these data highlight challenges in identifying vulnerable sexual partners and the need for differentiated approaches to avoid delays and curtail ongoing HIV transmission.

Figure - Time Between Index Testing Milestones by Type of Contact Elicited



153 ASSISTED PARTNER SERVICES FOR PWID TO IDENTIFY PARTNERS LIVING WITH HIV & HCV

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Background: People who inject drugs (PWID) experience high risk of both HIV and hepatitis C (HCV) but face barriers to testing and engagement in care. Assisted partner services (APS) is effective at case finding for HIV but has been understudied among PWID. We determined whether APS could find, test for HIV and HCV, and link to care the sexual and injection partners of PWID living with HIV in Kenya.

Methods: We conducted a prospective study in 8 sites in Kenya. Index participants—people living with HIV (PLHIV) actively injecting drugs-- were interviewed and provided locator information about sexual and injection partners. Peer educators located partners and brought them to study sites, where partners completed questionnaires and rapid HIV testing. All participants also had rapid HCV antibody testing and all participants positive for HIV or HCV antibodies underwent a blood draw for viral load testing. Intimate partner violence (IPV) was monitored for all participants at moderate or high risk. Data were entered into REDCap and analyzed using Stata. Numbers needed to interview (NNTI) to find partners in need of care were calculated.

Results: 989 index participants mentioned 4705 partners and 4588 (97%) of mentioned partners were located, of whom 18.0% were living with HIV and 11.8% were HCV antibody-positive. Of the 597 living with HIV, 85.2% already knew their status, of whom 91.3% reported currently taking ART and 77% were virally suppressed. NNTIs are shown in Table 1. Of 393 partners positive for HCV antibodies, 53.7% were viremic, 26.5% already knew their antibody status, and 1% had previously been treated. Prevalence of both HIV and HCV differed by partner type. 6-month follow-up completion was 86%. Over 70% of index participants and partners who were not on antiretroviral therapy at enrollment were taking it at 6-month follow-up visits. No IPV or adverse events, including violence or death, occurred due to study procedures.

Conclusion: When used among PWID, APS for PLHIV is safe and effectively identifies partners living with both HIV and HCV. Although many partners were already aware of their HIV status, APS also increased engagement in care for both index participants and partners over a 6-month period.

Table 1. Numbers of index participants interviewed to find partners in different categories

	Index Number Needed to Interview (NNTI)
All Partners	
Any partner living with HIV (LHIV)	1.66
A partner LHIV unaware of status	11.24
A partner LHIV unaware of status, not on ART or not virally suppressed	4.14
Injecting Partners	
Any partner LHIV	2.57
A partner LHIV unaware of status, not on ART or not virally suppressed	6.18
Sexual Partners	
Any partner LHIV	8.17
A partner LHIV unaware of status, not on ART or not virally suppressed	19.8

154 HIV INCIDENCE DIFFERENCES MEASURED BY SERIAL CROSS-SECTIONAL TESTING: HPTN 071

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HPTN 071 (PopART study team)
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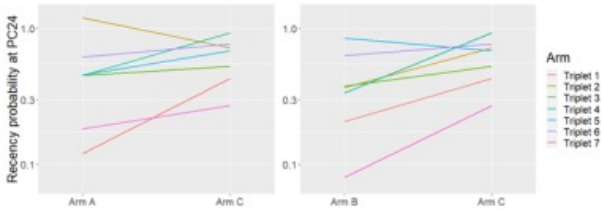
Background: HPTN 071 (PopART) was a community-randomized trial conducted in Zambia and South Africa (2013-2018); 21 communities were randomized into three arms in 7 triplets matched on baseline HIV prevalence and location (Arm A: combination prevention intervention with universal antiretroviral treatment [ART]; Arm B: combination prevention intervention with ART provided according to local guidelines; Arm C: standard of care). In the primary analysis, intervention effect was assessed using longitudinal observed HIV seroconversion. Arm B had 30% lower incidence than Arm C, in contrast, the intervention effect was similar in Arms A and C. In this report, we used cross-sectional incidence (CSI) testing to estimate HIV incidence in each community at baseline (PC0) and two-year visit (PC24).
Methods: CSI was estimated using the LAg assay and HIV viral load (mean duration of recent infection: 130 days; false recent rate: 0.2%). This method was shown to accurately estimate incidence in this cohort. The Sedia Incidence Calculator was used to determine incidence estimate. Intervention effect compared CSI at PC24 between arms, adjusted for community age and sex composition and PC0 CSI.
Results: At PC0, 37,128 individuals were surveyed; 7,998 were HIV+ and 187 were classified as recently infected. At PC24, 27,896 individuals were surveyed; 6,254 were HIV+ and 73 were classified as recently infected. CSI testing was performed for 99.5% of all HIV+ samples. HIV incidence at enrollment was highest in Arm A in 4 of 7 triplets. The unadjusted incidence estimates for Arms A, B and C were 1.95, 1.49 and 1.58 at PC0 and 1.03, 0.90 and 1.55 /100py at PC24, respectively. Based on CSI, the adjusted HIV incidence ratio for Arm A vs. C was 0.69 (95% CI: 0.44-1.07, p=0.095) and for Arm B vs. C was 0.54 (95% CI: 0.34-0.84, p=0.011).
Conclusion: In this large community-randomized trial, HIV incidence decreased over time in both study arms that included a combination prevention intervention. The decrease in incidence was similar in communities with universal ART (Arm A, 31% reduction) and ART provided according to local guidelines (Arm B, 46% reduction). The methods used for the intervention assessment using CSI align with those used for the primary study analysis and suggest that intervention was similarly effective in both intervention arms. Additionally, the apparent dissonance in the effects in Arms A and B (in the primary analysis) may have been due to a chance imbalance in HIV incidence at baseline.



155 INCIDENCE OF CANCER AMONG MEDICAID BENEFICIARIES WITH AND WITHOUT HIV: 2001-2015

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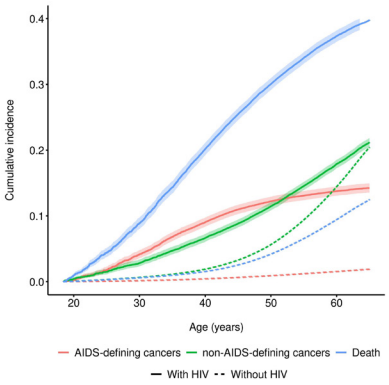
Background: Life expectancy among people living with HIV (PLH) is approaching the general population, and chronic conditions associated with aging—including cancer—are increasingly relevant. Among PLH, incidence of AIDS-defining cancers (ADCs) has decreased, and the cancer burden has shifted toward non-AIDS-defining cancers (NADCs). Medicaid provides insurance for 40% of PLH in the US and may offer a better comparator group for PLH than the general population. Thus, we compared the incidence of cancer among Medicaid beneficiaries with and without HIV.
Methods: We used data on Medicaid beneficiaries enrolled in 14 US states in 2001-2015. We included beneficiaries aged 18-64 years, who had >6 months of continual enrollment in Medicaid without dual enrollment in Medicare. We excluded beneficiaries with a history of cancer prior to baseline. We estimated cumulative incidence of first cancer by HIV status at baseline, with age as the time scale, accounting for death and incidence of other cancer types as competing risks. Cancer types examined included all ADCs (Kaposi's sarcoma, cervical, and non-Hodgkin's lymphoma) and NADCs that are high burden in the general population (breast, colon, head/neck, kidney, larynx, leukemia, liver, lung, oropharynx, pancreatic, prostate) and among PLH (anal, Hodgkin's lymphoma). We estimated cumulative incidence overall and stratified by sex, race/ethnicity, and calendar period.
Results: We included 43,925,817 beneficiaries in the analysis, of whom 181,030 had HIV. Across all ages, beneficiaries with HIV had a higher incidence of ADCs, as well as some NADCs (lung, leukemia, head and neck, liver, oropharynx, larynx, and anal cancer). Breast cancer incidence was similar until age 42, after which beneficiaries without HIV had a higher incidence. For colon, prostate, and pancreatic cancers, beneficiaries with HIV had higher incidence at younger ages; at older ages, incidence was similar or higher among beneficiaries without HIV.
Conclusion: We compared cancer incidence by HIV status within a geographically diverse sample of Medicaid beneficiaries. We examined incidence across much of the beneficiaries' adult lives, allowing us to see trends in how incidence of cancers (especially NADCs) varied by HIV status and age. Our findings may suggest an increased risk of certain NADCs (e.g., colon, head/neck, and leukemia) at younger ages among PLH, even when compared against other Medicaid beneficiaries, and highlight the importance of monitoring PLH for both ADCs and NADCs.

Incidence of AIDS-defining cancers, non-AIDS-defining cancers, and death by HIV status in all eligible Medicaid beneficiaries, 2001-2015



156 CAUSES OF DEATH AMONG ADULTS WITH HIV ON ART IN EUROPE AND NORTH AMERICA: 1996-2019

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Background: Mortality rates among persons with HIV (PWH) have fallen since widespread availability and use of effective antiretroviral therapy (ART) in 1996. Patterns of cause-specific mortality continue to change as the population of PWH ages.
Methods: We investigated longitudinal patterns in causes of death in Europe and North America among PWH aged ≥16 years old who started ART 1996-2019, using data from the Antiretroviral Therapy Cohort Collaboration. Cohorts gathered information on mortality through hospitals or physician reports, linkage with vital statistics agencies and active follow-up. Causes of death were coded using adaptation of the Coding of Death in HIV protocol. Causes were mostly classified by both a clinician and an algorithm using available ICD9/10 data on cause of death and otherwise two clinicians using clinical data with

all disagreements being resolved through panel discussion. We used Poisson models to compare cause-specific mortality rates over time-periods, adjusted for time-updated CD4, age and whether ART-naïve at the start of each follow-up period.

Results: Among 189,916 PWH, 16,897 died. Age at death increased from 42.2 years in 1996-99 to 56.2 years in 2016-19. Rates of all-cause mortality per 1000 person-years decreased from 16.9 (95% confidence interval [95%CI]: 15.4-18.4) during 1996-99, to 7.9 (7.6-8.2) during 2016-20. The adjusted all-cause mortality rate ratio [aMRR] per 4-year calendar period was 0.86 (95%CI 0.85-0.87), see table. Mortality rates declined with time for almost all causes of death. The decline over time was most pronounced for AIDS-related mortality (aMRR per 4 years 0.82; 95%CI 0.80-0.84). There were also reductions in cardiovascular, liver-related, non-AIDS infection, non-AIDS, non-hepatocellular carcinoma malignancy, and suicide/accident mortality (corresponding aMRRs per 4 years 0.83 (0.79-0.87), 0.90 (0.85-0.94), 0.93 (0.88-0.98), 0.95 (0.91-0.98), and 0.90 (0.84-0.96), respectively). There was little evidence of declines in central nervous system, respiratory, and substance use-related mortality.

Conclusion: Improvements in ART and HIV care have led to reductions in rates of all major causes of death, particularly AIDS-related deaths, among PWH taking ART. These results highlight the further potential for reducing mortality through hepatitis treatment, targeted cancer screening, and preventing late HIV diagnosis.

Adjusted cause-specific mortality rate ratios (MRRs) per 4-year period.

Cause of death	Deaths	MRR per 4 years
Overall	16897	0.86 (0.85, 0.87)
AIDS	4222	0.82 (0.80, 0.84)
Cardiovascular/heart (including stroke)	1406	0.83 (0.79, 0.87)
Central nervous system (including Parkinson's and Alzheimer's)	184	1.02 (0.90, 1.16)
Liver (including hepatocellular carcinoma)	1167	0.90 (0.85, 0.94)
Non-AIDS infection	1048	0.93 (0.88, 0.98)
Non-AIDS, non-hepatocellular carcinoma malignancy	2314	0.95 (0.91, 0.98)
Other	1481	0.84 (0.80, 0.88)
Respiratory	362	1.06 (0.96, 1.17)
Substance abuse	380	0.94 (0.86, 1.03)
Suicide/accident	651	0.90 (0.84, 0.96)
Unknown/unclassifiable	3682	0.83 (0.81, 0.85)

157 MOLECULAR HIV CLUSTERING OF INDIVIDUALS WITH MPOX/HIV COMORBIDITY

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Background: HIV cluster detection and response (CDR) is a key part of the federal Ending the HIV Epidemic initiative in the United States. HIV molecular clusters are thought to preferentially include individuals that are at highest risk of HIV transmission and the most stringent clusters are assumed to indicate recent and rapid transmission. The global monkeypox (MPOX) outbreak, starting in 2022, created an opportunity to test the utility of molecular HIV surveillance (MHS) to identify high risk transmission networks.

Methods: In New York State (NYS) outside New York City - (Rest of State - ROS) there were 282 individuals diagnosed with MPOX from June 2, 2022 through September 9, 2022. Individuals diagnosed with MPOX were matched to the NYS HIV and sexually transmitted infection (STI) registries. The data were analyzed to examine and compare demographic characteristics of those diagnosed with MPOX alone and those diagnosed with both HIV and MPOX. In addition, the HIV-MPOX co-morbid individuals were analyzed for HIV molecular cluster characteristics.

Results: The demographic characteristics of individuals diagnosed with MPOX, including HIV-MPOX co-morbid individuals, mirror national trends: most were male, with a history of male-to-male sexual contact (MSM) and were likely to have received a recent STI diagnosis (DX). Individuals diagnosed with both HIV and MPOX were more likely to be included in HIV molecular clusters compared to three comparison groups: persons living with diagnosed HIV (PLWDH) in ROS overall, MSM in ROS, and age-adjusted MSM (to match individuals with MPOX DX) in ROS. For the 3-year 0.5% clusters, which are used to define national priority clusters, the HIV-MPOX co-morbid individuals clustered 2.4 times more frequently than the age/risk-adjusted control group.

Conclusion: This study supports to the use of HIV molecular clustering to identify individuals for priority public health interventions, including MPOX vaccination and testing.

158 ISOLATING THE EFFECT OF COVID-19 RELATED DISRUPTION ON HIV DIAGNOSES IN THE US, 2020

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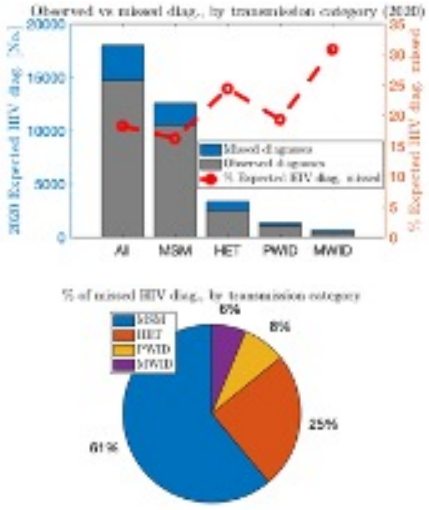
Background: Diagnoses of HIV in the US decreased by 17% in 2020 due to COVID-related disruptions. The extent to which this decrease is attributable to changes in HIV testing versus HIV transmission is unclear. We seek to better understand this issue by analyzing the discrepancy in expected versus observed HIV diagnoses in 2020 among persons who acquired HIV between 2010-2019, as changes in diagnosis patterns in this cohort cannot be attributed to changes in transmission.

Methods: We developed three methods based on the CD4-depletion model to estimate excess missed diagnoses in 2020 among PWH infected from 2010-2019. We stratified the results by transmission group, sex assigned at birth, race/ethnicity, and region to examine differences by group and confirm the reliability of our estimates. We performed similar analyses projecting new diagnoses in 2019 among PWH infected from 2010-2018 to evaluate the accuracy of our methods against surveillance data.

Results: There were approximately 3100-3300 fewer diagnoses than expected in 2020 among persons who acquired HIV from 2010-2019. Females (at birth), heterosexuals, persons who inject drugs, and Hispanic/Latino PWH missed diagnoses at higher levels than the overall population. By transmission category, MSM accounted for the highest percentage (61%) of missed diagnoses. Validation and stratification analyses confirmed the accuracy and reliability of our estimates.

Conclusion: PWH infected from 2010-2019 showed a significant drop in diagnosis rate during 2020, suggesting that changes in testing played a substantial role in the observed decrease in new HIV diagnoses. Levels of missed diagnoses differed substantially across population subgroups. These analyses may be used to inform future estimates of HIV transmission during the COVID-19 pandemic and prioritize populations with increased testing needs.



159 CABOTEGRAVIR PHARMACOLOGY IN THE BACKGROUND OF DELAYED INJECTIONS IN HPTN 084

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Background: HPTN 084, a Phase 3 randomized, placebo-controlled trial, demonstrated the superiority of long-acting injectable cabotegravir (CAB) compared to daily oral TDF/FTC for HIV prevention in individuals assigned female at birth. Injections were provided at 8-week intervals after the first two

injections were separated by 4 weeks. While there were protocol-specified visit windows for injections, some participants received injections outside of the visit schedule. Although CAB correlates of protection are unknown, we evaluated CAB concentrations in those with delayed injections during the blinded phase of HPTN 084 to assess the impact of less frequent dosing on CAB pharmacology.
Methods: Participants randomized to the CAB arm with at least one delayed injection were included in the analysis. Delayed injections were defined as type 1 (if the second injection occurred 8-14 weeks after the first injection; 4 weeks + 4-10) or type 2 (if a subsequent injection occurred 12-18 weeks after the preceding injection; 8 weeks + 4-10). CAB concentrations were measured at visits before and after an injection delay. Drug concentrations were evaluated relative to the 4x (0.664 mcg/mL) and 8x (1.33 mcg/mL) $PAIC_{90}$ (1.33 mcg/mL).
Results: One participant acquired HIV after a 16.1-week delay between injections 8 and 9; CAB concentrations were < 4x PA-IC_{90} at the first HIV positive visit. We identified 194 participants who had at least one delayed injection (n=224 occurrences): 19 type 1 and 205 type 2 delays. For type 1 delays, 100% and 91% of occurrences yielded CAB concentrations ≥ 4x PA-IC_{90} and ≥ 8x PA-IC_{90} when an injection was given 8-10 weeks (4 weeks + 4-6) after the first injection; 75% were < 4x PA-IC_{90} when the delay was 12-14 weeks (4 weeks + 8-10). For type 2 delays, when the time between injections was 12-14 weeks (8 weeks + 4-6; n=109 occurrences), 98% and 87% of CAB concentrations were ≥ 4x PA-IC_{90} and ≥ 8x PA-IC_{90}, respectively; this fell to 90% and 62% when injections were delayed 16-18 weeks (8 weeks + 8-10). Up to eight weeks post-administration of a type 2 injection delay, CAB concentrations were ≥ 4x PA-IC_{90} and ≥ 8x PA-IC_{90} in 100% and 94% of occurrences, respectively.
Conclusion: Pharmacologic analyses suggest there may be up to 6 weeks of forgiveness in persons assigned female at birth who received delayed CAB-LA injections. These data suggest that quarterly CAB-LA dosing in this population may be feasible and warrant further investigation.

160 THE LEVI SYNDROME: CHARACTERISTICS OF EARLY HIV INFECTION WITH CABOTEGRAVIR FOR PrEP

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Background: HPTN 083 and HPTN 084 demonstrated that long-acting injectable cabotegravir (CAB-LA) pre-exposure prophylaxis (PrEP) was superior to daily oral tenofovir disoproxil fumarate/emtricitabine (TDF/FTC) for HIV prevention. Twenty HIV infections were detected in the cabotegravir (CAB) arm during the blinded phase of the trials (5 baseline infections; 15 incident infections; 16 in HPTN 083 over 3,205 person-years; 4 in HPTN 084 over 1956 person-years). Characterization of these infections led to recognition of a novel syndrome that occurs in persons who acquire HIV infection in the setting of CAB-LA PrEP.
Methods: Virology assessments included use of an antigen/antibody test, a discriminatory test, RNA assays, an ultrasensitive HIV DNA test, and HIV genotyping with standard and low viral load testing. Liquid chromatography-tandem mass spectrometry was used to measure CAB concentrations.
Results: Infections that occurred within six months of CAB-LA exposure had clinical and laboratory features that were distinct from those usually seen in acute HIV infection and had minimal or no clinical symptoms. In most cases, viral replication was suppressed and antibody production was diminished/delayed for long periods. HIV DNA levels were undetectable or low in half of the cases where testing was performed. Seven infections occurred with no recent CAB exposure; these infections were detected using standard HIV testing algorithms. In contrast, detection of infection was delayed using standard HIV testing algorithms in 12 of 13 remaining cases. Major integrase strand transfer inhibitor (InSTI) resistance mutations were observed in seven cases. Delayed detection of infection in this setting led to inadvertent administration of CAB-LA to persons with undiagnosed infection in 11 cases.
Conclusion: Detailed characterization of HIV infections in the setting of CAB-LA PrEP defined a new syndrome which we term the long-acting early viral inhibition syndrome (LEVI). This syndrome was associated with diagnostic delays using standard local HIV testing algorithms, InSTI resistance risk, and CAB-LA administration after infection. The prolonged viral suppression observed with CAB-LA PrEP suggests that there may be limited seeding of the HIV reservoir in early infection. Future studies are needed to evaluate the potential for HIV cure in this setting.

161 CABOTEGRAVIR FOR HIV PrEP IN US BLACK MEN AND TRANSGENDER WOMEN WHO HAVE SEX WITH MEN

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Background: HIV infections are disproportionally higher among Black cisgender men and transgender women who have sex with men (MSM and TGW) compared with other racial/ethnic groups in the US. Long-acting injectable cabotegravir (CAB-LA) for HIV pre-exposure prophylaxis (PrEP) was shown to be safe and effective across populations globally. We evaluated HIV incidence and prevention efficacy of CAB-LA among US Black MSM and TGW who were enrolled in HPTN 083.
Methods: HPTN 083 is an ongoing randomized controlled trial comparing CAB-LA to daily oral tenofovir disoproxil fumarate/emtricitabine (TDF/FTC) for HIV prevention in MSM and TGW. Eligible participants were randomized 1:1 to CAB-LA or TDF/FTC and followed for 153 weeks for incident HIV infection; TDF/FTC adherence was assessed among a subset of TDF/FTC-arm participants via plasma and dried blood spots (DBS). This pre-specified subanalysis included participants at US sites who self-identified as Black/African American, or mixed race including Black.
Results: At US sites, 1698 MSM and TGW enrolled: 844 (49.7%) Black and 852 (50.2%) non-Black. The majority were MSM (92.6%), < 30 years old (61%), and non-Hispanic (82%). At study enrollment, Black and non-Black participants reported a similar number of sexual partners (mean: 3 vs 4), receptive anal sex acts in the past month (mean: 2 vs 3), and recreational drug use in the past 6 months (62.4% vs 72.6%); baseline prevalent syphilis was higher among Black participants (4.0% vs 1.9%). Among Black MSM and TGW, HIV incidence was 2.11% [95% Confidence Interval (CI): 1.18-3.48%] in the TDF/FTC arm and 0.58% (95% CI: 0.16-1.49%) in the CAB-LA arm [Hazard Ratio (HR): 0.28 (95% CI: 0.096-0.83)]. Among non-Black MSM and TGW, HIV incidence was 0.63% (95% CI: 0.21-1.48%) in the TDF/FTC arm compared with 0.00% (95% CI: 0.00-0.44%) in the CAB-LA arm [HR: 0.086 (95% CI: 0.004-2.060)]. In a subset of 151 participants, DBS-based metrics consistent with >4 doses/week of TDF/FTC were lower among Black (64.7%) than non-Black (81.2%) MSM and TGW. On-time CAB-LA injection was high (89.7%) and similar among Black and non-Black MSM and TGW.
Conclusion: In this US cohort of MSM and TGW, while HIV incidence was higher among Black participants in both study arms, the protective efficacy of CAB-LA vs. TDF/FTC was consistent. CAB-LA is a powerful HIV prevention tool to reduce HIV incidence among Black MSM and TGW, and implementation must focus on ensuring access and addressing disparities in HIV incidence among these populations.

162 CAB LA FOR HIV PREVENTION IN AFRICAN CISGENDER FEMALE ADOLESCENTS (HPTN 084-01)

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Background: While adolescents represent a key population in need of HIV prevention worldwide, daily oral TDF/FTC pre-exposure prophylaxis (PrEP) confers adherence challenges that limit effectiveness. This single arm, open-label Phase 2b safety study (HPTN 084-01) examined the safety, tolerability and acceptability of long-acting injectable cabotegravir (CAB-LA) among adolescent cisgender females in South Africa, Uganda and Zimbabwe.

Methods: Sexually active, HIV-uninfected females under 18 years of age, willing to use reliable long-acting contraception and weighing at least 35kg were eligible to participate. Parental/guardian consent was required for participation unless youth were considered emancipated minors. Step 1 involved a 5-week oral CAB 30mg QD lead-in, followed by 5 intramuscular gluteal injections of 3 mL (600 mg) of CAB-LA administered at weeks 5, 9, 17, 25 and 33 (Step 2). Participants then switched to daily oral TDF/FTC for 48 weeks of follow-up (Step 3) or opted to continue CAB-LA via open label extension (HPTN 084 OLE). We present safety data, injection tolerability, product acceptability, and adverse events (AEs) of special interest (Table 1).

Results: From November 2020-August 2021, 69 individuals were screened and 55 were enrolled (mean age=16, age range 12-17; 100% Black African). At baseline, most had a primary sexual partner in the past month (71%), 22% reported transactional sex, 31% had genitourinary chlamydia and 7% had gonorrhea. Fifty-two (95%) of participants completed Step 1 and 2; two participants discontinued during Step 1 for AEs unrelated to CAB and 1 participant who started Step 2 stopped CAB-LA after 3 injections due to incident pregnancy. There were no product-related serious AEs nor discontinuations from product due to AEs. No one acquired HIV on study. CAB-LA injections were well tolerated overall. Fourteen participants (26%) experienced 20 injection site reactions (ISR) – all Grade 1 or 2. For acceptability, 62% of participants reported via survey that they would consider using CAB-LA for HIV prevention in the future and 94% of participants went on to continue CAB-LA via HPTN 084 OLE.

Conclusion: CAB LA for HIV PrEP was found to be safe, tolerable and acceptable to sexually active adolescent females under the age of 18 in 3 African countries. Concurrent evaluation of CAB-LA for adolescents and adults has allowed for simultaneous licensure in several countries to date, expanding the HIV prevention options available to youth in circumstances of heightened risk.

Table 1. Adverse Events of Special Interest during Steps 1 and 2 (n=55 enrolled pts)

Adverse Events of Special Interest during Steps 1 and 2 (n=55 enrolled pts)	Frequency (# of pts reporting)	Severity – # of pts	Detail
Creatinine renal clearance decreased	41	Grade 2—39 Grade 3—2	All resolved without intervention
Blood glucose increased	22	Grade 1—21 Grade 2—1	All resolved without intervention
Blood creatinine increased	9	Grade 1—1 Grade 2—6 Grade 3—2	All resolved without intervention
Neuropsychiatric events	3	Grade 1 – 1 Grade 2—1 Grade 4—1	Depressive symptoms. Resolved Anxiety (stress). Resolved with counselling Suicidal ideation/behavior (suicide attempt). Resolved with counselling
Rhabdomyolysis	1	Grade 2	Myalgia resolved without intervention

*There were no events of weight gain, hepatoxicity, hypersensitivity, rash, seizures or pancreatitis

163 8+ YEARS POOLED ANALYSIS: ADHERENCE AND HIV INCIDENCE IN 6000 WOMEN ON F/TDF FOR PrEP

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Background: Daily emtricitabine/tenofovir disoproxil fumarate (F/TDF) for HIV pre-exposure prophylaxis (PrEP) substantially reduces HIV acquisition. This multinational pooled analysis summarizes data from >6000 women followed since F/TDF for PrEP approval in 2012 to better understand adherence and HIV prevention.

Methods: We obtained demographic, adherence, and HIV-1 status for cisgender women on F/TDF for PrEP at baseline and follow-up visits of 11 demonstration projects in 6 countries from 11/2012 to 12/2020. We evaluated adherence using long- or short-term measures of tenofovir-diphosphate (TFV-DP) in dried blood spots or TFV in plasma, respectively, and by electronic pill cap-monitoring, pill-counts, self-report, and/or study-reported adherence scale. We used group-based trajectory modelling to identify adherence trajectories over 96 weeks and assigned women into 4 latent adherence groups (Table). We used multinomial logistic regression adjusted for study clustering to estimate odds ratios (OR) of adherence, and Poisson regression to calculate HIV incidence rates (IR) per 100 person-years (PY).

Results: Among 6296 women, median age at PrEP initiation was 23 y (IQR 20—29, range 10—69) with mean 0.7 y (range 0.01—1.89) of follow-up. 78% were from Africa and 21% from Asia. 32 women acquired HIV, with overall IR of 0.72/100 PY (95% CI 0.51—1.01). Age was inversely associated with HIV incidence. Numerically higher HIV IR occurred in women who were married or had no children. Marital/parity status and HIV incidence associations were attenuated after adjusting for age, but for married or nulliparous women remained higher than for unmarried women or those with children.

Of 2954 women with adherence data, 17% were highly adherent, 22% consistently moderate, 39% moderate and declining, and 21% consistently low adherence. Women >25 y were more likely to remain highly adherent than those <18 (OR=2.28, 95% CI 1.35—3.85). No new HIV infections were observed in women with high, steady adherence. HIV IRs (95% CI) were 0.13 (0.02—0.92), 0.49 (0.22—1.1), and 1.27 (0.53—3.04) with consistently moderate, moderate and declining, and consistently low adherence, respectively.

Conclusion: This diverse multinational pooled analysis of F/TDF for PrEP is the largest assessment of real-world adherence to PrEP and HIV incidence in cisgender women and supports the high effectiveness of F/TDF for PrEP in women with consistent adherence. Efforts to support real-world adherence are critical to maximizing PrEP efficacy in women.

Incidence Rates (95% Confidence Intervals) of New HIV-1 Diagnosis for Women Used F/TDF for PrEP*

Table. Incidence Rates (95% Confidence Intervals) of HIV-1 Diagnosis for Women Used F/TDF for PrEP*

	Number of Participants	Total Person Years	HIV-1 Diagnosis	Incidence rate (95% CI) per 100 person-years
All	6296	4466.11	32	0.717 (0.507, 1.013)
Adherence Trajectory † (N = 2954)				
High and Steady	498 (7.9%)	556.71	0	0
Moderate and Steady	658 (10.5%)	770.72	1	0.130 (0.018, 0.921)
Moderate but Declining	1166 (18.5%)	1235.02	6	0.486 (0.218, 1.081)
Consistently Low	632 (10.0%)	395.37	5	1.265 (0.526, 3.038)
Age at Enrollment (N = 6296)				
<18	319 (5.1%)	117.7	2	1.699 (0.425, 6.794)
18-24	3515 (55.8%)	1842.41	24	1.303 (0.873, 1.943)
25+	2462 (39.1%)	2506	6	0.239 (0.108, 0.533)
Baseline Marital Status (N = 5941)				
Married	3256 (51.7%)	1739.15	20	1.150 (0.742, 1.782)
Single	1791 (28.4%)	1522.87	10	0.657 (0.353, 1.220)
Separated/Divorced/Widowed	894 (14.2%)	1009.9	1	0.099 (0.014, 0.703)
Baseline Parity (N = 4591)				
Nulliparous	1816 (28.8%)	834.95	14	1.677 (0.993, 2.831)
1 Child	1506 (23.9%)	985.63	7	0.710 (0.339, 1.490)
2+ Children	1269 (20.2%)	1288.23	7	0.543 (0.259, 1.140)

*Includes women in Botswana, Kenya, India, South Africa, Uganda, USA.
†Weekly adherence measures were categorized into 4 levels: High (≥1250 fmol/punch in dried blood spot (DBS), or 7+ tablets per week in electronic pill cap-monitoring [EM], pill counts [PC], or self-report [SR], or study summarized adherence evaluation [SS] as excellent), Moderate (700-<1250 fmol/punch in DBS, or ≥40 ng/ml in plasma or 4-7 tablets per week in EM, PC or SR, or SS as very good or good), Moderate but Declining (350-<700 fmol/punch in DBS or 2-3 tablets per week in EM, PC or SR, or SS as Fair), and Low (<350 fmol/punch in DBS or <40 ng/ml in plasma or 0-1 tablet per week in EM, PC or SR, or SS as no/poor/very poor). Average ordinal adherence level for women with adherence data was 2.8, equivalent to moderate adherence, 4-7 tablets per week in DBS, or very good/good in other adherence measures. Group-based trajectory modelling was performed to identify trajectories of PrEP adherence over 96 weeks and assigned women to the 4 latent adherence groups.

164 SAFETY AND PK/PD OF A TENOFOVIR ALAFENAMIDE/ELVITEGRAVIR INSERT ADMINISTERED RECTALLY

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Background: On-demand topical products for rectal use are desired by the community and could be an important tool for HIV prevention. A tenofovir alafenamide/elvitegravir (TAF/EVG) fast-dissolve insert has demonstrated protective efficacy in a NHP SHIV rectal challenge model. We evaluated the safety and pharmacokinetics (PK) of the TAF/EVG insert administered rectally at two dose levels.

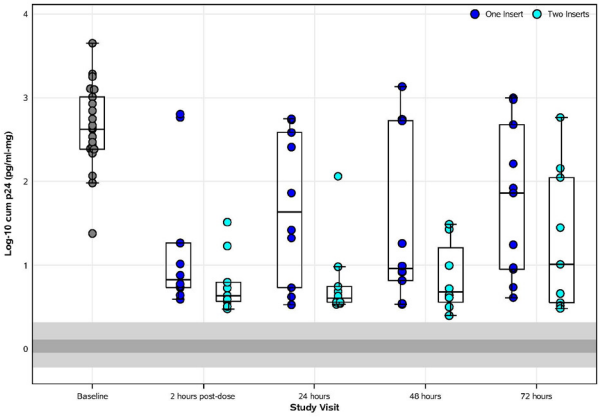
Methods: MTN-039 was a Phase 1, two-site, open-label, single arm, two-period study of rectal administration of one TAF/EVG insert (20/16 mg), followed by ≥7 day washout, then two TAF/EVG inserts. Inserts were administered in the clinic; blood, rectal fluid (RF), and rectal tissue (RT) were collected over 72 hours

following administration (participants randomized to RT collection at 2h/48h or 24h/72h). EVG, TAF, and tenofovir (TFV) levels were measured in plasma, RF and RT homogenates; and TFV-DP in RT mononuclear cells. *Ex vivo* HIV infectivity of RT explants was done pre- and post-dosing as a pharmacodynamic (PD) measure.

Results: Twenty-one participants without HIV (71% male) were enrolled and received study product (n=21 for 1 insert; n=19 for 2 inserts). TAF/EVG inserts were safe; 9 participants reported 17 adverse events (AEs); one mild AE (anal erythema) was related. Median peak plasma EVG, TAF and TFV concentrations (conc) for 1/2 inserts were 1.73/2.39, 29.5/41.9, and 2.64/4.42 ng/mL, respectively. EVG and TFV were detected in RF in all samples at 2h; median values for 1/2 inserts at 24h were EVG 2234/2597 ng/mL and TFV 2909/8277 ng/mL. EVG and TFV were detected in nearly all RT homogenates at 2h post-dose; EVG conc declined and were BLQ in 50%/30% for 1/2 inserts at 24 hours whereas TFV was measurable in the majority of samples for 72h. Median RT cell TFV-DP conc exceeded target levels for 72h. Compared to baseline, median cumulative $\log_{10}$ HIV p24 antigen was significantly reduced at all timepoints for both 1 and 2 inserts ($p< 0.032$ and $p< 0.02$, respectively), with median $\log_{10}$ declines with 2 inserts of -2.0, -1.8, -1.9, -1.7 at 2, 24, 48, and 72 h, respectively (Figure).

Conclusion: Rectal administration of 1 or 2 TAF/EVG inserts was safe and achieved high RF and RT levels of EVG and TFV with low systemic drug exposure. RT cell TFV-DP concentrations were higher than observed at steady-state with oral TDF dosing, with demonstrable inhibition of HIV infection for up to 72h. These results indicate that the TAF/EVG insert has great potential as an on-demand rectal microbicide for HIV prevention.

Explant Challenge in Rectal Biopsy Supernatant: Median and inter-quartile range (boxplots) of the median $\log_{10}$ cumulative, weight-adjusted p24 levels from up to four rectal tissue explant supernatants per participant-timepoint.. The gray horizontal bars represent the inter-quartile range (dark gray) and overall range (light gray) of the weight-adjusted LLOQ of cumulative p24 concentrations.



165 ULTRA LONG-ACTING REFILLABLE ISLATRAVIR IMPLANT FULLY PROTECTS NHP AGAINST SHIV

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Background: When taken as prescribed, antiretroviral (ARV) drugs are effective as pre-exposure prophylaxis (PrEP) against human immunodeficiency virus (HIV) transmission. However, consistent adherence to daily dosing regimen is challenged by issues such as pill fatigue, forgetfulness, stigma or lifestyle discordance. To this end, long-acting approaches with infrequent dosing intervals aim at improving therapeutic adherence and uptake. Among these, however, long-acting injectables suffer drawbacks of burst release, site-specific adverse reactions, and risky year-long sub-therapeutic tails. Moreover, injectables cannot be removed in the event of medical complications. Subdermal long-acting polymeric implants are also under investigations for HIV PrEP. However, such systems are commonly limited by decaying release profiles and require repeated surgical procedures for implantation and replacement upon drug exhaustion. To overcome these limitations, we developed a transcutaneously refillable ultra-long-acting islatravir delivery implant for HIV PrEP, based on a nanofluidic silicon membrane technology.

Methods: We developed nanofabricated, biocompatible, silicon nanochannel membrane implants with channels in size of 280 nm. The implants achieved constant and sustained islatravir release via electrostatic confinement on molecules diffusing along the nanochannel path. The implant allowed for the transcutaneous loading and refilling of islatravir. A 20-month PK study was performed *in vivo* in rhesus macaques with implant subcutaneously inserted in the animal's dorsum. Preventive efficacy was evaluated against rectal and vaginal infection using repeated SHIV challenges model in male and female rhesus macaques, respectively. Finally, implant toxicity and tolerability were assessed.

Results: Implants achieved constant islatravir plasma (median 3.14 nM) and islatravir-triphosphate (ISL-TP) (median 0.16 pmol/10^6 cells) levels for over 20 months uninterrupted, above the established PrEP protection benchmarks. In the PrEP efficacy studies with repeated low-dose SHIVSF162P3 challenges, the implants conferred 100% protection against rectal and vaginal infection. The implants were well tolerated with mild local tissue inflammation and no signs of systemic toxicity.

Conclusion: Our nanofluidic islatravir implant is a promising technology for HIV prevention, which may improve PrEP uptake, adherence and implementation.

166 ENSITRELVIR FOR MILD-TO-MODERATE COVID-19: PHASE 3 PART OF PHASE 2/3 STUDY

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Background: Ensitrelvir is a SARS-CoV-2 3CL protease inhibitor approved in Japan under emergency regulatory approval system as an oral treatment for COVID-19. Here we report the key analysis results of 125 mg group of phase3 part (SCORPIO-SR).

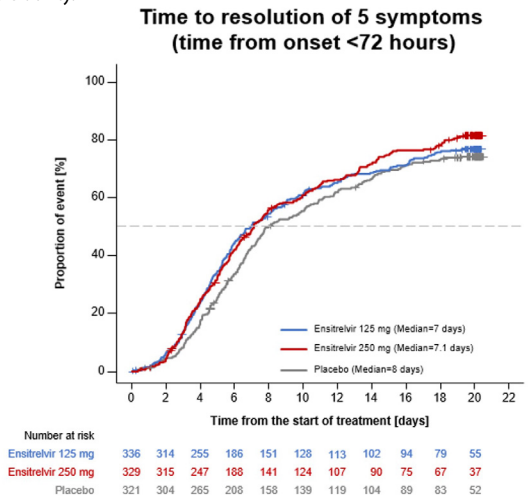
Methods: This study was a multicenter, randomized, double-blind, placebo-controlled study. Regardless of SARS-CoV-2 vaccination status and presence of risk factors for severe disease, patients with mild-to-moderate COVID-19 within 120 hours from onset were randomized to oral administration of ensitrelvir 125 mg (375 mg loading dose on Day1), ensitrelvir 250 mg (750 mg loading dose on Day1), and placebo once daily, for 5 days. The primary endpoint was time to resolution of 5 symptoms of COVID-19 (stuffy or runny nose, sore throat, cough, feeling hot or feverish, and low energy or tiredness), and the key secondary endpoints include change from baseline on Day4 in the amount of SARS-CoV-2 viral RNA and time to first negative of viral titer. The primary population for the primary and key secondary endpoints was patients with <72 hours from onset to randomization.

Results: Median time to resolution of 5 symptoms was significantly shorter in 125 mg group (n=336, 167.9 hours) than placebo group (n=321, 192.2 hours) ($p=0.0407$). Mean change of viral RNA levels from baseline ($\log_{10}$ copies/mL) on Day4 was significantly greater in 125 mg group (-2.48) than in placebo group (-1.01) ($p< 0.0001$). The time to first negative of viral titer was significantly shorter in 125 mg group (n=199, 36.2 hours) compared to placebo group (n=211, 65.3 hours) ($p< 0.0001$). Mean changes from baseline in viral titers [$\log_{10}$(TCID$_{50}$)/mL] were significantly greater in 125mg group on Day2 (-0.807, n=196) and Day4 (-1.108, n=197) than in the placebo group (-0.395, n=208 and -0.850, n=207, respectively) ($p< 0.0001$).

	Ensitrelvir 125mg	Ensitrelvir 250mg	Placebo
N	336	329	321
Median Time (hours) to Resolution of 5 COVID-19 Symptoms	167.9	171.2	192.2
Difference vs placebo	-24.3	-21.0	-
p-value	0.0407	0.0203	-

In the patients randomized within 120 hours of onset, median time to resolution of 5 symptoms was 189.7 hours in 125 mg group (n=582) and 200.3 hours in placebo group (n=572) ($p=0.4352$). No deaths or serious adverse drug reactions were reported in either group, and the incidence of serious adverse events between the two groups was comparable.

Conclusion: Ensitrelvir demonstrated a significant reduction in the time to resolution of 5 typical symptoms of COVID-19, robust antiviral effects and good tolerability.



167 EFFECT OF EARLY TREATMENT WITH PEGYLATED INTERFERON LAMBDA FOR COVID-19

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*Presented at CROI by a nonauthor colleague

Background: We assessed the efficacy of a single dose of peginterferon lambda in preventing clinical events among acutely symptomatic COVID-19 outpatients.
Methods: We conducted a placebo-controlled, randomized, adaptive platform trial among predominantly vaccinated SARS-CoV-2-positive adults in Brazil and Canada receiving either one subcutaneous injection of peginterferon lambda or placebo. The primary composite endpoint was medical admission to hospital, defined as either observation in a COVID-19 emergency setting for > 6 hours, or transfer to a tertiary hospital due to symptomatic COVID-19 within 28 days post-randomization.
Results: For this evaluation, 931 patients received peginterferon lambda and 1018 received placebo. 84% of the population were vaccinated and the trial occurred across multiple COVID-19 variants. In the primary analysis of patients, the primary outcome was reduced by 51% in the peginterferon lambda vs. placebo groups (relative risk 0.49 [25/916 vs 57/1003], 95% Bayesian credible interval 0.30-0.76, posterior probability >99.9%). This effect was maintained in subgroup analyses including COVID-19-related hospitalization alone (relative risk 0.57, 95% Bayesian credible intervals 0.33-0.95,) and COVID-19-related hospitalization or death (Hazard ratio 0.59, 95% Bayesian credible interval 0.35-0.97). The effects were consistent across dominant variants and vaccination status. Among individuals with a high viral level at baseline, peginterferon lambda resulted in lower viral loads by Day 7, compared to placebo. The incidence of adverse events was similar in the two groups.
Conclusion: Among predominantly vaccinated outpatients with COVID-19, single-dose of peginterferon lambda resulted in significantly decreased clinical events.

168 CHARACTERIZATION OF SINGLE VERSUS DUAL ACTIVE mAB AGAINST SARS-CoV-2

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Background: Amubarvimab and romlusevimab are anti-SARS-CoV-2 monoclonal antibodies (mAbs) that significantly reduced the risk of hospitalizations or death in the ACTIV-2/A5401 trial. SARS-CoV-2 variants (e.g., Delta, Epsilon, Lambda) harbor mutations against romlusevimab. We evaluated viral kinetics and resistance emergence in individuals treated with mono versus dual-active mAbs.
Methods: The study population included 789 non-hospitalized participants at high risk of progression to severe COVID-19 enrolled in the ACTIV-2/A5401 platform trial (NCT04518410) and received either placebo (n=400) or amubarvimab plus romlusevimab (n=389). Anterior nasal (AN) swabs were collected for SARS-CoV-2 RNA testing on days 0-14, and 28. Spike (S) gene next-generation sequencing were performed on samples collected at study entry and the last sample with viral load ≥2 $\log_{10}$ SARS-CoV-2 RNA copies per ml. We compared viral load kinetics and resistance emergence with single versus dual-active mAbs by categorizing participants as harboring variants sensitive to amubarvimab alone (Delta, Epsilon, Lambda, Mu) versus those sensitive to both mAbs (Alpha, Beta, Gamma, Others).
Results: Study participants receiving single and dual-active mAbs had similar demographics, baseline AN viral load, baseline symptom score and duration since symptom onset. The most common SARS-CoV-2 variant in the study population was Delta (26%) followed by Gamma (19%), Alpha (12%), and Epsilon (10%). In those with successful sequencing, 37% (N=111) were infected with a variant sensitive to amubarvimab alone and 63% (N=188) were infected with a variant sensitive to both mAbs. Compared to treatment with a single-active mAb, treatment with dual-active mAbs led to faster viral load decline at study day 3 (p=0.0001) and day 7 (p=0.003). Treatment-emergent resistance mutations were significantly more likely to be detected after amubarvimab plus romlusevimab treatment than placebo (2.6% vs 0%, P=0.0008). mAb resistance was also more frequently detected in the setting of single-active mAb treatment compared to dual-active mAb treatment (7.2% vs 1.1%, p=0.007). Participants with emerging mAb resistance had significantly higher pre-treatment SARS-CoV-2 nasal viral RNA levels.
Conclusion: Compared to single-active mAb therapy, dual-active mAb therapy led to significantly faster viral load decline and lower risk of emerging mAb resistance. Combination mAb therapy should be prioritized for the next generation of mAb therapeutics.

169 SAFETY AND EFFICACY OF INHALED INTERFERON-β1A (SNG001) IN OUTPATIENTS WITH COVID-19

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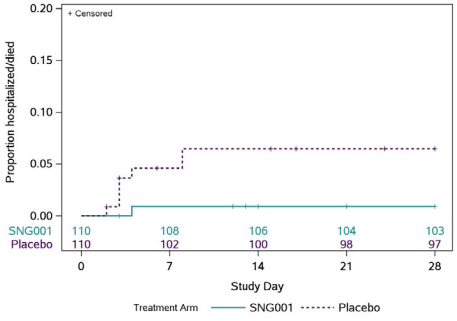
Background: SARS-CoV-2 variants resistant to monoclonal antibodies, and drug-drug interactions and potential mutagenicity of direct acting antivirals, heightens the need for additional therapeutics to prevent progression to severe COVID-19. Exogenous interferon beta is a promising therapeutic option against SARS-CoV-2 given its broad-spectrum antiviral activity and data suggesting impaired endogenous IFN production in individuals with severe disease.

Methods: The safety and efficacy of orally inhaled nebulized interferon-β1a (SNG001) was evaluated in a Phase II randomized controlled trial on the ACTIV-2/A5401 platform (NCT04518410). Adult outpatients with confirmed SARS-CoV-2 infection within 10 days of symptom onset were randomized to SNG001 once daily for 14 days or blinded pooled placebo. Primary outcomes included treatment-emergent Grade ≥3 adverse event (TEAE) through day 28; time to symptom improvement of 13 targeted COVID-19 symptoms collected by daily study diary through day 28; and SARS-CoV-2 RNA < lower limit of quantification (LLoQ) from nasopharyngeal (NP) swabs at days 3, 7, and 14. All-cause hospitalization or death through day 28 was a key secondary outcome.
Results: Of 221 participants enrolled at 25 US sites between February and August 2021, 220 (110 SNG001, 110 placebo) initiated study intervention, with a median age of 40 years, 55% female, and 20% SARS-CoV-2 vaccinated. There was no significant difference between SNG001 and placebo in Grade ≥3 TEAEs (4% vs 8%, Fisher's exact test p=0.25). Median time to symptom improvement was 13 days for SNG001 and 9 days for placebo (Gehan-Wilcoxon test p=0.17). There was no difference in the proportion of participants with SARS-CoV-2 RNA < LLoQ at day 3, 7 or 14 (SNG001 vs placebo, Day 3: 28% vs. 39%; Day 7: 65% vs. 66%; Day 10: 91% vs. 91%; joint Wald test p=0.41). There were fewer hospitalizations with SNG001 (n=1; 1%) compared with placebo (n=7; 6%), but this difference was not statistically significant (Fisher's exact test p=0.07; Figure). All hospitalizations were due to COVID-19 and occurred among unvaccinated participants without protocol-defined high-risk factors.
Conclusion: Inhaled nebulized SNG001 was safe and well tolerated but did not reduce SARS-CoV-2 RNA levels in the nasopharynx nor decrease time to improvement of COVID-19 symptoms in outpatients with mild-to-moderate COVID-19. The non-statistically significant decrease in hospitalizations among SNG001 participants warrants further investigation in a phase 3 clinical trial.

Cumulative incidence of hospitalization or death comparing SNG001 vs. placebo



Cumulative incidence of hospitalization or death is estimated by Kaplan-Meier method. Hospitalization is defined as ≥24 hours of acute care, in a hospital or similar acute care facility, including Emergency Rooms or temporary facilities instituted to address medical needs of those with severe COVID-19 during the COVID-19 pandemic, through day 28. There were no deaths through day 28. Numbers above the x-axis indicates the number of participants still in follow-up who have not been hospitalized or died.

170 METFORMIN REDUCED SARS-CoV-2 VIRAL LOAD IN A PHASE 3 RANDOMIZED CLINICAL TRIAL

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Background: Metformin has *in vitro* activity against SARS-CoV-2. In a published phase 3, quadruple-blinded, placebo-controlled randomized trial of outpatient COVID-19 therapy, metformin resulted in a 42% reduction in ER visits/hospitalizations/deaths by day 14, 58% reduction in hospitalizations/death by day 28, and 42% reduction in Long Covid through 10 months. This analysis presents the results of viral load sampling performed during that clinical trial.
Methods: Covid-Out trial (NCT04510194) enrolled adults aged 30 to 85 within 3 days of a documented SARS-CoV-2 infection and < 7 days after symptom onset. The trial randomized 1323 participants to metformin (1000mg/day days 2-5; 1500mg/day days 6 to 14), ivermectin, fluvoxamine, and/or exact-matching placebo in a 2x3 factorial trial design. Nasal swabs for viral load were an optional component, self-collected from the anterior nares on day 1, 5, and 10. Viral loads were measured via RT-qPCR using N1 and N2 targets in the SARS-CoV-2 nucleocapsid protein, with relative Ct values converted to absolute copy number via calibration to droplet digital PCR. A linear Tobit regression model was used to assess change over time while accounting for left censoring due to the viral load limit of detection. Results were adjusted for other treatment allocations within the factorial design, vaccination status, and baseline viral load. Repeated measures were accounted for using clustered standard errors within participants.
Results: Samples were available from n = 945, 871, and 775 participants on days 1, 5, and 10, respectively. The mean change from baseline to follow-up was -0.64 $\log_{10}$ copies/mL (95%CI, -1.16 to -0.13) for metformin versus placebo, which equates to a 4.4-fold greater decrease. The mean change in SARS-CoV-2 from baseline to day 5 was -0.48 $\log_{10}$ copies/mL, and was -0.81 $\log_{10}$ copies/mL from baseline to day 10. The anti-viral effect increased with increased metformin dosing days 6-14. The antiviral effect was larger in those unvaccinated (mean -0.95 log copies/mL) than vaccinated (mean -0.39 log copies/mL). There was no change in viral load vs. placebo for ivermectin or fluvoxamine.
Conclusion: Metformin lowered SARS-CoV-2 viral load in this quadruple-blinded, randomized clinical trial. The temporal relationship to dose titration suggests a dose-dependent effect. The magnitude of antiviral effect was similar to nirmatrelvir at day 5, greater than nirmatrelvir at day 10. Metformin is safe, widely available, and has few contraindications.

171 SYMPTOM AND VIRAL REBOUND IN UNTREATED COVID-19 INFECTION

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Background: Rebound of SARS-CoV-2 RNA and symptoms has been reported in people treated with nirmatrelvir/ritonavir. Since the natural course of viral and symptom trajectories during COVID-19 have not been well described, we evaluated the incidence of viral rebound and symptom relapse in untreated individuals with mild-to-moderate COVID-19.
Methods: This analysis included 563 participants randomized to placebo in the ACTIV-2/A5401 platform trial. Participants recorded the severity (scored as 0-3) of each of 13 targeted symptoms daily from days 0-28, with symptom score being the summed score (0-39). Symptom rebound was defined as ≥4 point increase in symptom score between the maximum and the preceding minimum score. Anterior nasal (AN) swabs were collected for SARS-CoV-2 RNA testing on days 0-14 and 28. Viral rebound was defined as a ≥0.5 $\log_{10}$ RNA copies/mL increase from the immediately preceding time point to a level ≥3.0 $\log_{10}$ RNA copies/mL, with high-level rebound defined as an increase of ≥0.5 $\log_{10}$ copies/mL to a level ≥5.0 $\log_{10}$ RNA copies/mL. To mirror the timing of a 5-day nirmatrelvir/ritonavir course, a supportive analysis was conducted where participants were only classified as rebounders if their rebounds occurred on or after day 5.
Results: Symptom rebound was identified in 26% of participants at a median [Q1, Q3] of 6 [4, 9] days after study entry and 11 [9, 14] days after initial symptom onset. Individuals with symptom rebound were more likely to be female, at high risk for progression to severe disease, have shorter time since symptom onset at study entry, and have higher symptom score and higher AN viral levels day 0. Viral rebound was detected in 32%, with high-level rebound in 13% of participants. Participants with viral rebound were older, more likely to be at low risk for progression to severe disease and had higher median AN viral level at day 0. Most symptom and viral rebound were transient with 89% of symptom rebound and 95% of viral rebound events occurring for only a single day before improving. The combination of symptom and high-level viral rebound was observed in 3% of participants. In the supportive analysis of rebound occurring ≥5 days after study entry, 22% and 20% of participants met symptom and viral rebound criteria, respectively, but only 1.2% of participants met criteria for both symptom and high-level viral rebound.
Conclusion: Symptom or viral rebound in the absence of antiviral treatment is common, but the combination of symptom and viral rebound is rare.

172 COVID-19 HOSPITALIZATION RISK AFTER SARS-CoV-2 VACCINATION AND OUTPATIENT TREATMENT

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Background: Given effectiveness of SARS-CoV-2 vaccines and outpatient antiviral and monoclonal antibody therapy for reducing progression to severe COVID-19, we sought to estimate the impact of these interventions on risk of hospitalization following SARS-CoV-2 infection in a large US healthcare system.
Methods: All patients ≥18 of age in the UNC Health system, with first positive SARS-CoV-2 RT-PCR test or U07.1 ICD-10-CM (diagnosis date) during 07/01/2021-05/31/2022, were included. The outcome was first hospitalization with U07.1 ICD-10-CM primary diagnosis ≤14 days after SARS-CoV-2 diagnosis date. SARS-CoV-2 vaccinations were included if received ≥14 days prior to diagnosis. Outpatient therapies were included if administered after diagnosis date and before hospital admission. Age, gender, race, ethnicity, and comorbidities associated with COVID-19 (using ICD-10-CM, if documented ≥14 days prior to diagnosis date) were also evaluated. Risk ratios for hospitalization were estimated using generalized linear models, and predictors identified using extreme gradient boosting using feature influence with Shapley additive explanations algorithm.
Results: The study population included 54,886 patients, 41% men and 27% ≥60 years of age. One-third of SARS-CoV-2 diagnoses occurred July-December 2021 and 67% December-May 2022 (predominantly Delta and Omicron variants, respectively). Overall 7.0% of patients were hospitalized for COVID-19, with median hospitalization stay of 5 days (IQR: 3-9). 32% and 12% of patients received ≥1 SARS-CoV-2 vaccine dose and outpatient therapy, respectively. Unadjusted and age-adjusted hospitalization risk decreased with vaccination and outpatient therapy (TABLE). Comparing patients who received 3 vaccine doses versus none we observed a 66% relative reduction in risk, with stronger association for more recent vaccination. For patients who received nirmatrelvir/ritonavir versus no therapy we observed a 99% relative reduction in risk.
In predictive models, older age was the most influential predictor of being hospitalized with COVID-19, while vaccination and outpatient therapy were the most influential factors predicting non-hospitalization.
Conclusion: The impact of recent SARS-CoV-2 vaccination and outpatient antiviral and monoclonal antibody therapy on reducing COVID-19 hospitalization risk was striking in this large healthcare system covering Delta and Omicron variant timeframes. SARS-CoV-2 vaccinations and outpatient therapeutics are critical for preventing severe COVID-19.

Unadjusted and age-adjusted risk ratios for hospitalization among patients with SARS-CoV-2

	N	Risk Ratio (95% CI) Unadjusted	Age adjusted
SARS-CoV-2 vaccine doses vs. no vaccine			
1	2,129	0.38 (0.30-0.48)	0.38 (0.30-0.48)
2	10,099	0.40 (0.36-0.45)	0.37 (0.33-0.41)
3	5,010	0.34 (0.28-0.40)	0.24 (0.20-0.28)
Time from last SARS-CoV-2 vaccine dose vs. ≤90 days			
91-180 days	4,964	1.08 (0.85-1.38)	1.16 (0.91-1.48)
181-270 days	4,636	1.13 (0.89-1.44)	1.29 (1.01-1.65)
>270 days	3,654	1.42 (1.12-1.81)	1.27 (0.99-1.62)
Outpatient SARS-CoV-2 therapy vs. no therapy			
Casirivimab/imdevimab	3,589	0.27 (0.21-0.34)	0.19 (0.15-0.24)
Nirmatrelvir/ritonavir	1,280	0.01 (0.001-0.04)	0.01 (0.00-0.03)

173 MPOX IN PEOPLE LIVING WITH HIV AND CD4 COUNTS < 350 CELLS/MM3: A GLOBAL CASE SERIES

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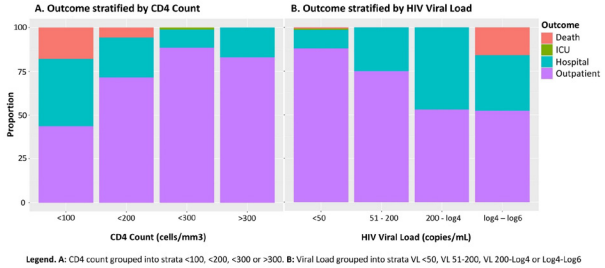
Background: People living with HIV (PLWH) represent 38-50% of the 2022 global MPOX outbreak. Most PLWH included in case series had CD4 counts >500 cells/mm^3 and similar outcomes to persons without HIV. Existing data suggest poorer outcomes in immunosuppressed PLWH. 60 deaths with MPOX outside of Africa were reported in 2022 – only 9 have been described and published. We describe clinical characteristics and deaths in PLWH with low CD4 cell counts (< 350 cells/mm^3) and MPOX.
Methods: International collaborators from 18 countries contributed data from PLWH with CD4 counts < 350 cells/mm^3 & confirmed MPOX between May 11th and December 24th, 2022. We describe in detail the clinical course, complications & causes of death with respect to both CD4 & viral load (VL) strata. Analyses were descriptive (continuous variables described as mean and standard deviation (SD); categorical variables as counts & percentages).
Results: We report on 258 persons (mean age 36 years): 251 cisgender men, 2 cisgender women, 5 transgender women. At (MPOX) diagnosis, 234 were known PLWH (205/234 on ART); 24/258 were undiagnosed, 26/258 had a concurrent opportunistic illness. Mean CD4 count was 210 cells/mm^3 (SD 96); mean VL was 1.6 log c/mL (SD 2). A total of 39 (15%), 70 (27%), 87 (34%), 53 (21%) persons had CD4 counts of < 100, 101-200, 201-300, & 301-350 cells/mm^3, respectively. 66/258 persons were hospitalised with MPOX, of whom 1 survived an ITU admission & 14 died. Among those who died, the mean CD4 count was 63 cells/mm^3, mean VL was 4.5 log c/mL. 13/14 had severe coalescing/necrotising skin lesions, secondary bacterial infections and rectal complications, 10/14 had respiratory symptoms and respiratory failure, 5/14 had neurological involvement (all described as confusion not encephalitis). More deaths occurred in persons with lower CD4 counts and higher viral loads (CD4< 100, 18% vs. CD4 >300, 0%), & (VL ≥4 log 16% vs. VL< 50 c/mL 0.7%) respectively (Figure). More complications occurred in 39 persons with CD4< 100 compared to 53 persons with CD4 >300 cells/mm^3: respiratory (59% vs 25%), rectal (59% vs 25%), skin (51% vs 8%), bacterial (38% vs 9%), gastrointestinal (26% vs 6%), CNS (10% vs 2%). Immune reconstitution inflammatory syndrome was suspected in 15/46 persons started or re-started on ART with MPOX.
Conclusion: In our case series in PLWH with MPOX, severe systemic complications and deaths occurred most commonly in persons with CD4 < 100 cells/mm^3 and viraemia.

FIGURE. OUTCOME BY CD4 COUNT (A) AND HIV VIRAL LOAD (B)



Legend. A: CD4 count grouped into strata <100, <200, <300 or >300. **B:** Viral Load grouped into strata VL <50, VL 51-200, VL 200-Log4 or Log4-Log6

174 CD8+ T CELLS INDUCE HIV LATENCY IN CD4+ T CELLS THROUGH THE DOWNMODULATION OF NF-κB

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Background: The key barrier to achieving either a cure for HIV infection or a remission in the absence of antiretroviral therapy (ART) is the presence of cells harboring integrated, replication competent virus (i.e. the reservoir) that persists despite long-term, fully suppressive ART. Although previous studies have demonstrated that CD8+ T cells negatively regulate HIV expression and may influence HIV latency, the exact mechanism is unknown. Here we identify the HIV transcriptional regulator NF-kB as a key target modulated by non-cytolytic CD8+ T cells.
Methods: We adapted our previously developed primary cell-based *in vitro* model of HIV latency to study the molecular mechanism exerted by CD8+ T cells for the suppression of HIV expression in memory CD4+ T cells (mCD4+). Resting or TCR-activated mCD4+ T cells were HIV infected *in vitro* and then co-cultured with autologous activated total CD8+ T cells in the presence of ART. mCD4+ T cell monocultures were included as controls. After 24-hour co-culture, mCD4+ and CD8+ T cells were sorted by FACS and mCD4+ were returned to *in vitro* culture for an additional 72h hours. HIV expression was monitored by

intracellular Gag and infection frequency was quantified by integrated HIV DNA quantitative PCR. Modulation of NF-kB was monitored by RT-PCR of NF-kB targets at 24, 48 and 72 hours post co-culture.

Results: Following co-culture with autologous activated CD8+ T cells, both resting and activated mCD4+ T cells showed a significant reduction in Gag expression compared to the monocultures. The downmodulation of HIV expression was comparable among the mCD4+ T central, transitional and effector subsets. To determine if the suppression of HIV expression exerted by CD8+ T cells is NF-kB dependent, we measured the expression of the NF-kB targets IL-6, IFN-γ, and the canonical p65. The NF-kB activity was significantly reduced in both resting and activated mCD4+ T cells following exposure to CD8+ T cells and its downmodulation was maintained after CD8+ T cells removal from coculture.

Conclusion: Our results show that CD8+ T cells play a pivotal role in the establishment of HIV latency by downmodulating HIV expression. CD8+ T cells modulate the NF-kB transcriptional activity in mCD4+ T cells independently from HIV infection, thus suggesting that this pro-latency activity might be due to the NF-kB suppression. Understanding the mechanism responsible for the NF-kB modulation in mCD4+ T cells may represent a tool to reverse the HIV latency and develop a new cure strategy.

175 BLOCKING CD4+T CELL MIGRATION DELAYS VIRAL SPREAD FOLLOWING VAGINAL SIV CHALLENGE

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Background: Nearly 2 million new HIV infections occur each year from sexual transmission, yet little is known about the anatomic steps that lead to systemic dissemination following vaginal exposure. We previously showed that following SIV vaginal challenge, CD4+ T-cell density increases in the female genital tract (FGT), and that local viral replication in FGT necessarily precedes dissemination. We hypothesize that cells harboring infectious virus are the predominant mechanism of viral dissemination.

Methods: To address this, we vaginally challenged eight rhesus macaques (RM) with the sequence tagged synthetic swarm SIVmac239X. Six animals were pre-treated with fingolimod (FTY720) to block the egress of leucocytes out of tissues. Animals were euthanized two weeks post-challenge. Plasma viral load was monitored frequently, and sequence analysis was used to assess the number of transmitted/founder lineages. T-cell populations were assessed using flow cytometry and immunohistochemistry.

Results: We observed a significant delay in the time to measurable viremia in animals receiving fingolimod (up to 5 days) as well as a drastic reduction in viral load magnitude at the time of necropsy (up to 5 logs). We observed a striking reduction in the number of CD4+T cells (and all leucocytes) in the blood following fingolimod treatment with an abundance of CD4+T cells retained in lymph nodes. However, when quantifying the density of CD4+T cells within the FGT, there was no significant difference in treated vs non-treated animals. In contrast, CD8+T cells were more abundant in the vagina tissue of non-treated animals. Sequencing of plasma virus revealed that animals treated with fingolimod were systemically infected with only one to two different variants, whereas the non-treated animals were infected with an average of five distinct variants.

Conclusion: Restricting trafficking of CD4+ T cells impeded the transition of local infection to systemic infection as demonstrated by significantly decreased and delayed plasma viremia. These differences were not due to differences in the availability of target cells at the challenge site nor were they likely due to any potential adaptive immune effects prior to dissemination. These observations highlight the importance of the mobility of productively infected cells and that systemic spread of virus via cell-free virion dissemination is slower and less efficient.

176 DEPLETION OF SIV-SPECIFIC CD8+ T CELLS DOES NOT ALTER VIRAL LOAD DURING SIV INFECTION

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Background: The emergence of SIV-specific CD8+ T cells coincides with declining viremia in monkeys acutely infected with SIV. Antiviral CD8+ T cells may also contribute to immune control in chronically infected animals treated with antiretrovirals (ARVs). We explored these relationships using toxin-conjugated MHC class I tetramers to deplete Gag CM9-specific CD8+ T cells in Mamu-A01+ rhesus macaques infected with a pathogenic strain of SIV.

Methods: Mamu-A*01+ rhesus macaques were infected with SIVmac239. Gag CM9 (CTPYDINQM) tetramers conjugated to saporin were administered to animals with progressive infection and animals with spontaneous control of viremia to < 10,000 copies/mL. Lymphocyte populations in blood, bronchoalveolar lavage fluid, lymph nodes, colon, and jejunum were enumerated via flow cytometry. Plasma viremia was measured via quantitative RT-PCR.

Results: Immunotoxin-conjugated CM9/Mamu-A*01 tetramers induced a transient and significant depletion of CM9-specific CD8+ T cells in blood with lesser effects in tissues. This manipulation resulted in viral recrudescence in one animal with spontaneous control of viremia but did not alter the kinetics or magnitude of viremia in other animals during acute or chronic infection, irrespective of treatment with ARVs.

Conclusion: Immunotoxin-conjugated MHC class I tetramers effectively induced a transient depletion of circulating SIV-specific CD8+ T cells. Our results suggest that CM9-specific CD8+ T cells are important for elite control of viral replication but play a minimal role in the transition from acute to set-point viremia in animals with progressive infection. No evidence was found to support the notion that SIV-specific CD8+ T cells contributed to the reduced viremia observed in animals treated with ARVs.

177 PROTECTION AGAINST HTLV-1 CHALLENGE BY VACCINATION INDUCING ANTIBODIES IN MACAQUES

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Background: Human T-cell leukemia virus type 1 (HTLV-1) causes severe diseases such as adult T-cell leukemia (ATL) and HTLV-1 associated myelopathy in some individuals after long-term asymptomatic phase of latent infection. Control of horizontal HTLV-1 transmission is a globally important issue, and there is a demand for the development of an effective HTLV-1 vaccine. In HTLV-1 transmission, latently HTLV-1-infected cells are transmitted into the donor, resulting in cell-to-cell virus transmission. It is a great challenge to determine whether vaccine-induced anti-Env antibodies can protect the cell-to-cell HTLV-1 transmission. In the present study, we examined the protective efficacy of a vaccine inducing anti-Env antibodies against HTLV-1 challenge.

Methods: We have recently developed a Sendai virus (SeV) vector expressing a chimeric antigen consisting of the HTLV-1 gp63 ectodomain and the SeV F transmembrane-cytoplasmic domain (HtlvEnvF), which can be incorporated into the SeV virion. A vaccine using the SeV-HtlvEnvF and a non-infectious SeV particle carrying HtlvEnvF (NVP-HtlvEnvF) has been shown to induce anti-HTLV-1 neutralizing antibodies in mice (Vaccine, 40:2420-2431, 2022). In this study, we examined the protective efficacy of the vaccine using SeV-HtlvEnvF against an intravenous challenge with 108 HTLV-1-producing cells (an ATL cell line provided by Dr. Yuetsu Tanaka) in cynomolgus macaques.

Results: In the first experiment, three of the five cynomolgus macaques vaccinated with SeV-HtlvEnvF and NVP-HtlvEnvF induced substantial anti-HTLV-1 neutralizing antibodies (NAbs) and were protected from the challenge. In the second experiment, all the five cynomolgus macaques vaccinated subcutaneously with SeV-HtlvEnvF induced substantial anti-HTLV-1 NAbs and were protected from the challenge. In contrast, all the unvaccinated cynomolgus macaques (n = 10) were infected with detectable proviruses.

Conclusion: These results indicate that neutralizing antibody induction by vaccination can result in protection from HTLV-1 transmission, implying

the rationale for the development of an HTLV-1 vaccine inducing anti-Env antibodies.

178 SHIFTS IN SYSTEMIC INFLAMMATION AFTER FECAL MICROBIOTA TRANSPLANT IN PEOPLE WITH HIV

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Background: Whether interventions on the microbiota can help reduce chronic inflammation during treated HIV infection remains unclear. In a fecal microbiota transplant (FMT) trial in PWH, we found that Lachnospiraceae and Ruminococcaceae families–with known anti-inflammatory properties– were the taxa more robustly engrafted across time points. Here, we aimed to better characterize the FMT effects on systemic inflammation.

Methods: We randomized 30 PWH on ART to either weekly fecal microbiota capsules or a placebo for eight weeks. Stool donors were selected based on anti-inflammatory microbiota profiles (high Faecalibacterium and butyrate abundance). We measured the plasma expression of 368 inflammatory proteins at weeks 0, 1, 8, and 24 using the Proximity Extension Assay by Olink. We fitted mixed models to compare the protein trajectories and selected the most significant to explore their correlations with Lachnospiraceae and Ruminococcaceae families. We performed a functional analysis using Gene Set Enrichment Analysis.

Results: FMT resulted in a significant decrease of 24 proteins related to cytokines and leukocyte activation compared to placebo. CCL22, CD22, FGF5, and JUN showed the most consistent pattern of decline after each FMT; CCL22, IL20, and JUN were those with the most apparent effect at week 24 (17 weeks after the last FMT); and AOC1 and IL13 showed the most significant differences between groups (p=0.0045 and p=0.0003)(**Figure 1A**). From these 24 proteins, increases in Lachnospiraceae and Ruminococcaceae families correlated with increased CCL22 (p=0.0094) and decreased IL20 expression (p = 0.0255) (**Figure 1B-C**).

Conclusion: Repeated FMT downregulated the expression of inflammatory proteins related to cytokines and leukocyte activation. The effects of FMT on Lachnospiraceae and Ruminococcaceae abundance correlated with CCL22 and IL20 kinetics, with known roles on Th17 cell preservation in HIV and the immune response against bacterial infections. Our results support investigating interventions on the microbiome to modulate systemic inflammation in PWH on effective ART.

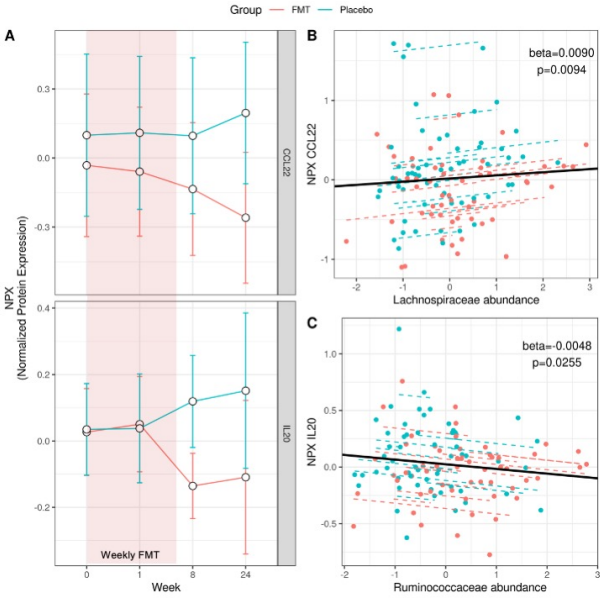

Figure 1. A. Observed changes in normalized CCL22 and IL20 expression in each group. B. Associations between weekly changes in Lachnospiraceae and Ruminococcaceae (scaled abundance) and CCL22 and IL20 (normalized expression) weekly changes estimated from linear mixed models with interaction terms with time. Dashed lines represent individual correlations between bacteria and protein changes and black lines the coefficients obtained from mixed models.

179 AUTOLOGOUS NEUTRALIZING ANTIBODY RESPONSES IN bNAb-TREATED RHESUS MACAQUES

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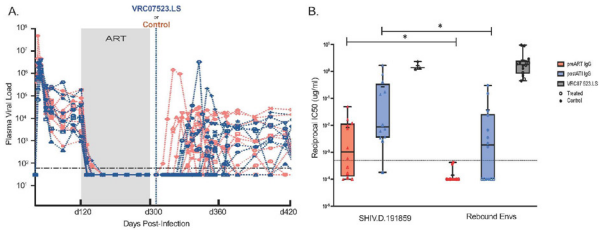
Background: Broadly neutralizing antibodies (bnAbs) are important tools for HIV-1 therapy and cure strategies, yet the role of autologous neutralizing antibodies (anAbs) during bnAb therapy is unclear. We studied the kinetics of anAb responses during VRC07523.LS therapy at analytical treatment interruption (ATI) in a robust SHIV-infected Rhesus Macaque (RM) model of HIV-1.

Methods: 18 RMs infected IV with $1x10^6$ infectious units of SHIV.D.191859 (SHIV.D) initiated antiretroviral therapy (ART) at 120 days post-infection (dpi). After 6 months of ART, all 18 RM underwent ATI, during which 9 were administered 30 mg/kg VRC07.523LS. Plasma virus env sequences were derived by single genome sequencing. SHIV.D and rebound Envs were tested for neutralization sensitivity.

Results: 18 RM experienced peak and pre-ART viral loads of $4.91x10^6$ and $3.94x10^4$ copies/mL, respectively. Virus was suppressed within 3 weeks of ART and rebounded in all RM following ATI, with a significant delay in VRC07.523LS-treated RM (median 41 vs. 28 days, p=0.016). At 120dpi, 56% (10/18) of RMs had detectable anAb responses against SHIV.D, with median 50% inhibition of 1:47 plasma dilutions (ID_{50}) and 87 µg/mL IgG (IC_{50}), with strong correlation between plasma and IgG (r_s =0.85, p=1E-5). AnAb responses were stable over 6 months of ART. Plasma virus env sequenced pre-ART and at rebound (median 31 sequences per RM) revealed 1-5 virus lineages at rebound. Rebound Envs were universally resistant to 120dpi plasma IgG (p=0.0051, vs. SHIV.D anAbs). Eight weeks post-rebound, plasma anAb responses rose up to 1000-fold against both SHIV.D and rebound Envs, with greater magnitude vs. SHIV.D than rebound Envs (p=0.0053). In treated RMs, plasma VRC07523.LS was detectable at rebound in 7/9 RM and undetectable 8 weeks post-ATI in 9/9. Rebound Envs in bnAb-treated RM were more VRC07523.LS-resistant than controls (p=0.0316). Modeling of virus evolution indicated similar rates of virus diversification in treated and control RM.

Conclusion: SHIV.D-infected RMs demonstrate viral kinetics, anAb responses, and effects of CD4bs bnAb monotherapy that closely mirror human trials. Rebound virus escaped baseline anAb responses, suggesting ongoing humoral immune pressure at ATI. Virus rebound preferentially boosted anAbs against inoculum vs. rebound virus, indicating antibody imprinting, or original antigenic sin. AnAb potencies approaching those of VRC07.523LS suggest a potential role for anAbs to restrict archived virus and complement bnAb-based interventions.

SHIV.D Study Schema and Autologous Neutralizing Antibody Responses



A. Study Schema. 18 RM were IV inoculated with SHIV.D.191859 and started on ART at day 120. After 6 months ART, 9 RM were given 30 mg/kg VRC07.523LS and all RM underwent ATI. VRC07.523LS-treated RM experienced delayed rebound (median 41 vs. 28 days, p=0.0164). **B. Autologous neutralizing antibody responses vs. inoculum SHIV.D.191859 and each RM's rebound Env**. Reciprocal IC50 on Y-axis and responses against SHIV.D shown as triangles on left and against Rebound Envs as circles on right. Pre-ART (day 120) IgG responses shown in red, 8-weeks post-ATI (day 360) shown in blue, VRC07.523LS responses in black.

180 ANALYSIS OF EPITOPE-SPECIFIC T CELLS IN SARS-CoV-2 INFECTION AND VACCINATION

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Background: T cells play a critical role in the adaptive immune response to SARS-CoV-2 in both infection and vaccination. Identifying T cell epitopes and understanding how T cells recognize these epitopes can help inform future vaccine design and provide insight into T cell recognition of newly emerging variants. Here, we identified SARS-CoV-2 specific T cell epitopes, analyzed epitope-specific T cell repertoires, and characterized the potency and cross-reactivity of T cell clones across different common human coronaviruses (HCoVs).

Methods: SARS-CoV-2-specific T cell epitopes were determined by IFNγ ELISpot using PBMC from convalescent individuals with mild/moderate disease (n=25 for Spike (S), Nucleocapsid (N) and Membrane (M)), and in vaccinated individuals (n=27 for S). Epitope-specific T cells were isolated based on activation markers following a 6-hour peptide stimulation, and scRNAseq was performed for TCR repertoire analysis. T cell lines were generated by expressing recombinant TCRs in Jurkat cells and activation was measured by CD69 upregulation.

Results: We identified multiple immunodominant T cell epitopes across S, N and M proteins in convalescent individuals. In vaccinated individuals, we detected many of the same dominant S-specific epitopes at similar frequencies as compared to convalescent individuals. T cell responses to peptide S205 (amino acids 817-831) were observed in 56% and 59% of individuals following infection and vaccination, respectively, while 20% and 19% of individuals responded to S302 (a.a. 1205-1219) following infection and vaccination, respectively. For S205, a CD4+ T cell response, we confirmed 8 unique TCRs and determined the minimal epitope to be a 9mer (IEDLLFNKV). While TCR genes TRAV8-6*01 and TRBV30*01 were commonly utilized across the TCRs, we did identify TCRs with unique immunogenetic properties with different potencies of cross-reactivity to other HCoVs. For S302, a CD8+ T cell response, we identified two unique TCRs with different immunogenetic properties that recognized the same 9mer (YIKWPWYIW) and cross-reacted with different HCoV peptides (Figure 1).

Conclusion: These data identify immunodominant T cell epitopes following SARS-CoV-2 infection and vaccination and provide a detailed analysis of epitope-specific TCR repertoires. The prospect of developing a vaccine that broadly protects against multiple human coronaviruses is bolstered by the identification of conserved immunodominant SARS-CoV-2 T cell epitopes that cross react with multiple other HCoVs.

S302 TCR1

Chain	V gene	J gene	CDR3
TCRα	12-1*01	34*01	CVVDYNTDKLIF
TCRβ	20-1*01	2-1*01	CSARDQGLAGPEQFF

S302 TCR2

Chain	V gene	J gene	CDR3
TCRα	8-4*01	4*01	CAVSDIGNKLIF
TCRβ	5-6*01	2-1*01	CASSVLANEQFF

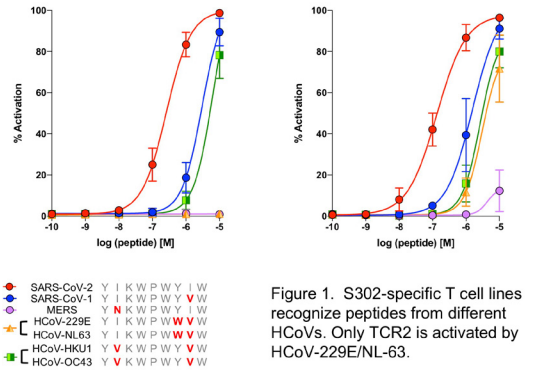

Figure 1. S302-specific T cell lines recognize peptides from different HCoVs. Only TCR2 is activated by HCoV-229E/NL-63.

181 ANTI-PD-1 THERAPY INDUCED RAPID INNATE INTERFERON RESPONSES DRIVE HIV RESERVOIR DECAY

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Background: Antiretroviral therapy (ART) is not curative and HIV patients continue to present with co-morbidities including cancer. Persistence of HIV in latently-infected CD4 T cells remains a major impediment to eradication. These cells express high levels of inhibitory receptor PD-1, which is associated with immune dysfunction in both HIV infection and cancer. Inhibitors that target PD-1 have been successful against cancers and have proven to be safe/can effectively target the HIV reservoir in cancer patients living with HIV. The mechanisms associated with HIV reservoir decay in these patients remain unknown.

Methods: Immune responses from 30 cancer patients living with HIV who received Pembrolizumab monoclonal antibody against PD-1 every 3 weeks for up to 2 years (Cancer Immunotherapy Network-12 trial) were profiled using an integrated multiomic approach. Plasma and PBMC responses (assessed using flow cytometry and single-cell/bulk RNA-sequencing) were measured at baseline, 24 hours, and 1 week following therapy and at the end of treatment (EOT) to identify molecular and cellular mechanisms associated with decay of the HIV reservoir.

Results: Anti-PD-1 therapy was associated with a further decrease in HIV reservoir in patients that had reduced HIV reservoir at baseline; and increase in HIV RNA within 1 week ($P < 0.05$) that remained significant at EOT ($P < 0.05$). Our multiomic analyses shows that anti-PD-1 therapy leads to a rapid increase (within 24h) in effector CD8 T cell function gene expression concomitant with increased plasma viral RNA, and reduced TGF-bsignaling (GSEA; $P < 0.05$). Higher frequencies of classical monocytes with augmented anti-viral functions and increased transcription of interferon-stimulated genes (IRF1, 7, 9 and higher plasma IFN-b/g), chemokine secretion (CXCL9, 10), restriction factors (TRIM21, 22), and TLR signaling (TLR4 and high plasma IL-6) were also observed 24h after therapy initiation. Importantly, this early monocyte specific antiviral signature persisted only in the 8 participants that maintain reduced HIV reservoir levels at EOT.

Conclusion: Our data demonstrate that anti-PD-1 therapy rapidly induces sustained antiviral innate responses as early as day 1 post treatment initiation that can lead to long-term reservoir reduction by limiting infection of new target cells and priming effector HIV specific T cell responses. Our findings pave the way for mechanism-based therapeutic opportunities that can help eradicate HIV.

182 SINGLE INFUSION OF STEM LIKE CCR5-MODIFIED CD4 T CELLS PROVIDE LONG-TERM HIV CONTROL

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Background: Antiretroviral therapy (ART) fails to fully restore immune function and is not curative, therefore more effective therapies are required for people with HIV (PWH). A cure for HIV has previously been observed in several individuals in which bone marrow transfer of CCR5-modified stem cells for leukemia treatment was also found to eliminate HIV. While these results are encouraging, a less invasive and more broadly applicable curative strategy is warranted. Transfer of autologous CCR5-modified CD4 T cells has been found to be safe and well-tolerated in PWH. However, whether this treatment re-programs the immune response to provide long-term viral control is unknown.

Methods: We performed two clinical studies, SB-728-902 (n = 9) and SB-728-1101 (n = 9), in which participants were provided a single infusion of autologous CCR5-modified T cells and ART was either maintained or interrupted (ATI), respectively. At 3-6 timepoints over 6 years, we collected blood samples and comprehensively profiled the immune response using multi-parameter flow cytometry and single-cell RNA sequencing.

Results: A single infusion of autologous CCR5-modified CD4 T cells led to a significant increase in absolute CD4 T cell count (+162 cells/µL, P = 0.02), reduced integrated HIV DNA (P = 0.004) in patients on ART (SB-728-902) and control of plasma viremia (for 1 to 6 years) upon ATI in 5 participants (SB-728-1101). These outcomes were associated with high frequencies of CCR5-modified CD45RA^{int}CD45RO^{int} CD4 T cells that had a quiescent metabolic profile (high oxidative phosphorylation) and were enriched in pathways/markers that regulate stemness (i.e., TCF1 protein, WNT/b-catenin signaling and TGF-b cascades). Single-cell trajectory analyses showed that this population gave rise to an effector CD4 T cell population which expressed high interferon inducible anti-viral genes. Higher frequencies of this subset were associated with both heightened effector CD8 T cell responses and reduced viral load.

Conclusion: Our results indicate that a single infusion of autologous CCR5-modified CD4 T products that are enriched in the novel CD45RAintCD45ROint stem-like phenotype are protected against HIV "re-infection" because they express mutated CCR5, which favors this anti-viral signature. This protection from infection promotes long-lasting effector CD4/8 T cell responses that can control viremia and facilitate a functional cure against HIV.

183 SEX MODIFIES THE ASSOCIATION OF AGE AND VIREMIA WITH STROKE RISK IN HIV

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CFAR Network of Integrated Clinical Systems (CNICS) Network

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Background: The increased risk of stroke conferred by HIV may be greater for women than for men. Little is known about potential mechanisms driving the differential stroke risk by sex in people with HIV (PWH). We examined whether sex modifies the effect of traditional and HIV-related risk factors associated with stroke in PWH.

Methods: We analyzed the Centers for AIDS Research Network of Integrated Clinical Systems (CNICS) cohort of PWH receiving HIV care. Strokes occurring in PWH from 5 sites across the U.S. were centrally adjudicated by neurologists. Follow-up in care was from ~2005-2020 (end dates varied by site). The observation period began at the date of stroke surveillance by site or the initial CNICS visit date plus 6 months and ended at the earliest of: stroke, last visit plus 9 months, death, or administrative censoring date. Data from the CNICS central data repository included demographics, laboratory values, medication prescriptions, and diagnoses. Substance use, depression, and physical activity were from the CNICS clinical assessment of patient-reported outcomes collected as part of care visits. Cox survival models were used to assess the hazard ratio of stroke for predictors of interest, female sex, and the interaction between predictors of interest and female sex adjusted for age, race/ethnicity, and site.

Results: Among 13,584 PWH (mean age 44 years, 19% women, 40% Black, 81% with viral load < 400 copies/mL), there were 147 incident strokes during follow-up (mean follow-up 5.8 years for women, 5.5 years for men). In the overall cohort, age (HR 1.63 per 10 years, 95% CI 1.34-1.98, p< 0.001) but not sex (HR 1.19 for women, 95% CI 0.77-1.82, p=0.43) was a risk factor for stroke. However, a statistically significant age-by-sex interaction was observed (p=0.005). At younger ages, the risk of stroke was higher for women compared with men (HR 2.09 for women versus men at age 40, 95% CI 1.27-3.44, p=0.004), whereas with older age, this difference was no longer present. Conversely, the risk of stroke associated with having a detectable viral load or using methamphetamine was greater for women than for men (Table).

Conclusion: Stroke risk was higher for some women with HIV compared with men, although this effect declined with older age. The effect of other risk factors on stroke, including viremia, differed between women and men with HIV. Investigation into the mechanisms underlying these differences and how this may translate into sex-specific stroke treatment and prevention is warranted.

Differences in the associations of risk factors with stroke by sex

Table: Differences in the associations of risk factors with stroke by sex[1]

		Adjusted Hazard Ratio	P value	95% CI
Model 1	Age (per 10 years)[2]	2.03	<0.001	1.69-2.44
	Age*female sex[3]	0.60	0.005	0.42-0.85
	Female sex at age 40[4]	2.09	0.004	1.27-3.44
Model 2	Current methamphetamine use[2]	1.16	0.7	0.59-2.25
	Current meth use*female sex[3]	4.26	0.04	1.09-16.62
	Female sex[4]	1.17	0.5	0.77-1.76
Model 3	Viral load >400 copies/mL[2]	1.39	0.2	0.88-2.21
	Viral load*female sex[3]	3.98	0.001	1.80-8.81
	Female sex[4]	0.78	0.4	0.46-1.33
Model 4	BMI (per 5 kg/m^2)[2]	1.10	0.4	0.89-138
	BMI*female sex[3]	1.07	0.7	0.79-1.46
	Female sex[4]	0.79	0.8	0.13-4.73
Model 5	Diabetes mellitus[2]	1.96	0.009	1.18-3.26
	Diabetes mellitus*female sex[3]	1.13	0.8	0.46-2.79
	Female sex[4]	1.22	0.4	0.78-1.91
Model 6	Treated hypertension[2]	1.89	0.002	1.28-2.81
	Treated hypertension*female sex[3]	1.42	0.4	0.65-3.08
	Female sex[4]	1.03	0.9	0.56-1.91
Model 7	Statin use[2]	1.52	0.047	1.00-2.30
	Statin use*female sex[3]	1.33	0.5	0.61-2.89
	Female sex[4]	1.16	0.6	0.71-1.89
Model 8	CD4 count (per 100 cells/mm^3)[2]	0.85	<0.001	0.79-0.92
	CD4 count*female sex[3]	1.02	0.8	0.89-1.17
	Female sex[4]	1.29	0.5	0.62-2.67

[1]All models are adjusted for age, race/ethnicity, and site.

[2]The HR for the predictor among men (e.g., among men, there is a 2.03-fold higher hazard of stroke for every 10 years of age; among men, methamphetamine use is associated with a non-statistically significant 1.16-fold higher hazard of stroke).

[3]The predictor*female sex term represents the interaction between those variables. To evaluate the hazard associated with each predictor for women, the HR for the interaction term must be multiplied by the HR for the predictor (e.g., among women, there is a 1.22-fold [0.60 multiplied by 2.03] higher hazard of stroke for every 10 years of age; among women, there is a 4.94-fold [4.26 multiplied by 1.16] higher hazard of stroke [95% CI 1.46-16.60, p=0.01] associated with methamphetamine use).

[4]In Model 1, the effect of female sex on stroke risk is shown for individuals at age 40. In Models 2 to 8, the effect of female sex on stroke risk is shown for individuals with the predictor set to 0 (e.g., no diabetes mellitus, CD4 count=0).

184 INCREASED IMMUNE ACTIVATION IN HIV+ MSM ON ART, BUT NOT WHEN COMPARED TO MSM ON PrEP

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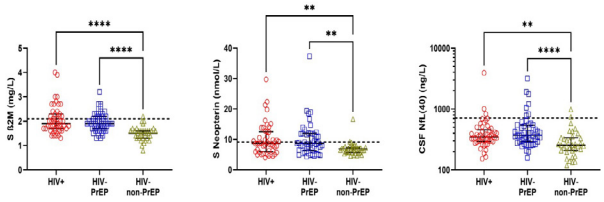
Background: Persistent systemic and CNS immune activation, as well as signs of neuronal injury, are commonly found in people living with HIV (PLWH) despite suppressive antiretroviral therapy. We have previously shown that HIV-negative persons on PrEP had higher levels of biomarkers for immune activation, blood-brain barrier (BBB) impairment and neuronal injury, compared with volunteers without PrEP. The aim of this study was to explore markers of immune activation and neuronal injury in ART-treated PLWH compared to controls with similar lifestyle-related factors.

Methods: Cerebrospinal fluid (CSF) and blood were collected from 50 men who have sex with men (MSM) treated with ART >12 months (median age 37.8, 24-68y), 50 HIV-negative MSM on PrEP (35.5, 22-68y), and 35 HIV-negative healthy volunteers (44.8, 22-66y). Biomarkers of immune activation (β2-microglobulin and neopterin), BBB integrity (CSF/plasma albumin ratio) and neuronal injury (neurofilament light protein, NfL) were analyzed.

Results: All 50 HIV-infected MSM on ART had HIV-RNA < 50 c/mL in plasma and CSF. Their CD4-cell counts (median 670, IQR 482-895 cells/µL) and CD4/CD8 ratio (0.94, 0.74-1.16) were significantly lower (p< 0.001) than the PrEP (850,

620-1100 and 1.33, 1.0-1.7) and volunteer (810, 660-1100, 1.52, 1.4-1.9) groups while no significant difference was seen in CD8 cell counts.
No significant differences in serum and CSF β2-microglobulin or neopterin were found between the PLWH and PrEP groups. However, both groups had significantly higher serum levels of β2-microglobulin (1.9, 1.7-2.3 and 1.9, 1.7-2.2 mg/L, p< 0.001) and neopterin (8.6, 6.0-12.6 and 8.65, 6.3-11.9 nmol/L, p< 0.01) compared to HIV-negative volunteers not on PrEP (1.5, 1.3-1.6 and 6.9, 5.7-7.3). Age adjusted CSF NfL was also higher in the PLWH (347, 294-456 ng/L, p< 0.01) and MSM PrEP (371, 290-544, p< 0.001) groups compared to voluntary controls (255, 208-338), while no significant differences were found in CSF β2-microglobulin, CSF neopterin or albumin ratio.
Conclusion: We found increased markers of immune activation and neuronal injury in both virologically suppressed PLWH and HIV-negative persons on PrEP compared to HIV-negative volunteers. These results indicate that factors unrelated to HIV-infection may contribute to the persistent immune activation and CNS injury commonly seen in PLWH on ART and highlights the importance of using appropriate control groups with comparable lifestyle-related factors.
Figure



185 CEREBROSPINAL FLUID HIV RNA AND VIRAL NUCLEIC ACID DETECTION IN PERSONS WITH HIV

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Background: Data on the prevalence of cerebrospinal fluid (CSF) HIV RNA escape and other viral nucleic acid detection in the modern anti-retroviral therapy (ART) era are sparse. Our aim was to determine the recent incidence of CSF HIV RNA escape and other viral nucleic acid detection in persons with HIV undergoing a lumbar puncture examination for clinical indications over a 5-year period and assess the associated clinical factors.
Methods: Persons with HIV with CSF virology results at a large London centre were identified from pathology records between 2017-2022 and clinical data recorded. CSF HIV RNA escape was defined as CSF HIV RNA concentrations greater than concurrent plasma HIV RNA. CSF viral screen included herpes simplex virus types 1 (HSV-1) and 2 (HSV-2), varicella zoster virus (VZV), Epstein Barr virus (EBV), cytomegalovirus (CMV), human herpes virus 6 (HHV-6), JC virus, adenovirus, enterovirus and parechovirus. For viruses that were detected in >5 individuals, associated clinical factors were assessed using linear regression modelling.
Results: Of 114 individuals, clinical indication for lumbar puncture examination included new onset neurological symptoms (n=83), investigation for neurosyphilis (n=24), new onset psychiatric symptoms (n=6) and new findings on brain MRI (n=1). CSF HIV RNA escape was observed in 19 (17%, table) and was associated with low level plasma viraemia, the presence of HIV-drug-resistance mutations and non-InSTI based ART. Viral nucleic acid testing was performed in 98 individuals with positive findings of EBV (n=10), VZV (3), CMV (2), HHV-6 (2) and JCV (4). Detectable EBV in the CSF was not clinically considered to be related to neurological symptoms in any individual and was associated with CSF pleocytosis (median 26 cells/cmm (range (r) 1-223) vs 1 cells/cmm (r 1-81), $p< 0.001$), higher rates of previous AIDS illness (60% vs 17%, $p=0.005$), lower nadir CD4 T cell count (87.5 cells/μL (r 3-380) vs 200 cells/μL (r 8-968), $p=0.038$) and lower current CD4 T-cell count (129 cells/μL (r 55-758) vs. 540 cells/μL (r 12-2390), $p=0.036$) when compared to those without detectable EBV, respectively.
Conclusion: In persons with HIV with neurological symptoms undergoing CSF examination, the incidence of CSF HIV RNA escape remains similar to historical reports. Detectable EBV viral nucleic acid in the CSF was observed frequently and in the absence of clinical manifestations may be a consequence of CSF pleocytosis and trafficking of viral nucleic acid into the CSF compartment.

Table 1: Baseline demographic, clinical and laboratory characteristics of the total cohort and those with and without CSF HIV RNA escape

Characteristic	Value	Total cohort *n*=114	CSF HIV RNA escape *n*=19	No-CSF HIV RNA escape *n*=95	p-value
Age, years	mean (SD)	48.8 (± 13)	51.6 (13.1)	48.3 (13)	0.306
Gender, male	*n* (%)	81 (71)	10 (53)	71 (75)	0.058
Ethnicity, white	*n* (%)	49 (43)	7 (37)	42 (44)	0.555
Absolute CD4 count, cells/μL	median (range)	546 (12-2390)	698 (42-1311)	510 (12-2390)	0.223
Nadir CD4 count, cells/μL	median (range)	248 (3-968)	190 (10-600)	250 (3-968)	0.410
Plasma HIV RNA viral load,	*n (%)*				
<20 copies/mL		53 (46)	9 (47)	44 (46)	0.866
20-200 copies/mL		27 (24)	8 (42)	19 (20)	**0.044***
>200 copies/mL		34 (30)	2 (11)	32 (34)	0.060
Previous AIDS	*n (%)*	27 (24)	6 (32)	21 (22)	0.378
ART regimen,	*n (%)*	**n=93**			
INSTI-containing		42 (45)	3 (16)	39 (42)	**0.019***
PI-containing		39 (42)	10 (53)	29 (32)	0.133
Current plasma/CSF HIV drug mutations	*n (%)*	10 (9)	4 (21)	6 (6)	**0.038***

Abbreviations: ART Antiretroviral therapy; INSTI Integrase-strand-transfer-inhibitor; PI protease inhibitor.
p-value significance of *≤0.05.

186 HIV CLINICAL, COMORBID, AND SOCIAL DETERMINANTS OF HEALTH ARE LINKED WITH BRAIN AGING

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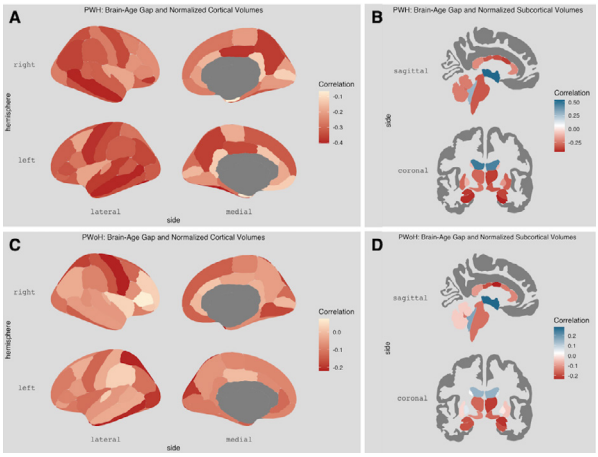
Background: Neuroimaging reveals brain changes linked with HIV infection and neurocognitive disorders. However, group-level differences between persons with HIV (PWH) and persons without HIV (PWoH) conceal substantial within-group heterogeneity in risk factor exposures. PWH experience elevated comorbidities such as cardiovascular disease and socioeconomic deprivation. However, the contribution of such factors to brain aging in PWH and PWoH remains to be quantified.
Methods: PWH (n=379; age=44.8±15.5 yr.; 78.1% biologically male; 68.6% African-American; 77.8% undetectable viral load [< 50 copies/mL]) and PWoH (n=259; age=38.3±17.1 yr.; 49.8% male; 56.4% A.A.) were clinically characterized and underwent 3-Tesla T1-weighted magnetic resonance imaging (MRI). DeepBrainNet, a publicly available machine learning algorithm, was applied to estimate brain-predicted age from MRI. The brain-age gap (BAG), defined as the difference between brain-predicted age and true chronological age, was modeled as a function of clinical, comorbid, and social factors for PWH and PWoH separately using linear regression and variable selection. To identify spatial patterns relevant to pathological aging, BAG values were correlated with regional brain volumes quantified with FreeSurfer v5.3.
Results: BAG was significantly elevated in PWH compared to PWoH (p=0.001). In PWH, BAG was positively associated with Framingham cardiovascular risk score (p=0.002), detectable viral load (p=0.006) and hepatitis C co-infection (p=0.006). After variable selection, the model for PWH retained Framingham score and hepatitis C, and added early life stress and area deprivation index, a socioeconomic measure combining geospatial data on housing, employment, education, and income. Educational attainment was linked with reduced BAG (p=0.016) for PWoH but not PWH, indicating a potential resilience factor. Elevated BAG was associated with reduced regional gray matter volumes and larger ventricles, with distinct spatial patterns by serostatus. PWH showed more negative BAG-volume associations in cortical regions such as precuneus and posterior cingulate gyrus, and subcortical structures including putamen, globus pallidus, and cerebellum (see **Figure**).
Conclusion: These findings confirm the hypothesis that comorbid and socioeconomic factors are associated with brain aging alongside clinical metrics such as viral load. A broadened clinical perspective on healthy aging with HIV may require increased focus on such non-traditional determinants of health. Regional correlations between brain-age gap (BAG) and cortical or subcortical volumes.



187 CHANGES TO MICROGLIAL GENOME STRUCTURE AND FUNCTION IN THE HIV-INFECTED HUMAN BRAIN

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Background: HIV infection of microglia in the central nervous system can lead to HIV associated neurocognitive disorder (HAND) and contributes to the formation of a potentially large reservoir, but the mechanisms of these processes remain poorly understood. Studies of genome organization and function in the HIV-infected brain are critical to aid in the development of HAND treatments and HIV cure strategies. Here we performed cell-type specific studies of 3D genome architecture, viral integration, and single nucleus transcriptomics in the HIV infected human brain with and without encephalitis.
Methods: Postmortem frontal cortex samples from the Manhattan HIV Brain Bank were processed for 10X Chromium single nucleus RNA-sequencing (snRNA-seq; n=3 HIV-, n=3 HIV+ without HIVE [HIV+], and n=7 HIV+ with HIVE [HIVE]). In situ Hi-C was performed on fixed Irf8+ microglial and NeuN+ neuronal nuclei sorted using fluorescence activated nuclei sorting (FANS; n=2 HIV-, n=2 HIVE, n=1 HIV+). Integration site sequencing (IS-seq) was performed on FANS isolated NeuN+ neuronal and NeuN- non-neuronal nuclei for a total of 27 samples (n= 6 HIV-, n= 18 HIV+, n= 7 HIVE).
Results: Reorganization of open/repressive (A/B) compartment structures in HIVE microglia encompassing 6.4% of the genome was linked to transcriptional activation of interferon (IFN) signaling and cell migratory pathways and was partially recapitulated by IFN-g stimulation of cultured microglia. In contrast, decreased expression and repressive compartmentalization of genes regulating neuronal health and signaling was seen in both HIVE and HIV+ microglia. IS-seq recovered 1,221 integration sites in the brain that displayed distinct genomic patterns as compared to peripheral lymphocyte integration and were enriched for chromosomal domains newly mobilized into a permissive chromatin environment in HIVE microglia. Viral transcription occurred in a subset of highly activated microglia comprising 0.003% of all nuclei in HIVE brain.
Conclusion: Our findings point to a disruption of microglia-neuronal interactions in the HIV infected brain and an interrelation of retroviral integration and expression with interferon-associated remodeling of the microglial 3D genome during progression to HIVE. Funded by R61DA048207, R01DA054526, and U24MH100931.

188 BRAIN AND BEHAVIOR PREDICTORS OF SARS-CoV-2 INFECTION AMONG PEOPLE WITH HIV

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Background: Recent findings from the UK Biobank revealed that healthy adults who later became infected with SARS-CoV-2 had lower brain volumes in regions involved in risk-taking behavior and olfaction compared to individuals who did not become infected. We examined if similar pre-existing differences in brain regions correspond to SARS-CoV-2 infection among people with HIV (PWH) receiving suppressive ART.
Methods: Participants included adult Thai MSM enrolled in the acute HIV (AHI) cohort (RV254/SEARCH010) in Bangkok, Thailand. Participants underwent 3T MRI and clinical assessments (i.e., HIV disease metrics, cognitive testing, and self-reported mood and substance use). ART initiation occurred within 5 days of the MRI (median=same day). Regional brain volumes were summed across hemispheres and corrected for head size. Brain volumes and clinical indices were compared between participants with laboratory confirmed SARS-CoV-2 and those without a diagnosis of SARS-CoV-2 following ART initiation. Machine learning was utilized to identify variables at the time of enrollment into the cohort that predicted subsequent SARS-CoV-2 infection status.
Results: 112 participants were included in the analysis. All study participants achieved viral suppression after ART and received SARS-CoV-2 vaccinations. Fifty-four participants became infected with SARS-CoV-2 during the observation period (median=79 weeks from ART initiation). Study participants who became infected with SARS-CoV-2 after ART had lower volumes at the time of enrollment in several subcortical brain regions with the most pronounced effect in the pallidum (p=.025). There were no associations between brain volumes and ratings of mood, demographics, or HIV disease indices. SARS-CoV-2 infection was two-fold higher among individuals who reported use of amyl nitrites (i.e., poppers) during "chemsex". Machine learning with repeated cross validation revealed that lower orbital and medial frontal lobe, anterior cingulate, pallidum, vermis, and olfactory volumes, worse motor function, and higher education collectively predicted co-infection status (average AUC of 85%).
Conclusion: Study findings point toward a risk phenotype for SARS-CoV-2 infection among PWH defined by pre-existing differences in brain volumes relevant to risk-taking behavior, emotion, and neuroHIV as well as behavioral factors such as inhalant use and lack of social distancing during "chemsex".
Table 1. Demographic and HIV disease indices.

	Full Sample	HIV + SARS-CoV-2	HIV	*p* value
Sample size	112 (100%)	54 (48%)	58 (52%)	n/a
Age, Mean (SD)	27.62 (6.38)	27.11 (5.80)	28.09 (6.89)	.421
CD4+ T-cell count, Median (IQR)	324 (248-457)	328 (272-506)	314 (233-417)	.180
CD8+ T-cell count, Median (IQR)	523 (325-831)	520 (342-785)	540 (313-970)	.852
CD4/CD8 T-cell Ratio, Median (IQR)	.64 (.35-1.05)	.68 (.42-1.11)	.61 (.33-1.03)	.381
Plasma Viral Load (log10), Median (IQR)	6.25 (5.44-6.85)	6.24 (5.34-6.85)	6.32 (5.44-6.94)	.691
Fiebig I-II, n (%)	32 (28.6%)	17 (53.1%)	15 (46.9%)	.511
Fiebig III-V, n (%)	80 (71.4%)	37 (46.3%)	43 (53.8%)	.511

189 NO CSF BIOMARKER EVIDENCE OF PERSISTING CNS INFECTION AFTER SARS-CoV-2 INFECTION

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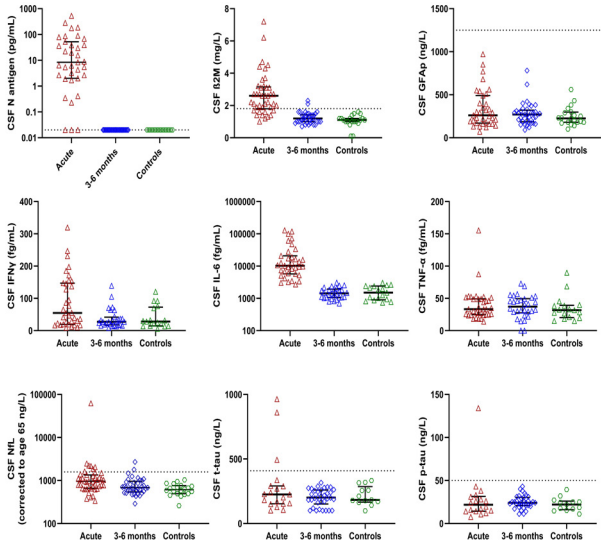
Background: Neurocognitive symptoms are common in acute as well as convalescent (post-acute sequelae of COVID-19 [PASC]) COVID-19, but mechanisms of CNS pathogenesis are unclear.
The aim of this study was to investigate cerebrospinal fluid (CSF) biomarker evidence of CNS infection, immune activation and neuronal injury in convalescent compared with acute infection.

Methods: We included 68 (35% female) patients ≥18 years with CSF sampled during acute (46), 3-6 months after (22) SARS-CoV-2 infection or both (17), and 20 (70% female) healthy controls from longitudinal studies. The 22 patients sampled only at 3-6 months were recruited in a PASC protocol. CSF N-Ag was analyzed using an ultrasensitive antigen capture immunoassay platform (S-PLEX SARS-CoV-2 N Kit, Meso Scale Diagnostics, LLC. Rockville, MD). Additional analyses included CSF β2-microglobulin (β2M)], IFN-γ, IL-6, TNF-α neurofilament light (NfL), and total and phosphorylated tau. Log-transformed CSF biomarkers were compared using ANOVA (Tukey post-hoc test).
Results: Patients sampled during acute infection had moderate (27) or severe (19) COVID-19. In patients sampled at 3-6 months, corresponding initial severity was 10 (mild), 14 (moderate), and 15 (severe). At 3-6 months, 31/39 patients reported neurocognitive symptoms; 8/17 patients also sampled during acute infection reported full recovery after 3-6 months. CSF biomarker results are shown in Figure 1. SARS-CoV-2 RNA was universally undetectable. N-Ag was detectable only during acute infection (32/35) but was undetectable in all follow up and control samples. Significantly higher CSF concentrations of β2M ($p < 0.0001$), IFN-γ ($p = 0.02$), IL-6 ($p < 0.0001$) and NfL ($p = 0.04$) were seen in acute compared to post-infection. Compared to controls, β2M ($p < .0001$), IL-6 ($p < 0.0001$) and NfL ($p = 0.005$) were significantly higher in acute infection. No biomarker differences were seen post-infection compared with controls. No differences were seen in CSF GFAp, t-tau or p-tau.
Conclusion: We found no evidence of residual infection (RNA, N-Ag), inflammation (β2M, IL-6, IFN-γ, TNF-α), astrocyte activity (GFAp) or neuronal injury (NfL, tau) 3-6 months after initial COVID-19, while significantly higher concentrations of several markers were found during acute infection, suggesting that PASC may be a consequence of earlier injury rather than active CNS damage. CSF β2M, IL-6, IFN-γ and NfL were significantly lower after 3-6 months than during acute COVID-19 and not different from healthy controls.
Figure 1. CSF Biomarker Concentrations



190 CSF & PLASMA SOLUBLE BIOMARKERS IN NEURO-PASC: PRELIMINARY RESULTS FROM COVID MIND

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Background: It is unknown whether individuals with neurological post-acute sequelae of COVID-19 (NeuroPASC) display altered levels of neuroimmune activity or neuronal injury.
Methods: Participants with new or worsened neurologic symptoms at least 3 months after laboratory-confirmed COVID-19 were enrolled in The COVID Mind Study at Yale. "Never COVID" controls (no history of COVID-19; nucleocapsid (N) antibody negative) were pre-pandemic or prospectively enrolled volunteers. CSF and plasma were assessed for neopterin and for IL-1β, IL-1RA, IL-2, IL-4, IL-5, IL-6, IL-8, IL-10, IL-12p40, IL-12p70, IL-13, MCP-1, TNFα by bead-based multiplex assay; and for anti-SARS-CoV-2 N antibodies by Luminex-based multiplex assay in technical replicate, normalized against bovine serum albumin conjugated beads. Plasma concentrations of D-dimer, C-reactive protein, neurofilament light chain (NFL), and glial fibrillary acid protein (GFAP) were measured using high-sensitivity immunoassays. Group comparisons used non-parametric tests.
Results: NeuroPASC participants (n=38) were studied 329 (median) days (range 81-742) after first positive test for acute COVID-19. Cognitive impairment (84%) and fatigue (82%) were the most frequent post-COVID symptoms. NeuroPASC and controls (n=22) were median 49 vs 52 yrs old ($p = 0.9$), 74% vs 32% female ($p < 0.001$), 76% vs 23% white race ($p < 0.001$), and 6% vs 57% smokers ($p < 0.001$). CSF white blood cells/mL, CSF protein, and serum:CSF albumin ratio were normal in both groups.
CSF TNFα (0.66 vs 0.55 pg/ul) and plasma IL12p40 were higher (103.3 vs 42.7); and MCP-1 (503 vs 697 pg/ul) and IL-6 (1.32 vs 1.84 pg/ul; $p < 0.05$ for IL-6) were lower in NeuroPASC vs controls ($p < 0.05$); but none of these differences were significant after adjusting for multiple comparisons. Plasma GFAP was elevated in NeuroPASC vs controls (54.4 vs 42.3 pg/ml; adjusted $p < 0.03$). There were no differences in the other biomarkers tested. 10/31 and 7/31 NeuroPASC had anti-N antibodies in CSF and plasma, respectively.
Conclusion: When comparing NeuroPASC to "never COVID" controls, we found no evidence of neuroinflammation (normal CSF cell count, inflammatory cytokines) or blood-brain barrier dysfunction (normal albumin ratio), and no support for ongoing neuronal damage (normal plasma NFL). Future studies should include better gender and race matched controls and should explore the significance of a persistent CNS humoral immune response to SARS-CoV-2 and elevated plasma GFAP after COVID-19.
Figure 1

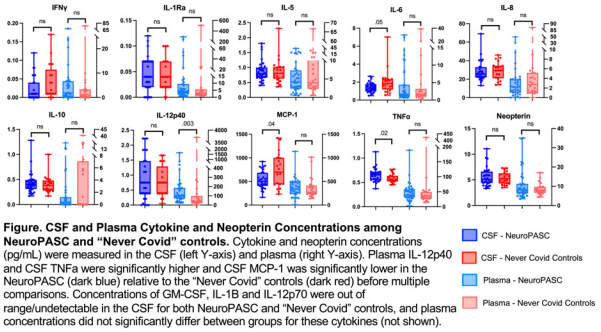

Figure. CSF and Plasma Cytokine and Neopterin Concentrations among NeuroPASC and "Never Covid" controls. Cytokine and neopterin concentrations (pg/mL) were measured in the CSF (left Y-axis) and plasma (right Y-axis). Plasma IL-12p40 and CSF TNFα were significantly higher and CSF MCP-1 was significantly lower in the NeuroPASC (dark blue) relative to the "Never Covid" controls (dark red) before multiple comparisons. Concentrations of GM-CSF, IL-1B and IL-12p70 were out of range/undetectable in the CSF for both NeuroPASC and "Never Covid" controls, and plasma concentrations did not significantly differ between groups for these cytokines (not shown).

191 SOLAR 12-MONTH RESULTS: RANDOMIZED SWITCH TRIAL OF CAB+RPV LA VS ORAL B/FTC/TAF

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Background: Cabotegravir (CAB)+rilpivirine (RPV) administered monthly or Q2M is a complete long-acting (LA) regimen for maintaining HIV-1 suppression. We present results from SOLAR, the first randomized comparison of CAB+RPV LA Q2M vs. continued daily oral bictegravir/emtricitabine/tenofovir alafenamide (B/FTC/TAF).
Methods: SOLAR (NCT04542070) is a Phase 3b, randomized (2:1), open-label, multicenter, noninferiority (NI) study assessing switching virologically suppressed adults to CAB+RPV LA (with/without oral lead-in [OLI]) Q2M vs. continuing B/FTC/TAF. The primary analysis was based on the pre-specified modified intention-to-treat exposed (mITT-E) population (n=11 excluded from the ITT-E for protocol deviation). The primary endpoint was the proportion with plasma HIV-1 RNA ≥50 c/mL (FDA Snapshot, 4% NI margin) at M11 (LA without OLI)/M12 (LA with OLI and B/FTC/TAF). Other endpoints were the proportion with plasma HIV-1 RNA < 50 c/mL (FDA Snapshot, –12% NI margin), incidence of confirmed virologic failure (CVF; 2 consecutive HIV-1 RNA ≥200 c/mL), safety, tolerability, treatment satisfaction (HIV Treatment Satisfaction Questionnaire status version [HIVTSQs]), and preference.

Results: Of 670 participants (mITT-E), 447 switched to LA (n=173 [39%] with OLI; n=274 [61%] without OLI) and 223 (33%) continued B/FTC/TAF. Baseline (BL) characteristics were similar between arms; 18% were female sex at birth, 21% were Black, median age (range) was 37 years (18–74). At M11/12, noninferior efficacy of LA vs. B/FTC/TAF was demonstrated for the proportion with HIV-1 RNA ≥50 c/mL (**Table**). 2 (0.4%) and 3 (0.6%) participants receiving LA had CVF in the mITT-E and ITT-E populations, respectively; all developed resistance at failure. Excluding injection site reactions (ISRs), AEs and serious AEs were comparable between arms, although drug-related AEs were more frequent in the LA arm (20% vs. <1%). More LA arm participants had AEs leading to withdrawal (6% vs. <1%). Most ISRs were Grade 1 or 2 (98%). Mean adjusted HIVTSQs scores improved significantly (p< 0.001) for LA (+3.36) vs. B/FTC/TAF (–1.59) participants from BL (LA, 57.88; B/FTC/TAF, 58.38; descriptive) to M11/12. Most (90%, n=382/425) participants preferred LA vs. oral therapy (5%, n=21/425) at M11/12 or withdrawal.

Conclusion: At M11/12, CAB+RPV LA Q2M demonstrated noninferior virologic efficacy vs. B/FTC/TAF. Switching to CAB+RPV LA from B/FTC/TAF was efficacious, well tolerated, improved treatment satisfaction, and was preferred by most participants.

SOLAR Key Efficacy and Safety Outcomes at Month 12

Outcome	mITT-E* Q2M (n=447)	mITT-E* B/FTC/TAF (n=223)	ITT-E Q2M (n=454)	ITT-E B/FTC/TAF (n=227)
Primary endpoint† HIV-1 RNA ≥50 c/mL (FDA Snapshot), n (%)	5 (1)	1 (<1)	6 (1)	1 (<1)
Adjusted difference (95% CI)	0.7 (–0.7, 2.0)		0.9 (–0.5, 2.2)	
Data in window not below 50 c/mL	3 (<1)	1 (<1)	3 (<1)	1 (<1)
Discontinued for lack of efficacy	1 (<1)	0	2 (<1)	0
Discontinued for other reason while not below 50 c/mL	1 (<1)	0	1 (<1)	0
No virologic data, n (%)	39 (9)	15 (7)	42 (9)	15 (7)
Discontinued due to AE or death	13 (3)	1 (<1)	14 (3)	1 (<1)
Discontinued for other reason	24 (5)	13 (6)	26 (6)	13 (6)
On study but missing data in window	2 (<1)	1 (<1)	2 (<1)	1 (<1)
Key secondary efficacy endpoint‡ HIV-1 RNA <50 c/mL (FDA Snapshot), n (%)	403 (90)	207 (93)	406 (89)	211 (93)
Adjusted difference (95% CI)	–2.7 (–7.0, 1.7)		–3.5 (–7.9, 0.9)	
CVF, n (%)	2 (<1)	0	3‡ (<1%)	0

Safety summary§

Outcome	Q2M (n=454)	B/FTC/TAF (n=227)
All AEs, n (%)	405 (89)	172 (76)
Excluding ISRs	349 (77)	172 (76)
Any Grade 3–5	55 (12)	26 (11)
Grade 3–5 excluding ISRs	42 (9)	26 (11)
Drug-related AEs, n (%)	327 (72)	2 (<1)
Excluding ISRs	90 (20)	2 (<1)
Any Grade 3–5	22 (5)	0
Grade 3–5 excluding ISRs	7 (2)	0
Serious AEs, n (%)	21 (5)	15 (7)
Drug-related	4 (<1)	0
AEs leading to discontinuation, n (%)	25 (6)	2 (<1)
Discontinued for ISR-related reasons,¶ n (%)	11 (2)	NA
Number of injections	5952	NA
Number of ISR events	1915	NA

*After Month 6, due to critical findings related to significant and persistent non-compliance to protocol requirements, the primary analysis population was modified to exclude all 11 participants from one study site.
†Per-protocol analyses were consistent with mITT-E.
‡Two participants in the mITT-E population had CVF. An additional participant with CVF was in the ITT-E population. All three participants had emergent RPV and/or INI RAMs while on LA therapy.
§Maintenance Phase; safety population (n=681; includes the 11 participants excluded from the mITT-E population).
¶Includes participants who discontinued due to ISR AEs, and an additional participant who withdrew from the study citing injection intolerability. This also includes one participant who was excluded from the primary analysis (mITT-E) population.
AE, adverse event; B/FTC/TAF, bictegravir/emtricitabine/tenofovir alafenamide; CI, confidence interval; CVF, confirmed virologic failure; FDA, U.S. Food and Drug Administration; INI, integrase inhibitor; ISR, injection site reaction; ITT-E, intention-to-treat exposed; LA, long-acting; mITT-E, modified intention-to-treat exposed; NA, not applicable; Q2M, every 2 months; RAM, resistance-associated mutation; RPV, rilpivirine.

192 EFFECT OF ISLATRAVIR ON TOTAL LYMPHOCYTE AND LYMPHOCYTE SUBSET COUNTS

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Background: Islatravir (ISL) is a nucleoside reverse transcriptase translocation inhibitor (NRTTI) being studied for HIV-1 treatment and prevention. Decreases in total lymphocyte counts and CD4+ T-cell counts were observed in several ISL clinical trials. We conducted comprehensive lymphocyte and lymphocyte subset analyses in Phase 2 and Phase 3 clinical trials evaluating oral ISL with doravirine (DOR) once daily (QD), oral ISL with MK-8507 once weekly (QW), or oral ISL alone once monthly (QM).

Methods: These analyses included 4 studies of ISL for HIV-1 treatment: one Phase 2 dose-ranging study of ISL 0.25, 0.75, and 2.25 mg QD with DOR 100 mg (±3TC) in treatment-naïve adults (P011), one Phase 2 dose-ranging study of ISL 20 mg with MK-8507 QW in virologically suppressed adults (P013), and two Phase 3 switch studies of DOR/ISL 100 mg/0.75 mg QD in virologically suppressed adults (P017 and P018); as well as 3 studies of ISL for pre-exposure prophylaxis (PrEP): one Phase 2 dose-ranging study of ISL 60 mg and 120 mg QM (P016) and two Phase 3 studies of ISL 60 mg QM (P022 and P024). For each study, the mean percent change from baseline in total lymphocyte counts and lymphocyte subset counts (CD4+ and CD8+ T-cells, B-cells, and NK-cells) were calculated by treatment group.

Results: In treatment-naïve participants (P011), increases in total lymphocyte counts (Table) and lymphocyte subset counts were similar for the ISL 0.25-mg group and the DOR/3TC/TDF group and were more favorable than changes observed in the ISL 0.75-mg or 2.25-mg groups. In participants switched to DOR/ISL 100 mg/0.75 mg QD (P017 and P018), decreases in total lymphocyte counts and lymphocyte subset counts reached a nadir on average between Weeks 48 and 72. In participants switched to ISL 20 mg + MK-8507 100, 200, or 400 mg QW (P013) and participants receiving ISL 60 or 120 mg QM for PrEP (P016, P022, and P024), decreases in total lymphocyte counts (Table) and lymphocyte subset counts were greater than those in participants receiving DOR/ISL 100 mg/0.75 mg QD (P017 and P018).

Conclusion: The magnitude of decreases in total lymphocyte counts and lymphocyte subset counts observed with ISL is exposure-dependent, with the 0.25-mg QD dose having lymphocyte changes comparable to standard of care antiretroviral therapy.

Total Lymphocyte Counts, Mean Percent Change from Baseline (95% CI) in Phase 2 and Phase 3 Clinical Trials of Oral Islatravir

HIV-1 Treatment in Adults			Pre-exposure Prophylaxis in Adults	
Treatment-naïve	Virologically suppressed		At risk for HIV-1 acquisition	
ISL+DOR 100mg QD	DOR/ISL 0.75mg QD	ISL 20mg + 8507 QW	ISL 60mg QM	ISL 60mg QM
Phase 2 (P011)	Phase 3 (P017, P018)	Phase 2 (P013)	Phase 2 (P016)	Phase 3 (P022, P024)
Week 72 (prior to 0.75 mg dose conversion)	Week 84	Week 24	Week 24	Month 3
DOR/3TC/TDF (n=22): +15.9% (2.0, 29.9)	P017 G1*: DOR/ISL (n=266): -6.3% (-9.3, -3.3)	BIC/FTC/TAF (n=34): +2.6% (-4.2, 9.5)	Placebo (n=42): +4.4% (-3.6, 12.5)	P022: FTC/TDF (n=228): -9.8% (-12.8, -6.7)
ISL 0.25mg (n=19): +20.5% (4.3, 36.6)	P018: BIC/FTC/TAF (n=295): +6.4% (3.6, 9.1)	ISL + 8507 100mg (n=27): -15.1% (-23.0, -7.3)	ISL 60mg QM (n=83): -21.3% (-25.7, -17.0)	ISL 60mg QM (n=219): -21.3% (-23.8, -18.7)
ISL 0.75mg (n=19) -0.4% (-14.9, 14.1)	DOR/ISL (n=296): -6.3% (-8.9, -3.7)	ISL+ 8507 200mg (n=27): -26.7% (-36.0, -17.4)		P024: FTC/TDF or FTC/TAF (n=119): -3.1% (-7.3, 1.1)
ISL 2.25mg (n=16) -15.9% (-31.9, 0.1)		ISL+ 8507 400mg (n=25): -30.9% (-39.6, -22.2)		ISL 60mg QM (n=231): -7.0% (-10.1, -4.0)

BIC/FTC/TAF=bictegravir/emtricitabine/tenofovir alafenamide; DOR/ISL=doravirine/islatravir; FTC/TDF=emtricitabine/tenofovir disoproxil fumarate. *G1=Group 1; Group 2 (Baseline ART) was censored from this analysis because participants switched to DOR/ISL at Week 48.

193 LENACAPAVIR WITH bNAbs GS-5423 AND GS-2872 DOSED EVERY 6 MONTHS IN PEOPLE WITH HIV

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Background: Lenacapavir (LEN) is a first-in-class HIV-1 capsid inhibitor in development for long-acting HIV treatment and prevention. GS-5423 and GS-2872 are broadly neutralizing antibodies (bNAbs). GS-5423 is derived from 3BNC117 and targets the CD4 binding site of HIV-1 glycoprotein (gp) 120; GS-2872 is derived from 10-1074 and binds to the V3 loop of gp120. Both bNAbs were modified to extend their half-life to allow less frequent dosing. We conducted a phase 1b randomized clinical trial to evaluate the safety and efficacy of LEN + GS-5423 + GS-2872 dosed every 6 months in people with HIV.

Methods: Participants were adults living with HIV virologically-suppressed ≥ 2 years (HIV-1 RNA < 50 copies/mL) on ART, sensitive to both bNAbs by HIV proviral DNA phenotype (PhenoSense mAb IC_{90} ≤2ug/mL, Monogram Biosciences), a CD4 nadir ≥350, and CD4 count ≥500 at study entry. Participants were randomized 1:1 to two active treatment groups consisting of LEN (927 mg subcutaneous after oral loading) + GS-5423 (30mg/kg IV) + GS-2872 (10 mg/kg in Group 1 and 30 mg/kg in Group 2 IV). Participants were monitored clinically with plasma HIV-1 RNA every four weeks until the primary endpoint at Week 26. The primary endpoint was safety; secondary endpoints included virologic outcomes by FDA Snapshot analysis.

Results: Of 124 screened participants, 55 were sensitive to both bNAbs, 21 were randomized, and 20 received the complete study regimen. The median age was 44 yrs (IQR 34, 51); 14% were female; 14% Black, 14% Asian, 33% Hispanic/Latinx; median CD4 count was 909 (IQR 687, 1270). There were no serious adverse events (AEs), no grade 4 or 5 AEs, and no AEs leading to study drug discontinuation. Two participants had grade 3 AEs: one with injection site cellulitis and one with injection site erythema at the site of LEN injection.

One participant in Group 1 had a confirmed HIV RNA ≥ 50 copies/mL (155 copies/mL, confirmed 524 copies/mL) at Week 16 and resuppressed with reinitiation of baseline ART; one participant in Group 2 withdrew consent at Week 12 (with HIV-1 RNA < 50 copies/mL). 18/20 (90%) participants had HIV-1 RNA < 50 copies/mL at Week 26. (Table 1).

Conclusion: The combination of LEN + GS-5423 + GS-2872 was well-tolerated with high efficacy for 6 months in selected virologically-suppressed persons living with HIV. These results provide a proof-of-concept that this combination could provide long-acting treatment for HIV with twice-yearly dosing.

Table 1: Efficacy as determined by the US FDA-defined Snapshot Algorithm at Week 26

Table 1: Efficacy as determined by the US FDA-defined Snapshot Algorithm at Week 26

	LEN + GS-5423 + GS-2872 10 mg/kg	LEN + GS-5423 + GS-2872 30 mg/kg
	(N=10)	(N=10)
HIV-1 RNA ≥50 copies/mL, N (% [95% CI])	1^ (10%, [0.3%, 44.5%])	0
HIV-1 RNA <50 copies/mL, N (% [95% CI])	9 (90%, [55.5%, 99.7%])	9 (90%, [55.5%, 99.7%])
Discontinued Study Drug Due to Other Reasons[$] and Last Available HIV-1 RNA <50 copies/mL	0	1 (10%)*

^ Resistance tests pending
*Withdrew from the study after week 12
[$] Reasons other than AE/Death or lack of efficacy

194 TARGET3D: GLECAPREVIR-PIBRENTASVIR FOR FOUR WEEKS IN PEOPLE WITH RECENT HCV INFECTION

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Background: Glecaprevir-pibrentasvir for eight weeks is recommended for treatment of chronic HCV infection and in recent infection has been shown to be highly effective as a six-week regimen. Shortened treatment duration may assist in elimination efforts among key populations. The aim of this analysis was to evaluate the efficacy of glecaprevir-pibrentasvir for four weeks in people with recent HCV infection.

Methods: In this open-label single-arm multi-centre international pilot study, adults with recent HCV infection (duration of infection < 12 months) received glecaprevir-pibrentasvir 300mg-120mg daily for four weeks. Recent primary infection was defined by first positive anti-HCV antibody and/or HCV RNA within six months of enrolment and either acute clinical hepatitis within the past 12 months (symptomatic seroconversion illness or ALT > 10 X ULN), or anti HCV antibody seroconversion within 18 months. Recent re-infection was defined as a new positive HCV RNA within six months of enrolment and evidence of prior spontaneous or treatment induced clearance. The primary endpoint was sustained virological response at 12 weeks post-treatment (SVR12).

Results: Twenty three participants (96% men, median age 46 years) received treatment, of whom 70% (n=16) had HIV, 57% (n=13) had ever injected drugs, and 35% (n=8) had recent reinfection. The majority had HCV genotype 1 infection (74%) followed by genotypes 3 (9%), 4 (9%) and 2 (4%). At baseline median estimated duration of infection was 7 weeks (IQR 11,29) and median HCV RNA was 5.8 log 10 IU/ml (range 4, 7.5). Virological suppression at week two and week four (end of treatment) was seen in 65% (15/23) and 87% (20/23) respectively. SVR12 in the intent-to-treat and per-protocol populations was achieved in 78% (18/23; 95% CI 56%,93%) and 82% (18/22; 95% CI 60%,95%) respectively. There were four cases of virological failure (all confirmed as relapse by sequencing), 3 genotype 1 and 1 genotype 4d. Median baseline HCV RNA in relapsers was 7.3 $\log_{10}$ IU/ml. Adherence was suboptimal in one patient. Three of the four relapse cases received re-treatment with 12 weeks sofosbuvir-velpatasvir or grazoprevir-elbasvir (outside of the study protocol; SVR, n=2, lost to follow-up, n=1). There were no treatment-related serious adverse events.

Conclusion: Glecaprevir-pibrentasvir for four weeks was safe and well tolerated among people with acute and recent HCV infection, but efficacy was lower than seen with longer treatment duration (>= 6 weeks).

195 LOW CONCENTRATIONS OF LONG-ACTING CABOTEGRAVIR AND RILPIVIRINE IN PATIENTS WITH HIV

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Background: Low cabotegravir and rilpivirine trough concentrations have been associated with virological failure in patients with HIV switching to long-acting cabotegravir and rilpivirine treatment in clinical trials. We wished to assess drug trough concentrations in patients initiating long-acting therapy.

Methods: Starting in March 2022, we prospectively monitored all patients initiating long-acting cabotegravir and rilpivirine in two University Hospitals in Paris. To be eligible, patients had to have a plasma HIV RNA < 50 copies/ml for at least 6 months, no major InSTI or NNRTI resistance-associated mutations and immunity against HBV infection. Intramuscular injections of long-acting cabotegravir 600 mg and rilpivirine 900 mg were administered at the first visit, 4 and 12 weeks later. These first three injections were administered in the hospital as recommended, with monitoring of plasma HIV RNA and trough plasma concentrations of cabotegravir and rilpivirine.

Results: Forty-nine patients were enrolled from March to August 2022, 89.8% male, median age 30.3 years. They were mostly men who have sex with men (73.5%), heterosexuals (22.4%), or IV drug user (4.1%) and 6.1% had BMI ≥ 30 kg/m^2. Median time since HIV diagnosis was 11.4 years. HIV-1 subtypes were B (61.2%), C (4.1%), F (2%), CRF02_AG (16.3%), or other recombinants (14.1%). Median CD4 T-cell count was 680/mm^3. With a median time of follow-up of 3.9 months, all patients received two injections, and 38 (84.4%) the Week-12 injection. Median cabotegravir concentration was 972.5 ng/mL (IQR: 719.2;1449.2) at Week 4, and 629.5 ng/mL (IQR: 467.8;920.0) at Week 12, with respectively 61.2% and 81.1% of patients below the 1120 ng/mL threshold. Median rilpivirine concentration was 49.6 ng/mL (IQR: 28.6;65.5) at Week 4, and 43.3 ng/mL (IQR: 31.6;53.6) at Week 12, with respectively 28.6% and 27% of patients below the 32 ng/mL threshold. Virological failure without resistance mutation occurred in one patient at Week 4 (plasma HIV RNA: 2820 c/mL) with cabotegravir and rilpivirine concentrations at 701.3 ng/mL and 27.7 ng/mL respectively at Week 4. This patient had no other risk factor for virological failure.

Conclusion: A significant proportion of patients starting long-acting cabotegravir and rilpivirine treatment have low trough concentrations that may increase the risk of virological failure and require careful monitoring.

196 SWITCH TO DOR/ISL (100/0.75MG) QD: WEEK 48 RESULTS FROM AN OPEN-LABEL PHASE 3 TRIAL

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Background: Doravirine (DOR), an approved NNRTI, and Islatravir (ISL), an investigational nucleoside reverse transcriptase translocation inhibitor (NRTTI), have complementary mechanisms of action and resistance profiles. We report week 48 results from a phase 3, open-label, non-inferiority trial (P017, NCT04223778) evaluating a switch from oral combination ART to DOR/ISL (100/0.75mg), a once-daily single-tablet regimen.

Methods: Virologically suppressed adults on any stable oral 2- or 3-drug ART for ≥3 months with no history of treatment failure or virologic resistance to DOR were randomized (1:1) to switch to DOR/ISL or continue baseline ART (bART), stratified by bART regimen (PI-based, InSTI-based, Other). The primary endpoint was % of participants (pts) with HIV-1 RNA ≥50 c/mL at week 48 (FDA Snapshot; non-inferiority margin 4%). Resistance was assessed in pts with

clinically significant confirmed viremia (CSCV; 2 consecutive measures of HIV-1 RNA ≥200 c/mL).

Results: 672 pts were randomized and treated with open-label DOR/ISL (n=336) or bART (n=336); 37% were female, 27% Black, mean age 45.5 (±11.7) years. bART was PI-based in 14%, InSTI-based in 52%, and Other (mainly NNRTI-based) in 34%; mean duration before study 39.4 months. At week 48, 0% on DOR/ISL and 1.5% on bART had HIV-1 RNA ≥50 c/mL (difference -1.5; 95%CI -3.4, -0.3), while 95.2% and 94.3% respectively had HIV-1 RNA < 50 c/mL (Table). CSCV occurred in 3 pts (1%) on bART (1 InSTI-based; 2 NNRTI-based), all had resistance to ≥1 component of their regimen. Mean change from baseline in CD4+ T-cell count at week 48 was -30.3 and +38.8 cells/mm^3 for DOR/ISL and bART, respectively (difference 66.7, 95%CI -95.8, -37.7). Total lymphocyte count was also significantly reduced in the DOR/ISL group (Table). Rates of drug-related adverse events (AEs) (19.6%, 8.9%) and discontinuation due to AEs (2.1%, 0.3%) were higher in the DOR/ISL group. Rates of Grade 3-4 AEs (6.8%, 7.4%) and serious AEs (4.2%, 3.9%) were similar between groups. One death occurred (in bART group) due to motor vehicle accident. Infection rates were comparable between treatment groups (33.6% each) and no CDC AIDS-defining Category C events occurred.

Conclusion: Switching to DOR/ISL (100/0.75mg) was non-inferior to continuing bART for maintaining viral suppression at week 48 and was generally well tolerated. No virologic failure was observed with DOR/ISL. Decreases in CD4+ T-cells and total lymphocytes with DOR/ISL were not associated with differences in infection-related AEs.

Table. Selected Efficacy & Safety Outcomes, DOR/ISL (100/0.75mg) P017

	DOR/ISL 100/0.75mg	Baseline ART
Week 48 Virologic Outcomes, n (%)	N=336	N=336
HIV-1 RNA ≥ 50 copies/mL	0 (0.0)	5 (1.5)
HIV-1 RNA < 50 copies/mL	320 (95.2)	317 (94.3)
No virologic data in window	16 (4.8)	14 (4.2)
CD4+ T-cell Count (cells/mm^3)[a]	N=313	N=311
Baseline mean	707.6	692.7
Week 48 mean	677.3	731.5
Week 48 mean change (95% CI)	-30.3 (-51.8, -8.7)	38.8 (17.4, 60.3)
Total lymphocyte count (10^9/L)[a]	N=297	N=302
Baseline mean	1.97	1.92
Week 48 mean	1.71	1.94
Week 48 mean change (95% CI)	-0.26 (-0.31, -0.20)	0.01 (-0.04, 0.07)
Week 48 mean % change (95% CI)	-10.7% (-13.3, -8.0)	2.3% (-0.4, 4.9)

[a] Data as Observed approach. The within-group 95% CIs were calculated based on the t-distribution.

197 SWITCH TO DOR/ISL (100/0.75MG) QD FROM B/F/TAF: WEEK 48 RESULTS FROM A PHASE 3 TRIAL

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Background: Doravirine (DOR), an approved NNRTI, and islatravir (ISL), an investigational nucleoside reverse transcriptase translocation inhibitor (NRTTI), have complementary mechanisms of action and resistance profiles. We report Week 48 results from a phase 3, non-inferiority trial (NCT04223791) evaluating a switch from bictegravir/emtricitabine/tenofovir alafenamide (B/F/TAF) to DOR/ISL (100/0.75mg), a once-daily single tablet regimen.

Methods: Adults with HIV-1 RNA <50 c/mL for ≥3 months on B/F/TAF without history of treatment failure were randomized 1:1 to switch to DOR/ISL or continue B/F/TAF in this double-blind, active-controlled study. The primary efficacy endpoint was % of participants with HIV-1 RNA ≥50 c/mL at Week 48 (FDA snapshot; non-inferiority margin 4%). Resistance was assessed for clinically significant confirmed viremia (CSCV, 2 consecutive HIV-1 RNA ≥200 c/mL).

Results: 643 participants were randomized; 641 received at least 1 dose (322 switched to DOR/ISL; 319 continued B/F/TAF). Mean age of participants was 47.8 (±12.2) years, with 72% male at birth, 75% White, 18% Black/African American, and 4% Asian. At Week 48, 2 participants (0.6%) on DOR/ISL and 1 (0.3%) on B/F/TAF had HIV-1 RNA ≥50 c/mL (difference 0.3, 95%CI -1.2, 2.0), demonstrating non-inferiority. HIV-1 RNA was < 50 c/mL in 93.8% of participants on DOR/ISL and 94.4% of participants on B/F/TAF (Table). One DOR/ISL participant had CSCV at Week 12; ISL plasma concentration was undetectable, and no resistance mutations were identified. Mean change in CD4+ T-cell count was -19.7 and 40.5 (difference -68.1, 95%CI -94.8, -41.4) cells/mm^3, respectively. Total lymphocyte count was also reduced in the DOR/ISL group (Table). Rates of AEs (71.1%, 74.6%) and drug-related AEs (9.9%, 11.9%) were similar between groups, with low rates of discontinuation due to AEs (both 2.5%). The most common AE in both groups was headache (7.8%, 7.2%). Infection rates were comparable between treatment groups (31.4%, 30.7%) and there was 1 CDC AIDS-Defining Category C event in each group (esophageal candidiasis in DOR/ISL, recurrent Kaposi sarcoma in B/F/TAF).

Conclusion: Switching to DOR/ISL (100/0.75mg) was non-inferior to continuing B/F/TAF for maintaining viral suppression through Week 48 with an AE profile comparable to B/F/TAF. No treatment-emergent resistance was detected in the DOR/ISL group. Observed decreases in CD4+ T-cells and total lymphocytes on DOR/ISL were not associated with differences in infection-related AEs.

Table. Selected Efficacy and Safety Outcomes, DOR/ISL (100/0.75mg) in P018

	DOR/ISL (100/0.75mg)	B/F/TAF
Week 48 Virologic Outcomes, n (%)	n=322	n=319
HIV-1 RNA ≥50 copies per mL	2 (0.6)	1 (0.3)
HIV-1 RNA <50 copies per mL	302 (93.8)	301 (94.4)
No virologic data in window	18 (5.6)	17 (5.3)
CD4+ T-cell Count (cells/mm^3)[a]	n=301	n=298
Baseline mean	680.4	720.7
Mean at week 48	660.7	761.2
Mean change from baseline (95% CI)	-19.7 (-39.8, 0.5)	40.5 (20.7, 60.4)
Lymphocyte Count (x 10^9/L)[a]	n=301	n=298
Baseline mean	1.90	1.98
Mean at week 48	1.70	2.00
Mean change from baseline (95% CI)	-0.20 (-0.25, -0.15)	0.02 (-0.03, 0.07)
Mean percent change from baseline (95% CI)	-8.4 (-11.0, -5.8)	3.5 (0.7, 6.2)

[a]Data as observed approach. The within-group 95% CIs were calculated based on the t-distribution.
CI=confidence interval; B/F/TAF=bictegravir/emtricitabine/tenofovir alafenamide; DOR/ISL=doravirine/islatravir.

198 D2EFT: DOLUTEGRAVIR AND DARUNAVIR EVALUATION IN ADULTS FAILING FIRST-LINE HIV THERAPY

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Background: Randomised comparative data on efficacy and safety of second-line antiretroviral (ARV) regimens, after failure of non-nucleoside reverse transcriptase inhibitors (NNRTIs) across diverse geographical settings are limited.

Methods: D^{2}EFT is an international randomised open-label trial comparing dolutegravir (DTG) with ritonavir boosted darunavir (DRV/r) versus DTG with fixed tenofovir and lamivudine or emtricitabine (TDF/XTC) versus standard of care (SOC: DRV/r+2NRTIs with a rotation of nucleosides or in adaptation to HIV genotyping) in adults living with HIV-1 whose first-line NNRTI therapy has failed. The study initially compared DTG+DRV/r vs SOC (stage 1) but later added a third arm (DTG+TDF/XTC, stage 2). Study was designed to show non-inferiority against SOC in terms of HIV-RNA< 50c/mL at 48 weeks using a delta=12%. Primary outcome data are presented as modified intent to treat analysis including all available data.

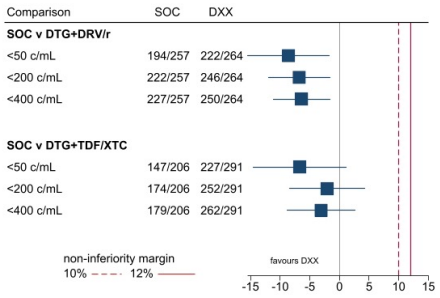
Results: 831 participants from 14 countries across Asia, Africa and Latin America, were randomised: Stage 1 DTG+DRV/r (n=56) vs SOC (n=53); Stage 2 DTG+DRV/r (n=216) vs SOC (n=210) vs DTG+TDF/XTC (n=296). Median age was 55 years and 54% were female. Median CD4 was 206 cells/mm^3 and median HIV-RNA was 4.2log$_{10}$c/ml. First-line failing regimen was efavirenz based in 85%. At 48 weeks the percentage with HIV-RNA< 50c/ml in Stage 1 was 75.4% SOC vs 84.1% DTG+DRV/r; in Stage 2: 71.4% SOC, 84.7% DTG+DRV/r, 78.0% DTG+TDF/XTC. Compared to SOC, the % difference in HIV-RNA < 50c/ml was -8.6% (95%

confidence interval; -15.5, -1.7, p=0.02) for DTG+DRV/r, and -6.7 (-14.4, 1.2, p=0.09) for DTG+TDF/XTC (Figure 1). 143/169 (85%) of virological failure was due to rebound.

Mean CD4 gain to week 48 was significantly greater in both DTG+DRV/r (56.0 cells/mm^3 (26.5, 85.5) p< 0.001) and DTG+TDF/XTC (39.9 cells/mm^3 (9.6, 70.2) p=0.01) compared to SOC. 14 deaths (none treatment related) and 97 SAEs (14 possibly treatment related) occurred. 35 pregnancies (24 deliveries) occurred with no congenital defects. Compared to SOC, mean weight gain was greater in both DTG+DRV/r 2.7kg (1.5, 3.8kg, p< 0.001) and DTG+TDF/XTC 1.7kg (0.5, 2.9kg, p=0.006) arms.

Conclusion: In failing NNRTI-based first-line ARV, a switch to either DTG+DRV/r or DTG+TDF/XTC, without universal access to genotyping, was non-inferior in achieving viral suppression compared to DRV/r+2NRTIs, with DTG+DRV/r also achieving superiority.

Undetectable HIV RNA at week 48 by randomised treatment arm



199 HIV RECENCY TESTING WITH INDEX TESTING CAN IDENTIFY NEW INFECTIONS EARLIER IN RWANDA

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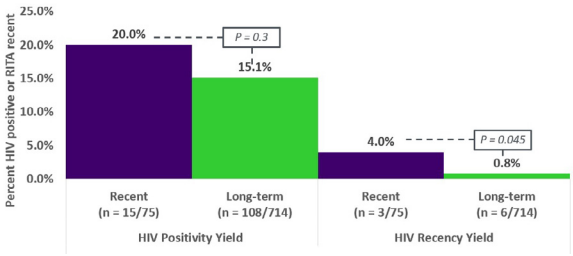
Background: In 2018, Rwanda implemented HIV recency testing as part of active case surveillance and index testing to inform prevention strategies. Recency testing can shed light on transmission dynamics by helping to distinguish recent and long-term (LT) infections among newly diagnosed people. We examined yields of HIV positivity and HIV recency among sexual partners of newly diagnosed people in Rwanda.

Methods: We conducted a prospective cohort study of 1,238 newly diagnosed people undergoing recency and index testing at 60 health facilities selected using probability sampling in all five provinces in Rwanda from August 2021–October 2022. We classified recent and LT infections based on a rapid test for recent infection (RTRI) followed by baseline viral load (VL). RTRI recent with a VL of ≥1000 copies/mL were classified as a recent case. RTRI LT with a VL of ≥1000 copies/mL were classified as a newly diagnosed LT case. We compared the average number of sexual contacts elicited, and HIV positivity and HIV recency yields among the sexual contacts of recent vs. LT cases over a 6-month period using Fisher's exact test. HIV positivity yield was defined as the number of new HIV positive sexual contacts identified among all sexual contacts tested for HIV. HIV recency yield was defined as the number of sexual contacts with a recent infection identified among all sexual contacts tested for HIV.

Results: We enrolled 98 recent and 1,140 LT newly diagnosed people who identified 1,738 sexual contacts as part of index testing. Index cases had an average of 6.6 clinic visits during study follow up. Recent Index cases were more likely to be female compared to LT cases (79% vs. 62%), under 35 years of age (72% vs. 60%), single (38% vs. 30%), and men who have sex with men or female sex worker (22% vs. 9%) (p< 0.01 for all comparisons). For every recent index case, 1.67 sexual contacts were elicited compared to 1.38 contacts per LT case (p=0.06). HIV positivity yield among sexual contacts of recent and LT index cases were 20% and 15%, respectively (p=0.3) while HIV recency yield was 4% vs. 0.8% (p=0.045).

Conclusion: Newly diagnosed people with recent infections compared to those with LT infections were associated with more sexual contacts with recent infections. HIV recency with index testing provides an important opportunity to identify new infections earlier and timely offer prevention resources to curb onward transmission.

Figure 1: HIV Positivity Yield and HIV Recency Yield among Sexual Contacts of Study Index Cases by RITA Status (n=789)



200 RANDOMIZED TRIAL OF DYNAMIC CHOICE HIV CARE FOR HIGHLY MOBILE PERSONS IN EAST AFRICA

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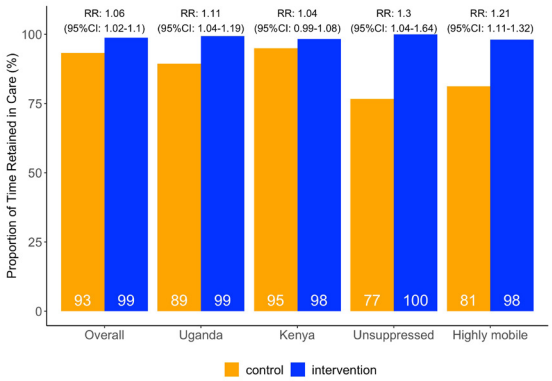
Background: Persons with HIV (PWH) with high mobility face multiple obstacles to HIV care engagement and viral suppression due to planned and unplanned travel away from their clinics' catchment areas.

Methods: In an individual randomized trial, we evaluated the effect of a mobile PWH-centered HIV care intervention on viral suppression vs. Ministry of Health standard care (control) among mobile adults (≥15 years old; and ≥2 weeks out of community in prior 12 months) with either viral non-suppression or recent missed visits in Kenya and Uganda (SEARCH NCT04810650). The intervention included dynamic choice of a "travel pack" (emergency 14-day ART supply, discrete ART packaging and travel checklist), multi-month (up to 6-month) and offsite medication refills, facilitated transfer to out-of-community clinics, and routine screening for travel and hotline access to a mobility coordinator who oversaw intervention delivery. The primary outcome was HIV viral suppression (viral load < 400 c/mL) at 48-weeks. Secondary outcomes included retention in care (proportion of time in care; "out of care" time starting 14-days after missed scheduled visit) and ART possession over 48 weeks. Outcomes were compared by arm with targeted minimum loss-based estimation.

Results: From April-July 2021, 201 participants (102 intervention, 99 control) were enrolled: 109 (54%) were female, 101 (50%) from Kenya, median age was 37 (IQR: 29-43), and 91 (45%) of participants (46% intervention, 44% control) had a VL >400 c/mL in the year prior to enrolment. At enrolment, viral suppression was 80% in intervention and 85% in control. Of 196 (98%) participants analysed at 48 weeks, there was no significant difference in viral suppression between the intervention (85%) vs. control (86%) arms. Viral suppression by arm did not differ significantly in subgroup analyses by sex, country or age (< 30 vs ≥30). Retention in care was higher in intervention vs control (98.8% vs. 93.2%, aRR: 1.06 (1.02-1.1); p< 0.001; most notably in the unsuppressed and highly mobile populations [**Figure**]), as was ART possession (97.5% vs. 91.4%, aRR: 1.07 (1.03-1.11); p< 0.001) over 48-weeks.

Conclusion: A person-centered intervention designed to overcome barriers to HIV care and viral suppression among mobile PWH did not result in significant improvements in viral suppression vs. standard care, but significantly improved retention in care and ART possession, which may confer long term benefit.

Mean proportion of time retained in care by arm, including subgroup analyses in a randomized trial of a person-centered HIV care delivery intervention for mobile PWH. Highly mobile was defined as >14 nights outside of community in 3 months prior to enrolment.



201 THE IMPACT OF PATIENT-CENTRED CARE ON HIV TREATMENT IN ZAMBIA: A STEPPED-WEDGE TRIAL

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Background: Patient-provider interactions drive HIV-care retention. How to change HCW attitudes, communication, and practice is poorly understood. We evaluated a multicomponent patient centred care (PCC) intervention comprising HCW training, practice facilitation, and incentives, to improve patient-experience in Zambia.

Methods: 24 clinics in Lusaka, Zambia, participated in a stepped wedge trial (August 2019-November 2021), over approximately four six-month periods. Treatment failure (HIV RNA > 400 copies/ml or disengagement) was our primary outcome at 15 months. Secondary outcomes were retention at 15 months (i.e., a visit between 11 and 19 months) in waves one and four, late for an appointment (> 30 days) in all waves, and trained patient experience survey (providers were blinded). The intervention included 1) systematic measurement and response to patient experience (satisfaction, HCW attitude/communication, timeliness), 2) PCC training and mentoring and 3) small incentives to enhance performance improvement. In primary analysis for treatment failure, we used mixed-effects logistic regression, accounting for clustering at facility-level using random effects, to assess the effect of PCC on our outcomes adjusting for sex, age, and care status. www.pactr.org registered the study (PACTR202101847907585)

Results: 933 (58% female, median age 37 (IQR:30-44)) participants were recruited in 16 facilities for our primary outcome. We found no difference in treatment-failure between control (N=453) and intervention (N=480) (RD=0.9%, 95% CI: -5.4 - 7.2). Under-25s experienced the greatest improvement in treatment-success (RD 13.6% [95% CI: -1.4 - 28.6]). Among all individuals, retention increased in intervention group (RD 4.7% [95% CI: -0.3 - 9.7]) [wave 1 and 4, N=84,926], this effect was greatest among reengaged (RD 5.2% [95% CI: 0.1 - 10.3], N=17,276) and new ART patients (RD 11.3% [95% CI: 0.2 - 22.5], N=8,817). Intervention patients missed fewer visits than control (waves 1 and 4, RD -3.3% [95% CI: -3.7 - 2.9], N=1,087,809 visits). The effect on missed visits was greatest among new ART patients (RD -5.5 % [95% CI: -7.3 - 3.6], N=54,886 visits). After 6 months of intervention, patient experience improved considerably (Sum score mean, 0.85; 95% CI: 0.37 - 1.32).

Conclusion: A multi-component, participatory intervention improved patient experience and retention, but not treatment-success. Improving patient experience through PCC practice facilitation can complement differentiated HIV care delivery techniques.

202 A RANDOMIZED CONTROL TRIAL OF MHEALTH TOOL EFFECT ON VIRAL SUPPRESSION IN YOUTHS

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Background: Adherence to antiretroviral therapy (ART) is the principal determinant for achieving and sustaining viral suppression, which decreases progression to AIDS, and reduces mortality and transmission risk. Whilst burden of HIV is increasing in adolescents and youth, adherence to medications, retention in care and self-management is still a challenge. It is important to evaluate if the emerging capacity in mHealth technology could support youth living with HIV. We evaluated whether Call for life-interactive voice response (CFL-IVR; Johnson & Johnson) mHealth tool improves ART adherence and retention in care among youth receiving ART at a rural district in Uganda.

Methods: This was a randomized trial in a rural Ugandan district, 225 KM away from the capital. Recruitment was from three ART clinics, youth living with HIV 15-24 years, initiating or on ART for ≤ 6 months were eligible for randomization at a ratio of 1:1 to either Standard of Care (SoC) which is usual care or the intervention "CFL-IVR plus SoC". Participants were seen at baseline, month 06, and month 12. Data collection included socio-demographics, medical history, HIV basic Knowledge, and sexual behaviors. Blood for viral load testing was drawn at all 3 clinic visits. Data was entered in REDCap and exported to stata 15. The CFL-IVR tool offered; individualized pill reminders, clinic visit reminders, health tips messages, and functionality to support self-reported symptoms. Descriptive and regression analysis were done to identify factors related to ART adherence, viral suppression and retention in care.

Results: We randomized 206 participants in a ratio 1:1 to either CFL-IVR intervention or SoC. Participants mean age were 22.3yrs, 167 (81%) were females, 183 (88%) had a sexual partner, 174 (84%) were working, 63 (30%) had monthly household income of at least 26 USD and 52 (25%) had secondary level of education. Retention in care at month 6 was 93.2% in intervention vs 84.3% in SoC (p=0.046) and at 12 months 94.8% in intervention vs 89.5% in SoC (p=0.122).Viral suppression: At 12 months, 67.4% (60) of those on intervention had a suppressed VL compared to 54.7% (41) SoC, which was statistically significant P=0.009. Factors related to viral suppression were age above 22yrs, being female, and having a partner (Table 1: Factors associated with VLS).

Conclusion: mHealth has demonstrated significant potential to improve medication adherence and retention in care.

Table of factors associated with viral load suppression at 12 months

Table 1.0: **Factors associated with viral load suppression at 12 months**

Variable	Risk Ratio	P>z	[95% Conf. Interval]	
Age				
< 22yrs	0.977	**0.000**	0.677	0.999
Gender				
Female	1.200	**0.000**	1.128	1.289
Having a partner				
No	1.230	**0.000**	1.123	1.330
Baseline VL Results				
Detectable				
Suppressed	0.253	**0.000**	0.169	0.379
simply_forgot Pills				
Yes	1.179	**0.000**	1.145	1.188
Fear of rejection				
No	0.682	**0.041**	0.472	0.984

203 SUPPRESSING VIRAL LOAD IN PEOPLE WITH HIV WHO INJECT DRUGS IN RUSSIA: LINC-II RCT

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Background: Over 1.4 million people with HIV (PWH) live in Russia; only 56% are on antiretroviral therapy (ART). Substance use is associated with delayed linkage to HIV care and suboptimal use of ART. In Russia, routine HIV testing is the norm in addiction treatment systems, but if positive, linkage to HIV care is limited.

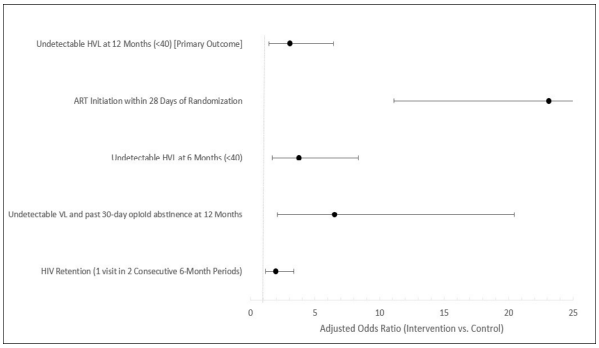
Methods: We conducted a two-arm, randomized controlled trial in St. Petersburg assessing the effectiveness of a multi-faceted intervention (rapid access to ART while admitted to an addiction hospital, provision of depot naltrexone for opioid use disorder, and 12-months of strengths-based case management) compared to usual care. Study eligibility included: PWH, past drug injection, currently not on ART, and an addiction hospital inpatient.

The primary outcome was undetectable HIV viral load (HVL) at 12 months. Secondary outcomes included undetectable HVL at 6 months, initiation of ART ≤28 days of randomization, retention in HIV care at 12 months, change in CD4 count, and a composite outcome of HVL suppression and past 30-day opioid abstinence. We performed adjusted logistic and linear regression analyses controlling for past ART use using an intention-to-treat approach.

Results: Among 225 (N=111 intervention; N=114 control) participants (60% male, mean age 37, mean baseline CD4 count 420 cells/mm3) nearly all (99%) had severe opioid use disorder, 33% reported previous ART use, and 76% had depressive symptoms. Compared to the control group, intervention participants had higher odds of achieving the primary outcome, undetectable HVL at 12 months (48% intervention vs. 22% controls; adjusted odds ratio [AOR] 3.04; 95% confidence interval [CI]: 1.44, 6.44; p=0.004). Secondary outcomes were undetectable HVL at 6 months (35% vs 13%; AOR 3.76; CI: 1.7, 8.34; p=0.001), initiating ART within 28 days of randomization (74% vs. 11%; AOR 23.13; CI: 11.13, 48.07; p< 0.001), retention in HIV care at 12 months (51% vs. 35%; AOR 1.97; CI: 1.15, 3.37; p=0.014), change in CD4 counts (+59 vs. 0; adjusted mean difference 63.95; CI: -2.36, 130.25; p=0.059), and achieving the composite outcome HVL suppression and past 30-day opioid abstinence at 12 months (27% vs. 5%; AOR 6.51; CI: 2.08, 20.40; p=0.001).

Conclusion: Among PWH who inject drugs in Russia, a multi-faceted intervention combining rapid, in-hospital ART initiation, naltrexone, and case management was more effective than standard of care for achieving undetectable HVL, initiating ART, retention in HIV care, and reducing opioid use.

Effect of LINC-II intervention compared with standard of care on HIV and substance use outcomes, adjusted for history of ART use



204 URINE TENOFOVIR LEVELS PREDICT VIRAL SUPPRESSION IN PATIENTS ON TENOFOVIR ALAFENAMIDE

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Background: We previously developed a point-of-care (POC) assay to measure urine tenofovir (TFV) levels among patients on tenofovir disoproxil fumarate (TDF), with a cut-off of 1500 ng/ml indicating adequate adherence. Since tenofovir alafenamide (TAF) results in lower plasma concentrations than TDF, the clinical utility of the existing assay for patients on TAF is unknown. We thus explored whether urine TFV levels above the 1500 ng/ml cut-off correlate with future virologic suppression (VS) (< 200 copies/mL) among people living with HIV (PLWH) on TAF.

Methods: We collected urine samples from patients with HIV on TAF-based regimens at two San Francisco HIV primary care clinics from 06/2019-12/2021. We used our electronic medical record to describe sociodemographic/clinical characteristics, then measured continuous urine TFV levels via liquid chromatography/tandem mass spectrometry. Finally, we used generalized estimating equations to fit a model comparing urine TFV levels (above and below 1500 ng/ml) for samples with and without VS on the first viral load measured after urine collection.

Results: Our analysis included 83 samples (68 suppressed and 15 unsuppressed) from 67 unique PLWH. Samples from person-visits with/without VS were similar in age (median 55 vs 45 years), sex (88% vs 100% male), gender (75% vs 67% cis-male), race/ethnicity (46% vs 33% Black; 37% vs 33% White), glomerular filtration rate (GFR, 84% vs 87% >60 ml/min), creatinine (1.02 vs 0.85 mg/dL), and weight (81.6 vs 73.7 kg); all with p >0.05. The median (interquartile range) urine TFV levels by LC-MS/MS were respectively 3190 (1460, 5720) ng/ml in samples from visits with VS and 690 (70, 2100) ng/ml from visits without suppression. In adjusted modeling accounting for age, race/ethnicity, and GFR (Table 1), urine TFV levels >1500 ng/ml were strongly associated with future VS (OR 5.66; 95% CI 1.59-20.14; p=0.007). The sensitivity/specificity/PPV/NPV at the 1500 ng/ml cut-off were respectively 75%, 67%, 91%, and 63%.

Conclusion: Urine TFV levels above 1500 ng/ml were strongly predictive of future VS among patients on TAF, suggesting that individuals taking TAF who flag below 1500 ng/ml on POC testing would benefit from enhanced adherence counseling. Our results further imply: (1) that the existing POC assay originally developed for TDF may have real-world applicability to predict VS among people with HIV on TAF, and (2) that a single POC assay may support adherence monitoring for patients on both TAF and TDF worldwide.

Table 1: Adjusted Generalized Estimating Equations Model for Future Virologic Suppression by Urine Tenofovir (TFV) Levels (above 1500 ng/ml) among People with HIV on TAF-based Antiretroviral Therapy

Table 1: Adjusted Generalized Estimating Equations Model for Future Virologic Suppression by Urine Tenofovir (TFV) Levels (above 1500 ng/ml) among People with HIV on TAF-based Antiretroviral Therapy

Variable	Odds ratio	Robust Standard Error	95% Confidence Interval	P-value
Urine TFV level above 1500 ng/ml by LC/MS/MS*	5.66	3.67	1.59-20.14	0.007
Age per ten years	0.90	0.25	0.52-1.55	0.71
Race/Ethnicity				
White	Reference	--	--	--
Black	1.09	0.88	0.22-5.29	0.92
Latinx	0.28	0.30	0.04-2.20	0.23
Other/Missing	0.56	0.65	0.06-5.51	0.62
GFR	1.43	1.19	0.28-7.32	0.67

*LC/MS/MS: liquid chromatography tandem mass spectrometry

205 TENOFOVIR DIPHOSPHATE IN DRIED BLOOD SPOTS AND HIV-1 RESISTANCE IN SOUTH AFRICA

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Background: Suboptimal antiretroviral (ART) adherence can lead to virologic failure with consequent HIV-1 resistance. Tenofovir diphosphate (TFV-DP) in dried blood spots (DBS) is a powerful biomarker of cumulative ART adherence that is predictive of present and future viremia in persons with HIV (PWH) in South Africa (SA) and the US. This study explored the relationship of TFV-DP concentrations with antiretroviral drug resistance at the time of treatment failure in SA.

Methods: Adult PWH from health clinics in Cape Town, SA on efavirenz-based first-line ART containing tenofovir disoproxil fumarate, who had an undetectable (< 50 copies/mL) HIV viral load (VL), were prospectively enrolled in an observational cohort for 12 months. Monthly study visits included blood collection for HIV VL and DBS for TFV-DP. Viral breakthrough (VB) was defined as the first confirmed HIV VL >400 copies/mL, and HIV-1 genotyping was completed at the next visit after VB. ART adherence was monitored using an electronic adherence (EA) monitor, and estimated as a percent for the 30-days prior to VB. Non-parametric statistics were used to compare median [IQR] TFV-DP by genotype outcome.

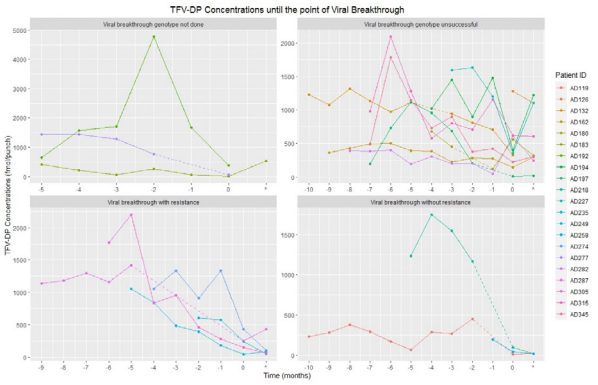
Results: Of 250 participants (n=195, 78% women), 21 experienced VB, with a median (IQR) of 5 [4;7] months on study, and a median EA of 33.3 [13.3;53.3] %. There were no demographic differences between those with and without VB. Median (IQR) VL at VB was 4.0 [3.2;4.5] log copies/mL. TFV-DP concentrations trended downwards towards the VB visit (Figure). Median [IQR] TFV-DP concentrations were compared (p=0.035) and were significantly higher those whose HIV-1 genotype did not amplify due to being virally suppressed at the subsequent visit (n=10; 380 [227-661] fmol/punch, ; EA 45 [24.9; 59.2]%); than in participants who were successfully genotyped with evidence of drug resistance (n=5, 241 [150-247] fmol/punch, EA 20 [6.7;36.7]%) and in participants who were genotyped and did not have resistance (n=3, 39.9 [16.6; 93.9] fmol/punch; EA 33.3 [16-38]%). Five genotypes were missed. Only non-nucleoside reverse transcriptase inhibitor-associated mutations were identified at VB (K103N, E138K, Y118H).

Conclusion: TFV-DP in DBS showed a step-wise inverse relationship with VB and drug resistance, with evidence of low (but not completely absent) cumulative low ART adherence in PWH who developed antiretroviral resistance

in SA. Monitoring TFV-DP concentrations could be a valuable tool not only for predicting future VB but also for predicting future resistance.

Figure 1

Figure: Concentration of tenofovir diphosphate those with VB, categorised by genotype outcome: amplified with HIV-1 resistance mutations, amplified without resistance, unsuccessful amplification and missed genotype. The graph is right justified, x-axis is time to first confirmed VB (months), with VB at month 0. The asterisk represents the visit at which genotyping was done, 1 month following confirmed VB.



206 ART SHARING IS COMMON AND ASSOCIATED WITH VIREMIA: A POPULATION-BASED STUDY IN UGANDA

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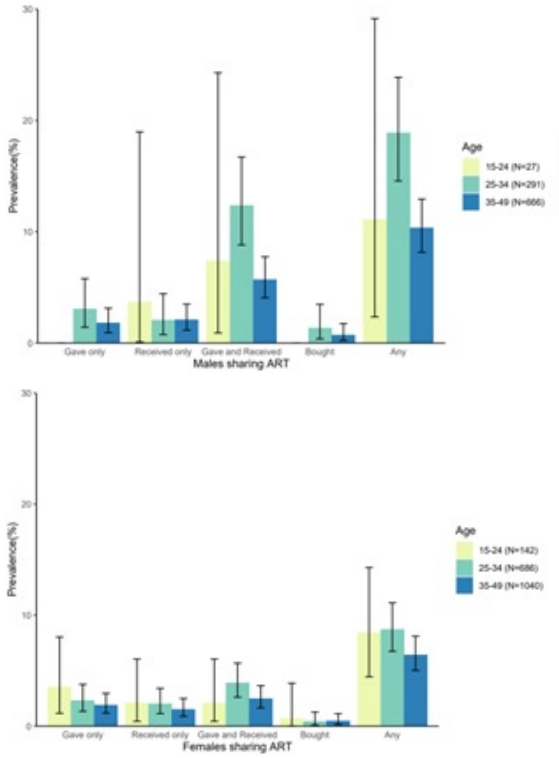
Background: Antiretroviral treatment (ART) sharing has been reported among fisherfolk and sex workers in Uganda and South Africa. However, to date, no population-based studies have documented the prevalence of ART diversion (including sharing [giving or receiving], buying, and selling ART pills) among men and women living with HIV in Africa, or its relationship with HIV viremia in these groups.

Methods: From 2018-2020, we surveyed all people living with HIV aged 15-49 in 40 communities in the Rakai Community Cohort Study (RCCS), a population-based cohort in south-central Uganda. We assessed prevalence and correlates of self-reported ever and past-year ART diversion. We stratified data by age and gender, and documented diversion partners. We used log-binomial regression to assess the relationship between diversion patterns and viremia (viral load >1000 copies/ml), reported as risk ratios (RR) with 95% confidence intervals (CI).

Results: Of 2,852 people living with HIV, 266 (9.3%) reported ART diversion. Giving and receiving were most common: 62 (2.2%) reported giving only, 54 (1.9%) reported receiving only, and 132 (4.6%) reported both giving and receiving. Few participants reported buying (n=18, 0.6%) and none reported selling. Men were more likely to report any diversion than women (12.9% vs. 7.4%), with men aged 25-34 reporting particularly high levels of sharing (18.9%) (Figure). Friends were the most common sharing partners, followed by spouses/sexual partners. Patterns of ever and past-year diversion were similar for age and gender. Among participants with viral load results, 8.6% (234/2,725) were viremic. People who reported only giving ART to others were twice as likely to be viremic than those who reported no diversion (RR:2.04, 95% CI:1.14-3.63), while those who reported only receiving ART had a non-significant lower prevalence of viremia (RR:0.48, 95% CI:0.12-1.89). Reporting both giving and receiving was not associated with viremia (RR:0.90, 95% CI 0.49-1.66).

Conclusion: This first population-based assessment of ART diversion found that ART sharing is fairly common in rural Uganda, particularly among men. While receiving pills may support viral suppression, giving pills is associated with viremia. HIV programs may benefit from considering drug sharing in counseling messaging. Future longitudinal studies are needed to assess temporal relationships.

Prevalence of ART giving, receiving, buying, and selling by age category and gender among people living with HIV ages 15-49 in 40 study communities in south-central Uganda



207 EFFECTIVENESS OF SMALLPOX VACCINATION TO PREVENT MPOX IN MILITARY PERSONNEL

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Background: The effectiveness of Smallpox vaccines against Mpox is unknown. In the global outbreak of Mpox, these vaccines are being used as prevention in individuals with high-risk of exposure to Mpox. There is an urgent need to determine their effectiveness.

Methods: We conducted a retrospective, test-negative case-control study among US current and former military personnel. The goal of the study was to evaluate the vaccine effectiveness (VE) of smallpox vaccines against Mpox . Uni- and multivariate logistic regressions were used to calculate odds ratios (ORs) with 95% confidence interval (CI) for the association between positive Mpox testing and receipt of Smallpox vaccine. Vaccine effectiveness (VE) was estimated as (1– OR of Mpox in vaccinated/OR of Mpox in unvaccinated) x 100%. Models for adjusted analyses included covariates for potential confounders of the association between vaccination status and testing positive for Mpox. The adjustment covariates included age, race, sex, and HIV status. Among individuals tested in the VA system, severity of disease was defined by admission to the hospital for Mpox. This information was not available for individuals outside of a VA facility. Analyses were conducted using Stata17 and SAS9.4 software.

Results: The analysis included 959 military personnel and Veterans who were tested for *Orthopoxvirus* between July 1-October 31, 2022, 188 (19.6%) of whom had a documented Smallpox vaccination. Among the 290 individuals who tested positive for *Orthopoxvirus*, 24 (8.3%) were previously vaccinated with ACAM2000 ("2nd-generation" Smallpox vaccine) and 12 (4.1%) were previously

vaccinated with Dryvax ("1st-zzgeneration" Smallpox vaccine). The median time from receipt of Smallpox vaccination to Mpox diagnosis was 12-years (range:35, IQR:6.5). Individuals with prior ACAM2000 (OR=0.28; 95%CI: 0.17-0.47) or Dryvax (OR=0.36; 95%CI 0.18-0.73) vaccination were less likely to test positive for *Orthopoxvirus* compared to unvaccinated individuals. The estimated VE rate was 72% for ACAM2000 and 64% for Dryvax . Among those who tested positive for orthopoxvirus within the VA, 14/183 (7.7%) required hospitalization; Of those who tested positive, 126 (43.4%) were people with HIV (OR: 2.30, 95% CI:1.63 – 3.25).

Conclusion: Vaccination with Smallpox vaccines reduces the likelihood of testing positive for Orthopoxvirus. Our study provides the largest evaluation of the effectiveness of earlier smallpox vaccines against Mpox, supporting their usefulness in containing the global outbreak.

Table 1: Demographic and clinical characteristics of individuals tested for Non-variola *Orthopoxvirus* (NVO) across DoD and VHA (July 1 – October 31, 2022)

	Positive for NVO	Negative for NVO
	N=290	N=669
Age (date of PCR test)		
median	37	49
18-34	126 (43%)	175 (26%)
34-44	79 (27%)	125 (19%)
45-64	80 (28%)	232 (35%)
≥ 65	5 (2%)	137 (20%)
Male	287 (99%)	596 (89%)
Race Ethnicity		
Black	141 (49%)	254 (38%)
Hispanic	39 (13%)	79 (12%)
White	88 (30%)	265 (40%)
Other/Unknown	22 (8%)	71 (11%)
Tested at VHA Facility	183 (63%)	567 (85%)
Previously received SPX vaccination	36 (12%)	152 (23%)
ACAM2000®	19 (66%)	49 (58%)
DRYVAX®	10 (34%)	35 (42%)
Number of years since receipt of last dose of SPX vaccination		
none	254 (88%)	517 (77%)
<5 years	7 (19%)	25 (16%)
5-10 years	7 (19%)	26 (17%)
11-15 years	14 (39%)	63 (41%)
16+ years	7 (24%)	24 (29%)
HIV positive	126 (43%)	141 (21%)
Hospitalized with Monkeypox*	14 (5%)	4 (1%)
Data on Hospitalization pending	107 (37%)	102 (15%)

Table 2: Multivariate analysis of variables associated with Human Monkeypox diagnosis

	Odds Ratio (95% CI)	
	Crude	Adjusted
ACAM2000®	0.49 (0.31 - 0.78)	0.28 (0.17 - 0.47)
Dryvax®	0.47 (0.25 - 0.90)	0.36 (0.18 - 0.73)
Age Groups		
35-44	0.88 (0.61 - 1.26)	0.73 (0.48 - 1.11)
45-64	0.48 (0.34 - 0.67)	0.33 (0.23 - 0.49)
65+	0.05 (0.02 - 0.13)	0.03 (0.01 - 0.09)
Race and Ethnicity		
Black	1.67 (1.22 - 2.30)	1.32 (0.92 - 1.90)
Hispanic	1.49 (0.94 - 2.34)	1.17 (0.71 - 1.92)
other / unknown	0.93 (0.55 - 1.59)	0.66 (0.37 - 1.17)
Sex and HIV		
Male Sex	11.72 (3.66 - 37.50)	11.71 (3.59 - 38.24)
HIV Diagnosis	2.88 (2.14 - 3.87)	2.30 (1.63 - 3.25)

208 IMPACT OF VACCINATION ON MPOX INCIDENCE IN MSM ON PrEP IN THE ANRS 174 DOXYVAC TRIAL

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Background: Mpox was first reported in France on May 19, 2022 and third-generation live Modified Vaccinia Ankara (MVA-BN) vaccination of multiple-partner MSM was recommended as of July 11, 2022. We assessed the impact of vaccination on incidence of mpox in MSM on PrEP participating in a clinical trial.

Methods: ANRS-174 DOXYVAC is an ongoing trial enrolling MSM on PrEP with history of STI in the past year. We compared socio-behavioral characteristics of mpox cases and mpox-free controls in the pre-epidemic period (up to May 8 2022). Then we compared the incidence of mpox between May 9-July 10 2022 (before recommendation of vaccination for MSM) and July 11-September 20 2022 (after vaccination launch). Incidence rates (IRs) of mpox per 1000 person-months (p-m) over periods were calculated as the total number of mpox divided by the p-m of observation. IRs of mpox were compared between periods using a Poisson regression model with random intercepts to account for within-subject variability.

Results: At the time of mpox outbreak, 546 MSM had been randomized including 472 with available data before and after May 9, 2022, with median age 39 years, median of 10 sexual partners during last 3 months, median of 5 condomless anal intercourses during last month and 20% received smallpox vaccine during childhood. Mpox occurred in 77/472 participants. Prior to the epidemic, cases were younger (37 vs 40, p=0.0179), had more sexual partners during last 3 months (15 vs 10, p=0.0022), more condomless anal intercourses during last month (7 vs 5, p=0.0244) and were less vaccinated during childhood (4% vs 23%, p< 0.0001) than controls. A significant change in sexual behavior was seen before and after May 9, 2022 only among the proportion of controls with > 10 partners during last 3 months (45% vs 38%, p=0.0035). Mpox incidence was 67.4 per 1000 p-m (95%CI 51.6-86.6) between May 9 and July 10, and 24.4 per 1000 p-m (95%CI 13.9-39.6) between July 11 and September 20 2022, with an IRR of 0.44 [0.24-0.81], with only one case reported after August 8, 2022. In multivariable Poisson regression model (see Table), only MVA-BN vaccination in 2022 remained significantly associated with mpox infection, with a 99% risk reduction (95%CI 96.6-99.7).

Conclusion: In France, MVA-BN vaccination in summer 2022 conferred high-level protection against mpox infection in highly-at-risk MSM on PrEP. In this study population, sexual behavior change did not seem to play a role in reduction of mpox incidence.

Table: Poisson regression model

Variable	Pr > |t|	Relative risk (RR)	lower RR	higher RR
period July 11-Sept 20 versus period May 9-July 10 2022	0.371	0.775	0.443	1.360
Smallpox vaccination during childhood	0.808	0.861	0.258	2.876
Smallpox vaccination in 2022	<.0001	0.0103	0.003	0.034
Median number of sexual partners	0.094	1.008	0.998	1.019

209 HOUSEHOLD TRANSMISSION OF MPOX TO CHILDREN AND ADOLESCENTS

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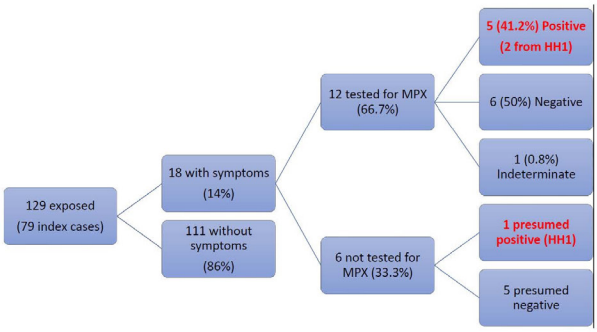
Background: In California, 5572 cases of Monkeypox (MPOX) were identified in California as of November 28, 2022, approximately 20% of the US case count; 0.3% of cases were among children < 16 years old. We analyzed routinely collected contact tracing data in California to assess the secondary attack rates (SAR) among pediatric household contacts exposed to MPOX.

Methods: Using data from California's public health database, and data separately provided by San Diego and Los Angeles counties, we created a line list of all pediatric MPOX contacts aged < 16 years reported through August 31, 2022. Contacts to a non-confirmed or probable case of MPOX and non-household contacts were excluded from analysis. All pediatric contacts were reviewed to ascertain whether symptoms developed during their incubation period (21 days after last exposure) and outcomes of testing; pediatric contacts that did not report symptoms were assumed to have been asymptomatic.

Results: We identified 129 pediatric household contacts exposed by 79 adult index cases. The median age of contacts was 7 years (range 0-15 years). Eighteen children (14%) exposed by 14 adult index cases reported symptoms consistent with MPOX during their incubation period; their median age was 6 years (range 1-11 years). All symptomatic children reported a rash; other symptoms included adenopathy, fever, fatigue, and myalgia. Among 18 symptomatic contacts, 12 (66.7%) underwent MPOX testing; 5 (41.2%) were confirmed cases, 6 (50%) were negative, and 1 (0.8%) had an indeterminate result. Two of the confirmed infected pediatric contacts came from a single household (Household 1). Six symptomatic children were not tested for MPOX (33.3%). One of these children, also a resident of Household 1, was considered to be a probable case due to consistent rash and systemic symptoms. Overall, six infected contacts were identified through August 2022, resulting in a SAR of 4.7% (6 of 129). Among infected contacts, median age was 4.5 years (range 2-9 years) and three of six resided in the same household (Household 1).

Conclusion: Among children with household contact to an adult with MPOX in California, only 14% developed symptoms consistent with MPOX, and less than 5% ultimately tested positive. The secondary attack rate may have been underestimated because one-third of symptomatic children were not tested. While the risk of household transmission is low, pediatric household contacts should be offered post-exposure prophylaxis to prevent MPOX spread.

Figure 1. Outcomes of monkeypox contact tracing among pediatric household contacts in California (July-August 2022)



MPOX: Monkeypox, HH (household)

210 ASSOCIATION BETWEEN OBSERVED MASKING AND SARS-CoV-2 PRESENCE IN SCHOOL WASTEWATER

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Background: The SARS-CoV-2 virus is airborne and highly transmissible. Masking is an important strategy for source control and personal protection. The American Academy of Pediatrics recommends masking as part of a comprehensive strategy to reduce the spread of COVID-19 and respiratory diseases in school settings, however the effectiveness of school masking policies has been heavily debated. Previous studies of masking effectiveness have been limited by the use of self-reported masking behavior, policies as a proxy for masking behaviors, and/or case surveillance data that are biased by access to testing

Methods: The Safer at School Early Alert (SASEA) project provided daily wastewater SARS-CoV-2 surveillance for elementary schools serving historically marginalized communities in San Diego County. We previously found that daily wastewater surveillance can identify 95% of PCR-detectable COVID-19 cases on campus. Between March 2 and May 27, 2022, we randomly selected 10 schools from the SASEA project for bi-weekly systematic observations of masking behaviors of students, staff, and parents. Each school was observed by 4 trained observers from the time school let out until all individuals had left. Observers counted the total number of adults and children and whether they were fully masked (nose and mouth covered), partially masked, or unmasked. We built a logistic regression model to measure the association between positive wastewater signals in the 5 days following an observation event (outcome) and the percentage of individuals who were observed fully masked vs partially or unmasked (primary predictor).

Results: We conducted 60 observation events over 6 weeks, during which positive wastewater signals— suggesting the presence of at least one COVID-19 case on campus—occurred on 9 days. On average, 38.6% of individuals were observed fully masked. After adjusting for intra-site correlation, observation week, current case rate per 100,000 in the school ZIP code and vaccination rate in the school ZIP code, we found that the odds of a positive wastewater signal in the 5 days after observation decreased by 47% (aOR 0.53, 95% CI: 0.28 – 0.99) for each 10% increase in the proportion of fully masked individuals.

Conclusion: Masking is an effective strategy to prevent the spread of COVID-19 in school settings. Even a relatively small increase in the proportion of individuals masking can potentially lead to a significant difference in epidemic spread

211 VARIABLE REDUCTIONS IN SARS-CoV-2 VARIANT IMPORTATIONS FOLLOWING TRAVEL RESTRICTIONS

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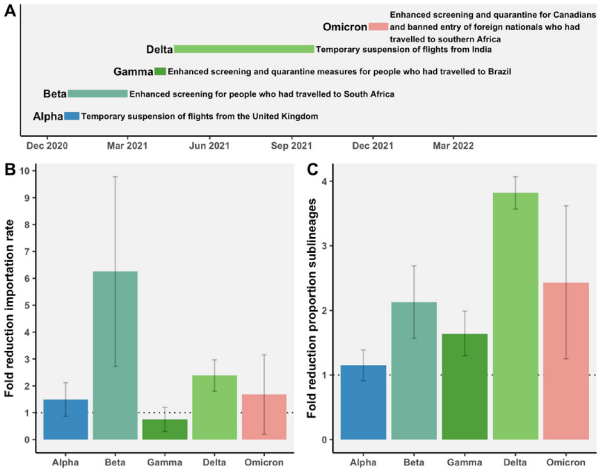
Background: Retrospectively quantifying effectiveness of interventions such as travel restrictions to counter viral introduction and transmission is critical to inform public health policy. Phylogenetic analyses of SARS-CoV-2 variants were undertaken to quantify the effects Canadian COVID-19 travel restrictions had on variant importation and transmission dynamics.

Methods: Global and Canadian GISAID sequences available up to March 2022 were subsampled proportionally to variant-specific case counts and ten phylogenies were inferred for each variant. Trees, dates, and geographies were inferred using maximum likelihood.

Results: In response to Alpha, Canada implemented a UK flight ban from December 20, 2020–January 6, 2021, resulting in a 1.5-fold reduction in UK sublineage importation rate, with subsequent rebound (**Fig. 1**). Enhanced screening measures were implemented on December 24, 2020 for South African arrivals to counter Beta. Although there was a 6.3-fold reduction of Beta sublineages per week from South Africa following enhanced screening, there is low confidence in rare events. For Gamma, enhanced screening for arrivals from Brazil was implemented March 31–April 13, 2021. Proportion of Gamma sublineages from Brazil was reduced 1.6-fold within 2 weeks of the intervention, but the weekly importation rate was not significantly changed from start to end of intervention. In response to Delta, Canada issued a suspension of flights from India from April 22–September 23, 202, coinciding with a 2.4-fold reduction in sublineage importation and 3.8-fold reduction in proportion of sublineages from India. Increased importations from the USA and Europe progressively negated the ban's effectiveness. Against Omicron, Canada banned entry of all foreign nationals who had travelled through southern Africa and implemented enhanced screening for Canadians from November 26–December 18, 2021. Subsequently, the BA.1 sublineage importation rate from South Africa was maintained at a low level amid rising cases, while importations from other sources increased, reducing the proportion of sublineages from South Africa and diluting the measure's effectiveness.

Conclusion: Flight bans and enhanced screening against SARS-CoV-2 variants were most effective when implemented rapidly and for lengthier time; however, effectiveness declined as variants became globally widespread. Ongoing genomic surveillance programs incorporating phylodynamic analyses can inform travel restriction and non-pharmaceutical intervention policy.

Figure 1. Reduction of variant of concern (VOC) introductions from source nations following Canadian COVID-19 travel restrictions. A) The timing of travel restrictions in Canada against VOC. B) Fold reduction in sublineage importation rates and C) proportion of sublineages from source nations 2 weeks after restriction implementation. Error bars depict t-distribution 95% confidence intervals across ten bootstraps.



212 INTERVENTION EFFICACY ON COVID-19 TESTING AND VACCINATION IN PEOPLE WHO INJECT DRUGS

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Background: People who inject drugs (PWID) are vulnerable to SARS-CoV-2 and severe disease but have low rates of COVID-19 testing and vaccination due to multilevel barriers. We partnered with a mobile syringe service program (SSP) in San Diego County, CA, to develop the theory-informed "LinkUP" intervention to increase COVID-19 testing and vaccination among PWID.

Methods: From March-June 2022, we conducted a pilot randomized controlled trial (RCT; ClinicalTrials.gov #NCT05181657) to assess efficacy of LinkUP vs. a

didactic attention-matched control condition in increasing COVID-19 testing uptake and acceptance of vaccination referrals. Based on Social Cognitive Theory, trained, SSP-hired peer counsellors delivered tailored education, motivational interviewing, and problem-solving and planning to the active LinkUP intervention arm. We referred eligible participants (PWID, ≥18 years old, San Diego County residents without recent voluntary COVID-19 testing or fully vaccinated status) to mobile SSP sites that had been randomized by week to offer LinkUP or the control condition; all participants were then offered on-site rapid COVID-19 antigen testing and vaccination referrals. Our intent-to-treat analysis used Chi-square tests to compare intervention groups' outcomes and log-binomial regression to estimate preliminary intervention efficacy and explore potential moderation.

Results: Among 150 participants, median age was 41 years, 33% identified as Latinx and 65% as male, 73% were experiencing homelessness, and 45% had prior mandatory COVID-19 testing. Overall, we only detected one SARS-CoV-2 case. However, more active intervention vs. control participants agreed to COVID-19 testing (77.3% vs. 22.7%; $p < .001$) and vaccine referrals (32.4% vs. 13.3%; $p = 0.006$). Homelessness moderated intervention effects: LinkUP increased COVID-19 testing uptake more among participants experiencing homelessness (adjusted risk ratio [aRR]: 1.64; 95% CI: 1.27-2.12) than those not experiencing homelessness (aRR: 1.25; 95% CI: 0.99-1.56).

Conclusion: Findings from this RCT support the efficacy of LinkUP in increasing COVID-19 testing and acceptance of vaccination referrals among PWID presenting at mobile SSP sites, particularly for those experiencing homelessness. This research underscores the significance of community-academic partnerships when working with PWID and identifies a promising model that could be adapted to increase access to other underutilized vaccines in this vulnerable population.

213 CLUSTER-RANDOMIZED TRIAL COMPARING TWO SARS-CoV-2 TESTING MODELS IN AFRICA

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Background: Most programs use a screen and test strategy to identify SARS-CoV-2 infection, but this strategy does not identify individuals with asymptomatic infection. We determined the SARS-CoV-2 case detection rates in a test-all model compared to the standard screen-and-test model in Kenya and Cameroon.

Methods: A cluster-randomized trial was conducted in 20 health facilities between May-October 2022. In each country, 5 facilities were randomized to test all (testing offered regardless of screening outcome) or screen and test (testing offered if screened positive) arms. Additional staff were hired to support implementation of the two models in Kenya (K) and the test all model in Cameroon (C). Clients age>2 years attending HIV, TB and MNCH clinics were tested using SARS-CoV-2 rapid antigen tests. We estimated case detection rates (CDR) with facility level weighted averages and used a weighted t-test with robust standard errors for between arm comparison.

Results: Overall, 80,828 attendee visits were reported in the test-all arm (63,492 C and 17,336 K) and 71,254 attendee visits were reported in the screen-and-test arm (56,589 C and 14,665 K). In the test-all arm, 42,325 (52.4%) were screened for COVID-19 symptoms (46.7% C and 73.2% K) and 21,536 (26.6%) were tested (29.2% C and 17.4% in Kenya) with a positivity rate of 1.4% (2.0% C and 1.1% K). In the screen-and-test arm, 48,314 (67.8%) were screened (72.8% C and 48.6% K), and 3,629 (7.5%) were eligible for testing (8.2% C and 3.7% K) - of those, 2,139 (58.9%) were tested (57.1% C and 82.4% K) with a positivity rate of 4.1% (3.4% C and 10% K). The estimated CDR was 3.59 (95% CI:1.55-5.64) per 1,000 attendee visits in the test-all arm and 1.46 (95% CI:0.60-2.32) per 1,000 attendee visits in the screen-and-test arm. Compared to the screen-and-test arm, the test-all arm had significantly higher COVID-19 CDR in MNCH clinics (3.57 vs.1.29, p=0.034). There were no significant differences in COVID-19 CDR between the two arms in HIV (4.20 vs.1.98, p=0.174) and TB (10.33 vs. 5.03, p=0.283) clinics, though the number of SARS-CoV-2 infections was small.

Conclusion: The test-all arm identified more SARS-CoV-2 cases than the routine screen-and-test model, despite overall low testing coverage. The test-all model should be considered in future epidemics to improve early detection of SARS-CoV-2 infection among vulnerable populations, but effective implementation requires additional human resources to manage the clinic volumes.

COVID-19 Case Detection Rates Per 1,000 Attendees: Comparison of Screen-and-Test and Test-All Arms

	Screen-and-Test (N=10 facilities)			Test-All (N=10 facilities)			P-value
	Attendees	Positives	Rate	Attendees	Positives	Rate	
Overall							
Totals	71,254	88	1.24 (0.10 – 1.52)	80,828	312	3.86 (3.44 – 4.31)	
Cluster means			1.50			3.54	0.031
Weighted means			1.46 (0.60 – 2.32)			3.59 (1.55 – 5.64)	0.058
Cameroon							
Totals	56,589	66	1.17 (0.90 – 1.48)	63,492	279	4.39 (3.89 – 4.94)	
Cluster mean			1.19			5.22	0.012
Weighted mean			1.19 (0.69 – 1.69)			5.17 (1.35 – 8.980	0.044
Kenya							
Totals	14,665	22	1.50 (0.94 – 2.27)	17,336	33	1.90 (1.31 – 2.67)	
Cluster mean			1.82			1.87	0.676
Weighted mean			1.68 (0 – 3.60)			1.88 (0.89 – 2.87)	0.833

214 COVID-19 BIVALENT BOOSTER EFFECTIVENESS IN PEOPLE WITH AND WITHOUT IMMUNE DYSFUNCTION

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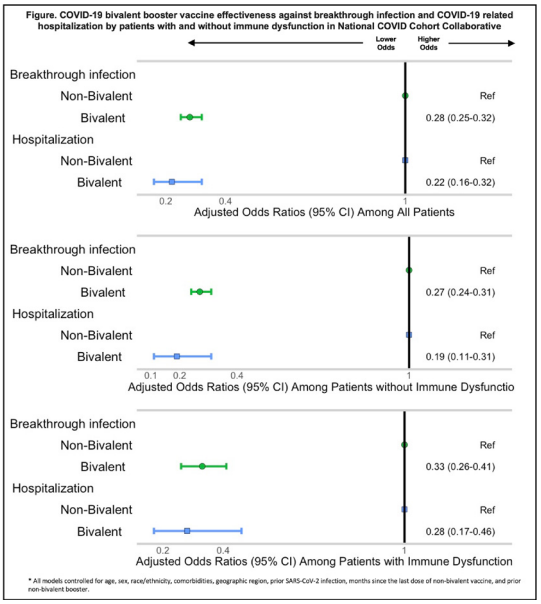
Background: Data on the effectiveness of the bivalent booster vaccine against COVID-19 breakthrough infection and severe outcomes is limited.

Methods: Using patient-level data from 54 sites in the U.S. National COVID Cohort Collaborative (N3C), we estimated bivalent booster effectiveness against breakthrough infection and outcomes between 09/01/2022 (bivalent vaccine approval date) to 12/15/2022 (most recent data release of N3C) among patients completed 2+ doses of mRNA vaccine. Bivalent booster effectiveness was evaluated among all patients and patients with and without immunosuppressed/compromised conditions (ISC; HIV infection, solid organ/bone marrow transplant, autoimmune diseases, and cancer). We used logistic regression models to compare the odds of breakthrough infection (COVID-19 diagnosis after the last dose of vaccine) and outcomes (hospitalization, ventilation/ECMO use, or death ≤28 days after infection) in the bivalent boosted vs. non-bivalent boosted groups. Models controlled for demographics, comorbidities, geographic region, prior SARS-CoV-2 infection, months since the last dose of non-bivalent vaccine, and prior non-bivalent booster.

Results: By 12/15/2022, 2,414,904 patients had received 2+ doses of mRNA vaccination, 75,873 of them had received a bivalent booster vaccine, and 24,046 of them had a breakthrough infection. At baseline, the median age was 52 (IQR 36-67) years, 40% male, 63% white, 10% Black, 12% Latinx, 3.5% Asian American/Pacific Islander, and 14% were patients with ISC. Patients received a bivalent booster were more likely to be female and had comorbidities. Bivalent booster was significantly associated with reduced odds of breakthrough infection and hospitalization (Figure). The adjusted odds ratios comparing bivalent vs. non-bivalent group were 0.28 (95% CI 0.25, 0.32) for all patients and 0.33 (95% CI: 0.26, 0.41) for patients with ISC. Compared to the non-bivalent group, the bivalent group had a lower incidence of COVID-19-related hospitalization (151 vs. 41 per 100,000 persons), invasive ventilation/ECMO use (7.5 vs. 1.3 per 100,000 persons), or death (11 vs. 1.3 per 100,000 persons)

in all patients during the study period; the incidence of severe outcomes after bivalent boosting was similar among patients with and without ISC.
Conclusion: A bivalent booster vaccine was highly effective against COVID-19 breakthrough infection and severe outcomes among patients received 2+ doses of mRNA vaccine and offered similar protection in patients with and without ISC.

Figure. COVID-19 bivalent booster vaccine effectiveness against breakthrough infection and COVID-19 related hospitalization by patients with and without immune dysfunction in National COVID Cohort Collaborative



POSTER ABSTRACTS

215 LENACAPAVIR DISRUPTS HIV-1 CORE INTEGRITY WHILE STABILIZING THE CAPSID LATTICE

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Background: Lenacapavir (LEN) is a potent HIV-1 capsid inhibitor (Gilead Sciences) currently in phase 2/3 clinical trials. Structural studies indicate that LEN binds two neighboring capsid subunits and stabilizes the cone-shaped capsid lattice, but its mechanism of viral inhibition and effect on capsids remain elusive. We recently utilized two different capsid-labeling approaches and demonstrated that intact HIV-1 capsids enter the nucleus and retain their integrity until just minutes before capsid disassembly (uncoating). Here, we sought to determine the effects of LEN on viral core integrity and kinetics of uncoating using isolated viral cores and cell-based assays.
Methods: We used two capsid-labeling methods: green fluorescent protein (GFP) fused to capsid (GFP-CA) and GFP as a fluid phase content marker (iGFP) by inserting GFP between matrix and capsid (GagiGFP) that was proteolytically cleaved from Gag during virion maturation. Some of the GFP remains trapped inside capsids and serves as a reporter of capsid integrity loss. HIV-1 viral cores isolated through sucrose gradient fractionation were characterized by immunostaining and single virion analysis (SVA). SVA and live-cell imaging were then used to investigate the effects of LEN on isolated capsids and nuclear capsids in infected HeLa cells, respectively.
Results: Immunostaining showed that only capsids labeled with GFP-CA, not iGFP, were stained with anti-GFP antibody. In addition, GFP-CA, but not iGFP, inhibited Mx2 restriction of HIV-1 infection, indicating that GFP-CA is incorporated into the capsid lattice and exposed on the outside. The number of GFP-CA-labeled capsids either increased or remained constant upon LEN treatment, while the number of iGFP-labeled capsids was significantly reduced in a dose-dependent manner. Live-cell imaging showed that upon LEN treatment, GFP-CA-labeled nuclear capsids remained detectable for >1 hour, while iGFP-labeled nuclear capsids disappeared within 5 minutes.
Conclusion: Our results show that GFP-CA is an HIV-1 capsid lattice marker and iGFP is a reporter of core integrity. LEN treatment stabilizes the capsid lattice while disrupting core integrity. These results highlight the importance of retaining an intact capsid until shortly before integration. The high potency of LEN inhibition of HIV-1 replication may be explained in part by the disruption of core integrity, rather than inhibition of capsid disassembly.

216 SINGLE-VIRUS IMAGING OF HIV-1 NUCLEAR IMPORT

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Background: In search of a cure for HIV infection, understanding of all molecular determinants resulting in HIV persistence is warranted. The mechanism of the early steps of HIV-1 replication including capsid uncoating, nuclear import, and integration remain poorly understood. In particular, the intracellular localization and timing of capsid uncoating is a matter of debate. Evidence is emerging that nuclear import and integration sites determine the transcriptional state of the provirus. Viral infection is essentially heterogeneous in nature as only a few particles yield an integrated provirus. Conventional molecular biology techniques provide a limited understanding of the process at the ensemble level. Advanced microscopy methods offer the advantage to study the mechanism of viral replication at single virus level.
Methods: Our group has established an imaging platform to study viral infection at the single-particle level. We use fluorescently labelled integrase and time-lapse imaging to analyze the different steps of the replication cycle of HIV-1 in living cells. We follow the trajectory of the individual particles and their change in fluorescence intensity during their transport to the nucleus. We have also optimized super-resolution microscopy, STED (stimulated emission depletion) to estimate and compare the size of cytoplasmatic and nuclear preintegration complexes (PICs) with a high spatial resolution. To study the role of host factors TRN-SR2, TNPO1, and CPSF6 in nuclear import we generated cell lines depleted for each of these factors.
Results: We observe a 2-fold decrease in the fluorescence intensity signal and a 1.5-fold decrease in the size of nuclear PICs by confocal and STED imaging. Moreover, the nuclear import takes place after transient docking of one to two minutes of the viral particles at the nuclear membrane. In TNPO1, TRN-SR2, and CPSF6-depleted cell lines a 2 to 3-fold increase in the docking time, the time spent in the cytoplasm, and the overall import time of PICs were observed confirming their role in nuclear import.
Conclusion: A decrease in the fluorescence intensity and size of nuclear PICs corroborates that uncoating mainly takes place at the nuclear membrane. The depletion of TRN-SR2 hampered single-round infection by 60% whereas, the decrease in single-round infection in cell lines depleted for TNPO1 or CPSF6 was not significant pointing to a possible redundancy for the use of host factors in the process of nuclear import.

217 RESTRICTION OF LENTIVIRAL CAPSIDS BY PRIMATE TRIM34

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Background: Human immunodeficiency virus (HIV) and other lentiviruses evolved to evade restriction factors, a type of germline-encoded, host innate immune proteins that inhibit viral replication. Understanding how restriction factors constrain lentivirus replication and transmission is key to understanding the emergence of pandemic viruses like HIV-1. The restriction factor TRIM5α can both mediate HIV capsid (CA) sensing and subsequent innate immune signaling and directly inhibit viral replication. Specifically, TRIM5a-mediated ubiquitination has been shown to induce downstream immune activation, while TRIM5α blocks replication by multimerizing onto the HIV core, inducing aberrant capsid uncoating. TRIM34, a paralog of TRIM5α, is a restriction factor of certain HIV and SIV capsids. Notably, TRIM34-mediated restriction requires TRIM5α, and TRIM5α-mediated restriction requires multimerization of TRIM5α monomers. Thus, we propose that TRIM34 requires multimerization with TRIM5α to restrict lentiviral capsids. The goals of this work are to identify determinants of antiviral specificity for TRIM34-mediated restriction, to identify domains of TRIM34 that are required for lentiviral restriction, and to examine TRIM34 and TRIM5α interactions.
Methods: To study the roles of TRIM5α and TRIM34 in restricting divergent lentiviruses, we co-expressed primate orthologues of TRIM5α and TRIM34 to test their ability to restrict a variety of lentivirus capsids. We generated chimeric and mutant TRIM proteins to identify regions of TRIM34 and TRIM5α that are necessary or sufficient for TRIM34-mediated restriction. To address whether TRIM34 is involved in signaling, we immunoprecipitated TRIM34 and TRIM5α to assess their capacity for ubiquitination.
Results: We found that diverse primate TRIM34 orthologues can restrict SIVagm and SIVmac capsids. This restrictive capacity appears broadly conserved across primates: all primate TRIM34 orthologues that we tested, regardless of species of origin, were able to restrict in the presence of human TRIM5α. Furthermore, we found that TRIM5α is necessary, but not sufficient, for restriction of these capsids. Finally, we found that TRIM34 is not polyubiquitinated to the same extent that TRIM5α is.
Conclusion: These data suggest that TRIM34 is a conserved primate lentiviral restriction factor. These studies will elucidate how TRIM34 and TRIM5α interact with each other and capsids, leading to a better understanding of TRIM34's role in host-pathogen evolutionary history.

218 HIV INFECTION OF TFH: INTERROGATING THE SAMHD1 CONTRIBUTION THROUGH HIV-2

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*Presented at CROI by a nonauthor colleague

Background: SAMHD1 is a host restriction factor with recognized impact in HIV reservoir establishment and suggested to be involved in follicular helper T cell (Tfh) biology. We explore here the ability of HIV-2 to counteract SAMHD1 due to the expression of Vpx, to further investigate the interplay of SAMHD1 and HIV in Tfh.
Methods: We sort-purified two distinct subsets of CD4+ T-cells from tonsillar tissue (n=6) known to feature distinct levels of SAMHD1, namely: Tfh, defined

as CXCR5^{bright}ICOS^{bright}PD-1^{bright}, and quiescent triple negative (TN), defined as CXCR5^{neg}ICOS^{neg}PD-1^{neg}, using FACS Aria (BD). Both Tfh and TN subsets were infected with HIV-2 and HIV-1 primary isolates with either CXCR4 or CCR5 co-receptor tropism. In parallel, CD4+ naïve T-cells were magnetically sorted from buffy-coats and differentiated into Tfh using a standardized protocol of TCR stimulation and cytokine exposure (TGF-β, IL-12, IL-6, IL-1β) upon infection with HIV-2 or HIV-1 dual-tropic virus. Cell associated total viral DNA and gag mRNA levels were quantified by qPCR, as well as SAMHD1 and Bcl6 expression. Cell phenotype was assessed utilizing high dimensional spectral flow cytometry (Cytek, Aurora), and the data was visualized utilizing the dimension reduction technique UMAP.

Results: We observed significantly higher levels of proviral DNA in Tfh as compared to TN upon 24h for all the viral isolates. Nevertheless, despite the high expression of SAMHD1 in TN, the levels of both proviral DNA and gag mRNA were comparable upon HIV-2 and HIV-1 infections. Contrarily to HIV-1, CXCR4 usage in the case of HIV-2 was not associated with higher proviral DNA in both subsets, suggesting a minor impact of the type of co-receptor. Then, we asked whether HIV-2 infection biased Tfh generation using a standardized protocol for in-vitro Tfh differentiation from circulating naïve CD4 T cells. Of note, the levels of cell-associated proviral DNA were similar 72h post-infection with dual-tropic HIV-2 and HIV-1 primary isolates. Surprisingly, the frequency of the generated Tfh and their detailed phenotype were remarkably similar in all conditions.

Conclusion: HIV-2, despite harboring Vpx, did not feature a significant advantage to infect tonsillar CD4 T cells, irrespectively of their SAMHD1 levels, as well as to modulate in-vitro Tfh differentiation. These first data using HIV-2 primary isolates prompt the investigation of additional paths in the establishment of Tfh reservoirs, and their implications for the benign course of HIV-2.

219 NEF FROM PRIMARY HIV INFECTION COUNTERACTS IFITM3 AND RESTORES VIRION INFECTIVITY

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Background: Interferon-induced transmembrane protein 3 (IFITM3) is a restriction factor that reduces HIV-1 infectivity by incorporating into virions, inhibiting Env function, and reducing virion entry into cells. We previously found that the accessory protein of murine leukemia virus, glycogag enables viral evasion of IFITM3. However, whether other retroviruses encode the means for IFITM3 counteraction was unclear. Here, we investigated whether HIV-1 Nef reduces the impact of IFITM3 on virion infectivity.

Methods: Nef-deficient HIV-1 (NL4.3) was produced by transient transfection of HEK293T cells –/+ pCMV-hIFITM3 and –/+ pBJ-HA-Nef. Infectivity of produced virions was measured by infecting TZM.bl cells (input virus normalized by p24 CA ELISA). Interactions between Nef and IFITM3 were determined by co-immunoprecipitation and western blot analysis. The impact of Nef on IFITM3 subcellular localization was determined by immunofluorescence microscopy of cells transfected with EEA1-GFP.

Results: Expression of IFITM3 in cells producing Nef-deficient NL4.3 HIV resulted in a 4-6 fold loss of virion infectivity. Using Nef from HIV-1 isolated ranging from transmitted/founder to lab-adapted molecular clones, we found that certain Nef variants exhibit the capacity to restore virion infectivity in the presence of IFITM3. Nef derived from primary infection (97ZA012, Clade C) fully restored HIV-1 infectivity in presence of IFITM3, while the effect of NL4.3 Nef was modest. Mutagenesis of Nef revealed that membrane anchoring and interactions with endocytic machinery were critical for overcoming IFITM3. Furthermore, Nef from at least some transmitted/founder strains (including CH040 and SUMA) also conferred resistance to IFITM3. Mechanistically, the relative ability of Nef variants to co-immunoprecipitate IFITM3 was associated with their ability to restore virion infectivity. Furthermore, co-expression of Nef and IFITM3 resulted in the enrichment of IFITM3 in early endosome and a reduction of IFITM3 at the cell surface.

Conclusion: Our results reveal a previously unrecognized activity of Nef that contributes to our understanding of how this accessory protein promotes virion infectivity. Furthermore, our work suggests that Nef restores infectivity not only by antagonizing SERINC family members but also by counteracting IFITM3. From an evolutionary point of view, multiple retroviruses appear to have independently evolved a means to overcome IFITM3 in virus-producing cells.

220 Vpu OF AN SIV ISOLATE CAN TARGET HUMAN BST-2

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Background: HIV-1 Vpu enhances the release of viral particles from infected cells by interfering with host factor BST-2/tetherin, which tethers nascent virions to the cell surface. The activity of Vpu is species-specific. Indeed, Vpu derived from HIV-1 but not SIV could target human BST-2, whereas some SIV Vpus but not HIV-1 Vpu could counteract monkey BST-2. HIV-1 is believed to have derived by zoonosis of SIVcpz. However, since Vpu encoded by SIVcpz neither antagonizes chimpanzee BST-2 nor human BST-2, HIV-1 Vpu was thought to have acquired the activity after virus transmission to humans. Interestingly, Vpu of SIVgsn-99CM71 (SIVgsn71) isolated from Greater Spot-Nosed monkey (*Cercopithecus nictitans*; GSN monkey) counteracted human as well as GSN BST-2. The purpose of our current research therefore was to gain a more in depth understanding of how SIVgsn71 Vpu antagonizes human BST-2 and whether it could indeed be the prototype of HIV-1 Vpu.

Methods: To identify amino acids in SIVgsn71 Vpu critical for downregulation of human BST-2, cells expressing endogenous human BST-2 were infected with HIV-1 carrying WT or mutants of the SIV *vpu* gene. The downregulation efficiency of BST-2 was assessed by flow cytometry. We also performed a gain-of-function study using SIV Vpus normally inactive against human BST-2 (e.g., Vpu derived from SIVgsn166) to assess whether these Vpus can acquire activity against human BST-2 through targeted mutagenesis.

Results: We identified L21, A22, A25, A29, W30, K32, and W33 as important amino acids for SIVgsn71 Vpu to counteract human BST-2. The AxxxAxxxW motif in SIVgsn71 Vpu (A25, A29, and W33) was conserved in HIV-1 Vpu (A14, A18, and W22), but the other identified amino acids (L21, A22, W30, and K32) were unique to SIVgsn71 Vpu. Interestingly, a single amino acid replacement in SIVgsn166 Vpu was sufficient to render it active against human BST-2.

Conclusion: We found that Vpu of the SIVgsn71 isolate can target BST-2 from humans as well as from its natural host. In contrast, Vpu from a related virus isolate, SIVgsn166, was unable to target human BST-2. However, a single mutation in the SIVgsn166 *vpu* gene rendered it active for human BST-2. Our results suggest that the origin of HIV-1 may be more complex than thought and involve contributions from other Simian immunodeficiency viruses.

221 STINGING CD4+ T CELLS TO RENDER THEM REFRACTORY TO HIV INFECTION

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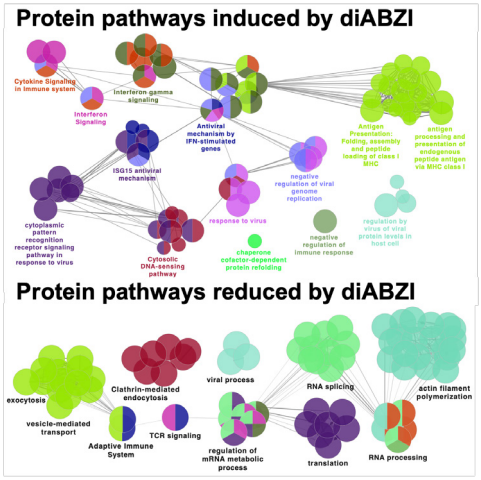
Background: HIV rapidly infects CD4+ T cells where it can establish latent infection. Identifying immune mechanisms which can render CD4+ T cells refractory to infection represents a critical step in limiting infection and viral spread during acute infection. In this study, we identify that the STING signaling pathway functions in CD4+ T cells and can be activated to mediate a cellular state refractory to HIV infection.

Methods: Using purified memory CD4+ T cells from healthy human donors, we stimulated cells with titrating doses (0.1 mM-50 mM) of the STING agonist diABZI for 18 hours followed by infection with HIV 89.6. p24 levels were quantified by flow cytometry (FCM) after 72 hours of infection. We next identified the critical role for STING sensing of HIV in limiting infection by CRISPR mediated knockdown (KD) of STING in purified CD4+ T cells. Control (CTL) and STING KD cells were infected and p24 quantified, as described before. Finally, purified memory CD4+ T cells were treated with 1 mM diABZI for 24 hours and global proteomics performed by Mass Spectrometry to identify the protein signatures induced and suppressed by STING activation.

Results: We found that 0.5 mM diABZI was sufficient to induce a state of refractoriness to HIV infection equivalent to IFN-a2a treatment in central memory CD4+ T cells, a major source of the HIV reservoir (Fig. 1A). We have also shown that diABZI induces Type I IFN production from CD4+ T cells and activates p-IRF3. CRISPR KD of STING in memory CD4+ T cells was shown to significantly enhance the level of HIV infected cells *in vitro*. Proteomics analysis revealed that HIV restriction factors and proteins involved in antiviral immunity and IFN signaling were significantly induced by diABZI. Importantly, proteins that were significantly reduced mapped to pathways including RNA processing and

protein translation which are aspects of the host machinery which HIV needs to co-opt to replicate and produce infectious virions.
Conclusion: Our data provide mechanistic insight into the STING pathway in CD4+ T cells as a means to mediate refractoriness to HIV infection and shows this pathway lands a "1-2" punch of heightening antiviral immunity while suppressing host machinery needed for viral replication. The prospect of treating with a STING agonist as part of post-exposure therapeutics represents a novel and impactful means of helping stop HIV infection in its tracks while restoring the normal antiviral immune response need to control the remaining virus.
Pathway analysis of proteins induced and reduced by diABZI treatment of memory CD4+ T cells



222 PAN-CASPASE INHIBITION PREVENTS HIV REPLICATION BY THE INDUCTION OF THE IFN I PATHWAY

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Background: Viral infection can trigger apoptosis and pyroptosis, which may limit viral replication. However, cleavage of critical molecules of the innate immune signaling pathways by activated caspases may also be of benefit for the virus. We hypothesize that inhibition of caspase activity by the pan-caspase inhibitor Q-VD-OPh can prevent HIV infection by the upregulation of the IFN I antiviral pathway.
Methods: We have determined the effects of Q-VD-OPh on HIV infection in a human tonsil *ex vivo* culture system. Caspase activation, cell death and viral replication have been analyzed in HIV-infected tonsil cells. Expression of activation markers, IFN and IFN-stimulated genes, as well as mitochondrial status have been assessed in uninfected tonsil cells.
Results: Q-VD-OPh prevented HIV-induced CD4+ T cell depletion and severely inhibited viral replication, decreasing the amount of viral p24 and total and integrated DNA in CD4+ T cells. This inhibitory effect was shown to be envelope-independent, as Q-VD-OPh could block infection by VSV-pseudotyped HIV viruses. Additionally, the mechanism of action was found to be caspase-dependent, since the effect was not observed with Q-VE-OPh, which lacks caspase inhibitory activity. Remarkably, HIV infection was still inhibited even when the compound was removed at the time of infection, suggesting Q-VD-OPh induces intrinsic cellular changes that render cells less susceptible to infection. Surprisingly, when evaluating the effect of Q-VD-OPh on cells in the absence of infection, Q-VD-OPh treatment resulted in the modulation of the IFN Type I pathway, leading to increased expression of IFNβ and other IFN-stimulated genes, both in CD3+ and CD3- cells. This type IFN induction was responsible for the inhibition of HIV replication, as a cocktail of neutralizing anti-IFN and anti-IFN receptor antibodies could abrogate Q-VD-OPh restriction. Mechanistically, the activation of the IFN pathway by Q-VD-OPh was linked to changes in mitochondrial membrane potential., as this compound triggered a sublethal mitochondrial depolarization, which did not involve cell death or mitochondrial structure defects.
Conclusion: We propose that Q-VD-OPh induces sublethal mitochondrial depolarization, leading to the release of mitochondrial DNA into the cytosol- This mtDNA can then be detected by cGAS/STING, resulting in the upregulation of type I IFN pathway genes. In summary, Q-VD-OPh inhibits HIV infection by a novel mechanism of action, driving cells into a potent anti-viral state.

223 THE SPIKE OF SARS-CoV-2 VARIANTS ALLOWS FOR MORE EFFICIENT COUNTERACTION OF BST2

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Background: BST2/Tetherin is an interferon-stimulated gene with antiviral activity against enveloped viruses. Particularly, BST2 tethers virions at their site of assembly, preventing their release and spread. In addition to this primary role, BST2 is as an important bridge between the innate and adaptive immune system, since (i) BST2 routes tethered particles to lysosomes, which generates viral breakdown products that engage pattern recognition receptors; and (ii) trapped virions facilitate antibody-dependent cell-mediated cytotoxicity (ADCC). In turn, viruses have evolved mechanisms to bypass BST2, either by targeting BST2 for proteasomal/lysosomal degradation or by removing BST2 from sites of virion assembly. However, the role of BST2 in SARS-CoV-2 replication, spread, evolution, and pathogenesis remains largely unknown.
Methods: The antiviral potential of BST2 against SARS-CoV-2 was investigated by infecting different SARS-CoV-2 isolates (Hong Kong, Alpha, Beta, Delta, and Omicron) in BST2+ and BST2- cells. Culture supernatants were collected to assess virion production by ELISA and infectivity by TCID50. Infected cells were analyzed by western blot and flow cytometry to examine viral and cellular protein levels, including BST2. Transfection of individual SARS-CoV-2 ORFs and mutagenesis studies allowed us to identify the genes that the virus uses to downregulate BST2. Immunoprecipitation assays revealed protein-protein interactions and changes in ubiquitination patterns. Experiments with proteasomal and lysosomal inhibitors furthered our mechanistic understanding of how SARS-CoV-2 counteracts BST2. Finally, fluorescence microscopy studies uncovered changes in the subcellular distribution of BST2 in SARS-CoV-2 infected cells.
Results: While BST2 reduces virion release, SARS-CoV-2 has evolved to counteract this effect. Specifically, SARS-CoV-2 uses the Spike to interact with BST2, sequester the protein at perinuclear locations, and ultimately route it for lysosomal degradation. By surveying different SARS-CoV-2 variants of concern (Alpha-Omicron), we found that each variant is more efficient than the previously circulating strain at downregulating BST2 and facilitating virion production, and that mutations in the Spike account for their enhanced BST2 antagonism.
Conclusion: As part of its adaptation to humans, SARS-CoV-2 is improving its capacity to counteract BST2, highlighting that BST2 antagonism is important for SARS-CoV-2 infectivity and transmission.

224 cGAS-STING PATHWAY LIMITS SARS-CoV-2 REPLICATION IN ACE2+ AIRWAY CELL LINES

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Background: We previously screened 10 human lung and upper airway cell lines expressing variable levels of endogenous ACE2/TMPRSS2. We found that H522 human lung adenocarcinoma cells supported SARS-CoV-2 replication independent of ACE2, whereas the ACE2 positive cell lines were not permissive to infection. Type I/III interferons (IFNs) potently restrict SARS-CoV-2 replication through the actions of hundreds of interferon-stimulated genes (ISGs) that are upregulated upon IFN signaling. Here we report that a number of ACE2 positive airway cell lines are unable to support SARS-CoV-2 replication due to basal activation of the cGAS-STING DNA sensing pathway and subsequent upregulation of IFNs and ISGs which restrict SARS-CoV-2 replication.
Methods: SARS-CoV-2 WT strain 2019-nCoV/USA-WA1/2020 viral replication was detected through analysis of cell associated RNA. RNA sequencing was used to study the basal level of genes in the type-I IFN pathway in the 10 cell lines, which was further validated by western blotting and qRT-PCR. A panel of 5 cell lines, with varying expression levels of *ACE2* and *TMPRSS2*, were pre-treated with Ruxolitinib, a JAK1/2 inhibitor. A siRNA-mediated screen was used to determine the molecular basis of basally high expression of ISGs in cell lines. CRISPR knockout of IFN-alpha receptor and cGAS-STING pathway components was conducted in parallel
Results: Here we show that higher basal levels of IFN pathway activity underlie the inability of ACE2+ cell lines to support virus replication. Importantly, this IFN-induced block can be overcome by chemical inhibition and genetic disruption of the IFN signaling pathway or by ACE2 overexpression, suggesting

that one or more saturable ISGs underlie the lack of permissivity of these cells. Ruxolitinib treatment increased SARS-CoV-2 RNA levels by nearly 3 logs in OE21 and SCC25. Furthermore, the baseline activation of the STING-cGAS pathway accounts for the high ISG levels and genetic disruption of the cGAS-STING pathway enhances levels by nearly 2 and 3 logs of virus replication in the two separate ACE2+ cell line models respectively.
Conclusion: Our findings demonstrate that cGAS-STING-dependent activation of IFN-mediated innate immunity underlies the inability of ACE2+ airway cell lines to support SARS-CoV-2 replication. Our study highlights that in addition to ACE2, basal activation of cGAS-STING pathway, IFNs and ISGs may play a key role in defining SARS-CoV-2 cellular tropism and may explain the complex SARS-CoV-2 pathogenesis *in vivo*.

225 LONG NON-CODING RNA REGULATES IFN-I RESPONSE AND SARS-CoV-2 REPLICATION

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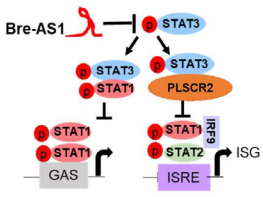
Background: Infection with SARS-CoV-2 triggers reprogramming through global transcriptomic changes that drive the development of Coronavirus disease 2019 (COVID-19). Although the expression and functions of protein-coding transcripts have been widely studied in SARS-CoV-2 infection, most of the transcriptome consists of non-protein-coding RNAs (ncRNAs). Long noncoding RNAs (lncRNAs), which constitute a large proportion of the transcriptome, regulate immune responses and play prominent roles in health and disease. However, the impact of lncRNAs on SARS-CoV-2 infection is poorly understood. Our study will provide fundamental insights into the role of lncRNAs in SARS-CoV-2 infection.
Methods: We hypothesized that SARS-CoV-2-induced lncRNAs are critical regulators of viral replication and immune response. To test our hypothesis, we identified lncRNAs with significant differential expression in SARS-CoV-2 infected vs. uninfected cells across two cell types (A549-hACE2 and Calu) from published transcriptome data. We silenced the expression of the top lncRNA *Bre-AS1* (BA) a human lung epithelial cell model (A549 cells stably expressing hACE2 and hTMPRSS2, A549^{AT}) using lncRNA-specific ASO (lncsi) or negative control (NC) and compared viral replication in lncsi vs. NC cells. BA-silencing (BA-si) increased SARS-CoV-2 replication. and inhibited the expression of antiviral interferon-stimulated genes (ISG). (Tyr 705) pSTAT3 forms suppressor molecular complexes (pSTAT3-pSTAT1 or pSTAT3-PLSCR2) that inhibit ISG transcription. Using molecular methods such as gene-silencing, immunoprecipitation, western blot, and measuring promoter activity, we further show that Bre-AS1 inhibits the phosphorylation of STAT3 and enhances ISG transcription.
Results: Our data show that cellular lncRNA, Bre-AS1 enhances antiviral interferon-stimulated genes (ISG) expression and inhibits replication of SARS-CoV-2. Our data show that Bre-AS1 inhibits the (Tyr705) phosphorylation of STAT3 that forms ISG repressor complexes (pSTAT3-pSTAT1 or pSTAT3-PLSCR2) and thus enhances ISG transcription.
Conclusion: Cellular lncRNA Bre-AS1 enhances expression of antiviral interferon-stimulated genes and inhibits the replication of SARS-CoV-2. Our data show that cellular lncRNAs could play significant roles in immune response and viral propagation. Thus, unraveling the mechanisms of lncRNA-mediated regulation of virus replication and immune response may lead to identifying new, highly selective therapeutic targets
Bre-AS1 inhibits STAT3 phosphorylation and enhances ISG transcription



Phosphorylated STAT3 (pSTAT3) inhibits transcription by both GAS and ISRE elements in the promoter of interferon stimulated genes (ISG genes). Bre-AS1 inhibits STAT3 phosphorylation and enhances ISG expression by inhibiting formation of repressor complexes (pSTAT3-STAT1; pSTAT3-PLSCR2).

226 ELEVATED HIV VIRAL LOAD IS ASSOCIATED WITH HIGHER VIRAL RECOMBINATION RATE *IN VIVO*

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Background: Intra-host recombination of HIV generates new mutational combinations which enable immune escape and multidrug resistance within people living with HIV (PLWHIV). Because HIV recombines via coinfection, we hypothesize that denser HIV populations may have higher rates of coinfection and therefore recombination. However, this potential impact of viral density on recombination has not been previously quantified due to a lack of methods that can sensitively estimate recombination without extensive genetic data.
Methods: To bridge this gap, we develop a method to quantify recombination in genetic time series data based on the autocorrelation of linkage between SNPs across timepoints. We validate this method on extensive simulated data and confirm its accuracy at recovering recombination rates under widely used short read sequencing conditions.
Results: We apply our new method to longitudinal, high-throughput viral sequencing data from PLWHIV, stratifying populations by viral load (a proxy for density) to investigate whether density impacts recombination rate. In populations with viral loads below 5×10^4 copies/mL, we estimate a recombination rate of 2.4×10^{-5} events/bp/generation (95% CI 1.5×10^{-5} - 3.9×10^{-5}), similar to existing estimates. However, in populations with viral loads above 5×10^4 copies/mL, we estimate significantly higher rates of viral recombination (7.5×10^{-5} events/bp/generation, 95% CI 5.5×10^{-5} - 9.8×10^{-5}). This elevation of viral recombination rate in populations with high viral loads persists across a number of viral load thresholding choices. We find a similar association of viral load and recombination rate within a single individual with varying viral load over time.
Conclusion: Our findings suggest that recombination rates can vary across PLWHIV and within those people over time, deepening our understanding of this otherwise static parameter. Elevated recombination rate during periods of high viral load provides an additional hypothesized mechanism for how HIV diversifies during acute and/or uncontrolled infection and suggests that incorporating variation in recombination rate estimates could lead to new insights from intra-host genetic data.

227 Vpr ENHANCES HIV REPLICATION BY INHIBITING T CELL PROLIFERATION

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Background: The resting HIV reservoir is a major obstacle towards curing HIV+ people. The reservoir is composed of clonally expanded T cells that predominantly harbor defective proviruses. A few infected cells containing replication-competent provirus are responsible for rebound viremia after treatment interruption. It is known the Vpr protein inhibits proliferation in cell lines. However, the timing of Vpr expression in resting infected cells is unknown and whether it will prevent proliferation of cycling primary CD4 T cells with replication-competent HIV.
Methods: We explored this question by direct infection of primary resting CD4 T cells with a CCR5-tropic replication-competent GFP reporter virus. We measured GFP expression by flow cytometry over 5 days. We performed bulk and single cell RNAseq of sorted GFP+ cells to measure host and virus mRNAs. We measured proliferation by first labelling resting infected cells with violet CellTrace and then stimulating them for 10 days with anti-CD3/CD28 beads and ART. We infected cells with wild-type Vpr, without Vpr, and with Vpr mutants known to affect T cell proliferation. We measured cell cyle progression using the mitosis marker phospho-Ser31 in histone 3.3 in both resting and stimulated cells with ART. Finally, we assayed HIV replication through co-culture of sorted infected cells with autologous or heterologous target primary CD4 T cells.
Results: We detected resting GFP+ cells 3 to 4 days after infection. Transcriptome analysis of resting GFP+ revealed infected cells expressed mRNAs coding for Vif, Vpr, VpuEnv and Nef. We confirmed Vpr modulates progression through the cell cycle and prevents T cell proliferation. Infected cells lacking Vpr contained transcriptionally-silent proviruses in the divided cells. In contrast, transcriptionally-active proviruses were present in the divided cells that expressed non-functional Vpr, because of mutations that prevented its binding to the host ubiquitin chaperone protein DCAF1. Lastly, we found replication-competent HIV originated from the undivided cells instead of the divided cells.
Conclusion: We conclude HIV can directly infect primary resting CD4 T cells. After T cell stimulation, Vpr prevents infected primary CD4 T cells from proliferating, which enhanced HIV replication. Surprisingly, two distinct effects on the provirus occurred after release of T cell proliferation based on whether Vpr was not expressed or non-functional.

228 A HUMAN-SPECIFIC CARD8 MUTATION AFFECTS INFLAMMASOME ACTIVATION AFTER HIV-1 INFECTION

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Background: Humans have a variety of innate immune sensors including inflammasomes which are cytosolic innate immune complexes that can sense and respond to pathogens. It was recently shown that the caspase recruitment domain-containing protein 8 (CARD8) inflammasome is activated by recognizing the enzymatic activity of HIV-1 protease (HIV-1PR), resulting in a lytic form of cell death called pyroptosis and the release of proinflammatory cytokines when a nonnucleoside reverse transcriptase inhibitor (NNRTI) was used to enforce protease dimerization (Wang et al 2021). Here, we took an evolution-guided and virological approach to infer the significance of CARD8's interaction with different lentiviral proteases in the context of intact proviruses.
Methods: Among available primate CARD8 sequences, only human CARD8 has a phenylalanine at the P1′ site of the HIV-1 protease cleavage site. We assessed the ability of HIV^{PR} and SIVcpz protease to cleave different CARD8 variants using an overexpression system. Additionally, we assessed whether or not CARD8 sensing and inflammasome activation occurs during HIV-1 infection using THP-1 cells that were knocked out for the *CARD8* gene and then complemented back with different variants of CARD8.
Results: We demonstrated that human CARD8 has a unique motif among hominoids, Old World monkeys and gibbons that renders it susceptible to cleavage by $HIV\text{-}1^{PR}$ and SIVcpz protease, indicating that the precursor viruses to HIV-1 were poised to cleave human CARD8, but do not cleave chimpanzee CARD8. Further, we show that human CARD8, but not chimpanzee CARD8, can sense lentiviral protease activity and induce inflammasome activation in the context of HIV-1 infection *in vitro*, but only if the target cells are first transcriptionally primed with toll-like receptor (TLR) stimulation prior to viral challenge.
Conclusion: As a major hallmark of acute HIV-1 disease is circulating microbial ligands like lipopolysaccharides caused by the breakdown of the gut epithelial barrier, we hypothesize that CARD8-induced pyroptosis may be a major driver of HIV-1 pathogenesis contributing to depletion of the T cell population and chronic inflammation that characterize HIV/AIDS disease and may partially explain increased pathogenesis of HIV-1 in humans relative to SIVcpz in chimpanzees.

229 CARD8 INFLAMMASOME MODULATES HIV-1 INFECTION IN CD4+ T CELLS

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Background: CARD8 is an innate immune sensor that can be activated through proteolytic cleavage. Recently, we reported that induction of HIV-1 protease activation leads to CARD8 inflammasome-mediated pyroptosis of infected macrophages and CD4+ T cells. However, it remains unclear whether natural HIV-1 infection can activate the CARD8 inflammasome to trigger pyroptosis of CD4+ T cell and thereby modulating HIV-1 replication.
Methods: We co-cultured HIV-1-infected CD4+ T cells with CFSE-labeled control PBMCs (target cells) to assess the CD4+ T cell death and inflammasome activation. We also infected CD4+ T cells with replication-competent HIV-1 *in vitro* and *in vivo* to examine the role of CARD8 inflammasome in viral replication.
Results: We found that HIV-1 infection induces rapid CARD8-dependent pyroptosis of CD4+ T cells in peripheral blood, tonsil tissues, and humanized mice. Mechanistically, the N-terminus of CARD8 is cleaved by HIV-1 protease encapsulated in the incoming viral particles immediately after viral entry, which creates an unstable neo-N terminus, resulting in proteasome degradation of CARD8 and release of the bioactive C-terminal fragment for inflammasome assembly and pyroptosis. We also observed that deletion of CARD8 significantly reduced HIV-1-triggered cell death, leading to increased susceptibility to HIV-1 infection in CD4+ T cells. Furthermore, we showed that sensitization of CARD8 by DPP9 inhibitor suppressed HIV-1 infection in CD4+ T cells.
Conclusion: This study demonstrates that HIV-1 infection activates the CARD8 inflammasome in CD4+ T cells, which provides critical insights into how the CARD8 modulates HIV-1 infection and pathogenesis. This work elucidates sensitization of CARD8 by DPP9 inhibitor restricts HIV-1 infection, suggesting that targeting CARD8 inflammasome may facilitate the development of new therapeutics for HIV-1.

230 VHH DIMER P559-R45L NEUTRALIZES SARS-CoV-2 BY STABILIZING SPIKE IN UP CONFORMATION

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Background: SARS-CoV-2 Omicron subvariants are highly resistant to vaccine-induced immunity and therapeutic monoclonal antibodies. We previously reported anti-SARS-CoV-2 spike alpaca nanobodies (VHHs) P86 and P17 that potently neutralize the wild type and VOCs from Alpha to Omicron BA.1 and BA.2, but not Omicron subvariants after that such as BA.4/5. Thus, we tried to establish a new VHH that can neutralize all the variants including BA.4/5.
Methods: We developed VHH trimers and heterodimers based on the structural and computational analysis of Delta spike-immunized alpaca VHH library. We tested representative VHHs against SARS-CoV-2 spike by pseudovirus assays and generated VHH heterodimers. We further obtained Cryo-EM structure of Spike trimer and VHH monomer or heterodimer.
Results: First, we generated series of P86 mutants to counteract L452R mutation in Delta or Omicron BA.5 subvariants and found that P86 R45L was most potent against D614G with an IC_{50} of 0.03 µg/mL. From the Delta spike-immunized VHH library, we also identified that homo-trimer of a new clone P559 neutralized SARS-CoV-2 Delta and Omicron BA.5 variants with an IC_{50} of 0.077 and 0.54 µg/mL, respectively. We finally generated P559-R45L heterodimer that neutralized all the variants so far including Omicron BA.5 with an IC_{50} of 0.39 µg/mL. Cryo-EM structure revealed that three molecules of P559-R45L heterodimer bridged two RBD molecules in the spike trimer and stabilized spike timers with RBD in the up conformation.
Conclusion: We developed VHH P559-R45L heterodimer that potently neutralized all the variants including Omicron subvariants through unique structural interaction.

231 Fc RECEPTOR-MEDIATED INFECTION OF MYELOID CELLS BY SARS-CoV-2

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Background: The role of myeloid cells in the pathogenesis of SARS-CoV-2 is well established, in particular as drivers of cytokine production and systemic inflammation characteristic of severe COVID-19. However, the potential for myeloid cells to act as bona fide targets of productive SARS-CoV-2 infection remains unclear.
Methods: Using anti-SARS-CoV-2 mAbs with a range of neutralisation potencies and binding specificities, we performed a detailed assessment of mAb-mediated infection of monocytes/macrophages. THP-1 cells were used as a model system, with results confirmed in primary macrophages.
Results: Infection of THP-1 cells was seen via mAbs targeting the spike RBD, but not with those targeting the NTD or S2 subunit. mAbs with the most consistent potential to mediate infection targeted a conserved region of the RBD (group 1/class IV). No infection was seen with the same quantity of virus but in the absence of antibody, and pre-treating the cells with FcγRI and -II blocking antibodies inhibited infection. Thus, antibody-FcR interactions are able to expand the tropism of SARS-CoV-2. Time-course studies demonstrated high-level and productive infection. Studies performed in human iPSC-derived macrophages and primary monocyte-derived macrophages paralleled results seen in THP-1 cells but with lower infection levels. Up to 2% of macrophages were infected, with infected cells appearing multinucleated and syncytial. Addition of ruxolitinib, an inhibitor of JAK1/2 signalling, increased infection up to 10-fold, indicating limitation of infection through innate immune mechanisms. Sera from primary infections (n=80) mediated rare infection events, with a minority of samples (n=3) promoting significant infection. Competition assays confirmed results seen in sera, with the addition of neutralising mAbs diminishing the infection seen with infection-mediating mAbs. Thus, the presence of antibodies with potential to mediate infection is not sufficient to predict myeloid cell infection, rather, the context in which the antibodies are produced is key.
Conclusion: We hypothesise that a nascent antibody response during peak viral replication in primary infection presents a window of opportunity for myeloid cells to become infected, while establishment of a robust polyclonal response via vaccination or prior infection reduces the likelihood of this occurring.

Infection via antibody-FcR interactions could contribute to pathogenesis in primary infection, systemic virus spread or persistent infection.

232 OMICRON SPIKE ENDOWS SARS-CoV-2 WITH ENHANCED INFECTIVITY IN NASAL EPITHELIA

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Background: Omicron lineages, including BA.1 and BA.2, emerged following mass COVID-19 vaccination campaigns, displaced previous SARS-CoV-2 variants of concern worldwide, and gave rise to sublineages that continue to spread among humans. Previous research has shown that Omicron lineages exhibit a decreased propensity for lower respiratory tract (lung) infection compared to ancestral SARS-CoV-2, which may explain the decreased pathogenicity associated with Omicron infections. Nonetheless, Omicron lineages exhibit an unprecedented transmissibility in humans, which until now has been solely attributed to escape from vaccine-induced neutralizing antibodies.
Methods: We comprehensively analyzed BA1 and BA2 infection in primary human nasal epithelial cells cultured at the air-liquid interface, which recapitulates the physiological architecture of the nasal epithelium *in vivo*. Meanwhile we also took advantage of the VSV-based pseudovirus decorated with different Spike variants.
Results: In primary human nasal epithelial cells cultured at the air-liquid interface, which recapitulates the physiological architecture of the nasal epithelium *in vivo*, BA.1 and BA.2 exhibited enhanced infectivity relative to ancestral SARS-CoV-2. Using VSV-based pseudovirus decorated with different Spike variants, we found that increased infectivity conferred by Omicron Spike is due to superior attachment and entry into nasal epithelial cells. In contrast to ancestral SARS-CoV-2, invasion of nasal epithelia by Omicron occurred via the cell surface and endosomal routes of entry and was accompanied by elevated induction of type-I interferons, indicative of a robust innate immune response. Furthermore, BA.1 was less sensitive to inhibition by the antiviral state elicited by type-I and type-III interferons, and this was recapitulated by pseudovirus bearing BA.1 and BA.2 Spike proteins.
Conclusion: Our results suggest that the constellation of Spike mutations unique to Omicron allow for increased adherence to nasal epithelia, flexible usage of virus entry pathways, and interferon resistance. These findings inform our understanding of how Omicron evolved elevated transmissibility between humans despite a decreased propensity to infect the lower respiratory tract. Additionally, the interferon insensitivity of the Omicron Spike-mediated entry process may explain why Omicron lineages lost the capacity to antagonize interferon pathways compared to ancestral SARS-CoV-2.

233 SARS-CoV-2 REPLICONS REVEAL SPIKE-INDEPENDENT ATTENUATION OF THE OMICRON VARIANT

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Background: The SARS-CoV-2 Omicron variant is highly immune evasive but is attenuated in cell and animal models of infection, which many reports attribute to spike mutations. However, the phenotype and contribution to viral fitness of Omicron non-spike mutations remain unknown.
Methods: To study mutations across the entire genome independent of spike, we developed a novel cloning and replicon system capable of generating mutants within 6 hours and obtaining phenotypic results within 3-4 days.
Results: Using a series of Omicron replicons, we found that ORF1ab harbors critical mutations, especially in the nonstructural protein 6 (NSP6), which lower viral fitness and are currently evolving in Omicron subvariants. In addition, Omicron mutations in several NSPs epistatically interact and are critical for viral replication and polyprotein processing.
Conclusion: Collectively, we describe a robust replicon technology to study mutations across the genome and our data highlight the need to vigilantly study and monitor non-spike mutations in emerging Omicron subvariants.

234 SARS-CoV-2 USES ENDOSOMAL MEMBRANES TO BUILD REPLICATION ORGANELLES

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Background: The health emergency caused by the COVID-19 pandemic has evidenced that the frequency of spillover episodes of viruses infecting bats to other species, including humans, has significantly increased compared to previous decades. Besides SARS-CoV-2, six other human coronaviruses (NL63, 229E, OC43, HKU1, SARS-CoV and MERS-CoV) emerged in the 20th and 21st century, most likely because of cross-species transmission events from bats. While many of these coronaviruses cause mild respiratory infections, MERS-CoV, SARS-CoV and SARS-CoV-2 can cause severe respiratory distress, particularly in immunocompromised individuals. However, unlike SARS-CoV and MERS-CoV, SARS-CoV-2 is highly contagious, very stable, with many person-to-person transmissions, which can occur even before individuals exhibit any symptoms. While vaccines are readily available, the emergence of new SARS-CoV-2 variants along with the increasing incidence of individuals developing long COVID urge to develop antivirals specific to treat COVID-19. To reach this goal, we need to have a working knowledge of the host-SARS-CoV-2 interactions to identify targets for therapeutic intervention.
Methods: Following that rationale, we focused on understanding how SARS-CoV-2 generates replication organelles (ROs). All coronaviruses need to remodel cellular membranes to create these structures to allow the active replication and transcription of their genome. Due to their relevance for virus replication, disabling RO formation represents a promising strategy to fight SARS-CoV-2. However, the biogenesis mechanism, the origin, and type of these replication organelles are still a major focus of debate. To identify the cellular membranes that SARS-CoV-2 uses to generate ROs we used multiple cell lines and primary cells that were evaluated by fluorescence microscopy, genetic engineering, compounds that specifically inhibit cellular processes, and immunoprecipitation assays to validate protein-protein interactions. We also used RT-qPCR to assess viral genome replication.
Results: SARS-CoV-2 uses the viral protein NSP6 to remodel endosomal membranes juxtaposed to the ER to generate replication organelles. Specifically, the virus depends on Clathrin, COPB1, and Rab5 for efficient SARS-CoV-2 RNA synthesis.
Conclusion: Uncovering the origins and mechanism(s) by which SARS-CoV-2 assembles ROs opens new avenues to develop strategies to interfere with RO biogenesis and halt virus replication.

235 WITHDRAWN

236 MPOX VIRUS SEQUENCES DIVERSITY IN PARIS AREA DURING THE 2022 OUTBREAK

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Background: Since May-2022, non-endemic countries reported mpox cases with no epidemiological link to Africa, mostly affecting men-who-have-sex-with-men (MSM). We deciphered genetic variability of epidemic mpox from French infected patients and compared sequences with pre-epidemic Western-African sequences.

Methods: Sequences generated from 12 PCR-amplified fragments (~30,000 base-pairs) included -outside terminal repeats- 28/35 mutation sites previously reported in epidemic isolates compared to reference clade-3 MT903344_2018_UK_P2 pre-epidemic strain. All 7 unexplored mutations were synonymous.

Results: We studied 130 mpox-infected patients attending Bichat University-Hospital, Paris, France: 110 sampled during the early 2022 outbreak period (24/05-04/07) and 20 later on (16/08-10/09), from which we produced 162 sequences. Available medical records showed that 95.0% were men, 5% transgenders (M to F), and 90% MSM of whom 50% on HIV pre-exposure prophylaxis. Among these 25% lived with HIV and 25% had travelled within 3 weeks prior to mpox diagnosis (>85% to Europe, none to Africa); 5% were hospitalized, mostly for severe pharyngeal/tonsils. We observed 32 different mutational patterns (pattern#1 in 120 sequences; #9 in 10; and #13 in 2; others in 1). All included a 17nt-deletion (pos. 150,621, intergenic) previously observed in a French sequence (ON602722) but present in only 37% of epidemic strains. Pattern#8 included a previously unreported 4nt-deletion (pos. 14,509, ORF OPG25). Overall, 55% of single-nucleotide mutations were non-synonymous, 30% synonymous, 10% non-coding. There was a majority of transitions (15 GèA; 8 CèT), confirming a highly specific mutational typology.

In a patient returning from Asia, we identified a profile (pattern# 26), closely related to clade-3 pre-epidemic and N674051_2022_USA. This suggests a baseline circulation of non-epidemic mpox in Western countries, probably underdiagnosed and detected here due to attention generated by the outbreak.

Conclusion: This rapid parsimonious mpox sequencing strategy in 130 mpox-infected patients provided a unique insight into the genomic variability of an epidemic DNA virus, confirmed the existence of epidemic strain-specific mutational patterns and quantified the overall genomic variability of circulating strains. It highlights, although rare, the non-epidemic circulation of mpox and the need to more frequently consider mpox diagnosis.

237 WITHDRAWN

239 GENOMIC SURVEILLANCE OF SARS-CoV-2 REVEALS SEVERITY OF DELTA VARIANT IN CAMEROON

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*Presented at CROI by a nonauthor colleague

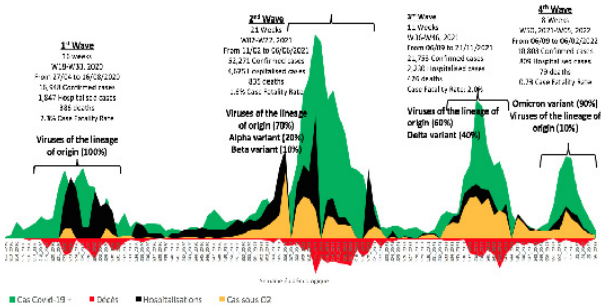
Background: At the global level, the dynamics of the COVID-19 pandemic have been driven by several epidemiological waves, determined by the emergence of new SARS-CoV-2 variants from the original viral lineage from Wuhan, China. While the SARS-CoV-2 dynamic has been described globally, there is a lack of data from Sub-Saharan African.

Methods: A laboratory-based survey was conducted in Cameroon, from March 1, 2020 to March 30, 2022, through an assessment of the evolutionary patterns of SARS-CoV-2 lineages across the four COVID-19 waves in the country. Data on full-length sequencing from all four sequencing laboratories were consecutively entered into the GISAID platform. These data were downloaded, and the molecular phylogeny of the SARS-CoV-2 sequences was performed using Nexstrain. The Mann–Whitney U test was used to calculate the correlation between the duration of each outbreak and the number of confirmed cases and between hospitalised cases and CFR, with a p value < 0.05 considered statistically significant.

Results: A total of 3,881 samples were successfully processed, of which 38.9% (n=1,509) using PCR mutation assay, 41.5% (n=1,612) using targeted sequencing, and 19.6% (n=760) using whole-genome sequencing. The mean age of the study population was 36 years (min–max: 2–86), and 45% were within the age range 26–45. Regarding gender distribution, 50.9% were male, and 49.1% were female. Phylogenetic analysis of the 760 whole-genome sequences generated from March 2020 to March 2022 revealed that the greater proportion of SARS-CoV-2 circulating in Cameroon belonged to the viral sub-lineages of the original strain from Wuhan (74%), 15% Delta variant, 6% Omicron variant, 3% Alpha variant and 2% Beta variant.The pandemic was driven by SARS-CoV-2 lineages of origin in Wave 1 (16 weeks, 2.3% CFR), the Alpha and Beta variants in Wave 2 (21 weeks, 1.6% CFR), Delta variants in Wave 3 (11 weeks, 2.0% CFR), and Omicron variants in Wave 4 (8 weeks, 0.73% CFR), with a declining trend over time (p=0.01208).

Conclusion: In a nutshell, the SARS-CoV-2 epidemic in Cameroon appears to have been driven by the SARS-CoV-2 lineage of origin in Wave 1, the co-introduction of the Alpha and Beta variants in Wave 2, the Delta variant in Wave 3, and the Omicron variant in Wave 4, with an overall declining trend in the wave duration, confirmed cases and hospitalisations over time.The SARS-CoV-2 lineage of origin and the Delta variant appeared to be the drivers of COVID-19 severity in Cameroon.

SARS-COV-2 lineage dynamics per wave in Cameroon



240 EARLY EVOLUTION OF HIV-1 FROM TRANSMITTED FOUNDERS DURING ACUTE INFECTION

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Background: To better define the number of transmitted founder variants and sequence divergence from founders in the first few weeks following HIV-1 transmission, we performed ultra-sensitive single genome sequencing (SGS) of pol and env HIV-1 RNA in plasma samples from individuals with acute HIV-1 infection.
Methods: HIV-1 RNA was extracted from plasma samples of donors with acute CRF01_AE infection (Fiebig II-IV) enrolled in the RV254/SEARCH010 Cohort (NCT00796146). Five of the donors had been identified by standard SGS as having multiple transmitted founders (TFs) and 10 as single TFs, consistent with the prior report showing 70% having single TFs in RV254. Our ultrasensitive SGS method with primer IDs and 500 bp paired-end Illumina sequencing was applied to identify >10,000 independent *pol* and *env* sequences per sample. We used radial trees (Figure 1) and star phylogeny to identify TFs, calculated transition/transversion (Ti/Tv) and non-synonymous/synonymous (dN/dS) ratios, identified drug resistance mutations (DRMs), and analyzed the phylogenetic relationships between emergent variants.
Results: An average of 12,823 pol and 11,249 env independent RNA sequences determined from consensus building of millions of barcoded reads were obtained from the plasma samples of the 15 donors. In single TF infections, an average of 85% of the genomes were identical to the TF. An average of 13% of the genomes contained only a single mutation. 1% of the genomes contained 2 mutations and 1% had 3-6 mutations, with 2 samples containing up to 12 mutations in a few genomes. Ti/Tv ratios were 5.5 and 3.4 in *pol* and *env* respectively. DRMs were found at very low frequency (0.01-0.09%) in all samples. Mutations predicted to confer resistance to the antibody VRC-01 were also present in all samples. The dN/dS in *env* (M=2.83, SD=0.90) was greater than *pol* (M=1.47, SD=0.74; t(9)=3.31, p=0.009). Mutation frequency was higher in both genomic regions in samples from later Fiebig stages.
Conclusion: Overall, ultrasensitive SGS (>10,000 genomes per sample) did not identify more transmitter founder variants than low depth (10 genomes) SGS, verifying that HIV-1 infection is most commonly established by a single variant. By contrast, ultrasensitive SGS revealed viral evolution from the founder variants in all samples including those from as early as Fiebig stage II, indicating rapid evolution of HIV-1, including appearance of DRMs soon after transmission.

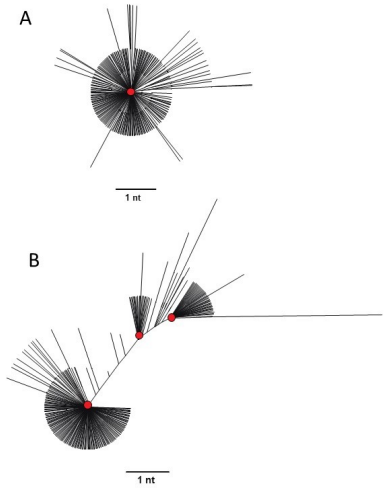

Figure 1. Phylogenetic analyses of ultrasensitive SGS data on one donor previously identified by standard SGS as having a single founder (A) and one previously identified by standard SGS as having multiple founders (B). The red circles show the consensus sequences of the predicted transmitted founders. More detailed phylogenetic analyses will be presented.

241 ASSOCIATION OF MBL2 GENE POLYMORPHISMS WITH HIV-1 INFECTION IN MOROCCO

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Background: Human Mannose-binding lectin (MBL) is a serum protein secreted by the liver. It is encoded by the *MBL2* gene and participates in the activation of the innate immune defense system through the lectin-complement pathway. Several studies showed that the deficiency of the *MBL2* gene is correlated to several infectious and autoimmune diseases susceptibility, including HIV-1 infection. The present study aims to investigate the impact of six MBL2 gene polymorphisms (rs11003125, rs7096206, rs7095891, rs5030737, rs1800450, and rs1800451) located in the promoter, 5' UTR and exon 1 regions on HIV-1 infection susceptibility, AIDS development and the antiretroviral treatment response outcome among Moroccan population.
Methods: This case-control study involves 400 consenting individuals, including 200 HIV-1 infected patients and 200 healthy controls. The genotyping of *MBL2* gene polymorphisms was performed by gene amplification using conventional PCR followed by DNA sequencing.
Results: After the Bonferroni correction, the statistical analysis showed that the GG genotype of rs7096206 polymorphism has a protective association with HIV-1 infection susceptibility with a *p*.adjust-value of 0.028 (OR=0.50 ; 95% CI=0.29-0.85). While the TT genotype of rs503037 and AA genotype of rs1800451 polymorphisms are associated with an increased risk of HIV-1 infection susceptibility (*p*.adjust=0.042 ; OR=3.30; 95% CI=1.21-9.00 and *p*.adjust< 0.001 OR=3.07; 95% CI=1.71-5.51, respectively). Moreover, a significant association between CGA haplotype in the first exon and HIV-1 infection susceptibility was found. It has been associated with an increased risk of acquiring HIV-1 with a *p*.adjust=0.014; OR=1.89; 95% CI=1.27-2.82. However, no significant difference in the frequency distributions between all studied polymorphisms and AIDS development or antiretroviral treatment response was detected (*p*.adjust > 0.05).
Conclusion: Our findings highlight the contribution of the homozygote mutated polymorphisms of the *MBL2* gene in the modulation of HIV-1 infection susceptibility.

242 DIFFERENTIAL INFECTION OF ECTO- AND ENDOCERVIX BY TRANSMITTED/FOUNDER HIV-1 *Ex vivo*

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Background: Characterization of the targets and kinetics of HIV infection within mucosae is key to assessing novel prevention agents. The identification and characterization of the TF HIV-1 replication in human explant cultures

provide an important foundation to study HIV pathogenesis in humans and design interventional measures to curb/reduce HIV transmission.
Methods: Full length infectious molecular clones of viruses were derived from people with acute HIV-1 clade C infection from IAVI Protocol C cohort. Two viruses, HIV-$1K_{4790}$ and HIV-$1K_{4791}$ were generated by plasmid DNA transformation, purification, and propagation in PBMCs. Donor-matched ecto- and endocervical explants derived from HIV-1-negative volunteers from Chicago and Nairobi, were then infected with HIV-1_{BaL}, HIV-$1K_{4790}$ and HIV-$1K_{4791}$ using nevirapine as a control. The explants were then incubated at 37°C, 90% humidity and 5% CO_2 for 12 days. DNA was extracted and HIV-1 replication assessed by RT-qPCR.
Results: There was no significant differences in rate of infection between HIV-1_{BaL} and HIV-$1K_{4791}$ in the ectocervical tissues. However, HIV-$1K_{4791}$ produced less virus in the ectocervix compared to HIV_{BaL} ($p< 0.01$). HIV-$1K_{4790}$ had a lower rate of infection in the ectocervix compared to HIV_{BaL} ($p=0.03$, $n=36$). In the endocervical tissues, HIV-$1K_{4791}$ infected less compared to HIV_{BaL} ($p=0.03$, $n=36$). However, the rate of infection between HIV-1_{BaL} and HIV-$1K_{4790}$ in the ectocervix was similar ($p < 0.01$). HIV-$1K_{4790}$ had a lower rate of infection in the ectocervix compared to HIV_{BaL} ($p=0.03$, $n=36$). In the endocervical tissues, HIV-$1K_{4791}$ infected less compared to HIVBaL ($p=0.03$, $n=36$). However, the rate of infection between HIV-1_{BaL} and HIV-$1K_{4790}$ in the ectocervix was similar. Further, HIV-$1K_{4790}$ and HIV-1_{BaL} replicated similarly in endocervix and ectocervix.
Conclusion: We demonstrate that the endocervix and ectocervix are differently infected with TF HIV-1, indicating that these two compartments are distinct. In addition, we demonstrate a potential assay capable of testing potency of HIV antiviral drugs at mucosal surfaces *ex vivo*. In the next phase, using the same model, we will use imaging techniques to characterize the initial immune targets of HIV-$1K_{4790}$ and HIV-$1K_{4791}$ in the human cervix. Taken together, the discovery and characterization of TF HIV-1 replication in human mucosal explant cultures may serve as a crucial reference point for investigating HIV pathogenesis and developing interventional strategies to prevent HIV transmission.

243 PD-1 IS AN INSENSITIVE MARKER FOR HIV/SIV RNA+ LYMPH NODE TFH IN UNTREATED INFECTION

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Background: Follicular T helper cells (TFH) are the major viral RNA expressing (vRNA+) cells in secondary lymphoid tissues during chronic HIV/SIV infection prior to AIDS/SAIDS. TFH are variably defined based on location in germinal centers (GC), and/or expression of the canonical transcription factor BCL6 and multiple cell surface markers including PD-1. In some *in vitro* systems, HIV downregulates PD-1, but whether this occurs *in vivo* is unknown. We investigated the distribution and expression of BCL-6 and PD-1 by HIV/SIV RNA+ cells in lymph nodes of untreated people living with HIV (PLWH) and SIV-infected rhesus macaques (RM).
Methods: Inguinal LN frozen in OCT from 7 PLWH (3 female; median age 42y; median viral load $4.35log_{10}$; median CD4 706) and 5 RM (4 female; median age 3y; median viral load $6.0log_{10}$) was sectioned (10µm) and fixed in paraformaldehyde. In situ hybridization for vRNA and BCL6 mRNA (ACDbio), and immunofluorescent antibody staining for PD1 and CD20 was performed. Slides were imaged (Aperio scanner), vRNA+ cells identified (median vRNA+ cells, 59/92 in PLWH/RM) and phenotypes determined. CD20+ areas defined follicles (F), CD20- areas extrafollicular (EF), and clusters of BCL6 in F defined GC. Nonparametric statistical analyses were performed; data reported are medians.
Results: In PLWH, most (78%) GC vRNA+ cells were BCL6+ and comparatively fewer nonGCF (60%; $p=0.03$) and EF (50%; $p=0.03$). PD-1 was present on 72% of GC, 53% of nonGCF, and 23% of EF vRNA+ cells ($p=0.01$). Percentages of BCL6+ vRNA+ cells that were PD-1+ were highest in GC (75%), and relatively lower in nonGCF (56%; $p=0.2$) and EF (11%; $p=0.03$). In RM, similar trends in BCL6 expression in vRNA+ cells were observed; 90% of GC, 48% of nonGCF and 50% of EF vRNA+ cells were BCL6+. PD-1 expression was substantially lower in RM than in PLWH; PD-1 was found on only 36% of GC, 15% of nonGCF, and 4% of EF vRNA+ cells. Percentages of BCL6+vRNA+ cells that expressed PD-1 were 38% in GC, 25% in nonGCF and 5% in EF.
Conclusion: PD-1 was not found on 25% of vRNA+ GC TFH in PLWH and 62% in RM, when defining TFH as BCL6+ vRNA+ cells in GC. Whether BCL6+ cells outside of the GC are TFH is unknown, but decreased PD-1 expression on BCL6+ vRNA+ cells outside of the GC is consistent with a model of downregulation of PD-1 on vRNA+ TFH infected in the GC as they migrate into nonGCF and EF. Sorting strategies to quantify vRNA that identify TFH utilizing PD-1 expression likely underestimate TFH contribution to viral burden.

244 IDENTIFICATION OF HIV-2 EXTREME ELITE CONTROLLERS OFFERS INSIGHT TO FUNCTIONAL CURE

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Background: HIV-2 is less pathogenic compared to HIV-1, and HIV-2-infected individuals usually have undetectable or low plasma RNA viral loads. Thus, many HIV-2 aviremic individuals resemble a rare group of HIV-1-infected elite controllers (ECs) that spontaneously control their infection and clinical progression. Although there is a significant compilation of studies on HIV-1 ECs, the characterization of HIV-2 ECs remains scarce. Here, we set out to study levels of viral control and immune modulation in HIV-2-infected individuals to identify traits that could be linked to spontaneous functional cure.
Methods: HIV-2-infected and HIV seronegative individuals were recruited from an occupational cohort in Guinea-Bissau. HIV-2 control was determined by quantifying plasma viral RNA load (pVL) and cell-bound viral DNA load. Immune modulation was analyzed by protein profiling of plasma and phenotyping of T-cell subsets, using markers previously linked to HIV disease progression and immune exhaustion.
Results: The HIV-2-infected individuals were stratified into the following groups: i) viremic with pVL above the qPCR quantification level (>75 copies/ml); ii) low viremic with pVL above the detection level but below the quantification level (5-75 copies/mL); iii) elite controllers (ECs) with undetectable pVL (< 5 copies/mL) and detectable cell-bound DNA load (>1 copy/10^6 leukocytes); iv) extreme elite controllers (EEC) with undetectable pVL and undetectable cell-bound viral DNA load (< 1 copy/10^6 leukocytes). Thus, the EEC definition contrasts with that of HIV-1 EC, where cell-bound viral DNA is detected. Further characterization showed that HIV-2 EECs could not be distinguished from HIV seronegative individuals by neither CD4+ T-cell level, concentrations of plasma markers previously linked to HIV disease progression, nor frequencies of chronically activated and exhausted T cell populations. Moreover, plasma proteome profiling and unsupervised hierarchical clustering revealed that reduced plasma concentrations of soluble co-inhibitory receptors differentiated the EEC group from the other groups.
Conclusion: EECs represents a previously undefined group of HIV-2-infected individuals able to spontaneously control their HIV infection. Further characterization of host responses and genetics in this unique group of HIV-infected individuals could reveal new insights into HIV extreme elite control, and spur novel functional cure strategies.

245 T CELLS HOMEOSTASIS DISTURBANCES IN A COHORT OF LONG-TERM ELITE CONTROLLERS

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Background: Elite controllers (EC) are an exceptional group of people living with HIV (PLWH) able to control HIV replication without antiretroviral therapy and have been proposed as a model of functional HIV cure. However, several evidence suggest that this spontaneous control of HIV has a cost in terms of systemic inflammation and immune activation. Herein we have performed a deep phenotypic study to get insight into the T-cells homeostasis disturbances in EC maintaining long-term virologic and immunologic control of HIV (long-term elite controllers; LTEC).
Methods: Forty-three PLWH were included:20 LTEC, 14 non-controllers under successful cART (TX), 9 non-controllers cART-naïve with replicating HIV (TP). Nineteen healthy participants (HC) were included as reference. T-cells homeostasis was analysed by spectral flow cytometry using a panel of 22

different T-cells markers. A minimum of 25,000 CD4 and CD8 T cells were acquired. Data were analyzed using an omic approach in R software. The analysis included batch correction, tsNE dimensionality reduction and Louvain clustering. Abundance of T-cells clusters was compared between groups by Mann-Whitney test and an adjusted p-value< 0.05 was considered as significant.

Results: Median follow-up maintaining virologic (undetectable plasma HIV load) and immunologic (stable CD4 counts) control in LTEC was 13 [7-16] years. Dimensionality reduction and clustering yielded 71 and 68 different CD4 and CD8 T cells clusters respectively.TP patients showed the highest level of T-cells disturbances with 21 CD4 clusters and 26 CD8 clusters significantly different from HC. Most of these alterations were reverted in TX who presented only 2 CD4 clusters and 1 CD8 cluster different from HC. Interestingly, LTEC presented a high level of CD4 and CD8 T-cells disturbances with 15 CD4 clusters and 23 CD8 clusters different from HC. Altered CD4 clusters included an increase of exhausted central memory cells and a decrease of naïve cells and peripheral follicular T helper (pTfh) cells. Altered CD8 clusters included an increase in exhausted and senescent terminally differentiated cells, and a decrease of naïve cells.

Conclusion: Our results suggest that, compared to cART-mediated control of HIV, the spontaneous control of HIV is associated with several disturbances in CD4 and CD8 T cells homeostasis. The impact of these alterations in both the loss of spontaneous HIV control and in the state of persistent systemic inflammation need to be further analyzed.

246 LOW TRYPTOPHAN CATABOLISM MARKS IMMUNE PRESERVATION IN HIV+ VIREMIC NON-PROGRESSORS

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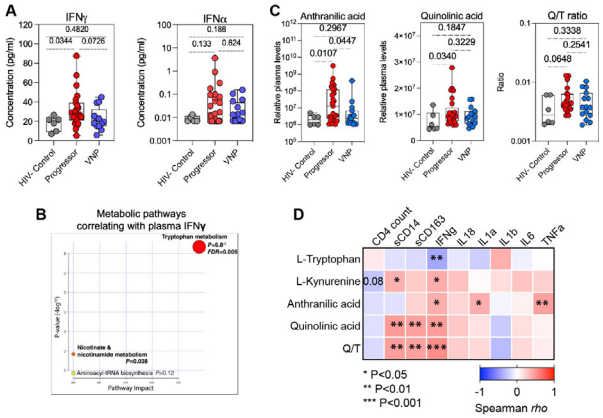
Background: Viremic Non-Progressors (VNPs) is a rare subgroup of HIV+ individuals who maintain high CD4 counts despite high viremia in the absence of antiretroviral treatment (ART), resembling SIV infection in natural hosts. The mechanisms underlying this phenotype are unclear; however, the VNP phenotype has been associated with lower expression of Interferon (IFN)-stimulated genes across multiple immune cells. Elevated IFN responses can alter host metabolism to impact immune homeostasis. However, the potential link between IFN responses, host metabolic alterations, and immune homeostasis in VNPs is unknown.

Methods: We retrospectively selected plasma samples from 16 VNPs and 29 HIV progressors with similar viral load (VL; median log VL >4) but different CD4 decay rates (median annual CD4 loss < 10% and >10%, respectively) before ART initiation. Plasma samples from six HIV-1 seronegative individuals (HIV-) were included as a reference. Soluble plasma markers of inflammation and microbial translocation were measured using ELISA and multiplex cytokine arrays. Untargeted plasma metabolomic analysis was performed by mass spectrometry. Metabolic pathway analysis was performed using MetaboAnalyst 5.0.

Results: Plasma levels of the proinflammatory type II IFN (IFNγ) were similar in VNPs and HIV–, but increased in Progressors ($P < 0.05$; **Fig. 1A**). However, no difference in the levels of the antiviral type I IFN (IFNα) was observed among the three groups. Levels of plasma IFNγ were strongly associated with an upregulation of tryptophan (Trp) catabolism and nicotinamide metabolism pathways (FDR=0.006 and $P=0.038$, respectively, **Fig. 1B**). Consistently, levels of metabolites within the Trp catabolism pathway (including anthranilic acid, quinolinic acid (Q), and the ratio of Q/Trp), with established immunomodulatory roles, were increased in Progressors, but not in VNPs, compared to HIV-controls (**Fig. 1C**). Finally, high Trp catabolism correlated with high levels of proinflammatory cytokines and low CD4 counts (**Fig. 1D**).

Conclusion: Increased Trp catabolism, as observed in HIV Progressors, is known to restrain CD4 T-cell function and decrease T cell survival. Conversely, unaltered Trp metabolic profile was linked to immune preservation in VNPs. Additional investigations are warranted to examine the mechanistic links between this pathway and the desirable phenotype of VNPs. Unraveling these mechanisms may guide the development of novel therapeutic strategies to maintain immune homeostasis during HIV infection.

Figure 1



247 PHENOTYPE OF SIV-INFECTED CELLS IN BLOOD AND TISSUES USING A NEW SINGLE-CELL APPROACH

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Background: CD4+ T cells are the main cellular targets of both HIV and SIV. While the phenotype of HIV-infected cells has been extensively reported, the cellular subsets in which SIV actively replicates in blood and tissues from non-human primates (NHPs) remain largely unidentified. We developed a novel flow-based approach to identify the phenotype of SIV-infected cells during untreated SIV infection. By using two different antibodies specific for the p27 SIV protein (2F12 and 4B7) we enumerated and phenotyped productively infected cells with high specificity. The assay (SIV-Flow) can detect a single infected cell in a million CD4+ T cells and has a large dynamic range (1 to 100,000 infected cells/10^6 CD4+ T cells).

Methods: We analyzed infected cells in multiple tissues from 4 SIVmac239-infected ART-naïve rhesus macaques, including blood, spleen, axial, mesenteric and inguinal lymph nodes. CD4+ T cells were isolated by negative magnetic selection and stained with a combination of antibodies to obtain the phenotype of p27+ cells (CTLA-4, PD-1, Ki67, CD69, CD127, CD45RA, CCR7, CD27, CD95, CD3, CD4, CD8).

Results: In all animals, the highest frequencies of p27+ cells were measured in the spleen (mean 1887 cells/10^6 CD4+ T cells), whereas blood and lymph nodes displayed similarly lower frequencies (842 and 848 cells/10^6 CD4+ T cells, respectively). p27+ were under represented in the naïve compartment in both blood and tissues (fold enrichment of 0.6 and 0.3, respectively). In the blood, p27+ cells were highly enriched in the central memory subset (fold enrichment of 3.8), whereas p27+ cells frequently displayed a transitional and effector memory phenotype in lymphoid tissues (fold enrichment of 2.3 and 2.9, respectively). Overall, when compared to their uninfected counterparts, p27+ cells expressed higher levels of several cellular markers including PD-1 (68% vs 32%), CD69 (47% vs. 23%), Ki67 (38% vs. 12%) and CTLA-4 (21% vs. 12%). Of note, enrichment of p27+ cells subsets expressing these activation and exhaustion markers was more pronounced in lymphoid tissues.

Conclusion: In untreated SIV-infected NHPs, productively-infected cells are found at higher frequencies in the spleen, which can be explained by the high percentages of PD-1+ and effector memory cells and the relatively low proportion of naïve cells in this tissue. Our results suggest that activated CD4+ T cells in the spleen are important contributors to SIV replication in chronically infected NHPs.

248 CHANGES IN GUT MICROBIOTA PROFILE IN PWHIV WHO SWITCH FROM EFV/FTC/TDF TO BIC/FTC/TAF

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Background: Weight gain is often reported when virologically suppressed people living with HIV (PWHIV) switch to integrase inhibitors (INSTI). Reasons linking INSTI to weight gain are unclear and might be attributed to this HIV

drug class, to coformulation with tenofovir alafenamide, and/or influenced by medications, lifestyle and environmental factors. One factor that could impact weight gain is the gut microbiota. Ample evidence exists on the reciprocal causal relationship between the gut microbiome and host metabolism. Here, we evaluated changes in the gut microbiota in aviremic PWHIV who switched from EFV/FTC/TDF to BIC/FTC/TAF.

Methods: This is a prospective single-center cohort study. A total of 27 PWHIV, 14.8% females (n=4), median age of 42 (26-53) years, virologically-suppressed (mean of 8.51 ± 4.98 years), were included. Fecal samples were obtained pre and one-year (mean of 367.3 ± 10.52 days) postswitch, and subjected to 16S rRNA sequencing.

Results: Alpha diversity (shannon) increased significantly postswitch (median 3.9 [3.5-4.1] compared to 2.8 [2.1-3.4] preswitch, p< 0.0001), this increase was observed for both sexes. *Bacteroidota* dominated, averaging 57.43% abundance preswitch, decreasing to 47.10% postswitch, with a concomitant increase in *Firmicutes* abundance (27.16% to 43.12%). The *Firmicutes* to *Bacteroidota* ratio, a putative marker of obesity and weight gain, increased postswitch (median 1.024 [0.50-1.739] versus 0.34 [0.146-1.023] preswitch, p=0.02). At genus level, *Prevotella* (males) and *Bacteroides* (females) dominated, *Faecalibacterium* (both sexes) and UCG_002 (males) increased while *Fusobacterium* (females) and *Succinivibrio* (both sexes) decreased postswitch. Principle-coordinate analysis revealed that microbial community clustering was mostly influenced by intra- and interpersonal variation (subjects) and sex, explaining 67.5% and 6.5% of the variance (PERMANOVA p=0.0001 and p= 0.002, respectively).

Conclusion: The complex nature of weight gain associated with HIV drug classes remains to be elucidated, and might reflect contextual host-gut microbiota adaptations. The work presented here expands our understanding of weight gain associated with INSTI. Our findings suggest that switching to INSTI might modulate the gut microbiota, increasing its diversity and the abundance of *Firmicutes* in both sexes, favoring weight gain by affecting energy extraction. Long-term health implications and therapeutic avenues should be further investigated to prevent or manage weight gain on INSTI.

249 PROTEOMIC ANALYSIS OF TRANSLOCATING BACTERIAL TAXA REVEALS NOVEL THERAPEUTIC TARGET

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Background: Microbial translocation contributes to inflammation in HIV-infected humans and has been associated with increased mortality and morbidity in individuals treated with antiretrovirals. Thus, there is interest in understanding the mechanisms underlying microbial translocation. To characterize translocating bacterial populations, we isolated and identified translocating bacteria from chronically SIV-infected macaques and characterized their genomes and proteomes. Proteome profiling identified a cytosine-specific DNA methyltransferase as being enriched in translocating taxa. We hypothesized that inhibiting this enzyme with the cytidine analog 5-Aza-2'-deoxycytidine would more strongly inhibit the growth of translocating bacteria compared to non-translocating bacteria.

Methods: Liver, mesenteric lymph node, and spleen samples were taken during necropsy from twenty chronically SIV- or SHIV-infected RM. Tissue samples were homogenized and plated under aerobic and anaerobic conditions. Isolates were identified using MALDI-TOF and/or 16S rDNA sequencing. Bacterial proteomes were analyzed by tandem mass spectrometry and genomics by next generation sequencing. 5-Aza-2'-deoxycytidine mediated growth inhibition was determined *in vitro* via longitudinal OD600 readings. Area under the curve was used to determine inhibitory effects between species, Welch's t test or Mann-Whitney test used to compare results depending on normal distribution.

Results: Thirty-six translocating bacterial taxa were identified from 4 bacterial phyla. Translocating bacteria showed different proteome features from non-translocating bacteria with 47.21% of proteins identified as being unique. Top hits included cytosine-specific DNA methyltransferases and copper homeostasis protein CutC, which were found in five of the eight translocating bacterial species. 5-Aza-2'-deoxycytidine preferentially inhibited the growth of translocating bacterial species compared to non-translocating species.

Conclusion: Microbial translocation does not seem to be stochastic and unique taxa of translocating bacteria commonly express DNA methylation enzymes. Inhibition of these enzymes *in vitro* results in significant reduction of growth in these taxa. Blocking activity of these enzymes *in vivo* may offer unique treatment modalities to reduce microbial translocation and improve the prognosis of HIV-infected individuals.

250 THE EFFECTS OF CD4+ LYMPHOPENIA ON THE HUMAN SKIN MICROBIOME

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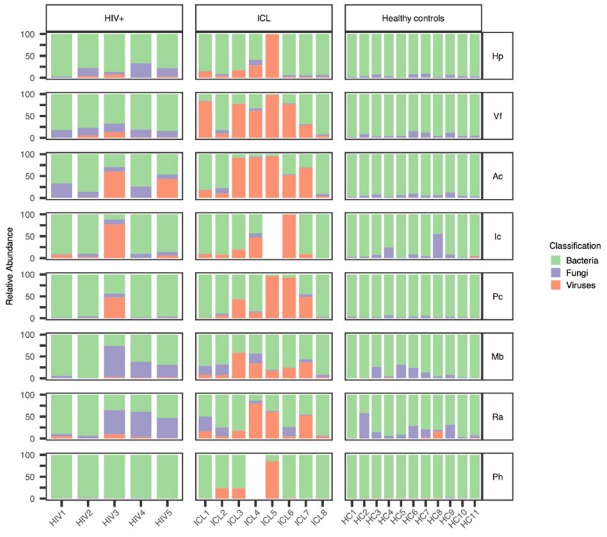
Background: The role of specific immune components in maintaining host-microbial homeostasis remains poorly defined. People with HIV (PWH) and Idiopathic CD4 Lymphocytopenia (ICL) patients exhibit low CD4 T cells in distinct clinical contexts providing a unique opportunity to decipher the role of helper CD4 T cells in skin host-microbial interactions. These patients' increased risk of comorbidities includes opportunistic fungal, mycobacterial and viral infections, neoplastic, and autoimmune or inflammatory skin disorders. We hypothesized ICL and PWH have prominent skin microbiome shifts, related to immune dysfunction and clinical cormobidities.

Methods: Skin microbiome topographical diversity (shotgun metagenomics) was analyzed in PWH, ICL and healthy controls (HCs).

Results: We collected skin samples from PWH naïve to any antiretroviral therapy (ART) (PWH-naïve, n=5, median CD4 48cells/mL, median plasma (p) HIV RNA=361206 copies/mL), ICL (n=8, median CD4 65cells/mL), and HC. PWH samples 2 (n=5) and 15 mos (n=4) after ART initiation were collected. HCs typically demonstrated shared microbiome features; PWH and ICL exhibited greater inter-individual heterogeneity in their microbiomes, consistent with prior studies in immunodeficiencies. As hypothesized, PWH and ICL had notable skin microbiome shifts: PWH-naïve had higher fungal relative abundances, and ICL exhibited higher DNA viral relative abundances. Mean fungal relative abundances of inner forearm were significantly higher on PWH-naïve than on ICL (18% and 3%, respectively; p=0.00002) and HCs (7%; p=0.00009), while mean relative abundances of viruses on PWH-naïve were lower than those on ICL (4% and 55%, respectively; p=0.06). Interestingly, PWH-naïve and HCs across all sites had significantly different microbiomes, compared to PWH on ART (n=4, median CD4 338cells /mL, median time on ART=15 mos, pHIV RNA < 40 copies/mL) and HCs (mean Bray-Curtis distances 0.52 and 0.39, respectively; p=0.0004).

Conclusion: Our data suggest that CD4 T cell lymphopenia may differentially affect skin microbiomes and consequent clinical manifestations based on underlying immune deficiency. ART plays a pivotal role in shifting PWH skin microbiomes towards HCs. Studying human skin microbiomes in such contexts can provide insights into susceptibility to microbial diseases (i.e. viral *vs* fungal) as well as the interactions between the skin microbiome and host immune deficiency and reconstitution.

Skin microbiomes of HIV, ICL, and healthy controls



251 COMMENSAL BACTERIA WITHIN THE FAMILY LACHNOSPIRACEAE ROBUSTLY INHIBIT HIV INFECTION

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Background: The microbiota, the vast collection of microorganisms residing in our body, regulates the susceptibility to and severity of various infectious diseases. In HIV infection, HIV-induced dysbiosis of the gut microbiota is well-recognized. However, it is less clear whether the gut microbiota—and which specific microbes and microbial mechanisms—impacts susceptibility to HIV.
Methods: To identify bacterial taxa associated with HIV susceptibility, we analyzed 16S rRNA gene sequences generated from stool of infant nursery-reared rhesus macaques collected before they were orally challenged with SHIV. For bacterial taxa identified to be associated with protection against SHIV, we obtained the corresponding human-derived isolates and experimentally validated their inhibitory effects on HIV pathogenesis by treating TZM-bl reporter cells with heat-killed bacteria before infecting with HIV. Additionally, we performed time-of-addition assays to identify the specific steps of HIV replication targeted by these bacteria.
Results: We bioinformatically identified two bacterial taxa, *Lactobacillus gasseri* and the family Lachnospiraceae, that are associated with protection against HIV. Although strains of *L. gasseri* demonstrated variable inhibitory effects against HIV infection, *Clostridium immunis* and *Ruminococcus gnavus*, two species within the family Lachnospiraceae, robustly inhibited HIV infection of TZM-bl cells. Based on time-of-addition assays, *C. immunis* inhibited viral entry and reverse transcription, while *R. gnavus* inhibited integration in addition to these steps. Given that tryptophan metabolism is known to be critical in regulating the severity of HIV infection, we developed bacterial genetics for *C. immunis* and inactivated the aromatic amino acid aminotransferase (ArAT) gene, which metabolizes tryptophan into 3-indolelactic acid. Intriguingly, *C. immunis*ΔArAT was a less potent inhibitor of HIV infection compared to its wild-type parental strain, a finding that indicates the ArAT gene is critical for inhibition of HIV.
Conclusion: We bioinformatically identified and experimentally validated three different commensal bacterial species as being able to inhibit HIV infection. Moreover, we established that metabolism of tryptophan by a commensal bacterium impacts HIV infection. More broadly, our results provide mechanistic insight into how commensal bacteria affect HIV pathogenesis and may inform new therapies for the prevention of HIV.

252 BACTERIAL DYSBIOSIS PERSISTS IN WOMEN LIVING WITH HIV-1 AFTER ART

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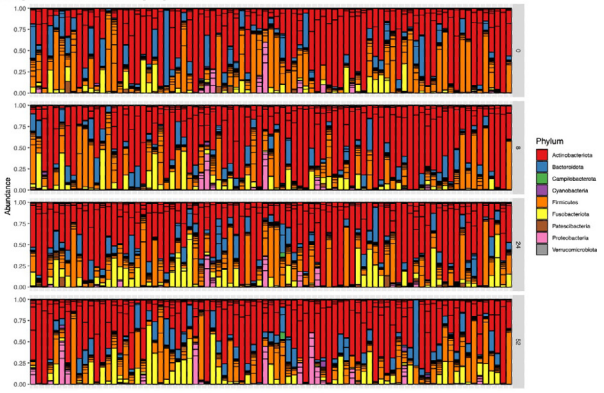
Background: The cervicovaginal (CV) microbiome has a critical role in women's health and disease, including HIV acquisition and progression. A healthy cervicovaginal (CV) microbiome is dominated by a single Lactobacillus species that helps maintain a low vaginal pH, prevent outgrowth of harmful bacteria, and regulate immune homeostasis. Bacterial vaginosis (BV) occurs when Lactobacillus is depleted and replaced by an outgrowth of facultative or obligate anaerobes. Women living with HIV (WLWH) have high prevalence of BV-associated bacteria that are linked to vaginal inflammation, higher genital HIV viral loads, and greater HIV shedding. However, the impact of antiretroviral treatment (ART) on the CV microbiome has not been described in depth. In this study, we sought to evaluate the CV microbiome of ARV-naïve WLWH over their first year of ART.
Methods: CV pellets were collected longitudinally from 83 ART-naïve cisgender Ugandan WLWH at week 0, 8, 24, and 52 of ART. After DNA extraction, the V3-V4 region of the bacterial 16S rRNA gene was amplified by PCR and sequenced using an Illumina NovaSeq platform. Paired end FASTQ files were analyzed using the DADA2 package in R. Reads were binned into amplicon sequence variants (ASVs) and the SILVA taxonomic framework were used to taxonomically annotate them. ASVs were analyzed using the PhyloSeq and DeSeq2 packages in R.
Results: The median age of participants was 31 years and median HIV plasma viral load was 4.4 $\log_{10}$ copies/ml with a CD4 count of 400 cells/ml. ART resulted in a restored median CD4 count of 687 cells/ml after 52 weeks ($p< 0.0001$) and undetectable viremia in 86% of participants (43/50). *Gardnerella* was identified as the most abundant family in our dataset with a median relative abundance of 35% at week 0. *Gardnerella* maintained a high prevalence throughout the study with a median relative abundance of 46, 35, and 35% at week 8, 24, and 52, respectively. Bacterial diversity, measured by Shannon Diversity, at week 52 did not differ from week 0 ($p=0.91$), although seven genera were significantly less abundant at week 52 compared to baseline including the BV-associated bacteria *Peptostreptococcus* ($\log_2$FC= -4.01, $p=< 0.0001$) and *Prevotella* (-1.09, $p=0.01$).
Conclusion: Our findings indicate that ART alone does not effectively modulate compositional diversity of the CV microbiome, however, abundance of some BV-specific bacteria was reduced following treatment. These data support exploration of targeted therapeutics to restore the CV microbiome.

Phylum Abundance, by week



Differentially expressed taxa, wk 52 to baseline

Family_Genus	log2 FC	p_value
Peptostreptococcaceae_Peptostreptococcus	-4.01	<0.0001
Lachnospiraceae_Howardella	-3.55	<0.0001
Mycoplasmataceae_Mycoplasma	-3.51	<0.0001
Fusobacteriaceae_Fusobacterium	-3.35	0.02
Streptococcaceae_Streptococcus	-2.65	0.01
Porphyromonadaceae_Porphyromonas	-2.49	0.004
Prevotellaceae_Prevotella	-1.09	0.01

253 BODY MASS INDEX AND INFLAMMATION IN PEOPLE LIVING WITH HIV AND UNINFECTED CONTROLS

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Background: In the present study we aimed to explore differences in inflammatory markers between people living with HIV (PLWH) and uninfected controls before and after stratification according to body-mass-index.
Methods: 710 well-treated PLWH and 86 uninfected controls where included from the Copenhagen Comorbidity in HIV infection (COCOMO) study. Study participants were stratified into overweight/obese and normo-/underweight according to their BMI (< 25 and ≥ 25, respectively). Hypotheses were tested by linear and logistic regression analyses adjusted for age and sex.
Results: PLWH had lower BMI compared to uninfected control (25.1 vs 26.2, p-value 0.004), but no difference in prevalence of overweight/obesity was found between the two groups (43% vs 53%, p-value 0.086). While no differences in IL-6, IL-10, IFN-γ and hs-CRP were found, PLWH had higher levels of TNF-alfa (7.9 (4.6) vs 6.7 (2.6), p-value 0.041) compared to uninfected controls. After stratification according to BMI and adjustment for confounders HIV infection was associated with excess risk of high levels of IL-6 (aOR 5.82 [1.69 – 20.05]) and IFN-γ (aOR 3.41 [1.01 – 11.46]) in normoweight/underweight, but not among overweight/obese individuals (aOR 2.03 [0.91 – 4.55] and aOR 2.46 [0.93 – 6.49], respectively). When restricting the analyses to normoweight/underweight individuals, age, smoking and waist-to-hip ratio were associated with higher concentrations of IL-6 in PLWH, but not in uninfected controls (Table 1).
Conclusion: In the present study, HIV was associated with higher levels of IL-6 and IFN-γ in normoweight/underweight but not in overweight/obese individuals. Interestingly, waist-to-hip ratio was a predictor of higher IL-6 in normoweight PLWH and not in uninfected controls. Taken together,

our results may suggest a pivotal role for adipose tissue deposition in the early establishment of a pro-inflammatory milieu, even in individuals not clinically overweight or obese. Given the well-known association of systemic inflammation with non-AIDS associated cardio metabolic comorbidities, our results may suggest the need of more intensive monitoring for comorbidities in a subgroup of PLWH otherwise described at low risk.

Predictors of IL-6 and Interferon-γ levels in PLWH and uninfected controls after stratification according to BMI

Table 1 – Predictors of IL-6 and Interferon-γ levels in PLWH and uninfected controls after stratification according to BMI

	Interleukin-6			
	Normoweight/underweight		Overweight/obese	
	PLWH *Beta [95% CI]*	Uninfected controls *Beta [95% CI]*	PLWH *Beta [95% CI]*	Uninfected controls *Beta [95% CI]*
Age, per year	**0.06 [0.03;0.10]***	0.07 [-0.02;0.16]	**0.09 [0.06;0.12]***	0.04 [-0.03;0.11]
Sex, male vs female	0.34 [-0.64;1.32]	0.51 [-1.00;2.02]	-0.05 [-1.09;0.99]	-1.78 [-3.41;-0.16]
WHR, per 1 unit change	**5.69 [0.41;10.97]***	2.95 [-8.24;14.15]	0.34 [-4.55;5.23]	3.56 [-9.33;16.46]
Smoking, yes vs no	**1.38 [0.69;2.07]***	0.89 [-1.89;3.66]	0.53 [-0.26;1.31]	-0.38 [-2.70;1.93]

	Interferon-γ			
	Normoweight/underweight		Overweight/obese	
	PLWH *Beta [95% CI]*	Uninfected controls *Beta [95% CI]*	PLWH *Beta [95% CI]*	Uninfected controls *Beta [95% CI]*
Age, per year	-0.01 [-0.03;0.00]	0.00 [-0.02;0.02]	-0.01 [-0.07;0.05]	-0.01 [-0.05;0.02]
Sex, male vs female	-0.18 [-0.70;0.33]	-0.41 [-0.77;-0.05]	0.38 [-1.42;2.17]	-0.65 [-1.48;0.17]
WHR, per 1 unit change	0.16 [-2.63;2.96]	1.31 [-1.33;3.95]	4.14 [-4.41;12.68]	**8.64 [2.11;15.17]***
Smoking, yes vs no	-0.09 [-0.45;0.27]	-0.16 [-0.81;0.48]	-0.17 [-1.54;1.21]	-0.69 [-1.87;0.48]

*, p-value < 0.05

Levels of iron metabolism markers and their associations, in young, HIV, elderly and ferropenic subjects

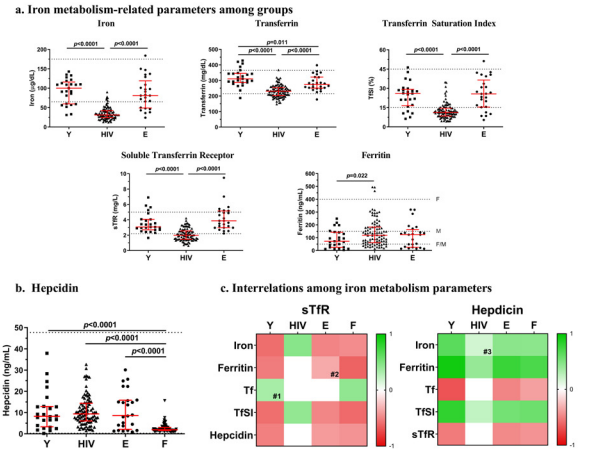

Figure 1. Iron-related parameters. a) Levels of iron metabolism-related parameters (iron, transferrin, TfSI, sTfR and ferritin) in Young non-HIV (Y), HIV, and Elderly non-HIV (E) groups. b) Hepcidin levels in Y, HIV, E and F (ferropenia with ferritin <50 ng/mL) groups. Comparisons were assessed using nonparametric Kruskal-Wallis/Mann–Whitney U tests. Variables with a p-value <0.05 were considered statistically significant. Grid lines represent minimum and maximum standard values. c) Associations between sTfR/Hepcidin and the rest of iron metabolism parameters in Y, HIV, E and F groups. Color intensity of boxes represents Spearman's rank correlation coefficient value as indicated in the color legend. All colored boxes represent statistically significant correlations, excepting for those noted as # ($0.05 \leqslant p \leqslant 0.1$). White boxes represent correlations with *p*-values >0.1. #1, p=0.092; #2, p=0.100; #3, p=0.096. Abbreviations: Tf, transferrin; TfSI, transferrin saturation index; sTfR, soluble transferrin receptor.

254 IRON METABOLISM IN CHRONIC HIV: IMPAIRED HEPCIDIN-SOLUBLE TRANSFERRIN RECEPTOR AXIS

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Background: Chronic HIV-infected subjects under effective antiretroviral treatment (ART) exhibit an immune dysfunction leading to comorbidities. Since iron metabolism plays an essential role in immune cell function, its regulation may be relevant in this context.

Methods: We included 92 asymptomatic chronic HIV-infected subjects under suppressive treatment (HIV), 25 age-matched non-HIV healthy donors (< 65 years old; Young, Y), and 25 non-HIV elderly subjects (>65 years old; Elderly, E). For partial analysis, 84 patients with iron deficiency and ferritin< 50 ng/mL were also included (Ferropenic, F). Traditional biomarkers of iron metabolism, as well as soluble transferrin receptor (sTfR), hepcidin, and inflammatory markers were determined in plasma.

Results: Compared to both healthy (Young and Elderly) controls, HIV subjects exhibited decreased iron (Y, 100[60-116]; HIV, 31[24-42]; E, 81[49-119] µg/dL), transferrin saturation (Y, 26[16-29]; HIV, 11[8-15]; E, 26[15-37] %) and sTfR (Y, 3.1[2.7-4.1]; HIV, 2.0[1.5-2.6]; E, 3.9[3.0-5.2] mg/L), although increased ferritin (Y, 72[25-142]; HIV, 119[61-183] ng/mL), but similar hepcidin levels (Figure 1A and B). As expected, ferropenic subjects showed the lowest levels of hepcidin (HIV, 9.4[6.1-14.4]; F, 1.9[1.6-3.0] ng/mL). Interestingly, HIV showed altered relationships between iron parameters and their regulators unlike young, elderly, or even the ferropenic group (Figure 1C). Specifically, associations between sTfR and iron or transferrin saturation index were negative in healthy and ferropenic groups, while positive in HIV. Moreover, the expected negative correlation between hepcidin and sTfR, observed in healthy and ferropenic groups, was absent in HIV. Interestingly, the HIV inflammatory profile differed from the Elderly one (with an inflammaging-related profile), showing high levels of homocysteine (HIV, 3.2[2.4-4.3] vs. Y, 1.8[1.6-2.2] mg/L, p< 0.0001) and β2-microglobulin (HIV, 2.1[1.9-2.5] vs. Y, 1.8[1.6-2.3] mg/L, p=0.018) compared to young.

Conclusion: Chronic HIV-infected patients under ART exhibit an imbalanced regulation of iron metabolism-related components, including hepcidin and sTfR, suggesting a complex functional iron deficiency that could contribute to their persisting immune dysfunction.

255 ENDOTHELIAL GM-CSF IN PLWH CONTRIBUTES TO PROINFLAMMATORY VASCULAR MICROENVIRONMENT

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Background: People living with HIV (PLWH) show clinical and radiological findings of persistent endothelial dysfunction (ED), and twice-higher incidences of critical cardiovascular emergencies which is independent of other general risk factors. The effects of endothelium derived granulocyte macrophage colony stimulating factor (GM-CSF) on infiltrating immune cells that infiltrate the endothelium in PLWH are unknown, as is the role of bacterial translocation on GM-CSF expression. Here, we investigated the quantitative changes of toll-like receptor-4 (TLR4) and GM-CSF expression in the vascular endothelium in PLWH to understand the biological significance of TLR ligands and endothelium-derived GM-CSF.

Methods: Immunofluorescence microscopy and digital image data quantification, FISH, RNA-Seq Western blot, and Standard Statistical tests using GraphPad Prism v6.02.

Results: Using immunofluorescence microscopy of primary human aortic endothelial cells (ECs) and of arterial tissue microarray slides from PLWH, SIV/SHIV-infected Rhesus macaques (RMs), and respective uninfected controls, we confirmed that GM-CSF and TLR4 are detectable in primary human aortic ECs and in aortic tissues irrespective of age or gender variability. In our *ex vivo* studies, the TLR4 ligand LPS induced EC expression of GM-CSF (Fig. 1A). In addition, we observed overall increased TLR4 on the aortic endothelium of SIV/SHIV infected RMs and PLWH, compared to uninfected controls (Fig. 1B, 1C).

Conclusion: Inadequate intestinal mucosal barrier function is responsible for bacterial translocation in PLWH. Detection of increased GM-CSF and TLR4 in the endothelium of PLWH or in SIV/SHIV infected RMs indicate that ED in HIV infection would potentially create a perpetuated supportive microenvironment for the infiltrating inflammatory immune cells. This work suggests that suppressing endothelium-derived GM-CSF might be an important direction for the development of future therapeutics to combat chronic ED in PLWH.

ENDOTHELIAL GM-CSF IN PLWH CONTRBUTE TO PROINFLAMMATORY VASCULAR MICROENVIRONMENT

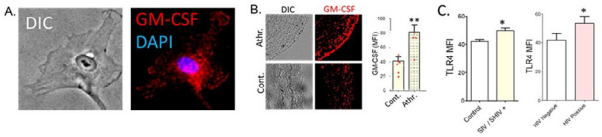

Figure 1: A. Endothelial cells express GM-CSF. B. Significantly high GM-CSF in the endothelium of atherosclerotic plaque (n = 18). C. High TLR4 expression in the vascular endothelium of SIV/SHIV infected Rhesus macaque (left; n = 37), and the endothelium of PLWH (right: n = 22).

256 EFFECT OF P. FRAGILE COINFECTION ON ART AND IMMUNITY IN SIV-INFECTED RHESUS MACAQUES

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Background: HIV and malaria are endemic in similar geographical areas. Previous work indicates that co-infection increases the risk for transmission of both HIV and malaria, however the mechanisms by which co-infection accelerates disease pathogenesis are unknown. Neutrophils have been implicated in adverse outcomes in HIV and malaria separately, but the role they play in co-infection is unclear. We hypothesized that *P. fragile* co-infection of ART-treated, SIV+ rhesus macaques (RMs) would result in elevated viral load (VL), decreased CD4+ T-cell counts, and increased neutrophil frequencies.
Methods: Male RMs (n=4) were intravenously (i.v.) inoculated with SIVmac239 (TCID50=50); initiated daily ART at Week (W)8 post-SIV infection (post-SIV); were i.v. inoculated with *P. fragile* ($20x10^6$ infected erythrocytes [iRBCs]) at W12 post-SIV; and were treated with anti-malarials at W14 post-SIV. Plasma VL and peripheral parasitemia were monitored via qPCR and Giemsa-stained blood smears, respectively. CD4+ T-cell absolute counts and neutrophil frequencies were assessed via flow cytometry
Results: Peak VL (median=$9.92x10_6$ RNA copies/ul) was reached by W3 post-SIV. Upon ART initiation, VLs decreased, with 2/4 RMs becoming undetectable by W12 post-SIV. Within two weeks of *P. fragile* inoculation, parasitemia reached peak levels (W14 post-SIV median %parasitemia=25.5% iRBCs), which declined after anti-malarial treatment. At W13 post-SIV, RMs exhibited detectable VLs, which were sustained until W17 post-SIV (median=$9.34x10^{02}$ RNA copies/ul). Compared to baseline (median=306.905 cells/ul), CD4+ T-cell counts declined by W8 post-SIV (median=140.5 cells/ul), increased after ART (median=193.5 cells/ul), followed by a sustained decline (median=173.59 cells/ul) after P. fragile inoculation. Neutrophil frequencies non-significantly increased at W14 post-SIV (median=71%), as compared to baseline (median=56.65%) and W3 post-SIV (median=55.35%).
Conclusion: In this pilot study, our observations suggested that *P. fragile* co-infection lowered ART efficacy, characterized by lesser SIV viral suppression and poorer CD4+ T-cell reconstitution. Additionally, we observed an increase in neutrophils after co-infection as compared to both baseline and peak SIV infection, potentially implicating a role for neutrophils in accelerated pathogenesis during co-infection. More work will be needed to confirm and characterize the mechanisms by which neutrophils may contribute to disease pathogenesis during SIV/malaria co-infection.

257 INNATE IMPAIRMENT DURING SIV INFECTION ALTERS ZIKV VIRAL PATHOGENESIS

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Background: Flaviviruses are circulating in >100 countries across the globe and in areas with endemic HIV. Despite the occurrence of large flavivirus outbreaks and geographic overlap in countries with high HIV prevalence, there is insufficient research to determine the risks of flavivirus co-infection in people living with HIV and impact on co-morbidities. Here, we establish and define a model featuring SIV-infected pigtail macaques with ZIKV co-infection. We investigated the hypothesis that enhanced ZIKV pathogenesis occurs in people living with HIV.
Methods: Pigtail macaques (n=7) were infected with SIVmac239M and co-infected with ZIKV at 9 weeks post-SIV infection (SIV+/ZIKV+). Animals were compared to control animals (n=7) only infected with ZIKV (SIV-/ZIKV+). SIV and ZIKV viral loads in plasma and peripheral tissues were measured by qRT-PCR. Blood/peripheral blood mononuclear cells (PBMCs), lymph node, and rectal tissues collected pre- and post-SIV and/or ZIKV infection were evaluated for innate and adaptive immune responses by flow cytometry. Alterations in host responses to infection were measured in PBMC using NanoString gene analysis.
Results: At the time of ZIKV co-infection, SIV+ animals had severe CD4 depletion and had reached viral setpoint. ZIKV was detected on average for 1.43 days longer in SIV+/ZIKV+ animals in comparison to SIV−/ZIKV+ control animals and peak viremia was shifted on average 1.81 days later in SIV+/ZIKV+ animals. ZIKV viral dissemination to tissues was less evident the SIV+/ZIKV+ animals. Post-ZIKV infection, peripheral recruitment of CD16+ monocytes, the *in vivo* blood target of ZIKV infection, was dampened and delayed in SIV+/ZIKV+ vs SIV−/ZIKV+ animals and corresponded to the delayed ZIKV viremia in SIV+/ZIKV+ animals. Furthermore, PBMC gene expression analysis post-ZIKV infection revealed sustained and hyperactivation of the innate immune response, including interferon-alpha signaling, in SIV+/ZIKV+ animals.
Conclusion: Here, we provide evidence that ZIKV viremia is delayed and more persistent in SIV-infected macaques. Characterization of the host response revealed chronic innate immune activation and constitutive type I IFN signaling, concomitant with impaired tissue recruitment of innate immune cells during SIV-ZIKV co-infection. Collectively, these findings suggest that untreated SIV/HIV infection could create an environment of immunological tolerance that may lead to poor ZIKV viral clearance and promote pathogenesis.

258 LYMPHOID TISSUE VOLUMES AND GLUCOSE METABOLISM IN EARLY SIV INFECTION OF AGM AND RM

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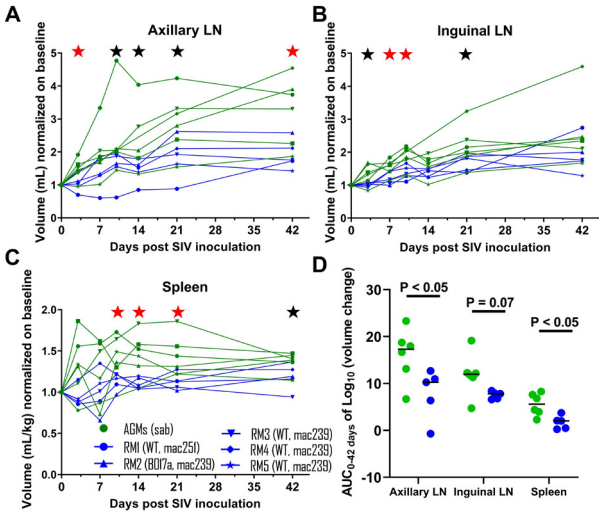
Background: Early establishment of an effector function following viral inoculation has been proposed as a major driver of viral reservoir control in nonpathogenic SIV infection. The capability of lymphoid tissues (LT) to promptly expand following antigen presentation (LT elasticity) has not been studied in natural and non-natural hosts of SIV infection. In this study, we investigated changes in LT volumes and tissue glucose metabolism in African Green Monkeys (AGMs) and Rhesus Macaques (RMs) during the early days following SIV inoculation, using ^{18}F-Fluordeoxyglucose (FDG)-Positron Emission Tomography (PET)\Computed Tomography (CT).
Methods: Six AGMs and 5 RMs were inoculated intravenously with 300TCID50 SIVsab and 300-1000TCID50 SIVmac viruses, respectively. We here report image analyses up to Day 42 post-infection (p.i.). Whole-body PET\CT scans were administered at baseline, Day 3, 7, 10, 14, 21, and 42 p.i. LT volumes of interest and radiotracer uptakes (reported as standardized uptake value, SUV) were obtained by two independent operators by drawing regions in MIM software. Plasma viral loads and peripheral blood CD4+ T-cell counts were monitored throughout the follow-up.
Results: Plasma viremia at each timepoint, peak, and area under the curve ($AUC_{0\text{-}42day}$s) was similar between AGM and RM groups. Based on the CD4 count crash at Day 42 (20-80% drop, $P< 0.05$) and all available follow-up (5-19 months p.i.), all RMs displayed normal disease progression (>65% CD4 drop at nadir). Starting at Day 3 p.i., a statistically significantly higher expansion of LTs was observed in the AGM group (Figure 1A, B, and C; $P< 0.05$ (red star), $P< 0.1$ (black star)). Consistently, $AUC_{0\text{-}42days}$ of the relative expansion of LTs was higher in the AGM group (Figure 1D). Compared to baseline, tissue glucose metabolism levels in LTs at Day 42 p.i. were statistically significantly higher in both groups ($P< 0.05$), with a higher increase observed in the AGM group ($P< 0.05$ for spleen and inguinal lymph node (LN)).
Conclusion: PET\CT imaging during the early days of SIV infection revealed a prompter expansion of LTs in the AGM group compared to the RM group, accompanied by an increase in tissue glucose metabolism. Future studies will focus on mechanisms responsible for LN expansion\contraction (e.g. molecular pathways governing the elongation of fibroblastic reticular cells) as well as on longer follow-up of LT volumetric analyses coupled with ^{18}F-FDG-PET imaging to suggest alternative functional cure strategies.

Figure 1



259 THE BREADTH AND POLYFUNCTIONALITY OF T CELL RESPONSES TO CMV DIFFER BY HIV STATUS

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Background: Chronic cytomegalovirus (CMV) infection elicits large T cell responses with significant biological and clinical implications (chronic inflammation and frailty) in HIV infection. Such T cell responses have been shown to target a wide range of CMV proteins. Building on our prior work, we postulated that the breadth and polyfunctionality of T cell responses to an extensive panel of CMV antigens would differ by HIV status.

Methods: CD4 and CD8 T cell responses to peptide pools spanning 19 CMV open reading frames (ORFs) were measured by intracellular cytokine staining for production of IFN-γ, TNF-α and IL-2 in 42 men (20 HIV- and 22 virologically suppressed HIV+) in the Multicenter AIDS Cohort Study. Polyfunctionality of T cell responses was assessed by mean polyfunctionality index of responding cells (= .33 for cells producing 1 cytokine and 1.00 for cells producing 3 cytokines). Differences between HIV– and HIV+ men were assessed by non-parametric Mann-Whitney test. Differences between bivariate Spearman's correlation coefficients were assessed by Fisher's Z test, and differences in slope of regressions by least-square linear regression.

Results: Median numbers of CMV ORFs triggering CD8 T cell responses in HIV+ men were significantly higher than in HIV- men (10 vs. 7, respectively; p=.04). This was primarily due to an excess of responses to late-expressed CMV antigens in HIV+ men. In HIV– men, the numbers of ORFs responded to were strongly and positively correlated with total T cell responses for both CD4 and CD8 T cells (r=0.73, p< .001, and r=0.88, p< 0.00001, respectively); these correlations were present but weaker in HIV+ men (r=0.56, p=.007, and r=0.59, p=.004, respectively; p=.04 for the difference in correlation in CD8 responses by HIV status). Slopes of the regression of total CD4 responses against the number of CD4 responses were lower in HIV+ men than in HIV– men (p=.06). Polyfunctionality of CD4 responses to CMV ORFs was significantly lower in HIV+ men than in HIV- men (mean PI = .33 vs. .59, respectively; p< .001).

Conclusion: The breadth of CMV-specific CD8 T cell responses was higher and its correlation with the total magnitude of these responses was weaker in HIV+ men than in HIV– men. These results, along with the lower polyfunctionality of CD4 responses and the greater response to late CMV antigens in HIV+ men, suggest that immune control of CMV infection may be different in HIV+ men receiving antiretroviral therapy than in HIV- men with similar lifestyle.

260 GLYCOMIC BIOMARKERS OF BIOLOGICAL AGING ARE ALTERED DURING SUPPRESSED HIV INFECTION

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MACS/WIHS Combined Cohort Study

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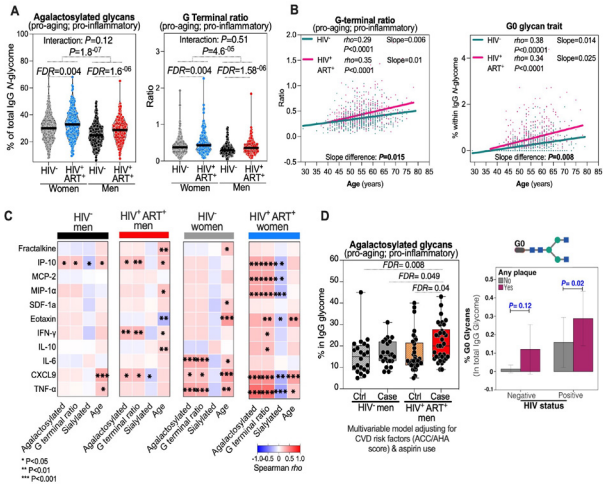
Background: In the general population, host glycomic alterations – including loss of galactose (agalactosylation; measured as high levels of G-terminal ratio and G0 glycan groups) – on circulating IgGs drive inflammation and precede the onset of premature aging-associated diseases. However, the impact of antiretroviral therapy (ART)-suppressed HIV infection on these glycomic biomarkers of biological aging is unknown.

Methods: Using capillary electrophoresis, we analyzed the IgG glycomes of 988 samples from participants of the MACS/WIHS Combined Cohort Study: 237 HIV-negative men and 254 HIV+ ART+ men (age/race matched); 254 HIV-negative women and 243 HIV+ ART+ women (age/race matched). HIV+ individuals were ART suppressed for ≥5 years with undetectable viral load and CD4 count of ≥ 350 cells/mm3. We also analyzed the IgG glycomes of 112 samples from HIV- and HIV+ ART+ male cases and controls; cases had coronary stenosis ≥50% in ≥1 coronary segments and controls had no coronary plaque (by CT angiography). Soluble markers of inflammatory aging (based on PMID:34888528) were measured using multiplex cytokine arrays on a subset of 400 samples. Comparisons between women and men were performed using multivariate models adjusting for age, race, and body mass index.

Results: Treated HIV infection was associated with pro-biological aging glycomic alterations; induction of the pro-inflammatory agalactosylated (false discovery rate (FDR)< 0.05; **Fig.1A**) and bisected GlcNAc glycans in both women and men, and a reduction of the anti-inflammatory sialylated glycans in men. Compared to men, women exhibited higher levels of the pro-inflammatory agalactosylated glycans (FDR< 0.05; **Fig. 1A**) and lower levels of the anti-inflammatory sialylated glycans. HIV infection accelerated the pace of age-associated agalactosylation compared to HIV- controls ($P < 0.02$, **Fig.1B**). HIV-associated IgG agalactosylation correlated with higher inflammatory markers of aging (including CXCL9 and IP-10), especially in HIV+ ART+ women ($P < 0.05$; **Fig.1C**). Finally, agalactosylated glycans were higher in HIV+ men with coronary stenosis compared to controls (FDR< 0.05; **Fig.1D**).

Conclusion: Sex-dependent premature-aging-associated glycomic dysregulation is accelerated during ART+ HIV infection and is associated with inflammatory aging (inflammaging) and subclinical atherosclerosis. These HIV and/or ART-promoted inflammaging-associated glycomic alterations warrant further investigation to examine their potential prognostic and functional significance.

Figure 1: Sex-dependent IgG glycomic dysregulations are accelerated during ART-suppressed HIV infection



261 SEX DIFFERENCES IN CYTOKINE DYNAMICS IN PEOPLE WITH HIV ON ART DURING AGING

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Background: Sex-based differences affect the natural and treated history of HIV infection and immune responses. We previously described that women undergoing reproductive aging have a progressive increase in inducible HIV reservoirs (PMID: 34612493), in sharp contrast to the steady decline in the reservoir size in men. Here we investigate possible underlying immunologic mechanisms.

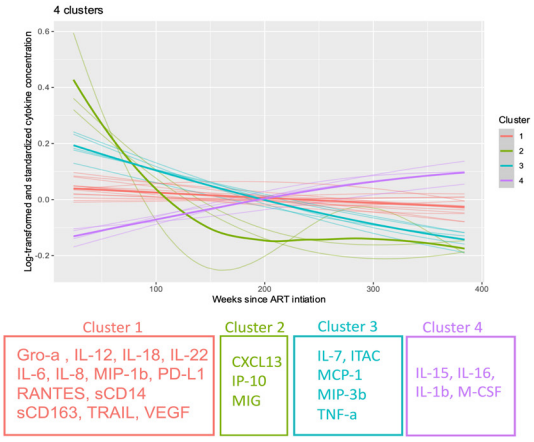
Methods: Longitudinal stored samples (N=422) from virally suppressed cisgender women (N=60) and age-matched men (N=31) were identified from the AIDS Clinical Trials Group Longitudinal Linked Randomized Trials (ALLRT). Selected participants were between the ages of 40-53 at the time of antiretroviral treatment (ART) initiation and virally suppressed (<20 cp/ml) throughout the study period. Participants did not report taking any hormonal therapy. At each timepoint we measured concentrations of 39 cytokine/chemokines by Luminex. Cytokines with <70% of values below the limit of detection across all participants and time points were included (N=25). Cytokines were clustered based on trajectories using the kmlShape package and the Frechet distance method. Within each cluster of cytokines, we fit a longitudinal mixed effects model to investigate the effect of sex on their trajectory.

Results: At baseline, median (range) CD4+ were 210 (3, 659) cells/ml for women and 238 (7.5, 450) for men. Median follow up (range) was 101 (52, 230) months for women and 83 (28, 179) for men. Cytokines were clustered into 4 groups with distinct trajectories. The average cytokine value in cluster 1 (n=13 cytokines) remained relatively stable throughout the study period, while cluster 2 (n=3) showed high values at baseline with a rapid decline, cluster 3 (n=5) showed a steady decrease, and cluster 4 (n=4) showed low values at baseline with a steady increase over time (**Figure**). Two clusters showed significant sex differences in their trajectories. Specifically, cluster 1 (which included multiple proinflammatory cytokines, including markers of monocyte activation) and cluster 3 (which included the T cell homeostatic factor IL-7) started higher in men but declined significantly slower in women during follow up.

Conclusion: Sex specific features to the inflammatory response could influence HIV reservoir formation, latency maintenance and reversal. Persistent increased levels of IL-7 and proinflammatory cytokines in women suggest that homeostatic proliferation may have a differential contribution to HIV reservoir maintenance in female during aging.

Longitudinal clustering of cytokines based on trajectories over time

Figure 1: Clustering of longitudinal cytokine trajectories of 26 cytokines into 4 clusters using kmlShape to cluster cytokine trajectories based on shape using the Frechet distance. Y-axis is log-transformed and normalized cytokine concentration and x-axis is weeks since ART initiation. Bold colored lines are average value of all cytokines within a cluster. Thin colored lines are single cytokine trajectories with color indicating cluster membership.



262 AGING IN WOMEN WITH HIV: SINGLE-CELL TRANSCRIPTOME ANALYSIS OF THE IMMUNE SYSTEM

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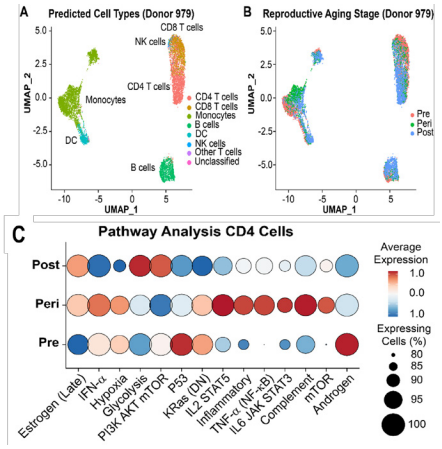
Background: Reproductive aging in women with HIV (WWH) introduces significant therapeutic challenges due to the progressive decline in blood levels of estrogen, a known negative regulator of HIV transcription. Our group recently described how the inducible HIV RNA reservoir, as measured by the EDITS assay, increased progressively in women during reproductive aging (PMID: 34612493). Here, we explore possible underlying mechanisms with detailed studies at a single-cell level, which will account for the heterogeneity of the immune cell populations.

Methods: We selected biorepository samples carefully staged across reproductive stages from cisgender women with HIV from the Chicago Women's Interagency HIV Study (WIHS). Specifically, we first selected cross-sectional samples from eight WWH, four pre- and four postmenopausal. To account for donor variability, we further selected 3 longitudinal samples (pre-, peri-, and postmenopausal) from 2 WWHs. Blood samples were collected during a ten-year period during viral suppression. To identify differentially expressed (DE) genes, surface protein markers, and pathway enrichment (PE) along the timeline of aging, we used the BD Rhapsody scRNAseq-ABseq platform. For cell typing, we performed ABseq using 30 antibodies to major diagnostic surface antigens of immune cells.

Results: The resulting integrated datasets consisted of >100,000 transcriptome (>500 genes/cell) and ABseq profiles. We performed detailed DE gene and PE analyses in CD4 and CD8 T-cells, monocytes, NK, DC, and B-cells, and their sub-populations (CD4 Naïve, TCM, TEM, and CTL). The most significant changes were between pre- and perimenopausal participants and less so between peri- and postmenopausal. Thus, TNFα signaling via NFκB, Interferon-α, p53, and complement showed significant enrichment in the cells of perimenopausal participants. Premenopausal CD4 T cells showed enriched PI3K/AKT/MTOR and androgen pathways, whereas genes of the late estrogen response, KRAS signaling, and glycolysis marked the postmenopausal stage (**Figure 1**). We observed similar DE genes and pathways in cross-sectional and longitudinal datasets.

Conclusion: Reproductive aging in WWH shifts transcriptome signatures in the immune cells toward innate immune pathways and antiviral cytotoxicity, possibly in response to the rise of inducible HIV reservoir. Future scRNAseq studies including matching males with HIV are necessary to further decipher sex-specific differences.

Figure 1. Immunophenotyping and differential pathway enrichment analyses in aging WWH by scRNAseq-ABseq. (A) An integrated UMAP plot of pooled single cell scRNAseq/ABseq profiles of total PBMC from donor 979 at pre-, peri- and post- menopause. Cell types were predicted by mapping against the reference PBMC dataset based on cell type-specific gene transcripts and further confirmed by the detection of 30 diagnostic immune cell surface markers using ABseq. (B) UMAP plot of that data from donor 979 highlighting cells obtained from each stage. (C) Dotplot showing pathway enrichment analysis in CD4 T-cells from longitudinal samples collected from three pre-, peri- and postmenopausal participants. Pathways were based on the Molecular Signature Hallmark database. The dot size represents the percentage of cells expressing the pathway-related genes, and the dot color shows log-normalized average expression of each pathway.



263 **MULTIPARAMETRIC CHARACTERIZATION OF TELOMERE LENGTH IN T CELLS FROM PLWH BY Flow-FISH**

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Background: People living with HIV (PLWH) on antiretroviral therapy (ART) present higher prevalence of ageing-associated morbidities than uninfected individuals. We assessed markers of immunosenescence in CD4 and CD8 T cells from well clinically characterized older PLWH and HIV-negative individuals.
Methods: We included 27 PLWH on ART and 24 HIV-negative controls (HNC) from the OVER50 cohort. We performed a multiparametric flow-FISH technique on frozen PBMCs to simultaneously assess the relative telomere length (RTL) of T cells with a telomere-specific peptide nucleic acid probe by spectral flow cytometry, using 1301 cells as reference. We studied the frequency and RTL of CD4 and CD8 T cell subsets (CD45RA, CCR7, CD27, CD28 CD25, CD127), and activated (HLA-DR+CD38+), senescent (CD57+, KRLG1+) and exhausted (PD-1+) cells.
Results: PLWH were 85% males with a median age of 72 IQR [70-75] years and on suppressive ART for a median of 16 IQR [8-20] years. HNC were matched by age and gender (79% males, median age 73 IQR [69-75] years). Clinically, there were no significant differences in the number of comorbidities between PLWH and HNC (median 3.6 IQR [2-5] and 3.25 IQR [2-5], respectively). Only dyslipidemia was significantly higher in PLWH (70%) compared with uninfected group (17%, $p< 0.01$). The frequency of total CD4 T cells was lower in PLWH compared to HNC group ($p< 0.01$), while no major differences in the CD4 T-cell maturation subsets or T-regulatory cells were found. No differences were observed in the RTL in total or CD4 T cell subsets, except for transitional memory (TM, $p=0.09$) and effector memory ($p=0.06$) cells from PLWH, which tended to have shorter RTL than HNC. PLWH show higher frequencies of total CD8 T cells than HNC ($p< 0.01$), but CD8 T-cell distribution was similar between groups. We did not observed differences in RTL in total CD8 T cell between groups, whereas naïve ($p=0.06$), central memory (CM, $p=0.03$) and TM ($p=0.05$) CD8 T cell subsets showed shorter RTL in PLWH compared to HNC. The frequencies of senescent, exhausted and activated CD4 and CD8 T cells were similar between groups, and no differences in the RTL in these subsets were observed.
Conclusion: Flow-FISH technique using full spectrum flow cytometry allowed a deep immune-characterization of the RTL in total and CD4 and CD8 T cell subsets from older PLWH and uninfected controls. Limited differences in RTL were observed between groups, suggesting similar immunoageing status in older individuals independently of HIV serostatus.

264 **DURABLE ART SUPPRESSION IN AGED RHESUS MACAQUES IS ASSOCIATED WITH MHC-I ALLELES**

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Background: Aging is associated with impairments in immune function that greatly increase the risk of viral infection and disease progression. However, the effects of CD8+ T cell-restricted MHC-I haplotypes on viral dynamics in old age remain undefined. We investigated how MHC-I alleles associated with spontaneous control of viral replication impact primary SIVmac239 infection and viral suppression in plasma and central nervous system (CNS) with ART in aged rhesus macaques (RM).
Methods: 16 aged RM (17-23 years old), with markedly reduced naïve T and B cells, were stratified into two groups based on expression of either Mamu A*01, B*08 or B*17 (protective MHC; n=8) or controls (no protective MHC; n=8) and IV inoculated with 2 IU of SIVmac239. At 70 days post-infection (dpi), a subset of 8 RM (n=4; protective MHC and n=4; controls) received daily ART consisting of dolutegravir, emtricitabine and tenofovir disoproxil (TDF) for 15 weeks followed by TDF monotherapy for a further 21 weeks. SIV loads in plasma (pvl) and cerebrospinal fluid (CSF) were assessed using real-time RT-qPCR.
Results: Upon SIV infection, pvl at peak, set point and total viral burden, as measured by area under curve (AUC) between 0 – 70 dpi were significantly lower in RM with protective MHC alleles relative to controls. Following ART, we observed a rapid decrease in pvl in RM with protective MHC, with all achieving pvl below threshold (15 RNA copies/ml) prior to TDF and this stringent viral suppression was maintained in plasma and CSF during TDF. In contrast, RM with no protective MHC alleles had significantly reduced viral suppression in response to ART and substantial viremia in plasma and CSF during TDF monotherapy.
Conclusion: Aged RM with CD8+ T cell-restricted MHC-I alleles associated with viral control demonstrated reduced SIV replication following primary infection and rapid suppression following ART that was maintained despite suboptimal therapy. Our results suggest that enhancing CD8+ T cell immunity may promote durable viral suppression, including in the CNS, in older HIV+ individuals.

265 **GERMINAL CENTER B CELLS INDUCE TFH ACTIVATION AND HIV REPLICATION**

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Background: T follicular helper cells (TFH) are major sources of HIV replication in people living with HIV infection. T cell activation enhances HIV replication, cytokine secretion including IL-2 and TNF, and expression of several receptors including OX40, CD25, CD69 and 4-1BB. In *ex vivo* infected tonsils, HIV replication is elevated in activated T cells expressing OX40 and reduced levels of CD127. Although much is known of the impact of TFH on germinal center B cell (GCB) activation and function, little is known of the influence of GCB on the activation state of TFH in HIV infection. We hypothesized that GCB induce activation and HIV replication in TFH.
Methods: TFH (7-AAD-CD3+CD8-CXCR5hiPD-1hi) and GCB (7-AAD-CD19+IgD-CD38+) were sorted from tonsils of individuals at low risk of HIV infection undergoing routine tonsillectomies. TFH were spinoculated with X4- or R5-tropic GFP reporter virus and cultured for 3 days in the presence or absence of GCB in media with saquinavir. Percent GFP+TFH and GFP MFI were measured by flow cytometry. In a subset of experiments, TFH were isolated after culture and RNA was extracted. Individual transcripts for 785 genes were quantified using an nCounter Host Response Panel and analyzed using Rosalind. Fold changes and p-values were calculated and p-value adjustment was performed using the Benjamini-Hochberg method of estimating false discovery rates.
Results: Compared to TFH alone, percent GFP+TFH and GFP MFI were elevated by a median of 11% and 28%, respectively, in X4-tropic infection when cultured with GCB (n=34; 12 female; $p< 0.0001$, $p< 0.0001$, respectively). Elevations in GFP+TFH (median, 37%) and GFP MFI (median, 48%) were also seen in R5-tropic

infection (n=8; 3 female; p=0.0078, p=0.0078, respectively). Multidimensional scaling of RNA profiles in six X4-tropic infections indicated separate clustering of TFH cultured alone and TFH cultured with GCB. Of the 785 genes analyzed, 101 genes were significantly upregulated >1.5 fold, and 10 genes were downregulated >1.5 fold in TFH in the presence of GCB. Genes associated with cellular activation including *TNF, IL2, TNFRSF9* (4-1BB), *TNFRSF4* (OX40), *IL2RA* (CD25), *HLA-DRA*, and CD69 were significantly upregulated in TFH cultured with GCB, while *IL7R* (CD127) expression was reduced.

Conclusion: GCB cells increase TFH activation and amplify HIV replication. A better understanding of the mechanisms that drive GCB mediated effects on TFH could suggest new targets for suppression of HIV replication in TFH.

266 SIALIDASE INHIBITION PREVENTS HIV-MEDIATED INFLAMMATION AND IMMUNE ACTIVATION IN VIVO

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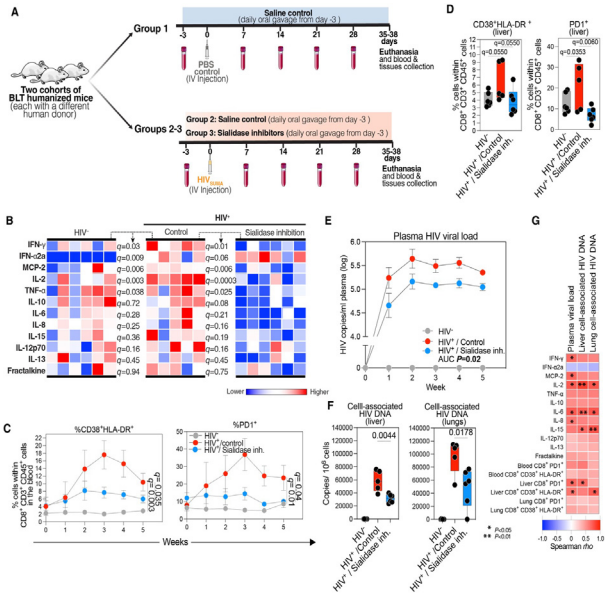
Background: Sialylated glycoproteins (proteins containing the glycan sialic acid) are reduced during HIV infection (viremic and antiretroviral-therapy (ART)-suppressed), and levels of sialidase (enzyme cleaving sialic acid) are elevated. Sialylated glycoproteins initiate anti-inflammatory immune responses by engaging the inhibitory sialic-acid binding proteins (Siglecs) expressed on several immune cells. We tested whether inhibiting sialidase, via sialidase inhibitors commonly used clinically to treat influenza (oseltamivir and DANA), would attenuate HIV-mediated immune activation/inflammation *in vivo*.

Methods: Two independent cohorts of bone-marrow-liver-thymus (BLT) humanized mice were infected or not with HIV_{SUMA} (a transmitter-founder virus) at 3,500 $TCID_{50}$. Infected mice were treated (via daily oral gavage) with a combination of oseltamivir and DANA (25mg/kg; a clinically comparable dosage) or saline control (**Fig. 1A**). Plasma markers of inflammation were measured by multiplex cytokine arrays five weeks post-infection. T cell activation (co-expression of CD38 and HLA-DR) and exhaustion (PD1) were measured by flow cytometry in the blood (weekly) and in the liver, lungs, and spleen (at endpoint). Plasma viral load (weekly) and levels of cell-associated HIV DNA in the liver, lungs, and spleen (at endpoint) were measured by qPCR.

Results: Sialidase inhibition significantly attenuated HIV-mediated induction of several markers of inflammation and immune activation, including markers of the pro-inflammatory type-II interferon responses ($q < 0.05$; **Fig. 1B**). In contrast, sialidase inhibition induced levels of the antiviral type-I interferon-α ($q=0.06$). Consistently, sialidase inhibition significantly attenuated HIV-mediated induction of CD8+ T cell activation and exhaustion in the blood ($q < 0.05$; **Fig. 1C**) and tissues ($q < 0.05$; **Fig. 1D**). This reduction in HIV-mediated inflammation and immune activation was accompanied with a decrease in plasma viral load ($P=0.02$; **Fig. 1E**) and levels of cell-associated HIV DNA in the liver and lungs ($P < 0.02$; **Fig. 1F**). The degree of immune activation and inflammation significantly correlated with higher levels of HIV viral load in plasma and tissues ($P < 0.05$; **Fig. 1G**).

Conclusion: Normalizing glycosylation patterns (in particular sialylation) represents a novel approach to prevent the development of inflammation during HIV infection. Future studies are warranted to examine the potential impact of sialidase inhibition on HIV-mediated inflammation during suppressive ART.

Figure 1: Sialidase inhibitors attenuate immune activation/inflammation and reduce levels of tissue-associated HIV DNA in humanized mice.



267 EXPRESSION OF UNSPLICED HIV-1 RNA INDUCES INFLAMMASOME ACTIVATION IN MYELOID CELLS

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Background: Despite the success of combination antiretroviral therapy, persistent viral RNA expression in tissue macrophages such as CNS-resident microglia and associated chronic inflammation still remain a major barrier to HIV-1 cure strategies. Our recently published studies reported that cytoplasmic expression of unspliced or intron-containing viral RNA (icRNA) leads to innate immune activation in human macrophages and microglia, though the icRNA sensing mechanism has remained unclear. Inflammasomes are known to play an important role in regulating immune response and secretion of pro-inflammatory cytokines, IL-1β and IL-18, in response to diverse stimuli. In this study, we focused on the role of HIV icRNA expression in triggering innate immune receptors and inducing inflammasome activation.

Methods: Monocyte-derived macrophages (MDMs), iPSC-derived microglia, and CHME3 microglial cell line were infected with replication-competent HIV-1 or reporter viruses expressing icRNA accessing distinct nucleocytoplasmic RNA export pathways. Infections were performed in the presence or absence of small molecule inhibitors targeting virus replication cycle, or upon knock-down of innate immune sensing pathways. Inflammasome activation was determined by qRT-PCR, immunoblotting, caspase-1 activation (FLICA) and IL-1β ELISA.

Results: Infection of MDMs and microglia with WT HIV-1, but not M10/Rev-mutant HIV-1 (that lacks cytoplasmic icRNA export) induced NLRP3 expression and IL-1β secretion. Interestingly, MPMV constitutive transport element (CTE)-mediated rescue of icRNA export in Rev/M10 HIV-1 also primed NLRP3 expression and triggered secretion of IL-1β. IL-1β production was independent of viral icRNA sequence, viral protein (Gag-Pol, Vif, Vpr, Vpu, Nef and Env) expression, and was attenuated upon pre-treatment with HIV-1 RT (Efavirenz), integrase (Raltegravir), transcription (Spironolactone) or icRNA export (KPT335) inhibitors, or treatment with a pan-caspase inhibitor (z-VAD). Importantly, knockdown of MAVS, but not STING or abrogation of endosomal TLR nucleic acid sensing pathways, significantly attenuated IL-1β production, confirming that cytosolic HIV-1 icRNA sensing is required for inflammasome activation in macrophages and microglia.

Conclusion: These results suggest that provirus establishment and persistent cytoplasmic expression of HIV-1 icRNA alone, even in the absence of viral protein expression, is sufficient to activate inflammasomes and might contribute to chronic innate immune activation.

268 IMPACT OF EARLY ART ON TISSUE RESIDENT MEMORY T CELLS IN THE GASTROINTESTINAL TRACT

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RV254/SEARCH010 and SEARCH013/RV304 Study Groups
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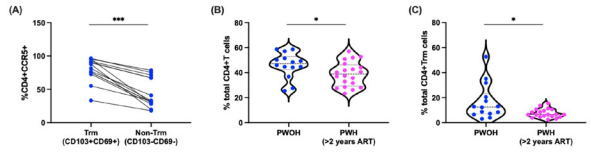
Background: Depletion of mucosal CD4 T cells during acute HIV infection (AHI) impairs mucosal homeostasis, leading to microbial translocation and ongoing immune activation. Tissue resident memory CD4 T cells (Trm) are long-lived non-circulating cells residing in different tissues that may be early targets of HIV and/or sources of the latent reservoir. We sought to determine the impact of early initiated ART on these cells.
Methods: We used an optimized flow cytometry panel to characterize CD4 Trm in colonic biopsies from people without HIV (PWOH, n=14, RV304 cohort) and people with HIV (PWH) who initiated ART during AHI treated for ≥ 2 years (n=21, RV254 cohort). CD4 Trm were defined by the expression of early activation marker CD69 and tissue retention integrin αEβ7 (CD103). Soluble markers of immune activation were assessed by ELISA, and mucosa-associated microbiome was characterized using 16S rRNA sequencing.
Results: In PWOH, CCR5 expression was higher in colonic CD4 Trm (CD69+CD103+) compared to non-Trm (CD69-CD103-; median 81.4% vs 33.1%, p< 0.0001), supporting the hypothesis that Trm have increased HIV susceptibility. In PWH who initiated ART during AHI, the frequency of colonic CD4 Trm was significantly reduced when compared to PWOH (p=0.016), with similar trends observed for absolute numbers (abs CD4 Trm; p=0.067); Trm reduction was mainly dependent on reduced CD103 expression. While a 22% decrease in the frequency of total CD4 T cells was observed between PWH who initiated ART early and PWOH (median 38.8% vs 47.2%, p< 0.0001), a 64% decrease in CD4 Trm was observed between groups, suggestive of preferential depletion of CD4 Trm cells. Abs CD4 Trm, but not total CD4 T cells, correlated inversely with plasma levels of MDC (r=-0.494, p=0.023) and MCP-1 (r=-0.513, p=0.017). Interestingly, mucosa-associated microbiome abundance clustered by CD4 Trm frequency more closely than by HIV status, with higher abundance of bacteria in the *Lachnospiraceae* family corresponding to higher CD4 Trm in PLWH on ART.
Conclusion: CD4 Trm may have increased susceptibility to HIV and are not restored to normal levels despite early ART, which may indicate a combination of preferential depletion and/or partial restoration. Reduction of CD4 Trm during ART was associated with elevated plasma cytokines and differences in gut microbiome composition. Interventions to fully restore CD4 Trm at mucosal sites could be important for normalizing inflammation in the context of early HIV treatment.



Expression of CCR5 on colonic CD4 Trm (CD69+CD103+) and non-Trm (CD69-CD103-) in PWOH (A), and frequency of total colonic CD4 T cells (B) and colonic CD4 Trm (C) in PWOH and PWH. P-values were calculated using Wilcoxon (paired) and Mann-Whitney (unpaired) test, with *p≤0.05 and ***p<0.001.

269 MULTIOMIC BIOMARKERS ACROSS ART INITIATION TIMEPOINTS REVEAL INTERFEROME ENRICHMENT

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Background: People with HIV (PWH) have increased risk of comorbidities even with antiretroviral therapy (ART). Based on our prior studies, we hypothesized that persistent immune activation in PWH, particularly in the monocyte compartment, undermines immunoregulation in some PWH. We analyzed peripheral blood gene expression profiles of monocytes and lymphocytes from PWH before and after ART to assess regulation of the interferome in chronic immune dysregulation after ART.
Methods: We included cryopreserved PBMC from PWH before starting ART (preART; with CD^4 > 200 cells/mL, n=17) and < 1 year after starting ART (postART, n=17); as well as matched HIV-negative individuals (HN, n=12). RNASeq was performed on PBMCs and flow-sorted cells to identify longitudinal changes in gene expression. Samples were further subgrouped to early postART (sampled ≤60 days after ART initiation), and late postART (>100 days after ART initiation). Low input RNASeq was performed (Illumina NextSeq 550 platform) on flow cytometry-sorted cell subsets. Linear contrasts were performed to identify differentially expressed genes (DEG, p≤0.05, n≥3) between preART, postART and HN. We employed single cell multiomic analysis (10X Genomics, ATAC) to delve deeper into possible mechanisms of epigenetic accessibility impacting gene expression in PWH before vs after ART administration.
Results: Overall, 237 interferon response genes (IRGs) in monocytes were differentially expressed in postART vs HN but not preART vs HN (p≤0.05). However, expression of gene sets representing IFN pathways and key regulators of immune responses, notch signaling, cell cycle, and intercellular communication were enriched in both postART and preART samples relative to HN (adj. p<0.05), indicating enrichment of these pathways during ART use. We also found significantly expressed IRG unique to monocyte subsets when comparing the postART versus earlyART PWH, with additional epigenetic molecular phenotypes distinguishing PWH endotypes before and after starting ART. Importantly, these molecular phenotypes persisted with ART.
Conclusion: These multiomic phenotypes represent candidate biomarkers and a growing understanding of the role monocytes play in immune dysfunction observed in some PWH endotypes with ART. Validation of these signatures in an independent cohort is needed to pursue these potential translational targets.

270 HIV SUPPRESSSION IS LINKED TO SHIFTING EPIGENETIC/TRANSCRIPTOME FEATURES IN MONOCYTES

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Background: The broad susceptibility to multiple pathogens in progressive HIV infection suggests that innate immune function is dysregulated. We sought to characterize the impact of HIV viral suppression on monocytes.
Methods: 20 participants (19M, 1F) with paired cryopreserved PBMCs from before and after the initiation of ART were selected. PBMCs were thawed, monocytes were isolated and were divided into two analyses (1) transcriptional response (RNAseq) after 24 hours of culture with or without LPS stimulation (2) direct *ex vivo* analysis of chromatin accessibility with ATACseq. All sequencing was performed on the NovaSeq6000 platform. ATACseq analysis of mapped reads used Genrich for peak finding, Motif-discovery using MEME-chip, visualization of peak regions with ChIPseeker, and DiffBind was used to compute differentially bound sites between the pre and post-ART samples. RNAseq data was analyzed for differential gene expression both at baseline and after LPS stimulation between the pre and post-ART conditions.
Results: Study participants had a median pre-ART HIV VL of 209,000 (IQR 48,900; 2,130,000) and a median CD4 count of 492 (IQR 386,589) with >95% with a viral load of< 50 copies at the second time point and a median CD4 of 716 (IQR 485,867) at the post-ART sample point. After quality control and data analysis, a median of 46,000 chromatin peaks were identified with a median of 2700 unique peaks pre-ART and 6,400 peaks post-ART. Combining the individual data, 88 chromatin peaks showed statistical differential accessibility pre and post-ART across the cohort. Among the top differentially accessible peaks were two peaks related genes in the acyl-coA synthetase family involved in fatty acid metabolism and a peak proximal to *IFI27*, a putative adaptor protein implicated in interferon signaling in innate cells (all at FDR< 0.01). The RNAseq analysis supported the significance of this chromatin feature; although global transcriptional profiles were similar before and after ART, *IFI27* was among the top differentially expressed genes between pre and post-ART samples in both media alone conditions and after LPS stimulation(logFC 3.4, FDR< 0.01 for both).
Conclusion: Suppression of HIV viremia is linked to changes in chromatin accessibility in and differential expression of IFI27 in monocytes. Chromatin

patterns also indicate a change in fatty acid metabolism. HIV viremia may impact innate function through metabolic and epigenetic regulatory pathways.

271 PLASMA LIPIDS AND AMINO ACIDS LINKED TO LOW SARS-CoV-2 SUSCEPTIBILITY

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Background: The mechanisms driving SARS-CoV-2 susceptibility remain poorly understood, especially the factors determining why a subset of unvaccinated individuals remain uninfected despite high-risk exposures.
Methods: We studied an exceptional group of unvaccinated healthcare workers heavily exposed to SARS-CoV-2 ('nonsusceptible') from April to June 2020, who were compared against 'susceptible' individuals to SARS-CoV-2, including uninfected subjects who became infected during the follow-up, and hospitalized patients with different disease severity providing samples at early disease stages. We analyzed plasma samples using different mass spectrometry technique and obtained metabolites and lipids profiles.
Results: We found that the metabolite profiles were predictive of the selected study groups and identified lipids profiles and metabolites linked to SARS-CoV-2 susceptibility and COVID-19 severity. More importantly, we showed that non-susceptible individuals exhibited unique metabolomics and lipidomic patterns characterized by upregulation of most lipids —especially ceramides and sphingomyelin—and amino acids related to tricarboxylic acid cycle and mitochondrial metabolism, which could be interpreted as markers of low susceptibility to SARS-CoV-2 infection. Lipids and metabolites pathways analysis revealed that metabolites related to energy production, mitochondrial and tissue dysfunction, and lipids involved in membrane structure and virus infectivity were key markers of SARS-CoV-2 susceptibility.
Conclusion: Lipid and metabolic profiles differ in 'nonsusceptible' compared to individuals susceptible to SARS-CoV-2. Our study suggests that lipid profiles are relevant actors during SARS-CoV-2 pathogenesis and highlight certain lipids relevant to understand SARS-CoV-2 pathogenesis.

Lipid profiles from COVID19 patients obtained by LC-MS

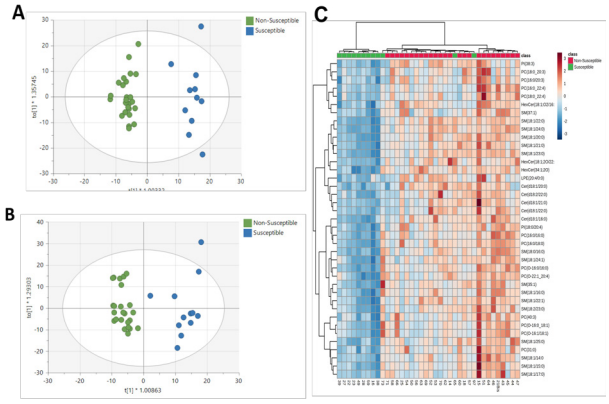

Figure 1. Lipid profiles from COVID19 susceptible and non-susceptible individuals obtained by LC-MS at positive and negative ionization modes. A. OPLS-DA score plot of LC-MS (ESI+) R2 = 0.945; Q2 = 0.699; CV-ANOVA = 6.79e-7. **B.** OPLS-DA score plot of LC-MS (ESI-) R2 = 0.903; Q2 = 0.687; CV-ANOVA = 3.17e-6. **C. Heatmaps of common significant lipids obtained by LC-MS for susceptible and non-susceptible groups.** The scale color on the right represents the relative abundances. Samples for susceptible individuals are depicted in green. Samples for non-susceptible individuals are depicted in red.

272 EARLY INFLAMMATORY PROFILES PREDICT MAXIMAL DISEASE SEVERITY IN COVID-19

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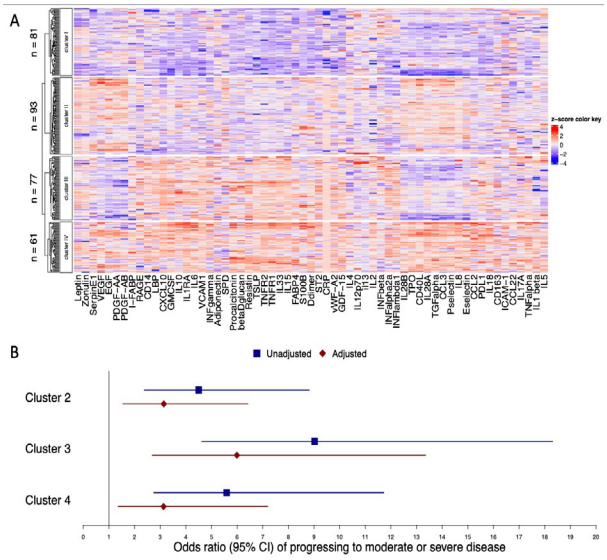
Background: Better understanding of host inflammatory changes that precede development of severe COVID-19 could improve delivery of available antiviral and immunomodulatory therapies, and provide insights for the development of new therapies.
Methods: In plasma from individuals with COVID-19, sampled ≤10 days from symptom onset from the All-Ireland Infectious Diseases Cohort study, we measured 61 biomarkers, including markers of innate immune and T cell activation, coagulation, tissue repair, lung injury, and immune regulation. We used principal component analysis (PCA) and k-means clustering to derive biomarker clusters, and univariate and multivariate ordinal logistic regression to explore association between cluster membership and maximal disease severity, adjusting for risk factors for severe COVID-19, including age, sex, ethnicity, BMI, hypertension and diabetes.
Results: From March 2020-April 2021, we included 312 individuals, (median (IQR) age 62 (48-77) years, 7 (4-9) days from symptom onset, 54% male) in the analysis. PCA and clustering derived 4 clusters. Compared to cluster 1, clusters 2-4 were significantly older and of higher BMI but there were no significant differences in sex or ethnicity. Cluster 1 had low levels of inflammation, cluster 2 had higher levels of markers of tissue repair and endothelial activation (EGF, VEGF, PDGF, TGFα, serpin E1 and p-selectin). Cluster 3 and 4 were both characterised by higher overall inflammation, but compared to cluster 4, cluster 3 had downregulation of growth factors, markers of endothelial activation, and immune regulation (IL10, PDL1), but higher alveolar epithelial injury markers (RAGE, ST2). In univariate analysis, compared to cluster 1, cluster 3 had the highest odds of severe disease (OR (95% CI) 9.02 (4.62-18.31), followed by cluster 4: 5.59 (2.75-11.72) then cluster 2: 4.5 (2.38-8.81), all $p < 0.05$). Cluster 3 remained most strongly associated with severe disease in fully adjusted analyses; cluster 3: OR(95% CI) 5.99 (2.69-13.35), cluster 2: 3.14 (1.54-6.42), cluster 4: 3.13 (1.36-7.19), all $p< 0.05$).
Conclusion: Distinct early inflammatory profiles predicted maximal disease severity independent of known risk factors for severe COVID-19. A cluster characterised by downregulation of growth factor and endothelial markers and early evidence of alveolar injury was associated with highest risk of developing severe COVID19. Whether this reflects a dysregulated inflammatory response that could improve targeted treatment requires further study.

Heatmap of biomarker derived clusters and forest plot of association between clusters and disease severity. A: Heatmap demonstrating differences in biomarkers between clusters B: Forest plot demonstrating odds ratio of specific clusters for progressing to moderate or severe disease (reference Cluster 1), calculated using ordinal logistic regression. Odds ratio (95% CI) presented as unadjusted and fully adjusted (for age, sex, ethnicity, BMI, hypertension, diabetes, immunosuppression, smoking and baseline anticoagulant use). Maximal disease severity graded per the WHO severity scale.



273 DIFFERENTIAL ASSOCIATION OF CYTOMEGALOVIRUS WITH ACUTE AND POST-ACUTE COVID-19

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IMPACC, COMET, and LIINC study teams
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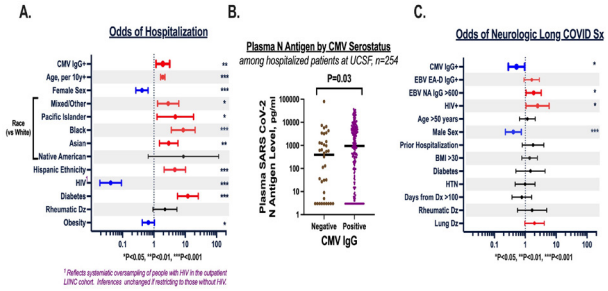
Background: Asymptomatic Cytomegalovirus (CMV) infection reshapes systemic immune responses and its replication can be both a consequence and cause of inflammation. As CMV resides in the same tissues affected by SARS-CoV-2, we hypothesized that asymptomatic CMV co-infection might modify the pathogenesis of both acute and post-acute COVID-19.
Methods: Participants had current or prior nucleic acid-confirmed SARS-CoV-2 infection in the COVID-19 Multi-Phenotyping for Effective Therapies (COMET, n=219), Immunophenotyping Assessment in a COVID-19 Cohort (IMPACC, n=244) or the Long-term Impact of Infection with Novel Coronavirus (LIINC, n=327) cohorts. We assessed the relationship between CMV serostatus and odds of hospitalization and plasma SARS-CoV-2 N antigen levels during acute COVID-19 as well as post-acute "Long COVID" symptoms, defined as >=1 of 32 COVID-19-attributed symptoms present at least 60 days following initial symptom onset.
Results: Among 758 participants, 518 were hospitalized for their acute COVID-19 episode. CMV seropositivity was independently associated with a 1.9-fold increased odds of hospitalization for acute COVID-19, after adjustment for age, sex, race, ethnicity, HIV status, prior autoimmune disease, diabetes, and obesity (p=0.01, A). Among those hospitalized, CMV seropositivity was also associated with higher plasma SARS-CoV-2 N antigen levels (median 936 vs. 323 pg/ml, P=0.03, B), which remained significant after adjustment for potential confounders, but not with ICU admission (n=209), death (n=58), or thrombotic events (n=31). In contrast to its relationship to acute COVID-19 disease severity, CMV seropositivity was independently associated with a 48% decreased odds of having neurocognitive Long COVID symptoms such has headache and brain fog 4 months after initial COVID-19 diagnosis (P=0.036). Conversely, serologic evidence of Epstein-Barr Virus (EBV) reactivation and HIV both increased the odds of these symptoms (C).
Conclusion: CMV seropositivity is associated with a 1.9-fold higher odds of hospitalization in people with acute COVID-19 and a nearly 3-fold higher SARS-CoV-2 antigen burden in hospitalized patients. In contrast, CMV seropositivity is associated with a decreased odds of neurocognitive Long COVID symptoms, while other chronic viral co-infections like EBV reactivation and HIV are associated with an increased odds of this complication. The biologic mechanisms mediating these relationships are unknown, but warrant further investigation.

Association of demographic and disease factors with acute and post-acute COVID-19 outcomes.



274 BASELINE AND TEMPORAL DIFFERENCES IN PROTEOMICS FOLLOWING SARS-CoV-2 INFECTION IN PWH

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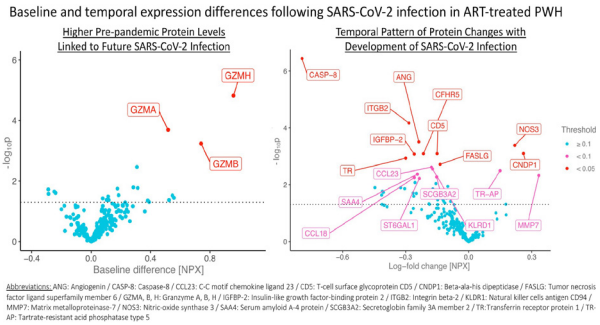
Background: COVID-19 may be more severe in persons with HIV (PWH). However, underlying biological mechanisms associated with the development of COVID-19 and its clinical severity among antiretroviral therapy (ART) treated PWH are largely unknown. Therefore, we wished to evaluate temporal changes in plasma proteins following SARS-CoV-2 infection and identify pre-infection proteomic markers associated with future COVID-19.
Methods: We analyzed the data of clinical, antibody-confirmed COVID-19 ART-treated PWH from the global Randomized Trial to Prevent Vascular Events in HIV (REPRIEVE). Individuals were matched on geographic region, age, and sample timing to antibody-negative controls. For cases and controls, pre-COVID-19 pandemic specimens were obtained prior to January 2020 to assess temporal changes and baseline differences in protein expression in relationship to COVID-19 severity, using mixed effects models adjusted for false-discovery rate.
Results: We compared 257 unique plasma proteins (Olink Proteomics) in 94 COVID-19 antibody-confirmed clinical cases and 113 matched antibody-negative controls, excluding COVID-19 vaccinated participants (median age 50 years, 73% male). 40% of cases were characterized as mild; 60% moderate to severe. Median time from COVID-19 infection to follow-up sampling was 4 months. Temporal changes in protein expression differed based on COVID-19 disease severity. Among moderate to severe cases vs. controls, NOS3 increased, whereas ANG, CASP-8, CD5, GZMH, GZMB, ITGB2, and KLRD1 decreased. Higher baseline circulating concentrations of granzymes A, B and H (GZMA, GZMB and GZMH) were associated with the future development of moderate-severe COVID-19 in PWH and were related to immune function, including CD4, CD8 and the CD4/CD8 ratio.
Conclusion: We identified temporal changes in novel proteins in closely linked inflammatory, immune, and fibrotic pathways which may relate to COVID-19-related morbidity among ART-treated PWH. Further, we identified key granzyme proteins, serine proteases expressed by cytotoxic T lymphocytes and NK cells in response to foreign antigens, associated with future COVID-19 in PWH. Our results provide unique insights into the biological susceptibility and responses to COVID-19 infection in PWH.

Baseline and temporal expression differences following SARS-CoV-2 infection in ART-treated PWH



Abbreviations: ANG: Angiogenin / CASP-8: Caspase-8 / CCL23: C-C motif chemokine ligand 23 / CD5: T-cell surface glycoprotein CD5 / CNDP1: Beta-ala-his dipeptidase / FASLG: Tumor necrosis factor ligand superfamily member 6 / GZMA, B, H: Granzyme A, B, H / IGFBP-2: Insulin-like growth factor-binding protein 2 / ITGB2: Integrin beta-2 / KLDR1: Natural killer cells antigen CD94 / MMP7: Matrix metalloproteinase-7 / NOS3: Nitric-oxide synthase 3 / SAA4: Serum amyloid A-4 protein / SCGB3A2: Secretoglobin family 3A member 2 / TR: Transferrin receptor protein 1 / TR-AP: Tartrate-resistant acid phosphatase type 5

275 SARS-CoV-2 BA.5 CAUSES HIGHER REPLICATION AND LETHAL INFECTION IN K18-hACE2 MICE

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Background: The continuous evolution of SARS-CoV-2 in the diverse immune landscape (natural, vaccine, hybrid) is giving rise to novel immune escape mutations. So far, the resulting new variants (BA.1, BA.2, BA.2.12.1) were observed to cause mild infections, however, BA.5 infections are associated with

an increased risk of hospitalization.[1] Therefore it is essential to investigate the pathogenesis of BA.5.

Methods: Here we compared the pathogenicity of Pre-Omicron (B.1.351) and Omicron (BA.1, BA.2.12.1, and BA.5) variants in wild-type C57BL/6J mice and K18-hACE2 mice. The virus replication kinetics was also studied in human Calu3, pulmonary alveolar type 2 (AT2) cells, and airway organoids (HAO). Cell-to-cell spread of virus was measured by syncytia formation assay and immunohistochemistry (IHC) of infected lungs.

Results: In the results, infection in C57BL/6J mice showed severe weight loss (>15%) for B.1.351 infected mice and moderate (>5%) for BA.5 infected. C57BL/6J mice showed higher virus replication of B.1.351 followed by BA.5, BA.1, and BA.2.12.1. At the peak of virus replication (2 days) plaque-forming units from lung extract of BA.5 infected mice were two, and three logs higher compared to BA.1 and BA.2.12.1 respectively. BA.5 infection was lethal to 80% of infected K18-hACE2 mice, whereas the mice looked normal after infection with BA.1 and BA.2.12.1. BA.5 infected mice showed high virus replication in brain tissue. Surprisingly the syncytia formation assay and IHC for BA.5 was comparable to that of B.1.351, indicating the higher cell-to-cell spread of BA.5 and B.1.351 compared to BA.1 and BA.2.12.1, which is one of the measures of pathogenicity. Calu3 and HAO showed the same trend of virus replication as was observed in-vivo experiments however AT2 cells were found to be resistant to BA.5 replication.

Conclusion: These results suggest that the BA.5 variant (lineage) of Omicron has the potential to regain the pathogenicity as it shows increased virulence compared to other Omicron sub-variants. Lethal infection of BA.5 in K18-hACE2 mice may be attributed to catastrophic encephalitis and increased cell-to-cell spread.

276 AUTOPHAGY AND Acyl-CoA-BINDING PROTEIN INFLUENCE COVID-19 SEVERITY

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BQC-19 Biobank
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Background: Autophagy, a cytosolic-structure degradation pathway, allows production of IL21 by CD4 T-cells and efficient cytolytic responses by CD8 T-cells. Autophagy is in part regulated by acyl-CoA-binding protein (ACBP) which has two functions. Intracellular ACBP favors autophagy, whereas secreted extracellular ACBP inhibits autophagy. Herein, we assessed whether autophagy and the ACBP pathway were associated with COVID-19 severity.

Methods: Through the BQC-19 Quebec biobank, somalogic proteomic analysis was performed on 5200 proteins in plasma samples collected between March 2020 and December 2021. Plasma from 903 patients (all data available) during the acute phase of COVID-19 were assessed. COVID-19 severity was stratified using WHO criteria. *In vitro*, ACBP intracellular levels, autophagy levels (LC3II) and IL21 production were assessed by flow in PBMCs after a 24h stimulation with IL6, phorbol myristate acetate (PMA)+ionomycin or lipopolysaccharide (LPS). Plasma levels of anti-SARS-CoV-2 (full spike protein or RBD) IgG were assessed by ELISA.

Results: Median age of the cohort was 62 yo, 48% were female, 55% had comorbidities (see table). Increasing plasma levels of ACBP were found with severity (mild, moderate, severe and fatal groups having 5.3, 7.3, 9.5 and 10.6 RFU/50µL of plasma, respectively, $p< 0.001$ for all comparisons). Patients with comorbidities had higher plasma ACBP levels (7.4 vs 6.4 RFU/50µL, $p< 0.001$). Plasma ACBP levels were higher during the delta and omicron-variant periods (8.4 vs 6.8 RFU/50µL; $p< 0.001$). Plasma ACBP levels correlated with LC3II levels ($r=0.51$, $P< 0.001$) and IL6 ($r=0.41$, $p< 0.001$), but neither with markers IL1β nor IL8. ACBP levels negatively correlated with IL21 levels ($r=-0.27$, $p< 0.001$), independently of age, sex, and severity. ACBP levels were not associated with levels of anti-SARS-CoV-2 IgG levels.

In vitro, IL6 stimulation of healthy control PBMC induced extracellular ACBP release. Moreover, adding recombinant ACBP: 1) reduced autophagy in lymphocytes and monocytes upon polyclonal stimulation with PMA/ionomycin or LPS; 2) reduced intracellular production of IL21 in T-cells after PMA/ionomycin stimulation.

Conclusion: Plasma ACBP levels were inversely linked with IL21 levels, suggesting that autophagy and IL21 allow control of SARS-CoV-2 infection, independently of the level of SARS-CoV-2 antibody secretion. ACBP is a targetable autophagy checkpoint and its extracellular inhibition may improve SARS-CoV-2 immune control.

Table 1: Demographic and results summary

	COVID-19+				
Groups	Mild	Moderate	Severe	Fatal	**All**
n	259	384	236	24	**903**
Age (median, years)	54.3	67.3	65.6	74.3	**61.9**
% Female	58	49	33	42	**48**
% with comorbidities	46	58	55	75	**55**
Plasma ACBP (median, RFU/50µL)	5.3	7.3	9.5	10.6	**7.0**
Plasma IL6 (median, RFU/50µL)	0.34	0.60	0.85	1.6	**0.54**
Plasma IL21 (median, RFU/50µL)	0.76	0.72	0.66	0.65	**0.71**

277 INFLAMMATORY PATHWAYS ASSOCIATED WITH COVID-19 SEVERITY DIFFER BASED ON OBESITY STATUS

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All Ireland Infectious Diseases Cohort
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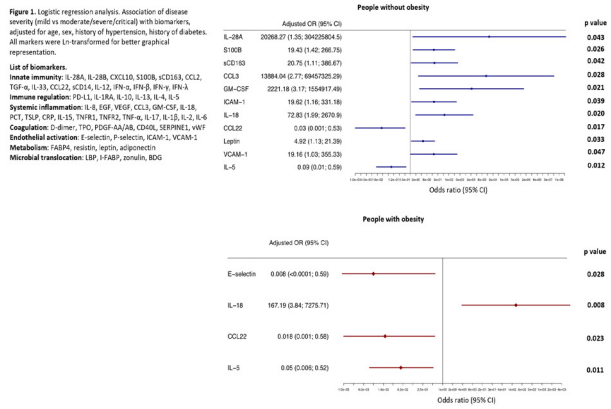
Background: Severe COVID-19 and obesity are characterized by higher inflammation. We aimed to examine early inflammatory patterns in people with (Ob) and without (NOb) obesity and COVID-19 and how they relate to COVID-19 disease severity

Methods: Ob (BMI >30 Kg/m^2) and NOb with COVID-19 matched for age, sex and WHO disease severity provided blood early after diagnosis. Immunoassays measured 57 plasma biomarkers reflecting innate immune and endothelial activation, systemic inflammation, coagulation, metabolism and microbial translocation (Fig 1). Between-group differences were assessed by Mann-Whitney. Associations between subsequent maximal COVID-19 severity (mild vs moderate/severe/critical) and biomarkers were explored by logistic regression adjusted for age, sex, hypertension (HTN) and diabetes (DM). Data are median pg/mL [IQR] or n [%] unless stated

Results: Of 100 subjects (50 Ob and 50 Nob) presenting between April 2020 and March 2021, characteristics (Ob vs Nob) included: age 65 [23-91] vs 65 [21-95]; female sex 27 (48%) vs 28 (56%); BMI 33.7 [30.0-71.8] vs 23.3 [15.3-25.9]; disease severity mild 22 [48%] vs 23 [46%], moderate 15 [30%] vs 13 [26%], severe 6 [12%] vs 7 [14%]; HTN 30 (60%) vs 17 (34%); DM 19 [38%] vs 6 [12%]; days from symptom onset 7 [2-17] vs 8 [1-15]; vaccinated 3 (6%) vs 0 (0%). Compared to NOb, Ob had higher IFN-α (1.8 [0.6; 11] vs 0.9 [0.1; 4.7]), CRP (10 mAU/mL [9.6; 10.2] vs 9.7 [7.2; 10]), IL-1RA (197 [122; 399] vs 138 [88; 253]), IL-4 (288 AU/mL [161; 424] vs 205 [82; 333]), vWF (252 [166; 383] vs 163 [96; 318]), Zonulin (114 ng/mL [77; 131] vs 57 [18; 106]), Resistin (956 [569; 1153] vs 727 [712; 1525]), Leptin (3482 [1513; 5738] vs 848 [249; 2114]), and lower Adiponectin (1.12 mg/L [0.09; 1.5] vs 1.5 [1.18; 1.93]), all $p< 0.05$.
In both groups higher, proinflammatory IL-18 and lower levels of anti-inflammatory CCL22 and IL-5 were associated with higher odds of disease severity, and lower E-selectin with higher disease severity only in Ob. However, in NOb higher type 3 interferons (IL-28A), macrophage activation (sCD163, CCL3) and vascular inflammation markers (ICAM-1, VCAM-1), along with higher S100B, GM-CSF and leptin were also associated with disease severity, a pattern not observed in Ob (Fig 1)

Conclusion: Although Ob had higher overall levels of inflammation than NOb, few biomarkers predicted subsequent COVID-19 severity in Ob. These differential inflammatory patterns suggest dysregulated immune responses in Ob with COVID-19

Figure 1. Logistic regression analysis



278 SARS-CoV-2 VARIANTS-DEPENDENT INFLAMMASOME ACTIVATION

Elisa Teyssou[1], Stephane Marot[2], Adelie Gothland[1], Isabelle Malet[1], Karen Zafilaza[2], Valentin Leducq[2], Theophile Cocherie[1], Cathia Soulié[2], Anne-Geneviève Marcelin[2], Vincent Calvez[2]

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Background: Innate immunity is the first line of defense in response to pathogens, which acts locally and also leads the stimulation of adaptive immunity through at least with IL-1β secretion. It has been shown that SARS-CoV-2 infection triggered the NLRP-3 inflammasome activation and the IL-1β secretion. The aim of this study was to analyze and compare the level of IL-1β secretion that is one of the most important innate immunity cytokines, in monocyte-like cells infected with 6 different variants of the SARS-CoV-2.

Methods: Six SARS-CoV-2 variants (historical (B.1, D614G), Alpha, Beta, Gamma, Delta and Omicron BA.1) were isolated from COVID-19 hospitalized patients. Viral stocks were obtained by inoculation in Vero and Vero-TRMPSS2 cells. THP-1 monocyte-like cells were cultured with RPMI-hepes 10% FBS-0.05 mM 2-mercaptoethanol. A total of 5 x 10^4 of THP-1 cells was plated per well in 96-wells plate and differentiated with 10nM of PMA for 24h. Differenciated-THP-1 were first primed with LPS 1µg/ml for 2h and infected with different SARS-CoV-2 variants with a MOI 0.1. IL-1β was measured by luminescence in the supernatant after 24 h of infection.

Results: We analyzed and compared IL-1β secretion between SARS-CoV-2 virus 6 sublineages after infection of monocytes like THP-1. We observed that THP-1 cells infected with SARS-CoV-2 variants presented a significantly higher IL-1β secretion than non-infected cells.

Moreover, some SARS-CoV-2 variants led to a stronger IL-1β secretion, and particularly we observed a significantly higher level of IL-1β cells infected with Omicron BA.1 sublineage compared to other variants.

Indeed, Omicron BA.1 infected cells presented the higher IL-1β secretion (median 385.7 pg/ml IQR[302.6–426.3]) follows by the Delta variants and the historical variants (median 303.6 [266.3–391.9] and 281.9 [207.2–410], respectively). Alpha, Beta and Gamma variants presented the lowest IL-1β secretion (median 228.1 [192.5–276.4], 219.1 [185.1–354.2] and 211 [149.8–228.8]).

Conclusion: We observed the inflammasome activation for the 6 SARS-CoV-2 sublineages with a variation in level of IL-1β secretion. Indeed, our results suggested that Omicron BA.1 was more recognized by the innate immune cells than other SARS-CoV-2, which could in part, with its upper respiratory tract tropism, possibly explain its less clinical virulence. Taking together, these results suggest that the innate immunity response and precisely, IL-1β secretion pathways were activated in a SARS-CoV-2 variants-dependent manner.

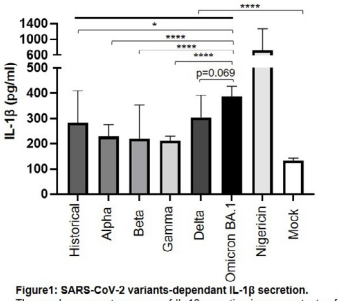

Figure1: SARS-CoV-2 variants-dependant IL-1β secretion.
The graph represent measure of IL-1β secretion in supernatants of non (mock) or SARS-CoV-2 infected or treat Nigericin (positive control for NLRP-3 activation) differenciated-THP-1 cells. *p<0.05 ; ****p<0.0001. Data shown result from multiple independent experiments.

279 HIGH FAT AND SUGAR DIET INDUCES GUT LEUKOCYTE DISRUPTIONS EXACERBATED BY SARS-CoV-2

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Background: The disparity in COVID-19 disease burden between European, Asian, and African countries is notable, with considerably higher morbidity and mortality in many European countries as well as the U.S. Dietary differences between regions could play a role in differential COVID-19 pathogenesis, as Western diets high in fat and sugar have been implicated in enhancing gut damage and pathogenesis during viral infections. Here we investigate the effect of diet on gut immunity and SARS-CoV-2 infection.

Methods: Six pigtail macaques were fed a commercial monkey chow diet, then transitioned to a high fat and sugar chow diet (HFD) for approximately two months prior to infection with Delta strain SARS-CoV-2. Animals were sampled prior to HFD initiation, during HFD administration but prior to infection, and for approximately one month post-infection. HFD was maintained following infection and animals were euthanized at the study conclusion.

Results: Viral RNA was detected for up to 28 days post-infection in nose swabs, with peak viral load at day 2 at a mean of 8.2x10^9 copies/mL of swab fluid. Subgenomic RNA (sgRNA, indicating viral replication) decayed more rapidly, with all animals having undetectable sgRNA by day 21, and a lower peak of 2.6x10^9 copies/mL swab fluid on day 2. Viral RNA load was approximately 3.5 logs greater and sgRNA load approximately 3 logs higher at day 2 than in rhesus macaques infected with WA2020 SARS-CoV-2 and fed standard monkey chow. Mucosal rectal biopsies indicated significantly lower B cell frequencies from baseline to approximately two months following HFD administration (p=0.04, Dunn's), and frequencies had not recovered approximately one month post-infection. GI tract-resident IgG+ B cells were nearly absent at necropsy, with mean frequency 0.03% of total B cells. B cell loss was coupled with modest T cell expansion during HFD administration, though frequencies declined following infection. Furthermore, NK cell frequencies tended to decline from baseline throughout HFD administration, and were further depleted at necropsy one month post-infection.

Conclusion: SARS-CoV-2 infection can induce lymphopenia, and our sampling of gut mucosal tissue indicates B cell depletion and NK cell loss with a HFD that is further exacerbated by SARS-CoV-2 infection. Excess dietary fat and sugar may disrupt gut barrier integrity and immunity, in turn predisposing the tissue to pathology of viral infection.

280 ACE2 SUBSTRATE CLEAVAGE EFFECT ASSOCIATED WITH COVID-19 PATIENT PLASMA IMMUNOGLOBULIN

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Background: Many mechanisms responsible for COVID-19 pathogenesis are well-known, but COVID-19 includes features with unclear pathogenesis, like autonomic dysregulation, coagulopathies, and high levels of inflammation. The SARS-CoV-2 spike protein receptor binding domain (RBD) receptor is angiotensin converting enzyme 2 (ACE2). We hypothesized that some COVID-19 patients may develop immunoglobulins (Igs) that have negative molecular image of

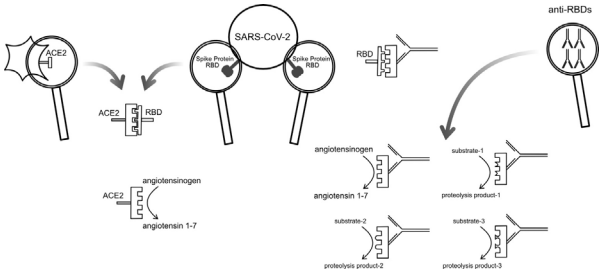
RBD sufficiently similar to ACE2 to yield ACE2-like catalytic activity – ACE2-like 'abzymes'.

Methods: To explore this hypothesis, we studied 67 patients hospitalized with COVID-19 who had disodium ethylenediaminetetraacetate (EDTA) anticoagulated plasma samples available, obtained about 7 days after admission. We used commercially available fluorometric ACE2 assays (Abcam), and a SpectraMax® M5 microplate reader (Molecular Devices), measuring Relative Fluorescent Unit (RFU, Ex/Em = 320/420 nm; RFU) in a kinetic mode every 20 min at 37C. ACE2 inhibitor provided in the assay kit was used for additional controls. In some control experiments, we added Zn^2+ to plasma, or conducted serial dilutions to decrease Zn^2+. To deplete Igs, we passed plasma samples through a 0.45 µm filter to remove large particles, then passed the material through 100kDa cut-off ultrafiltration membrane (Pierce™) columns, and finally used protein A/G Magnetic Beads (Life Technologies) to specifically deplete Ig, removing >99.99% of Ig as assessed with a human IgG ELISA Kit (Abcam).

Results: ACE2 is a metalloprotease that requires Zn^{2+} for activity. However, we found that the plasma of 11 of the 67 patients could cleave a synthetic ACE2 peptide substrate, even though the plasma samples were collected using EDTA anticoagulant. When we spiked plasma with synthetic ACE2, no ACE2 substrate cleavage activity was observed unless Zn2+ was added, or the plasma was diluted to decrease EDTA concentration. After processing samples by size exclusion and protein A/G adsorption, the plasma samples did not cleave the ACE2 substrate peptide.

Conclusion: The data suggest that some patients with COVID-19 develop Igs with activity capable of cleaving synthetic ACE2 substrate. Since abzymes can exhibit promiscuous substrate specificities compared to the enzyme whose active site image they resemble, and since proteolytic cascades regulate physiologic processes, anti-RBD abzymes may contribute to some otherwise obscure features of COVID-19 pathogenesis.

Hypothesized Anti-RBD Antibodies with Catalytic Activity: Anti-RBD Abzymes



281 SARS-CoV-2 VARIANTS' TEMPORAL AND VL DISTRIBUTIONS IN IMMUNOCOMPROMISED PATIENTS

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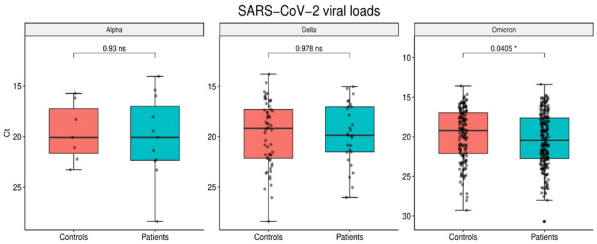
Background: The COVID-19 pandemic has been striking for three years and, despite the regular arise of new variants, populations are now widely immune and protected from severe symptoms. However, immunocompromised patients still have worse clinical outcomes, higher mortality and rarely develop effective immunity through vaccination or infection. Here, we studied the temporal distribution of infections, viral loads (VL) as well as the viral genetic diversity among an immunocompromised patient cohort, between January 2021 and September 2022.

Methods: Overall, 478 immunocompromised patients (solid organ transplant, HIV positive, cancer, autoimmune disease) and 234 controls (healthcare workers) from Pitié-Salpêtrière and Bichat Claude-Bernard University hospitals (Paris, FRANCE) were diagnosed with SARS-CoV-2 infection by RT-qPCR. Whole genome sequencing was performed according to ARTIC protocol on Oxford Nanopore platform. All 712 full viral genomes were used to determine lineages and mapped to Wuhan-Hu-1 reference to produce a maximum likelihood phylogenetic tree (IQTree, 1000 bootstraps). Differences in temporal distributions of infections and VL were assessed using nonparametric statistical tests.

Results: According to phylogenetic analysis, genomes from SARS-CoV-2 infecting immunocompromised patients and those infecting healthy individuals are distributed in a similar way. No significant genetic differences can be observed between viral genomes from patients and controls within the different lineages. Temporal distribution of COVID-19 infections were also similar between immunocompromised patients and controls, with the exception of BA.2 variant for which controls were infected earlier ($p< 0.001$). VL were significantly lower in immunocompromised patients infected with Omicron variants ($p=0.04$). No differences in VL were observed for Alpha and Delta variants.

Conclusion: At diagnosis, no intrinsic genetic divergence was observed in virus infecting immunocompromised patients compared to those circulating in the general population. Similarities in temporal distribution of infections between controls and patients suggest that these different groups become infected concomitantly. VL appeared to be lower for Omicron variants in immunocompromised patients. An earlier VL peak of Omicron and a testing of immunocompromised patients hospitalized once severe symptoms have appeared could indicate a delayed testing in these patients, once the replicative phase over.

SAR-CoV-2 viral loads in immunocompromised patients vs controls



282 PLASMA-BASED ANTIGEN PERSISTENCE IN THE POST-ACUTE PHASE OF SARS-CoV-2 INFECTION

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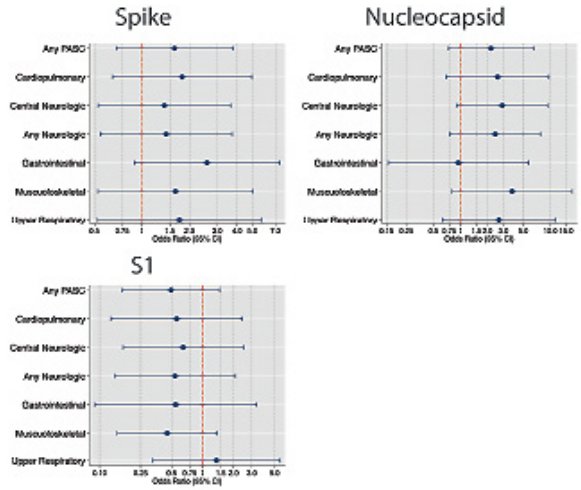
Background: There is mounting evidence regarding the frequency and spectrum of post-acute sequelae of SARS-CoV-2 infection (PASC), but a search for causes has been elusive. Recently, a plasma-based assay for SARS-CoV-2 antigen has been developed, which in initial use revealed that a high fraction of severely affected patients with PASC had circulating antigen. It is unknown whether detectable SARS-CoV-2 antigen is specific for PASC or how the assay performs in a broader clinical spectrum of patients with PASC.

Methods: We evaluated a cohort of patients with RNA-confirmed SARS-CoV-2 infection enrolled ≥3 weeks following initial symptoms. Participants, both with and without PASC at enrollment, were identified via facility- and community-based advertising and examined every 4 months. An interviewer-administered questionnaire ascertained presence of 30 different symptoms (new or worse compared to pre-COVID) in the prior 2 days at each exam. Using the single molecule array (Simoa) assay, we measured spike, S1, and nucleocapsid SARS-CoV-2 antigens in plasma collected at time of symptom assessment.

Results: We examined 172 participants (50% men, 46% non-white, median age 46 years) who contributed 667 timepoints from 0.7 to 15.4 months following infection, at which 66% featured report of ≥1 symptom. Sixty-one of 667 timepoints (9.1%) representing 24% of persons had ≥1 detectable SARS-CoV-2 antigen. Among the 437 timepoints at which ≥1 symptom was present, 9.8% had ≥1 detectable antigen; this compares to 7.8% of timepoints at which symptoms were absent. In comparison to those without symptoms, individuals with several specific symptom complexes (gastrointestinal, musculoskeletal, and central neurologic) more commonly had detectable antigen (Figure). Hospitalization during acute COVID-19 was strongly related to antigen detection.

Conclusion: Among a diverse group of SARS-CoV-2-infected persons in the post-acute phase of infection, SARS-CoV-2 antigen is detectable in plasma in both those with and without symptoms but more commonly in those with gastrointestinal, musculoskeletal, and central neurologic complaints. The findings indicate that antigen persists in at least some persons and suggest (but do not prove) that antigen is causally related to symptoms. That antigen is found in only a fraction of those with PASC indicates either that not all symptoms are driven by antigen, current plasma antigen detection is insensitive relative to tissue, or nominal PASC symptoms are sometimes unrelated to SARS-CoV-2.

Associations between SARS-CoV-2 antigen and COVID-attributed symptoms during the post-acute phase



283 PLASMA ANTIBODY AND N ANTIGEN STATUS PREDICT OUTCOMES IN OUTPATIENTS WITH COVID-19

Nikolaus Jilg[1], Mark Giganti[2], Kara W. Chew[3], Katy Shaw-Saliba[4], Justin Ritz[2], Carlee Moser[2], Teresa H. Evering[5], Eric S. Daar[6], Joseph J. Eron[7], Judith S. Currier[3], Michael D. Hughes[2], Henry C. Lane[8], Robin Dewar[9], Davey M. Smith[10], Jonathan Z. Li[11]

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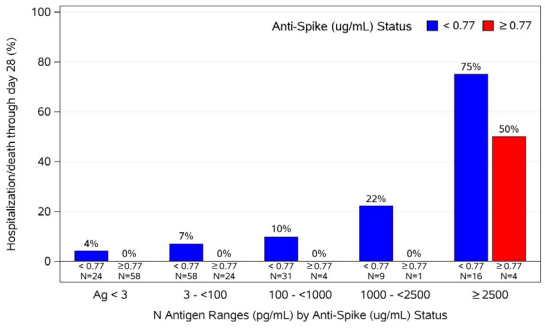
Background: Reliable biomarkers of COVID-19 severity and outcomes are critically needed for clinical and research applications. We evaluated associations between anti-Spike IgG and SARS-COV-2 nucleocapsid antigen (N Ag) in plasma with clinical outcomes in outpatients with COVID-19.

Methods: We used data from 229 non-hospitalized, US-based adults with COVID-19 who enrolled between January and July 2021 into the placebo arm of the ACTIV-2/A5401 platform trial within 10 days of symptom onset. Pre-treatment (day 0) plasma was analyzed by the quantitative Simoa SARS-CoV-2 IgG antibody (anti-Spike) assay (lower limit of quantification [LLoQ] 0.77ug/mL), and the quantitative Simoa SARS-CoV-2 N Protein Advantage (Quanterix) measuring N Ag (LLoQ 3pg/mL). In addition to analyses for < LLoQ vs ≥LLoQ anti-Spike and N Ag, we categorized participants into five N Ag groups (< 3 pg/ml; 3-< 100 pg/ml; 100-< 1,000 pg/ml; 1,000-< 2,500 pg/ml; ≥2,500 pg/ml). Associations between SARS-CoV-2 anti-Spike and N Ag levels and clinical outcomes (all-cause hospitalization/death through day 28 and time to symptom improvement or resolution for two consecutive days from day 0 status) were estimated using log-binomial and Cox regression models, respectively.

Results: At day 0, 40% had anti-Spike levels ≥LLoQ and 64% of participants had plasma N Ag levels ≥LLoQ. Participants with anti-Spike levels < LLoQ compared to those who had quantifiable anti-Spike at day 0, had an increased risk of hospitalization/death (16% vs 2%, RR [95% confidence interval (CI)]: 7.3 [1.8, 30.1]), and a significantly longer time to symptom improvement (median [Q1, Q3] 14 days [8, >27] vs 9 days [4, 16], hazard ratio [HR]: 0.6 [95%: CI: 0.4, 0.8], p< 0.001). Participants with higher N Ag levels at day 0 had an increased risk of hospitalization or death, ranging from 1% for < 3 pg/ml to 70% for ≥2500 pg/ml (Figure). Compared to individuals who had N Ag levels < LLoQ at day 0, those in the highest category of N Ag levels (≥2500 pg/mL) experienced a significantly longer time to symptom improvement (median [Q1, Q3]: 25 days [13, >27] vs 10 days [5, 20]; HR: 0.4 [95% CI: 0.2, 0.7]; p=0.04).

Conclusion: At study entry, the absence of Spike antibodies and higher levels of plasma SARS-CoV-2 N Ag predicted hospitalizations and death in untreated outpatients with COVID-19. These parameters may serve as informative biomarkers for risk stratification in the evaluation of outpatients with COVID-19.



284 VIRAL DYNAMICS AND FACTORS FAVOURING THE DURATION OF COVID-19 POSITIVITY IN CAMEROON

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Background: Evolution evidence of Coronavirus disease 2019 (COVID-19) and viral clearance time remains limited in tropical settings. Understanding this is crucial for public health control measures at community-level. We evaluated the viral dynamics of SARS-CoV-2 infection and factors associated with positivity duration in COVID-19 cases in Cameroon.

Methods: We conducted a prospective cohort-study of SARS-CoV-2 positive cases from the first to third wave (March 2020-October 2021) in Yaounde-Cameroon. RT-PCR was performed on nasopharyngeal swabs. SARS-CoV-2 positivity duration was evaluated from the first to last positive test before a negative result. Epi-info V.7.0 was used for data analyses with p< 0.05 considered statistically significant

Results: A total of 282 participants were enrolled. The mean age was 41±14 years, with male predominant (62.1%). We had 15.6% symptomatic cases and cough most common (59.09%). The overall median positivity duration was 15[IQR: 9-23] days with 15[IQR: 13-16] in the first, 17[IQR: 11-26] in the second and 8[IQR: 4-12] in the third wave (p= 0.007). Positivity duration was significantly higher in males (16 versus 14 days, p=0.03) and people aged >40 years (15 versus 14 days, p=0.02). Positivity duration was not affected by presence or absence of symptoms (p=0.80). No significant correlation was found with viral load (r=0.03; p=0.61). Considering baseline (24.7±7.2Ct) and last viral load (29.3±5.9 Ct), the ΔCt (4.6±1.3) and positivity duration (15 days) revealed a kinetic in viral decay of 0.3±0.087 Ct/day.

Conclusion: A median positivity duration of 15 days is in accordance with viral clearance around 2 weeks for optimal confinement at community-level. Men and/or the elderly stand at higher risk of prolonged infection. Given the viral decay (0.3 Ct daily), we suggest personalized confinement periods. The variability of positivity duration according to phases could be function of strains which could be a factor of positivity duration.

285 MITOCHONDRIAL DYSFUNCTION IS ASSOCIATED WITH POST-ACUTE SEQUELAE OF COVID-19

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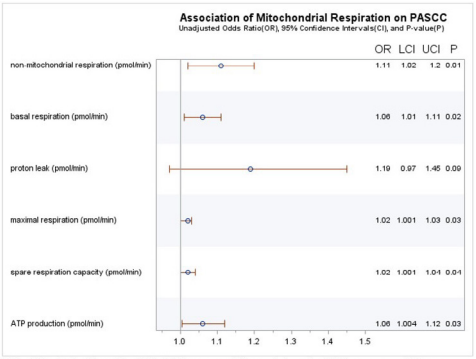
Background: Mitochondrial (mt) dysfunction has been described in acute severe SARS-CoV2 infection. It remains unclear whether the disturbances in mt are also present in post-acute sequelae of COVID-19 (PASC).

Methods: We analyzed cross-sectional data from participants without history of COVID and SARS-CoV2 antibody negative (COVID-), with documented prior COVID and full recovery (COVID+ PASC-), and with prior COVID with PASC as defined by the CDC (COVID+PASC+). Mt respiration was measured from peripheral blood mononuclear cells utilizing the Seahorse XFe96 analyzer. Generalized linear regression was used to compare estimates of mt and non-mt respirations, and unadjusted odds ratios using multinomial logistic regression to assess if mt respiration were associated with PASC.

Results: For this analysis, 59 participants were enrolled, 71.19% (n=42) had a confirmed COVID-19 diagnosis. The overall mean age was 47.47 ± 14.86 years, 69.49% (n=41) were females and 33.90% (n=20) were non-white race. There was no difference in demographics between participants with and without COVID (p≥0.72). Amongst all COVID+ participants, 19% (n=11) had hypertension and 8% (n=5) had diabetes. Among all COVID+, the median time between COVID diagnosis and study evaluation was 210 (IQR: 119, 453) days, and 50% (n=21) of COVID+ experienced persistent symptoms consistent with PASC. PASC participants had the highest observed values in non-mt respiration (21.57 ± 10.77 pmol/min), basal respiration (38.95 ± 17.58 pmol/min), proton leak (10.41 ± 3.1), maximal respiration (103.91 ± 58.63 pmol/min), spare respiratory capacity (64.96 ± 41.82 pmol/min), and ATP production (28.55 ±14.85 pmol/min). Basal respiration, ATP production, maximal respiration, and non-mt respiration were highest in PASC compared to COVID- (p≤0.02). There was marginal evidence (p=0.05) of a mean difference (8.09 pmol/min) in ATP production between COVID+PASC+ and COVID+PASC-, without differences in proton leak (p=0.23) or spare respiration capacity (p=0.07). Every unit increase in non-mt respiration, basal respiration, maximal respiration, and ATP production increased the predicted odds of PASC by 10.99, 5.6, 1.6 and 6.2%, respectively (Figure).

Conclusion: Individuals with PASC are consuming more oxygen and producing more ATP in the PBMCs compared to controls. There also appears to be increased PBMC ATP production between PASC and COVID+. We hypothesize that this may reflect a crucial pathogenic mechanism in PASC that may be associated with ongoing inflammation.

Figure : Association of mitochondrial respiration on PASC-



OR: Adjusted odds ratio, 95% CI (lower confidence interval = LCI; upper confidence interval = UCI), p-value

286 SINGLE-CELL ANALYSIS REVEALS CHARACTERISTICS OF MYELOID CELLS IN PULMONARY PASC

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Background: Although our understanding of immunopathology in the risk and severity of COVID-19 disease is evolving, a detail of immune response in long-term consequences of COVID-19 infection remains unclear. Recently, few studies have detailed the immune and cytokine profiles associated with PASC. However, dysregulation of immune system driving pulmonary PASC is still largely unknown.

Methods: To characterize the immunological features of PPASC, we performed droplet-based scRNA-sequencing using 10X genomics to study the transcriptomic profiles of peripheral blood mononuclear cells (PBMCs) from participants naïve to SARS-CoV-2 (NP, n=2) and infected with SARS-CoV-2 with chronic pulmonary symptoms (PPASC, n=2).

Results: Analysis of more than 34,000 PBMCs by integrating our dataset with previously reported control datasets generated cell distribution and identified 11 immune cell types based on canonical gene expression. The proportion of myeloid-lineage cells (CD14+monocyte, CD16+monocyte, and dendritic cells) and platelets were increased in PPASC compared with those of NP. Specifically, PPASC displayed up-regulation of *VEGFA* and transcription factors, such as *ATF2*, *ELK*, and *SMAD* in myeloid-lineage cells. Also, *TGF-β* and *WNT* signaling pathways were up-regulated in these cell population. Cell-cell interaction analysis identified that myeloid-lineage cells in PPASC participated in regulation of fibrosis and immune response, such as *VEGFA* (increased) and *MIF* (decreased) interactions.

Conclusion: Together, this study provides high-resolution insights into immune landscape in PPASC. Our results emphasize differences in myeloid lineage-mediated fibrosis and immunity between PPASC and NP, suggesting they could act as potential pathological drivers of PPASC.

Figure 1

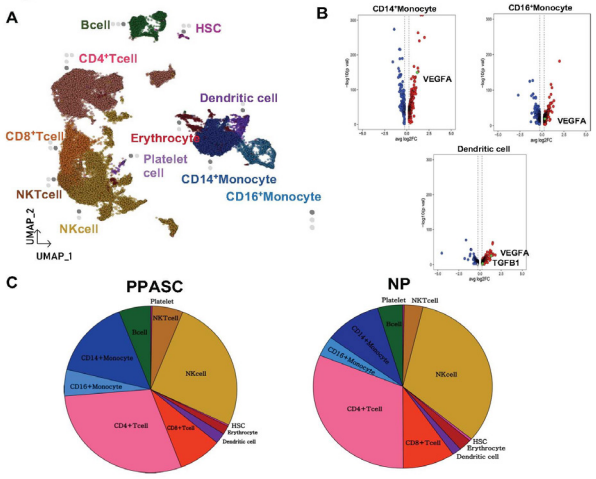

Figure 1. Elevated proportion of myeloid-lineage cells and their increased VEGFA and TGF-beta expressior in PPASC. A. The UMAP and cell type composition of the PPASC and NP groups were integrated. B: The expression of VEGF and TGF-beta was differentially regulated in the PPASC group compared to the NP group. C: The relative cell type proportions of the PPASC and NP groups were analyzed.

287 ADAPTIVE IMMUNITY DYSREGULATION IS ASSOCIATED TO THE DEVELOPMENT OF LONG COVID

Roberta Rovito[1], Valeria Bono[1], Matteo Augello[1], Francesca Bai[1], Camilla Tincati[1], Guillaume Beaudoin-Bussières[2], Alexandra Tauzin[2], Silvia Bianchi[1], Joanna Mikulak[3], Elisa Borghi[1], Antonella D'Arminio Monforte[1], Silvia Della Bella[4], Andrés Finzi[2], Domenico Mavilio[3], **Giulia C. Marchetti**[1]

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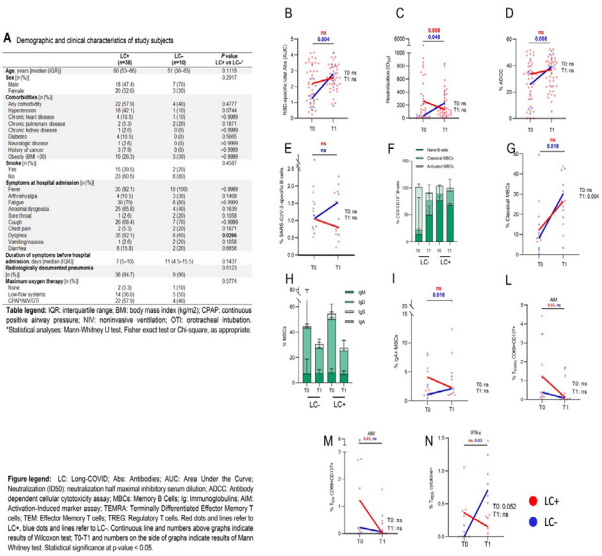
Background: The pathogenetic mechanisms behind the development of long-COVID (LC) are largely unknown. Because both plasma SARS-CoV-2 RNAemia and dysregulated immunity have been correlated with COVID-19 severity, we evaluated whether they are associated with LC.

Methods: We consecutively enrolled unvaccinated hospitalized COVID-19 patients during acute-COVID-19 (T0) in March-October 2020 who either developed LC at a follow-up visit 2-3 months from virologic clearance (T1) or did not. LC was defined as persistence ≥2 months after recovery of ≥1 symptom: anosmia, dysgeusia, fever, gastrointestinal symptoms, dyspnoea, fatigue, musculoskeletal pain, muscle weakness, brain fog. We measured: SARS-CoV-2 RNAemia (RT-qPCR, $\log_{10}$(copies/mL)), magnitude (ELISA, AUC) and functionality (pseudovirus neutralization, ID_{50}; Fc-mediated functions, %ADCC) of SARS-CoV-2-specific antibodies, SARS-CoV-2-specific B and CD4-T-cells (Immunophenotype, AIM and ICS assays).

Results: We enrolled 48 COVID-19 individuals, 38/48 (79.2%) developed LC (LC+) and 10 did not (LC-). LC+ and LC- had similar co-morbidities and symptoms in the acute phase (Fig.1A), and the majority showed a radiologically documented SARS-CoV-2 pneumonia. The SARS-CoV-2 RNAemia did not differ between groups at both time points. The levels of RBD-specific Abs, as well as their functionality, appeared to increase over time in the LC- group but not in the LC+ (Fig.1B-D). Similarly, a trend towards increased RBD-specific B-cells was observed over time in the LC- group but not in LC+ (Fig.1E). B-cell immunophenotyping showed a significant increase over time of classical memory B cells (MBCs) at the expenses of activated MBCs (Fig.1F-G) as well as an IgA class-switching in the LC- group compared to LC+ (Fig.1H-I). Furthermore, LC+ showed a faster decline of SARS-CoV-2-specific (CD69+CD137+) CD4-TEMRA and CD4-TEM (Fig.1L-M). Finally, IFN-γ-producing TREG of LC- individuals increased over time (Fig.1N).

Conclusion: Acutely ill, hospitalized COVID-19 patients developing LC feature a dysregulated SARS-CoV-2-specific humoral as well as B- and T-cell response, in both magnitude and functionality, suggesting a link between dysregulated SARS-CoV-2-specific adaptive immunity and LC development. The fine understanding of the factors contributing to such dysregulation in LC patients is strongly needed, that might further inform targeted therapeutic interventions.

Figure 1



288 INCREASED GUT PERMEABILITY AND OXIDIZED LIPIDS IN PASC

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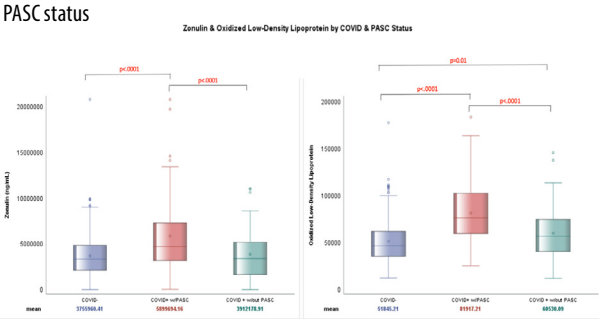
Background: Post-acute sequelae of COVID-19 (PASC) is marked by persistent or newly developing symptoms beyond 4 weeks of infection. Investigating gut integrity, oxidized lipids and inflammatory markers is important for understanding PASC pathogenesis.

Methods: A cross-sectional study including COVID+ with PASC, COVID+ without PASC, and COVID- participants. We measured plasma markers by enzyme-linked immunosorbent assay to assess gut-barrier integrity: zonulin for intestinal permeability, lipopolysaccharide-binding protein (LBP) for microbial translocation, and fatty acid binding protein I-FABP for intestinal integrity, and to assess inflammation: high-sensitivity C-reactive protein (hsCRP) and oxidized low-density lipoprotein (Ox-LDL) assays.

Results: 415 participants were enrolled in our study. 62.17% (n=258) were COVID- and 20.48% (n=85) had PASC. COVID- participants had lower age (43.68±13.69 vs. 46.45±13.45 years; p=0.04), lower BMI (27.91±6.05 vs. 31.28±9.03; p< .0001), 39.15% (n=101) were female sex [vs. 54.14% (n=85); p=0.003], and 41.86% (n=108) were non-white race [vs. 32.48% (n=51); p=0.06] compared to COVID+. Zonulin (p< .0001), and Ox-LDL (p< .0001) were associated with COVID and PASC status. The mean Zonulin among COVID- was 3755960.41±2541177.0 ng/mL, 3912178.91±2649882.95 ng/mL among COVID+ without PASC, and the highest (5899694.16±4110456.4 ng/mL) among PASC. The mean Ox-LDL was lowest (51845.21±24328.46 U/L) among COVID-, 60530.09±26497.47 U/L among COVID+ without PASC, and 81917.21±32148.59 U/L among PASC. The estimated mean difference in Zonulin among PASC compared to COVID- was 2143734±368522 ng/mL (p< .0001) and compared to COVID+ without PASC was 1987515±471965 ng/mL (p< .0001). The estimated mean difference in Ox-LDL among PASC compared to COVID- was 30072±3311.02 U/L (p<.0001) and compared to COVID+ without PASC was 21387±4240.41 (p<.0001). Zonulin was positively associated with hs-CRP and Ox-LDL. For every unit increase in Zonulin we would expect hsCRP to increase by 86.14±15.09/100000 ng/mL (p<.0001) and OX-LDL to increase by 22.2±4.05/10000 ng/mL (p<.0001).

Conclusion: PASC is associated with increased gut permeability, which in turn is associated with oxidized LDL and hsCRP.

Zonulin (ng/mL) and Oxidized Low-Density Lipoprotein (U/L) by COVID-19 and PASC status



289 NONHUMAN PRIMATE MODEL OF LONG COVID: IMMUNE INSIGHTS OF GLYCOMETABOLIC DYSFUNCTIONS

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Background: A major consequence of COVID-19 is long-term metabolic complications (metabolic PASC or Long COVID) following acute disease resolution leading to hyperglycemia, increased risk of diabetes or defects in glucose metabolism. However, the mechanisms underlying the links between COVID-19 and glycometabolic disruptions remain unclear.

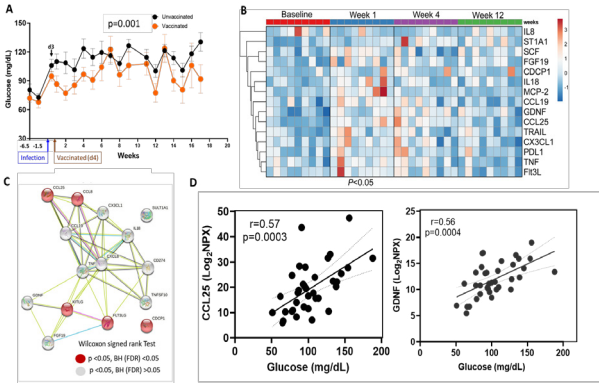
Methods: 15 African green monkeys (AGM; Chlorocebus aethiops) were infected with SARS-CoV-2 (Wuhan stain) and divided into two groups: unvaccinated (n=10) and vaccinated (BNT162b2 (Pfizer) 4-days post infection; n=5). Subgenomic SARS-CoV-2 mRNA (sgRNA) reflecting active replication was quantified in nasal and pharyngeal swabs, and blood chemistry analysis was performed longitudinally up to 18 weeks post-infection. We quantified liver glycogen at necropsy using Periodic acid–Schiff staining. Finally, we longitudinally analyzed 96 plasma proteins using a proximity extension assay (Olink). STRING was used to identify enriched protein networks. Comparisons between the two groups over time were performed using PERMANOVA.

Results: All animals had detectable sgRNA (>3.64x10^6) at day 3, and only two were undetectable at week 5. Post-infection BNT162b2 vaccination partially inhibited the SARS-CoV-2 mediated disruption of glucose levels (P=0.001, **Fig. 1A**). Liver glycogen levels following necropsy correlated positively with blood glucose levels at week 12 (r=0.74, P =0.003). Histopathological analysis revealed no marked evidence of long-term inflammation or fibrosis of pancreatic islets. Using the plasma proteomic data, we identified a signature of 15 SARS-CoV-2-modulated plasma proteins coinciding with early onset hyperglycemia during acute infection (P=0.001, **Fig. 1B**). These proteins are enriched for biological processes linked to chemotaxis (FDR=1.38E-06), and viral protein interaction with cytokines (FDR=1.01E-12) (**Fig. 1C**). Of these, CCL25 and glial cell derived neurotrophic factor (GDNF) remained persistently elevated post-acute infection and correlated with blood glucose levels (r=0.57, P =0.0003; and r=0.64, P <0.0001, respectively, **Fig. 1D**).

Conclusion: Our AGM model validates phenotypes of metabolic PASC and offers an opportunity to mechanistically study the manifestations of PASC. Our preliminary data suggest that vaccine-preventable early insults by metabolic-regulating immune factors may contribute to long-term dysregulated liver

and systemic glucose homeostasis during PASC. These immune factors warrant further investigation for their mechanistic links to PASC.

SARS-CoV-2 infection of AGM is associated with early-onset hyperglycemia that persists



290 PROLONGED SARS-CoV-2 VIRAL BURDEN IN SIV-SARS-CoV-2 COINFECTED MACAQUES

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Background: Individuals living with HIV are at increased risk of morbidity and mortality from COVID-19. Furthermore, SARS-CoV-2 infection in immunocompromised HIV infected individuals poses a risk to prolonged infection and viral shedding and the emergence of new variants of concern (VOCs). Using the SIV macaque model for AIDS, we are investigating the hypothesis that immune dysfunction during HIV infection will prolong SARS-CoV-2 viral infection, promote enhanced COVID-19 disease, and accelerate viral evolution. Here, we report the impact of SIV-CoV-2 co-infection on immune responses and pathogenesis.

Methods: Eight female rhesus macaques (aged 7-15 years, 5.5-9.9kg) were infected with SIVmac251 via low dose intravaginal challenge and then inoculated with 6.5x105 TCID50/mL SARS-CoV-2 (WA-1) at 17-34 weeks post-SIV infection via combined intranasal and intratracheal routes. Blood, bronchoalveolar lavage (BAL), stool, and nasal, oral, and rectal swabs were collected pre-infection through 14 days post-infection (DPI) to measure immune responses and viremia. ELISAs, ELISPOT, qRT-PCR, lung pathology, cytokine multiplex, and virus neutralization assays were performed to measure viral loads, pathogenesis, and immune responses.

Results: Three days post-SARS-CoV-2 infection, we observed a transient decrease in CD4 counts, but there were no changes in clinical symptoms or plasma SIV viral loads. However, SARS-CoV-2 replication persisted in the upper respiratory tract, but not the lower respiratory tract. In addition, SARS-CoV-2 IgG seroconversion was delayed and antigen-specific T-cell responses were dampened. Notably, viral RNA levels in nasal swabs were significantly higher 7-14 DPI in SIV+ compared to previously published results using the same SARS-CoV-2 challenge virus in SIV- rhesus (PMCID: PMC8462335, PMC8829873). In addition, SIV/CoV-2 co-infected animals exhibited elevated levels of myeloperoxidase (MPO), a marker of neutrophil activation and increased lung inflammation.

Conclusion: Here we provide evidence for the utility of the rhesus macaque in modeling human HIV-SARS-CoV-2 co-infection. Our results suggest that immunosuppression during SIV infection impairs de novo generation of anti-SARS-CoV-2 immunity, that may contribute to prolonged SARS-CoV-2 viral shedding, increased transmission windows, altered disease pathogenesis, and lower protection against subsequent SARS-CoV-2 exposures. Studies in progress will determine if SARS-CoV-2 viral evolution is accelerated in SIV-infected macaques.

291 DELAYED POSITIVIZATION OF NON-LESION SPECIMENS AMONG INDIVIDUALS WITH MPOX

Angelo Roberto Raccagni[1], Davide Mileto[2], Alberto Rizzo[2], Nicola Gianotti[3], **Vincenzo Spagnuolo**[3], Caterina Candela[1], Elena Bruzzesi[1], Riccardo Lolatto[3], Benedetta Trentacapilli[1], Emanuela Messina[3], Maria Rita Gismondo[2], Antonella Castagna[1], Silvia Nozza[4]

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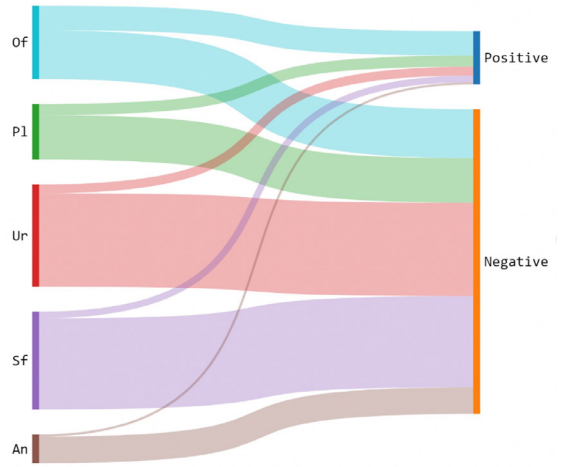
Background: Viral dynamics of non-lesion mpox specimens is uncertain, with possible community implications regarding mpox transmission. The aim was to investigate the delayed positivization of non-lesion specimens among individuals diagnosed with mpox.

Methods: We included individuals diagnosed with mpox at San Raffaele Scientific Institute, Milan; all individuals had mpox positive lesions at time of mpox diagnosis. Delayed positivization was defined as mpox detection at virological re-evaluation in a non-lesion specimen which was previously negative at time of mpox diagnosis; plasma (Pl), urines (Ur), seminal fluids (Sf), oropharyngeal (Op) and anal (An) swabs were collected among all people. Individuals were virologically re-assessed until mpox clearance.

Results: Overall, 1836 total samples (1246 non-lesion specimens, 478 positive and 768 negative) from 140 MSM diagnosed with mpox were considered. Viral dynamics of non-lesion specimens negative at time of mpox diagnosis are illustrated in Figure 1. Observed delayed positivizations were 24 (11 Op, 5 Pl, 4 Ur, 3 Sf, 1 An) among 10% of included individuals. Among them, the median time to mpox diagnosis from symptoms onset was 2 days (interquartile, IQR 1-3, range 1-5): all were already in care at our center for HIV/PrEP and half were sexual contacts of mpox cases. Median cycle thresholds (Ct) of samples at time of delayed positivazion were: Op 31 (IQR 26-33), Pl 34 (IQR 33-36.5), Ur 33 (IQR 32-35), Sf 36 (IQR 35-37), and An 36. Median days to positivization from mpox diagnosis were: Op 7 (IQR 7-9), Pl 7 (IQR 3.5-10), Ur 7 (IQR 6.5-8), Sf 9 (IQR 8-10), and An 7. In Of, Ur, Sf, and An samples with delayed positivization, plasma was already positive at time of mpox diagnosis (median Ct 34, IQR 33-35). The median Ct of mpox lesions at time of mpox diagnosis was 24 (IQR 19-28), at time of delayed positivization 20.5 (IQR 17-25); among all individuals appearance of new mpox lesions was documented following mpox diagnosis.

Conclusion: Delayed positivization can occur in non-lesion specimens among individuals diagnosed with mpox; high Ct values, positivization at first virological re-evaluation and more often at the oropharyngeal site were observed. We hypothesize that individuals received a prompt mpox testing and that the delayed positivization followed bloodstream viral dissemination. Given the community implications on transmission, these data reinforce the need of repeated mpox testing of non-lesion specimens.

Figure 1. Mpox testing dynamics at virological re-evaluation of non-lesion specimens which tested negative at mpox diagnosis; all individuals had positive mpox lesions at time of mpox diagnosis. Left: Non-lesion specimens which tested negative at mpox diagnosis (Negative). Right: Viral dynamics at virological re-evaluation (Positive or Negative).



292 LONGITUDINAL ASSESSMENT OF VIRAL SHEDDING AMONG PATIENTS WITH MPOX IN TORONTO, CANADA

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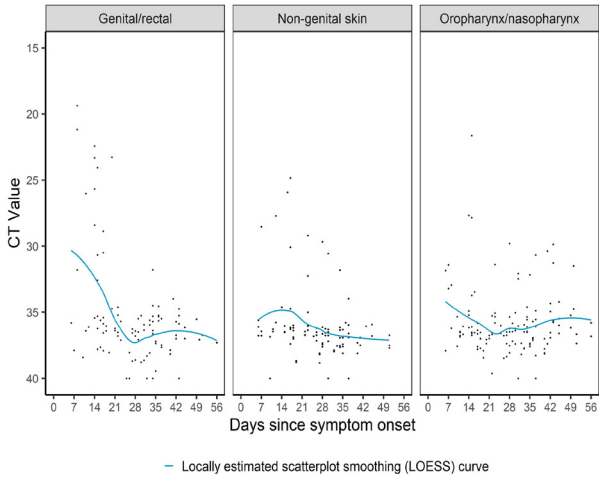
Background: Patients with human Mpox infection may have detectable virus in multiple anatomic compartments including skin, mucosal sites, blood, urine and semen. Longitudinal data on viral shedding are scarce.

Methods: We conducted a prospective cohort study of adults with confirmed or suspected Mpox infection at an academic hospital in Toronto, Canada. Participants underwent swabs of skin lesions (up to three anatomic sites per visit), the nasopharynx (NP), the oropharynx, and the rectum, as well as urine and semen sampling, regardless of symptom status, at weekly (±3 days) visits until one week after complete resolution of the last skin lesion. Refrigerated specimens were transported to the laboratory within 24 hours of collection, frozen at –80C, and batch tested for Mpox virus using quantitative polymerase chain reaction (qPCR) targeting the viral polymerase gene E9L. We report serial cycle threshold (CT) values for specimens taken from participants with confirmed infection.

Results: Between 21JUN2022-12OCT2022, we enrolled 28 participants, all of whom were cisgender men who have sex with men. Median (range) age was 38 (29, 60) years, and 12/28 (43%) were HIV-positive, all but one of whom had an undetectable viral load at the time of enrollment. Clinical manifestations ever reported included skin lesions (100%), headache (75%), fatigue (68%), fever (64%), myalgias (54%), rectal pain/discharge (46%) and sore throat (39%). After excluding specimens collected during or after use of tecovirimat, 21 participants provided a median (range) of 3 (1, 7) sampling visits per participant, beginning 14 (7, 35) and ending 34.5 (6, 56) days from symptom onset. The proportion of participants with evidence of viral shedding for at least one timepoint was 100% for skin specimens, NP swabs, rectal swabs and urine, but lower in semen (76%). Shedding was most pronounced in genital skin/rectal specimens, followed by oro/nasopharyngeal swabs and non-genital skin swabs (Figure). Shedding typically declined in the second week of illness in non-cutaneous sites but persisted at the final sampling timepoint in 95% and 76% of participants' rectal swabs and semen samples, respectively.

Conclusion: Mpox virus genetic material may remain detectable in multiple anatomic compartments for up to 8 weeks after symptom onset. Correlation with infectivity requires further study.



293 MPOX DNA CLEARANCE IN SEMEN OVER SIX MONTHS FOLLOW-UP

Caterina Candela[1], Alberto Rizzo[2], Laura Galli[3], Davide Mileto[2], Diana Canetti[4], Nicola Gianotti[3], Maria Francesca Lucente[1], Costanza Bertoni[1], Angelo Roberto Raccagni[1], Maria Rita Gismondo[2], **Antonella Castagna**[1], Silvia Nozza[5]

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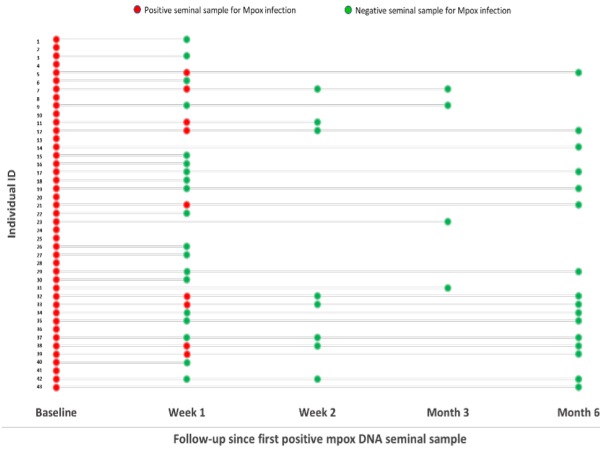
Background: During mpox outbreak, sexual intercourse demonstrates to be a well-established way of transmission. WHO recommends avoiding any sexual contact among mpox cases during the 21-days monitoring period, regardless of their symptoms. However, it is unknown whether seminal fluids might represent a viral reservoir. Therefore, we aimed at evaluating mpox DNA clearance in semen samples of people with mpox infection over six months of follow-up.

Methods: This is an observational, prospective, single-center study of outpatients diagnosed with mpox in IRCCS San Raffaele, Milan, Italy between May, 2022, and October, 2022. Samples were analyzed by a real-time polymerase chain reaction (RT-PCR) to detect the presence of non-variola DNA; a specific RT-PCR targeting mpox DNA was used for confirmation. The primary endpoint was time from the first positive test of seminal fluid (baseline, BL) to viral DNA clearance. Follow-up accrued from BL until the date of most recent test of seminal fluid (performed within 6 months).

Results: Overall, 164 seminal fluid samples were collected from 140 people diagnosed with mpox infection; mpox DNA was detected in seminal fluid of 43 people with a BL median cycle thresholds of 34 (IQR 31-36). At mpox diagnosis, median age was 36 (IQR 34-42) years, 98% were men who had sex with men (MSM), 23% had concomitant sexually transmitted infections (7 *C. trachomatis*, 4 *N. gonorrhoeae*, 2 syphilis) and 28% were living with HIV infection. To assess viral clearance in seminal fluid, 58 further seminal samples were collected in 32 individuals (11 people has only BL sample). Viral clearance was observed within 6 months in all these individuals in a median time of 10.5 days (IQR 7-33); 19/28 seminal samples tested within 1 week were negative (68%), 25/28 (89%) tested negative within 2 weeks, 26/29 (90%) within 3 months (**Figure 1**).

Conclusion: These preliminary findings from this cohort of individuals highlight that viral DNA clearance in seminal fluid samples from people diagnosed with mpox infection was mostly observed within 2 weeks since first positive test. These findings suggest that semen testing and prolonged use of condoms after mpox infection may be necessary.

Figure 1 - Time to viral clearance in study individuals



294 INNATE IMMUNITY IN HTLV-1 INFECTION: IFN-GAMMA LEVELS ARE UP-REGULATED IN EARLY HAM

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Background: HTLV-1 infection is responsible for two aggressive diseases, leukemia and neuronal inflammation (HAM), in 5-10% of the chronically-infected asymptomatic carriers (AC). However, some infected individuals present minor symptoms that do not meet the criteria for HAM, while not asymptomatic which we named Intermediate syndrome (IS). To determine whether immune responses could discriminate IS from AC and healthy carriers (HC), and could be used as biomarkers of disease progression, in this study, were analyzed the frequency of monocytes (cMono, intMono, and ncMono), dendritic cells (cDCs and pDCs), and NK cells and their cytokine production, before and after stimulation.

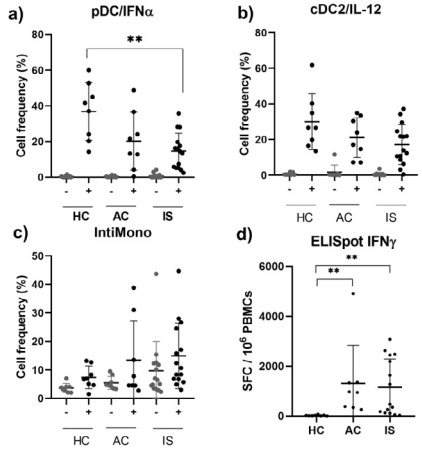
Methods: 23 HTLV-1-positive participants being followed up at the Institute of Infectious Diseases "Emilio Ribas" were invited to participate in this study. Whole fresh blood samples were collected from health controls (HC) (n=8), asymptomatic carriers (n=8), and individuals with the intermediate syndrome (n=15), and *in vitro* stimulated with R848, an agonist of TLR7/8 to evaluate the responsiveness of immune cells. Multi-parameter immunostaining was

performed to analyze the cytokine production of different cell subpopulations, here specifically the IFN-α production of pDC. In addition, we quantified the spontaneous IFN-γ production by peripheral blood mononuclear cells (PBMCs) using ELISPOT assay. One-way ANOVA or Kruskal-Wallis statistical analysis was performed using the software GraphPad Prism 8.0 to compare parametric or nonparametric variables.

Results: 31 volunteers were included (77% women and 23% men), with a median age of 56 years. No statistical difference was seen in the cell subpopulations of the three groups. However, IFN-α production by pDC cells (fig. 1a) was significantly reduced in the IS vs HC group (p=0.002). Moreover, spontaneous IFN-γ production (fig. 1d) was increased in both asymptomatic and IS individuals compared to HC, with a statistical difference of p=0.0013 between HC and AC and of p=0.0011 between HC and IS.

Conclusion: Changes in innate and adaptive immunity are observed in HTLV-1 infected individuals compared to healthy donors regardless of their disease status. A higher decrease of IFN-α-producing pDC and a higher increase of IFN-γ-producing PBMCs in IS compared to AC might be a signature of disease evolution to HAM.

Main changes observed in the immune response of this study



295 HIV COINFECTION INCREASES HBV-INDUCED HEPATIC FIBROGENESIS THROUGH HIF-1α

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Background: The progression of chronic HBV to cirrhosis is accelerated by HIV coinfection compared to HBV mono-infection. HIV and gp120 signal through CCR5 and CXCR4 on hepatocytes and hepatic stellate cells to promote cell growth and proliferation through hypoxia-inducible factor-1α (HIF-1α). HIF-1α has been shown to regulate expression of the pro-fibrogenic cytokine TGF-β1. We hypothesize that HIV and gp120 promote HBV-induced liver fibrosis in HIV/HBV coinfected cell culture models through HIF-1α signaling.

Methods: Infectious HBV viral particles (HBVvp) were purified from the HBV supernatant (HBVsup) of HepAD38 cells. HIV NL4-3 strains were propagated in U937 macrophage lines and directly incubated with LX-2 stellate cells and hepatoma HepG2 and HBV-infected NTCP-HepG2 cells. Cells were incubated with recombinant HIV proteins including Gp120, Tat, Vpr, Vif, Nef, Ref, Vpu, reverse transcriptase, protease, and integrase. HBV subgenomic constructs including S, Core, X, and P were transfected into NTCP hepG2 cells. CXCR4 (plerixafor) and CCR5 (maraviroc) inhibitors were used to block HIV-induced liver fibrosis. HIF-1a, CCR5 and CXCR4 were knocked-down via siRNA.

Results: HIV infection significantly increased expression of HIF-1α and TGF-β1 in U937 cells in a virus load-dependent manner. HIF-1α and pro-fibrogenic genes were also significantly upregulated in HBV-infected NTCP HepG2 cells compared to uninfected cells. HIV-infected U937 cell supernatant and recombinant HIV gp120 significantly increased expression of HIF-1α, TGF-β1 and profibrotic genes in HBV-infected NTCP-HepG2 and LX2 cells. The overexpression of HBV X protein significantly upregulated pro-fibrogenic gene expression and this can be enhanced by the exposure of HIV and gp120 peptide. HIF-1α siRNA transfection and CCR5/CXCR4 inhibitors neutralized the HIV- and HIV gp120-induced fibrogenic response.

Conclusion: HIV and HBV coinfection exacerbates liver fibrogenesis through upregulation of the HIF-1α pathway. This cooperative effect can be mitigated by disruption of the interaction between HIV/Gp120 and its coreceptors CCR5/CXCR4.

296 WITHDRAWN

297 ENDOGENOUS RETROVIRAL DYSREGULATED EXPRESSION IN PEDIATRIC CROHN'S DISEASE

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Background: Human Endogenous Retroviruses (HERVs) comprise 8% of the modern human genome and their dysregulated expression is linked to inflammation. Aberrant HERV expression was recognized in adult patients with Crohn's Disease (CD). We aimed to investigate the expression of HERVs in the

ileal mucosa of children with CD compared to healthy children and its correlation to the expression of genes involved in mucosal inflammation.
Methods: We used online available high throughput RNA-sequencing data of ileal biopsies of 26 children with CD and of 8 age-matched healthy controls. We used Bowtie2 for the alignment of these data against the hg19 human genome assembly; we used Samtools and Bedtools to retrieve read counts corresponding to 13 HERV families (HERV-H, HERV-W, HERV-L, HERV-E, HERV-I, HERV-9, HERV-FRD, HML-1/2/3/4/5/6) and a panel of 20 mucosal immunity genes. We evaluated HERV expression at a family level by summing the reads corresponding to each HERV family. HERV and immunity gene expression was normalized by means of four housekeeping genes (SDHA, HPRT1, RBX1, RRAGA). Normalized expressions were ln-transformed and we used independent sample t-tests, to compare the expression of HERV families and immunity genes in the ileal biopsies of children with CD and controls. Spearman's rho correlation coefficient was used to identify correlations between the expression of differentially expressed HERVs and immunity genes.
Results: We recognized upregulated expression of HERV-FRD (1.54-fold, p=0.031) and downregulated expression of HERV-9 (0.52-fold, p=0.013) in children with CD. Of the examined immunity genes, we found significant upregulation in the expression of CXCL-10 (5.9-fold, p< 0.001), CXCL-11 (4.3-fold, p=0.001), CXCL-16 (1.64-fold, p=0.002), SPAK (1.4-fold, p=0.014), ADAM-10 (1.5-fold, p=0.047), TLR-4 (2.1-fold, p=0.036) in CD. HERV-FRD expression correlated to the expression of SPAK (Rho=0.68, p< 0.001) and ADAM-10 (Rho=0.411, p=0.037), while HERV-9 expression correlated to the expression of CXCL-10 (Rho=-0.496, p=0.001), CXCL-11 (Rho=-0.5, p=0.009) and TLR-4 (Rho=-0.5, p=0.008).
Conclusion: We recognized dysregulated expression of HERV-FRD and HERV-9 in children with CD, correlated to the expression of genes involved in proinflammatory processes in ileal mucosa and the perpetuation of mucosal inflammation. These findings merit further research on the HERV role in intestinal mucosa fitness to confirm the HERV involvement in pediatric IBD.

298 MYCOBACTERIUM TUBERCULOSIS ASSOCIATES WITH HIGHER HIV-1-SPECIFIC ANTIBODY RESPONSES

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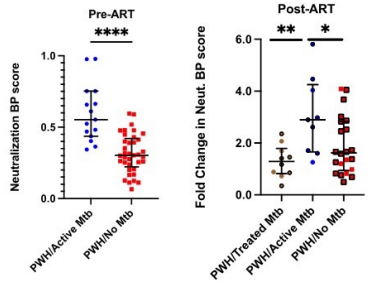
AIDS Clinical Trials Group A5274 (REMEMBER) Study Team
[1]Boston University, Boston, MA, USA, [2]Makerere University, Kampala, Uganda, [3]Boston Medical Center, Boston, MA, USA, [4]The Johns Hopkins University School of Medicine, Baltimore, MD, USA, [5]University of North Carolina at Chapel Hill, Chapel Hill, NC, USA, [6]University of Malawi, Blantyre, Malawi
*Presented at CROI by a nonauthor colleague

Background: Mycobacterium tuberculosis (Mtb) can enhance immune responses against unrelated pathogens. Mtb is the most common co-infection in people living with HIV (PWH), and the impact of active Mtb disease on HIV-1 immune responses has not been examined.
Methods: Neutralization and antibody dependent cellular cytotoxicity (ADCC) were compared among plasma samples from PWH and Mtb disease (PWH/Active Mtb) and PWH/No Mtb both prior to any treatment and after antiretroviral treatment (ART) and completion of Mtb therapy. Single genome amplification, flow cytometry and luminex-based assays were used to examine HIV-1 envelope sequences, antibody, and cytokine levels respectively. Wilcoxon-rank sum, Kruskal Wallis, and Student t-tests were used to compared different groups and multivariate linear regression analysis was used to account for baseline demographic differences.
Results: HIV-1 neutralizing antibodies (nAbs) were broader and more potent in PWH/Active Mtb (n = 15) as compared to PWH/No Mtb (n = 37, p < 0.0001) even after accounting for pre-treatment plasma virus level and CD4 counts. NAb breadth and potency significantly increased among the PWH who developed active Mtb after ART initiation (PWH/Active Mtb + ART, n = 9) as compared to the PWH/Treated Mtb + ART (n = 10) and PWH/No Mtb + ART (n = 22, p = 0.01). ADCC was higher in PWH/Active Mtb + ART as compared to PWH/Treated Mtb + ART and PWH/No Mtb + ART (p = 0.02), but ADCC was not different among PWH/Active Mtb and PWH/No Mtb prior to ART initiation. Before ART, PWH/Active Mtb as compared to PWH/No Mtb had unique HIV-1 envelope sequence motifs associated with neutralization resistance implying differences in humoral immune selection pressure. The Mtb-linked antibody augmentation associated with elevated plasma levels of interleukin-6, a proliferation-inducing ligand (APRIL), and B-cell activating factor (BAFF), but not other cytokines important for B cell development and maintenance. Active Mtb co-infection did not associate with non-specific elevation of all antibodies or cross-reactive responses.
Conclusion: Mtb disease enhances HIV-1 antibody responses primarily as a bystander effect on pathways important for antibody production. The Mtb enhanced humoral responses do not associate with increased virus levels or envelope antigen diversity. Understanding pathways perturbed by Mtb disease can provide unique insights for inducing optimal HIV-1 antibody responses.
Neutralization breadth and potency prior to (left) and post ART initiation (right)



299 IMPACT OF THE INTRAUTERINE HIV EXPOSURE ON THE INFANTS VIRUS ANTIBODY REPERTOIRE

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Background: Antibody responses to vaccines do not explain health outcomes disparities observed between infants who are HIV-exposed but uninfected (iHEU) and HIV-unexposed uninfected (iHUU). We investigated the effect of HIV-exposure on infant humoral immunity by comparing viral-specific antibody repertoires between iHEU and iHUU.
Methods: IgG against 206 eukaryote-infecting viruses was measured using Phage Immunoprecipitation Sequencing in plasma of iHEU (n=15) and iHUU (n=15) at birth and 36 weeks of life. Data analysis was performed using AntiViral Antibody Response Deconvolution Algorithm (ARVARDA). High-dimensional reduction analysis and pairwise comparison was performed in R with alpha< 0.05 as the significance level.
Results: We measured viral specific antibodies from 30 study participants at birth and 36 weeks of life, 42.85% of whom were female. High-dimensional reduction analysis revealed age-associated difference in the repertoire of virus-targeting antibodies between paired birth and week 36 samples (p=0.001). At birth, antibody repertoires were different between iHEU and iHUU ($p=0.002$), although they converged by week 36 ($p=0.790$). iHUU had a greater number of unique viral antibody targets per participant at birth than iHEU (*median; 9 vs. 6; p =0.035*), although there were no differences by week 36 (*median; 7 v.s 6; p=0.500*). Antibodies against HIV were detected in 10 and 1 iHEU at birth and at week 36, respectively, showing a >2-fold longitudinal decrease (p=< 0.001). Common viral targets at birth included Epstein-Barr virus (100%), herpes simplex-1 (90.0%) and -2 (73.3%), cytomegalovirus (93.3%), mastadenovirus C (63.3%) and rhinovirus A (96.6%), whereas antibodies against enterovirus B (70.0%) and C (70.0%), cytomegalovirus (76.6%), rhinovirus A (83.0%) and B (60.0%) were common at week 36. Mastadenovirus C antibody levels were higher in iHUU compared to iHEU at birth (*mean; 28.06 vs. 24.27; p = 0.048*).
Conclusion: Lower antibody repertoire breadth of iHEU at birth could have clinical significance including increased risk of infections, warranting further investigations. Further analysis of the maternal antibody repertoire is required to determine whether the differences observed between iHEU and iHUU at birth are as result of impeded transplacental antibody transfer or different antibody repertoire between women living with HIV and women living without HIV.

300 VIRUS PANEL CLASSIFICATION: A STRATEGY TOWARD DELINEATION OF PLASMA bNAb ACTIVITY

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Background: Dissecting broadly neutralizing antibody (bnAb) specificity in polyclonal plasma in HIV-1 infection and post vaccination remains challenging. Delineation methods comparing plasma neutralization patterns against large virus panels with those of epitope-mapped bnAbs are widely used. Common to the current approaches is their inability to resolve the presence of multiple bnAb specificities, or, in rare occasions, of novel bnAb types. Here we report on virus panel classification, a novel delineation method designed to overcome these limitations and probed its utility on the XbnAb cohort, a large cohort of bnAb inducers (N=304) identified in the Swiss 4.5K Screen (Rusert et al. 2016).
Methods: Plasma neutralization fingerprints of bnAb inducers (N=304) were evaluated using a 40-virus multiclade panel and compared to reference fingerprints of bnAbs (V1V2, V3 glycans, CD4bs, interface, fusion peptide, MPER) and broadly neutralizing DARPins (bnDs) (Friedrich et al. 2021). bnAb specificity was predicted using a maximum Spearman correlation method and the newly developed "*virus panel classification*" strategy. Creating thousands of random possible panels (size 10 to 35) from an existing data set, this method computationally identifies 20 to 30 virus sub-panels with optimal ability to classify bnAbs into their respective epitope clusters. Plasma specificity is predicted on each virus sub-panel using maximum Spearman correlation, plasmas clustered based on the percentages of prediction for each epitope in all virus panels and specificities defined based on the observed signatures in each plasma cluster.
Results: Compared to the classical Spearman approach, we find agreement in 94% of plasmas with the panel method including only bnAbs as reference fingerprints, and 91% of plasmas when additionally integrating bnDs. The virus panel classification allowed a more detailed allocation of bnAb specificity and identified bnAb sub-groups with V3 activity. Most notably, we identified 77 (bnAb reference) and 85 (bnAb plus bnD reference) patients with potentially multi-specific bnAb activity exhibiting MPER features in combination with V1V2, V3 glycan, and/or CD4bs patterns.
Conclusion: Application of the new viral panel classification to the XbnAb cohort provided a highly reliable prediction of bnAb specificity. In addition, the method provides insight into potential multi-specific bnAb responses, indicating its usefulness for analyzing bnAb responses in future vaccine trials.

301 INFERRING IMMUNOGENIC PROPERTIES OF ENV TRIMERS BY REACTIVITY TO bNAb INDUCER PLASMA

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Background: Identification of HIV-1 envelope (Env) trimers with the ability to induce broadly neutralizing antibodies (bnAbs) remains critical for HIV-1 vaccine development. Here, we used the XbnAb cohort, comprising bnAb inducers (N=304), and non-neutralizing (nnAb) controls (N=304) identified in the Swiss 4.5k study (Rusert Nat Med 2016), to investigate the reactivity of 29 candidate Env trimer antigens with polyclonal bnAb and nnAb responses in HIV-1 infection. Several of these trimer immunogens have been clinically tested or are in the testing phase, including BG505 SOSIP, BG505 DS-SOSIP.664, ConM SOSIP.v7, BG505 SOSIP.v4 1-GT1.1 and ConCv5_KIKO. Together with the wealth of available data on the XbnAb cohort, including information on the induced bnAb type, virus, disease parameters, and host demographics, this provided a unique framework to obtain information on the *in vivo* immunogenic potential of these Env trimers.
Methods: Patient plasma were assessed for IgG1, -2, and -3 against 29 stabilized soluble Env trimer variants in a Luminex based binding antibody multi-plex assay (BAMA). Plasma dilution curves were summarized into weighted MFI. We determined the quality of bnAb engaging trimer immunogens using the following criteria: i) MFI magnitude in bnAb inducers, ii) differentiation between bnAb inducers and nnAb controls, iii) reactivity with different subtype plasma, iv) reactivity with plasma with different predicted bnAb type.
Results: We first ranked Env trimers for their level of reactivity and capacity to differentiate between bnAb and nnAbs inducers based on IgG1. Trimers that stood out in this were BG505 SOSIP.v4 1-GT1.1 (and derivatives), ConM SOSIP.v7, and ConCv5 (and derivatives). Subtype reactivity (comparison of plasmas from subtype B versus non-B infection) was not significantly different in the majority of Envs when adjusting for ethnicity, and the few exceptions were modest in magnitude, confirming that antigenic features on the Env trimers are mostly conserved across subtypes. Stratifying plasma based on the bnAb type elicited provided insights into differential binding preferences of Env trimers, that are in part intended as in the case of germline targeting immunogens.
Conclusion: Weighting the antigens according to their ability to discriminate bnAb from nnAb inducers, as well as in-depth analysis of their reactivity patterns, provided unique clues to their immunogenic potential that can be exploited for vaccine development.

302 GLYCAN-DEFICIENT SHIVS TO ELICIT BROADLY NEUTRALIZING ANTIBODIES IN MACAQUES

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Background: Previous studies have shown that HIV-1 SOSIP Env trimers or cleavage-independent native flexibly linked trimers engineered to lack glycans surrounding the CD4 binding site (CD4bs) or Fusion Peptide (FP) can immunofocus potent NAb responses to these critical domains. However, such immunogens did not elicit neutralization breadth, possibly due to that Env epitopes could not co-evolve and sustain sufficient affinity gradients to select for antibody affinity maturation. Here, we designed novel replicating simian-human immunodeficiency viruses (SHIVs) to encode primary transmitted/founder Envs that lacked glycans at residues surrounding the CD4bs (197, 363, and 462) or the FP (88, 241, and 611) to test the hypothesis that native-like SHIV Envs could selectively prime, boost and affinity-mature neutralizing or broadly neutralizing antibodies (bNAbs) targeting these key epitopes.
Methods: We introduced mutations disrupting glycosylation sequons at the above residues to generate eight glycan-deficient SHIV designs in previously characterized transmitted/founder SHIVs. We infected a cohort of 16 Indian-origin rhesus macaques intravenously with one of eight designs and followed them longitudinally to evaluate viral kinetics, Env sequence evolution, and neutralizing antibody development.
Results: 11 of 16 animals exhibited ideal viral kinetics and were used for further analysis. 10 of 11 animals developed potent autologous neutralizing responses targeting peptides beneath the engineered glycan holes. 8 of 11 animals developed responses capable of neutralizing heterologous glycan-deficient viral strains. Longitudinal single genome sequencing revealed a rapid, sequential restoration of the deleted glycans, which enabled virus escape from neutralization. In a subset of animals, additional mutations known to affect CD4bs or FP bNAbs arose concordantly with rising neutralizing titers. 4 macaques developed antibody responses capable of neutralizing wild-type heterologous viruses: 3 targeting the CD4bs, and 1 targeting the FP.
Conclusion: These results demonstrate a highly dynamic process of Env-Ab coevolution leading to viral persistence and maturation of immunofocused B cell responses. A subset of animals developed CD4bs or FP targeted bNAbs. Ongoing work will continue to monitor these animals' neutralizing responses and isolate monoclonal antibodies from animals with wild-type heterologous neutralization. These studies will help inform the design of boosting immunogens to elicit CD4bs or FP bNAbs.

303 IDENTIFICATION OF HIV BROADLY NEUTRALIZING MONOCLONAL ANTIBODIES TARGETING MPER

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Background: Broadly neutralizing monoclonal antibodies (bNAbs) target sites of vulnerability on the HIV envelope, such as the gp41 membrane proximal external region (MPER). MPER-directed bNAbs, such as VRC42.01 and PGZL1, have been previously isolated from chronically subtype CRF_01 AE and subtype B infected donors, respectively, and are part of the 4E10-class of MPER-specific bNAbs. Here we report the isolation of MHRP.01 from a subtype B infected donor, as another 4E10-class bNAb. These data indicate that MPER-directed mAbs are found in multiple donors infected with different HIV subtypes.

Methods: Monoclonal antibodies (mAbs) were isolated from a subtype B infected donor using two parallel methods: high-throughput B-cell culture followed by microneutralization assays, and fluorescently labeled MPER peptide to capture antigen-specific B cells by cell sorting. B-cell receptors were sequenced, and heavy and light chain sequences were cloned into expression vectors and expressed in Expi293F cells. MAbs were then characterized for binding, epitope mapping, and neutralization across a panel of 208 diverse pseudoviruses (pSVs). MAbs with potent cross-neutralization were further characterized by crystal structure determination.
Results: MPER-specific mAbs were isolated using both MPER-specific B-cells and probe negative B-cells, and confirmed by neutralization using an HIV-2 chimera pSV containing HIV-2 backbone with HIV-1 MPER inserted. Two mAbs, MHRP.01 and MHRP.02 were able to neutralize 100% and 97% of the pSVs in a panel of 208, respectively with an average potency < 1ug/mL. MHRP.01 utilized VH1-69 and VK3-20, the same gene usage as other MPER-specific mAbs VRC42, and PGZL1. MHRP01-GW was produced to include shared amino acid residues with VRC42, glycine (G) and tryptophan (W), and exhibited more robust binding to the MPER peptide but did not improve neutralization compared to MHRP.01. Crystallization of MHRP.01 revealed residues important for MPER binding, which bound in the same conformation as MPER-directed bNAbs 4E10 and VRC42 (Fig. 1).
Conclusion: These data reveal that similar monoclonal antibodies targeting MPER have been isolated from multiple individuals infected with different HIV subtypes. These mAbs, VRC42.01 (subtype CRF01_AE), PGZL1 (B) and now MHRP.01 (B) have identical gene usage, targeted epitope, angle of binding, and neutralization profiles, suggesting that individuals from different demographic areas could elicit B-cell clones targeting this epitope through vaccination efforts.

Structural comparisons of MHRP.01 with 4E10 and VRC42

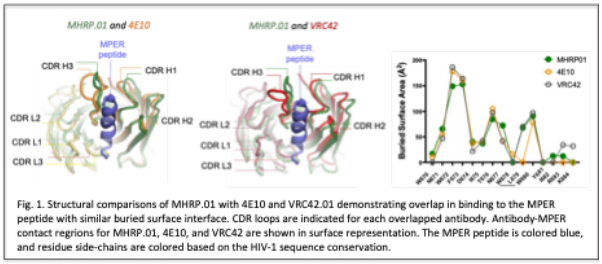

Fig. 1. Structural comparisons of MHRP.01 with 4E10 and VRC42.01 demonstrating overlap in binding to the MPER peptide with similar buried surface interface. CDR loops are indicated for each overlapped antibody. Antibody-MPER contact regrions for MHRP.01, 4E10, and VRC42 are shown in surface representation. The MPER peptide is colored blue, and residue side-chains are colored based on the HIV-1 sequence conservation.

304 NASCENT HIV-1 ENV-REACTIVE bNAb INDUCTION IN SHIV-INFECTED NEONATAL RHESUS MACAQUES

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Background: Recent studies have indicated that HIV-1 infected infants and children more frequently develop broadly neutralizing antibodies (bnAbs) and do so faster than adults. However, the cellular and molecular mechanisms of infant bnAb development are not fully understood. We sought to develop a neonatal model to reproducibly study bnAb induction.
Methods: Thirteen therapy-naïve infant rhesus macaques (RMs) were infected soon after birth with a pathogenic Simian-HIV (SHIV) designed to elicit V2-apex and V3-glycan bnAbs. Viral load was monitored by quantification of plasma SIV RNA. Envelope (Env) evolution was evaluated by single genome sequencing of circulating viral envs, and plasma Abs were functionally characterized. We performed flow-cytometry phenotyping of lymph node (LN)-derived germinal center (GC) cells, and single-cell transcriptomics of peripheral blood cells (PBMCs) to interrogate neonatal host immunity associated with bnAb induction.
Results: All infant RMs were successfully infected; 8 RMs had viral loads ranging from 10^3-10^7 RNA copies/ml for 12-24 months of infection, but 5 RMs developed partial or full control of viremia. In 11 RMs studied, we observed rapid onset of mutations at glycan hole sites D133, T138, H289, and P291. By month 6 post-infection, a fraction of circulating viruses in 8/11 RMs studied carried env mutations in and around the C-strand of the V2-apex (residues 166-172), and by 18-24 months post-infection, the majority of sequences from 7/8 RMs contained mutations at residue 169 that is a key contact residue of V2-apex bnAbs. Additionally, mutations D325N and I326T in V3 ^{324}GDIR^{327}-motif also emerged in two RMs, indicative of possible development of GDIR-targeted and polyclonal b/NAbs in these two RMs. Of 13 RMs, all of them generated plasma Abs that neutralized tier 2 or difficult-to-neutralize autologous SHIV, while 8/13 (62%) RMs also generated Abs that potently neutralized 1-4 heterologous tier 2 HIV-1 isolates. RMs that developed heterologous NAbs had increased frequency of GC Env-reactive B cells and total follicular-helper CD4 T cells overtime, as well as increased expression of genes in PBMCs associated with activated immune cells and inflammation.
Conclusion: Thus, SHIV infection of neonatal RMs elicited plasma nascent bnAbs that may affinity mature overtime to develop neutralization breadth. Moreover, we define a neonatal model of nascent bnAb induction that may provide insights for pediatric HIV-1 vaccine designs.

305 AUTOLOGOUS NEUTRALIZING ANTIBODIES DEVELOP AFTER EARLY BUT NOT ACUTE ART INITIATION

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Background: ART initiation (ARTi) in acute/early HIV limits reservoir size and diversity, preserves host immunity, and limits transmission risk, but may also limit development of HIV-specific immune responses. While the kinetics of HIV-specific immunity with ongoing viremia is described, the effect of early ARTi on autologous neutralizing antibody (anAb) development and persistence is less clear. Here, we tested for antibody responses to the identified transmitted/founder (TF) or early virus populations in individuals with acute/early ARTi.
Methods: Among 15 participants from the UCSF Treat Acute HIV study of individuals with acute/early ARTi, plasma was obtained at day of ARTi and longitudinally for 6-36 months. Single genome sequencing (SGS) of early plasma virus was used to identify TF viruses or representative early viruses, which were cloned and pseudotyped. Plasma IgG from longitudinal timepoints was used to test for autologous neutralization by TZM.bl assay. In parallel, plasma IgG was assessed for gp120-specific binding antibodies by ELISA and neutralization of tier 1 MN and SF162 strains.
Results: SGS of gp160 env was performed on first available plasma from 15 participants with ARTi in Fiebig stages I-V and estimated date of diagnostic infection (EDDI) ranging from 17-128 days. SGS (n=311 total, median=22/participant) identified 8 single and 7 multiple virus transmissions. In all 15 participants, plasma IgG from the day of diagnosis/ARTi did not neutralize the contemporaneous autologous TF/early virus. In 7 participants with ARTi < 60 days from EDDI who maintained suppression on ART, no anAbs developed in up to 3 years of sampling. In contrast, 2 of 3 participants with EDDI < 60 days who experienced viral rebound (weeks 16 and 96 after ARTi) subsequently developed anAbs. In participants with ARTi at EDDI >60 days, 5 of 6 developed anAbs 12-80 weeks post-ARTi, which increased in potency on continued ART. AnAb potency at week 24 post-ARTi correlated with time to ARTi (r=-0.69, p=0.006), and with binding antibodies at ARTi (r=-0.79, p< 0.001) and 24 weeks later (r=-0.86, p< 0.0001).
Conclusion: AnAbs developed only in those initiating ART >60 days after EDDI or following rebound viremia after initial ARTi, suggesting that anAb development is dependent on a threshold of viral exposure. In participants for whom this virus exposure threshold was met, anAb potency increased over years of suppressive ART. Results have implications for humoral immunotherapy approaches in PLWH with early ARTi.

Plasma IgG Neutralization of Transmitted/Founder or Early Virus.

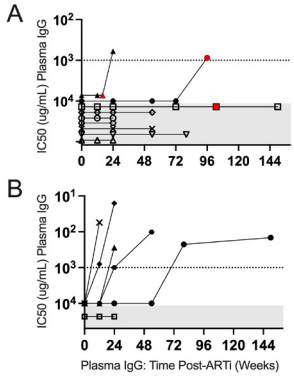

Figure 1. Plasma IgG neutralization of transmitted/founder or early virus. Participants with ART initiation <60 days post-estimated date of infection (**A**, n=9), or >60 days post-estimated date of infection (**B**, n=6). 50% inhibitory concentration titer in TZM.bl assay on Y axis, time post-ART initiation on X-axis. Red shapes indicate documented viremia after initial virus suppression on ART. Values greater than limit of detection (IC50=10^3) indicate lack of neutralization. Open symbols designate participants who do not develop neutralization at any time point.

306 ART-DIX: A NOVEL STRATEGY TO MONITOR BROADLY NEUTRALIZING ANTIBODY ACTIVITY ON ART

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Background: Therapeutic application of broadly neutralizing antibodies (bnAbs), either passively administered or elicited by therapeutic vaccines, offers new possibilities in the quest for an HIV-1 cure. One difficulty in implementing such cure strategies is the need for concurrent antiretroviral (ARV) therapy (ART). Therefore, monitoring bnAb activity under these conditions requires assays that are unaffected by ARVs. Here we report on the development of novel, cost-effective, and scalable strategies to remove inhibition by ARVs without compromising Ab-based neutralization.

Methods: The ART-compatible neutralization assays were conducted on TZM-bl cells and compared to the standard NLuc-based pseudovirus neutralization assay. We included 13 multi-clade viruses and MuLV as control. Inhibition in presence of common ARVs, bnAbs, and plasma from ART-treated patients (N=23) was assessed.

Results: To eliminate the impact of ART on neutralization assays, we investigated two basic strategies, namely using ART-resistant viruses or removing ARVs. We used two different approaches for each strategy and compared all four methods for efficacy and suitability for high-throughput screening. To generate ART-resistant viruses, we developed NLuc variants with multiple ART-resistance mutations (HIV-Luc-res). However, full resistance was not achieved as combined resistance mutations affect infectivity too severely. Exploiting the inherent resistance of vesicular stomatitis virus (VSV) to ARVs proved not satisfactory as VSV-based Env pseudotypes displayed increased neutralization sensitivity to certain Abs, suggesting more open trimer conformations in the VSV context. Next, to remove ARVs from plasma, we fine-tuned the purification of plasma Abs by protein A/G to ascertain full Ab recovery. However, while the approach was successful, it is not scalable and costly. Finally, we developed a novel ARV removal strategy to separate ARVs by size exclusion after pH-dependent dissociation of plasma proteins (ART-DIX: **D**issociation and s**I**ze-e**X**clusion). ART-DIX proved to be highly effective in removing ARVs, with only the most potent drugs showing some residual activity that can be overcome when using ART-DIX in combination with HIV-Luc-res viruses.

Conclusion: The method portfolio presented here offers versatile options to reduce confounding effects of ARVs in neutralization assays. Depending on the ART scheme, research question, and required throughput, alternative test formats may prove beneficial.

307 EFFICACY AND COMPLEMENTARITY OF HIV-1 SUPPRESSION BY CD4-BINDING bNAbs

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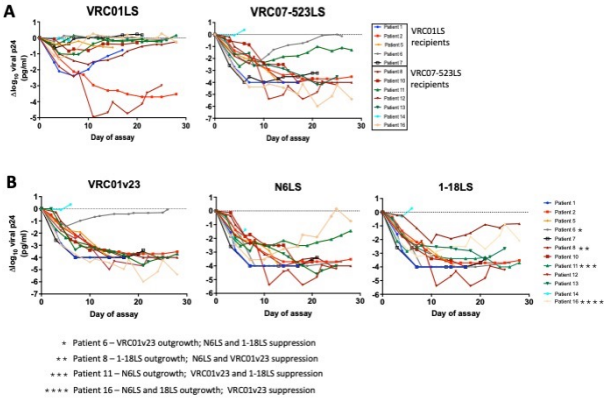
Background: Broadly neutralizing antibodies (bNAbs) show potential as complementary immunotherapy to combination anti-retroviral therapies for HIV-1 treatment yet infusion of a single bNAb selects for resistant variants. We developed an *ex vivo* assay that predicts bNAbs potential to achieve *in vivo* virologic response in people with HIV and allows investigation of viral resistance signatures.

Methods: The *ex vivo* assay used pre-infusion CD4+ T cells from VRC607/ACTG5378 patients, a phase I study of the CD4 binding site (CD4bs) bNAbs VRC01LS (n=7) or VRC07-523LS (n=9) antiviral efficacy. Cells were activated and treated with various CD4bs bNAbs. Viral titers were assessed by p24 ELISA, escape variant signatures were characterized by sequencing and neutralization assays.

Results: In VRC607/ACGT5378, 2 patients infused with VRC01LS and 8 with VRC07-523LS showed viremia decrease > 1 $\log_{10}$. *Ex vivo* assays using samples from 9 patients whose viremia decreased after VRC01LS (n=2) or VRC07-523LS (n=7) infusion evidenced >10-fold reduction in viral replication by the corresponding bNAb relative to assay control. Four patients that did not show an *in vivo* response post-bNAb infusion did not show viral suppression *ex vivo* by the respective bNAb indicating *ex vivo* assays recapitulated virological outcome observed *in vivo*. We also assessed more potent and broader next generation CD4bs bNAbs: VRC01v23, 1-18 and N6 in this assay. We found that there were complementary suppression profiles for these 3 bNAbs with some assays showing suppression by 1 or 2 but not all 3 bNAbs dependent on the patient sample used. Further, most VRC01LS or VRC07-523LS escape strains were neutralized by 1-18, N6 or VRC01v23, supporting potential for combined therapy with these bNAbs. 1-18, N6 and VRC01v23 escape variants had charge changes, glycan loss or shifts in the ß23-V5. Resistant strains to 1-18 lacked R308 while N6 escape strains lacked glycan N276 or D279. Moreover, genetic signatures in *ex vivo* outgrowth viruses were also found in plasma viral sequences, suggesting that the *ex vivo* assay can identify circulating bNAb resistant variants in these patients.

Conclusion: *In vivo* and *ex vivo* effect of HIV-1 bNAbs comparison suggest that the *ex vivo* assay shows potential to reliably predict bNAbs antiviral effect in clinical trials and contribute to analysis of resistant strains that could emerge *in vivo*. Our data indicate that optimal combinations of CD4bs bNAbs can be used to mitigate viral resistance to bNAb-based immunotherapies.

Comparative suppression profiles of VRC01LS, VRC07-523LS, VRC01v23, N6LS and 1-18LS treated conditions in *ex vivo* assay



Comparison of *ex vivo* virologic effect by p24 ELISA between **(A)** VRC01LS and VRC07-523LS evidencing improved suppression by the latest and **(B)** VRC01v23, N6LS and 1-18LS showing complementary suppression profiles between the three bNAbs. Patients showing different suppression profiles by these bNAbs are indicated by *. P24 ELISA titers have been normalized to assay control.

308 ASSESSING IMMUNOGENICITY BARRIERS OF THE HIV-1 ENVELOPE TRIMER

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Background: Understanding the counterbalance of epitope shielding and accessibility on HIV-1 envelope (Env) trimers is essential to guide immunogen selection for broadly neutralizing antibody (bnAb) based vaccines. To investigate the antigenic space of highly stabilized Env trimers, we here created a novel strategy, DARPin Antigenicity Analysis (DANA), based on synthetic, high diversity Designed Ankyrin Repeat Protein (DARPin) libraries. We show that DANA, a purely in-vitro screening tool, has the means to inform on the antigenic properties of Env immunogens by recapitulating the difficulty of the human immune system to generate antibodies recognizing prefusion closed Env *in vivo*.

Methods: High diversity DARPin libraries consist of ~19kDa-sized synthetic proteins with a consensus-designed framework and randomized residues in the binding surface. We performed 12 independent DANA screens using different SOSIP-type Env trimers as panning targets to select Env-specific DARPins from DARPin libraries by ribosome display. 190 DARPins from each DANA screen were sequenced and analyzed for trimer and V3 loop reactivity by ELISA and neutralization breadth using a 5-virus panel in the standard TZM-bl based pseudovirus neutralization assay.

Results: Comparison of Env trimers in DANA screens revealed that stronger trimer stabilization, occluding the V3, lead to the selection of highly mutated DARPins with length variations and framework mutations. This is highly reminiscent of the extensive affinity maturation and framework mutations reported for bnAbs, indicating that DARPins and antibodies, despite their genuinely different binding architecture, have the same underlying biophysics of interaction and thus similar limitations in recognizing the shielded trimer. Notably, by exploring different selection regimens, we showed that in DANA reduction of V3 dominance benefits the selection of trimer-reactive clones, reaffirming current concepts of vaccine design. As we show, DANA screens have, next to investigating single immunogens, the capacity to mimic heterotypic prime-boost immunization regimens and to select immunogen combinations that favor the selection of trimer reactive binders.

Conclusion: Our results demonstrate the utility of DANA screens as a versatile tool for basic antigenicity screening of immunogen candidates, which may substitute for some of the early-stage animal testing required in vaccine development.

309 ISOLATION OF PAN-SARBECOVIRUS mABs THAT NEUTRALIZE SARS-CoV-1 AND SARS-CoV-2 VARIANTS

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Background: The continued emergence of severe acute respiratory syndrome coronaviruses (SARS-CoVs) and recent explosion of the SARS-CoV-2 pandemic highlights the need for broad and potent antibody recognition and understanding the contexts in which they may develop. Antibodies with cross reactivity across SARS lineages may be of particular value in preparing for future outbreaks of new sarbecoviruses.

Methods: We isolated monoclonal antibodies (mAbs) from an individual 60-days post-vaccination, 30-days post Delta-infection. Reconstructed antibodies were screened for binding to a panel of prefusion-stabilized Spike trimers from SARS-CoV-2 and other β-coronaviruses using enzyme-linked immunosorbent assay (ELISA). Neutralization potency and breadth was assessed using a spike-pseudotyped lentivirus neutralization assay. Additionally, epitope and escape mutant profiling was conducted by deep mutational scanning (DMS) to identify mutations that affect antibody binding. Lastly, binding breadth was further evaluated using a yeast display library of RBDs from SARS-CoV-2 variants and related sarbecoviruses.

Results: We identified several SARS-CoV-2-specific mAbs that neutralized SARS-CoV-2 variants of concern (VOCs) and SARS-CoV-1. Notably, two of these mAbs (C68.61 and C68.185) neutralized SARS-CoV-1 with an IC_{50} = 307 and 139 ng/mL (respectively) that is similar to or better than the potency of S309 (IC_{50} = 206 ng/mL) and CR3022 (IC_{50} = 981 ng/mL), which are mAbs isolated from individuals with SARS-CoV-1 infections. C68.61 also neutralized all Omicron VOCs tested and retained neutralization activity against currently circulating variants BQ1.1 (IC_{50}=790 ng/ml) and XBB (IC_{50}=590 ng/ml). Key C68.61 mAb-escape mutations identified by DMS in the Omicron BA.2 background yeast display library included sites K462, E465, R466, and I468, which are conserved sites across all VOCs and SARS-CoV-1. The isolated mAbs displayed cross-reactive binding to RBDs from diverse SARS-CoV-1-related CoVs and African and European sarbecovirus isolates as well as SARS-CoV-2 VOCs.

Conclusion: Here we describe mAbs from a SARS-CoV-2-infected individual that bound and neutralized both SARS-CoV-2 and SARS-CoV-1, including one that showed breadth across recent VOCs. Given their breadth, these SARS-CoV-2 cross-reactive mAbs may be robust to viral escape and thus could contribute to therapeutic efforts. In addition, these mAbs displayed broad cross-reactive activity across sarbecoviruses and may be beneficial against future spillover events.

310 BROAD ANTIBODIES TO FUNCTIONALLY CONSTRAINED REGIONS OF SARS-CoV-2 SPIKE

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Background: While remarkable and rapid progress was made in fighting the SARS-CoV-2 pandemic with vaccines and therapeutic antibodies, these approaches were quickly compromised by viral evolution. Therapeutic monoclonal antibodies (mAbs) that were once authorized for clinical use, which all target the receptor binding domain (RBD), are no longer effective against current variants of concern (VOCs) due to mutations in this region of Spike. Thus, to achieve durable protection against SARS-CoV-2, novel mAbs need to show breadth and potency across VOCs and target epitopes that are more constrained.

Methods: mAbs from an individual who had a breakthrough Delta VOC infection after vaccination were isolated from Spike-specific memory B cells. mAbs were assessed for binding affinity and neutralization potency using Spike-pseudotyped lentivirus (PSV) and live SARS-CoV-2 virus neutralization assays. Epitopes were mapped using deep mutational sequencing (DMS) and structural-based methods.

Results: Three novel mAbs (C68.3, C68.13, C68.59) demonstrated binding breadth to Spikes from various VOCs including Omicron VOCs despite that C68 had not yet been exposed to Omicron. These mAbs potently neutralized the Wuhan-Hu-1 vaccine and Delta strains (IC_{50} = 9-61ng/mL), and early Omicron strains BA.1, BA.2, BA.5 (IC_{50} = 12-149 ng/mL). C68.3 and C68.59 retained potency against recent VOCs BQ.1.1 and XBB (IC_{50} = 121-122 ng/mL and 56-82 ng/mL, respectively) in the PSV assay. Similar neutralization activity was observed in the live virus assay. The potency of these mAbs was greater against Omicron VOCs than all but one of the mAbs previously authorized for treatment and they showed greater breadth. The mAbs target distinct epitopes on the Spike glycoprotein, two in the RBD (C68.3, C68.13) and one in an invariant region downstream of RBD in subdomain 1 (SD1) (C68.59). Structural analysis of C68.59 Fab binding to Spike trimer revealed significant allosteric changes to regions of Spike outside of the epitope in the S2 unit. Finally, DMS escape pathways showed these mAbs target regions highly conserved across VOCs that are also functionally constrained, suggesting escape could incur a fitness cost.

Conclusion: Overall, these mAbs are novel in their breadth across VOCs and include a potent mAb targeting a rare epitope outside of the RBD in SD1. These mAbs focus on diverse, functionally constrained regions in Spike making them candidates for development as combination therapeutics with good durability against future VOCs.

311 IL-15 DEPENDENT NK CELLS AND DENDRITIC CELLS CROSS-TALK IN HIV-1 ELITE CONTROLLERS

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Background: HIV-1-specific T cell responses are commonly regarded as the backbone of antiviral immunity in HIV-1 elite controllers (ECs), while the specific

contribution of innate immune cells is less clear. Natural Killer (NK) cells are of particular interest, as they can mount direct cytotoxic effects against HIV-1-infected cells that do not depend on MHC class I restriction and are less prone to viral mutational escape. Here, we investigated epigenetic, transcriptomic and metabolic characteristics of NK cells from ECs.

Methods: Epigenomic, transcriptomic and metabolic profiles of sorted CD56^{dim} CD16+ NK cells from HIV-1 ECs (n=20) were compared to antiretroviral-treated HIV-1-infected individuals (HAARTs; n = 21) and HIV-1 negative healthy donors (HIVNs; n = 18). CUT&RUN-Seq was used to assess DNA segments bound to activating and inhibitory histone modifications, while transcriptional signatures were analyzed by RNA-Seq. Seahorse assays were used to evaluate metabolic activities of NK cells.

Results: Compared to reference cohorts, epigenomic profiles of *ex vivo* sorted CD56^{dim} CD16+ NK cells from ECs showed statistically significant differential enrichments, with the activating histone H3K27ac and H3K4me3 marks in 546 and 391 gene loci, respectively. However, no differences were seen for the inhibitory H3K27me3 mark. Notably, within ECs, the IL-2Rb gene was enriched with activating histone modifications, and was more strongly expressed on the transcriptional and the protein levels in CD56^{dim} CD16+ NK cells. Correspondingly, IL-15, the physiological ligand for the IL-2Rβ chain, was more strongly expressed by myeloid dendritic cells (mDCs) from ECs compared to alternative study cohorts, and transcriptional signature pathways showed evidence for an improved cross-talk between mDCs and NK cells from ECs. Upon IL-15 stimulation to NK cells, an upregulation of the anti-apoptotic molecule BCL2 was seen in activated CD69+ CD56^{dim} CD16+ NK cells from ECs, compared to HAARTs (P = 0.011) and HIVNs (P = 0.001). Furthermore, IL-15-stimulated NK cells from ECs displayed an elevated level of glycolysis, compared to the other cohorts.

Conclusion: CD56^{dim} CD16+ NK cells from ECs are epigenetically poised to mount improved responses to IL-15 stimulation, allowing for improved survival and optimized metabolic activities. We propose that a distinct immune cross-talk between NK cells and mDCs may reflect features of trained innate immunity in ECs.

312 DISTINCT NK CELL RESPONSES DEFINE DURABLE CONTROL IN ELITE CONTROLLERS

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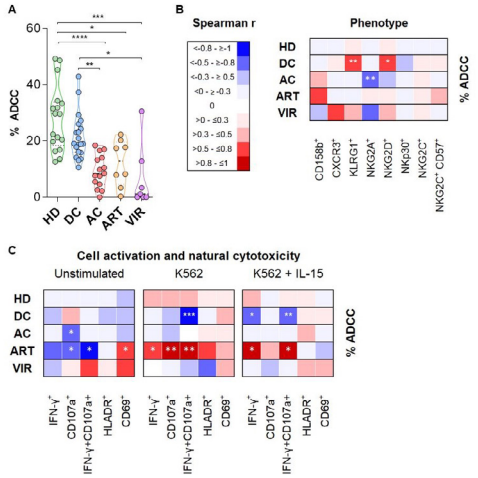
Background: Elite Controllers (EC) are PLWH that present drug-free control of the infection, representing a model for a functional cure. Hence, understanding their mechanisms of immune-mediated control is of considerable interest. We sought to characterize the NK cell repertoire in EC, including their memory-like properties and functional potential.

Methods: PBMC samples from n=33 EC (n=20 with durable control (DC), and n=13 with immunological aborted control (AC), defined by a progressive CD4+ T cell depletion (p< 0.05) during the patient's follow-up), n=25 healthy donors (HD), n=8 ART-suppressed (ART), and n=7 viremic (VIR) participants were included in the study. Phenotypic studies were performed by flow cytometry and included the markers CD57, CD56, Nkp30, NKG2C, NKG2A, CD16, CXCR3, KIR2DL2/L3, and KLRG1. Natural cytotoxicity and cell activation were evaluated by IFN-γ, CD107a, CD69 and HLA-DR expression by flow cytometry after co-culturing isolated NK cells with the MHC-devoid K562 cell line with and without IL-15. Antibody-dependent cell-mediated cytotoxicity (ADCC) was assessed after co-culturing NK cells with the latently-infected ACH-2 cell line and HIV+ plasma. P24 expression was measured by flow cytometry.

Results: NK cells from DC presented lower NKG2A expression (p=0.004) and basal cell activation, based on HLA-DR (p=0.033) and CD69 (p=0.042) expression, compared to AC. In addition, NKG2C+ NK cells, associated to memory-like NK cells, were expanded in DC compared to HD and AC (p_{HD}< 0.001 and p_{AC}=0.040), and were found to produce higher basal IFN-γ levels than AC (p=0.024). Although NK cells from DC showed a marked cytotoxic response to K562 in the presence (p< 0.001) or absence of IL-15 (p< 0.001) compared to unstimulated conditions, the response was significantly lower compared to HD (pK562= 0.001, pIL-15=0.049). However, NK cells from DC showed a strong ADCC response, similar to HD. Importantly, DC presented a remarkable ADCC response compared to AC (p=0.003) and VIR (p=0.013) participants (**Figure 1A**), which correlated positively with KLRG1 (p=0.008, r=0.57) and NKG2D expression (p=0.016, r=0.52) and inversely with the cytotoxic response presented upon K562 (p< 0.001, r=-0.80) and IL-15 (p=0.003, r=-0.74) stimulation (**Figure 1B**).

Conclusion: Our findings suggest that durable immune-mediated control of HIV infection in EC is defined by NK cell phenotypic and functional attributes, including lower cell activation, an increased memory-NK cell compartment and higher ADCC responses.

Figure 1. ADCC responses are associated to phenotypical and functional changes in the NK cell repertoire. (A) Summary graph of the ADCC activity mediated by NK cells from study groups in the presence of plasma from a viremic HIV+ participant. Statistical comparisons were performed using Kruskal-Wallis One-way ANOVA followed by Dunn's multiple comparisons test. *p<0.05, **p<0<01, ***p<0.001, ****p<0.0001. (B-C) Heatmaps summarizing the correlations between ADCC responses and (B) NK cell receptor expression (left to right: CD158b, CXCR3, KLRG1, NKG2A, NKG2D, Nkp30, NKG2C and CD57) in CD56total NK cells or (C) functional markers (IFN-γ, CD107a, HLA-DR and CD69) in (left to right): unstimulated, K562-stimulated and IL-15-K562-stimulated CD56total NK cells by study group. Statistical analysis was performed using two-tailed spearman rank correlation. *p<0.05, **p<0<01, ***p<0.001



313 MONOCYTES OF HIV-1 ELITE CONTROLLERS AND RELATIVES SHOW ENHANCED TRAINED IMMUNITY

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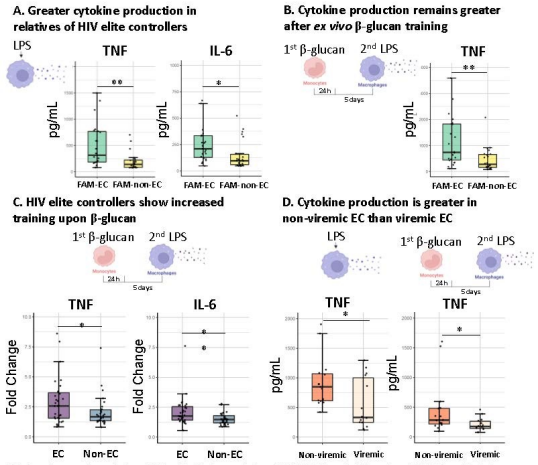
Background: Less than 1% of people living with HIV (PLHIV) spontaneously control HIV-1. Characterization of immune drivers eliciting this spontaneous control remain important. Monocytes can undergo long-term functional reprogramming after exposure to certain stimuli such as b-glucan, a process called trained immunity (TI), which confers heterologous protection against multiple pathogens. We hypothesized that spontaneous controllers show enhanced innate immune responsiveness and TI compared with noncontrolling PLHIV. Immune stimulations in the 1st degree relatives of both groups were used as surrogates of the immune reactivity without HIV.

Methods: In a double case control design, HIV-1 elite controllers (EC; N=31) and non-controlling PLHIV on suppressive antiretroviral therapy (ART) (non-EC; N=30) were recruited, as well as relatives from both groups (N=23 and N=22, respectively). Groups were similar in age, sex, BMI and vaccination history. EC were subdivided into non-viremic (N = 17) and viremic (N=14), based on viral load cutoffs < 75 and < 10,000 copies/mL, respectively. Adherent monocytes were exposed *ex vivo* to 1 ug/ml b-glucan (trained) or RPMI (control) for 24 hours at 37^{0}C. After 24 hours, the cells were washed and left to rest for 5 days,

followed by stimulation with 10 ng/mL LPS on day 6. TNF, IL-6 and IL-1RA were measured in supernatant at day 7 by ELISA.

Results: EC relatives had stronger TNF, IL-6 and IL-1RA production capacity of control monocytes after LPS stimulation than non-EC relatives (P = 0.0013, P = 0.013 and P = 0.013, respectively, Fig 1A). Induction of trained immunity was also stronger in EC relatives after b-glucan exposure and LPS stimulation (P = 0.0021, P = 0.078 and P = 0.0056 for TNF, IL-6 and IL-1RA, respectively, Fig 1B). Control monocytes responses of EC and non-EC PLHIV were similar after LPS stimulation (P = 0.54, P = 0.63 and P = 0.063 for TNF, IL-6 and IL-1RA, respectively). However, trained monocytes of EC showed greater induction of TNF, IL-6 and IL-1RA production (P = 0.047, P = 0.0054 and P = 0.043, respectively, Fig 1C). Both trained and control monocytes of non-viremic EC produced more TNF than viremic EC (P = 0.012 and P = 0.012, respectively, Fig 1D).

Conclusion: Elite controllers and their first-degree relatives show both increased innate immune responses and trained innate immunity compared to non-controlling PLHIV on ART and their first-degree relatives. Further studies on the role of trained innate immunity to control HIV-1 are warranted.



A. Adherent monocyte production of TNF and IL-6, between relatives of EC (FAM-EC) and relatives of non-EC (FAM-non-EC). Cells were exposed on day 1 with RPMI and stimulated on day 6 with LPS. B. Similar to A, yet after pre-exposure with β-glucan instead of RPMI on day 1 (training). C. Fold-to-RPMI ratio is calculated as cytokine production of trained monocytes divided by cytokine production of control monocytes. D. TNF production between non-viremic EC (viral cutoff <75 copies/mL) and viremic EC (viral cutoff <10,000 copies/mL). Left graph shows LPS responses of control monocytes and right graph LPS responses of trained monocytes.

314 TRAINED IMMUNITY FEATURES IN NK CELLS OF HIV-1 ELITE CONTROLLERS

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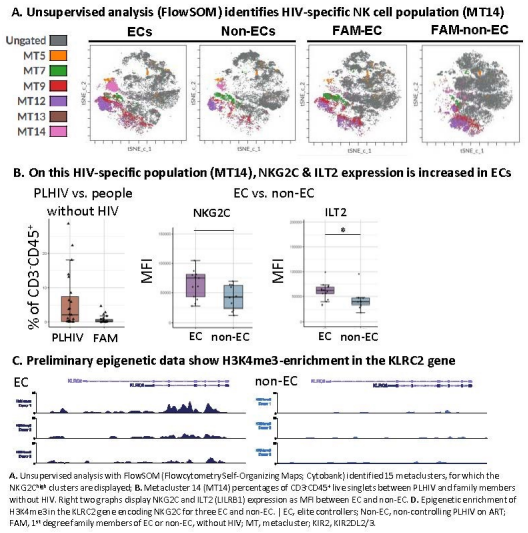
Background: It is unclear how elite controllers (EC) spontaneously control HIV in the absence of antiretroviral therapy (ART). NK cells significantly contribute to antiviral innate immune responses and can display memory characteristics mirrored by high NKG2C expression. We aimed to investigate the phenotype of NK cells in ECs and their memory features, which favor antiviral control.

Methods: NK flow cytometry analysis was performed on CD56+-sorted PMBCs from 15 EC and 12 non-controlling people living with HIV (PLHIV) on suppressive ART (non-EC), as well as 1st degree family members from both groups (N=10 and N=12, respectively): Live/Dead ViaKrome, HLA-DR, CD3, CD45, CD56, CD16, CD57, CD94, NKG2A, NKG2C, NKG2D, ILT2 (LILRB1), KIR2DL2/3, DNAM, NKp30, NKp46. Machine learning algorithms viSNE and FlowSOM were used to identify and analyze fifteen metaclusters. CMV IgG serology was measured with ELISA. Between-group comparisons were done with Mann-Whitney U tests.

Results: Through unsupervised analysis we identified two $CD57^{high}NKG2C^{high}$ metaclusters. One was characterized as $CD57^{high}NKG2C^{high}KIR2^{low}$ and exclusively present in CMV-seropositive individuals, from both the PLHIV and family members groups without HIV (MT12). The second $CD57^{high}NKG2C^{high}$ metacluster was $KIR2^{high}$ and specific to PLHIV (MT14, Fig 1B). In this subset, EC had a greater NKG2C and ILT2 (LILRB1) expression than non-EC (P=0.036 and P=0.012, respectively). EC family members had a higher percentage of CD56-CD16+$KIR2^{high}$ NK cells, a cytotoxicity subset, than non-EC family members (P = 0.0026, MT9). NKG2C expression on this subset was greater in EC family members (P = 0.036). Deposition of H3K4me3 mark of open chromatin at immune gene promoters is a hallmark of long-term innate immune memory (also called *trained immunity*). An increased H3K4me3 enrichment at the promoter of KLRC2 gene, the coding gene for NKG2C, was observed in 3 EC in comparison to 3 non-EC (Fig 1C).

Conclusion: Unsupervised analysis revealed the presence of two distinct memory NKs subpopulations in PLHIV. CD57highNKG2ChighKIR2high NK cells were specific to PLHIV and had greater NKG2C and ILT2 expression in EC. CD57highNKG2ChighKIR2low NK cells were only present in CMV-seropositive individuals. A high capacity for target cell-induced IFNγ production has been attributed to these NK cells. Increased NKG2C expression together with enrichment of H3K4me3 at the promoter of KLRC2 suggests improved antiviral control in ECs through induction of trained immunity.



A. Unsupervised analysis with FlowSOM (Flowcytometry Self-Organizing Maps; Cytobank) identified 15 metaclusters, for which the $NKG2C^{high}$ clusters are displayed. B. Metacluster 14 (MT14) percentages of $CD3^{-}CD45^{+}$ live singlets between PLHIV and family members without HIV. Right two graphs display NKG2C and ILT2 (LILRB1) expression as MFI between EC and non-EC. D. Epigenetic enrichment of H3K4me3 in the KLRC2 gene encoding NKG2C for three EC and non-EC. | EC, elite controllers; Non-EC, non-controlling PLHIV on ART; FAM, 1st degree family members of EC or non-EC, without HIV; MT, metacluster; KIR2, KIR2DL2/3.

315 ELITE CONTROLLERS WITH DISTINCT VIRAL RESERVOIR HAVE ROBUST CTL TO NETWORKED EPITOPES

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Background: A major objective for HIV cure research is treatment-free suppression of infection, which has been achieved by individuals who spontaneously control HIV to undetectable levels (elite controllers, ECs). Prior analyses of ECs demonstrated that functional cytotoxic T lymphocyte (CTL) responses towards epitopes derived from mutationally constrained ('networked') regions of the HIV proteome were a key distinguishing feature. Recent work has shown that a subset of ECs have distinct viral reservoirs where integrated near full-length HIV genomes are primarily within transcriptionally repressive chromosomal locations, representing an even more promising model of HIV cure, but for which immune correlates remain to be defined. Thus, we characterized HIV-specific CTL responses in ECs with distinct viral reservoirs (DVRs).

Methods: We evaluated the specificity and functionality of HLA-restricted HIV-specific CTL responses in 10 ECs with DVRs (Jiang et al, Nature 585:261) and 30 HIV+ individuals on long-term ART by IFN-g ELISpot, proliferation assay, T cell phenotyping and CTL elimination assay. Matched integration and proviral sequencing was performed on the entire cohort and was used to evaluate the sequence diversity of targeted epitopes.

Results: Evaluation of CTL immunodominance hierarchies by IFN-gamma ELISpot and tetramer staning revealed preferential targeting of networked epitopes by ECs with DPRs in comparison to individuals on ART ($p < 0.05$). Further assessment of the functionality of CTL responses targeting networked epitopes revealed highly significant differences in proliferative capacity ($p < 0.0001$) and primary CD4+ T cell elimination ($p < 0.0001$), with some proliferative networked CTL responses being among the highest observed to date. Evaluation of viral sequence diversity in near full-length provirus revealed an absence of immune escape mutations within networked epitopes despite the presence of highly functional CTL responses.

Conclusion: Our findings demonstrate that ECs with distinct viral reservoirs have highly functional CTL responses against networked epitopes in comparison to individuals on long-term ART. Moreover, these networked epitopes resist mutagenesis despite robust CTL pressure. These studies therefore indicate that induction of proliferative and cytotoxic T cell responses targeting mutationally constrained regions of HIV may be a viable strategy to restrict proviruses to transcriptionally repressed genomic regions and thereby durably suppress virus-producing cells.

316 DNA LAUNCHED BROADLY NEUTRALIZING KILLERS: A DOUBLE-EDGED THERAPEUTIC AGAINST HIV-1

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Background: Robust induction of CD8+ T cells play important role in control of HIV-1 viremia. Here, we describe design and implementation of approaches to recruit cytotoxic T-cell responses for achieving HIV-1 clearance. We have exploited a combination of two critical immune components, first is the HIV virus neutralization property of the Broadly Neutralizing Antibodies (bNAbs) and second – the killer potential of cytotoxic T cells as DNA launched therapeutic intervention against HIV-1.

Methods: We designed DNA launched broadly neutralizing killers (bNKs) which are single chain molecules, these engage CD3+ T cells from one arm and HIV-1 infected target cells using the other arm. Multiple bNKs for targeting various sites of vulnerabilities present on HIV-1 Env protein like CD4bs, V1/V2 loop, etc. have been developed. We evaluated the expression profiles of these DNA launched bNKs and characterized for functionality in terms of binding, neutralization and killing by recruitment of effector cells first *in vitro* and then *in vivo*. ELISA and flow cytometry was employed for binding studies, followed by pseudo-neutralization assays to test neutralizing potential of these therapeutics against global virus panel. A novel cell based Xcelligence assay was designed to use impedance as a readout for killing activity of bNKs in the presence of effector T cells and their potency were defined.

Results: PGDM1400-bNK and 3BNC117-bNK were designed and optimized for expression both *in vitro* and *in vivo*. These were found to be functional and bound CD3 expressing T cells along with capacity to neutralize HIV-1 Tier2/3 viruses with high potency and specificity. These were found to be extremely potent killers against HIV-1 infected target cells with picogram IC50 for killing. Further, IM administration in mice using electroporation was performed and the serum expressing the bNKs exhibited cytolysis and killing of HIV-1 infected cells in novel cell based Xcelligence assay.

Conclusion: Our data highlights the design and characterization of novel DNA launched bNKs which are potent double-edged therapeutics capable of broadly neutralizing difficult to neutralize Tier2/3 viruses and engaging effector T cells to their targets and mediate killing of HIV-1 infected cells with high potency and specificity. Further designs are being currently explored to use these molecules as combination therapies to engage various other effector cells of the immune system and target arresting HIV-1 virus escape using our robust HIV therapy.

317 LAIR-1: NEGATIVE REGULATOR OF SIV- SPECIFIC CD8 T CELLS DURING CHRONIC SIV INFECTION

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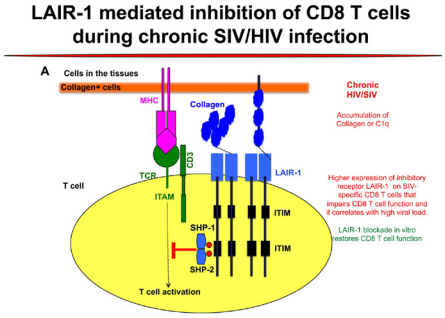
Background: HIV-1 specific CD8 T cells play an important role in controlling HIV infection. However, during chronic HIV infection, HIV-specific CD8 T cells undergo functional exhaustion, lose effector function and fail to control viral infection.Leukocyte-associated Ig-like receptor-1 (LAIR-1), a 32 kDa transmembrane glycoprotein, is a surface molecule expressed on human peripheral blood mononuclear leukocytes and act as an inhibitory receptor many immune cells. However, the role of LAIR-1 on CD8 T cells during SIV/HIV infection remains unknown.

Methods: A total of 14 macaques were infected with simian immunodeficiency virus(SIVmac251) and studied the temporal dynamics of LAIR-1+ SIV-specific CD8 T cells for their phenotypic and functional profiles using multicolor flow cytometry. We performed immunohistochemistry IHC to stain for LAIR-1 in LN tissues and used RNA sequencing to study the transcriptomic profile of LAIR-1+ CD8 T cells.

Results: Here, we report on the expression of LAIR-1 on virus-specific CD8+ T cells during chronic SIV infection and the effect of LAIR-1 blockade on the proliferation and cytokine function of these cells. LAIR-1 expression was found to be low on naive CD8+ T cells and increased on total and SIV-specific effector memory CD8+ T cells during chronic infection. In addition, the level of LAIR-1 expression in the lymph node during chronic infection was higher compared to naïve animals. Transcriptionally, these LAIR-1+ CD8 T cells exhibited a unique transcriptome characterized by with heightened type I IFN-signaling coupled with reduced TCR signaling, cell cycling and cell metabolism pathways. Importantly the expression of LAIR-1 on SIV-specific effector memory CD8 T cells correlated directly with the SIV viral RNA levels in plasma. Indeed, *In vitro* blockade of LAIR-1 using LAIR-1-Fc/anti-LAIR-1 antibody resulted in enhanced proliferation of SIV-specific CD8 T cells with cytotoxic function.

Conclusion: These results serve as a foundation for future *in vivo* trials of the use of LAIR-1 blockade to potentially enhance and/or restore antiviral SIV-specific CD8 T cells, especially in secondary lymphoid tissues which may be important for the HIV cure strategy.

LAIR-1 mediated inhibition of CD8 T cells during chronic SIV/HIV infection



318 TIGIT/CD155 BLOCKADE BOOSTS T-CELL IMMUNITY AND HIV-SPECIFIC DEGRANULATION IN PLWH

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Background: Exploring immune interventions, such as immune checkpoint blockade, is critical to attaining the HIV cure. To date, these strategies focus on a narrow set of targets using conventional monoclonal blocking antibodies. Although several studies have indicated the potential of targeting the TIGIT inhibitory pathway in people living with HIV (PLWH), no focus has been paid to its ligand CD155. Here, we propose to explore CD155 as an immunoregulatory target in PLWH.

Methods: We engineered two soluble Inhibitory Receptors (sIR) proteins (monomeric sIR1 and Fc-dimeric sIR2) with a sIR-Control. We determined SIRs affinity to CD155 by SPR and evaluated CD155 blockade in a coculture using a Jurkat-TIGIT+ and BW5417:OKT3-CD155+. Moreover, we assessed CD155 blockade by sIRs in PBMCs from PLWH on ART (n=17). Briefly, PBMCs were stimulated with sIRs in the absence or presence of an HIV-1 Gag peptide pool. After 16h, we analyzed antigen-independent and HIV-specific responses by flow-cytometry combining CD3, CD4, CD8, CD45RA, CCR7, CD16, CD56, CD155, TIGIT, IFNg, TNF, CD107a, IL-2, and IL-10 markers.

Results: We determined sIRs specific binding to CD155 and found an increased affinity in sIR2 (8.6nM) compared to sIR1. In coculture, only the blockade of CD155 with sIR2 increased the activation of NFkB ($p=0.043$) and the coactivation of NFkB:NFAT ($p=0.006$) in Jurkat-TIGIT+ cells. TIGIT blockade by mAb only produced NFkB:NFAT coactivation ($p=0.0045$). Using PBMCS from PLWH, we found in an antigen-independent manner, increased production of IFNg ($p=0.002$), TNF ($p=0.003$), IL-2 ($p=0.02$) and IL-10 ($p=0.0009$) in CD8+ T-cells and increased production of IL-2 ($p=0.055$) and IL-10 ($p\leq0.0001$) in CD4+ T-cells by sIR2. In addition, sIR2 increased the frequency of TIGIT+CD8+($p\leq0.0001$) and TIGIT+CD4+($p=0.002$) T-cells with augmented degranulation capacity.

However, the increase of TIGIT+ T-cells did not correlate with loss of IFNg, TNF, IL-2, IL-10 or CD107a production. In HIV-1 stimuli, sIR2 favored a specific increase of CD107a in TIGIT+CD8+(p=0.003) and TIGIT+CD4+(p=0.003) T-cells in the absence of IFNg, TNF, IL-2, and IL-10 production. No effect was found for sIR1.
Conclusion: We generate sIRs immunomodulatory proteins capable of binding CD155. Our data demonstrate blockade of CD155 and enhancement of T-cell cytokine production by sIR2. Moreover, sIR2 increased HIV-specific degranulation in TIGIT+CD4+ and TIGIT+CD8+ T-cells in PLWH on ART. Thus, we propose CD155 as a potential target for novel immunotherapeutics in PLWH.

319 EVALUATION OF HIV-SPECIFIC T CELL RESPONSE IN BEAT2 CLINICAL TRIAL

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Background: Passive administration of HIV-1 broadly neutralizing antibodies (bNAbs) can achieve durable viral suppression when replacing ART. Previous studies have suggested that ART substitution with bNAb administration can have a vaccinal effect on HIV-specific T cells, increasing response frequencies and improving functional properties during bNAb-mediated suppression. Here, we evaluated whether such a vaccinal effect occurred in the BEAT2 clinical trial, which tested a 26-week combination of bNABs (3BNC117 and 10-1074) and peg-IFN-α2b (IMM-Tx) off-ART, followed by an off-IMM-Tx follow-up non-intervention ATI (non-int. ATI).
Methods: Cryopreserved peripheral mononuclear cells were obtained from the BEAT2 study (NCT03588715) in which baseline bNAb-sensitive PLWH received 29 weekly doses of peg-IFN-α2b (1.5µg/kg) (4 wks on ART and 26 wks off ART), and seven IV infusions of the bNAbs 3BNC117 and 10-1074 (30 mg/kg during the 26 wks off ART). Ten participants received combined IMM-Tx, and one received only bNAbs infusions. Activation-induced marker (AIM) assay and flow cytometry were used to quantify HIV-specific immune responses in all 11 donors at several time points, including baseline (on ART), after 4x weekly peg-IFN-α2b on ART, after 26 weeks of IMM-Tx (7 bNABs infusions plus peg-IFN-α2b), and during the final non-int. ATI. HIV1-specific CD4+ or CD8+ T cells were identified as CD69+PDL1+ or CD69+CD137+ or PDL1+CD137+ after stimulation against HIV-1 Consensus B Gag peptide pool.
Results: We found no increase in Gag-specific CD4+ and CD8+ T cell responses during IMM-Tx (with or without peg-IFN-α2b) compared to baseline in most donors; increased CD8+ responses after peg-IFN-α2b were observed in a single participant. However, we did find an increase in the proportion of Gag-specific CD4+ and CD8+ T cells in 4 out of 11 individuals during the post-IMM-Tx non-int. ATI compared to earlier time points. These individuals showed sustained control of viremia (Viral load 20 c/ml for 3 participants and < 2000 c/ml for 1), suggesting an association between emerging T cell response and control of the viremia.
Conclusion: We found no detectable change in HIV-specific T cell responses after 26 weeks of IMM-Tx with 3BNC117+10-1074 bNAB plus peg-IFN-α2b immunotherapy; however, an increase in Gag-specific T cell responses was associated with viral control following the end of IMM-Tx in a subset of persons, suggesting a potential link between IMM-Tx and T cell-mediated responses in viral suppression.

320 ONE-YEAR TREATMENT WITH PONATINIB INDUCES SUSTAINED CYTOTOXIC ACTIVITY AGAINST HIV

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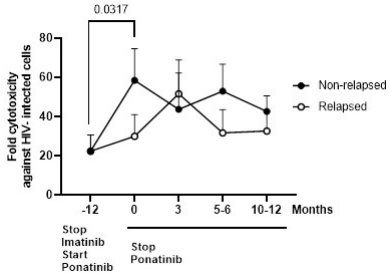
Background: Treatment with tyrosine kinase inhibitors (TKIs) protects CD4 cells from HIV infection, inducing functional cytotoxic populations that eliminate HIV-infected cells. PLWH on ART and dasatinib present reduced reservoir that is resistant to reactivation. We evaluated the persistence of HIV antiviral activity elicited in PBMCs of individuals with chronic myeloid leukemia (CML) after one-year treatment with ponatinib.
Methods: Nine participants of Phase II clinical trial NCT04043676 were recruited. They achieved deep molecular response against CML after 14 (IQR 5.5-15.5) years of treatment with imatinib before interruption and then received one-year consolidation treatment with ponatinib 15 mg/day. Blood samples were taken before starting ponatinib (t=-12 months), after one year of treatment (t=0), and 3, 6 and 12 months after interruption. PBMCs ntiviral activity was evaluated by measuring caspase-3 activity of NL4.3_wt-infected TZM-bl cells. Cytotoxic cell populations were characterized by flow cytometry.
Results: 1) 5 participants (55.5%) did not relapse from CML 12 months after ponatinib interruption (Non-relapsed), while 4 participants (44.4%) relapsed after 5.5 months (IQR 4.25-6.75) of ponatinib interruption (Relapsed). 2) PBMCs from Non-relapsed showed 2-fold increased antiviral cytotoxicity (p=0.0317) after 1-year of ponatinib, in comparison with Relapsed (Figure). Cytotoxic activity was similar in both groups 3-months after interruption and remained increased 1.7- and 1.3-fold for 5.5 and 11 months, respectively, in Non-relapsed after ponatinib withdrawal. 3) Degranulation activity (CD107a+) of CD8 was increased 4.08-fold (p=0.0317) in Non-relapsed and it was maintained 3-months after interruption. 4) CD3+CD8-TCRgd+ cells increased in both groups (p=0.0330) since treatment withdrawal but their degranulation capacity was only significantly increased 3.3-fold (p=0.0078) after ponatinib withdrawal in Non-relapsed. 5) NK cell count (CD3-CD56+) sustainably increased in Non-relapsed (p=0.0039); degranulation capacity of NKT cells (CD3+CD56+) was increased in Non-relapsed (p=0.0078).
Conclusion: Potent, sustained cytotoxic antiviral response against HIV-infected cells was induced after one-year treatment with ponatinib in non-relapsed individuals. Temporary intensification treatment with TKIs such as ponatinib could stimulate the antiviral response in PLWH during cure strategies.
Figure 1: Cytotoxic activity against HIV-infected cells of PBMCs from individuals with CML who were treated with ponatinib for one year as consolidation treatment before interruption



321 DECREASED HIV-SPECIFIC POLYFUNCTIONAL RESPONSES FOLLOWING DIPYRIDAMOLE TREATMENT

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Background: Decreases in extracellular adenosine (ADO) production are associated with increased inflammation and immune activation in ART-treated people living with HIV (PWH). We previously showed that 12 weeks (w) of treatment with dipyridamole (DP), which increases extracellular ADO levels, decreased CD8+ T cell activation in PWH. Here, we investigated if the decrease in activation also affected HIV-specific T cell responses.
Methods: PWH with viral suppression on ART were randomized to 12w of DP vs placebo (PL). Peripheral blood mononuclear cells were obtained pre- and post- DP treatment. Using flow cytometry, we evaluated changes in Gag- and Env-specific polyfunctional T cell responses (CD107a, TNFα, IFNγ, IL2, Granzyme B). We measured purine levels, soluble markers of inflammation, T cell immune activation (HLA-DR/CD38+) and cell cycling (Ki-67), and residual viremia by single copy assay to determine whether immune responses were associated with these parameters (using Spearman).
Results: Twenty of 40 participants enrolled (9 DP, 11 PL) had available specimens for this substudy (90% male; median age 57; median CD4+ 673 cells/mL; median 17 years on ART). There was a significant decrease in Gag-specific (% change from baseline (BL) to w12 -63.18% DP vs -28.14 PL; p< 0.001; Mann Whitney) and Env-specific (-57.5% DP vs -16.0% PL; p=0.025) CD4+ polyfunctional response (2 or more immune mediators expressed). No differences in HIV-specific CD8+ T cell responses were observed. Higher levels of inosine, a surrogate of ADO, at w 12 was associated with decreased CD4+ Gag-specific polyfunctional responses at w12 compared to BL (r= -0.56; p=0.04). Although there were no overall differences in BL to w 12 changes in cell cycling, change in the frequency of CD4+ and CD8+ cell cycling positively correlated

with change in Gag-specific CD4+ polyfunctional responses and Env-specific CD8+ polyfunctional responses, respectively (r=0.52, p=0.01 and r= 0.55; p=0.01). There were no associations between HIV-specific polyfunctional T cell and frequencies of activated T cells, levels of soluble inflammatory markers or residual viremia.

Conclusion: Increases in ADO production following treatment with DP were associated with reductions in HIV-specific CD4+ T-cell responses in this substudy. Although the clinical implications of this finding are unknown, trials of interventions targeting immune activation in PWH should evaluate their impact on HIV-specific immune responses.

322 URACIL TREATMENT DOES NOT INCREASE SUSCEPTIBILITY TO RECTAL SIV INFECTION

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Background: The intestinal microbiome of men who have sex with men (MSM) is distinct as compared to non-MSM and is suggested to increase susceptibility to rectal HIV infection. Indeed, we recently demonstrated that dysbiosis-associated disruptions in host antimicrobial immunity increase susceptibility to rectal SIVmac239X in rhesus macaques (RMs; Macaca mulatta). Central to the susceptibility-associated antimicrobial network is DUOX2 – an epithelial sensor that catalyzes reactive oxygen species (ROS) production upon sensing pathobiont-derived uracil. We hypothesize that uracil bioavailability may increase susceptibility to rectal HIV.

Methods: RMs were treated daily with (n=6) or without (n=8) oral uracil at 250 mg/m^2. Blood, mesenteric lymph nodes (MLN), stool, and intestinal biopsies were taken before and 28 days into treatment. Animals were challenged intra-rectally with 4 TCID50 of SIVmac239X 56 days into treatment and every 2 weeks thereafter. We assessed immunity by flow cytometry and high throughput quantitative RT-PCR (NanoString) and the intestinal microbiome by 16S Illumina sequencing.

Results: Oral uracil treatment reduced IFNγ, IL-17, IL-22, and TNFα expression by peripheral CD4+ and CD8+ T-cells. Isolated changes in cytokine expression were observed among MLN, jejunal, and rectal T-cells. Although uracil had limited effect on rectal T-cell function or transcript expression, we observed an increase in ROS production by rectal epithelial cells. Among the fecal microbiome, uracil-responsive taxa were largely restricted to *Prevotellaceae*, *Lachnospiraceae*, *Lactobacillaceae*, and *Ruminococcaceae*. No differences in time to infection or transmitter/founder variant acquisition were observed between control and treated RMs.

Conclusion: Oral uracil treatment in RMs does not alter susceptibility to SIV acquisition. Although treatment induced significant shifts in peripheral T-cell function, these effects were not systemic, suggesting limited intestinal dissemination. Future studies which evaluate the effects of intestinal uracil on host immunity should consider alternate delivery methods.

323 HETEROLOGOUS ChAd/samRNA SIV VACCINE INDUCES ROBUST T CELL RESPONSES IN MACAQUES

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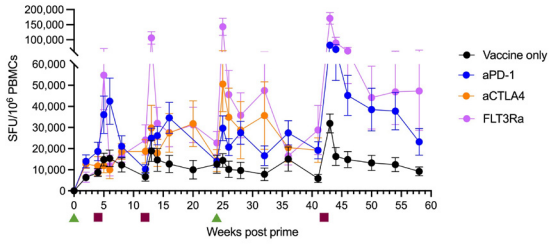
Background: Since the latent HIV reservoir persists on antiretroviral therapy (ART), additional interventions are needed to achieve remission and potentially HIV cure. Therapeutic vaccination to enhance HIV-specific T cell immunity is a focal strategy in the pursuit of the cure. Here, we evaluated safety and immunogenicity of a novel heterologous SIV vaccine in combination with immune modulators in macaques.

Methods: Naive rhesus macaques (n=6/group) were immunized with a chimpanzee adenovirus (ChAd) and self-amplifying mRNA (samRNA)-based vaccine alone or in combination with either anti-PD-1 antibody (aPD-1), anti-CTLA4 antibody (aCTLA4) or FLT3R agonist (FLT3Ra). ChAd and samRNA vectors encoding full length SIV Gag, Pol and Env antigens were administered intramuscularly on weeks 0 & 24 (ChAd) and 4, 12 & 42 (samRNA). aPD-1 and aCTLA4 were dosed subcutaneously and/or intravenously concomitant with immunization. FLT3Ra was dosed intravenously 1 week prior to immunization. Immunogenicity was characterized by IFNγ ELISpot and multi-parameter flow cytometry.

Results: All regimens were well tolerated with transient small increases in inflammatory markers and body temperature. The vaccine elicited strong IFNγ ELISpot responses 4 weeks post-ChAd prime (8,724±1,845 SFU/10^6 PBMCs, mean±SEM), which were further augmented by boosts with samRNA (mean 1.8, 3.7, and 11.5-fold increase post each boost, respectively) and ChAd (1.7-fold increase). The responses peaked at 32,234±4,433 SFU/10^6 PBMCs (mean±SEM) and were durable through at least 16 weeks post last immunization (range 3,398 – 15,360 SFU/10^6 PBMCs). Combination with either aPD-1, aCTLA4 or FLT3Ra further augmented mean peak T cell response magnitude by 2.8, 2.4 and 5.7-fold, respectively. When assessed using antigen-derived overlapping peptides, the breadth of responses at week 13 was greater in combination with aCTLA4 or FLT3Ra than with vaccine alone ($p < 0.05$). Vaccine alone elicited predominantly CD8+ T-cell responses (1.9% IFNγ+/CD8+ and 0.6% IFNγ+/CD4+, week 13), while FLT3Ra also robustly enhanced CD4+ T cell responses (2.0% IFNγ+/CD8+ and 3.5% IFNγ+/CD4+, week 13). T cell responses were polyfunctional (predominantly IFNγ+TNFα+) in all groups.

Conclusion: ChAd/samRNA heterologous SIV vaccine was well tolerated and induced robust and broad antigen-specific T cell responses. The immune responses were augmented by aPD-1, aCTLA4 or FLT3Ra warranting their further exploration as part of a combination therapeutic approach for HIV cure.

Figure 1. Strong and durable SIV-specific T cell response in rhesus macaques following vaccination with ChAd/samRNA is enhanced by co-administration of aPD-1, aCTLA4 or FLT3Ra. IFNgamma ELISpot, sum of Env, Pol and Gag overlapping peptide pools, background subtracted. Mean +- SEM. Green triangles represent ChAd immunizations and red squares represent samRNA immunizations.



324 CD40.HIVRI.Env VACCINE INDUCES STRONG AND DURABLE IMMUNE RESPONSES: ANRS VRI06 TRIAL

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Background: RV144 study identified anti-HIV Env V1/V2 binding IgG and Env-specific CD4 T cells as immune correlates of protection. We tested here a new way of antigen (Ag) delivery to improve vaccine immunogenicity by targeting Ag to CD40-expressing dendritic cells. CD40.HIVRI.Env vaccine is a fully humanized mAb fused to Clade C ZM96 Env. We hypothesized that administration of different doses of CD40.HIVRI.Env vaccine adjuvanted with TLR3 Poly-ICLC Hiltonol® will be safe and immunogenic.

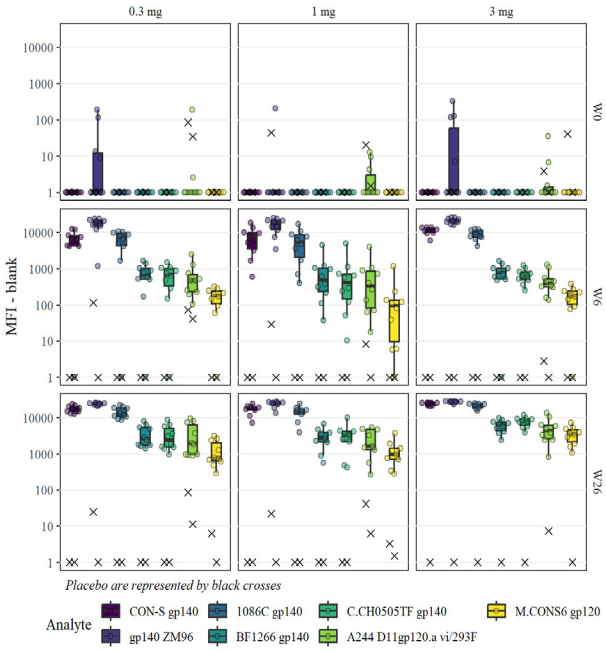
Methods: VRI06 is a first-in-human phase I, placebo-controlled, dose-escalation trial (NCT04842682) in France and Switzerland. Twelve healthy volunteers were included per group (randomized 5:1 active vs. placebo) to receive either 0.3, 1, or 3 mg CD40.HIVRI.Env SC with Hiltonol® (1mg) at weeks (W) 0, 4 and 24. Safety, immunogenicity (anti-Env and anti V1/V2 IgG assessed by binding antibody multiplex assay, Neutralizing Abs (nAbs), IgG functionality, T-cell responses) were evaluated at W6, W26 and W48.

Results: Thirty-six volunteers were enrolled (mean 34 years, 64% male). Vaccine was safe and well tolerated. Two SAE were not related to vaccination. IgG response rates (RR) against vaccine-matched (gp140 ZM96) and 6 mismatched gp140 and gp120 were 80-100% at W6 and 100% at W26 across groups. Magnitude of IgG responses (MFI) to Ags was high at all time points, peaked at W6 and/or W26 across groups (Figure) and remained flat or decreased slightly at W48. At W26, the RR to heterologous V1V2 Ags ranged from 60-100% (92TH02), 70-80% (CE1086), 50-100% (CaseA2) across groups. IgG3 anti-Env and

V1/V2 response kinetics were similar, although lower than total IgG. nAb IC_{50} titers against Tier1 MW965.26 were detected in 50 (0.3 mg group) and 100% (1 and 3 mg groups) vaccinees at W26. Polyfunctional Env-specific CD4 T cells (IL-2+ or IFN-g+ or TNF-α+) were detected in all vaccinees at all time points. At W26, median (%) [IQR]) were 0.14 [0.12-0.23]; 0.3 [0.19-0.44]; 0.4 [0.32-0.53] in 0.3, 1, 3 mg groups, respectively ($P < 0.05$ for all comparisons to W0).

Conclusion: CD40.HIVRI.Env was safe and induced early, potent and durable anti-Env and V1/V2 IgG and polyfunctional CD4 T-cell responses, markers associated with reduced risk of infection in RV144. Co-administration of CD40.HIVRI.Env with DNA HIV-PT-123 is currently assessed in additional groups of the trial. CD40-DC targeting Env-based vaccines may be instrumental in strategies combining vaccine regimens, particularly Env protein-based vaccines, to induce durable responses.

Magnitude of IgG responses across groups and time points



325 THE ROLE OF MYELOID-DERIVED SUPRESSOR CELLS IN STI-MEDIATED ENHANCED HIV INFECTION

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Background: Sexually transmitted infections (STIs) may affect the development and pathogenesis of other STIs, such as enhanced HIV infection. Understanding the mechanisms by which STIs enhance early events in HIV acquisition and replication would allow designing preventive strategies. Myeloid-derived suppressor cells (MDSCs) are a diverse population of immature myeloid cells that may exert immune-suppressive effects on other immune cells. Some of the cytokines produced during STIs have been involved in MDSC development. We therefore hypothesize that MDSCs expand in response to a primary STI, thereby increasing the risk of acquiring a secondary STI such as HIV by suppression of the mucosal immune response.

Methods: We obtained cervical samples from healthy women (HC, n=18), or women with acute *Chlamydia trachomatis* infection (CT, n=13), Human Papillomavirus infection (HPV, n=20), Bacterial Vaginosis (BV, n=14), or co-infected (n=12). In these samples, we assessed the cellular immune composition by flow cytometry and the level of eight cytokines. Additionally, cervical tissue (n=11) was obtained from patients undergoing non-oncogenic cervical surgery. Cervical tissue was *ex vivo* exposed to CT or GM-CSF+IL-6 cytokines to assess MDSC expansion and HIV infection by flow cytometry.

Results: In cervical samples from patients, we found higher frequencies of HLA-DR¬-CD14- MDSCs in CT compared to HC, whereas there was a trend towards higher levels of HLA-DR^{dim}CD14+ MDSCs in BV patients ($p=0.06$). Also, cervical BV samples showed higher levels of several MDSC-associated cytokines including M-CSF, IL-1β, GM-CSF, VEGF-A, and TGF-β, whereas CT samples showed increased levels of M-CSF. *Ex vivo* exposure of cervical tissue to CT or GM-CSF+IL-6 enhanced subsequent HIV infection (n=7-9, $p=0.02$ and 0.003, respectively). Moreover, exposure to CT showed a trend towards an increase of the proportion of CD15+ MDSC cells ($p=0.07$) and increased expression of suppressive mediators (e.g. PD-L1).

Conclusion: Distinct cytokine microenvironments and MDSC phenotypes may be involved based on the pathogen in promoting immune suppression in cervix in patients with STI. The enhancement of HIV infection after CT infection and the concomitant increase in MDSCs with a potentially suppressive phenotype, suggest a role for MDSCs in increasing the risk of secondary infection. Future efforts will include high-dimensional analyses of flow cytometry data and exploring the suppressive capacity of these cervical MDSCs.

326 BEAT2: PEG-IFN-ALPHA + 3BNC117 & 10-1074 REBOUND VIRUS PHENOTYPE AND EVOLUTION

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Background: BEAT2 (NCT03588715) tested combined peg-IFN-α2b with two broadly neutralizing antibodies (bnAbs) (3BNC117 and 10-1074) at antiretroviral treatment interruption (ATI) in 14 people living with HIV. Entry criteria included bnAb sensitivity by PhenoSense HIV mAb Assay ($IC_{90} < 2.0$ µg/mL (3BNC117) and < 1.5 µg/mL (10-1074)). Primary clinical outcomes are presented elsewhere; here, we report the plasma rebound virus phenotype and evolution.

Methods: HIV-1 env single genome sequencing (SGS) was performed at rebound and longitudinally through ATI. Rebound lineage consensus Envs were tested for neutralization sensitivity by TZM.bl assay and compared with PhenoSense results. Two participants withdrew during the study, 12 were analyzed.

Results: SGS of first detectable rebound virus (n=210 sequences) revealed a median of 1 (range 1-3) reactivating virus populations. Two participants rebounded with high levels of both bnAbs during the 26-week period of immunotherapy. Early rebound Envs had complete resistance to 10-1074 (IC_{90} >10µg/ml), and increased resistance to 3BNC117 compared to entry criteria (median IC_{90} of 5.9 µg/ml). Eight participants rebounded after cessation of immunotherapy, between 26 and 30 weeks post-ATI, with waning 10-1074 and 3BNC117 plasma levels (median of 71.0 and 8.1 µg/ml, respectively). Rebound Envs in 6/8 participants were resistant to 10-1074, while 5/8 retained sensitivity to 3BNC117 (median IC_{90} of 1.52 µg/ml). Finally, 2 participants with rebound >50 weeks post-ATI as both bnAb levels fell to < 5 µg/ml, retained sensitivity (median IC_{90}s=0.63 to 10-1074 and 0.28 µg/ml to 3BNC117). Rebound Env neutralization sensitivities largely agreed with PhenoSense cutoffs obtained from similar samples (100% concordance for 10-1074, 92% for 3BNC117). Rebound Env resistance to 3BNC117 correlated with time to rebound ($r_s=0.82$, $p=0.013$) and weakly correlated with concurrent 3BNC117 plasma levels ($r_s=0.67$, $p=0.069$). Longitudinal sequencing over ATI showed increasing env diversity via within-lineage evolution and addition of new rebound lineages, both of which led to further increases in resistance to 3BNC117 (median 2.5-fold increase in IC_{50}).

Conclusion: Parallel analyses of rebound Env sensitivity to administered bnAbs using independent research and commercial assays gave similar results. Rebound Env lineages revealed a high frequency of resistance to both bnAbs (10-1074 > 3BNC117), which increased over the duration of ATI and correlated with time to rebound and diminishing bnAb levels.

327 TIGIT BLOCKADE RESTORES FUNCTIONAL NKG2C+ NK CELLS AND LIMITS SPREAD OF HIV-1 EX VIVO

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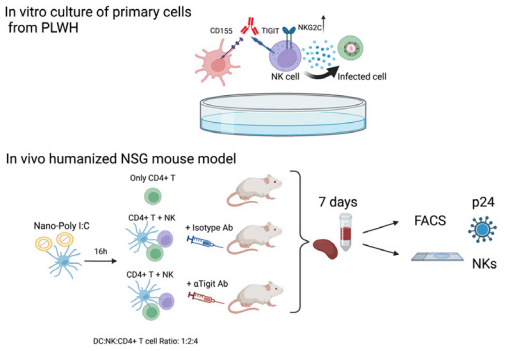
Background: Expression of TIGIT on Natural Killer (NK) cells from People living with HIV (PLWH) limits induction of adaptive NKG2C+ CD57- cells and promotes a dysfunctional state after stimulation with dendritic cell (DC) immunotherapy. Here, we asked whether blockade of TIGIT enhances functional adaptive NKG2C+ NK cells *in vitro* and *in vivo*.

Methods: Monocyte-derived dendritic cells (DCs) from n=9 PLWH on ART and activated with nanoparticle-loaded Poly I:C (Nano-PIC) were cultured with autologous NK cells in the presence of anti-TIGIT or isotypic control mAbs. Reduction of proportions of HIV-1 p24+ cells CD4+ T cells in the presence of NK cells, Romidepsin and Raltegravir was evaluated by FACS. *In vivo* efficacy of TIGIT blockade on NK cells was addressed by transplanting n=42 immunodeficient NSG mice with CD4+ T cells from the same PLWH alone (n=14) or with NK cells and Nano-PIC DC in combination with either anti-TIGIT (n=14) or Isotypic mAbs (n=14) in three independent experiments. After 7 days, mice were sacrificed and proportions of circulating human CD45+ p24+ CD4+ T cells were analysed by FACS. In addition, histological distribution of p24+ infected cells in the spleen was analysed by confocal microscopy.

Results: Blockade of TIGIT combined with Nano-PIC DC enhanced the ability of NK cells from PLWH to significantly reduce by 70% the proportions of autologous HIV-1 p24+ CD4+ T cells *ex vivo* compared to cells receiving an Isotypic mAb (p=0.0078). Importantly, i.p. administration of anti-TIGIT into NSG mice xenotransplanted with CD4+ T cells from PLWH and autologous NK cell and Nano-PIC-DC immunotherapy led to a more significant reduction of p24+ cells (mean reduction 57%, p= 0.0019) within human circulating CD4+ T cells compared to mice receiving only CD4+ T cells, in contrast to mice receiving isotypic control mAb (mean reduction 23.6%, p=0.0479). In addition, significantly lower areas of p24+ foci (Median 1,452 mm^2 vs 1,766 mm^2; p=0.0078) as well as a trend to larger areas free of infection (Median 1,296.308 mm^2 vs 862.210 mm^2) were detected in the spleen of mice injected with aTIGIT compared to Isotype mAbs. Interestingly, control of spread HIV-1 infection in spleen was associated with a reduction of CD57 expression (38% aTIGIT vs 63% Isotype mAbs; p=0.0011) on adaptive NKG2C+ cells in this tissue.

Conclusion: Collectively, combination of DC immunotherapies and TIGIT blockade is a promising strategy to enhance functional NKG2C+ NK responses and limit HIV-1 replication in tissue *in vivo*.

Schematic Representation of *in vitro* and *in vivo* models used to study impact of modulation of TIGIT in functional restoration of NKG2C+ NK cells



328 GERMLINE-TARGETING ENV TRIMER ELICITS bNAb PRECURSORS IN INFANT, NOT JUVENILE MONKEYS

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Background: An HIV vaccine that induces protective, broadly-neutralizing antibodies (bnAbs) prior to sexual debut is critical to eliminate the ~410,000 new infections annually that occur among youth aged 15 to 24 years worldwide, and provide lifelong immunity. Recent work has established that HIV-infected children develop bnAbs earlier and at a higher frequency than adults, suggesting that the infant immune landscape may be more amenable to the induction of bnAb B cell lineages by vaccination than that of adults. The goal of this study was to assess the ability of bnAb germline-targeting BG505 SOSIP trimers to induce precursor bnAb responses in early life.

Methods: Infant (n=5) and juvenile (n=4) rhesus macaques (RMs) received 3 immunizations of the germline-targeting BG505 GT1.1 SOSIP trimer (50mg) with the 3M-052-SE adjuvant 6 weeks apart. All RMs were then boosted 12 weeks later with the wildtype BG505.664 SOSIP trimer 3 times in 6-month intervals. Vaccine elicited antibody responses were monitored through 1.5 years.

Results: BG505 GT1.1 SOSIP trimer immunization induced consistently higher magnitude vaccine antigen-specific IgG responses after each immunization in infants compared to juvenile RMs. BG505 SOSIP immunization also induced similar plasma tier 2 autologous virus neutralization responses in both age groups, which were maintained through 1.5 years. Notably, by week 80 three GT1.1 SOSIP-immunized infants exhibited a plasma neutralization signature reflective of CD4 binding site-specific (CD4bs) bnAb precursor development, while none of the juvenile RMs had developed this response. Electron-microscopy based epitope mapping of polyclonal plasma confirmed the presence of CD4bs-targeting antibodies in the majority of immunized infant RMs.

Conclusion: Our data demonstrates that sequential immunization of infant RMs with germline-targeting and wildtype BG505 SOSIP trimers can induce high serum neutralizing antibody titers and CD4bs bnAb precursors, while these responses were not detectable in vaccinated juvenile RMs. Our results support observations in human studies suggesting that the infant immune environment is better suited for induction of plasma HIV bnAb responses.

329 DYNAMICS AND ROLE OF TOX+ TCF1+ CD39+ CD8 T CELLS IN LYMPHOID TISSUE IN SIV INFECTION

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Background: CD8 T-cell responses to HIV/SIV infection critically contribute to control of viremia, but lymph node (LN) CD8 T-cells have been shown to be phenotypically and functionally distinct from those in blood.

Methods: To characterize the unique populations in LN, we obtained LN samples from rhesus macaques during early chronic SIV infection (D42 post-infection) and performed flow cytometry, scRNA-seq and imaging to explore the dynamics of LN CD8 T-cells expressing Tox, TCF1 and CD39, three well-described markers delineating exhausted, stem-like and terminally-differentiated populations.

Results: Tox is upregulated after SIV infection and primarily expressed in PD-1+ and TIGIT+ cells. Notably, we observed high expression of Tox on a previously undescribed TCF1+CD39+ population, distinct from the known TCF1+CD39- stem-like and TCF1-CD39+ effector/exhausted CD8 T-cells, that significantly expands after infection. These TCF1+CD39+ cells expressed inhibitory receptors, intermediate levels of Ki-67, and are uniquely high in GzmK but low in GzmB, a profile consistent with a precursor effector cell. After SIV peptide stimulation, TCF1+CD39+ cells degranulated at similar levels to TCF1-CD39+ cells but produce less IFNγ. scRNA-seq of SIV-specific CD8 T-cells revealed an intermediate profile of TCF1+CD39+ cells between the stem-like TCF1+CD39- cells and the differentiated TCF1-CD39+ cells. Importantly, a higher frequency of both Tox+ (p< 0.0001) and TCF1+CD39+ (p=0.0003) CD8 T-cells in LN at d42 p.i. was strongly associated with lower plasma viremia, lower levels of cell-associated SIV-DNA (Tox p=0.0007; TCF1+CD39+ p=0.01) and better CD4 preservation (Tox p=0.02; TCF1+CD39+ p=0.065). After more than 1 year of ART, the level of TCF1+CD39+ LN CD8 T cells is associated with lower frequency of CD4 T cells harboring intact SIV-DNA (IPDA). Investigations into potential mechanisms contributing to viral control revealed that TCF1+CD39+ cells expressed elevated levels of CXCR5 compared to traditional effector cells, and expression of CXCR5 within TCF1+CD39+ cells was associated with lower plasma viremia. Imaging analysis confirmed increased presence of TCF1+Tox+ CD8 T-cells within B cell follicles compared to TCF1-Tox+ and TCF1+Tox- cells.

Conclusion: Overall, these data are consistent with a unique precursor effector CD8 T-cell population that expands in LN after SIV infection, have a better ability to access the LN BCF, and is associated with increased viral control and reduced disease progression.

330 SPATIAL MAPPING OF SIV-INFECTED RHESUS MACAQUE LYMPH NODE ENVIRONMENT DURING REBOUND

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Background: Lymphoid tissues are important sites of the HIV-1 reservoir that contribute to viral rebound after analytical treatment interruption (ATI). We hypothesize that different immune cell subsets exhibit distinct immune signatures during early versus late viral rebound. Understanding these immune signatures and their respective immune cell subsets throughout viral rebound provides mechanisms for immune control.
Methods: From 2 female rhesus macaques intravaginally infected with SIV_{mac239} and treated with suppressive antiretroviral therapy (ART) for 6 months from 4 days post-challenge, we obtained 2 mesenteric lymph nodes each at 4 days and 24 days after ATI. These lymph nodes were SIV+ by targeted PET-CT. To resolve lymphoid cell heterogeneity and their respective immune responses, particularly in the context of spatial interactions, we applied deterministic barcoding in tissues (DBiT-seq) to profile transcriptomes from 10 µm x 10 µm pixels. This state-of-the-art platform allows the closest estimate of single-cell transcriptomes at a genome-wide scale compared with currently available platforms. We used machine learning algorithms to assign cell type identities to pixels, created spatial maps overlaying the pixels on tissue images, and determined gene set enrichment in early versus late viral rebound with GSEA.
Results: To identify early and late viral rebound immune signatures, we profiled 9822 10 µm x 10 µm pixels. We captured a median of 265 RNA reads and 163 genes per pixel. At 4 days after ATI, we found enrichment in gene signatures for Tregs (GSE37605, leading edge genes: *IGFBP6*, *TAGLN*, *FHL1*, *MGP*, *HSBP1*), cytotoxic macrophages (GSE26912: *LPL*, *FASN*, *RRAS*, *S100A1*, *SPARC*; GSE22935: *MYL9*, *GSN*, *LPL*, *FABP4*, *WFDC1*), Tfh cells (GSE21379: *FHL1*, *DGAT2*, *S100A1*, *LAMB2*, *AKAP12*), and expanding CD4+ T cells (GSE32533: *HSBP6*, *IGF2*, *MLIXPL*, *CRIP2*, *NEXN*; GSE9316: *GSN*, *TNXB*, *VCL*, *LDB2*). At 24 days after ATI, we found upregulated gene signatures of stimulated neutrophils (GSE2405: *ACTG1*, *C3*, *CORO1A*, *CLU*, *RPL35*) and vaccine responses to Leishmania (Osman: *CXCL9*, *CD74*, *CTSH*, *LYZ*, *C3*), VEEV (Erwin Cohen: *LYZ*, *IFI27*, *RPL35*, *IFI6*, *CD52*), influenza (Nakaya: *CTSH*, *ITGB2*, *SPN*, *PSAP*, *CD84*, *LCK*), and HIV-1 (Zak MRKAd5: *C1QB*, *IFI27*, *IFI6*, *TNFRSF1B*, *TCIRG1*).
Conclusion: We identified CD4+ T cell and macrophage signatures early and immune effector cell responses later during viral rebound in lymph nodes. Further spatial analysis and validation could provide targets to improve immune control and function during rebound.

331 LYMPH NODE IMMUNE MICROENVIRONMENT FOLLOWING ART INITIATED DURING ACUTE HIV INFECTION

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Background: Persistence HIV reservoirs in lymphoid tissues is one of the main barriers to cure. We and others have shown that follicles within secondary lymphoid tissues are a major site of HIV persistence during antiretroviral therapy (ART).
Methods: We used spatial transcriptomics and several imaging approaches to spatially define cellular subsets and molecular pathways associated with HIV persistence in LNs. Study participants included 10 young women (16 to 24 years old) who initiated therapy in Fiebig stages I-V, and 10 age matched women who started therapy after Fiebig V. Excisional LN were obtained after a year or more on uninterrupted ART.
Results: Using multicolor immunofluorescence staining and *in situ* hybridization we were able to detect HIV Gagp24 protein and Gag-pol RNA in GC T follicular helper cells (GCTFH) and macrophages in 18 of 20 individuals studied. GCs had greater amounts of HIV Gag p24 protein and Gag-pol RNA compared to extrafollicular areas (p=0.0001). Very early ART was associated with more functional (proliferative) HIV-specific CD8+ T cells compared to late treated donors (p=0.002). However, most of the CD8+ T cells were spatially segregated fromHIV harbouring GCTFH and macrophages. The few CD8+ T cells within GCs lacked expression of cytolytic molecules granzyme B and perforin. Spatial transcriptomic analysis revealed lower expression of adaptive immune response genes in GCs harbouring HIV antigens relative to adjacent GCs without HIV antigens. Inversely, immunoregulatory genes namely, *Foxp3* and *Tbet (tbx21)* were upregulated in HIV positive GCs relative to HIV negative GCs.
Conclusion: We show that persistent HIV transcription in GCs generates spatially defined immunosuppressive microenvironment. These data suggest that reversing immunosuppressive environment within HIV infected GCs is critical to the development of CD8+ T cell-mediated strategies aimed at eliminating HIV infection in lymphoid tissue during ART.

332 DEVELOPMENT OF A LYMPHOID ORGAN-CHIP TO EVALUATE COVID VACCINE BOOSTING STRATEGIES

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Background: Secondary lymphoid organs provide the adequate microenvironment for the development of antigen (Ag)-specific immune responses. The tight collaboration between CD4+ T cells and B cells in germinal centers is crucial to shape B cell fate and optimize antibody maturation. Dissecting these immune interactions remains challenging in humans, and animal models do not always recapitulate human physiology. To address this issue, we developed an *in vitro* 3D model of a human lymphoid organ. The model relies on a microfluidic device, enabling primary human cells to self-organize in an extracellular matrix (ECM) under continuous fluid perfusion. We applied this Lymphoid Organ-Chip (LO chip) system to the analysis of B cell recall responses to SARS-CoV-2 antigens.
Methods: We used a two-channel microfluidic Chip S1® from Emulate, where the top channel is perfused with antigen (spike protein or SARS-CoV-2 mRNA vaccine), while the bottom channel contains PBMC (n = 14 independent donors) seeded at high-density in a collagen-based ECM. Immune cell division and cluster formation were monitored by confocal imaging, plasmablast differentiation and spike-specific B cell amplification by flow cytometry, antibody secretion by a cell-based binding assay (S-flow).
Results: Chip perfusion with the SARS-CoV-2 spike protein for 6 days resulted in the induction $CD38^{hi}CD27^{hi}$ plasmablast maturation compared to an irrelevant BSA protein (P< 0.0001). Using fluorescent spike as a probe, we observed a strong amplification of spike-specific B cell (from 3.7 to 140-fold increase). In line with this rapid memory B cell response, spike-specific antibodies production could be detected as early as day 6 of culture. Spike perfusion also induced CD4+ T cell activation (CD38+ ICOS+), which correlated with the level of B cell maturation. The magnitude of specific B cell amplification in the LO chip was higher than in 2D and 3D static cultures at day 6, showing the added value of 3D perfused culture for the induction of recall responses. Interestingly, the perfusion of mRNA-based SARS-CoV-2 vaccines also led to strong B cell maturation and specific B cell amplification, indicating that mRNA-derived spike could be expressed and efficiently presented in the LO chip.
Conclusion: We developed a versatile Lymphoid Organ-Chip model suitable for the rapid evaluation of B cell recall responses. The model is responsive to protein and mRNA-encoded antigens, highlighting its potential in the evaluation of SARS-CoV-2 vaccine boosting strategies.

333 AGING IMPAIRS HIV RESPONSES IN NEUTROPHILS FROM BLOOD AND THE FEMALE GENITAL TRACT

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Background: Women acquire HIV through sexual transmission, with HIV incidence increasing in older women (>50 years). However, low transmission rates per sexual act indicate local immune protection against HIV acquisition at the main portal of entry. We demonstrated that genital neutrophils respond to HIV stimulation with Neutrophil Extracellular Trap (NET)-release to inactivate the virus. However, the mechanisms involved in HIV recognition, molecular events that lead to NET-release, and how aging affects this protective mechanism are unknown.
Methods: Human neutrophils were purified from blood (n=36) and genital tract tissues (n=45) after digestion of hysterectomy samples (endometrium, ectocervix and endocervix). Neutrophils were stimulated *in vitro* with

GFP-labeled HIV to induce NET-release and quantified by time-lapse imaging and confocal microscopy. To study HIV-recognition and signaling mechanisms, prior to HIV stimulation, neutrophils were incubated with endosomal TLR7/8 inhibitors; Rhod-3 AM to stain cytosolic calcium; and Annexin V dye to assess cell death.

Results: Early NET-release (15min) was reduced in post- compared to pre-menopausal women (p=0.05) and progressively declined with aging (r=-0.6; p< 0.01). In pre-menopausal neutrophils, HIV stimulation significantly increased cytosolic calcium levels immediately after stimulation (p< 0.01), but HIV-induced calcium response declined with age (r=-0.6; p=0.02). In post-menopausal women, NET release was preferentially triggered by endosomal TLR recognition of HIV-RNA and TLR8 and TLR7 inhibition reduced early (15min) and late (2h) NET-release respectively. Reduced NET-release in post-menopausal women was not due to increased cell death. However, we identified a subset of NETs that incorporated Annexin V, were preferentially released at late time points by blood neutrophils, but not tissue neutrophils, and uniquely incorporated lactoferrin, with known proinflammatory properties.

Conclusion: HIV-induced NET-release is delayed and progressively declines in post-menopausal neutrophils from blood and genital tissues. In younger women, HIV triggers rapid cytosolic calcium increase, but this response is compromised with aging, leading to preferential endosomal TLR7/8 induced NET-release in post-menopausal women. Importantly, we identified differential responses in blood and tissue, with blood neutrophils more prone to release proinflammatory NETs, highlighting the need to study genital neutrophils to develop prevention strategies.

334 RAPID EXPANSION OF MEMORY NK CELLS IN ACUTE HIV INFECTION WHICH PERSIST DESPITE ART

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Background: HIV infection is associated with NK cell dysfunction including expansion of memory NK cells with heightened inflammatory and cytotoxic function which persist despite antiretroviral therapy (ART). We investigated the timing of NK cell activation following acute HIV infection (AHI) and explored the impact of early ART initiation on these parameters.

Methods: PBMC and plasma samples were obtained from people with acute HIV (PWAH) in the RV254 cohort who initiated ART during Fiebig stages I, II, III or IV/V (n=8-10 in each). Immunophenotyping was performed at AHI (pre-ART) and 4, 12 and 48 weeks after ART-initiation. IgG antibodies to cytomegalovirus (CMV) antigens were assessed by ELISA. Participants were all men who have sex with men (MSM), median age 26.0 (IQR: 22.8-30.0) years and all achieved viral suppression after 48 weeks of ART. Samples from people without HIV (PWOH) enrolled in the RV304 study (n=10 MSM, median age 27.0 [23.8 – 38.5]) were analyzed for comparison.

Results: Proportions of memory NK cells (defined by absence of the Fcg-receptor signal transduction chain FceR1g) were significantly expanded in PWAH in all Fiebig stages pre-ART (pooled median 66% vs 25% for controls, p< 0.001). Memory NK cells were not different between Fiebig stages and were not altered by ART. Plasma antibodies to the immediate early CMV protein were elevated in PWAH in Fiebig III and IV/V (p< 0.03 for both), suggesting more frequent CMV reactivations secondary to HIV-induced immunosuppression. Proportions of memory NK cells were significantly negatively associated with HIV DNA in PBMC at diagnosis (p=0.04) and trended towards an association after 48 weeks of ART (p=0.08). NK cells were activated in PWAH in all Fiebig stages including stage I (CD69+; p=0.02 and HLA-DR+/CD38; p=0.04), whilst activation of CD4 and CD8 T cell became evident at Fiebig stages II or after. Suppressive ART significantly reversed T cell activation to levels comparable to PWOH after 48 weeks whilst proportions of activated HLA-DR+/CD38+ NK cells remained elevated irrespective of when ART was initiated.

Conclusion: NK cell activation and expansion of memory NK cells occurs very early during AHI, prior to T cell activation and CMV reactivation, and is not reversed by early ART. The association of memory NK cells with lower HIV DNA levels may suggest a role in HIV control. These findings have implications for the long-term morbidity of PWH on ART.

335 HIERARCHICAL CLUSTERING SHOWS B-CELL PERTURBATIONS INDEPENDENT OF HIV-2 VIRAEMIA

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Background: Time to AIDS in HIV-2 infection is approximately twice as long compared to in HIV-1 infection. Still, and despite reduced viraemia, HIV-2 infected individuals display signs of chronic immune activation. In HIV-1 infected individuals, the expansion of hyperactivated B-cells, characterized by the expression of the transcription factor T-bet, is driven by continuous antigen exposure. However, the contribution of viraemia to B-cell perturbations in HIV-2 infected individuals remains largely unexplored. Here we set out to determine if B-cell hyperactivation is viraemia dependent during HIV-2 infection, as it has been described for HIV-1 infection.

Methods: We used polychromatic flow cytometry to immunophenotype B-cells from HIV-1 infected (viraemic (n=8) and successfully ART treated (n=7) individuals), HIV-2 infected (viraemic (n=8) and treatment naïve aviraemic (n=12) individuals), and HIV seronegative (n=25) individuals from Guinea-Bissau. We performed consensus hierarchical cluster analysis on the flow cytometry data, using the FlowSOM R packages, to define the impact of HIV-1 or HIV-2 infections on the expansion or depletion of B-cell populations. Plasma proteins were quantified using an Olink Proteomics panel. Frequencies of identified B-cell populations were correlated with concentrations of Th1 associated proinflammatory cytokines.

Results: We observed increased frequencies of clusters containing hyperactivated T-bet^{high}CD95+CD27^{int} and proliferating CD95+T-bet+CD27+CD71+ memory B-cells in viraemic HIV-1 (p< 0.001 and p< 0.001, respectively), viraemic HIV-2 (p< 0.001 and p=0.014, respectively), and in treatment naïve aviraemic HIV-2 (p=0.004 and p=0.020, respectively) infected individuals compared to seronegative individuals. In contrast, these expansions were not observed in successfully treated HIV-1 infected individuals. Finally, the frequency of the hyperactivated Tbet^{high} memory B-cells showed a moderate to strong correlation with plasma concentrations of proinflammatory Th1-associated cytokines, most prominently TNF-α (r=0.686; p=0.001), IFN-γ (r=0.530; p=0.020), CXCL9 (r=0.619; p=0.005) and CXCL10 (r=674; p=0.002) in HIV-2 infected individuals.

Conclusion: In contrast to successfully ART treated HIV-1 infected individuals; treatment naïve aviraemic HIV-2 infected individuals showed B-cell perturbations. Our data therefore suggest that aviraemic HIV-2 infected individuals are likely to benefit from antiretroviral treatment.

336 EARLY ART TREATMENT PREVENTS B CELL LOSS AND DYSFUNCTION IN PEOPLE LIVING WITH HIV

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RV217 and RV254/RV304 study groups

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Background: B cell populations significantly decline 2 weeks after initial HIV-1 infection in the absence of ART. However, few studies have characterized longitudinal B cell phenotypic changes after early ART initiation. Here, we compare longitudinal changes in B cell activation and differentiation in PWH in the presence and absence of ART starting from early acute infection in both the periphery and mucosal compartments.

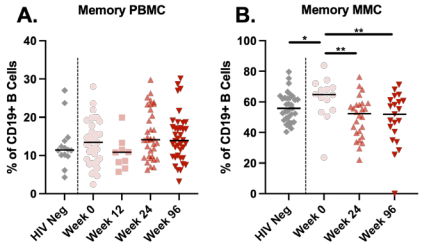
Methods: Specimens from participants in the RV217 Early Capture HIV Cohort (ECHO) and RV254 Acute HIV Infection (AHI) study were used to assess B cell changes in PWH who are therapy-naïve or treated during early AHI, respectively. Flow cytometry was employed to determine B cell counts and phenotypes in both peripheral blood mononuclear cells (PBMC) and mucosal mononuclear cells

(MMC) isolated from sigmoid biopsies at early and chronic infection time points including weeks 0 (AHI diagnosis), 2-4, 12, 24, and 52-96 after infection and in the presence or absence of ART. Healthy donors (RV304) or pre-infection time points (RV217) served as controls.

Results: PWH have reduced peripheral B cell counts at diagnosis of AHI; however, administration of early ART resulted in higher peripheral B cell counts and frequencies as early as 2 weeks after ART initiation compared to untreated PWH ($p< 0.05$). PWH treated during Fiebig stage II or III showed significant increases in peripheral B cell counts between week 0 and week 2 post ART ($p< 0.01$), whereas PWH treated during Fiebig stage I maintained similar B cell counts at both time points ($p >0.05$). In the absence of ART, the frequency of peripheral memory B cells decreased and plasmablast populations increased 2 weeks after infection ($p< 0.01$) compared to uninfected time points. However early administration of ART prevented these changes ($p >0.05$). Conversely, compared to healthy donors, frequencies of mucosal memory cells were expanded at HIV diagnosis during AHI (week 0) and then declined after ART administration. However, these memory B cell changes were not detected in the periphery (see Figure).

Conclusion: Early ART administration maintained similar peripheral B cell phenotypes compared to healthy donors whereas later treatment resulted in increased B cell activation and differentiation, likely due to increased antigen load. However, B cell population changes in the sigmoid mucosa were still detected despite early ART administration, suggesting early B cell responses to HIV in mucosal compartments.

The frequency of memory B cells from the periphery (A) or sigmoid biopsies (B) of uninfected (HIV Neg) or ART treated PWH (Week 0-96) was determined by flow cytometry. P-values were calculated using Mann-Whitney.



337 NK CELL BIOMARKERS THAT PREDICT TIME-TO-REBOUND IN HIV+ INDIVIDUALS UNDERGOING ATI

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Background: Most people with HIV exhibit viral rebound within weeks of analytical treatment interruption (ATI), but some can control replication for prolonged periods of time. The mechanisms mediating control upon ATI remain poorly understood, and may involve Natural Killer (NK) cells, potent antiviral immune effectors. The objective of this study was to use CyTOF to identify NK cell features that can predict time-to-rebound upon ATI.

Methods: We analyzed samples from two ATI cohorts: the REDUC cohort, which consisted of 17 participants that received therapeutic vaccination (Vacc4x) with the HDAC inhibitor Romidepsin prior to ATI, and the ACTG A5345 cohort, which consisted of 33 chronic- and 12 acute-treated participants that underwent ATI in the absence of any intervention. We phenotyped pre-ATI PBMCs using an NK cell CyTOF panel that includes markers of differentiation and activation states, homing receptors, inhibitory and activating receptors, and intracellular factors. We performed unsupervised clustering analyses to define NK cell clusters, optimized the number of clusters with a leave-one-out cross-validation model, and looked for associations with time-to-rebound, with HIV reservoir size as determined by IPDA, and with time of treatment initiation (chronic vs. acute).

Results: Clustering analyses for the REDUC cohort revealed a cluster that was significantly ($p< 0.05$) associated with increased time-to-rebound: an individual with 2.1 times the average number of cells belonging to this cluster rebounds on average 3 days later. The NK cells in this cluster were atypical in that they were CD56-CD16+ and exhibited a memory signature. Clustering analyses for the ACTG A5345 cohort revealed that individuals with a lower frequency of intact provirus were significantly ($p< 0.01$) associated with a different cluster of $CD56^{dim}CD16+$ NK cells expressing high levels of the inhibitory receptor Siglec-7 associated with functional NK responses. Acute-treated participants were also more likely to have NK cells that expressed high levels of the memory NK cell antigens CXCR6 ($p< 0.01$) and CD49a ($p=0.06$).

Conclusion: As CD56-CD16+ NK cells have been associated with bnAb production, these results suggest a potential role of NK cells and HIV-specific antibodies in control of viral replication. Siglec-7+ NK cells may temporarily control viral rebound during ATI. The findings with CXCR6 and CD49a implicate a role for memory NK cells in the preserved immune responses found in acute-treated individuals.

338 CHARACTERIZATION OF TISSUE-RESIDENT NK CELLS IN A TISSUE MODEL OF HIV INFECTION

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Background: NK cells are immune innate cells with important functions in controlling HIV infection. However, their role in the main tissues where HIV persists, such as the secondary lymphoid tissue and the gastrointestinal tract, is largely undefined. Here, we have characterized NK cells present in relevant tissues, particularly their memory-like and residency properties, and assessed their functionality in killing HIV-infected cells in a tissue model of HIV infection.

Methods: We obtained tissue resections from gut and tonsils from uninfected donors. We determined by flow cytometry the expression of the memory marker NKG2C, the residency markers CD49a, CD69, and CD103, and KIRs (KIR2DL1, S1, L2, L3, and S2). Natural cytotoxicity was evaluated by the expression of CD107a and IFN-γ after co-culturing disaggregated tissue cells with the HLA-negative K562 cell line (tonsil n=11, gut n=7). Last, using the tonsil explant model (n=16), the NK phenotype and natural cytotoxicity were characterized by flow cytometry after 5-7 days of HIVBAL *ex vivo* infection.

Results: Gut tissue had higher proportions of CD56+ NK cells (1.8%) in comparison with tonsils (0.38%). The distribution of the two main NK subsets was similar, showing a predominant population of $CD56^{bright}$ CD16−. However, their minority counterpart ($CD56^{dim}$ CD16+) was the subset more frequently expressing the residency markers CD49a and CD103, KIRs, and the NKG2C marker. Gut tissue had higher expression of the residency markers CD69 and CD103; however, they showed a reduced stimulatory potential compared with tonsils. In general, tonsil CD16+ NK cells expressing residency markers correlated with decreased levels of HIV in *ex vivo* infection. Furthermore, we detected two main tonsil populations associated with significant lower levels of HIV; the $CD56^{bright}$ CD16− CD103+ subset ($r=-0.54$, $p=0.014$), and the $CD56^{dim}$ CD16+ CD69+ KIR+ cells ($r=-0.61$, $p<0.01$), being the latest significantly expanded in the infected culture ($p<0.01$). Importantly, both subpopulations showed high basal production of CD107a and IFN-γ and increased functionality after K562 stimulation.

Conclusion: Relevant anatomic sites for HIV present different NK subset distribution and functional capacity. Our research indicates that higher numbers of cytotoxic NK-resident cells might have an important role in HIV control in lymphoid tissue. Hence, strategies aimed at expanding tissue-resident NKs may lead to the development of targeted therapies directed to the main sites of HIV persistence.

339 LOW-DENSITY GRANULOCYTES DISPLAY IMMATURE CELLS WITH PRIMED PHENOTYPE IN PLWH

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Background: While a protective role of neutrophil extracellular traps (NET) in limiting HIV spread to susceptible cells has been documented, there is comparatively little insight into whether NET formation may also be harmful in people living with HIV (PLWH) as a potential proinflammatory driver of HIV-associated comorbidities. To gain insight into this issue, we assessed the

frequency and characteristics of low-density granulocytes (LDGs), a subset of neutrophils and their NET forming capacity in PLWH on antiretroviral therapy (ART) and in HIV sero-negative (HIV-) individuals.

Methods: Utilizing banked PBMCs from the Hawaii Aging with HIV-Cardiovascular (HAHC-CVD) study, we identified and quantified circulating LDGs (CD14−CD16+CD15+) by flow cytometry. We compared LDG maturation and activation, assessing CD10 expression and mean fluorescence intensity (MFI) of cell surface markers, CD11b, CD66b, and MPO per LDG, respectively. NET forming LDGs (MPO+H3Cit+) were analyzed and plasma levels of NET (H3Cit and cfDNA) were measured to detect NET components in blood. We also measured circulating inflammatory (IL-6 and CRP) and prothrombotic markers (fibrinogen and d-dimer) to assess their relationship to plasma NET levels.

Results: A total 141 subjects, (HIV+; n=88 and HIV-; n=53) were included in this study. The median (IQR) age was 49 (45.0-57.0) years (87.8% male) in HIV+ individuals and 55 (47.5-60.0) years (84.9% male) in the HIV- individuals. Most participant (89.0%) had undetectable HIV RNA (less than 50 copies/mL) and the median CD4+ T cell count was 469 (294.5-605.5) cells/mm^3. The number of LDGs was significantly decreased in HIV+ (p=0.03) compared to HIV- individuals (495.7 [262.5-1585], 1038 [442.3-3714], respectively). We observed significantly higher NET forming capacity in HIV+LDG compared to HIV- LDG. Moreover, HIV+ LDG displayed immature CD10- neutrophils, but had heightened expression of CD66b and CD11b. Increased H3Cit levels ($p < 0.001$) were found in HIV+ individuals and these levels were positively associated with inflammatory and prothrombotic markers.

Conclusion: We found that LDGs from HIV+ individuals on ART display an immature and activated phenotype, and may exert proinflammatory effects. Plasma NET levels correlate with blood markers for inflammation and coagulation, which may yield insights into the pathologic role of LDGs at least in part mediated through NET formation in PLWH.

Comparison of LDG counts and the proportion of NET forming LDGs in HIV+ and HIV- individuals

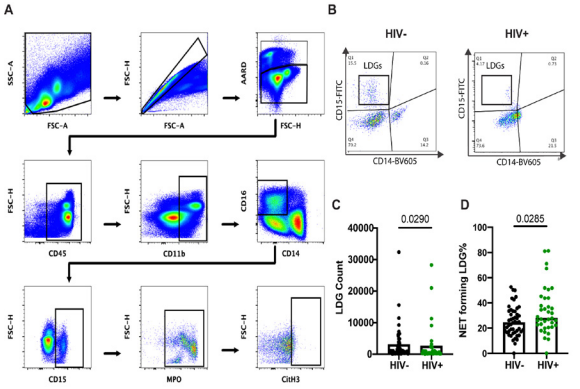

Figure 1.Comparison of LDG counts and the proportion of NET forming LDGs in HIV+ and HIV- individuals
Gating strategy for identifying LDG and NET forming LDGs. Leukocytes were selected by CD45 expression and CD11b CD14 CD16 fractions were finally identified for LDG based on CD15 expression. NETs were defined as MPO and CitH3 double positive events within the LDG population (A).
Flow cytometry analyzed the percentage of the LDGs (B-C) and NET forming LDG count. HIV- (n=48), HIV+ (n=37), Mann–Whitney U test.

340 NK CELLS ARE CRITICAL FOR *IN VIVO* CONTROL OF SARS-CoV-2 REPLICATION AND DISEASE

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Background: Natural killer (NK) cells play a critical role in control of viral infections. However, empirical evidence thus far has been unclear on the role of NK cells in pathogenesis and control of SARS-CoV-2 infection with some research suggesting NK cell accumulation as beneficial while others indicate it as deleterious. To address this crucial deficit in understanding, we employed a non-human primate infection model with a validated experimental NK cell depletion technique.

Methods: A total of 12 experimentally naïve (75% female) cynomolgus macaques (CM) of Cambodian origin were used in this study. Six CM were NK cell-depleted using an anti-IL-15 neutralizing antibody, while six controls received placebo, prior to intranasal and intratracheal challenge with the SARS-CoV-2 Delta variant at a TCID50 of 1X10^5. The cohort was monitored for five weeks with scheduled blood, colorectal (CR) biopsies, and lymph node (LN) collections. Total envelope and sub-genomic viral loads (VL) were measured in the nasal cavity, throat, and bronchoalveolar lavage (BAL). 23-color flow cytometry, pathology, and 27-plex inflammatory analyte Luminex analyses were conducted. Statistical tests used were Mann-Whitney U and Spearman's Correlation.

Results: Control CM exhibited an increase in the frequency of circulating NK cells, reaching a peak at 10 days post-infection (DPI) and returning to baseline by 22DPI. Simultaneously, NK cells expressing activation and tissue retention marker, CD69, also significantly increased. Cytotoxic NK cells were positively associated with VL (r=0.66; p=0.02), suggestive of a virus-induced mobilization.

Total experimental NK cell ablation was verified in blood, CR, and LN of NK cell-depleted CM, which had higher VL compared to controls in all tissues evaluated, reaching significance at 10DPI (p=0.01) and demonstrated a longer duration of viremia. Although Luminex measures were similar in plasma, BAL samples from NK cell-depleted CM had universally higher concentrations of inflammatory mediators, most notably a 25-fold higher concentration of IFN-α compared to controls. Lung pathology scores were also higher in NK cell-depleted CM with increased evidence of fibrosis, syncytia, pneumocyte hyperplasia, and endothelialitis.

Conclusion: Overall, we find significant and conclusive evidence for NK cell-mediated control of SARS-CoV-2 virus replication and disease pathology. These data suggest adjunct therapies for infection could largely benefit from NK cell-targeted approaches.

341 SIGLEC-9 RESTRAINS ANTIBODY-DEPENDENT NK CELL CYTOTOXICITY AGAINST SARS-CoV-2

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Background: SARS CoV 2 infection alters the immunological profiles of natural killer (NK) cells. However, whether NK anti-viral functions (direct cytotoxicity and/or antibody-dependent cell cytotoxicity (ADCC)) are impaired during severe COVID-19 and what host factors modulate these functions remain unclear.

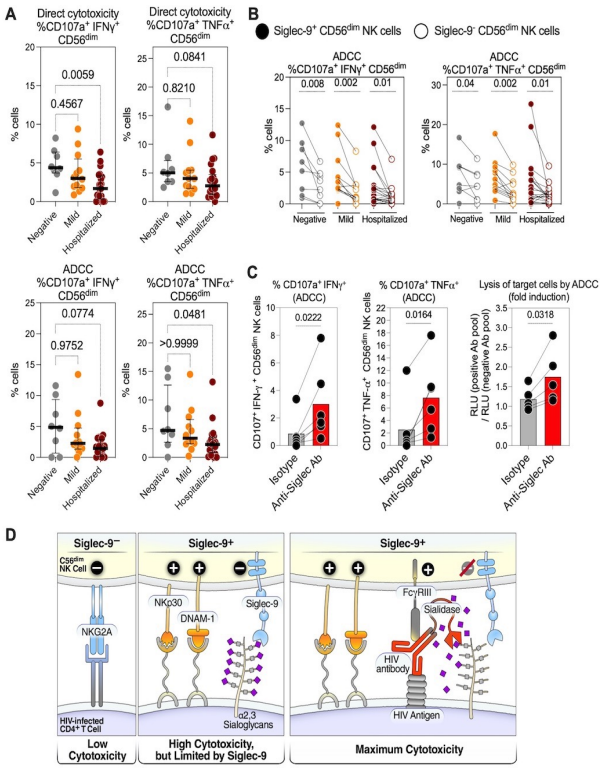
Methods: Using functional assays, we examined the ability of NK cells from SARS-CoV-2 negative controls (n=12), mild COVID-19 patients (n=26), and hospitalized COVID-19 patients (n=41) to elicit direct cytotoxicity and ADCC [NK degranulation by flow] against cells expressing SARS-CoV-2 antigens. SARS-CoV-2 N antigen plasma load was measured using an ultra-sensitive Simoa assay. We also phenotypically characterized the baseline expression of NK activating (CD16 and NKG2C), maturation (CD57), and inhibitory (NKG2A and the glyco-immune negative checkpoint Siglec-9) by flow cytometry. Finally, an anti-Siglec-9 blocking antibody was used to examine the impact of Siglec-9 expression on anti-SARS-CoV-2-specific ADCC [degranulation and target cell lysis].

Results: NK cells from hospitalized COVID-19 patients degranulate less against SARS-CoV-2-antigen-expressing cells (in direct cytolytic and ADCC assays) than did cells from mild COVID-19 patients or negative controls (**Fig. 1A**). The lower NK degranulation was associated with higher plasma levels of SARS-CoV-2 N-antigen ($P \leq 0.02$). Phenotypic and functional analyses showed that NK cells expressing Siglec-9 elicited higher ADCC than Siglec-9− NK cells (P<0.05; **Fig. 1B**). Consistently, Siglec-9+ NK cells expressed an activated and mature phenotype with higher expression of CD16, CD57, and NKG2C, and lower expression of NKG2A, than Siglec-9- NK cells (P≤0.03). These data are consistent with the concept that the NK cell subpopulation expressing Siglec-9 is highly activated and cytotoxic. However, the Siglec-9 molecule itself is an inhibitory receptor that restrains NK cytotoxicity during cancer and other infections. Indeed, blocking Siglec-9 significantly enhanced the ADCC-mediated NK degranulation and lysis of SARS-CoV-2-antigen-positive target cells ($P \leq 0.05$; **Fig. 1C**).

Conclusion: These data support a model (**Fig. 1D**) in which the Siglec-9+ CD56^{dim} NK subpopulation is cytotoxic even while being restrained by the inhibitory effects of Siglec-9. However, alleviating the Siglec-9-mediated restriction on NK cytotoxicity can further improve NK immune surveillance and

presents an opportunity to develop novel immunotherapeutic tools against SARS-CoV-2 infected cells.

Siglec-9 Restrains Antibody-dependent NK Cell Cytotoxicity Against SARS-CoV-2



342 **ICAM-1 MEDIATES PLASMACYTOID DENDRITIC CELL SENSING OF SARS-CoV-2-INFECTED CELLS**

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Background: Plasmacytoid dendritic cells (pDCs) are the major producer of type I IFNs (IFN-I), the critically important antiviral cytokines against SARS-CoV-2. Although pDCs can sense cell-free SARS-CoV-2 virions, it is unknown whether they can detect infected cells to produce IFN-I. Since cell-to-cell transmission accounts for 90% of SARS-CoV-2 infections (Zeng et al., 2022), we examined the relevance of pDC sensing of infected cells in SARS-CoV-2 infection and whether the virus exploits this pathway to evade IFN-I responses.

Methods: LSPQ1, the first SARS-CoV-2 clinical isolate received from the Public Health Laboratory of Quebec, was used as a prototype virus. SARS-CoV-2 variants of concerns (VOCs) were also used. PBMCs or enriched pDCs were cocultured with mock-infected or SARS-CoV-2-infected HeLa-hACE2 or Calu-3. Either PBMCs, enriched pDCs, or HeLa-hACE2 were pretreated with anti-human ICAM-1 antibody or isotype control. The conjugate formation was determined by flow cytometry. Polarized Caco cells were used to validate critical data.

Results: Upon sensing infected cells, PBMCs release 6-fold more IFN-I than they do when exposed to cell-free virions. Antibody-mediated depletion of pDCs from PBMCs abolishes IFN-I secretion. Direct contact of pDCs with infected cells is required for sensing since the use of a transwell membrane reduces IFN-I release by 85%. Infected cells form conjugates with pDCs more frequently (3.2-fold higher) than uninfected cells. Blocking ICAM-1 on infected cells or pDCs impacts conjugate formation and significantly suppresses IFN-I production by 55-80%, suggesting bidirectional interaction. Moreover, human lung cells infected with VOCs are sensed to a different extent with the alpha variant being the least efficiently sensed by pDCs compared to the delta or omicron strains. Even though SARS-CoV-2 is primarily released from the apical domain of polarized infected Caco cells, sensing of infected cells does occur upon direct contact of pDCs with the basolateral domain, highlighting how pDCs antiviral responses might be triggered in respiratory tissues.

Conclusion: pDC sensing of infected cells accounts for the vast majority of IFN-I released during SARS-CoV-2 infection. ICAM-1 promotes physical contact between pDCs and infected cells, thus leading to efficient sensing. Differential pDC sensing of SARS-CoV-2 VOC-infected cells suggests that some VOCs might manipulate the interactions of pDCs with infected cells to limit IFN-I responses.

343 **POLYFUNCTIONAL SARS-CoV-2-SPECIFIC T CELLS PERSIST IN TISSUE OF COVID-19 CONVALESCENTS**

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Background: T cells play an essential role in SARS-CoV-2 immunity, including in defense against severe COVID-19. However, most studies analyzing SARS-CoV-2-specific T cells have been limited to analysis of blood. Furthermore, the role of T cells in SARS-CoV-2 immunity in pregnant women, which are at disproportionately higher risk of severe COVID-19, is poorly understood.

Methods: Here, we quantitated and deeply phenotyped SARS-CoV-2-specific T cells from convalescent women (n=12) that had mild (non-hospitalized) COVID-19 during pregnancy. Endometrial, maternal blood, and fetal cord blood specimens were procured at term, which ranged from 3 days to 5 months post-infection. SARS-CoV-2-specific T cells were deeply analyzed by CyTOF using a tailored phenotyping panel designed to assess the effector functions, differentiation states, and homing properties of the cells.

Results: SARS-CoV-2-specific T cells were more abundant in the endometrium than in maternal or fetal cord blood. In a particularly striking example, in one donor sampled 5 months after infection, SARS-CoV-2-specific CD8+ T cells comprised 4.8% of total endometrial CD8+ T cells, while it only reached 1.4% in blood. Endometrial SARS-CoV-2-specific T cells were more frequently of the memory phenotype relative to their counterparts in maternal and fetal cord blood, which harbored higher frequencies of naïve T cells. Relative to their counterparts in blood, endometrial SARS-CoV-2-specific T cells exhibited unique phenotypic features, including preferential expression of the T resident memory marker CD69, inflammatory tissue-homing receptor CXCR4, and the activation marker 4-1BB. Endometrial T cells were highly polyfunctional, and could secrete IFNg, TNFa, MIP1b, IL2, and/or IL4 in response to spike peptide stimulation. By contrast, their counterparts in blood preferentially produced the cytolytic effectors perforin and granzyme B.

Conclusion: Polyfunctional SARS-CoV-2-specific T cells primed by prior exposure to the virus are abundant and persist in endometrial tissue for months after infection. These cells exhibit unique phenotypic features including preferential expression of select chemokine receptors and activation molecules. Compared to their blood counterparts, the effector functions of these cells are more cytokine-driven and less cytolytic. The long-term persistence of these cells in the endometrium may help protect future pregnancies from SARS-CoV-2 re-infection.

344 **HIGH RNAemia ASSOCIATES WITH SKEWED T-CELL RESPONSE IN PLWH HOSPITALIZED FOR COVID-19**

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Background: Severe COVID-19 outcomes have been reported in people living with HIV (PLWH). High SARS-CoV-2 RNAemia has emerged as a hallmark of severe COVID-19, yet its pathogenic role in the context of COVID-19 in PLWH is currently unknown. We hereby measured SARS-CoV-2 RNAemia and explored its association with T-cell/humoral responses and clinical severity in PLWH.

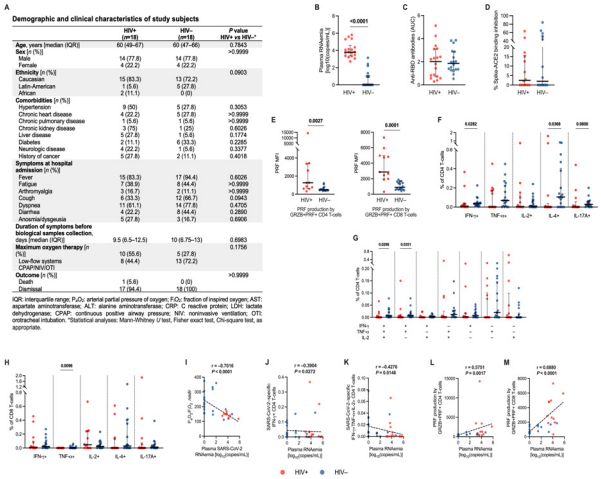
Methods: Unvaccinated PLWH and age/sex-matched people living without HIV (PLWOH) hospitalized for radiologically-confirmed COVID-19 pneumonia were consecutively enrolled (March 2020–January 2021). We measured: SARS-CoV-2 RNAemia (RT-qPCR); T-cell activation (HLA-DR+CD-38+), cytotoxic T-cells [granzyme-B(GRZB)+perforin(PRF)+], GRZB/PRF production (MFI) by cytotoxic T-cells (flow cytometry); SARS-CoV-2–specific cytokines (IFN-γ/TNF-α/IL-2/IL-4/IL-17A)-producing T-cells, after SARS-CoV-2 spike peptides challenge (flow cytometry); anti-RBD antibodies (ELISA), Spike-ACE2 binding inhibition (receptor binding inhibition assay). Statistics: Mann-Whitney test and Spearman's correlation.

Results: 18 PLWH (16 on cART; median CD4 361.5/mL; HIV-RNA< 50 cp/mL in 15/18) and 18 PLWOH were included at a median of 10 days from symptoms onset (**Fig.1A**). PLWH had lower P_aO_2/F_iO_2 [140 (122–151.5) vs. 207

(156.3–309.3); $P=0.0005$] and higher SARS-CoV-2 RNAemia (**Fig.1B**). While humoral responses were comparable between groups (**Fig.1C–D**), as was T-cell activation, PLWH showed skewed T-cell responses: higher perforin production by cytotoxic T-cells (**Fig.1E**); fewer SARS-CoV-2–specific IFN-γ+ and IL-4+ CD4 T-cells (**Fig.1F**); lower Th1 tri-functional (IFN-γ+TNF-α+IL-2+) and bi-functional (IFN-γ+TNF-α+) CD4 T-cells (**Fig.1G**); reduced TNF-α+ CD8 T-cells (Fig.1H). Interestingly, SARS-CoV-2 RNAemia correlated negatively with P_aO_2/F_iO_2 nadir and SARS-CoV-2–specific T-cells, yet positively with perforin production by cytotoxic T-cells (**Fig.1I–M**). No correlations between RNAemia and humoral responses were found.

Conclusion: As compared to HIV-uninfected patients, PLWH hospitalized for COVID-19 pneumonia feature high SARS-CoV-2 RNAemia which is linked to respiratory failure and skewed T-cell responses, with higher perforin production by cytotoxic T-cells, and yet fewer polyfunctional SARS-CoV-2–specific T-cells. Our data suggest a link between HIV-related T-cell dysfunction and poor control over circulating SARS-CoV-2 that may in turn influence COVID-19 severity in PLWH.

Figure 1



345 HIGH-RESOLUTION MAPPING OF T-CELL HYBRID IMMUNITY TO THE ENTIRE SARS-CoV-2 PROTEOME

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Background: To understand T-cell responses to SARS-CoV-2, it is essential to define the contribution of infection versus immunization to virus-specific hybrid immunity. Here, we characterized the breadth and magnitude of T-cell responses to the entire SARS-CoV2 proteome over a 2-year follow-up period in infected and vaccinated (CoV2+Vac+) and vaccinated and infected (Vac+CoV2+) individuals.

Methods: We selected samples from 38 (19 CoV2+ and 19 CoV2-, time1, T1) ProHEpiC-19 cohort participants, a prospective, longitudinal study starting in March 2020 involving 7,776 healthcare workers in Spain. Longitudinal samples were available from 10 of them after a 3-dose mRNA vaccination, including 5 CoV2+Vac+ and 5 Vac+CoV2+, at 824.5 and 250.5 days from symptoms onset (DfSO, time 2, T2). We measured the breadth and magnitude of IFN-γ T-cell responses by ELISpot assay in cryopreserved PBMCs, using a 15-mer overlapping peptide (OLP) library of 2,790 SARS-CoV-2 peptides in 100 pools.

Results: We identified immunodominant T-cell responses in S1, S2, nsp3, Env, NC, and M proteins across the SARS-CoV2 proteome. We observed an increased breadth of T-cell responses (responding pools over the entire region) to S1 (44 - 30%) and S2 (31 - 40%) in CoV2+Vac+ and Vac+CoV2+, respectively. In addition, CoV2+Vac+ had an exclusive and sustained response to M. We found significantly stronger responses in CoV2+Vac+ (P=0.0313). Particularly the total magnitude was greater in CoV2+Vac+ vs. Vac+CoV2+ in S1 (4476.88 vs. 1498.53), Env (457.34 vs. 250.50), and M (455.13 vs. 0.00) but not in S2 and nsp3. The total number of peptides for deconvolution was higher in CoV2+Vac+ (32 peptides) than in Vac+CoV2+ (3 peptides) during the follow-up. Seventy-five percent of the responses targeted S, and 25% M, ORF1a, and Env.

Conclusion: These results profile immunodominant T-cell responses in S1, S2, nsp3, Env, NC, and M proteins across the entire SARS-CoV2 proteome. The data delineate differences in the number of T-cell responses primed hybrid immunity by infection previous to vaccination (CoV2+Vac+), being broader and of higher magnitude and underlining an exclusive T-cell response to the M region. Overall, these findings identify differences in long-term T-cell hybrid immunity primed by infection or vaccination, which may have implications in protection from re-infection and vaccine design.

346 UNIQUE DIFFERENTIATION AND HOMING FEATURES OF T CELLS IN INDIVIDUALS WITH LONG COVID

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Background: A significant portion of individuals experience persistent symptoms months after SARS-CoV-2 infection, broadly referred to as Long COVID (LC). Although the frequencies of subsets of SARS-CoV-2-specific T cells have been shown to differ in individuals with LC relative to those with complete recovery, a deep dive into phenotypic and functional features of total and SARS-CoV-2-specific T cells from individuals with LC has yet to be performed.

Methods: Here, we used CyTOF to characterize the phenotypes and effector functions of T cells from LIINC cohort. The median age was 46, the cohort was 55.8% female, and 9/43 had been hospitalized. Participants were reported a median of 7 LC symptoms at 8 months. SARS-CoV-2-specific total antibody levels were also measured in concurrent sera. Manual gating was used to define T cell subsets, SPICE analyses for polyfunctionality, T cell clustering for phenotypic features, and linear regression for correlation. Permutation tests, Student's t tests, and Welch's t test were used for statistical analysis.

Results: SARS-CoV-2 total antibody responses were elevated in the LC group (p=0.043), and correlated with frequencies of SARS-CoV-2-specific T cells in those without LC (r=0.776, p< 0.001) but not those with LC. While the frequencies of total SARS-CoV-2-specific CD4+ and CD8+ T cells were similar between individuals with and without LC, those from individuals without LC tended to be more polyfunctional (co-expressing IFNγ, TNFα, IL2, and/or MIP1β). CD4+ T cells from individuals with LC harbored higher frequencies of Tcm (p=0.003), Tfh (p=0.037), and Treg subsets (p=0.0412), and preferentially expressed a variety of tissue homing receptors including CXCR4 and CXCR5 (p=0.037). SARS-CoV-2-specific CD4+ T cells producing IL6, albeit rare, were observed exclusively among those with LC (p=0.016). In addition, participants with LC harbored significantly higher frequencies of SARS-CoV-2-specific CD8+ T cells co-expressing exhaustion markers PD1 and CTLA4 (p=0.018).

Conclusion: Long COVID is characterized by global phenotypic differences in the CD4+ T cell compartment in ways suggesting preferential migration of these cells to inflamed mucosal tissues. Individuals with LC also harbor higher numbers of exhausted SARS-CoV-2-specific CD8+ T cells, potentially implicating viral persistence. Finally, our data additionally suggest that individuals with LC may uniquely exhibit an uncoordinated T cell and antibody response during COVID-19 convalescence.

347 LONGITUDINAL CORONAVIRUS ANTIBODY RESPONSES IN AFRICA BETWEEN 2013 AND 2021

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Background: Pre-existing coronavirus-specific antibody responses may affect SARS-CoV-2 responses. We evaluated longitudinal samples obtained before and during the pandemic in participants from Kenya, Nigeria, Tanzania and Uganda; 90% were people living with HIV.

Methods: Serum samples were tested using a multiplex bead-based immunoassay to measure antibody binding against 22 antigens including Nucleocapsid (N) and Spike (S) proteins of the 7 human coronaviruses and one malaria antigen.

Results: We tested 819 longitudinal samples from 80 participants collected between July 2013 and May 2021 (3-16 samples per participant). Using a signal to noise ratio (S/N) >10, 13, 1, and 5 participants showed at least one time point with IgG responses to S of SARS-CoV-2 (ancestral), SARS-CoV-1 and MERS-CoV respectively while 14, 8, and 11 participants showed responses to N before 2020. Across individuals, IgG binding to SARS-CoV-2 S subunit S2 was most frequently detected and it showed the highest within-host fluctuations over time. A few individuals had elevated responses that persisted over years towards multiple antigens, most frequently to different SARS-CoV-2 antigens and rarely to distinct viruses. One individual showed high RBD-specific IgG responses to distinct coronaviruses at a single time point before 2020. Responses against coronaviruses measured post-2020 generally correlated with responses measured before 2020, except for a subset of infected individuals whose responses against SARS-CoV-2 dramatically increased post-pandemic. IgG responses against the ancestral SARS-CoV-2 variant were most correlated with responses against Alpha and Gamma (then to Beta and Delta, rho >0.75) variants. Using an IgM S/N >10, 31 participants were Malaria positive and 22 showed concurrent elevated coronavirus IgM responses. However, about half of the malaria positive participants had no IgG responses against any coronavirus antigen and the rest presented limited and variable patterns of association between responses against coronaviruses and malaria.

Conclusion: Our study confirmed that a small subset of individuals in Africa had long-lasting IgG coronavirus-specific antibodies before the pandemic. While there was an association between coronavirus IgM responses and responses against malaria, there was no correlation between IgG responses and malaria infection. Further analysis is needed to better understand the interactions between antigens in the development of antibody immunity to coronaviruses.

Table 1. Numbers of the coronavirus responders in IgG by country

		Positive to Spike			Positive to Nucleocapsid		
Country	Total N	SARS-CoV-2	SARS-CoV-1	MERS-CoV	SARS-CoV-2	SARS-CoV-1	MERS-CoV
Kenya	34	5 (3*)	1	2	5 (2)	3 (1)	4 (2)
Nigeria	6	1 (1)	0	1	1	0	0
Tanzania	9	0	0	0	2	1	1
Uganda	31	7 (3)	0	2	6 (2)	4 (1)	6 (1)

*The values in parenthesis are the number of participants with S/N > 10 in more than half of the time points

348 IMPACT OF COVID-19 AND HOST FACTORS ON THE HUMORAL IMMUNE REPERTOIRE IN TREATED HIV

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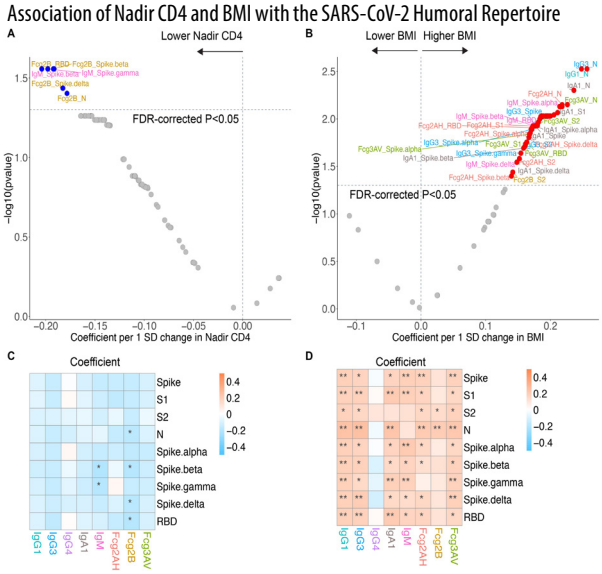
Background: People with HIV (PWH) on antiretroviral therapy (ART) appear to be at higher risk for worse COVID-19 outcomes, but the underlying mechanisms–including effects of COVID-19 and host factors on the broader humoral immune repertoire–are poorly understood.

Methods: REPRIEVE enrolled a global cohort of ART-treated PWH ages 40-75. COVID+ was defined by positive receptor binding domain IgG or IgA from annual visits 5/2020-2/2021. Antibody isotype, subclass, and Fc receptor Luminex arrays to SARS-CoV-2, CMV, EBV, HSV, HIV, influenza, pneumococcus, and RSV were assessed. Report of COVID diagnosis (collected every 4 months) was defined as mild, moderate, or severe (asymptomatic if no clinical diagnosis but IgG/IgA+). FDR-corrected regression was used to assess effects of 1) COVID+ on non-SARS-CoV-2 repertoire in full cohort and 2) host factors on non-SARS-CoV-2 and SARS-CoV-2 repertoire in COVID- and COVID+ cohorts, respectively, adjusted for age, sex, region, nadir CD4, and HIV VL at entry.

Results: Of 2,464 unvaccinated participants, 283 (11%) were COVID+; 260 (92%) were asymptomatic. Median age was 53, 35% were women, 50% had nadir CD4 < 200, median current CD4 was 649, and 97% had HIV VL < 400. In the full cohort, COVID+ was associated with higher CMV PP65 IgG3 and FcγRIIA (P< 0.05); COVID severity was not associated with the non-SARS-CoV-2 repertoire. Among COVID-, older age, female sex, and lower nadir CD4 were associated with higher EBV and CMV responses; IgG1 levels were higher in women for all non-SARS-CoV-2 antigens assessed (P< 0.05). Among COVID+, higher BMI was associated with amplified SARS-CoV-2 IgG, IgA, IgM, and FcγRIIA responses (P< 0.05). Lower nadir CD4 was associated with a SARS-CoV-2 repertoire shift toward IgM and FcγRIIB (P< 0.05). Age and sex were not associated with SARS-CoV-2-related repertoire changes in COVID+.

Conclusion: Our analysis presents a comprehensive view of host factors associated with the humoral immune repertoire among a global cohort of ART-treated PWH. COVID's association with higher CMV responses may suggest increased susceptibility to or a consequence of persistent inflammation after infection. The striking amplification of SARS-CoV-2 responses with higher BMI suggests an excessive inflammatory response. Lower nadir CD4 was related to uncontrolled extra-follicular and inhibitory SARS-CoV-2 responses, which are unlikely to be protective. These findings may suggest mechanisms underlying factors associated with worse COVID-19 outcomes among PWH.

Association of Nadir CD4 and BMI with the SARS-CoV-2 Humoral Repertoire



A,B: Association of nadir CD4 and BMI with SARS-CoV-2 repertoire among COVID+, adjusted for age, sex, region, HIV-1 RNA, and nadir CD4; C,D: heat maps of A,B; *P<0.05, **P<0.01.

349 LYMPHOCYTE TRAJECTORIES AND OUTCOMES OF COVID-19 INFECTION IN PEOPLE WITH HIV

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Background: Studies have shown that lymphopenia and a decreased CD4/CD8 ratio are correlated with the severity of COVID-19 infections. As people with HIV (PWH) can have altered CD4/CD8 ratios at baseline, this study examined the relationship between lymphocyte and T-cell subsets with COVID-19 disease outcomes among PWH.

Methods: This retrospective study included adult PWH (identified by HIV ICD codes, HIV RNA or antibody results, or antiretroviral therapy use excluding pre-exposure prophylaxis) in the Optum COVID-19 EHR database with positive SARS-CoV-2 PCR or antigen tests from February 2020 to December 2021. Outcomes included 30-day hospitalization, ICU stay, mechanical ventilation, and death from COVID-19. Absolute lymphocyte counts and percent and CD4:CD8 ratios were collected prior to SARS-CoV-2 positivity (baseline) and then weekly for four weeks post-SARS-CoV-2 positivity. We examined lymphocyte trajectories in PWH who had available data at all time points, and we compared changes in counts and percentages at each week post-SARS-CoV-2 to baseline values, using Wilcoxon rank sum test.

Results: Of a total of 4,525 PWH who tested positive for SARS-CoV-2, 102 PWH had available lymphocyte counts at all study time points. Compared to non-hospitalized PWH (n=38), hospitalized PWH (n=64) and PWH who were in the ICU (n=32) or ventilator dependent (n=27) experienced a larger drop in lymphocyte percentage in the first two weeks post-SARS-CoV-2 diagnosis with only a partial recovery in subsequent weeks. In patients who died (n=19), lymphocyte percentage recovered even more slowly. Hospitalized PWH, as compared to non-hospitalized PWH, had a significant decrease in lymphocyte percentage post-SARS-CoV-2 infection in the first week (-0.19 vs -0.05; < 0.001), second week (-0.23 vs -0.02; < 0.001), third week (-0.20 vs 0.00; < 0.001),

and fourth week (-0.10 vs 0.00; 0.001), a trend seen in the ICU, mechanically ventilated, and deceased groups as well (Table 1). By the first week, CD4/CD8 ratio in COVID-19 positive patients was lower in the deceased (-0.18 vs 0.00; p=0.4), ventilator dependent (-0.15 vs 0.00; p=0.2), and ICU (-0.15 vs 0.00; p=0.4) groups.

Conclusion: Our study showed that not only is lymphopenia a marker of COVID-19 disease severity in PWH but also a failure of lymphocyte percentage recovery is associated with worse outcomes. There was also a trend towards worse outcomes associated with a lower CD4/CD8 ratio in the first week after COVID-19 infection.

Median Lymphocyte Percent Delta Change Post COVID-19 Test Positivity Among PWH

Lymphocyte Percent Δ Change	Hospitalization		ICU Stay		Ventilator		Death	
	Non-Hospitalized	Hospitalized	Non-ICU	ICU	Non-Ventilator	Ventilator Support	Survived	Deceased
First Week vs Pre-COVID	-0.05	-0.19	-0.11	-0.23	-0.11	-0.34	-0.11	-0.33
P-value*	<0.001		0.007		0.003		0.028	
Second Week vs Pre-COVID	-0.02	-0.23	-0.07	-0.37	-0.06	-0.45	-0.06	-0.47
P-value*	<0.001		<0.001		<0.001		<0.001	
Third Week vs Pre-COVID	0.00	-0.20	-0.04	-0.32	-0.03	-0.51	-0.02	-0.63
P-value*	<0.001		<0.001		<0.001		<0.001	
Fourth Week vs Pre-COVID	0.00	-0.10	-0.01	-0.12	-0.01	-0.25	-0.01	-0.25
P-value*	0.001		0.4		0.048		0.2	

Table 1. Median Lymphocyte Percent Delta Change Post COVID-19 Test Positivity Among PWH

*Wilcoxon rank sum test

350 CHRONIC HIV INFECTION IMPACTS THE IMMUNE RESPONSE DURING ACUTE SARS-CoV-2

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Background: SARS-CoV-2 infection typically causes self-limited disease, but a subset of individuals experience more severe disease associated with respiratory manifestations, hospitalization and mortality. People living with HIV (PLWH) have been shown to have chronic immune activation and inflammation despite effective antiretroviral therapy. During the COVID pandemic, PLWH were found to have an increased risk of hospitalization and mortality with acute COVID-19. The immune response driving these worsened outcomes in PLWH is not defined. We analyzed immune activation and exhaustion markers, as well as antigen specific T cell responses during acute COVID-19 in PLWH versus HIV-seronegative controls to determine the impact of chronic HIV infection and inflammation on acute COVID-19.

Methods: We performed flow cytometric analyses on peripheral blood mononuclear cells from: 1) PLWH with acute COVID-19 (HIV+COVID), 2) HIV-seronegative individuals with acute COVID-19 (COVID) and 3) pre-COVID-19 pandemic PLWH (HIV). COVID(+) samples were collected at an average of 4.7 (range 0-16) and 5.5 (range 0-20) days post-symptom onset for the COVID and HIV+COVID cohorts, respectively. Cells were stained for surface markers of activation/exhaustion and intracellular cytokines (with and without SARS-CoV-2-specific antigen stimulation). Observed immune responses were correlated with disease severity.

Results: PLWH with acute COVID-19 had increased classical (CD14+) monocytes compared to HIV-seronegative individuals with acute COVID-19. The HIV+COVID cohort also had higher expression of activation (OX40, CD137) and exhaustion (PD1, TIGIT) markers on CD4+ and CD8+ T cells compared to HIV-seronegative individuals. SARS-CoV-2 antigen stimulation resulted in similar response frequencies between the HIV+COVID and COVID cohorts.

Conclusion: PLWH had increased activation and exhaustion and increased classical monocytes compared to HIV-seronegative presentations of COVID-19, highlighting the persistent immune dysregulation associated with chronic HIV infection. Our findings aid in further characterization of how chronic immune dysregulation impacts the immune response to acute SARS-CoV-2 infection. Future studies include characterizing the impact of acute SARS-CoV-2 infection duration, as well as how chronic immune dysregulation impacts the development of long COVID.

Table 1. Cohort demographics

	HIV+COVID (n=28)	HIV (n=12)	COVID (n=42)
Age	51 (30-76)	48 (24-72)	64 (25-93)
Male	16 (57.1%)	6 (50%)	17 (40.5%)
Race			
AA	17 (60.7%)	9 (75%)	26 (61.9%)
W	11 (39.3%)	2 (16.7%)	16 (38.1%)
Multiracial	0 (0%)	1 (8.3%)	0 (0%)
Clinical Outcome (severity)			
No O2 requirement	17 (60.7%)		13 (31%)
High flow	5 (17.9%)		4 (9.5%)
Ventilator	2 (7.1%)		3 (7.1%)
Deceased	1 (3.6%)		6 (14.3%)
Viral Suppression	26 (92.9%)	6 (50%)	
CD4			
Percent	31% (13-45%)	28% (10-44%)	
Count	722 (181-1619)	649 (170-1238)	
ART Regimen			
NRTI	24 (85.7%)	7 (58.3%)	
NNRTI	2 (7.1%)	3 (25%)	
INSTI	25 (89.3%)	4 (33.3%)	
PI	3 (10.7%)	0 (0%)	

AA – African American; W – White; NRTI – Nucleoside reverse transcriptase inhibitor; NNRTI – Non-nucleoside reverse transcriptase inhibitor; INSTI – Integrase strand inhibitor; PI – Protease inhibitor

351 PRIOR SARS-CoV-2 INFECTION PROTECTS AGAINST SYMPTOMATIC COMMON COLD CORONAVIRUSES

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Background: Current COVID-19 vaccines provide substantial protection against severe COVID-19, but they do not completely eliminate subsequent SARS-CoV-2 infections. We examined incidence of and immune differences against related but different common cold coronaviruses (ccCoV) as a proxy for response against a future emerging CoV among those with SARS-CoV-2 infection, COVID-19 vaccination, or neither exposure.

Methods: We assessed incidence of ccCoV (229E, HKU1, NL63, OC43) and rhinovirus/enterovirus infections among those with documented prior SARS-CoV-2 infection (n=493), prior COVID-19 vaccine, but no SARS-CoV-2 infection (n=1,568), or no prior SARS-CoV-2 infection or vaccination (n=2,874). We conducted a retrospective review of all individuals at Boston Medical Center that underwent a comprehensive respiratory panel polymerase chain reaction (CRP-PCR) test from November 30, 2020 to October 8, 2021 to estimate infection incidence. A subset within each group was assessed for coronavirus specific humoral and cellular immune responses, via pseudovirus neutralization and peptide stimulation T cell assays. Comparisons among the three groups were done using Chi-square and multi-variate Cox-proportional hazards models.

Results: Incidence of symptomatic ccCoV was lower in those individuals with documented prior SARS-CoV-2 infection (1.0%) compared to those with COVID-19 vaccination (2.9%) or no prior SARS-CoV-2 exposure (1.8%, $p = 0.01$). Rhinovirus/enterovirus incidence was similar in all three groups (range 6.2 – 8.7%). Individuals with prior SARS-CoV-2 infection and those with previous COVID-19 vaccination had similar plasma neutralization against SARS-CoV-2, OC43, and 229E spike bearing pseudoviruses. SARS-CoV-2 ($p = 0.01$) and OC43 nucleocapsid ($p = 0.02$), but not spike specific peptides, yielded higher T cell responses in individuals with a prior SARS-CoV-2 infection as compared to those with COVID-19 vaccination or no prior SARS-CoV-2 exposure.

Conclusion: Prior SARS-CoV-2 infection, but not COVID-19 vaccination, protects against subsequent related but different ccCoV symptomatic infection. This protection against symptomatic ccCoVs may be mediated by cellular responses to non-spike proteins. Future pan-coronavirus vaccines could be improved by including both spike and non-spike antigens.

352 RESPIRATORY DISEASE FACTORS LINK WITH REDUCED SARS-CoV-2 SUSCEPTIBILITY IN PWH

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Background: Despite favorable vaccine responses of people with HIV (PWH), susceptibility to SARS-CoV-2 (SCv2) infection and increased risk of COVID-19 in immunocompromised PWH continue to be of concern. Here, we searched the Swiss HIV Cohort Study (SHCS) with>9500 actively enrolled, optimally treated PWH to identify factors associated with SCv2 infection in the pre-and post-vaccination area.

Methods: We utilized information on SCv2 events reported to the SHCS in 2020 -2021. To detect asymptomatic infection, we screened pre-pandemic (2019) and

pandemic (2020-2021) bio-banked plasma for SCv2 antibodies (Ab). SCv2+ and matched SCv2– PWH were additionally screened for Abs to circulating human coronaviruses (HCoV). Data were compared to HIV negative (HIV-) controls. SCv2 data and >26 behavioral, immunologic and disease-parameters available in the SHCS data base were analyzed by logistic regression, conditional logistic regression, and Bayesian multivariate regression.

Results: Considering information on the SCv2 status of 6270 SHCS participants, neither HIV-1 viral load nor CD4+ T cell levels were linked with increased SCv2 infection risk. COVID-19-linked hospitalization (87/982) and case fatality rates (8/982) were low, but slightly higher than in the general Swiss population when stratified by age. Compared to HIV–, PWH had lower SCv2 IgG responses (median effect size= −0.48, 95%-Credibility-Interval=[−0.7, −0.28]). Consistent with earlier findings, high HCoV Abs pre-pandemic (2019) were associated with a lower risk of a subsequent SCv2-infection and, in case or infection, with higher Ab responses.

Examining behavioral factors unrelated to the HIV-status, people living in single-person households were less at risk of SCv2 infection (aOR= 0.77 [0.66,0.9]). We found a striking, highly significant protective effect of smoking on SCv2 infection risk (aOR= 0.46 [0.38,0.56], $p=2.6*10^{-14}$) which was strongest in 2020 prior to vaccination and was even comparable to the effect of early vaccination in 2021. This impact of smoking was highly robust, occurred even in previous smokers and was highest for heavy smokers.

Conclusion: Our unbiased cohort screen identified two controversially discussed factors, smoking and cross-protection by HCoV responses to be linked with reduced susceptibility to SCv2, validating their effect for the general population. Overall weaker SCv2 Ab responses in PWH are of concern and need to be monitored to ensure infection- and vaccine-mediated protection from severe disease.

353 DELINEATING FACTORS ASSOCIATED WITH ASYMPTOMATIC PRIMARY SARS-CoV-2 INFECTION

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Background: SARS-CoV-2 infection leads to a broad range of clinical manifestations, from no symptoms to critical illness. Pre-stimulated innate defenses, rapid induction of SARS-CoV-2 responses and pre-existing cross-reactive immunity to circulating human coronaviruses (HCoV) may early dampen SARS-CoV-2 infection, preventing symptomatic disease. Here we explore SARS-CoV-2 and HCoV antibody impact on asymptomatic infection in individuals first encountering SARS-CoV-2 in March 2020-March 2021 participating in a longitudinal pediatric cohort (n=2917) and a cross-sectional adult and children diagnostic cohort (n=882) in Switzerland.

Methods: Antibodies (Ab) to S1 of the four HCoV strains and SARS-CoV-2 antigens S1, RBD, S2 and N were determined in saliva (n=4993) and serum (n=7486) samples. Mucosal and systemic neutralization activity against wildtype SARS-CoV-2-Wuhan, and Alpha, Delta and Omicron (BA.2) variants of concerns (VoC) was assessed by pseudovirus neutralization in a subset of individuals.

Results: Analysis of simultaneously sampled saliva and plasma revealed a strong correlation of mucosal and systemic SARS-CoV-2 anti-spike responses in recent infection. Notably, pre-existing high HCoV antibody response was significantly associated with higher systemic (IgG, IgA, and IgM, p< 0.001) and mucosal (IgG, p=0.03) SARS-CoV-2 responses following SARS-CoV-2 infection. Adjusting for age and sex, we found four saliva SARS-CoV-2 Ab parameters, namely total Ig S2, total Ig S1, IgA S2 and IgM S1 (p< 0.001, p< 0.001, p=0.02, p=0.01 respectively), inversely associated with salivary viral load highlighting the impact of mucosal Ab response on viral suppression. Saliva neutralization activity was modest but surprisingly broad, retaining same level activity against Wuhan, Alpha and Delta, but not Omicron BA.2, whereas plasma neutralization activity showed the typical decrease for all three VoCs compared to Wuhan. Most interestingly, asymptomatic individuals presented with higher IgG S2 antibody reactivity in saliva (p=0.03) and higher pre-existing HCoV-S1 IgG activity in plasma (HKU1, p=0.04) and saliva (total hCoV, p=0.02) suggesting immune factors that restrict disease severity.

Conclusion: Focusing on a SARS-CoV-2 infection and vaccine naïve population, our study reveals interdependencies of systemic and mucosal SARS-CoV-2 and HCoV immunity following primary SARS-CoV-2 infection and locates reactivities linked with reduced viral load and asymptomatic infection.

354 HIGHER SPIKE GENETIC DIVERSITY OF DELTA/OMICRON VARIANTS IN IMMUNOCOMPROMISED HOSTS

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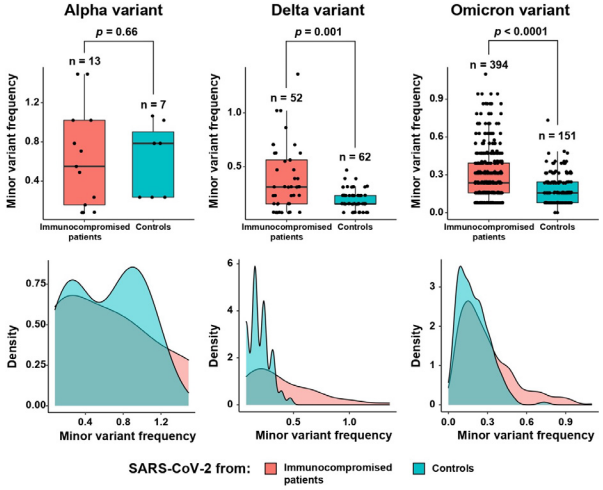
Background: Immunocompromised hosts with prolonged SARS-CoV-2 infections have been associated with the emergence of novel mutations, especially in the Spike protein, a key target for vaccines and therapeutics. Here, we conducted a case-control study to measure the genetic diversity of SARS-CoV-2 and to search for immunocompromised-specific minority variants.

Methods: SARS-CoV-2-positive patients with lung/cardiac/kidney transplant, HIV-positive, or treated with high doses of corticosteroids for auto-immune diseases were considered as immunocompromised hosts. SARS-CoV-2-positive healthcare workers with no auto-immune disease were used as controls. Samples were analyzed by RT-qPCR at Pitié-Salpêtrière and Bichat Claude-Bernard university hospitals (Paris, France). Samples with Cycle threshold < 30 were selected for SARS-CoV-2 whole-genome sequencing using Oxford Nanopore protocol. Raw sequence data were mapped onto the Wuhan-Hu-1 reference genome, and consensus sequences were produced to determine the lineage. Only sequences covering at least 95% at ≥50X depth of the Spike gene were investigated. In-house algorithms were developed to identify all majority and minority mutations in Spike. We defined a minority variant when it was present in ≥6% and < 50% of the reads; and a majority variant when it was present in >50%.

Results: We sequenced SARS-CoV-2 genome from 478 COVID-19-positive immunocompromised patients and 234 controls. More minority non-synonymous mutations in Spike were detected in viruses from immunocompromised hosts, compared to viral genomes from controls, in both Delta (p=0.001) and Omicron (p< 0.001) lineages, but not in Alpha (p=0.66) (Figure 1). Interestingly, among the 52 patients infected with the Delta variant, we concomitantly detected at low frequencies the mutations H655Y, N764K, D796Y, in three patients (associated with different auto-immune disease), that are part of Omicron variants signature mutations. Similarly, some patients (n=7) infected by Omicron BA.1 lineage had R346T at low-frequency, later fixed in Omicron BA.4.6 and BQ.1.1 lineages. None of these mutations were observed in the viral genomes from controls.

Conclusion: Here, we report a higher genetic diversity in Spike gene among SARS-CoV-2 sequences from immunocompromised hosts for Delta and Omicron lineages. These results suggest that immunocompromised patients are more likely to allow viral genetic diversification and are associated with a risk of emergence of novel SARS-CoV-2 variants.

Variable levels of Spike gene evolution for different SARS-CoV-2 lineages in immunocompromised hosts and care workers "controles" without autoimmune disease.



355 REAL-WORLD EFFECTIVENESS OF mRNA, SUBUNIT, AND VECTOR-BASED VACCINES AGAINST COVID-19

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Background: Limited Covid-19 vaccine effectiveness (VE) studies address the mRNA, adenoviral vector-based, and protein subunit vaccines and their mix and match in real-world settings. BNT162v2 (Pfizer-BioNTech), mRNA-1273 (Moderna), AZD1222 (AstraZeneca), and locally produced MVC-COV1901 (Medigen) are provided under the National Vaccination Program. Taiwan maintained a low circulation of Covid-19 infection until a major epidemic Omicron BA.2, began in April 2022. The study aimed to estimate the VE against moderate and severe (severity) and fatal diseases (death) associated with SARS-CoV-2 among individuals administered one, two, and three doses of vaccination and categorized by vaccine type combinations in this predominantly infection-naïve population.

Methods: The study included CDC's administrative records from National Immunization Information System and National Infectious Disease Reporting System from March 21, 2021, to September 30, 2022. Criteria for Covid-19 severity followed WHO's guidelines, and the committee reviewed the records. The study calculated each individual's last administered date to disease onset (incidence rate (IR) per 100,000 person-days) to explore the incidence rate to compare the presence of risk probabilities. Multiple logistic regression was used for vaccine effectiveness analysis.

Results: Of 23,933,482 individuals included in the study, and 6,202,496 infections, 30,976 severity, and 10,851 deaths were observed. Compared with three doses administered, three doses of AZD1222 or it as primary series plus mRNA or protein-based vaccines were at higher risk of severity (IR: 0.390-0.762), followed by mRNA-1273 (IR: 0.316-0.471), MVC-COV1901 (IR: 0.044-0.196) and BNT162v2 (IR: 0.061-0.197). As for the death outcome, AZD1222 was at higher fatal risk (IR: 0.127-0.269), followed by mRNA-1273 (IR: 0.086-0.125), MVC-COV1901 (IR: 0.013-0.064) and BNT162v2 (IR: 0.015-0.045). VE against the severity of AZD1222 or it as primary series ranged from 65.9% to 77.7%; mRNA vaccines ranged from 86.4% to 96.1%; and protein-based vaccines ranged from 91.4% to 96.2%. A similar pattern of VE against death ranged from 60.9% to 73.7%, 88.2% to 96.2%, and 90.3% to 95.6%.

Conclusion: Individuals who received their primary series as AZD1222 might not have adequate protection against Covid-19 severity so encourage those vulnerable groups to receive additional booster doses. The study also indicated that protein subunit vaccines provide similar protection against severity and death as mRNA vaccines.

Vaccine Effectiveness and Severity and Death Incidence Rate by Vaccine Type and Mix-and-Match Groups

Vaccines Effectiveness Analysis	Demography	Severity incidence	VE against severity		Death incidence	VE against death	
	Case number	Rate (per 10,000 person day)	Among all Ages	Among Elderly (65+)	Rate (per 10,000 person day)	Among all Ages	Among Elderly (65+)
Primary series: AZD1222 (AstraZeneca)							
AZ + AZ + AZ	12,540	0.762	65.9% (65.1%–70.8%)	46.2% (5.1%–69.5%)	0.269	60.9% (53.1%–63.1%)	45.1% (-32.3%–77.2%)
AZ + AZ + Moderna	4,652,714	0.507	69.8% (68.8%–70.8%)	44.2% (42.1%–46.2%)	0.191	61.1% (58.8%–63.2%)	44.6% (41.2%–47.7%)
AZ + AZ + BNT	1,598,320	0.390	74.9% (73.4%–76.3%)	32.1% (27.6%–36.3%)	0.127	71.0% (68.0%–73.8%)	39.1% (32.4%–45.2%)
AZ + AZ + Medigen	313,506	0.477	77.7% (74.5%–80.2%)	54.0% (47.2%–59.7%)	0.171	73.7% (68.0%–78.4%)	58.0% (47.8%–66.1%)
Primary series: mRNA-1273 (Moderna)							
Moderna+Moderna+Moderna	3,012,619	0.353	87.4% (86.8%–88.0%)	90.5% (90.0%–91.0%)	0.091	90.0% (89.1%–90.9%)	93.1% (92.4%–93.7%)
Moderna+Moderna+BNT	328,890	0.316	86.4% (84.4%–88.1%)	88.1% (86.2%–89.7%)	0.086	88.2% (84.7%–90.9%)	90.3% (87.3%–92.6%)
Moderna+Moderna+Medigen	107,957	0.471	84.9% (81.4%–87.7%)	89.1% (84.5%–91.3%)	0.125	87.7% (81.8%–91.7%)	92.3% (88.2%–95.0%)
Primary series: BNT162v2 (BNT)							
BNT + BNT + BNT	1,839,690	0.061	95.8% (95.1%–96.4%)	84.3% (79.8%–87.8%)	0.016	95.6% (94.0%–96.7%)	87.0% (79.6%–91.7%)
BNT + BNT + Moderna	2,510,303	0.064	96.1% (95.2%–96.7%)	81.8% (77.4%–85.3%)	0.015	96.2% (95.1%–97.1%)	86.5% (79.8%–91.0%)
BNT + BNT + Medigen	93,493	0.197	90.7% (89.3%–93.7%)	74.5% (53.0%–85.3%)	0.045	91.9% (82.0%–96.4%)	77.3% (59.3%–91.5%)
Primary series: MVC-COV1901 (Medigen)							
Medigen + Medigen + Medigen	341,841	0.196	91.4% (89.6%–92.8%)	87.0% (83.3%–89.8%)	0.064	90.3% (86.6%–93.0%)	86.9% (80.4%–91.2%)
Medigen + Medigen + Moderna	219,562	0.113	92.3% (89.7%–94.7%)	82.0% (70.6%–88.9%)	0.034	91.1% (85.9%–94.6%)	78.9% (55.9%–90.9%)
Medigen + Medigen + BNT	149,928	0.044	96.2% (93.3%–97.7%)	69.0% (40.4%–83.9%)	0.013	95.6% (89.2%–98.3%)	81.7% (26.6%–95.4%)

356 IMMUNOGENICITY OF SARS-COV-2 VACCINES BY VACCINE TYPE IN RANDOMISED CLINICAL TRIALS

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Background: Currently five SARS-CoV-2 vaccines are approved in North America (FDA) and Europe (EMA). Across the world other vaccines have been developed but not approved in high-income countries. Of the approved vaccines, 2 are mRNA vaccines, 2 are viral vectored vaccines, and 1 is a protein subunit vaccine. As immunogenicity markers are increasingly being used by regulatory agencies as surrogate markers for vaccine efficacy to inform authorization decisions, this meta-analysis compared the size of immunogenicity responses response elicited by the different COVID-19 vaccine types (mRNA, protein subunit, inactivated virus, viral vectors) and approved and unapproved COVID-19 vaccines.

Methods: Systematic review of trial registers and databases identified RCTs for SARS-CoV-2 vaccines. Risk of bias analysis was conducted using the Cochrane Risk of Bias tool. High risk of bias studies were excluded from analysis. Meta-analysis of seroconversion rates and geometric antibody titers (GMT) for neutralising (NAb) and anti-spike antibodies was conducted, each compared with a placebo using random effects model Cochrane-Mantel Haenszel Tests.

Results: All studies assessed immunogenicity of COVID-19 vaccines on healthy non-immunocompromised adults between the age of 18 and 59. Statistically significant difference was identified between the different vaccine types for NAb GMT, anti-spike GMT, NAb seroconversion, and anti-spike seroconversion ($P< 0.00001$ for all). Conversely, no statistical significant difference was identified between approved and unapproved vaccines for NAb seroconversion ($P=0.39$), Nab GMT ($P=0.36$), anti-spike seroconversion ($P=0.07$), and anti-spike GMT ($P=0.54$). mRNA vaccines had the best immunogenicity results for NAb seroconversion, GMT, and anti-spike seroconversion. Viral vector vaccines had the lowest results for NAb seroconversion and GMT, while inactivated viruses had the lowest result for anti-spike seroconversion and mRNA vaccines for anti-spike GMT. High heterogeneity was observed across the different studies.

Conclusion: This metanalysis of 35 randomised trials in 33,813 participants showed approved and unapproved vaccines to be comparable in post-vaccination GMT values and seroconversion for both NAb and anti-spike. However, while comparing COVID-19 vaccines by vaccine types, statistically significant differences are observed. Variations in study designs, populations enrolled, and infection prevalence during trial duration could have influenced results.

357 VSV-BASED COVID VACCINE FOR THE PREVENTION OF BREAKTHROUGH SARS-CoV-2 INFECTIONS

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Background: More than 12 billion doses of COVID-19 vaccine administrations and over 630 million natural infections should have developed adequate levels of herd immunity over the last three years. However, there have been many new waves of coronavirus infections. The development of safe and effective vaccines to control breakthrough SARS-CoV-2 infections remain an urgent priority. We have developed a recombinant VSV vector-based vaccine to fulfill this worldwide need.

Methods: We have used a recombinant vesicular stomatitis virus (rVSV)-based prime-boost immunization strategy to develop an effective COVID-19 recall vaccine candidate. We have constructed an attenuated recombinant VSV genome carrying the full-length Spike protein gene of SARS-CoV-2. Adding the honeybee melittin signal peptide (*msp*) at the N-terminus enhanced the protein expression and adding the VSV G protein transmembrane domain and the cytoplasmic tail (*Gtc*) at the C-terminus of the Spike protein allowed efficient incorporation of the Spike protein into pseudotype VSV.

Results: In immunized mice, rVSV with chimeric rVSV-*msp*-S-*Gtc* induced high levels of potent neutralizing antibodies (nAbs) and CD8+ T cell responses, while the full-length Spike with *Gtc* proved to be the superior immunogen. More importantly, rVSV-*msp*-S-*Gtc*-vaccinated animals were completely protected from subsequent SARS-CoV-2 challenges. Furthermore, rVSV-Wuhan and rVSV-Delta vaccines, and an rVSV-Trivalent (mixed rVSV-Wuhan, -Beta and -Delta) vaccine elicited potent nAbs against live SARS-CoV-2 Wuhan (USAWA1), Beta (B.1.351), Delta (B.1.617.2) and Omicron (B.1.1.529) viruses. Heterologous boosting of rVSV-Wuhan with rVSV-Delta induced strong nAb responses against Delta and Omicron viruses, with the rVSV-Trivalent vaccine consistently inducing effective nAbs against all the SARS-CoV-2 variants tested. All rVSV-*msp*-S-*Gtc* vaccines also elicited an immunodominant Spike-specific CD8+ T cell response.

Conclusion: rVSV vaccines targeting SARS-CoV-2 variants of concern can be considered as an effective booster vaccine in the global fight against COVID-19.

358 HOSPITAL PROTECTION CORRELATES IN OUTPATIENT COVID-19 CONVALESCENT PLASMA RECIPIENTS

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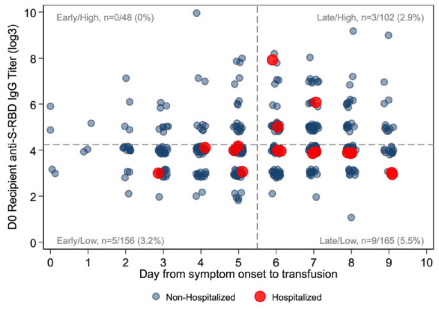
Background: High titer COVID-19 convalescent plasma (CCP) reduces hospitalizations among immunocompetent outpatients. This study evaluated recipient post-transfusion S receptor binding domain (S-RBD) IgG antibody levels and the association of progressing to hospitalization among unvaccinated outpatients with COVID-19 treated with CCP or control plasma.

Methods: This analysis focused on participants from a multicenter double-blind, randomized, controlled trial comparing treatment of outpatients with COVID-19 convalescent plasma (CCP) or control plasma without SARS-CoV-2 antibodies. Participants with confirmed SARS-CoV-2 infection were transfused within 9-days of symptom onset between June 2020 and October 2021 (n=110 vaccinated control; n=105 vaccinated CCP; n=464 unvaccinated control; n=472 unvaccinated CCP; total n=574 control and n=577 CCP recipients). All subjects had specimens collected the day prior to transfusion (D-1), within 30 minutes after transfusion (D0), 14 (D14), 28 (D28), and 90 (D90) days post-transfusion. Ancestral SARS-CoV-2 S-RBD was measured by an in-house validated ELISA. All 54 COVID-19-related hospitalizations occurred within 2 weeks of transfusion.

Results: Post-transfusion anti-S-RBD IgG levels on D0 were significantly greater for CCP (median=4 titer,$\log_3$) compared to control (median=2 titer,$\log_3$; $p < 0.001$) recipients. Neither sex nor age impacted antibody levels following CCP treatment at D14, D28, and D90. Vaccinated recipients had greater titers than unvaccinated recipients prior to transfusion with little change in titers post-transfusion. Unvaccinated recipients had low antibody titers on D-1 with CCP recipients exhibiting a significant increase in titer from D-1 to D0 compared to controls (mean fold change=1.89; $p < 0.001$). Among unvaccinated recipients, those who received CCP transfusion late (>5 days after symptom onset) and had low D0 antibody levels (< 4.24 titer, log3) had the greatest proportion of hospitalizations (5.5%). In contrast, those who received CCP transfusion early (< 5 days after symptom onset) with high D0 antibody levels (>4.24 titer, log3) had no hospitalizations. Unvaccinated CCP recipient anti-S-RBD IgG antibody levels on D0 correlated with donor anti-S-RBD IgG antibody levels (r=0.30, $p < 0.001$).

Conclusion: Among unvaccinated outpatients with COVID-19, CCP recipient antibody dilutional titers after transfusion over 540 titer correlated with protection against hospitalization when transfusion occurred within 5 days of symptom onset.

Figure of the proportion of hospitalizations by early vs. late transfusion and high vs. low recipient antibody levels



Analysis of anti-S-RBD IgG (titer, $\log_3$) in unvaccinated COVID-19 convalescent plasma (CCP) recipients at D0 grouped by number of days from symptom onset to transfusion. CCP recipients receiving high titer plasma early after COVID-19 symptom onset have the lowest proportion of hospitalizations.

359 SARS-CoV-2 INFECTIONS AMONG 275 PATIENTS WITH TIXAGEVIMAB/CILGAVIMAB PROPHYLAXIS

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Background: At the end of 2021, concomitantly with the beginning of Omicron variant circulation, pre-exposure prophylaxis with the dual monoclonal long-acting monoclonal antibodies tixagevimab/cilgavimab became available in France to protect patients non-responding or non-eligible to SARS-CoV-2 vaccination at risk of severe COVID-19.

Methods: This study included patients who received tixagevimab/cilgavimab for pre-exposure prophylaxis independently of vaccination status or previous SARS-CoV-2 infection. This prophylaxis strategy was implemented at the Bichat-Claude Bernard University Hospital, Paris since December 2021 Last date of follow-up was November 1st, 2022. Incident SARS-CoV-2 infections were detected based on positive RT-PCR result and/or anti-nucleocapsid antibodies seroconversion. Severe COVID-19 was defined as an infection leading to an hospitalization requiring oxygenotherapy and/or high dose corticotherapy.

Results: Among the 275 patients who received a tixagevimab/cilgavimab pre-exposure prophylaxis, 55% (n=153) were solid organ transplant recipients (50% lung, 46% kidney, 4% heart transplants), 42% (n=116) had an autoimmune disease, and 3% (n=6) had other indications. 51% (n=141) of all patients received rituximab. No severe adverse event of tixagevimab/cilgavimab was observed. Incident SARS-CoV-2 infection was diagnosed in 67 patients (24%). Among them, 59% (n=40) were solid organ transplant recipients, 36% (n=24) had an autoimmune disease and overall 52% had received rituximab. For the 56 patients whose infection date was available, the median delay between the last infusion of tixagevimab/cilgavimab and SARS-CoV-2 infection was 62 days (IQR=[30-97]). During the study period, 57% of incident infections occurred between December 17th, 2021 and May 31st, 2022, when BA.1 and BA.2 were the major Omicron sublineages in France, and 43% between June 1st, 2022 and November 2022 1st, a period during which BA.4 and BA.5 were predominant in France. Severe COVID-19 occurred in 6 patients out of 67 (9%); 5 were solid organ transplant recipients and 3 received rituximab. No death due to COVID-19 was reported.

Conclusion: Overall, 76% of patients receiving pre-exposure prophylaxis with tixagevimab/cilgavimab had no incident SARS-CoV-2 infection during the study period. Severe COVID-19 was observed in 9% of infected patients. These results suggest a potential protective effect in-vivo of tixagevimab/cilgavimab during the study period despite the circulation of different Omicron sublineages.

360 CD8+ T CELL CLONES FROM PRIOR SARS-CoV-2 INFECTION PREDOMINATE AFTER mRNA VACCINATION

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Background: Hybrid immunity is more protective than vaccination or prior infection alone. To understand the formation of hybrid immunity, we studied how SARS-CoV-2 mRNA vaccines interact with T cell memory by tracking spike (S) specific T cells in cohorts of hospitalized ($n = 19$) or non-hospitalized ($n = 34$) COVID-19 convalescents. We hypothesized that S-reactive CD4 and CD8 T cells would increase in response to serial vaccine doses and reflect prior immune exposure at the clonal level.

Methods: After vaccination, we stimulated PBMCs from 12 participants (8M/4F) with peptides spanning S. Activated cells (CD69+CD137+) were sorted and CD4/CD8 phenotype linked with paired TRB-TRA sequences at single cell resolution. S-reactive TRB sequences were mapped within 4-6 serial blood and post-booster nasal TRB repertoires to evaluate S-reactive CD4 and CD8 T cell clonotypic kinetics spanning convalescence to boost. PBMCs from 53 participants were sequenced with the ImmunoSEQ assay to evaluate S-reactive TRB breadth using a database of S-assigned TRB sequences (Adaptive Biotechnologies), comparing S-reactive TRB diagnostic breadth by hospitalization status (Wilcoxon test).

Results: SARS-CoV-2 mRNA vaccination provoked strong T cell clonal expansion in most participants. At 8-12 months after infection, each primary mRNA dose increased the abundance and diversity of S-specific T cells. Clonal and integrated expansions were larger in CD8 than in CD4 T cells. At the convalescent time point, we observed greater diagnostic S-reactive CD4 T cell breadth in hospitalized vs. non-hospitalized patients ($p< 0.01$). CD4 T cell S breadth was again higher in previously hospitalized persons after the 2nd primary ($p=0.02$) and booster ($p< 0.01$) doses, suggesting that diverse CD4 T cell memory after severe infection leads to increased repertoire diversity after vaccination. S-specific T cells with identical TCRs were detectable in blood and the nasal mucosa, with specificity confirmed using a TRA/TRB transgenic T cell with the matching receptor.
Conclusion: Although both S-specific CD8 and CD4 T cell memory are established by prior infection, S-specific CD8 T cells predominated in blood after primary vaccination, with some clonotypes showing up to 1000-fold expansion across 1-2 mRNA doses. Vaccine-reactive CD8 clonotypes were present at the barrier nasal site after booster mRNA dosing. Severe disease imprinted a highly diverse S-reactive CD4 repertoire persisting through vaccination.

361 LIMITED INDUCTION OF LUNG-RESIDENT MEMORY T CELLS BY SARS-CoV-2 mRNA VACCINATION

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Background: Resident memory T cells (T_{RM}) present at the respiratory tract may be essential to enhance early SARS-CoV-2 viral clearance, thus limiting viral infection and disease. While long-term antigen-specific T_{RM} are detectable beyond 11 months in the lung of convalescent COVID-19 patients after mild and severe infection, it is unknown if mRNA vaccination encoding for the SARS-CoV-2 S-protein can induce this frontline protection.
Methods: We obtained cross-sectional paired blood and lung biopsy samples from patients (n=30) undergoing lung resection for various reasons and assigned them to one of four groups: I.) uninfected unvaccinated individuals (n=5), II.) unvaccinated long-term SARS-CoV-2 convalescent individuals (between 6.0-10.5 months post-infection; n=9), III.) uninfected and long-term vaccinated individuals (between 6.0-7.7 months after the second or third dose; n=10), and IV.) uninfected and short-term vaccinated individuals (between 1.3-1.8 months after the third or fourth dose; n=6). We determined the presence of SARS-CoV-2-specific CD4+ and CD8+ T cells in blood and lung samples after exposure of cells to M, N, and S peptide pools, followed by flow cytometry to detect T_{RM} cells expressing interferon (IFN)γ and/or CD107a, as a degranulation marker.
Results: We found that the frequency of CD4+ T cells secreting IFNγ in response to S-peptides was variable but detectable in blood and lung up to 8 months after mRNA vaccination. Moreover, the IFNγ response of CD4+ T cells in the lung of mRNA-vaccinated patients was similar to the response found in convalescent patients. However, in mRNA-vaccinated patients, lung responses presented less frequently with a T_{RM} phenotype compared to convalescent infected individuals and, strikingly, polyfunctional CD107a+ IFNγ+ T_{RM} were virtually absent in vaccinated patients.
Conclusion: mRNA vaccines might induce memory responses within the lung parenchyma in some patients, potentially contributing to the overall disease control. However, the robust and broad T_{RM} response established in convalescent-infected individuals may offer advantages at limiting disease if the virus is not blocked by initial mechanisms of protection, such as neutralization. Our results warrant investigation of mucosal vaccine-induced resident T cell responses in establishing superior site-specific protective immunity.

362 CD40.SARS.CoV2 VACCINE, BUT NOT mRNA, INDUCES SPECIFIC CD8+ T MEMORY STEM CELLS

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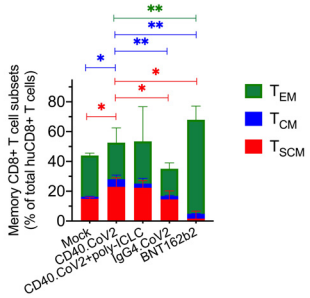
Background: Vaccination plays a major role in controlling SARS-CoV2 infection but faces the issue of short-term protection. Beyond the generation of Abs, induction of memory CD8+T cells with stem cell-like (Tscm) properties is essential for long-term immunity to viruses. We have designed a sub-unit CD40.CoV-2 vaccine which targets Spike (S) and nucleocapsid (N) regions from SARS-CoV-2 to antigen presenting cells with comparable immunogenicity and protective effect than mRNA BNT162b2 (Pfizer-BioNTech) in preclinical models (Coléon S. EBioMed 2022). We hypothesized that CD40.CoV2 vaccine will elicit CD8+ Tscm cells.
Methods: CD40.CoV2 vaccine is a fully humanized mAb fused to RBD (aa 318-541) and N (aa 276-411). Humanized (hu) NSG mice (HIS-mice) (n=6/group) received: i) CD40.CoV2 (10 µg equal to 1.3 µg of RBD, i.p.) +/- poly-ICLC (TLR3 agonist; 50µg) or ii) BNT162b2 (1µg, i.m.); iii) IgG4.CoV2 (10µg, i.p.) as non-CD40-targeting control. Phenotype and function of splenic S and N-specific T cells were assessed at W5.
Results: The CD40.CoV2 vaccine +/– poly-CLC induced significant S and N-specific Th1 huCD4+, cytokines-secreting huCD8+ T cells and RBD-specific IgG-switched huB cells as compared to mock injections and non-targeted IgG4.CoV2. CD40.CoV-2 vaccine +/– adjuvant induced higher frequencies of huCD8+ Tscm (CD95+ CD45RA+ CD62L+ ; median, (IQR) 22.4% (12.3-27.4) and 23% (20.7-29.1) +/– adjuvant, respectively) and central memory (T_{CM}; CD45RA- CD62L+) CD8+ T cells (2.7% (2.3-6.2) and 5.1% (3.8-7.8) +/– adjuvant, respectively). In contrast, BNT162b2 induced predominantly effector memory (T_{EM}, CD45RA– CD62L– ; median, (IQR) 63.1% (47.3-72.3)) but not Tscm (1.6% (0.9-6.6)) (figure). CD40.CoV-2 induced huCD8+ Tscm cells exhibit ; i) a higher proliferation index than T_{CM} and T_{EM}; ii) a functional profile secreting TNF and IFNγ after restimulation with RBD or N peptides; cardinal features of Tscm cells.
Conclusion: The CD40.SARS.CoV2, but not BNT162b2 vaccine, stimulates selective enrichment in S-and N-specific CD8+ Tscm cells that support long-lasting anti-viral immunity. CD40.CoV2 sub-unit is under clinical development as a booster vaccine aimed to maintain durable anti-viral T and humoral responses. The CD40.SARS.CoV2 vaccine specifically elicits huCD8 Tscm cells.



Frequencies of T_{SCM} (stem cell-like memory), T_{CM} (central memory) and T_{EM} (effector memory) cells among the human CD8 T cells in the spleen of HIS-mice, one week post-boost with indicated vaccines.

363 SARS-CoV-2 VACCINE-INDUCED T CELL RESPONSES IN CANCER PATIENTS UNDERGOING TREATMENT

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Background: mRNA vaccines have proven useful in protecting vulnerable populations against SARS-CoV-2 infection. However, certain therapeutics, specifically those used in cancer treatment, reduce mRNA vaccine-induced humoral responses against SARS-CoV-2. The effects on T cell responses are not well characterized. Here, we evaluate SARS-CoV-2 spike-specific T cell responses over the course of one year in solid tumor patients in BC, Canada.
Methods: 18 female, solid-tumor patients from the BC Cancer Agency were enrolled in this prospective, cohort study, with 7 patients receiving cytotoxic chemotherapy and 11 patients receiving non-cytotoxic treatments. Whole blood was collected 1-month (T1) and one-year +/– 1-month (T2) post series completion (2 mRNA doses). Antigen-induced marker assays (AIM assays) were used to quantify CD4+ and CD8+ T cell responses, where whole blood was stimulated with ancestral or omicron SARS-CoV2 Spike peptide pools or unstimulated for 48 hours at 37° C, fluorescently stained for activation markers CD25 and OX40 (CD4+ T cells) or CD69 and CD137 (CD8+ T cells), and analyzed using a 5-laser flow cytometer. Phenotyping of antigen-specific CD4+ T cells was done in parallel to assess the frequency of spike-specific Tregs, Th1, Th2, Th9, Th17, and Th17.1 cells.

Results: All individuals had detectable levels of spike-specific CD4+ T cells at T2, while only 72.2% of individuals had detectable levels of spike-specific CD8+ T cells. Treatment type did not significantly impact the magnitude or phenotype of T cell responses, including those to Omicron. However, increased age was associated with decreased ancestral CD8+ T cell responses at T2. Further, ancestral and omicron responses were significantly different at T2, with decreased magnitude and altered phenotype of omicron-specific CD4+ T cells.
Conclusion: Here, we report that solid tumor patients, treated with either chemotherapy or biologics, mount robust T cell immunity to SARS-CoV-2 following vaccination. Additional data is needed to determine if these responses correlate with antibody levels and clinical illness.

364 NEUTRALIZING ACTIVITY AND T CELL RESPONSE AFTER BIVALENT THIRD BOOSTER DOSE IN PLWH

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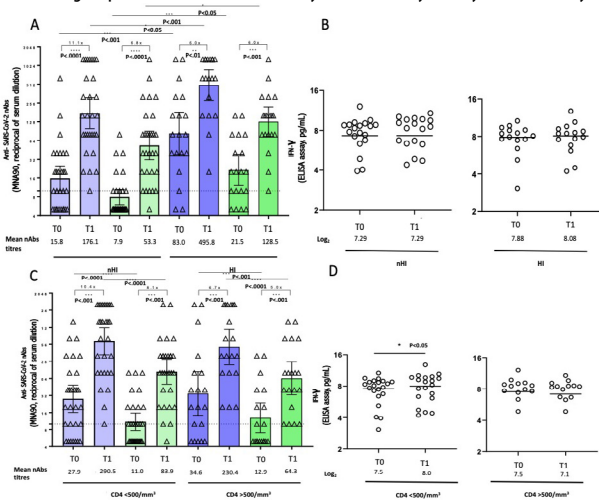
Background: Aim of the study was to analyze neutralizing activity against BA.5,BQ.1.1 and T cell response after 3rd booster dose [3BD (5th shot)] with BA.4/5 bivalent vaccine by hybrid immunity (HI) and CD4 count in advanced PLWH.
Methods: In PLWH with previous AIDS and/or CD4< 200/mm^3 receiving 3BD (original strain/BA.4/5),immunogenicity was assessed at time of 3BD (T0) and at day 15 (T1) by microneutralization assay [MNA90] against Omicron BA.5, BQ.1.1 and by IFNγ-ELISA. PLWH were stratified by HI vs. nHI and by CD4 count at T0 (>or< 500/mm^3). For crude mean comparisons, neutralizing antibodies (nAbs) were expressed in natural scale and fold changes, IFNγ and all values for regression analyses in log$_2$ scale, paired t-test used to test changes over T0-T1. Two 2-arms parallel trials were emulated: HI and CD4 count as exposure, log$_2$ nAbs and IFNγ as outcome. Average treatment effect (ATE) of the two exposures were estimated by marginal models weighted for potential confounders (age, CD4 nadir, years from AIDS; when HI was the exposure also CD4 count).
Results: N=48 PLWH on ART, 15% female, median age 56 yrs, 45% >1 comorbidity, 87% with previous AIDS, median CD4 nadir 44 cell/mm^3 (16-102), 98% with HIV-RNA < 50 cps/mL. A significant increase of nAbs against BA.5 (fold-increase 8.8,p< 0.0001) and BQ.1.1 (6.4, p< 0.0001) was observed from T0 to T1. At T1, in nHI (n=29), mean nAb was 176 and 53 against BA.5 and BQ.1.1, respectively, with a fold change reduction (FCR) vs BA.5 of 3.3; in HI (n=19), 496 and 128, respectively, with a FCR of 3.8 (Fig.1A). After controlling for confounders, HI was associated with a higher level of neutralizing response against BA.5 [ATE=1.17 log$_2$ (95%CI 0.34;2.00), P=0.006] but not against BQ.1.1 [0.65 log$_2$ (-0.18;1.48), p=0.124]. At T1, among PLWH with CD4 count< 500 (n=29), mean nAb was 290.8 and 83.9 against BA.5 and BQ.1.1, respectively, with a FCR of 3.4; in those with CD4 count >500 (n=19), 230.4 and 64.3, respectively, with a FCR of 3.6 (Fig. 1C).There was no impact of CD4 count on neutralization after controlling for potential confounding factors. No evidence for a difference between T0 and T1 was detected for IFNg (Fig.1B,D).
Conclusion: In PLWH with advanced diseases, bivalent BA.5 3BD elicited strong neutralization against BA.5, and retained cross-neutralization against BQ.1.1, even if 3 times lower. HI but not CD4 count >500 appeared to enhance neutralization against BA.5. Importantly, bivalent vaccine appeared to have no effect on T-cell mediated response.

Figure 1 A-D. Mean values of MNA90 and IFN-γ from T0 to T1 according to hybrid immunity (A,B) and CD4 count (C,D). Blue plots represent nAbs against BA.5, green plots represent nAbs against BQ.1.1. Wilcoxon test was used to compare nAbs, IFNγ in each group, Mann-Whitney test for comparisons between different groups. Abbreviations: nHI, no hybrid immunity ; HI, hybrid immunity.



365 12-MONTH HUMORAL RESPONSE AFTER mRNA COVID-19 VACCINATION IN PEOPLE LIVING WITH HIV

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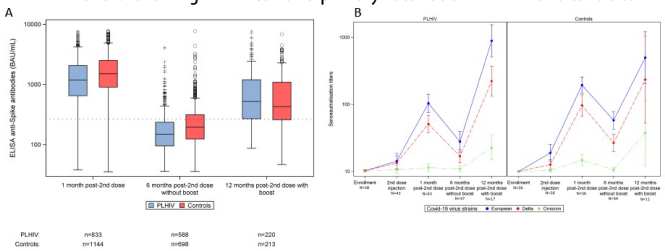
Background: We compared the 12-month post primary vaccination humoral immune response to mRNA COVID-19 vaccines in PLHIV and controls.
Methods: PLHIV and HIV-negative healthy controls included in the French national multi-center prospective COVID 19 vaccine cohort study ANRS0001S COV-POPART were analyzed. Percentage (95% CI) of responders (positive anti-Spike SARS-CoV-2 IgG antibodies) and geometric means titers (95% CI) of anti-Spike SARS-CoV-2 IgG antibodies (BAU/mL) were assessed at 1 month and 6 months (M) after the 2nd dose of the primary vaccination and at 12 months in those who received a booster dose. Specific neutralizing antibodies (nAbs) (*in vitro* neutralization assay against original, Delta and Omicron BA.1 strains) were estimated in a subset of participants. Serological tests (ELISA Euroimmun) and seroneutralization were performed centrally.
Results: Overall, 858 PLHIV and 1156 controls were included. PLHIV were older than controls: 55.2 years, (49.6-60.6) vs 46.6 years (36.3-56.6) and more frequently male (75.1% vs 48.9%). Among PLHIV at inclusion, 97.3% were under antiretroviral therapy, 95.6% had an undetectable viral load and 71.8% had CD4 counts above 500 cells/mm^3. Participants had namely received BNT162b2 as the primary vaccination (93% in PLWHIV vs 84% in controls) and 53.1% had received a booster dose (57.2% in PLHIV (median time after the 2nd dose: 6.1 M [5.9-6.7]) and 50.1% in controls (median time 6.0 M [5.5-6.2])). Percentage of responders after the 2nd dose was lower in PLHIV than controls ((98.7% [97.7; 99.3] *vs* 99.9% [99.5; 99.9], p=0.0001)). PLHIV had significantly lower levels of anti-Spike antibodies at 1 M ((1188 [650; 2067] vs 1506 [950; 2507] BAU/mL, p< 0.0001)) and 6 M (149 [95; 235] *vs* 194 [124; 314] BAU/mL, p=< 0.0001) but similar levels at 12 M (520 [269; 1198] vs 427 [259; 1087] BAU/mL, p=0.3387) (Figure A). PLHIV had significantly lower nAbs against original, Delta and Omicron BA.1 strains at 1, 6 and 12 M after primary vaccination compared to controls. The booster dose significantly increased the titers of nAbs against original and Delta strains and, to a lower extent, against Omicron (Figure B).
Conclusion: PLHIV had high response rates to mRNA COVID-19 vaccines but lower titers of antibodies and nAbs at 1 and 6 M after primary vaccination than controls. One mRNA booster dose increased SARS-CoV-2 IgG antibodies titers

to similar levels to controls but neutralizing activity especially against Omicron remained lower.

Median anti-Spike antibodies (A) and seroneutralization (B) titers at 1, 6 and 12 months following mRNA Covid-19 primary vaccination in PLHIV and controls.



366 SARS-CoV-2 LIVE VIRUS NEUTRALIZATION AFTER FOUR COVID-19 VACCINE DOSES IN PWH ON ART

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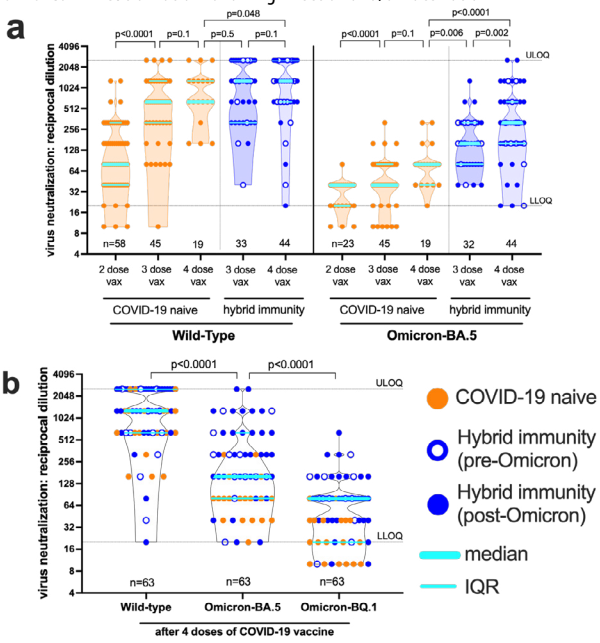
Background: Limited data exist regarding the immune benefits of fourth COVID-19 vaccine doses in people with HIV (PWH) receiving antiretroviral therapy (ART), particularly given that most have now experienced SARS-CoV-2 infection. We measured the effect of fourth doses on SARS-CoV-2 neutralization in 63 PWH, including 19 SARS-CoV-2-naive and 44 SARS-CoV-2-experienced participants.

Methods: Wild-type (WT)-, Omicron-BA.5 and Omicron-BQ.1-specific neutralization activities were longitudinally quantified using live virus assays up to one month post-fourth vaccine dose. Multiple linear regression was used to investigate the relationship between sociodemographic, health and vaccine-related variables and SARS-CoV-2 neutralization.

Results: Participants (54 male; 9 female) received monovalent (44%) or bivalent (56%) mRNA fourth doses. In COVID-19-naive PWH, a fourth dose enhanced WT- and BA.5-specific neutralization modestly above three-dose levels (p=0.1). In COVID-19-experienced PWH, a fourth dose enhanced WT neutralization modestly (p=0.1) and BA.5 neutralization significantly (p=0.002). Consistent with the humoral benefits of 'hybrid' immunity, the highest neutralization was observed in COVID-19-experienced PWH after a fourth dose. Of note, PWH with Omicron-era infections exhibited higher WT-specific (p=0.04), but comparable BA.5- or BQ.1-specific neutralization, compared to PWH with pre-Omicron-era infections. Overall, BA.5 neutralization was significantly lower than WT in all participants regardless of COVID-19 experience, and BQ.1 neutralization was significantly lower than BA.5 (all p< 0.0001). In multivariable analyses, fourth dose valency did not significantly affect neutralization magnitude, nor did sex, age nor CD4+ T-cell count (neither recent nor nadir). Rather, an mRNA-1273 fourth dose (versus a BNT162b2 one) was the strongest correlate of WT-specific neutralization, while prior COVID-19, regardless of infection era, was the strongest correlate of BA.5 and BQ.1-specific neutralization post-fourth dose.

Conclusion: Fourth COVID-19 vaccine doses, irrespective of valency, benefit PWH regardless of prior SARS-CoV-2 infection, but the highest neutralization of Omicron-BA.5 and BQ.1 variants post-fourth dose occurred in PWH with hybrid immunity. These results support existing recommendations that all adults receive a fourth immunization within 6 months of their third vaccine dose (or their most recent SARS-CoV-2 infection).

SARS-CoV-2 neutralization following infection and/or vaccination



367 IMMUNOGENICITY OF SARS-CoV-2 mRNA VACCINATION IN IDIOPATHIC CD4 LYMPHOPENIA

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Background: The rapid development of SARS-CoV-2 mRNA vaccines has been a remarkable success of the COVID-19 pandemic, but vaccine-induced immunity is heterogeneous in immunocompromised populations. We sought to determine the immunogenicity of SARS-CoV-2 mRNA vaccines in a cohort of people with idiopathic CD4 lymphopenia (ICL).

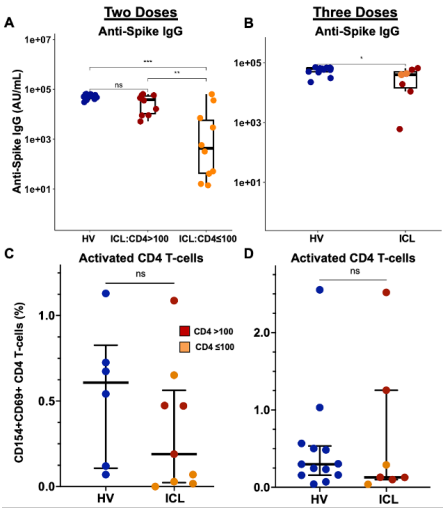
Methods: 25-patients with ICL followed at the National Institutes of Health on a natural history protocol were evaluated between 2020-2022. Blood and serum was collected within 4-12 weeks after their second and/or third SARS-CoV-2 mRNA vaccine dose. Twenty-three matched healthy volunteers (HVs) provided blood samples at similar timepoints post-mRNA vaccination on a separate clinical protocol. Pre-vaccine blood samples were also used when available. Anti-spike and anti-receptor binding domain antibodies were measured. T-cell stimulation assays were performed to quantify SARS-CoV-2 specific T-cell responses. Comparisons were made with Wilcoxon test.

Results: Twenty-participants with ICL had samples collected after their second mRNA vaccine and 7-individuals after the third dose. Median age at vaccination was 51-years (IQR: 44-62) and 12 were women (48%). Median CD4 T-cell count was 150 cells/μL (IQR: 85-188) at the time of vaccination, and 11-individuals (44%) had a baseline CD4 count ≤100 cells/μL. HVs had a median age of 54-years (IQR: 43-60) with 13-women (56.5%). Anti-spike IgG antibody levels were significantly greater in HVs than those with ICL after 2-doses. Lower SARS-CoV-2 IgG antibody production was primarily observed in those with baseline CD4 T-cells ≤100 cells/μl (Figure-1A). The decreased production in ICL remained after a third vaccine dose (Figure-1B). There was a significant correlation between anti-spike IgG and baseline CD4 count. Spike-specific CD4 T-cell responses in volunteers compared to those with ICL demonstrated similar levels of activation induced markers (CD154+CD69+) and cytokine production (IFNγ+, TNFα+, IL2+) after two or three mRNA vaccine doses. Quantitatively the smallest responses were observed in those with lower baseline CD4 T-cells (Figure 1C-D). Minimal SARS-CoV-2 CD8 T-cell responses were detected in both groups.

Conclusion: Patients with ICL and baseline CD4 T-cells >100 mount similar humoral and cellular immune responses to SARS-CoV-2 vaccination as healthy volunteers. Those with baseline CD4 T-cells ≤100 have impaired vaccine-

induced immunity and should be prioritized to additional boosters and continue other risk mitigation strategies.

Figure-1: SARS-CoV-2 specific antibody and T-cell responses after mRNA vaccination.



368 RESTORATION OF HUMORAL RESPONSE TO COVID-19 VACCINATION IN RITUXIMAB-TREATED PATIENTS

Wang-Da Liu, Tai-Chung Huang, Jann-Tay Wang, Hsin-Yun Sun, Shang-Ju Wu, Huai-Hsuan Huang, Chia-Yi Lin, Guei-Chi Li, Sui-Yuan Chang, Chien-Ching Hung
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Background: Previous studies had demonstrated that patients with hematologic malignancies had suboptimal antibody response after receiving COVID-19 vaccines, especially among those having previously treated with anti-CD20 monoclonal antibodies.

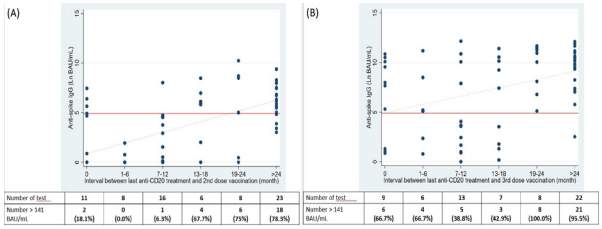
Methods: Adult patients with non-Hodgkin's lymphoma or chronic lymphocytic leukemia (CLL) were enrolled before receiving the second dose of SARS-CoV-2 vaccine. Determinations of anti-SARS-CoV-2 spike and nucleocapsid IgG titers were performed every 1-3 months, after they received the second and the third dose of SARS-CoV-2 vaccine, respectively. Patients were excluded from analysis if they were diagnosed with COVID-19. All serum samples were tested for anti-nucleocapsid antibody and those tested positive were excluded from subsequent analyses.

Results: A total of 85 participants were enrolled, including 42 (49.4%) with diffused large B-cell lymphoma, and 13 (15.3) with follicular lymphoma and 9 with CLL. 72 (84.7%) participants had received anti-CD20 monoclonal antibodies, with a median interval of 24 months between last anti-CD20 treatment and the second dose of vaccine, and 21 (24.7%) had HIV infection. Factors associated with failure to achieve an anti-spike IgG titer >141 BAU/mL within 12 weeks after the second dose of vaccine included HIV infection (adjusted odds ratio [aOR], 0.14; 95% CI, 0.04-0.51), active hematologic disease (aOR, 5.50; 95% CI 1.42-21.32), receipt of anti-CD20 monoclonal antibodies (aOR, 6.65; 95% CI 1.52-29.07), and receipt of two doses of homologous mRNA vaccination (aOR, 0.17; 95% CI 0.05-0.56).

In the participants having previously treated with anti-CD20 regimen, only 8.6% achieved an antibody response (>141 BAU/mL) in the first year, while 78.3% achieved anti-spike IgG titer > 141 BAU/mL after two years post B-cell depleting treatment. After the third dose of SARS-CoV-2 vaccine, 53.6% achieved an anti-spike IgG titer > 141 BAU/mL in the first year post anti-CD20 treatment.

Conclusion: Our study demonstrated that previous treatment with anti-CD20 monoclonal antibodies was associated a lower antibody response among patients with lymphoproliferative disorders receiving two doses of SARS-CoV-2 vaccine. While two doses of SARS-CoV-2 vaccines might not be sufficient even one year apart from the last dose of rituximab, a third dose of vaccine may boost anti-spike IgG particularly in the subset of recent exposure to rituximab.

Anti-spike IgG determined 1-3 months after the second (A) / third (B) dose of COVID-19 vaccine, stratified by the interval between last anti-CD20 regimen and the second / third dose of COVID-19 vaccine.



369 THREE DOSES OF COVID-19 VACCINES IN PWH: IMMUNOGENICITY AND EFFECTS ON HIV RESERVOIR

Vitaliy Matveev[1], Erika Benko[2], Erik Mihelic[1], Terry Lee[3], Karen Colwill[4], Robert Reinhard[5], Sebastian Grocott[6], Patrick Budylowski[1], Lela Kardava[7], Susan Moir[7], Jennifer Gommerman[1], Anne-Claude Gingras[1], Colin Kovacs[2], Mario Ostrowski[1]
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Background: People with HIV (PWH) older than age 55 have an enhanced risk of complications from SARS-CoV-2 infection. It is unclear whether COVID-19 vaccines with a booster are as durable in terms of immunogenicity in this cohort or whether these vaccines can destabilize HIV reservoirs.

Methods: We prospectively studied 91 PWH on cART aged 55 or over (n=91) and 23 age-matched individuals without HIV (control group, CG) who received three doses of COVID-19 vaccines (D1-D3) over 48 weeks. Participants received combinations of BNT162b2, mRNA-1273, and ChAdOx1. Of PWH, 42 were immune responders (IR), 20 were non-responders (INR), and 3 had a low-level viremia (LLV). Total and neutralizing Abs to SARS-CoV-2 spike (S) and RBD in sera and saliva, frequency of anti-RBD/NTD memory B cells (spectral flow cytometry), S-specific T cell immunity (IFN-g, IL-2 ELISpot) and HIV reservoirs in peripheral CD4+ T cells (IPDA) were measured.

Results: No significant differences in vaccine regimens or dosing intervals were observed between PWH and CG. Vaccines elicited equally strong anti-S IgG in PWH vs CG in serum and saliva, and RBD IgG in serum. Serum Abs peaked at 4w after D3. Week 48 serum IgG in PWH vs CG were 916 vs 919 BAU/mL for S ($p=0.624$) and 706 vs 752 for RBD ($p=0.198$), respectively. Week 48 median saliva S IgG: 48.1% AUC of the positive control in PWH vs 95.9% for CG ($p=0.384$). S IgA: 3.83 vs 20.5 in PWH vs CG ($p=0.039$). Median neutralizing titers post-D2 were significantly lower in PWH than in CG (NT50 82.9 vs 535, $p<0.001$). However, after D3, at 48w, PWH had similar titers as CG: 309 vs 269 ($p=0.745$), mirroring an increase in RBD/NTD-specific B cells in PWH. Anti-S T cell cytokine responses were stronger in IR PWH after D2 and D3 than in CG. Week 48 S IL-2 responses: median 135 SFC/10^6 PBMC vs 43.8 ($p<0.001$), but only 12.5 in INR ($p=0.001$ vs IR). COVID-19 vaccines did not affect the size of HIV reservoir in PWH (change in median frequency of intact proviruses from baseline: 95.0 vs 90.9, $p=0.952$), except in three LLV PWH (mean increase 93.7% at 48w).

Conclusion: PWH aged 55 and over show diminished neutralizing Ab responses to SARS-CoV-2 with two vaccine doses which are 'rescued' after a booster. PWH have lower S-specific IgA in saliva after vaccination which may affect protection. Enhanced S-specific T cell immunity in PWH suggests Th1 imprinting from pre-existent HIV infection. COVID-19 vaccines did not destabilize the HIV reservoir in most PWH but may pose potential risk in unsuppressed viremia.

370 EFFECTS OF COVID-19 mRNA VACCINATION ON HIV VIREMIA AND RESERVOIR SIZE IN PWH ON ART

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Background: Transient viremia has been reported after COVID-19 mRNA vaccination in ART-suppressed PWH, suggesting a stimulatory effect on the HIV reservoir. A recent study also reported that Nef-specific CD8+ T cells increased and acquired granzyme-B effector function following COVID-19 mRNA vaccination, and that this correlated with markers of immune-mediated suppression of HIV-transcribing cells. That study however did not investigate

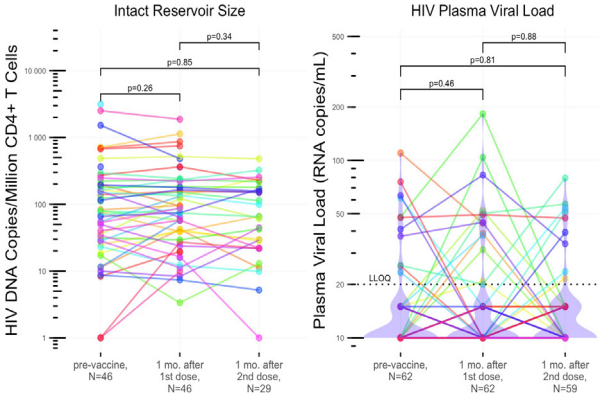
HIV viremia, nor did it detect significant reservoir size changes in the 13 participants assessed. We investigated changes in HIV viremia and reservoir size following COVID-19 mRNA vaccination in 62 ART-treated PWH.

Methods: Participants (55 male; 7 female) were sampled pre-vaccination, and one month after the first and second doses. Plasma HIV loads (pVL) were measured using the Cobas 6800 (LLOQ 20 copies/mL). Intact and total HIV copies/million CD4+ T cells were measured using the Intact Proviral DNA Assay. Anti-SARS-CoV-2 S serum antibody concentrations were measured using the Roche Elecsys Anti-S assay.

Results: Pre-vaccination, 82% of participants had pVL < 20 copies/mL (max 110 copies/mL). No significant changes in pVL were observed post-vaccination (all p >0.4): one month post-first and second doses, 79% and 85% of participants had pVL < 20 copies/mL (max 183 and 79 copies/mL), respectively. Pre-vaccination, the median intact reservoir size was 80 (IQR:28-197; n=46) HIV copies/million CD4+ T cells. Intact reservoir size did not change significantly post-vaccination (all p >0.2): one month post-first and second doses, medians were 85 (IQR: 29-184; n=46) and 65 (IQR:22-168; n=29) copies/million CD4+ T cells, respectively. No significant changes in total, nor 5' and 3' defective proviral burdens were observed post-vaccination (all p >0.1), nor were any significant changes observed in any outcome upon stratification by sex, COVID-19 vaccine regimen, or ART regimen (here, multiple tests were addressed using q-values). Finally, no correlations were observed between the SARS-CoV-2 anti-S antibody response magnitude, and either the magnitude of change in reservoir size, nor the observation of detectable viremia, following the first and second vaccine doses (all p >0.2).

Conclusion: Despite evidence that COVID-19 mRNA vaccination may induce HIV-specific immune responses, we observed no measurable changes in reservoir size nor lasting plasma viremia following COVID-19 mRNA immunization, regardless of anti-SARS-CoV-2 antibody response magnitude.

Intact HIV Reservoir Size and Plasma Viral Load following COVID-19 mRNA Vaccination



371 COVID-19 VACCINATION IMPACTS FUNCTIONAL IMMUNE RESPONSES AND PLASMA PROTEOME IN PLWH

Twan J.W Otten[1], Nadira Vadaq[1], Albert L. Groenendijk[1], Marc J. T. Blaauw[1], Willem A. J. W. Vos[1], Louise E. van Eekeren[1], Elise M. G. Meeder[1], Janneke E. Stalenhoef[2], Casper Rokx[3], Marvin A. H. Berrevoets[4], Leo A. B. Joosten[1], Mihai G. Netea[1], Andre J.A.M. van Der Ven[1]

2000HIV Functional Genomics Partnership Program

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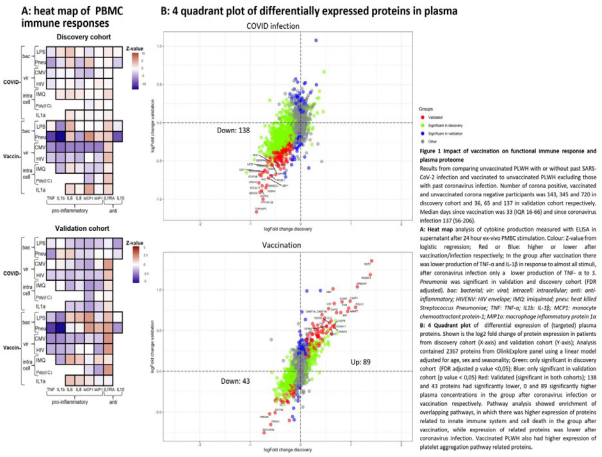
Background: The impact of COVID-19 infection or COVID-19 vaccination on the immune system of people living with HIV (PLWH) is unclear. We therefore studied the effects of COVID-19 infection or vaccination on functional immune responses and systemic inflammation in PLWH.

Methods: Between 2019 and 2021, 1985 virally suppressed, asymptomatic PLWH were included in the Netherlands in the 2000HIV study (NCT039948350): 1514 participants enrolled after the start of the COVID-19 pandemic were separated into a discovery and validation cohort. PBMCs were incubated with different stimuli for 24 hours: cytokine levels were measured in supernatants. ~3000 targeted plasma proteins were measured with Olink® Explore panel. Past COVID-19 infection was proven when a positive PCR was reported or when serology on samples from inclusion proved positive. Compared were unvaccinated PLWH with and without past COVID-19 infection, and PLWH with or without anti-COVID-19 vaccination excluding those with past COVID-19 infection.

Results: 471 out of 1514 participants were vaccinated (median days since vaccination: 33, IQR 16-66) and 242 had a past COVID-19 infection (median days since +PCR: 137, IQR 56-206). Alcohol, smoking, drug use, BMI, age, latest CD4 count and proportion with viral blips were comparable between groups. Systemic inflammation as assessed by targeted proteomics showed 89 upregulated and 43 downregulated proteins in the vaccinated participants. In contrast, individuals with a past COVID-19 infection display lower levels of 138 plasma proteins compared to the uninfected group (see figure). '*Innate immune system*' and '*cell death*' were upregulated in pathway analysis in vaccinated PLWH, but downregulated in COVID-19 infected participants. The increased systemic inflammation of the COVID-19 vaccinated group was accompanied by lower TNF-α and IL-1β production capacity upon restimulation with a range of microbial stimuli, while production of IL-1Ra was increased. In COVID-19 infected PLWH only a reduced production of TNF-α to *S. pneumonia* was significant. Vaccinated PLWH also showed upregulation of platelet aggregation pathways.

Conclusion: COVID-19 vaccination in PLWH leads to an increased systemic inflammation, but less effective cytokine production capacity of its immune cells upon microbial stimulation. This pattern is different from that of COVID-19 infection that leads to a decreased inflammatory profile and only minimal effects on cytokine production capacity.

Impact of COVID-19 and Vaccination on Functional Immune Response and Plasma Proteome



372 IMPACT OF GUT MICROBIOTA ON IMMUNOGENICITY TO COVID-19 VACCINES IN PLWH

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Background: Immune responses to SARS-CoV-2 vaccines in people living with HIV (PLWH) have been the focus of several recent studies. As the gut microbiome can influence vaccine immunogenicity, in this study we are the first to investigate whether the baseline gut microbiota can predict immune responses to the BNT162b2 SARS-CoV-2 vaccine in people living with HIV (PLWH) and healthy controls (HC).

Methods: Fecal samples were collected from PLWH (n=68) and HC (n=75) at baseline, prior to the first vaccine dose, to extract DNA for 16S rRNA sequencing. The individuals were part of the COVAXID Clinical trial, where humoral and cellular responses to SARS-CoV-2 vaccine were evaluated on day 35 after the first dose. Comprehensive bioinformatic tools were used for bacterial identification to further reveal the associations between gut microbiota and SARS-CoV-2 antibody, spike CD4+ T cell responses, and clinical parameters such as age, gender, CD4/CD8 ratio, and length of antiretroviral (ART) treatment.

Results: At day 35 post vaccination, HC showed significantly higher spike IgG titers than PLWH (p=0.0001). Interestingly, both phylogenetic and α-diversity were negatively correlated with antibody titers, in the whole cohort and

within groups. Similarly, individuals with low α-diversity had higher levels of spike specific CD4+T-cell responses. *Agathobacter*, *Lactobacillus*, *Bacteroides*, and *Lachnospira* were positively correlated with both antibody levels and spike-specific CD4+ T-cell responses while *Methanobrevibacter*, *Marvinbryantia*, *Cloacibacillus*, and *Succinivibrio* have a negative one. Within the PLWH group, the gut microbiota taxa associated with CD4+ counts, such as *Lachnospira* (p=0.002), *Oscillibacter* (p=0.019) and *Flavonifractor* (p=0.017), were found to be positively correlated with spike IgG levels. Additionally, the length of ART treatment and CD4/CD8 ratio displayed a positive association with bacterial diversity. Notably, different microbiome profiles and immune status in PLWH, affect their immune responses to vaccination.

Conclusion: Our results show potential associations between gut microbiota diversity and spike IgG responses after COVID-19 vaccination. These findings were consistent in the whole cohort, albeit group differences between the microbiome compositions in PLWH and HC were observed. Based on our findings, we propose that microbiome modulation could optimize immunogenicity to SARS-Cov-2 vaccines.

373 SEQUENTIAL IMMUNIZATION OF UPDATED COVID-19 DNA AND RNA VACCINES IN NONHUMAN PRIMATES

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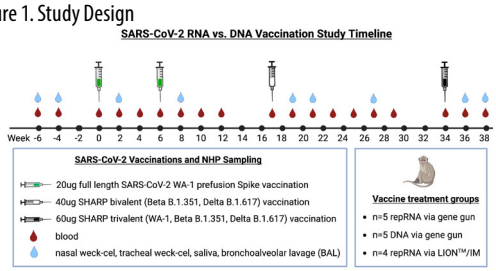
Background: COVID-19 vaccines that expand immunity against emerging variants of concern (VOC) are needed to protect against ongoing viral evolution. We investigated the impact of boosting nonhuman primates pre-immune to the original WA-1 strain with updated VOC vaccines on the breadth and magnitude of mucosal and systemic antibody (Ab) and T cell (Tc) responses.

Methods: Cynomolgus macaques were primed with 2 doses of WA-1 Spike protein encoded by either an IL-12 adjuvanted DNA vaccine administered by gene gun (GG) or a self-amplifying RNA vaccine (repRNA) delivered intramuscularly (IM) with a cationic nanocarrier (LION™/IM, HDT Bio) or by GG (**FIG 1**). A booster dose was administered at week 17 with DNA or repRNA vaccines expressing B.1.351 (Beta) and B.1.617 (Delta) Spike receptor-binding domains (RBDs) fused to influenza HA2 stem domain (SHARP, designed by AIR/JP) followed by a final Beta + Delta + WA-1 SHARP boost at week 34. Blood and bronchoalveolar lavages (BAL) were collected before and after each dose. Binding and neutralizing Ab to VOCs, including Omicron strains, were measured by ELISA and pseudovirus neutralization assays. Tc responses to Spike protein (WA-1 peptides) were measured by ELISpot. Immune responses were compared between groups and between blood vs lung using non-parametric statistical tests.

Results: Two doses of WA-1 DNA or repRNA vaccines induced broad Ab against all VOC with the repRNA vaccine inducing the highest titers. Boosting with VOC SHARP significantly increased mucosal and systemic Ab responses against all VOCs tested including Omicron. After final boost, all groups had comparable binding and neutralization Ab titers and Tc responses regardless of method of delivery (GG or LION™/IM) or formulation (DNA or repRNA). Tc responses were significantly higher in the BAL vs PBMC after WA-1 Spike doses (p=0.0420) and VOC SHARP boosters (p=0.0009).

Conclusion: The WA-1 strain primed for broad responses against VOCs that were significantly boosted with updated SHARP vaccines including responses against Omicron, even though this strain was not included in any dose. This suggests that sequential immunization with updated vaccines may broaden mucosal and systemic immunity against future VOCs. The repRNA vaccine initially induced the strongest responses, but there were no differences between RNA and DNA following additional booster doses, a result that supports development of a more cost-effective, room temperature stable DNA vaccine for worldwide boosters.

Figure 1. Study Design



374 NEUTRALIZING AND T CELL RESPONSE AGAINST MPOX VIRUS AFTER MVA-BN VACCINE

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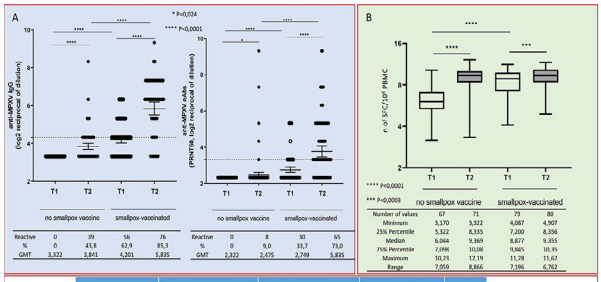
Background: Modified vaccinia Ankara-Bavarian Nordik (MVA-BN) was licensed for Mpox. Recent data estimated single dose effectiveness around 78%, whereas its ability to induce neutralising antibodies (nAbs) has been measured as relatively low. Whether historical smallpox vaccination (HiSXV) or HIV infection may impact MVA-BN response remains to be determined.

Methods: Blood samples collected from participants (pts) eligible for pre-exposure Mpox vaccination at the time of receiving the first dose (in non-primed) or single dose (in primed) of MVA-BN vaccine (T1) and one month later (T2). MPXV-specific IgG were measured by in-house immunofluorescence assay, using 1:20 as screening dilution; MPXV-specific nAbs by 50% plaque reduction neutralization test (PRNT50, starting dilution 1:10); IFN-γ-producing specific T cells to MVA-BN vaccine, by ELISpot assay. Probability of nAb response in primed vs non-primed at T2 was estimated in pts who had a titre < 10 at T1. McNemar test used to evaluate the overall response, while proportion becoming responders at T2 by exposure groups was compared by logistic regression. Average Treatment Effect (ATE) of the difference over T1-T2 by HiSXV was estimated after weighting for age using a linear predictor. Whether the effect of HiSXV on MVA-BN response may vary by HIV infection status was tested by including an interaction parameter in the models.

Results: Among the 180 persons self-identified as GBTMSM, 90 (50%) were historically smallpox vaccinated. Median age was 47 years (IQR 38-54). Among the 86 (48%) PLWH, 81% had a CD4 count of more than 500 cells/mm3. A significant increase in T-cell and nAb response over T1-T2 was observed (Fig.1A-B) and 46 of the 157 who were nAbs non responders at T1 became responders at T2 (McNemar p< 0.001). In this subset, the chance of achieving nAb response at T2 was higher in primed vs non-primed [OR=12.2 95% CI (3.4-44.0) after controlling for age]. Results were similar when comparing nAbs in ATE with a mean difference of 0.39 $\log_2$ (p=0.03). There was no evidence for a difference in T-cell response according to HiSXV (Fig.1C). There was no evidence that the effect of HiSXV on MVA-BN response varies by HIV status [OR in HIV-neg 18.3 vs HIV-pos 10.7, interaction p=0.54].

Conclusion: The first/single dose of MVA-BN triggers a humoral and cellular response with nAbs response greater in primed vs. non-primed participants independently of age. No evidence that HiSXV effect on nAbs response to MVA-BN differed by HIV status.

Figure 1. IgG, nAbs and T-cel response after first dose of MVA-BN A. Titers of MPXV-specific IgG and neutralising antibodies. IgG were measured by in-house immunofluorescence assay, using 1:20 as screening dilution; MPXV-specific neutralising antibodies (nAbs) by 50% plaque reduction neutralization test (PRNT50) starting dilution 1:10. Intra-group comparisons were performed with paired t-test; inter-group comparisons with unpaired t-test. B. Frequency of T cells responding to MVA-BN vaccine expressed as the number of SFC/10^6 PBMC was tested by interferon-γ ELISpot assay. Intra-group comparisons were performed with by Wilcoxon test; inter-group comparisons by Mann-Whitney test. C. Potential average change at time T2 post vaccine and Average treatment effect (ATE) from fitting a linear regression model (log_2 scale), weighted for age.



	Smallpox vaccine Yes vs. No	Mean (log2) in exposed (95% CI)	Mean (log2)in unexposed (95% CI)	ATE* (95% CI)	p-value
Elispot					
Double Robust		1.57 (-1.08, 4.22)	2.25 (-0.78, 5.27)	-0.68 (1.44, -2.79)	0.532
IGg					
Double Robust		1.06 (-0.82, 2.94)	0.38 (-0.51, 1.27)	0.68 (1.72, -0.36)	0.201
nAbs					
Double Robust		0.58 (0.01, 1.16)	0.20 (0.55, 0.94)	0.39 (0.73, 0.04)	0.029

375 COMPARISON OF SUBCUTANEOUS VERSUS INTRADERMAL ROUTE OF ADMINISTRATION OF MVA VACCINE

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MPOX Vaccine Lazio Study Group

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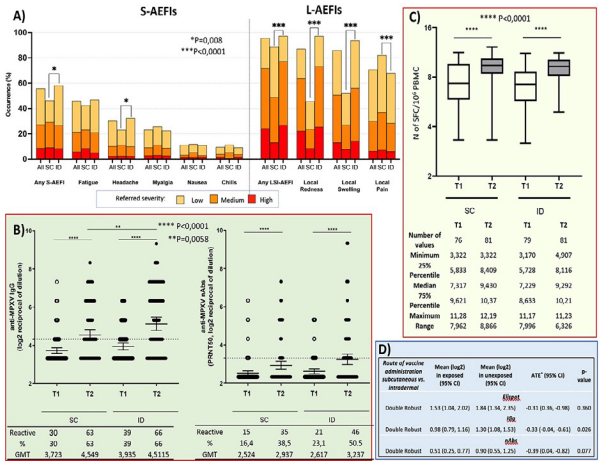
Background: Standard subcutaneous (SC) formulation of 3rd-generation modified vaccinia Ankara (MVA-BN) was replaced by the intradermal (ID) administration route (ad.r), owing to shortages in supplies, based on equivalent antibody responses with both (ad.r). Aim was to compare reactogenicity and immunogenicity of the SC vs. ID ad.r.

Methods: Self-reports of adverse effects following immunisation (AEFIs) were prospectively collected for 7 days from recipients (RCP) of the first MVA-BN dose (T1) as Mpox pre-exposure prophylaxis according to Italian Ministry of Health criteria. Systemic (S-AEFIs: fatigue, myalgia, headache, GI effects, chills) and local (L-AEFIs: redness, swelling, pain) AEFIs were graded as absent (grade 0), mild (1), moderate (2), or severe (3). AEFIs incidence, time of onset, and duration were compared according to ad.r, using chi-square, Fisher, or Mann-Whitney test, respectively. In a subgroup of 193 RCP, blood samples collected at T1 and one month later (T2) were tested for MPXV-specific IgG and neutralising antibodies (nAbs) by in-house immunofluorescence assay and PRNT50, respectively, and MVA-responsive T-cells by standard interferon-γ ELISpot. Average Treatment Effect (ATE) of the T1-T2 changes (log_2 scale) by ad.r were estimated after weighting for age using a linear predictor.

Results: 785 MSM with a median age of 38 y (IQR 33-45) received MVA either SC (151;19%) or ID (634;81%). S-AEFIs occurred in 56%, while LSI-AEFIs in 96% RCP with a 3-point grade in 9% and 24%, respectively. Fatigue was the most common (46%) S-AEFI, while local redness (87%) the local one. Compared to SC, a higher rate of both S-AEFIs and L-AEFIs, (27.0 vs 13.2 p< 0.001), especially local redness and swelling (25.6 vs 8.6, p< 0.001 and 14.5 vs 7.9, p=0.03) was seen with ID. No evidence for a difference in timing and duration was detected for S-AEFIs; median duration in ID vs. SC was 7 vs 4 days for redness, 6 vs 5 days for swelling, and 1 vs 2 days for local pain (p< 0.001). Compared to SC, change was 0.33 log_2 in IgG (p=0.03) and 0.39 log_2 in nAbs (p=0.08) (Fig.1B) larger when using ID. There was no evidence for a difference in Elispot changes by ad.r (Fig1D).

Conclusion: MVA-BN was generally well tolerated; S-AEFIs were reported more frequently by ID vaccine recipients as well as LSI-AEFI, apart from more frequent local pain after SC. A larger increase in immunological markers was observed with ID vs. SC administration, particularly for IgG and nAb. ID route proved to be safe and immunogenic.

Figure 1. A. Incidence of SAEFIs and LAEFIs. Comparisons were performed according to the administration route using the chi-square test. B. Titers of MPXV-specific IgG and neutralising antibodies. IgG were measured by in-house immunofluorescence assay, using 1:20 as screening dilution; MPXV-specific neutralising antibodies (nAbs) by 50% plaque reduction neutralization test (PRNT50) starting dilution 1:10. Intra-group comparisons were performed with paired t-test; inter-group (Sc vs ID) comparisons with unpaired t-test. C. Frequency of T cells responding to MVA-BN vaccine expressed as the number of SFC/10^6 PBMC tested by standard interferon-γ ELISpot. Intra-group comparisons were performed with by Wilcoxon test; inter-group comparisons by Mann-Whitney test. D. Potential average change at T2 and Average Treatment Effect (ATE) from fitting a linear regression model (log_2 scale) weighted for age performed by route of vaccine administration subcutaneous vs. intradermal.



376 HUMORAL AND CELLULAR IMMUNE RESPONSE AFTER 3 MONTHS FROM MPOX VIRUS INFECTION

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Background: Immunological signature of Mpox has been described in the early stages of infection. Analysis of its persistence could have implications for decision-making on the need and timing of vaccination in Mpox virus (MPXV) infected subjects. We described the kinetics of humoral and cellular immune response from symptoms onset (FSO) up to 3 months after Mpox.

Methods: 9 patients (pts) with Mpox confirmed diagnosis were enrolled from May to July 2022, and blood samples prospectively collected in the early phase of infection (0-20 days) and after 3 months (T90-140). Specific-MPXV IgM/IgG and neutralizing antibodies (nAb) titers were measured by immunofluorescence assay and by 50% plaque reduction neutralization test ($PRNT_{50}$). Interferon-γ producing specific T-cells to MVA peptides was assessed by ELISpot assay. In a subgroup of 6 pts, we analyzed the proportion of naïve, central memory (CM), effector memory (EM), and terminally differentiated (TEMRA) CD4+ and CD8+ T-cells and their expression of activation and exhaustion markers (CD38/CD57/PD-1) by flow cytometry. Kinetics of the cellular response were compared with 10 healthy donors matched by sex and age. Kruskal-Wallis and Dunn's tests, Mann-Whitney and Wilcoxon test were used for statistics, as appropriate.

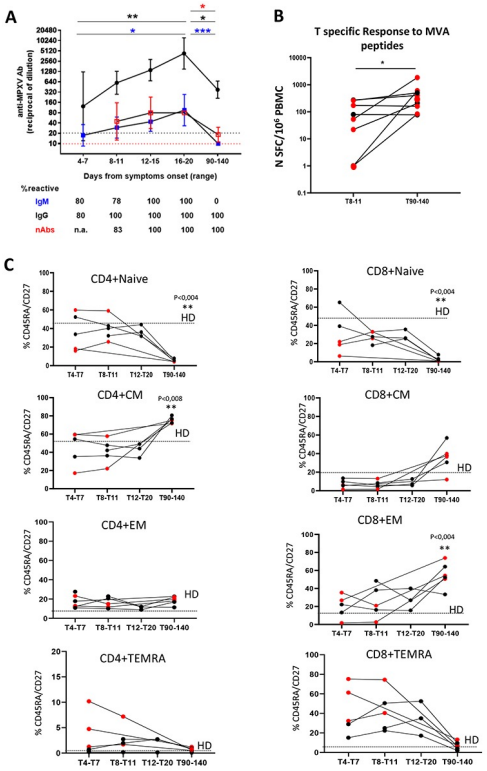
Results: All were MSM with a median age of 39 years (IQR 31-46). 6 were PLWH, all on ART with good viro-immunological status. Only one received smallpox vaccine during childhood.

In all samples, MPXV-specific IgG/IgM have been detected as early as 4 days FSO and peaked during the third week. nAb developed during the second week FSO. At T90-140, IgG and nAb were still detectable, even if at significantly lower levels than the peak (Fig1A). MVA-specific T-cells response significantly increased from T8-11 to T90-140 (Fig1B). Regarding T-cells differentiation profile, a significant expansion of CM and EM cells was observed at T90-140,

differently from the higher proportion of effector cells in the acute phase of infection (Fig1C). Exhaustion and activation markers (PD-1, CD57, CD38) were increased at the beginning of infection and resulted lower after three months. No differences were observed between PLWH and not.

Conclusion: Analysis of immune response after 3 months from MPXV infection showed detectable IgG and nAb and increased CM, EM, and MVA-specific responding T-cells, regardless of HIV infection, suggesting the possible expansion of a protective memory/effector T-cells phenotype and the persistence of immune protection.

Figure 1. A. Kinetics of anti-MPXV IgM/IgG and neutralizing antibodies (nAb). Geometric mean titers (GMT-95% CI) are shown for IgM (blue), IgG (black), and nAb (red). Dot lines represent the limit of detection for IgM/IgG (black) and nAb (red). Kruskal-Wallis and Dunn tests were performed to compare titers at different time points. P values are assigned as follows *<0.05, **<0.01, ***<0.001, and indicated in blue for IgM, black for IgG, and red for nAb. The percentage of reactive samples at each time point is displayed for the three humoral immunity markers. B. Specific T-cells response to MVA peptides was assessed by interferon-γ ELISpot assay. C. Proportion of naïve, central memory (CM), effector memory (EM), and terminally differentiated (TEMRA) CD4+ and CD8+ T-cells and their expression of activation and exhaustion markers (CD38/CD57/PD-1) assessed by flow cytometry. Kinetics of the cellular response were compared with 10 healthy donors matched by sex and age.



377 IMMUNOGENICITY OF MVA-BN VACCINATION WITH HYBRID ADMINISTRATION ROUTE

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Background: The limited availability of the Modified vaccina Ankara-Bavarian Nordic (MVA-BN) vaccine during the 2022 human monkeypox (HMPX) outbreak led to the adoption of the dose-sparing regimen of 0.1 ml/dose intradermally administered four weeks apart in two doses.

At the time of this decision, the local vaccination campaign was already ongoing, and a part of patients underwent a hybrid scheme consisting of a first subcutaneous administration (SC) followed by an intradermal one (ID) after 4 weeks.

Aim of our study is to assess the neutralization titers induced by a hybrid vaccination schedule.

Methods: We enrolled consecutive subjects who attended our Outpatient Clinic for Prevention and Assistance of Sexually Transmitted Infections in the period spanning from August to December 2022. One blood sample was collected at baseline (first dose, SC: T0), week 4 (2nd dose, ID: T1), and week 12 (T2). Virus-neutralizing antibodies titers were estimated by means of Plaque Reduction Neutralization Test (PRNT) against monkeypox virus (MPXV).

Results: For 78 patients a T2 sample was available and all of them showed a positive PRNT; of those, 43 patients did not have one of the previous two determinations (n 37) and 6 had a positive PRNT at T0. The remaining 35 patients were all male, with a median age of 35 years (IQR, 30-39), and among them, 9 people were living with HIV (PLWH) with an optimal viro-immunological control (undetectable HIV-RNA and CD4 cells count >500/mmc). At T1, 4/35 subjects showed no neutralization capacity (of whom 1 PLWH), and the median neutralization titer was 1:20 (IQR, 1:20 – 1:40). At T2, all the patients had a positive PRNT [median neutralization titer was 1:40 (IQR, 1:20 – 1:80)]. Most of the patients increased (21/35, 60%; 5 PLWH) or maintained (4/35, 11.4%; 1 PLWH) the neutralization titer. On the other hand, a 28.6% (10/35; 3 PLWH) showed a reduction of the neutralization titer when compared to T1. No difference in terms of median neutralization titer at T1 [1:20 (IQR 1:10-1:20) vs 1:20 (IQR 1:20-1:40)] and T2 [1:40 (IQR 1:10-1:80) vs 1:40 (IQR 1:20-1:40)] were observed between PLWH and non-PLWH, respectively.

Conclusion: A hybrid SC/ID MVA-BN vaccination schedule induced neutralizing antibodies against MPXV at T2. Nevertheless, one out of three subjects showed a decline in the neutralization titer which deserves further investigation.

378 IMMUNE RESPONSES AND VIRAL DYNAMICS AFTER MPOX INFECTION IN THE 2022 OUTBREAK

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Background: Human immunity to Monkeypox infection (Mpox) has not been extensively characterized in people with HIV (PWH). Here, we analyzed antibody responses in outpatients diagnosed with Mpox during the 2022 outbreak in Barcelona, Spain who had been enrolled in the MoViE study (NCT05476744, Suñer et al 2022)

Methods: Observational, prospective, multicentre study designed to evaluate time from symptom onset (SO) to viral DNA clearance. A severity score was generated based on the number of local and distal skin lesions and presence of systemic symptoms. Samples from multiple body sites were collected at diagnosis and weekly for one month. Blood was collected from an immune subset of 33 individuals at Mpox diagnosis, 1, 3 and 6 months. IgG and IgA titers in plasma were determined by ELISA against recombinant Mpox proteins A35, Envelope H3 and A29.

Results: All participants were male aged 25 to 58 years. Participants were diagnosed at a median of 5 days (range 1-10) since SO and had mild/moderate disease. Fourteen (42%) were PWH, with last CD4+ T cells >450/µL and all but 3 were ART-suppressed. Mpox clinical severity was similar between PWH and HIV negative individuals (HIVneg). At Mpox diagnosis, no differences in the breadth of reactivity or IgG titers to A35, H3 and A29 proteins were detected between PWH and HIVneg. IgGs to at least one Mpox antigen were detected in 11/13 PWH and 17/19 HIVneg. Anti-A35 IgGs in participants aged >48 years were significantly higher than in younger participants (p=0.01) suggesting potential pre-existing immunity due to previous smallpox vaccination, consistent with the time when immunizations were globally ceased. Despite anti-A35/H3/A29 IgGs did not correlate with days since SO or Mpox DNA levels in skin lesions or blood, higher titers of anti-A35/A-29 IgG were associated with a lower severity score (Rho -0,43 and -0.40 respectively, p< 0.05). Moreover, anti-A35/H3 IgG and IgA correlated with less days to negativization of viral DNA in skin lesions and higher DNA copies cleared per day. Longitudinal analysis at 1, 3 and 6

months after diagnosis, as well as viral neutralization and T-cell assays are ongoing at the time of submission.

Conclusion: In our cohort, PWH with CD4+ >450/μL had a similar clinical presentation of Mpox to HIVneg individuals. Magnitude of humoral immune responses at the time of diagnosis was associated with a milder presentation and a shorter and faster viral clearance of Mpox DNA in skin lesions. These results may inform isolation strategies.

379 NOVEL SEROASSAYS DETECT MPOX-SPECIFIC AND VACCINE-INDUCED ORTHOPOXVIRUS IMMUNITY

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Background: Mpox (previously known as monkeypox) is a disease caused by the mpox virus (MPXV) belonging to the orthopoxvirus (OPXV) genus which includes smallpox and vaccinia virus (VACV). VACV-based vaccines provide protection against mpox disease but complicate differentiation of infection-specific from vaccine-induced immunity. We tested the reactivity of serum from recently vaccinated or mpox-infected individuals and controls to a dozen MPXV/VACV proteins and developed and validated a novel immunoassay to measure vaccine response and distinguish mpox infection from vaccination.

Methods: Vaccine and control sera were obtained from ongoing studies with IRB approval. MPXV-vaccinated individuals (N=3) received MVA-BN (VACV-based) vaccine ≥ 2 weeks prior to serum collection and had no history of mpox infection. OPXV-naïve control sera (N=71) were collected prior to the global mpox outbreak from individuals < 40 years of age (born after routine smallpox vaccination ended). Mpox sera (N=5) were from individuals who recovered from PCR-confirmed mpox. Indirect IgG ELISAS were performed using conserved OPXV antigens: A27L, A29L, A30L, A33R, A35R, B16R, C19L, D6L, E8L, H3L, I1L. For the MPXV-specific assay we used the complete, 1879 amino acid B21R protein which is present in MPXV but absent in VACV. Statistical analyses were performed on background-reduced ODs with two-tailed Mann-Whitney tests for comparisons.

Results: Reactivity of vaccine serum was low or nonspecific for most antigens (A35R, L1R, B16R, A29L, A30L, A27L, I1L, D6L, A33R) (Fig 1a). E8L showed consistently high levels of reactivity in vaccine sera with low background. We re-ran the E8L assay with vaccine sera against a larger pool of controls and again found high levels of IgG in vaccinated but not in control sera (OD = 0.62 vs. 0.056, P < 0.0001) (Fig 1b). B21R IgG was detectable in all mpox sera but low in vaccine sera (OD 0.27 vs. 0.07, P < 0.05) (Fig 1c).

Conclusion: We developed and validated the first mpox-specific seroassay which uses the complete B21R peptide, which can distinguish recent infection from vaccination, which in turn was associated with a robust E8L antibody response. Collectively, our assays provide tools for conducting vaccine response and immunosurveillance studies to longitudinally detect immunity to MPXV, determine the true prevalence of MPXV infection and identify asymptomatic community spread.

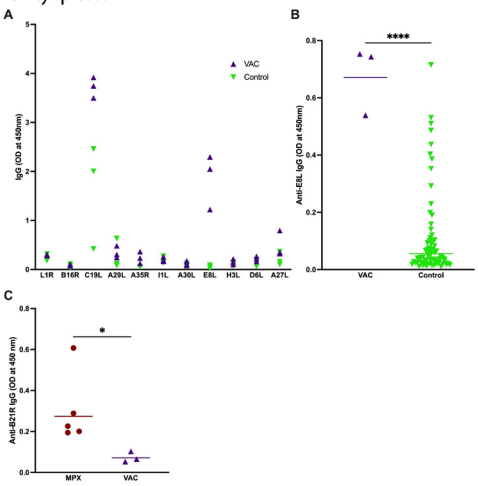

Figure 1. A) Levels of serum IgG to 11 MPXV/VACV antigens in MVA-BN vaccinated individuals (N=3) (purple) and OPXV-naïve controls (N=3) (green). **B)** Anti-E8L IgG levels in MVA-BN vaccinated individuals (N=3) and controls (N=71). **C)** Anti-B21R IgG levels in convalescent mpox patients (N=5) and in MVA-BN vaccinated individuals (N=3).
VAC = MVA-BN vaccinated; MPX = convalescent mpox patient.
*P < 0.05; ****P < 0.0001

380 CD103 EXPRESSION ON CD8 T CELLS PREDICTS LONGER TIME REBOUND OF HIV AFTER ATI

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Background: Antiretroviral therapy (ART) suppresses HIV replication in people living with HIV (PLWH), but is not curative. Upon interruption of ART, viral typically rebounds within a period of several weeks, although prolonged time-to-rebound occurs in some individuals through unclear mechanisms. In this study, we used CyTOF to identify phenotypic features of T cells associated with time-to-rebound in the ACTG 5345 analytical treatment interruption (ATI) cohort, which included both individuals who initiated treatment during the acute and chronic phases of HIV infection.

Methods: We designed a 40-parameter CyTOF T cell phenotyping panel, which included markers of T cell differentiation, activation, exhaustion, and homing. We applied the panel on pre-ATI blood specimens from 33 chronic-treated and 12 acute-treated individuals from the ACTG 5345 cohort. We then performed clustering analysis to identify associations with time-to-rebound upon ATI.

Results: 11 clusters were identified using a leave-one-out cross-validation model with a resolution of 0.2. Within the 11 clusters, 2 clusters were significantly ($p< 0.01$) and positively associated with longer time-to-rebound. One of these, Cluster 8, consisted of memory CD8+ T cells expressing high levels of CD49d, the integrin alpha subunit that makes up half of the α4β1 homing receptor associated with mucosal tissue homing, and that has been used as a marker of T resident memory (Trm) cells. Cluster 8 cells also expressed CD73, a hypoxia-regulated ectonucleotidase recently identified as host determinant of HIV latency. The second associated cluster, Cluster 10, were memory CD4+ T cells that expressed high levels of the co-stimulatory molecule CD28, and CD29, the beta 1 integrin chain of α4β1. Interestingly, T cells in both clusters, and not any of the other clusters, expressed high levels of CD103, a Trm marker.

Conclusion: These data demonstrate that expression of CD103 on T cells may serve as a marker predicting longer time-to-rebound. More broadly, the findings suggest that different subsets of CD4+ and CD8+ Trm with distinct features associate with temporary ART-free HIV control. To what extent these cells play an active role in this control remains to be deciphered.

381 THE CIRCULATING CELL-FREE DNA METHYLOME PREDICTS HIV POST-TREATMENT CONTROL

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Background: The development of HIV cure strategies depends on our capacity to predict HIV control when antiretroviral therapy (ART) is stopped. Motivated by the recent expansion of noninvasive cell-free DNA (cfDNA)-based cancer diagnostics, we performed multi-dimensional profiling of plasma cfDNA obtained from individuals who maintain HIV suppression following ART cessation termed post-treatment controllers (PTCs), to identify quantitative, genetic, and epigenetic signatures of PTC status.

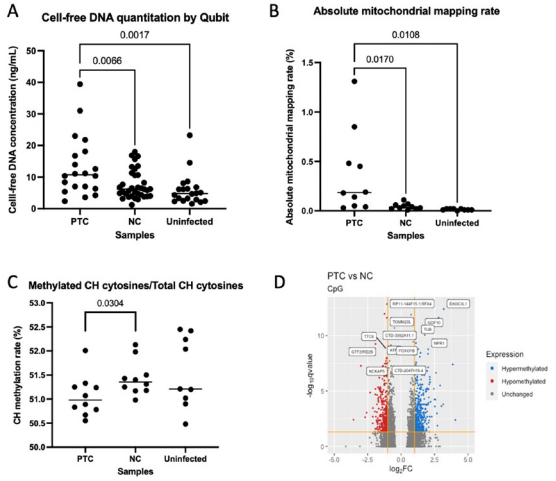
Methods: cfDNA was extracted from 1 ml of plasma collected prior to ART cessation from 20 PTCs (HIV RNA maintained at < 400 copies/ml for >24 weeks post-ART) and 20 non-controllers (NCs) enrolled in ACTG treatment interruption studies, and from 20 uninfected individuals enrolled in the SCOPE cohort. Plasma cfDNA was quantified using the Qubit fluorometer, and whole genome bisulfite sequencing (WGBS) was performed using the IDT Xgen Methyl-Seq kit and the Illumina NovaSeq platform. BSMap, BSBolt, and Metilene software tools were used for sequence alignment, methylation calls, and identification of differentially methylated regions (DMRs), respectively. Statistical analyses and data visualization were performed using the R computing environment.

Results: PTCs exhibited elevated levels of plasma cell-free DNA as compared to NCs ($p=0.007$, Mann-Whitney test) and uninfected individuals ($p=0.002$) (Fig.1A). Sequencing data revealed higher amounts of circulating mitochondrial DNA (mtDNA) in PTCs as compared to NCs ($p=0.017$) and uninfected individuals ($p=0.011$) (Fig.1B). WGBS data demonstrated that PTCs had significantly lower

genome-wide cytosine methylation rates as compared to NCs (p=0.03) (Fig.1C). 503 genes (DMRs) were hypermethylated and 397 genes were hypomethylated at CpG sites in PTCs as compared to NCs (using FDR q< 0.05 and $\log_2$ fold change >1 cutoff) (Fig.1D).

Conclusion: Elevated circulating levels of cfDNA and mtDNA during ART are predictors of HIV post-treatment control. Reduced genome-wide methylation and an abundance of cfDNA DMRs distinguishing PTCs from NCs further demonstrate the prognostic potential of cfDNA as a predictive biomarker of natural HIV control following ART cessation. Elevated levels of circulating hypomethylated DNA may reflect the death of infected cells, and may promote innate immune control of HIV via interactions with innate DNA sensors including TLR-9. Our data warrant continued investigation into cfDNA as a marker and modulator of HIV persistence and control *in vivo*.

Figure 1. Plasma cell-free DNA-based signatures of HIV post-treatment control.



382 WHICH ENDPOINT TO CHOOSE DURING ANTIRETROVIRAL TREATMENT INTERRUPTION?

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ANRS 118 ILIADE, ANRS 149 VRI02 LIGHT, ANRS VRI DALIA trials
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Background: The evaluation of strategies targeting HIV cure requires analytical antiretroviral treatment (ART) interruption (ATI) to measure the effect on viral load dynamics with the ultimate goal of maintaining viral control in the absence of ART. The objective of this study was to evaluate potential viral endpoints and the impact of the trial design using 3 ATI trials.

Methods: The ANRS 118 ILIADE is a phase 2 trial of 148 patients randomized to either IL-2 subcutaneous therapy (n=81) or placebo (n=67) and followed during 228-week ATI period. The VRI02 ANRS 149 LIGHT is a phase 2 trial of 103 patients randomized to either recombinant DNA vaccine (GTU-MultiHIV B) followed by lipopeptide vaccine (HIV-LIPO-5) or placebo and followed during a 12-week ATI period. The ANRS/VRI DALIA is a single arm phase I trial evaluating the effects of a dendritic cell vaccine in 19 infected patients followed over a 24-week ATI period. Various HIV RNA endpoints were calculated in each trial: time to rebound (TTR), the maximum observed value (peak), the slope of the initial increase of HIV RNA (slope), the area under the curve (AUC) and the stable level reached after rebound (setpoint).

Results: The median TTR, peak, slope, AUC and setpoint varied across arms from 2 to 6 weeks, 4.6 to 5 $\log_{10}$ copies/mL, 0.22 to 0.75 $\log_{10}$ copies/mL/week, 3.74 to 4.25 $\log_{10}$ copies/mL and 4.29 to 4.59 copies/mL, respectively. These endpoints were sensible to the design of the trial (sampling times and duration of ATI).

When estimating the correlations between endpoints within each trial, it appears that there was no correlation between the setpoint and the TTR or the slope (but in LIGHT vaccine arm) whereas the maximum correlation was always estimated between setpoint and AUC (r between 0.79 and 0.99, all p< .0001). Then, we simulated the impact of the threshold of HIV RNA defined to resume ART varying from 2 to 6 $\log_{10}$ copies/mL and whether a confirmatory measure is asked when the threshold is passed. The correlations between the AUC and the setpoint were the highest for a threshold of 5 $\log_{10}$ copies/mL and with a confirmatory measure (r >0.8).

Conclusion: The evaluation of time to rebound requires frequent monitoring of HIV RNA (at least once a week over 6 weeks) and does not reflect at all the viral setpoint in case of viral replication. For the evaluation of the capacity to control viral replication, we recommend to use of the AUC where ART are resumed if HIV RNA goes above 5 $\log_{10}$ copies/mL.

383 PREEXISTING HOST EPIGENETIC STATES ASSOCIATED WITH HIV REBOUND KINETICS

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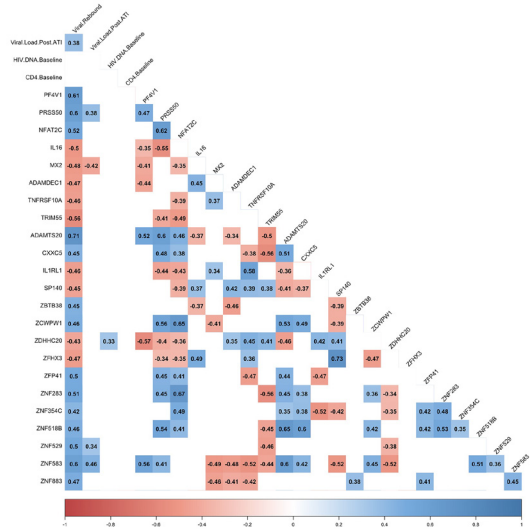
Background: Viral rebound with variable kinetics consistently occurs in people living with HIV (PLWH) after the discontinuation of ART during analytical treatment interruptions (ATI). In CD4 T cells, we previously identified candidate host epigenetic DNA methylation (DNAm) states correlating with time to viral rebound during ATI. Whether preexisting host DNAm states in bulk peripheral blood mononuclear cells (PBMCs) of PLWH participating in diverse curative interventions can reveal novel preexisting host epigenetic signatures related to time to viral rebound remains understudied.

Methods: Genome-wide DNAm profiling of PBMCs was obtained at study entry from 26 male PLWH on ART who participated in an ATI following combination interventions designed for eradicating residual plasma viremia and decreasing HIV reservoirs (NCT02961829). 15 early rebounding participants ranged in time to viral rebound from 14-24 days, 10 late rebounding participants from 33-102 days, and one exceptional participant (São Paulo Patient) rebounded at 511 days. Differentially methylated loci (DML) associated with the rebound group were identified by comparing early and late groups at a mean difference in methylation greater than 5% (Δβ-value) with FDR correction.

Results: Pre-ATI total HIV DNA at baseline and CD4 count did not significantly associate with time to viral rebound. At baseline study entry visit prior to intervention, we identified 2,694 DML (Δβ-value > |0.05|; P < 0.05) comparing early compared to late rebounding participants (Fig.1). These loci were enriched at intergenic regulatory regions and upstream of CpG islands in the human genome (P=0.001). Gene ontology and pathway enrichment analyses revealed DNAm differences at genes involved in the MHC class II protein complex, interferon-gamma-mediated signaling pathway, platelet activation, and Th17 cell differentiation. Among the top DML associated with rebound group were genes including *ADAMTS20* involved in HIV life cycle, *MX2* antiviral protein against HIV, epigenetic regulator of plasmacytoid dendritic cells *CXXC5*, and chemokine gene *PF4V1*. DNAm states of *PRSS50*, *MX2*, *ZNF529*, and *ZNF583* significantly associated with viral load post-ATI.

Conclusion: Fixed epigenetic features of innate and adaptive immune cells in PLWH may predetermine varying viral rebound kinetics during ATI despite multimodal therapies. These findings also suggest that an optimal host epigenetic landscape may exist to control HIV expression and silencing.

Correlogram plot of time to viral rebound, viral load post-ATI, HIV DNA pre-ATI, CD4 count pre-ATI, and pre-ATI DNAm states of host genes.



384 PARTICIPANT EXPERIENCES IN A CURE-DIRECTED LONG-TERM ANALYTIC TREATMENT INTERRUPTION

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Background: Most HIV cure-directed clinical trials require an analytical treatment interruption (ATI) to test the efficacy of interventions aimed at keeping HIV suppressed in the absence of antiretroviral treatment (ART). Little is known about how people with HIV (PWH) articulate or feel about having experienced extended ATIs.

Methods: From April – August 2022, we conducted two sequential qualitative interviews with participants in the BEAT-HIV-02 (NCT03588715) HIV cure-directed trial testing a combination of immunotherapy (peg-IFN-α2b) with two broadly neutralizing antibodies (3BNC117 and 10-1074) given for 26 weeks after ART interruption. Immunotherapy was followed by up to an additional 24-week follow-up ATI until ART re-start criteria was met. Interviews took place at study baseline and immediately after completion of study ATI when re-start ART criteria were met. Interviews elicited participant experiences during the ATI and the trial in general. Interviews were recorded, transcribed, and analyzed using directed content analysis.

Results: In total, 13 PWH, 77% male, 77% Black, completed sequential interviews. The mean ATI was 38 weeks in duration. Participants viewed the ATI as positive because they appreciated a respite from daily medication. Some reported increased self-confidence when their counts remained low during the ATI, before viral rebound. However, when viral counts rose, some expressed feelings of fear, frustration, anger and despair. Three expressed disappointment that they were not cured of their HIV. Rising viral loads led some to feel a sense of failure. All participants reported a positive and trusting relationship with the clinical trial team. Reciprocal respectful relationships between participants and study staff were noted as helping to mitigate participants' safety concerns.

Conclusion: Our socio-behavioral study identifies key points for intervention and participant support during HIV cure-directed studies including an extended ATI. Managing expectations, focusing on participants' contributions, and providing support to reduce feelings of having failed the research team and/or the HIV community following viral rebound should be part of study design. Continued efforts to understand how PWH experience ATIs will improve future designs of HIV cure-directed clinical trials.

Key Themes and Representative Quotes

Table 1: Key Themes and Representative Quotes

ATI experience was positive	*"It's hard to explain how good it feels not to take one pill... Every day I went without taking it, just makes it feel so good... **I am optimistic**."* *"This clinical study has **helped give me self-confidence, encouragement**. Before I got involved in this, I hadn't worked in 14 years due to being ill, but... it helped give me back my life."*
ATI was less positive	*"My viral load jumped up high...it had me a little **scared**, because I had never seen my numbers in that range since I've been diagnosed."* *"So, I was hoping that there was a rare chance that these antibodies... were really long lasting and that I would still be undetectable with just the antibodies."*
Research team conferred a sense of safety and trust that mitigated the sense of risk	*"So, **I felt like I was in safe hands and that always makes a person feel valued**. That makes them feel like, I'm not just a guinea pig or I'm not just a number and grand number of participants. I wasn't just a participant I was a person."*

385 PLASMA CD33 LEVEL IS A MARKER OF VIRUS CONTROL POST-KICK-AND-KILL CURE INTERVENTION

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Background: HIV cure strategies will require the elimination of latently HIV infected cells from all sites of the viral reservoir, including central nervous system. Latency reversing agents (LRA) that can reach all these sites may thus be needed. The BCN02 trial (NCT02616874) combined the HIVconsv T-cell vaccine with the latency reversing agent romidepsin (RMD), a LRA that also has been linked to beneficial effects in neurological diseases. To identify biomarkers associated with virus control during monitored antiretroviral pause (MAP), longitudinal proteomics screenings were conducted in plasma from BCN02 participants.

Methods: Plasma proteomes of longitudinal samples from 11 BCN02 participants, including 8 MAP-non controllers (MAP-NC, viral loads >2000 copies/ml < 4 weeks) and 3 MAP-controllers (MAP-C, viral load < 2000 copies/ml for >32 weeks) were determined. Integration data analysis (viral load, proviral levels, and neurocognitive assessments) was performed to identify candidates. For validation, untreated chronically HIV infected individuals (n=96) with different levels of virus control were included. Finally, *in vitro* viral replication assays and proviral quantification targeting CD33 in PHA-stimulated T-cells and macrophages derived monocytes were performed.

Results: During the BCN02 trial, plasma proteomes changed longitudinally, with most changes observed after RMD infusions and during MAP and significant differences between MAP-C and MAP-NC were observed already before the initiation of the intervention. CD33 protein was uniquely increased upon RMD administration and maintained during MAP and allowed to discriminate between MAP-C and MAP-NC, even when assessed before RMD treatment. CD33 plasma levels were positively associated with viral load and proviral levels in the BCN02 trial. Validation untreated chronically HIV infected individuals showed higher plasma levels of CD33 associated with reduced virus control. While neurocognitive assessments did not correlate with CD33 plasma levels in the BCN02 trial, positive correlations between CD33 protein and neurofilament light protein were observed after RMD administration and during MAP. *In vitro* targeting of CD33 showed reduced HIV replication and proviral levels, suggesting an important role of CD33 in the HIV life cycle.

Conclusion: This study identifies CD33 as key factor associated with virus control post Kick-and-Kill intervention and in natural HIV infection. Targeting CD33 may be considered for future HIV therapeutic cure strategies.

386 COMPREHENSIVE ANALYSIS OF VIRAL RESERVOIRS IN HIV-INFECTED ELITE CONTROLLERS

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Background: Antiretroviral therapy (ART) has greatly improved health outcomes in people living with the human immunodeficiency virus (HIV), but the persistence of viral reservoirs remains a barrier to viral eradication. Given that HIV-infected elite controllers (ECs) can naturally suppress plasma viremia to undetectable levels without ART, systematic analyses of their viral reservoirs may be key to understanding how to achieve ART-free virologic control in infected individuals. Previous studies have found that ECs have relatively small HIV DNA burdens, potent HIV-specific immunity, and integration patterns that contribute to long-term HIV control. However, few have compared the inducibility of infectious HIV between ECs and chronically infected, aviremic individuals receiving ART (CAs).

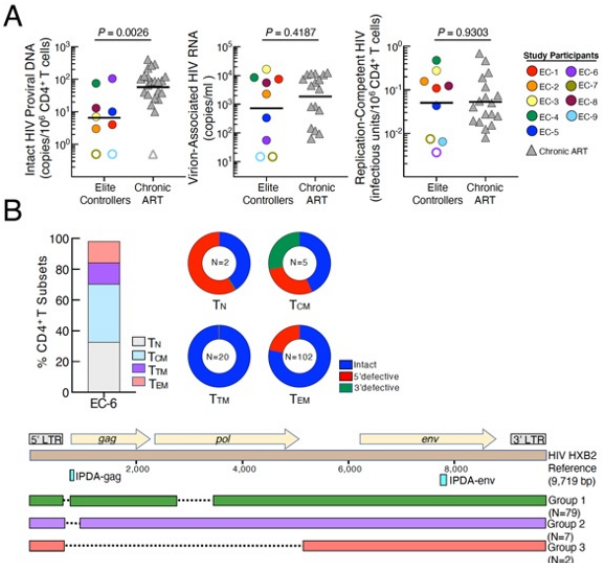
Methods: HIV reservoirs of 9 ECs and 22 CAs were compared by measuring intact proviral DNA, defective DNA, and cell-associated HIV RNA in CD4+ T cells with PCR-based assays. Cellular assays were used to measure inducible virion-associated HIV RNA and replication-competent virus. HIV-specific immune responses were measured following stimulation with HIV Gag peptides. Near-full length (NFL) sequencing of proviral DNA in effector memory CD4+ T cells was performed. Statistical analysis was performed with the Mann-Whitney test.

Results: Levels of intact proviral DNA, defective DNA, and cell-associated HIV RNA were lower in ECs compared to CAs. However, the levels of inducible and replication-competent virus were similar between both groups, and ECs had higher frequencies of HIV-specific CD8+ T cells, suggesting the presence of viral antigen expression. Of three ECs with extraordinarily low inducible/infectious viral reservoirs, one had high copy numbers of intact proviral DNA by IPDA, but NFL sequencing revealed that all clonotypes were defective.

Conclusion: We demonstrated that ECs have lower levels of intact proviral DNA and cell-associated HIV RNA but comparable levels of inducible and replication-

competent virus compared to CAs. The discordance observed between the PCR- and cellular-based assays may suggest that many identified intact proviral DNA in our CA group are, to a certain extent, replication-defective, as seen in one EC. Thus, although PCR-based methods provide insight into the composition of viral reservoirs, it is essential to perform assays that detect replication-competent virus in certain populations of HIV-infected individuals, such as ECs, to accurately estimate the size of the viral reservoir.

Analyses of HIV reservoirs in elite controllers and chronically infected aviremic study participants



387 PREDICTORS OF HIV REBOUND AFTER INTERRUPTION OF ART STARTED DURING PRIMARY INFECTION

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Background: Understanding factors that affect timing of viral rebound after antiretroviral treatment (ART) interruption will accelerate efforts toward inducing sustained HIV remission. Here, we evaluated whether HIV DNA size, activity, and molecular diversity as well as peripheral T cell phenotypes prior to treatment interruption predict time to HIV rebound in individuals interrupting ART initiated during primary infection.

Methods: The Zurich Primary HIV Infection Cohort (ZPHI) enrolled people with HIV (PWH) who started ART during primary infection and interrupted therapy after a median of 18 months of viral suppression. We selected stored cross-sectional samples (pre-ART interruption) from 70 ZPHI participants for this study. Using flow cytometry, we evaluated frequencies of T cell maturation subsets, levels of T cell activation (HLA-DR+CD38+), exhaustion (PD-1+, TIGIT+), proliferation (Ki67+) degranulation/cytotoxicity (CD107a+) and regulatory CD4+ T Cells (CD25+FoxP3+). On a subset of 38 individuals, we measured levels of cellular total HIV DNA (gag), HIV RNA (spliced and multiple spliced encoding *tatrev*) by digital droplet PCR, and molecular diversity by deep sequencing of HIV DNA (full length envelope). We evaluated associations between time to rebound (i.e., reaching 1,000 cps/ml) and each virologic and immunologic factors using univariate Cox proportional hazard models for interval censored outcomes without adjusting for multiple comparisons.

Results: Main cohort characteristics were 14% female, 70% Caucasians, median age 39, median Nadir CD4+ 289 cells/ml. Lower molecular diversity of HIV DNA envelope pre-ART interruption was significantly associated with longer time to rebound (p=0.048), but not the size (HIV DNA) or activity (HIV RNA) of the HIV reservoir. Among immunological factors, lower percentage of effector and terminally differentiated CD4+ and CD8+ T cells expressing markers of activation and degranulation/cytotoxicity were consistently associated with longer time to rebound (all P< 0.05, see **Table 1**).

Conclusion: We found viral and immune factors associated with delayed rebound of HIV RNA after ART interruption in PWH starting ART during early infection. Our results suggest that a combination approach will be necessary to boost viral control, including early ART start to limit viral diversity and additional interventions to reduce or reverse T cell activation and degranulation/cytotoxicity.

Table 1: Factors significantly predictive of time to viral rebound

Factor	Estimate	Standard Error	95% Confidence Limits		p-value
Terminally differentiated CD8 T Cells expressing CD38 and HLA-DR	0.0163	0.0068	0.003	0.03	0.017
Effector memory CD4 T Cells expressing CD38 and HLA-DR	0.0511	0.0224	0.007	0.095	0.0227
Central Memory CD8 T Cells expressing CD107a	0.0252	0.0113	0.003	0.047	0.0258
Terminally differentiated CD8 T Cells expressing CD107a	0.0164	0.0075	0.002	0.031	0.0278
Central memory CD4 T Cells expressing CD107a	0.0181	0.0082	0.002	0.034	0.0279
Effector Memory CD8 T Cells expressing CD107a	0.0196	0.0099	0	0.039	0.0491
Mean molecular diversity HIV DNA (env)	88.56	44.89	0.576	176.54	0.0485

Legend: *Estimate:* the estimated effect sizes of the factors on the hazard of viral rebound. An estimated effect greater/smaller than zero indicates that as the factor increases, the hazard of viral rebound increases/decreases and thus the time to rebound decreases/increases. *Standard Error:* the standard errors of the estimates. *95% Confidence Limits:* the lower and upper 95% confidence intervals for the estimates. The lower bound = Estimate - 1.96*Standard Error and the upper bound = Estimate + 1.96*Standard Error. *p-value:* the p-values from testing the significance of the effects. A p-value < 0.05 indicates a significant effect of the factor on the hazard of viral rebound.

388 SHORT- AND LONG-TERM DYNAMICS OF SIV-INFECTED CELL POPULATIONS ON ART

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Background: Antiretroviral therapy (ART) potently suppresses HIV-1 replication and prevents infection of new cells. Understanding changes in HIV-infected cell populations following ART initiation can inform design and evaluation of cure strategies by providing insights into the cells that enter the long-term reservoir. Recently, White et al. explored the decay kinetics of infected CD4+ T cells in people living with HIV-1 (PLWH) on ART and found that intact genomes decayed with biphasic kinetics characterized by a rapid initial phase, and a slower 2nd phase that was faster than the decay in PLWH on long-term ART. The decay of SIV-infected cells in macaques on ART has not been described. Analogous studies using the SIV/non-human primate model offer an opportunity for insights difficult to obtain in PLWH.

Methods: We characterized quantitative and qualitative changes in SIV-infected CD4+ T cells for 4 years following ART initiation. We used digital droplet PCR to compare the decay of intact and defective proviruses, as well as single-genome sequencing (SGS) of env from plasma virus and proviral DNA to look for qualitative changes during ART.

Results: By following treated macaques for 4 years, we observed both early and late phase dynamics of the latent reservoir. We found that the decay kinetics of cells harboring intact SIV proviruses are similar to those reported for HIV-1, characterized by multiphasic decay and a final phase representing stable persistence of a latent reservoir. *env* SGS revealed that ART potently stops viral evolution and that the composition of infected cell populations changes during ART. We found that the average pairwise distance from the stock decreased over time on ART, reflecting decay of recently infected cells. Ancestral variants with fewer mutations that had been archived in the latent reservoir were not present in the plasma at ART initiation and became prominent over time on treatment.

Conclusion: These data provide a baseline decay rate for SIV-infected cells in macaques on ART, which is critical to accurately evaluate cure strategies aimed at the latent reservoir. Our results show that variants enter the reservoir throughout untreated infection and not just at ART initiation. The population of SIV-infected CD4+ T cells is dynamic and changes both quantitatively and qualitatively for several years following ART initiation. These data provide a framework for evaluating and interpreting intervention trials utilizing the SIV/NHP model.

389 PRESENTATION OF COGNATE ANTIGENS BY DENDRITIC CELLS CAUSES STOCHASTIC HIV EXPRESSION

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Background: Encounter with cognate antigens (Ag) is a major cause of proliferation and persistence of HIV-infected CD4+ T cells. Understanding to which extent physiological T cell activation leads to latency reversal is key for cure efforts. However, due to the low frequency of HIV-infected Ag-reactive cells, previous studies failed to compare HIV reactivation mediated by Ag recognition versus global T cell activators.
Methods: CD8-depleted PBMCs from 10 PLWH on ART were stimulated with either CMV or HIV Gag Ag. Reactive cells (CD40L+) were isolated and expanded for 10-14 days. Expanded pools were characterized by TCR repertoire, total and intact HIV DNA, and proviral sequencing. After resting for 3 days, cells were re-stimulated with either PMA/Io, anti-CD3/CD28, or autologous dendritic cells (DCs) pulsed with cognate or an unrelated Ag (KLH). We measured T-cell activation by CD40L and CD69 expression, and profiled HIV RNA by bulk and limiting dilution digital PCR and sequencing.
Results: Our approach allowed us to isolate rare Ag-reactive CD4+ T cells (range 0.5-2%) and expand them while preserving their overall TCR repertoire. The frequency and composition of proviruses in the expanded pools were highly variable across participants. Although most HIV genomes were defective, we detected intact proviruses in 2/5 and 5/5 participants' CMV or Gag reactive cells, respectively. Upon re-stimulation with DCs, only cognate Ag caused significant T cell activation (CMV 69.57%, Gag 64.4%, KLH 4.08%, $p< 0.0001$). Although Ag stimulation increased HIV expression compared to baseline ($p=0.004$), HIV reactivation was variable (fold change 0.83-50.56). While CMV-reactive pools from 2 participants showed high induction of HIV expression (48- and 50-fold), 4/10 Ag-pools exhibited little HIV RNA increase compared to baseline (fold change 0.8-4). Conversely, treatment with PMA/Io or anti-CD3/CD28 caused significant HIV RNA production across all participants (fold change mean 13.5 and 6.5, respectively). Limiting dilution RNA assays showed similar breadth of proviruses induced across conditions, but only strong stimulation (PMA/Io) lead to high HIV RNA-producing cells ($>10^2$ cps/cell).
Conclusion: These results suggest that there are quantitative and qualitative differences in cellular and HIV transcriptional profiles when CD4+ T cells encounter their cognate Ag compared to global T cell activators. Our work suggests that, for some proviruses, physiological T cell activation is insufficient to fully reverse HIV latency.

390 STABILITY AND INSTABILITY OF THE CELLULAR HIV RESERVOIR AFTER REBOUND DURING ATI

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Background: The complex pool of infected cells that comprise the HIV reservoir can be distributed amongst CD4+ T subsets with varied functional and compartmental characteristics. Recent studies during treatment interruption in passive immunotherapy trials have demonstrated that reservoir reseeding can coincide with viral rebound. However, whether reseeding is associated with compositionally distinct cellular populations is unknown.
Methods: We profiled the reservoir from three participants of the clinical trial (ACTG A5340) who experienced viral rebound after receiving the broadly neutralizing antibody VRC01 during analytical treatment interruption (ATI). Pre-ATI and post-ATI blood samples were collected while viral load was fully suppressed. We applied viral single-cell Assay for Transposase Accessible Chromatin with Select Antigen Profiling by sequencing (ASAPseq) to identify HIV+ cells using accessible proviral DNA and their coordinate cell surface markers. Peripheral blood memory CD4+ T cells were enriched by bead separation and labeled with oligo-tagged antibodies for generation of viral ASAPseq libraries. Reads were processed using our custom pipeline which included alignments to consensus and autologous viral sequences.
Results: We profiled 136997 memory CD4+ T cells with viral ASAPseq, of which 205 cells (0.15%) were detected as HIV+. After clustering and annotating with epigenetic and surface antigen data, we compared the phenotypes between the pre-ATI and post-ATI timepoints for each individual. In one individual with a low viral rebound (as determined by area under the curve; AUC) during ATI, phenotypic composition of HIV+ cells was maintained. In contrast, the other individuals with higher viral load rebound had greater disruption of the phenotypic composition of HIV+ cells. Reservoir modulation was specifically associated with the emergence of recently activated Tcm/Ttm cells at the post-ATI timepoint.
Conclusion: Our observations suggest that the extent of viral rebound AUC is associated with greater changes in reservoir phenotype. These results suggest that incomplete viral suppression during clinical trial interventions can lead to diversification of the cellular phenotypes found in the HIV reservoir.

391 LACK OF DETECTABLE ONGOING REPLICATION ON ART IN SIV-INFECTED RHESUS MACAQUES

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Background: The capacity of HIV-1 to replicate during antiretroviral therapy (ART) remains controversial. Limitations of clinical sampling and the high background level of genetic diversity in most persons living with HIV make it challenging to detect additional substitutions on ART. To gain greater sensitivity to detect even small changes to the virus population on ART, we used an NHP model, which allows precise control over the level of pre-ART evolution and subsequent changes to the viral population.
Methods: We infected 21 rhesus macaques with the barcoded virus SIVmac239M to compare near-full-length (nFL) SIV DNA single genome sequences from PBMCs (and in some cases lymph nodes and spleen) obtained near the time of ART initiation and those present after long-term ART. Animals started ART between 10-27 days post infection (dpi) and were treated for 285-977 dpi. We obtained 25-200 intact nFL sequences per animal. We then assessed whether the viral populations differed significantly between the two time points in (i) genetic diversity, (ii) population structure, and (iii) genetic divergence from the founder.
Results: We found no evidence for replication on ART for any of the animals. The median average pairwise distance did not differ significantly between baseline and long-term ART samples (0.015% vs 0.015%; p-value = 0.23; two-tailed Wilcoxon-signed rank test.) The probability that sequences from the two samples came from different populations was not statistically significant in any animal (test for panmixia). Finally, the regression slope of p-distance over time did not differ significantly from zero in any animal. Neighbor-joining trees were also consistent with a lack of viral evolution, displaying no clustering of sequences from different time points, or longer branches associated with sequences obtained from long-term ART.
Conclusion: Overall, these data are consistent with the most recent papers in the field, which did not find evidence for evolution of HIV on ART. We cannot exclude the possibility of low-level ongoing viral replication not detectable in our study despite intensive sampling. For example, computational modeling suggests that ongoing replication in a theoretical sanctuary site could lead to viral evolution while maintaining the level of plasma viremia below the limit of detection. However, the potential contribution of such a small replicating population to the rebound-competent reservoir or as a source of drug resistance escape mutations would be limited.

392 SLOWING OR REVERSAL OF DECAY OF INTACT PROVIRUSES OVER 2 DECADES OF SUPPRESSIVE ART

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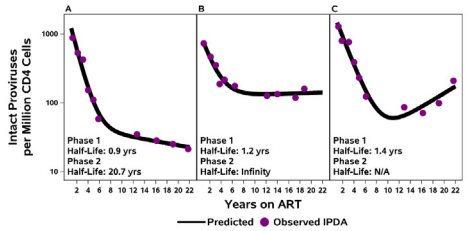
Background: The intact proviral DNA assay is a measure of the replication-competent HIV reservoir. Little is known about the decay patterns of intact proviral DNA (IPD) in people with HIV (PWH) during very long-term (15-20 yr) suppressive antiretroviral therapy (ART).
Methods: Participants in ACTG A5321 with chronic HIV and documented suppression of viremia (HIV RNA < 50 copies/mL) for >15 yr of ART had measurements on blood samples of IPD, 5′ or 3′ defective proviral DNA, and

total proviral DNA (sum of defective, hypermutated, intact proviruses). A biexponential model for intact proviral DNA was estimated using non-linear regression.

Results: Fourteen participants (5 female) were evaluated longitudinally from ART yr 1 to ART yr 17-23 (median 20 yr of ART; 8-10 timepoints). Median pre-ART plasma HIV RNA 4.2 log_{10} c/mL; median pre-ART CD4 cell count 377/mm^3. At yr 1 of ART, median intact proviruses were 204 copies/million CD4 cells; median (Q1, Q3) intact provirus percentage (intact/total) was 66% (41, 83). By the last time point (median 20 yr on ART), intact provirus percentage had fallen to 7% (4, 10), reflecting selective decay of intact proviruses (decay of intact proviruses was 13-fold compared with 3-fold for total proviruses). Over the two decades on ART, 5 participants had biphasic decay in IPD levels, 3 participants had biphasic decay with a second phase plateau (slope effectively zero), and 2 participants showed evidence of increased IPD levels during the second decade of ART (**see Figure**). The inflection or transition of decay occurred at a median of 5 yr after ART initiation (range 2-13 yr). The median IPD first phase half-life was 1 yr (n=10), whereas the median IPD second phase half-life was >25 yr (n=8). (For the 2 participants with late IPD increases, second phase half-life was undefined.) In the 4 other participants, there was a variable pattern of IPD decay, perhaps in part due to fewer cells assayed or low IPD levels.

Conclusion: In PWH on very long-term ART, three patterns of IPD decay were revealed despite continual suppression of viremia: 1) biphasic decline with markedly slower second phase decline; 2) initial decline that transitions to a zero slope plateau; and 3) initial decline followed by late increases in IPD. The mechanisms of markedly slower second phase decay or reversal are uncertain but may include the inability to clear cells with intact but transcriptionally silent proviruses and clonal expansion of cells with intact proviruses.

Examples of decay patterns in intact proviral DNA levels for participants on long-term ART. Five participants had a similar pattern as shown on left (A), with slowing decay of intact proviruses during the second decade of ART. Three participants showed plateauing of decay (slope effectively zero) (B) and two participants had patterns of late increases (C).



393 DIFFERENTIAL TRANSCRIPTION LEVELS OF HIV-1 FULL-LENGTH AND HIGHLY DELETED PROVIRUSES

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Background: HIV-infected cells during antiretroviral therapy (ART) carry intact or defective proviruses in genomes or in transcription/translation activity. Transcription activity contributes notably to differential dynamics of proviral populations. We aim to compare and identify viral determinants affecting transcription levels of intact, near-full length (NFL) defective, and total proviruses after long-term ART.

Methods: Blood cells were collected from 10 HIV-suppressed patients at pretherapy and after 4-20y on ART. We performed single genome sequencing (SGS) of proviruses >7kb by Illumina MiSeq and determined the genetic intactness. The total proviral *gag* and cell-associated RNA (caRNA) populations were obtained by SGS of 1.3kb *gag* region. We analyzed only sequences with no stop codons on *gag*. We measured the diversity using average pairwise distance (APD) and net divergence (% subs/site) of caRNA from NFL and from total gag populations (MEGAX). We analyzed HLA-associated escape mutations and reported mutations on proviruses with >1.5-fold difference compared to caRNA.

Results: We obtained a total of 1291 sequences without stop codons on gag, ranging from 0-57 NFL (both intact and defective), 5-42 total *gag*, and 3-39 caRNA sequences/patient/timepoint. There was no significant difference in the diversity of caRNA vs NFL or total proviruses from pretherapy to long-term ART. The median APD (interquartile range-IQR) of caRNA, NFL, and total *gag* populations after long-term ART were 1.66 (0.35-1.97), 1.10 (0.33-1.46), 1.39 (0.68-1.66) while NFL and total *gag* populations at pretherapy had a median APD of 1.62 and 1.64%, respectively. CaRNA were genetically closer to total *gag* than NFL populations with the median (IQR) divergence of 0.06 (0.005-0.19) vs 0.14 (0.03-0.5) (p=0.02). Interestingly, the diversity of intact was not different with NFL defective proviruses and caRNA populations were not differently divergent from intact or NFL defective proviruses, 0.04 (0.005-0.5) vs 0.2 (0.04-0.48) (p=0.46). We observed a >1.5-fold difference in frequency of some HLA-associated escape mutations in proviruses compared to caRNA in 6/10 patients (table1).

Conclusion: Transcription levels of intact and NFL defective proviruses are not significantly different. However, total gag proviruses i.e highly deleted, are more transcriptionally active than NFL proviruses and HLA escape mechanism does not explain this difference. The results suggest the advantage of highly defective proviruses in transcription elongation.

Table 1: Selection for or against of **> 1.5-fold** HLA associated wild-type or escaped epitopes.
The frequencies of wild-type (capital) and escaped mutations (lowercase) on HLA-associated epitopes in *gag* were not significantly different in NFL vs total *gag* vs caRNA populations after long-term ART. However, 6 patients had evidence of selection for or against some epitopes in proviral *gag* compared to caRNA.

Patient	HLA	HXB2 start on gag	Wildtype epitope	Variant epitope	Frequency of total proviral gag (n/N, %)	Frequency of intact and NFL defective gag (n/N, %)	Frequency of caRNA *gag* (n/N, %)
1	B*07:02	407	APRKKGCWK	APRKrGCWK	24/25, 96.0	18/33, 54.5	17/17, 100
2	A*02:23	77	SLYNTVATL	SLfNTVATL	18/25, 75.0	24/26, 92.3	7/13, 53.9
3	A*02:31	77	SLYNTVATL	SvYNTVATL	1/5, 20.0	1/1, 50.0	9/13, 69.2
4	A*02:74	433	FLGKIWPSYK	FLGKIWPSrK	3/19, 15.8	2/9, 22.2	1/25, 4.0
				FLGKIWPScK	5/19, 26.3	1/9, 11.1	13/25, 52.0
5	A*30:02	76	RSLYNTVATLY	kSLYNTVATLY	14/30, 46.7	27/34, 79.4	1/3, 33.3
6	A*02:01	77	SLYNTVATL	SLYNTiATL	9/33, 27.3	4/7, 57.1	0/34, 0

394 HUMAN GALECTIN-9 PROMOTES THE EXPANSION OF HIV RESERVOIRS IN VIVO IN HUMANIZED MICE

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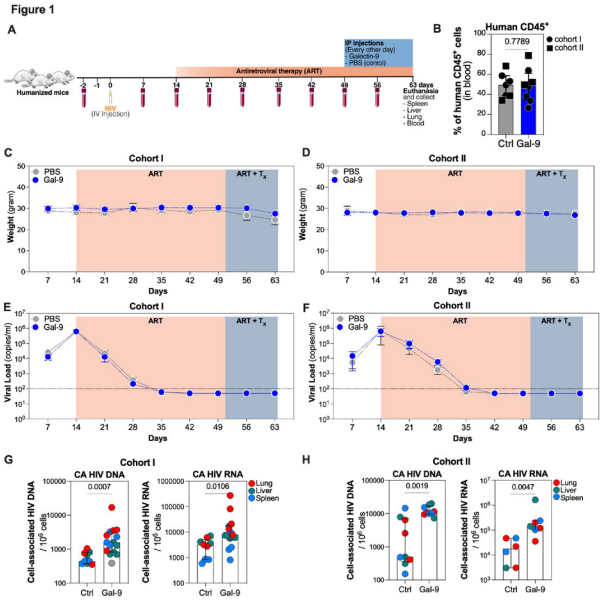
Background: The human endogenous β-galactoside-binding protein Galectin-9 (Gal-9) reactivates latently HIV-infected cells, which may allow for immune-mediated clearance of these cells. However, Gal-9 also activates T cell Receptor (TCR) signaling pathways, which could negatively affect HIV persistence by promoting T cell expansion and chronic immune activation and exhaustion. This potential "immunomodulatory" effect of Gal-9 during HIV infection raises the question of the overall impact of Gal-9 on HIV persistence *in vivo*.

Methods: We used the BLT (bone marrow, liver, thymus) humanized mouse model to evaluate the overall impact of Gal-9 on HIV persistence *in vivo* during antiretroviral therapy (ART). Two independent cohorts of BLT mice with high human immune reconstitution were infected with HIV, placed on ART, and then treated with either recombinant human Gal-9 or PBS during ART suppression. Plasma viral loads and levels of tissue-associated HIV DNA and RNA were measured by qPCR. Markers of T cell activation/exhaustion were measured by flow cytometry, and plasma markers of inflammation were measured by multiplex cytokine arrays.

Results: Gal-9 treatment was tolerable in ART-suppressed humanized mice and did not significantly induce plasma markers of inflammation or T cell markers of activation or exhaustion. However, Gal-9 treatment during ART significantly increased levels of tissue-associated HIV DNA and RNA compared to controls (P=0.0007 and P=0.011, respectively, for cohort I and P=0.002 and P=0.005, respectively, for cohort II).

Conclusion: Our study reveals a detrimental effect of Gal-9 on HIV persistence *in vivo*, suggesting instead for blockade of Gal-9 interactions as a strategy for reservoir reduction in PLWH.

Figure: Gal-9 treatment is tolerable *in vivo* but increased levels of tissue-associated HIV DNA and RNA during ART-suppressed HIV infection in Hu-mice.



395 HIV-1 CLADE C RESERVOIR CHARACTERISTICS IN EARLY AND CHRONIC TREATED INFECTION

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Background: Persisting HIV reservoir viruses in resting CD4 T cells and other cellular subsets remains a barrier to curative efforts. Early antiretroviral treatment (ART) has been shown to enable post-treatment viral control in some cases. We hypothesized that extremely early ART initiation will affect the size, decay dynamics and landscape characteristics of the HIV-1 subtype C viral reservoirs.
Methods: We studied 35 women from the FRESH cohort in Durban, South Africa diagnosed with hyperacute HIV infection by twice weekly testing for HIV-1 RNA. Study participants were divided into 2 groups where, 11 started ART at a median of 456 (297-1203) days post onset of viraemia (DPOV), while 24 started ART at a median of 1 (1-3) DPOV. We used PBMC to measure total HIV DNA by ddPCR and sequence viral genomes by full length individual proviral sequencing (FLIP-Seq) from detection of HIV up to 1 year post treatment.
Results: ART in hyperacute infection reduced peak viraemia compared to untreated infection ($p< 0.0001$), but there was no difference in total HIV DNA measured contemporaneously ($p=0.104$). There was a steady decline of total HIV DNA in the early treated group over 1 year that was not observed in the late treated group ($p=0.0004$). Total HIV DNA after 1 year of treatment was lower in the early treated compared to the late treated group ($p=0.02$). We generated 697 single viral genome sequences. There was a difference in the longitudinal proviral genetic landscape over 1 year between untreated, late treated and early treated infection, where the relative contribution of intact genomes to the total pool of HIV DNA after 1 year was higher in untreated infection (31%) compared to late treated (14%) and early treated infection (0%). Treatment initiated in both late and early infection resulted in a more rapid decay of intact ($T_{1/2}$=2 months and $T_{1/2}$=0.75 months) versus defective ($T_{1/2}$=25 months and $T_{1/2}$=8.54 months) viral genomes. However, intact genomes were still present 1 year post chronic treatment initiation in contrast to early treatment where intact genomes where no longer detectable. Also, early treatment reduced phylogenetic diversity of intact genomes as well as limited adaptation to cytotoxic T lymphocyte immune selection pressure.
Conclusion: Extremely early ART initiation in subtype C HIV-1 was associated with a more rapid decay of intact viral genomes, decreased genetic complexity and immune escape which could accelerate reservoir clearance when combined with other interventional strategies.

396 PERSISTANCE OF INDUCIBLE REPLICATION-COMPETENT HIV-1 AFTER LONG-TERM ART

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Background: Latent HIV-1 persists in a population of resting CD4+ T cells (rCD4s) harboring a transcriptionally silent provirus. It was previously shown that this latent reservoir decays slowly in individuals on antiretroviral therapy (ART) over the first seven years of therapy with a half-life of 44 months (Siliciano, *Nat Med*, 2003). However, it is unclear if the latent reservoir continues to decay in people on very long-term ART.
Methods: We recruited 11 people living with HIV (PLWH) who had been on suppressive ART for at least 20 years. To determine reservoir size and the frequency of inducible, replication-competent HIV-1, we performed quantitative viral outgrowth assays (QVOAs) with purified rCD4s. Wells scored positive for viral outgrowth were subjected to RNA extraction and full length env sequencing to explore the clonality of the reservoir. Additionally, we extracted genomic DNA from rCD4s to quantitate the proportion of intact and defective HIV proviruses using the intact proviral DNA assay (IPDA).
Results: Viral outgrowth was detected in all study participants in the QVOA. The frequency of rCD4s harboring inducible, replication competent HIV ranged from 0.03-16.2 infectious units per million (IUPM) and was highly correlated with the number of intact proviruses detected in the IPDA. Intact proviruses detected by the IPDA ranged from 2.8-168.1 copies per million cells and comprised < 10% of the total number of proviruses detected using this assay. Full-length *env* sequencing results suggest a trend in several individuals towards a high proportion of identical sequences.
Conclusion: In this study, we demonstrated that the latent reservoir in PLWH on ART for more than 20 years harbors inducible, replication-competent provirus. The range of IUPM values measured in this study are similar to those measured previously, indicating that over a very long time interval, the reservoir does not decay significantly. This is likely because decay processes are counterbalanced by infected cell proliferation. Full-length *env* sequences exhibited limited diversity in some individuals, implying that expanded T cell clones harboring identical proviruses contribute to long-term reservoir persistence. Ultimately, these data provide evidence that continued ART is necessary even following 20+ years of ART.

397 IN-DEPTH TRANSCRIPTOMIC ANALYSIS OF THE TRANSLATION-COMPETENT HIV-1 RESERVOIR

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Background: We previously described a Tat mimetic (Tat #1) that induces HIV reactivation in a higher fraction of latently-infected cells compared to PMA/ionomycin, without impacting cell viability nor modifying the transcriptome of the cells. Here we took advantage of these unique properties to study viral and cellular transcripts in p24+ cells following reactivation.
Methods: CD4 T cells from 5 ART-treated individuals were treated for 48h with Tat #1. A total of 108 p24+ cells and 109 p24- cells were single-cell sorted and subjected to single-cell RNA sequencing by Smart-seq2. Transcriptomic differences between p24+ and p24- cells were validated at the protein level using flow cytometry.
Results: Among p24+ cells, 6.7% of the detected reads mapped to the HIV reference genome HXB2, while HIV reads were not detected in p24- cells. Levels of HIV transcripts positively correlated with the intracellular p24 production per cell. Following de novo assembly of HIV transcriptional reads, complete reconstruction of the viral genome could be obtained in 36% of the p24+ cells, independently of the HIV subtype. Proviruses with a defective major splice donor (MSD) site and cryptic donor (CD) site utilized alternative splice sites up- and/or downstream of the MSD, highlighting the plasticity of MSD/CD defective proviruses. Compared to p24- cells, p24+ cells significantly expressed higher levels of a previously undescribed long non-coding (lnc) RNA, *SOD1P3*, *CCL5* and *GZMA*, while expressing lower levels of *ATG10* and *IL7R*. Flow cytometry analyses confirmed that p24+ cells expressed higher levels of CCL5 and GZMA proteins while expressing lower levels of IL7R and GZMB proteins compared to p24- cells.

In vitro infection of primary CD4 T cells with the virus strain 89.6 induced a strong upregulation of the lncRNA expression. Furthermore, pre-treatment of primary CD4 T cells with three different antisense oligonucleotides targeting the lncRNA prior *in vitro* infection resulted in the efficient silencing of the lncRNA while reducing the percentage of p24+ cells compared to the non treated control (≈3-fold, n=3 donors).
Conclusion: Using single-cell RNA sequencing, we unravelled alternative splicing mechanisms and showed that p24+ cells display a distinct transcriptional signature compared to non-infected cells. We identified a lncRNA as preferentially expressed by p24+ cells and provided evidence this lncRNA may play in role in regulating HIV gene expression.

398 CTL RESPONSES ARE NOT ASSOCIATED WITH DECAY OF INTACT PROVIRUSES OR HIV RNA ON ART

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Background: HIV-specific T-cells targeting Nef but not other HIV proteins are associated with levels of total HIV DNA and cell-associated (CA)-RNA that persist on ART, suggesting ongoing Nef antigenic stimulation. It is not known, however, if HIV-specific T-cells impact either proviral persistence or expression. We hypothesized that decay of intact proviral DNA and CA-RNA levels on ART would be associated with cytotoxic T-cell (CTL) responses.
Methods: 49 participants from the ACTG A5321 cohort on suppressive ART (plasma HIV RNA < 40 copies/mL) were studied at weeks 24 and 168 post-entry (median 7 years on ART at entry). HIV DNA and CA-RNA were measured by droplet digital PCR (IPDA for DNA, 5′ unspliced and 3′ total poly(A) for RNA). T-cell responses were measured by IFN-γ and granzyme B [GrB] ELISPOT to each HIV gene product (Gag, Env, Pol, Nef, Tat, Rev, and summed HIV). Non-parametric statistics were used to evaluate associations and to compare time points.
Results: 5′ unspliced CA-RNA decreased significantly from week 24 to 168 (p=0.001), and decline in intact (p=0.053) but not defective (p=0.22) HIV DNA approached significance. CA-RNA levels at weeks 24 and 168, and changes from 24 to 168 weeks were not found associated with IPDA levels or changes over time. There were no apparent associations between measures of HIV-specific T-cell responses (both IFN-γ-producing and GrB-producing) with the changes in intact or defective proviruses, nor with the changes in CA-RNA levels – including after controlling for time on ART, pre-ART viral load, and pre-ART CD4 count. As examples, the correlations between magnitudes of IFN-γ-producing Nef-specific responses and changes in intact HIV (r=-0.11, p=0.61) and 5′ CA-RNA (r=0.06, p=0.71), or GrB-producing Nef-specific responses and changes in intact HIV (r=0.10, p=0.66) and 5′ CA-RNA (r=-0.14, p=0.37), were small and not significant.
Conclusion: While both intact proviral DNA and CA-RNA levels (5′ unspliced) decayed over the 144-week period, contrary to our primary hypothesis no associations were observed between decay of intact HIV DNA or CA-RNA with HIV-specific T-cell responses, including with cytotoxic function (GrB) and despite controlling for time on ART. These findings suggest either a limited role for CTLs in reservoir decay after multiple years of suppressive ART, or that other unmeasured parameters are important, such as variation in susceptibility of reservoir cells to CTL-mediated killing.

399 TSCM/TCM-ENRICHED ANTI-HIV duoCAR-T CELLS EXERT POTENT HIV CONTROL

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Background: Anti-HIV chimeric antigen receptor (CAR) T cell therapies are candidates to functionally cure HIV infection in people with HIV (PWH). Translating such therapeutic candidates successfully into PWH will require anti-HIV CAR-T cells to persist long term and eliminate reactivated HIV-infected cells. Interestingly, recent clinical studies have shown a positive correlation between the early-memory phenotype of pre-infusion anti-CD19 CAR-T cell therapies and their long-term *in vivo* persistence and therapeutic efficacy. Here, we hypothesized that early-memory enriched anti-HIV duoCAR-T cells generated using a GMP-compliant CAR-T cell manufacturing process would exert potent HIV control in humanized mice with productive HIV-1 infection.
Methods: To test this hypothesis, we developed an 8-day CAR-T cell manufacturing process and profiled the T cell differentiation state of pre-infusion anti-HIV duoCAR-T cell products using multiparametric flow cytometry and CyTOF analyses. The therapeutic efficacy of early-memory enriched anti-HIV duoCAR-T cells was evaluated in a humanized NSG mouse model of intrasplenic HIV-1 infection (hu-spl-PBMC-NSG).
Results: CyTOF analyses of pre-infusion duoCAR-T cells revealed a unique early-memory phenotype composed predominantly of CCR7+ stem cell-like/central memory T cells (T_{SCM}/T_{CM}) with effector-like characteristics. We show that peripheral-injected T_{SCM}/T_{CM} enriched anti-HIV duoCAR-T cells localized to the site of active HIV infection in the spleen of humanized mice and eliminated HIV-infected PBMCs. In addition, anti-HIV duoCAR-T cells effectively recognized and killed productive HIV-infected monocytes/macrophages *in vitro*, a cell type that contributes to the latent HIV reservoir. Last, we demonstrate efficient genetic modification of T cells from PWH on suppressive ART into anti-HIV duoCAR-T cells that subsequently killed autologous PBMCs superinfected with HIV.
Conclusion: The observed early-memory phenotype of anti-HIV duoCAR-T cells combined with markers of T cell activation and effector function suggest that our 8-day CAR-T cell manufacturing process generates a product that is primed to attack cells with active HIV infection and may provide a durable therapeutic response over time in PWH. These studies support translation of anti-HIV duoCAR-T cell therapy to PWH in our presently open phase I/IIa clinical trial (NCT04648046).

400 bNAb ESCAPE HIV-ENV VARIANTS IN ORALLY SHIV-INFECTED, ART-TREATED INFANT MACAQUES

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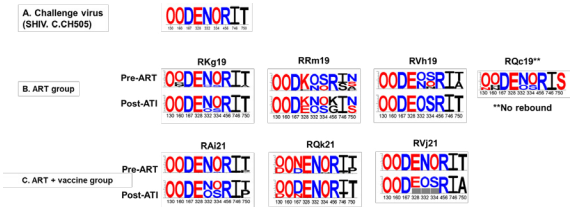
Background: Each year >150,000 children are newly infected with HIV, majority during breastfeeding. Early life infection forces adherence to life-long ART. Development of autologous virus neutralizing antibodies or broadly neutralizing antibody (bNAb) therapy has been associated with delay in viral rebound after analytical treatment interruption (ATI). However, viral variants that escape neutralization response limit the therapeutic potential of these strategies. Our objective is to map the neutralization escape mutations in orally SHIV-infected infant rhesus macaques (RMs) following ATI with and without therapeutic immunization.
Methods: Infant RMs (n=19) were orally challenged with SHIV.C.CH505 and started on triple ART at 8 weeks post-infection (wpi). Nine animals were immunized with two doses each of SHIV-DNA-rhCD40L, SHIV-MVA and CH505 Env SOSIP protein. At 60 wpi, ART was interrupted and all RMs were monitored for viral rebound. SHIV.C.CH505 virus neutralization titer in plasma was measured. To assess autologous virus neutralization escape variants, single genome amplification was performed on HIV-Env gene, and Env variants were compared to SHIV challenge stock. Finally, mutations previously associated with bNAb resistance were identified.
Results: While equivalent numbers of RMs from ART and ART+vaccine group developed autologous virus neutralizing antibodies (ART:5/10; ART +vaccine:5/9), the median titer was ~five-fold higher in the vaccine group (ID50=557) vs. the ART group (ID50=124) RMs, who developed response (p=0.4). However, there was no difference in median time to viral rebound post-ATI between ART (18 days) or ART+ vaccine group (14 days) (p=0.16). Individual assessment of HIV-Env sequences from animals who rebounded, even after development of autologous virus neutralization titers, demonstrated resistance against CD4bs (D130), V2 (N167) and V3-targeting bNAbs (T746). Interestingly, RMs showed a glycan gain at position 332, which is associated with V3 bNAb resistance, even before ART start (**Fig 1**). No specific differences in

patterns of mutation in the HIV-Env region was observed in ART vs. ART+vaccine group.

Conclusion: Using an infant RM model mimicking breast milk HIV transmission and therapy, we identified HIV-Env mutations associated with bNAb escape. Identifying specific neutralizing antibody escape-mutations will guide development of future active and passive immunization regimens that will minimize viral escape, leading to sustained drug-free HIV remission in infants.

Figure 1. BNAb resistance and sensitivity in HIV-Env variants in infant rhesus macaques (RMs). Logo plots of the viral sequences for (A) SHIV.C.CH505 challenge virus, (B) ART group and (C) ART+ DNA/MVA/SOSIP-based therapeutic vaccine group RMs. For each animal, pre-ART (top) and post-ATI (bottom) sequences are shown for panels B and C. Residues are color-coded red if they confer resistance to one of the broadly neutralizing antibody classes or blue if they confer sensitivity instead (Bricault et al. 2019 and Roark et al, 2021). O indicates a glycosylation site.



401 BISPECIFIC ANTIBODIES PROMOTE NK CELL-MEDIATED ELIMINATION OF THE HIV-1 RESERVOIR

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Background: The persistence of long-lived HIV-infected cells comprising the latent reservoir is the main barrier to an effective cure. One strategy for clearing the latent reservoir, known as "shock and kill," involves selective reactivation of HIV gene expression through treatment with a latency reversing agent (LRA) followed by immune-mediated elimination of HIV-infected cells. To ensure effective elimination of HIV-infected cells in the context of "shock and kill," novel immunotherapies must be developed to enhance HIV-specific cell-mediated cytolytic activity.

Methods: Here, we report single-chain diabody (scDb) constructs that target the HIV envelope protein (Env) and the human type III Fcγ receptor (CD16a). Two HIV-1-specific scDbs were designed based on PG16 and 3BNC117, broadly neutralizing antibodies specific for the V1/V2 and CD4 binding site regions of Env respectively. We evaluated the ability of the scDbs to promote HIV-specific natural killer (NK) cell activation and NK cell-mediated cytolytic killing of infected cells *in vitro*. Using the intact proviral DNA assay and viral outgrowth assays, we quantified changes in the frequencies of infected CD4+ T cells isolated from 10 virally suppressed PLWH following *ex vivo* reversal of latency and co-culture with autologous NK cells in the presence of the scDbs.

Results: Both scDbs promoted robust and HIV-specific NK cell activation and lysis of infected cells *in vitro*. These effects were not observed with an isotype control scDb targeting an irrelevant cancer epitope. Further, the Env-specific scDbs mediated remarkable *ex vivo* clearance of cells harboring intact proviruses (mean reduction 44%, range 20-67%, $p < 0.0001$). The observed clearance of reservoir cells was highly dependent on efficient latency reversal. Notably, we did not detect changes in cells harboring defective proviruses following *ex vivo* latency reversal and co-culture, suggesting that the scDbs are highly specific for cells expressing sufficient surface Env. Viral outgrowth assays revealed comparable scDb-mediated reductions in cells harboring inducible, replication-competent proviruses (mean reduction 40%, range 20-61%, $p < 0.001$).

Conclusion: Our study provides proof-of-concept evidence that the HIV-specific, NK cell-engaging scDbs described here are capable of mediating potent elimination of HIV reservoir cells. In combination with effective LRAs, the scDbs merit further preclinical evaluation as potential therapeutics for use in "shock and kill" HIV cure strategies.

402 DONOR-DERIVED ENV MUTATION SCANNING REVEALS aNAB AND bNAb VULNERABILITIES

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Background: Rapid viral evolution during untreated HIV-1 infection results in escape from autologous neutralizing antibodies (aNAbs). Escape often occurs within variable regions of the env gene, and at known epitopes of broadly neutralizing antibodies (bNAbs). Following ART initiation, viral evolution ceases, but aNAb activity persists against some viral variants in the latent reservoir. We hypothesized that identifying common escape mutations to aNAb will offer insight into the efficacy of passive and active immunization strategies.

Methods: We have previously characterized neutralizing activity of aNAbs against autologous envelope pseudo-typed viral particles from individuals suppressed on ART. Neutralization data were matched with the corresponding env sequence, and a genetic signatures analysis (Bricault et al., CHM 2019) was performed to identify putative determinants of aNAb resistance. Single amino acid sites of interest were altered using site-directed mutagenesis (SDM) in sensitive envs to adopt the resistant genotype. Changes in neutralizing activity of aNAbs and bNAbs against altered envelope pseudoviruses were investigated.

Results: Several amino acid sites were identified by bioinformatic analysis as having statistically significant association with aNAb resistance phenotype in a donor, 012. These single amino acid sites were altered by SDM in a sensitive env to reflect the resistant genotype. In this envelope sequence, a single alteration at the N332 glycan supersite- adding a glycan- significantly reduced the capacity of aNAb to neutralize the viral variant. Conversely, removal of the N332 glycan in a resistant envelope did not rescue neutralizing activity. Phenotypic changes were validated using the V3-glycan directed bNAb 10-1074, that is highly specific for the presence of a glycan at N332. Moreover, several other alterations did not impact aNAb neutralization capacity.

Conclusion: These studies confirm the use of our experimental protocol to identify sites of aNAb and bNAb vulnerability within select envelope sequences. Only a single amino acid modification had the capacity to induce significant change in aNAb activity. This suggests that vulnerability to aNAb in latent reservoir viral variants could be the result of only a few instances of immune escape. Thus, immunization-based strategies for a cure may involve targeting a few key vulnerabilities in env.

403 HIV-RESISTANT CAR T CELLS BY CRISPR/Cas-MEDIATED CAR INTEGRATION INTO THE CCR5 LOCUS

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Background: The HIV reservoir is a major barrier to a cure. To augment T cell mediated eradication of infected cells, we have engineered chimeric antigen receptor (CAR) T cells using a single-chain variable fragment (scFv) from the clinically potent broadly neutralizing antibody (bNAb) 10-1074. We used the CRISPR/Cas9 system to integrate the CAR expression cassette into either the AAVS1 locus (AAVS1-CAR) as a negative control or the CCR5 locus (CCR5-CAR) leading to concurrent CAR gene integration and CCR5 disruption, making the engineered CAR T cells resistant to HIV infection.

Methods: HIV-resistant CAR T cells were produced from healthy donor leukapheresis products and engineered by homology directed repair by delivering sgRNA/Cas9 ribonucleoprotein complexes by nucleofection and donor DNA templates by AAV6 viral vector transduction. CAR integration into T cells was evaluated by flow cytometry and droplet digital PCR (ddPCR). The cytotoxic capacity was assessed using HIV envelope-expressing cell lines and HIV-infected autologous PBMCs or CD4+ T cells.

Results: Engineered CCR5-CAR T cells showed complete CCR5 knock-out and protection from HIV infection. A mean of 20 % (range 10-35 %) of AAVS1-CAR and CCR5-CAR T cells expressed the CAR with precise CCR5 integration verified by ddPCR in CCR5-CARs. Both AAVS1-CARs and CCR5-CARs showed no off-target effects towards autologous B cells and reporter cells not expressing HIV Env in 24-hour cytotoxicity assays. Specifically, we show that our AAVS1-CAR and CCR5-CAR T cells lysed YU2-expressing Raji cells (81% and 77%, respectively) and R5-tropic NL4-3-infected autologous CD4+ T cells (67 % and 63 %, respectively) following 24-hours of co-culture in 2-4 biological replicates.

Finally, in a five-day co-culture with HxB2-infected CD8-depleted PBMCs, the AAVS1-CAR and CCR5-CAR T cells led to significant reductions (98.8 % and 93.3 % respectively, $p < 0.05$) of p24 levels in supernatants measured by ELISA.
Conclusion: In conclusion, we have developed HIV-specific CAR T cells with complete CCR5 disruption and protection from infection using the CRISPR/Cas9 system. Our cells showed no off-target effects and high cytotoxic capacity against HIV envelope-expressing cells. These data support the further development of gene edited cellular therapies to achieve an HIV cure.

404 GENERATING BROADLY NEUTRALIZING ANTIBODY-SECRETING CAR-T CELLS AGAINST HIV INFECTION

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Background: Treatment with HIV-specific CAR-T cells and broadly neutralizing antibodies (bNAbs) are both important approaches to potentially provide the sustained anti-HIV activity required to achieve ART-free HIV remission. We hypothesized that the anti-HIV activity of CAR-T cells could be further increased by enabling them to secrete bNAbs. As a proof-of-concept, we engineered a lentiviral vector (LV) encoding the BNC117 bNAb (3BNC) which was co-transduced with a LV encoding an anti-HIV duoCAR construct targeting two distinct HIV gp120 epitopes with potent anti-HIV activity (Sci Transl Med. 2019; 11:eaav5685) to generate 3BNC-secreting duoCAR-T cells.
Methods: CD3 T cells were purified from HIV-seronegative donors and transduced with 3BNC and/or HIV-duoCAR LV and evaluated for *in vitro* anti-HIV activity and 3BNC production. *In vivo* function was determined by intrasplenically co-injecting NSG mice with LV-transduced T cells and autologous PBMCs infected with an HIV infectious molecular clone expressing a luciferase-reporter (HIV-luc) and measuring *in vivo* viral suppression and 3BNC serum levels.
Results: *In vitro* studies demonstrated we could generate duoCAR-T cells capable of producing 3BNC that suppressed *in vitro* HIV infection. In the *in vivo* study, T cells transduced with the duoCAR and/or 3BNC LV (40×10^6 cells) were co-injected intrasplenically into NSG mice with autologous PBMCs infected with HIV-Luc (20×10^6 cells). Prior to injection, ~50% of T cells expressed 3BNC or duoCAR only with single LV transduction. In the T cells transduced with both LVs (duo-LV), ~40%, 5% and 15% of them expressed 3BNC alone, duoCAR alone or both, respectively. After 3 weeks, CD4 T cells were preserved in the spleens of mice treated with 3BNC- (35%), duoCAR- (36%) and duo-LV- (37%) transduced T cells, as compared to untreated mice (2%). In all treated mouse groups, HIV infection was suppressed by more than 90% as compared to untreated controls. Importantly, HIV levels in the duo-LV mice was 1.2 and 2.6 fold lower than 3BNC and HIV-duoCAR LV mice, respectively. Mice plasma 3BNC concentrations at 2 weeks after injection with 3BNC- or duo-LV-transduced T cells were 1.2 or 1.0 microgram/ml, respectively.
Conclusion: We successfully engineered HIV-CAR-T cells that secreted bNAbs which exhibited superior *in vivo* anti-HIV function as compared to single LV-transduced T cells. This "2 in 1" approach provides a new strategy to generate more potent immunotherapeutics to contribute to a functional cure of HIV infection.

405 CIRCULATING IMMUNE PREDICTORS OF INTACT HIV RESERVOIR DECAY DURING LONG-TERM ART

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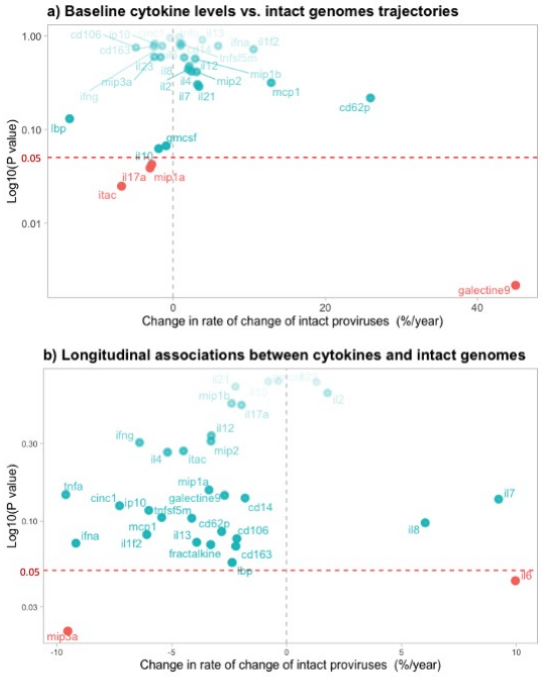
Background: The HIV reservoir is not stable during antiretroviral therapy (ART). Cells harboring intact genomes decay more rapidly than those with defective genomes, particularly during the first several years of therapy. The host factors associated with the rate of decay have not been characterized.
Methods: We measured intact proviruses in PWH on ART using the intact proviral DNA assay (IPDA) in peripheral blood. We used Luminex bead-based multiplexed immunoassay system to measure 32 pro-inflammatory and regulatory cytokines in plasma. Based on our previous study focused on total and intact HIV genome kinetics, we fitted linear spline models with a knot at seven years and a random intercept and slope up to the knot. We estimated the influence of baseline cytokine levels and their trajectories on intact HIV kinetics in separate models.
Results: We studied 76 PWH on effective ART for a median of 10.4 (range 4.3 -15.6) years, providing a median of 3 (2 – 4) samples during the follow-up. Their median nadir CD4 was 180 (0 – 644) cells/uL and their baseline CD4 counts were 591 cells/uL (173-1600). Baseline galectin-9 was the most predictive marker of intact HIV kinetics: per each 10-fold decrease at baseline, there was a mean 45% greater reduction of intact HIV genomes per year ($p = 0.0021$; after adjustment for CD4 nadir, $p = 0.005$). In contrast, lower baseline ITAC, IL-17, and MIP-1a were predictive of intact HIV increases (Figure 1a).
MIP-3a and IL-6 exhibited the strongest associations between longitudinal changes in cytokine level during ART and intact HIV kinetics. For each 10-fold increase of MIP-3a over time, we observed a concurrent 9.5% faster decay of intact HIV genomes ($p=0.021$), while for each 10-fold reduction of IL-6, intact genomes decreased 10% faster per year ($p=0.043$)(Figure 1b).
Conclusion: The extent of intact HIV decay was predicted by baseline galectin-9 levels, while MIP-3a and IL-6 correlated with intact HIV kinetics. Galectin-9 was the host factor most strongly associated with subsequent intact HIV decay, in alignment with its established roles in regulation of HIV expression and cytotoxic immunity.

Figure 1. Effects of baseline cytokine levels (a) and changes per year (b) on intact HIV reservoir kinetics.



406 THE LEAKY RESERVOIRS ARE ASSOCIATED WITH HIV-SPECIFIC CD4 AND CD8 T CELL RESPONSES

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Background: A major obstacle to an HIV cure is the persistence of latent viral reservoirs. When ART is interrupted, rare latently-infected cells revert to a state of productive infection fueling viral rebound. New sensitive assays clarified the misconception that latency implies a fully silent state of infection: most latently infected cells maintain a certain degree of transcriptional "leakiness", although the *in vivo* relevance of this phenomenon remains unclear.
Methods: We studied leaky latency in 18 people living with HIV on ART ^{3} 3 years (ART-PLWH) with optimal viral suppression. Purified CD4 T cells were either PMA/ionomycin-stimulated (inducible) or unstimulated (leaky) for 16h. Transcriptionally active (vRNA+) viral reservoirs were identified by single-cell flow cytometric fluorescent *in situ* RNA hybridization (RNAflow-FISH) using probes targeting LTR-gag, gag or pol regions. To assess if viral reservoirs were

associated with anti-HIV immune responses, HIV-specific CD4+ and CD8+ T cells were measured by activation induced marker (AIM) and intracellular cytokine staining (ICS) assays. Cells were stimulated with Gag, Pol, Env and Nef peptides.

Results: We detected leaky vRNA+ cells in samples from 14/18 (78%) ART-PLWH, compared to 16/18 (89%) for induced vRNA+. We measured a median of 21 leaky vRNA+ /10^6 CD4 T cells. Transcriptionally active reservoirs represented 30% of the inducible vRNA+ (median 62/10^6), and 4% of the cells containing integrated HIV DNA (median 686/10^6). Frequencies of transcriptionally active cells were associated with HIV-specific CD4 T cell responses as measured by AIM ($r=0.532$, $p< 0.05$). Similar associations were noted for HIV-specific CD8 T cells, although only Env-specific responses reached significance ($r=0.510$, $p< 0.05$). These results were confirmed by correlations between leaky reservoirs and CD4 T cell responses measured by ICS. Rare spontaneous p24-expressing CD4 T cells strongly correlated with HIV-specific CD4 T cell responses ($r=0.640$, $p< 0.01$).

Conclusion: We conclude that leaky latency is detectable in a majority of ART-PLWH, and at frequencies only three times lower than the inducible reservoirs. The correlations between leaky HIV reservoirs and antigen-specific CD4 and CD8 T cells suggest that residual HIV protein expression is a major driver of sustained HIV-specific CD4 and CD8 T cell responses during suppressive ART.

407 CTL EPITOPES FROM STRUCTURALLY IMPORTANT HIV PROTEINS ARE IDENTIFIED IN REBOUND HIV

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Background: During an analytic treatment interruption (ATI), the elimination of HIV-infected cells by HIV-specific cytotoxic CD8 T cells (CTLs) is required to control viral infection. However, unless treatment is initiated during acute infection, the HIV reservoir becomes dominated by CTL escape variants resistant to immune response. To address this issue, we applied a novel IMmunoinformatics Analysis Pipeline (IMAP) to identify CTL epitopes within structurally important HIV protein regions that avoid CTL immune escape mutations.

Methods: Employing the IMAP, we generated 8-14 mer overlapping peptides containing amino acid residues that are essential for HIV Gag protein structure and function. We excluded the peptides containing CTL escape mutations and those found within < 85% of all HIV-1 subtypes/recombinants. Using the Immune Epitope Database and NetMHCpan analysis tools, we selected the peptides that are predicted to be immunogenic and are binders to multiple HLA-I alleles. These peptides were compared to the Gag protein region extracted from HIV RNA sequences of five participants who underwent multiple ATIs.

Results: We identified a total of 32 overlapping peptides within the Gag protein from positions 150-166. Interestingly, when we compared this protein region to the Los Alamos HIV database, we observed 55% of the HIV sequences contained arginine (R) and 41% contained lysine (K) at position 154. Therefore, the R/K variant peptides combined (n=24) were identified within 96% of viral sequences worldwide. Of note, none of these peptides contained the R/K variations at positions critical for HLA-I anchoring. Eight additional overlapping HIV peptides identified within positions 155-166 of the Gag protein region were found within 95% of HIV sequences globally. These 32 HIV peptides were predicted to bind to multiple HLA-I alleles, resulting in 88% worldwide population coverage. When including the R/K variant forms of the HIV peptides, 100% of plasma-derived HIV RNA sequences from 5 participants, who experienced 3 separate treatment interruptions, contained our selected Gag peptides.

Conclusion: Applying the IMAP, we defined novel HIV peptides within a structurally important region of the Gag protein. Importantly, these peptides were genetically conserved and avoid known CTL escape mutations. The peptides were identified within ATI-derived plasma HIV RNA sequences, indicating these peptides as a pool are highly promising for eliciting a CD8 T cell immune response during treatment interruption.

408 IMMUNE FEATURES ASSOCIATED WITH HIGHER T CELL RESPONSES TO AN HIV THERAPEUTIC VACCINE

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Background: Eliciting a robust T cell response is a central goal of many HIV therapeutic vaccines, but T cell responses are often heterogenous. We conducted systems immunology analyses to identify the immunologic signatures, at the cellular and transcriptional level, that correlate with augmented HIV-specific T cell responses post-vaccination in 30 participants with HIV who received an HIV DNA vaccine/IL-12 in the PENNVAX clinical trial (NCT03606213).

Methods: Response to vaccination was defined as the fold change (FC) in the magnitude of HIV-specific T cell responses (averaged per HIV antigen) from pre-vaccination to 2 weeks post-boost (Week 14), as measured by IFNγ ELISpot using vaccine-matched peptide pools (median FC 2.1 [range 0.1-15.9). We characterized 473 innate and adaptive immune cell features using mass cytometry (CyTOF) and performed whole-blood RNA-sequencing. We then correlated CyTOF features and genes with ELISpot FC to identify cell subsets and immune pathways associated with enhanced vaccine responses.

Results: Pre-vaccination, higher expression of genes involved in T cell homeostasis (e.g., IL7, IL7R; adj. p=1e-04) and innate immune sensing (e.g., TLR9, IFNAR1, IL1R1; adj. p=8e-04) pathways were associated with a greater increase in HIV-specific T cell responses after vaccination (genes in Fig. 1A). Individuals with a larger FC in their T cell response between baseline and Week 14 also demonstrated greater induction of genes in IL-2/STAT-5 signaling (adj. p=0.003) and hematopoiesis (adj. p=4e-09). By CyTOF, larger IFNγ ELISpot responses post-vaccination were significantly ($p< 0.05$) associated with a greater increase in the frequency in cytotoxic-skewed CD4+, CD8+, and γδ T cells expressing Granzymes A/B, Perforin, CX3CR1, and Tbet (Fig. 1B)

Conclusion: Our data highlight that individuals who develop a larger T cell response to a DNA HIV therapeutic vaccine have a baseline immune environment that promotes T cell survival and responsiveness to innate immune signaling, and that they respond to vaccination with more robust IL-2 signaling and hematopoiesis. We also demonstrate that therapeutic vaccination with DNA/IL-12 induces not only cytotoxic CD8+ T cells, but also cytotoxic CD4+ and γδ T cells. These data provide insight into how differences in host immune responses pre- and post-vaccination can impact vaccine immunogenicity and highlight that modulation of the pre-existing immune environment (e.g., with different adjuvants) may be critical to conditioning better vaccine responses.

Immunologic features associated with a greater magnitude increase in T cell responses to therapeutic vaccination.

Fig 1A. Leading-edge genes from pathways significantly enriched in pre-vaccine whole blood that are associated with a higher T cell response post-vaccine.

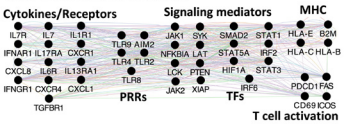
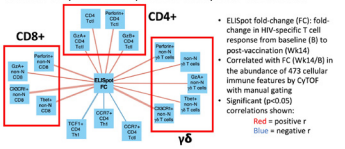


Fig 1B. Expansion of cytotoxic CD4, CD8 and γδ T cells correlates with the IFNγ ELISPOT response to therapeutic vaccination.



409 ANTIRETROVIRAL THERAPY REPAIRS CD4 T CELL DYSREGULATION IN PEOPLE LIVING WITH HIV

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Background: Recent studies show that the majority of the HIV reservoir is stabilized at the time of ART initiation. We hypothesized that ART in people

with HIV (PWH) contributes to this stabilization by restoring CD4 T cell memory formation.
Methods: We used a 32-marker mass cytometry panel to examine CD4 T cell memory dynamics in PWH who are durably (~5yrs) ART suppressed (PWHART, n=10) and PWH in the 1.5 years following ART initiation (n=10, ACTG5248). The panel included markers of activation (HLA-DR, CD38, CCR5), activation/exhaustion (PD-1), proliferation (Ki67), survival (Bcl-2) and long-lived memory (CD127). We paired these CD4 T cell studies with functional analysis of proliferation and T cell receptor (TCR) β clonotype sequencing.
Results: Using fixed effects models with indicators for participant ID, we found that frequencies of CD4 T cell memory subsets and expression of activation, exhaustion, cell cycling and long-liveness are remarkably stable in PWH-ART. In contrast, in the weeks after ART initiation, markers of activation and cell cycling decreased rapidly. Subsequently, slower but sustained increases in frequency of markers of T cell long liveness, CD127 and Bcl-2, were observed. Elastic net regression analysis was complementary, finding that CD127 Bcl-2 expression on both CD4 and CD8 central memory T cells increased post-ART initiation. TCR sequencing in PWHART found that dominant CD4 TCR clonotypes were not stable over time (17-19 months), however clonotypes that dominated (2-10%) at ART initiation were maintained for the first 18 months. To assess functionality of CD4 T cells post-ART, we measured CD4 T cell proliferation in response to pp65/IE1 CMV and mitogen stimulation. Proliferation was clearly detectable at ART initiation and decreased over time as viral load decreased. After viral suppression, proliferation began to recover. By contrast, we did not detect HIV Gag/Nef-specific CD4 T cell proliferation over background.
Conclusion: In our study population (CD4 nadir 77-453), CD4 T cells were highly activated but retained proliferative capacity at ART initiation. ART resulted in rapid decreases in cell cycling and activation. Interestingly, restoration of CD4 T cell memory phenotypes was much slower, occurring over the months-years following virus suppression. CD4 T cell restoration likely supports maintenance of dominant CD4 T cell clonotypes at ART initiation. Overall, our data suggest that immune changes at ART initiation help stabilize the HIV reservoir in CD4 T cells.

410 REPROGRAMMING CMV-SPECIFIC CD8+ T CELLS TO TARGET HIV USING TCR GENE TRANSFER

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Background: Due to the chronic nature of HIV infection, cytotoxic CD8 T lymphocytes (CTL) are limited in their capacity to provide sustained control of HIV infection in part due to exhaustion. In contrast, chronic cytomegalovirus (CMV) infection induces a unique CTL response termed memory inflation characterized by continued expansion following priming, maintained "effector-memory" phenotype, and sustained functionality. As T cell activation is crucial to enable lentivector transduction, we hypothesized that we could selectively transduce CMV-specific CTL with a lentivector expressing an HIV-specific TCR by using a novel immunotherapeutic, CMV-synTac, which selectively activates and expands CMV-specific CTL (JCI 2021;131:e141051). This would convert CMV-specific CTL into bispecific CTL capable of suppressing HIV infection while exhibiting the memory inflation phenotype.
Methods: After CMV-synTac treatment, CMV-specific CTL were selectively transduced with a lentivirus encoding a chimeric T cell receptor (TCR) containing a murine constant region fused to a human variable region specific for the HIV-1 Gag epitope, SL9. Use of the mouse constant region prevents mispairing of endogenous and lentivector-encoded alpha and beta TCR chains. TCR Expression was determined by tetramer staining and functional activity of the bispecific CTL was detected by ELISpot.
Results: CMV-specific CTL were selectively transduced with an SL9-specific TCR lentivector after activation with CMV-synTac, but not after anti-CD3/CD28 activation. Lentivector-encoded SL9-TCR function was demonstrated by markedly increased luciferase expression after coculturing SL9-TCR lentivector-transduced Jurkat T cells with an NFAT-regulated luciferase reporter with SL9-peptide but not irrelevant peptide-loaded T2 cells. Dual expression of the exogenous SL9-TCR and endogenous CMV-TCR in transduced donor CD8 T cells was detected by tetramer staining and flow cytometry. Lastly, functionality of both SL9- and CMV- TCRs were validated by interferon-gamma ELISpot assays after either SL9 or CMV peptide stimulation.
Conclusion: CMV-synTac enables antigen-specific transduction of CMV-specific CTL with a lentivector expressing an SL9-TCR which confers them with additional functional activity against HIV-infected cells. We anticipate that these bispecific CTLs should also express the memory inflation phenotype of the CMV-specific CTL enabling them to display sustained anti-HIV activity after infusion into PWH and thereby contribute to a functional cure.

411 NOVEL BISPECIFIC ENGAGER REDIRECTS CMV-SPECIFIC CTL TO ELIMINATE HIV-INFECTED CELLS

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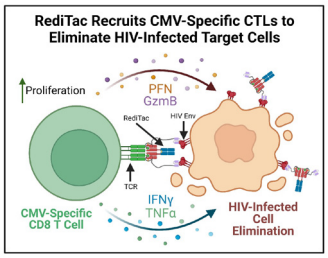
Background: We developed a novel biologic (RediTac) to selectively activate and expand virus-specific memory CD8 T cells (CTLs), redirect them to eliminate HIV-infected cells, and thereby eliminate reactivated latent HIV-infected cells. RediTac employs a bispecific Fc-fusion protein scaffold to dimerize HLA-A2 pMHC linked to HIV bNAb scFvs. The pMHC presents a tethered viral peptide for selective binding and stimulation of cognate TCR on virus-specific CTLs, while the scFv redirects the CTL to eliminate HIV-infected cells. As a proof-of-concept, we constructed RediTac with pMHC presenting a CMV-derived peptide, NLV, which is associated with a well-described memory inflation phenotype. The NLV-pMHC was linked to an scFv derived from VRC01, an HIV-1 Env-specific bNAb. This NLV-VRC01 RediTac was tested to determine its ability to redirect CMV-specific CTLs to eliminate HIV-1 Env-expressing cells and suppress HIV-1 infection.
Methods: Donor PBMC treated with NLV-VRC01 RediTac to expand NLV-specific memory CTLs were cocultured with either an Env-expressing 293T cell line or autologous CD4 T cells infected with an HIV infectious molecular clone expressing a luciferase reporter. NLV-VRC01 RediTac or control treatments were administered and Env-expressing 293T cell killing or luciferase activity reduction was measured as a readout for anti-HIV function.
Results: Two weeks after NLV-VRC01 RediTac treatment, NLV-specific CTLs expanded by >50-fold compared to untreated controls. Following a two-day coculture, these CTLs eliminated ~40% of Env-expressing 293T cells when treated with fresh NLV-VRC01 RediTac. No elimination was observed when control non-cognate-VRC01 RediTac or NLV-antiCD19 scFv RediTac was added instead. The addition of NLV-VRC01 RediTac without NLV-specific CTLs suppressed HIV infection of donor CD4 T cells by ~35%, indicating neutralizing activity of the VRC01 scFv domain. When NLV-VRC01 RediTac was administered to HIV-infected donor CD4 T cells with syngeneic NLV-specific CTLs, the infection was suppressed by ~70% as compared to untreated cultures.
Conclusion: NLV-VRC01 RediTac selectively expands CMV-specific memory CTLs and redirects their cytotoxic activity to eliminate HIV-infected cells, and in parallel, also functions as a bNAb to inhibit HIV-1 infection. These results support virus-specific CTL redirection as a novel approach to eliminate latent HIV-infected cells reactivated by LRAs. This approach could contribute to new strategies for a functional HIV-1 cure.



412 HIV-1 RESISTANCE PROFILES AGAINST bNAb IN INTACT VS DEFECTIVE GENOMES ARE DISTINCT

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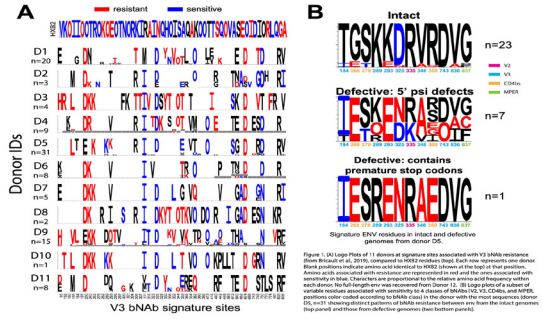
Background: Broadly neutralizing antibodies (bNAbs) targeting HIV-1 Env are under study as a strategy in cure research. Viral env is genetically diverse, with distinct bNAb sensitivity profiles across hosts. Here, we developed a pipeline to analyze bNAb-associated resistance genotypes in intact and defective HIV DNA genomes. We hypothesize that intact genomes will have distinct bNAb resistance profiles relative to defectives.

Methods: HIV-1 DNA genomes were sequenced from 1 viremic and 11 virologically suppressed individuals on long-term ART via single genome amplification (HXB2 638-9632). Genomes were classified as intact or defective using HIVSeqinR software. Resistance features against CD4 binding site-, V2-, and V3-targeting bNAbs examined include specific env residues, as well as hypervariable loop characteristics such as total length, number of N-linked glycosylation sites (PNGs), and electric charge.
Results: Of the 477 genomes obtained, 72 were intact, while full-length HIV-1 env was only present in 26% (10^6/405) of defective genomes. All 12 study donors displayed distinct resistance profiles against CD4bs-, V2- and V3-targeting bNAbs (Figure 1A), and all env in intact genomes were genetically unique compared to env in defective genomes within host. In the viremic donor, 91% defective viruses lacked env, whereas the 20 intact genomes had two distinct bNAb resistance profiles, equally split, one with significantly more resistant residues, as well as longer V1+V2 loop lengths and a higher number of PNGs ($p< 0.004$) – all characteristics associated with higher V3 bNAb resistance (Bricault et al., 2019). In-depth analysis of the virologically suppressed donor with the most sequences revealed that resistance profiles in intact env were more homogeneous and displayed more sensitive profiles when compared to the defective envs (Figure 1B). Env in defective genomes had significantly longer V1+V2 hypervariable loops than intact env ($p=0.005$) and were more negatively charged ($p=0.002$). Two glycans, at positions 289 and 743, both associated with increased V3 bNAb resistance, were exclusively found in defective genomes.
Conclusion: Our results reveal that resistance profiles across all bNAb classes in env are diverse across hosts and distinct between intact and defective genomes within host, and highlight the importance of understanding intact-genomes resistance profiles when screening individuals for enrollment in bNAbs clinical trials.
Figure 1.



413 KIR+RA+CD8 T CELLS EXHIBIT ANTIGEN INDEPENDENCE AND CORRELATE WITH HIV RESERVOIR SIZE

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Background: CD45RA+CD8+ T cells that express killer cell immunoglobulin-like receptors (KIRs) (KIR+RA+) are active during autoimmunity and infectious disease, contain restricted TCR repertoires, and elicit IL-15-dependent protective immunity. We sought to reveal these features in ART-treated HIV+ individuals and further hypothesized KIR+RA+ harbor antigen-independent activity and would negatively correlate with reservoir size.
Methods: CD8+ T cells from HIV+ individuals were sorted into distinct CD3+CD8+ subsets: TN (CD45RA+panKIR-CD27+), KIR+RA+ (CD45RA+panKIR+), TEMRA (CD45RA+ panKIR-CD27-), TCM (CD45RA-CD27), and TEM (CD45RA-CD27-); RNA was sequenced (NovaSeq6000; n=3). In PBMCs from HIV+ individuals (n=15), RNA profiles were validated via flow cytometry, and subsets were correlated to reservoir size using the intact proviral DNA assay (IPDA). We developed an antigen-independent Viral Inhibition Assay (VIA) which abrogated surface expression of MHC I on CD4+ T cells by CRISPR/Cas9 (n=7). Activated cells were infected with HIV and cocultured for 7 days with CD8+ T cell subsets then assessed for HIV Gag via flow cytometry. The impact of IL-15 superagonist (N803) on KIR+RA+ was also assessed (n=5).
Results: KIR+RA+ cells contained high levels of cytotoxic and NK-associated transcripts and protein expression. Perforin and GZMA/B expression was comparable to TEMRA and TEM cells, and higher than TCM. Expression of CD56, CD16, and NKG2D was limited to KIR+RA+ cells. KIR+RA+ cells had restricted TCR repertoires, comparable to TEMRA. Only KIR+RA+ cells correlated inversely with intact (spearman $r = -0.54$; $P=0.04$), gag ($r = -0.53$; $P=0.05$) and env ($r = -0.63$; $P=0.01$) proviral DNA. In the VIA, KIR+RA+ cells did not reduce Gag expression in MHCpos CD4+ T cells compared to CD4-only cultures (median FC 0.76; ns), but did in conditions with MHCneg CD4+ T cells (FC 0.45; $P=0.01$), including marked reductions in cell number (FC 0.33; $P=0.0002$). In response to 2 weeks of N803 stimulation, KIR+RA+ numbers significantly increased (mean FC 11.92; $P=0.02$) and accumulated cytotoxic profiles (i.e., GZMA 9.3 mean FC, $P=0.03$).
Conclusion: KIR+RA+ cells harbor cytotoxic profiles and negatively correlate with intact proviral DNA. KIR+RA+ cells respond to N803 and diminish the number of primary MHCneg CD4+ T cells infected with HIV. Our data demonstrate that KIR+RA+ cells are associated with smaller HIV reservoirs and exhibit antigen-independent, innate-like antiviral activity during HIV infection.

414 IMPACT OF SARS-CoV-2-MEDIATED CD4 T CELL ACTIVATION AND HIV DNA PERSISTANCE *IN VIVO*

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Background: Antigen-driven CD4+ T cell proliferation is a proposed mechanism of HIV-1 reservoir persistence. We previously reported that SARS-CoV-2 infection leads to increased detectable low-level HIV-1 plasm RNA blips months after COVID-19, but the impact of SARS-CoV-2-mediated T cell activation on expansion of HIV-1 reservoirs is not known. We sought to identify if SARS-CoV-2 infection leads to expansion of preferentially HIV-infected CD4+ T cells in people with HIV (PWH) on ART.
Methods: Five PWH with samples collected prior to and approximately two months after SARS-CoV-2 infection were identified. We performed a surface activation induced marker (AIM) assay using a CD4-optimized overlapping SARS-CoV-2 peptide pool to measure OX40/CD137 expression following peptide stimulation and sorted CD4+ T cells based on surface marker expression. ddPCR quantification of genomic HIV-1 DNA was performed on sorted subsets.
Results: We observed an increase in the frequency of SARS-CoV-2 AIM+ non-naive CD4+ T cells following COVID-19 in samples from 4 of 5 participants (mean AIM+ % 0.13 pre- vs 0.31 post). A large percentage of non-naive AIM+ CD4+ T cells expressed PD1 compared with total non-naive cells before (76% vs 36%) and after (65% vs 19%) COVID-19; PD1 expression was lower following SARS-CoV-2 in both AIM+ and AIM- CD4+ T cell subsets (although very few cells were AIM+ prior to COVID-19). HIV-1 DNA levels in non-naive AIM- CD4+ T cells prior to COVID-19 unexpectedly decreased following infection (mean 3,522 to 766 copies/10^6 cells). The numbers of AIM+ cells obtained by cell sorting were overall low (3,863 mean) and only one participant had detectable DNA in post-COVID AIM+ CD4+ T cells. However, a large majority of this participant's post-COVID AIM+ cells harbored HIV-1 DNA (0.89 copies per cell) whereas HIV DNA in their AIM- cells decreased from 8,387 to not detected following SARS-CoV-2 infection. No HIV-1 DNA was detected in the small number of AIM+ cells obtained prior to COVID-19 in this participant.
Conclusion: COVID-19 in PWH led to a modest SARS-CoV-2-specific CD4+ cell response approximately two months following acute presentation. One participant may have preferentially expanded HIV-1-infected, SARS-CoV-2-specific CD4+ T cells following COVID-19 but studies involving larger numbers of participants and larger numbers of cells will be needed to fully understand the impact of SARS-CoV-2 on clonal expansion and HIV persistence.

415 UNRAVELING ONGOING INFLAMMATION AFTER EARLY ART BY IN-DEPTH ANALYSIS OF LYMPH NODES

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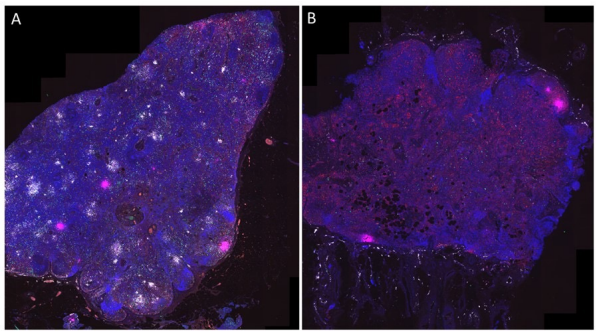
Background: Antiretroviral therapy (ART) initiation during acute HIV-1 infection limits HIV reservoir seeding and favors immune restoration, however there are concerns of remaining increased systemic inflammation, despite intervention with very early ART. In-depth analysis of lymph nodes during and after acute HIV-infection, may provide insight into the drivers of this inflammation.
Methods: Samples were selected from a multi-centric Belgian cohort study (ACS), in which blood and inguinal lymph nodes (LNs) were collected during acute HIV infection (T0), upon reaching an undetectable plasma viral load on ART (UD) and 1 year later (UD+1). We performed multiplex immunoassay (Mesoscale Discovery) on plasma of 25 participants at T0 and UD. A total of 15 T0 and 8 UD+1 formalin-fixed paraffin embedded inguinal LNs were analyzed by multiplex immune fluorescence (IF) to determine inflammatory changes and activation. In addition, HIV DNAscope was used to quantify the frequency of HIV DNA+ (vDNA) cells. To maximize the sensitivity of the assay, coverage of subtype-specific probe sets was predicted based on near full-length sequences. In case < 20 ZZ pairs were predicted to bind, custom probe sets were used.
Results: Plasma levels of CXCL10 and CXCL11 at UD were significantly higher in ACS-participants compared to healthy controls (p=0.018, p=0.015). CXCL10 was detected in a highly focal pattern within LNs and was positively correlated with pSTAT1 expression (r=0.614, p=0.001). Both showed a non-statistically significant downward trend between T0 and UD+1 (p=0.46, p=0.09) and foci of CXCL10 remained detectable in most LNs at UD+1. CXCL10-expressing cells consisted of 37.8% macrophages and 13.9% neutrophils at T0. Neutrophil counts within the LNs were elevated at T0, and were significantly reduced at UD+1 (p=0.031). Expression of CXCR3, the CXCL10 receptor, was significantly higher at T0 versus UD+1, in both T-cells, B-cells, and other cells (p=0.031), and was enriched in proliferating (Ki67+) cells. Initial quantification of vDNA showed a decrease between T0 (median 482/10^6 cells) and UD+1 (median 75/10^6 cells), however no significance was reached (p=0.0625). No correlation could be found with expression levels of pSTAT1 or CXCL10.
Conclusion: During acute HIV infection, lymph nodes are in a hyperinflammatory state. Foci of CXCL10 did not significantly decrease at UD+1, suggesting ongoing inflammation within the lymphoid tissues as a source for increased systemic CXCL10, despite suppressive ART.

Representative IF images on inguinal lymph nodes of an early treated participant (ACS005) for CXCL10 (magenta), pSTAT1 (white), neutrophil marker (MPO, green), pan-macrophage marker (Iba1, red) and nuclei (DAPI, blue) at the T0 timepoint (A) and UD+1 timepoint (B).



416 UNEQUAL DISTRIBUTION OF INTACT HIV PROVIRUSES IN CELLS EXPRESSING PD-1 AND/OR CTLA-4

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Background: HIV persists in CD4 T-cells of people with HIV (PWH) on antiretroviral therapy (ART). Determining cell surface markers that enrich for genetically-intact HIV genomes is vital in developing curative strategies. The immune checkpoint markers programmed cell death protein-1 (PD-1) and cytotoxic T-lymphocyte associated protein-4 (CTLA-4) have been identified as potential markers for enrichment of HIV provirus.
Methods: We obtained peripheral blood (PB) from 16 PWH under effective ART. Memory CD4 T-cells were FACS-sorted into 4 populations: PD-1-CTLA-4- (double negative, DN), PD-1+CTLA-4- (PD-1+), PD-1-CTLA-4+ (CTLA-4+) and PD-1+CTLA-4+ (double positive, DP). Using the full-length individual proviral sequencing assay, we identified genetically-intact and defective genomes from each subset (954 total genomes; 56 intact). We also identified proviruses with intact p24 open reading frames (ORFs), as p24 protein expression is used to identify replication-competent HIV provirus, and proviruses with an intact nef ORF due to the role of Nef in HIV persistence.
Results: We observed that DN and PD-1+ cells had a higher estimated intact infection frequency compared to CTLA-4+ and DP cells, with evidence for PD-1+>CTLA-4+ (p=0.04), DN >CTLA-4+ (p=0.01) and DN >DP cells (p=0.03). However, the difference in intact infection frequency between DN and PD-1+ cells was variable across different participants (p=0.009). When we investigated the infection frequency of proviruses with an intact p24 ORF, we observed the order of PD-1+>DN >DP >CTLA-4+, with evidence for PD-1+>DN, PD-1+>CTLA-4+ and PD-1+>DP (all p< 0.00001). These differences were also participant-dependent (all p< 0.001). We found that CTLA-4+ and DP cells had the lowest estimated intact nef infection frequency compared to DN and PD-1+, with evidence for PD-1+>CTLA-4+, PD-1+>DP and PD-1+>DN (all p< 0.00001), and DN >CTLA-4+ (p=0.002). These differences all varied across participants (p≤0.02 for all).
Conclusion: PD-1+ cells contain HIV proviruses that are likely to have intact ORFs for genes such as p24 and nef in the PB, which may affect studies of HIV persistence. Conversely, we have found that CTLA-4 expression is a marker for HIV provirus that is more likely to be defective and contain low levels of these intact ORFs. However, all differences were highly variable between participants, and consideration of additional cellular markers will likely be needed to consistently identify cells harbouring potentially replication-competent, HIV.

417 DECIPHERING THE SOURCE OF VIRAL REBOUND IN SIV-INFECTED RHESUS MACAQUES

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Background: An HIV cure is elusive due to the viral persistence in tissue reservoirs. Upon antiretroviral therapy (ART) interruption (ATI), the virus can reemerge from tissue reservoirs and spread through the body. In order to develop better HIV therapies, a deeper understanding of the tissue and cellular origin of early rebound is critical.
Methods: In this study, the barcoded virus SIVmac239M was used to infect 7 Chinese rhesus macaques. The animals were treated with ART for 42 weeks beginning at 12 weeks post-infection, and followed by a 3-week ATI (ATI1). ART resumed for 9-16 weeks, and a second ATI (ATI2) was started one week before each individual necropsy. To evaluate potential sources of viral rebound, and possible cellular factors contributing to viral reactivation, we used deep sequencing, single genome amplification, quantitative real-time PCR, intact proviral DNA assay, immunofluorescence analysis, combined CODEX/RNAscope/*in situ* hybridization (Comb-CODEX-RNAscope) analysis, and single-cell RNA sequencing (scRNA-seq).
Results: All animals rebounded within 20 days after the start of ATI1. In addition, despite PVL levels were < 15 copies/ml during ART and at necropsy after ATI2, a total of 11 viral barcodes were detected across the 4 animals, with mesenteric lymph node (mesLN), inguinal lymph nodes (ingLN), and spleen exhibiting viral barcode clonotype overlap with plasma virus. These tissue sites also had higher viral barcode clonotypic diversity, larger intact proviral reservoir size, and consistent production of vRNA detected by Comb-CODEX-RNAscope. Moreover, scRNA-seq analysis of these sites revealed expression of genes related to immune activation, mitochondria damage, and epigenetic modulation in these 4 animals. While the remaining 3 animals had no measurable plasma rebound viremia at ATI2, similar viral reservoirs were identified in lymphoid tissues comparable to those found in rebounding animals.
Conclusion: Our results suggest that tissues with higher levels of virus, particularly mesLN, ingLN, and spleen, appear to be potential sources of early viral rebound during the first week after ATI, despite PVL levels below 15

copies/ml, with transcriptomic profiles providing hints of potential cellular correlates of viral reactivation. Further validation of these findings may help guide efforts to develop targeted strategies to reduce or eliminate rebound-competent viral reservoirs.

418 AN INTESTINAL TISSUE MODEL FOR TARGETED STRATEGIES DIRECTED TO TISSUE RESERVOIRS

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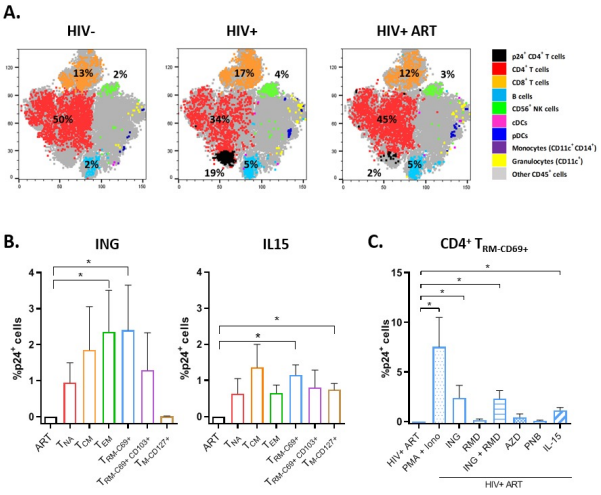
Background: The gastrointestinal (GI) tract constitutes one of the main anatomical sites in which HIV establishes persistence, mainly during acute infection and when ART is initiated. However, sample availability from PLWH limits its study. Here, we have developed an intestinal explant model to study tissue cell reservoirs and assess strategies directed to impact viral persistence.
Methods: Human intestinal tissue resections from uninfected donors were obtained from routine surgeries. To develop the best model, we assayed different times for HIV infection, ART initiation and duration, and LRA treatment, in addition to different doses of IL-2 and IL-7. HIV-reservoir cells were first identified by quantification of intracellular p24 in CD4+ T subsets in the presence of ART, after viral reactivation with PMA+Ionomycin. Furthermore, the effect of different LRAs, including Ingenol (ING), Romidepsin (RMD), Panobinostat, AZD5582, IL-15, and the combination of RMD+ING, was evaluated in Naïve (TNA), Central Memory (TCM), Effector Memory (TEM), Resident Memory (TRM, CD69+ and/or CD103+) and Memory CD127+(TM-CD127+) CD4+ T cells.
Results: The optimal model consisted in 9 days of HIVBAL infection of unstimulated tissue blocks on top of gelatin sponges and the introduction of ART from day 6. HIV caused a significant decline in CD4+ T cells (p=0.03), an increase of NK cells (p=0.06), and an expansion of B cells (p= 0.03) (Figure 1A). ART significantly reduced HIV replication (from 10.5 to 1.9% p=0.03), and partially reverted the changes observed in the immune populations. Addition of LRAs on day 8 revealed the presence of viral reservoir cells in all tested CD4+ T subsets, which differed in their reactivation potential (example in Figure 1B). Viral reactivation was observed in TEM (p= 0.03) and TRM-CD69+ (p=0.03) using ING; in TCM (p=0.03), TEM (p= 0.01) and TRM-CD69+ (p= 0.01) cells with the combination of ING+RMD; and in TRM-CD69+ (p=0.03) and TM-CD127+ (p=0.03) with IL-15 (example in Figure 1C). No significant changes were observed for the remaining LRAs.
Conclusion: Despite the limited lifespan of the tissue culture, the model recapitulates major features of HIV infection, ART treatment, and viral reactivation. Besides identifying LRAs acting in different tissue CD4+ T cells, the model may be useful for testing tissue-specific immune-related approaches. Efforts directed to molecularly characterize both different cell reservoirs and signatures of immune cells are currently ongoing.

Figure 1. Effect of HIV infection, ART treatment and viral reactivation in the intestinal model. (A) t-distributed Stochastic Neighbour Embedding (t-SNE) representations displaying the major cell clusters present in live CD45+ gate, based on FSC and SSC, of a representative human intestinal tissue uninfected, HIV-infected and HIV-infected and ART-treated. HIV-infected cells are displayed in black. Main immune cells are shown. (B) HIV reactivation of CD4+ T subsets in the intestinal tissue model (n=7) using ING and IL15. Means with SEM are represented and statistical comparisons were performed using the Wilcoxon test. *p<0.05. (C) Reactivation of CD4+ TRM-CD69+ viral reservoir cells (n=7) with the different LRAs. Data is normalized to the unstimulated condition (ART). Means with SEM are represented and statistical comparisons were performed using the Wilcoxon test. *p<0.05.



419 MONOCYTE-DERIVED MACROPHAGES CONTAIN LONG-LIVED LATENT HIV RESERVOIRS

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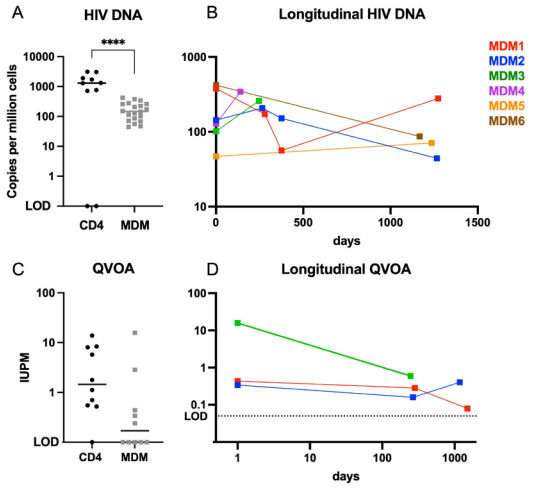
Background: There is substantial evidence that HIV persists in myeloid cells (monocytes/macrophages) in blood and tissues in virologically suppressed people with HIV (vsPWH). However, despite the likelihood that myeloid cells contribute to the size of the HIV reservoir and will likely rebound during treatment interruption, little is known about this reservoir. Specifically, there are limited studies investigating whether HIV within myeloid cells can be reactivated to produce functional virus in vsPWH. Here we report the implementation of a novel human monocyte-derived macrophage quantitative viral outgrowth assay (MDM-QVOA) in a longitudinal cohort of vsPWH.
Methods: The cohort included 10 vsPWH. All subjects were male, had undetectable viral loads, median CD4 levels of 708 cells/µl (range 450-1086), on long-term suppressive ART (range 4-14yr), and had no reported viral blips. The MDM and CD4 replication-competent and DNA reservoirs were assessed via MDM or CD4-QVOA and qPCR for HIV gag. QVOA virus functionality was assessed via sequencing and subsequent infection of a CD4 T cell-line. T cell contamination was assessed by flow cytometry and TCRβ qPCR.
Results: 10/10 subjects had detectable HIV gag DNA in MDM (median[m]=147cp/1e6) at approximately 10-fold lower levels than their CD4 counterparts (m=1514cp/1e6). MDM and CD4 had undetectable levels of HIV RNA (gag and tat/rev), suggesting that the cells were latent at time of sampling. 6/10 subjects were assessed longitudinally (150-1250 days) and had stable levels of HIV gag DNA. 5/10 subjects had detectable IUPM in the MDM-QVOA (m=0.44 infectious units per million [IUPM]) and 9/10 in the CD4-QVOA (m=1.6 IUPM). 3/5 subjects with detectable IUPM in the MDM-QVOA were assessed longitudinally and had latent reservoirs that were consistently reactivated over several years. Additionally, higher HIV DNA levels in MDM stratified with detectable latent reservoirs. The virus produced in MDM-QVOA was infectious and capable of spread in a CD4 T cell-line. Nef sequences from QVOA showed distinct viruses released from MDM compared to subject matched CD4. There was no detectable T cell contamination in the MDM-QVOA or DNA assays.
Conclusion: The proposed definition of a viral reservoir in the context of eradication, is a cell type that allows the persistence of replication-competent HIV on a time scale of years in patients on optimal ART. The data presented here provide evidence that MDMs should be considered an HIV reservoir as they now meet the proposed definition.

Monocyte-derived macrophages from vsPWH have consistent levels of HIV DNA and reactivatable reservoirs overtime.



420 SYSTEMIC INFLAMMATION, GUT DYSBIOSIS AND GUT MICROBIOME IMPACT HIV MIGRATION DYNAMICS

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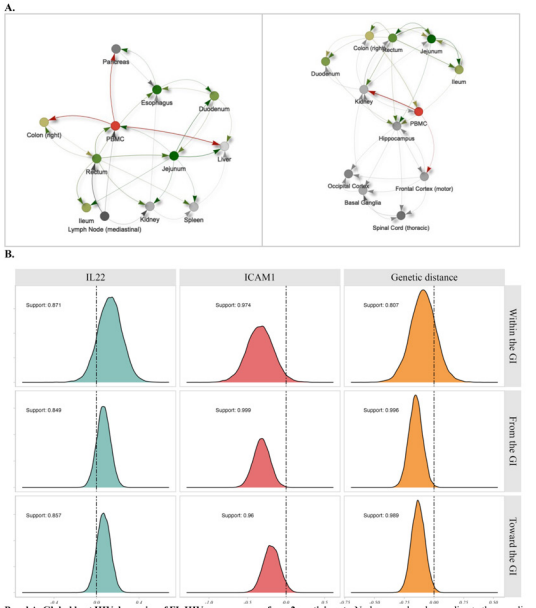
Background: HIV persists in the human body, including the gastrointestinal (GI) tract where the virus causes cellular damage, microbial translocation and inflammation. The GI tract also act as a source of rebounding virus upon cessation of ART. We investigate HIV dynamics within host between tissue reservoirs and evaluate biomarkers, viral reservoir characteristics and microbiome composition associated with viral dynamics in 8 participants of the Last Gift cohort.

Methods: To infer HIV dynamics within each participant, Bayesian discrete trait analyses (DTA) were conducted using HIV DNA single genome full env sequencing data across 33 tissues (10 to 25 per participant) including 7 GI tissues. A panel of 44 cytokines were measured perimortem in blood (ELISA and Luminex assays). Microbiome was characterized in GI tissue (bacterial 16S-rDNA sequencing). Bayesian hierarchical models were used to interrogate the association between viral migration between tissues and (1) HIV reservoir characteristics (size measured by ddPCR, diversity and genetic distance), (2) microbiome composition and (3) soluble biomarkers. The models included predictors of the source and recipient tissues, whether the tissues are within the same biological system, and host- and tissue- level effects.

Results: For inflammatory markers, our DTA showed that viral migration within, from or toward GI tissues (Fig.1A) was consistently associated with higher levels of markers of inflammation and homeostasis (e.g.IL22, RANTES) and lower blood levels of ICAM1, a regulator of cellular responses in inflammation (Fig.1B). For viral characteristics, our DTA showed strong associations between lower genetic distance between viral populations at anatomical sites and increased viral migration between those sites. Among GI tissues, viral diversity in source and recipient tissues was also positively associated with viral migration. Finally, there was a positive association between viral migration and the abundance of Fusobacteria (marker of inflammation) in the source tissue, and Actinobacteria in the recipient tissue. There was also more viral migration from tissues with lower Firmicutes/ Bacteroides ratio, a marker of gut dysbiosis.

Conclusion: This study further supports the impact of HIV reservoir composition on viral dynamics. We showed that systemic inflammation and microbial gut environment also impacted HIV dynamics. Our approach provides a robust way to evaluate host and tissue level markers associated with directional HIV dispersal within host.

A. Global host HIV dynamics of FL HIV env sequences from 2 participants.
B.Posterior distribution of the estimates for three selected biomarkers (predictors) associated with viral movement (outcome) obtained from a Bayesian hierarchical model (BHM).



Panel A. Global host HIV dynamics of FL HIV *env* sequences from 2 participants. Nodes are colored according to the sampling location with gastrointestinal tissues in shades of green, blood samples in red and other tissues in shades of grey. Edges are colored according to the tissue sources. Results from Bayesian discrete diffusion models performed with BEAST. Only migration events with Bayes Factors ≥ 3 are considered. We showed viral migration between GI tissues (green lines between green dots) but also migration from GI tissue toward other systems (green lines toward green or red dots) or from PBMC (red) or other tissues (grey) toward the GI (red and grey lines).

Panel B. Posterior distribution of the estimates for three selected biomarkers (predictors) associated with viral movement (outcome) obtained from a Bayesian hierarchical model (BHM). The model was developed to assess the association between viral movement and host and tissue level predictors. Predictors included 44 cytokines measured in blood plasma close to the time of death, virological measures of gastrointestinal (GI) tissue reservoirs including HIV DNA level (ddPCR), viral diversity and genetic distance between tissue (inferred from single genome sequencing data) and GI microbiome (16S-rDNA-pyrosequencing). Here we show a positive association between IL22 levels and viral movement within the GI, and from/toward the GI (green). There was also a negative association between level of ICAM1 (red) and genetic distance between tissue (orange) and viral movement. The support represents the probability that estimates are greater or less (depending on the assumed association) than 0.

421 T-TRACE ENABLES SINGLE-CELL MULTI-OMICS ANALYSIS OF HIV RESERVOIR CELLS FROM TISSUES

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Background: Single-cell sequencing of HIV-infected cells from people with HIV (PWH) has for the most part been restricted to analyses of viremic individuals and of *ex vivo* stimulated reservoir cells from ART-suppressed individuals and limited to blood.

Methods: We describe T-TRACE as a multiomics approach to simultaneously characterize the transcriptome (scRNAseq), surface proteome (CITE-seq), and clonal expansion (VDJ-seq) of unstimulated HIV reservoir cells, from both blood and tissue cells of ART-suppressed individuals. To enable more efficient identification of transcriptionally active reservoir cells in the context of ART-suppression, bead-based cell purification was used to enrich for reservoir cells prior to single-cell analysis, HIV capture sequences were incorporated during library preparation, and a subtype B consensus was created and used in read alignments. Fresh tissue & blood specimens from the SCOPE and the MACS-WIHS Combined Cohort Study were used.

Results: HIV capture sequences enabled the identification of more HIV+ cells from PWH, enabling for the first time scRNAseq/CITE-seq interrogation of HIV reservoir cells from tissues in the context of ART-suppression. Transcriptionally active reservoir cells from the gut of ART-suppressed PWH exhibited phenotypes distinct from their blood counterparts, including features of T resident memory cells. VDJ sequences of reservoir cells shared between gut and blood were identified. For analysis of the inducible reservoir, a fraction of the cells was stimulated with PMA/ionomycin for 40h, and then analyzed by scRNAseq/ CITE-seq/VDJ analyses, resulting in identification of reactivated reservoir cells expressing high levels of HIV transcripts. Matching of their TCR sequences to those from unstimulated cells from the same specimen identified hundreds of clonally expanded, inducible reservoir cells in their original (pre-stimulated) state. These inducible reservoir cells preferentially expressed low levels of CD62L and high levels of cytolysis-associated transcripts (PRF1, GNLY, GZM).

Conclusion: Implementation of T-TRACE with HIV capture sequences allows efficient in-depth transcriptomic and surface phenotypic analysis of transcriptionally-active reservoir cells, along with inducible clonally-expanded reservoir cells prior to *ex vivo* stimulation. Application of the approach on specimens from ART-suppressed PWH revealed clones of HIV reservoir cells shared between gut and blood which differ markedly in their transcriptomes and surface phenotypes.

422 HIV VIRION PROFILING SUGGEST THAT CXCR3+CD4 T CELLS ARE THE MAIN HIV-PRODUCING CELLS

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Background: The identification of markers of the HIV reservoirs represents a key step towards a HIV cure. In the present study, we postulated that the identification of host molecules incorporated into HIV virions may help to identify their cellular origin.

Methods: We therefore assessed the incorporated protein profiles of plasmatic HIV virions of untreated viremic HIV-infected individuals collected during acute (N=10), chronic (N=10) or AIDS phases (N=10) or at the time of viral rebound post analytical treatment interruption (ATI; N=8). Briefly, HIV virions were captured using anti-gp120/41 coated beads and characterized using mass cytometry panels composed of 57 isotope-labelled mAbs.

Results: We showed that HIV virions collected during AIDS or post ATI harbored distinct incorporated protein profiles as compared to HIV virions from plasma collected during acute or chronic phases ($P< 0.05$). Interestingly, a large proportions (70-85%) of virions collected during acute, chronic or post ATI harbored CXCR3, while other molecules expressed on activated CD4 T cells (ICOS, Lag-3 or CD40L) were less frequently detected (30-40%; $P< 0.05$). We therefore conducted a series of *in vitro* experiments to determine whether the incorporation of the aforementioned molecules may rely on passive and/or active mechanisms. We investigated the potential interactions between the intracellular tails (ic) of CXCR3, ICOS, Lag-3 or CD40L with immobilized recombinant p17 or p24 proteins using biolayer interferometry-based assay. The data demonstrated that p17 protein interacted with the icCXCR3, while no other interaction was detected between icICOS, icLag3 or icCD40L and p17. Notably no interaction was detected between p24 protein and any host molecules tested, demonstrating the specificity of p17/icCXCR3 interactions. To further determine the affinity of p17/icCXCR3 interactions, p17 was immobilized and exposed to various concentrations of icCXCR3 ranging from 0 to 450 nM. The data demonstrated that p17 protein interacted with icCXCR3 protein with a constant of dissociation (KD) value of 0.3 10−6 M (300nM) (±2.05−11).

Conclusion: Taken together, the developed experimental strategy indicate that CXCR3 expressing CD4 T cells may serve as a major HIV cellular compartment for HIV production.

423 GLYCOENGINEERING ENHANCES HIV 10-1074 bNAb-DEPENDENT NATURAL KILLER CELL CYTOTOXICITY

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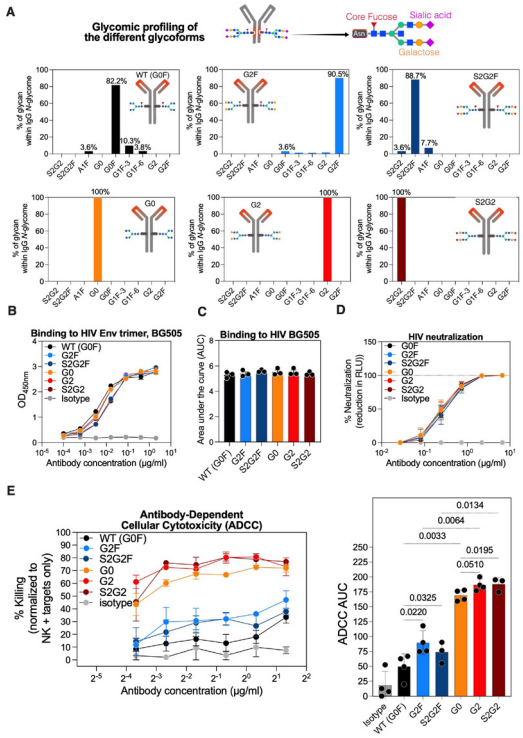
Background: Broadly neutralizing antibodies (bNAbs) are being clinically tested to cure HIV. Such bNAbs are recognized for their potent neutralizing activity. However, beyond neutralization, the constant domains (Fc) of antibodies can elicit several innate immune functions, such as antibody-dependent cellular cytotoxicity by natural killer (NK) cells (ADCC). Antibody Fc glycosylation impacts these functions; however, whether Fc glycans (fucose, galactose, and sialic acid) impact the ADCC of bNAbs currently being tested clinically to cure HIV, such as the V3-glycan targeting antibody 10-1074, is unknown.

Methods: We chemoenzymatically glycoengineered 10-1074 to yield six highly homogenous (>80% purity) antibody glycoforms, as determined by capillary electrophoresis (Fig. 1A). The glycoforms either expressed or not fucose (F), galactose (G), and/or sialic acid (S): wild type (WT) 10-1074 (mainly G0F); G2F; G2S2F; G2; and G2S2. Using these glycoforms, we examined the impact of glycosylation on 10-1074 binding to the HIV envelope glycoprotein (Env) using a clade A gp140 BG505 SOSIP trimer [ELISA] and to the Fcγ3a receptor [ELISA], neutralization of HIVJR-CSF [TZM-bl assay], and ADCC [using primary NK cells from healthy donors and HIVIIIB-infected CEM.NKR CCR5+ Luc+ cells].

Results: Glyco-engineering 10-1074 did not impact its ability to bind to Env or neutralize live virus (Fig. 1B-D). However, non-fucosylated glycoforms exhibited higher levels of ADCC compared to fucosylated glycoforms (Fig. 1E; $P< 0.013$). Galactosylated glycoforms also exhibited higher ADCC than agalactosylated glycoforms within fucosylated and non-fucosylated glycoforms ($P\leq0.05$). Furthermore, the G2 glycoform (non-fucosylated, galactosylated, non-sialylated) exhibited ~4-fold enhancement of ADCC compared to WT 10-1074 (from 17.46% cytotoxicity with WT 10-1074 to 68.02% cytotoxicity with the G2 glycoform; Fig. 1E). As expected, the ADCC activity correlated strongly with antibody binding to Fcγ3a receptor ($P< 0.0001$; not shown).

Conclusion: Removing fucose and adding galactose to 10-1074 can significantly enhance its ADCC activity, which may improve its overall efficiency. Further studies are warranted to examine the impact of bNAbs glycosylation on other innate immune functions, such as antibody-dependent cellular phagocytosis and antibody-dependent complement deposition *ex vivo* and *in vivo*. Together, these findings highlight the importance of optimizing bNAb glycosylation to potentially eliminate or functionally cure HIV.

[1:05 PM] Mohamed Abdel-Mohsen Removing Fucose and Adding Galactose Significantly Enhance the Antibody-dependent Cellular Cytotoxicity of the HIV Broadly Neutralizing Antibody 10-1074



424 SINGLE-CELL QUANTIFICATION OF HIV-1 AND LENTIVIRAL VECTOR IN GENE THERAPY STUDIES

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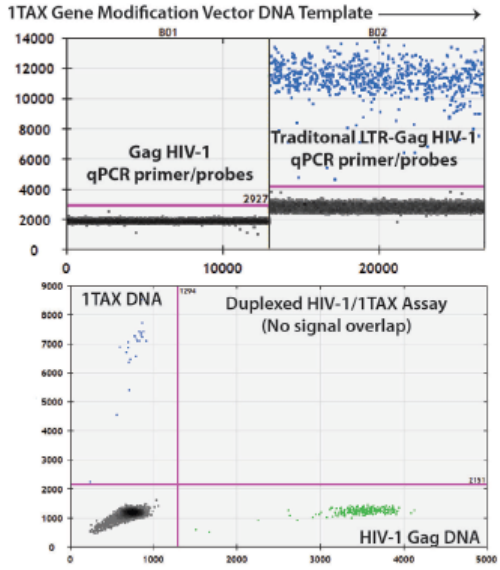
Background: Lentiviral-based vector therapies, which include many CAR-T and gene-modified cell therapies, are at the forefront of HIV-1 cure research. However, sequence homology between these lentiviral vectors and HIV-1 creates challenges with quantifying both cellular HIV burden or lentiviral DNA. As a result, we developed a novel single-cell in droplet (scd)PCR method to co-quantify genomic HIV-1 DNA and lentiviral vector DNA (from CAR-T and gene-modified autologous stem cell transplant) with single-cell resolution. This approach provides a high-throughput platform to determine if gene-modified cells can become infected *in vivo*, a critical unknown question.

Methods: We adapted a multiplexed scdPCR method to co-quantify genomic HIV-1 DNA and the MNDU3 promoter, a common component of lentiviral gene delivery vectors. In addition, we screened over 30 existing HIV-1 DNA quantitative assays to determine the optimal method to quantify HIV DNA in cells from human studies.
Results: First, we show in the figure that commonly used lentiviral vectors directly cross-react with the HIV-1 LTR, LTR-Gag junction/Psi, and Env regions. Second, we observed that the intact proviral DNA assay (IPDA), co-targeting Psi and Env, quantified nearly 100% of lentiviral vector DNA. Third, of over 30 screened HIV-1 qPCR assays, we identified only one, targeting the downstream Gag region, that did not have significant cross-amplification with lentiviral vector DNA. Fourth, we successfully duplexed the HIV-1 and MNDU3 DNA assays for droplet-digital (dd)PCR with minimal cross-amplification (Figure) using both physiological and super-physiological levels of HIV-1 and vector DNA in bulk cell lysates from combinations of 293T cells transfected with: a) HIV-1 plasmid alone, b) 1TAX (lentiviral vector, c) HIV-1 and 1TAX, d) not transfected. Finally, we have successfully applied the duplexed ddPCR assay in our scdPCR platform for use with individually encapsulated transfected 293 T cells. The multiplexed ddPCR assay is now being implemented on participant-derived cells from a multiple gene modification study in autologous SCT (AMC097) and a duoCAR-T cell study in people with HIV.
Conclusion: The multiplexed scdPCR assay can reliably quantify both HIV-1 DNA and lentiviral vector DNA in both bulk cell lysates and in individual, encapsulated cells. This method also allows in-depth characterization of residual HIV-1 burden and the potential for infected, transduced cells *in vivo*/*ex vivo* across a range of gene modification studies.
Example of Cross Reactivity of Traditional LTR-Gag HIV-1 Region (Top) and Duplexing MNDU3 Viral Promoter and HIV-1 Gag Region (Bottom)



425 MULTI-SEROTYPE NANOBODY-ENGINEERED AAV VECTORS FOR CD4 TARGETED GENE THERAPY

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Background: HIV cure approaches involving *in vivo* gene therapy have the potential to target prominent tissue-resident HIV reservoirs. Virus-based vectors are most common in clinical studies, with Adeno-associated Virus (AAV) being the vector of choice. Effectiveness of *in vivo* gene therapy largely correlates with high vector doses, but must be balanced to avert unwanted effects including immune responses and transgene activity in non-target cells. Modulating receptor binding specificities of therapeutic vectors increases on-target effectivity while reducing off-target effects. So far, no robust viral gene therapy vector specific for CD4-positive HIV target cells has been described. We here show that coupling of AAV capsid surfaces with CD4-specific nanobodies mediates retargeting of AAVs to CD4-positive cells. These CD4-AAVs could provide an invaluable vector for anti-HIV therapeutic approaches.
Methods: We used structure-based rational design to genetically fuse CD4-specific nanobodies into AAV capsid proteins VP1 and VP2. We examined optimal nanobody/insertion-site combination for targeted reporter transgene delivery *in vitro* and *in vivo*. We applied our engineering platform to multiple AAV serotypes, proving system versatility. Electron microscopy (EM) and biochemistry analyses were used to investigate particle characteristics.
Results: Functional competition assays with CD4-AAV vectors revealed highly specific transduction of CD4-positive cells *in vitro*. Isolated human primary CD4-positive T cells from multiple donors are effectively transduced compared to wild-type AAV serotypes. CD4-positive cells were transduced with 5-fold higher specificity compared to CD4-negative cells *in vitro*. CD4-specific transduction was also observed in humanized mice after IV delivery. EM and biochemical characterization of CD4-AAV particles revealed overall beneficial features: regular morphology, increased capsid stability, nanobody presentation on the capsid outer shell, exceeding titers and unaffected genome packaging compared to wild-type AAVs.
Conclusion: We provide proof-of-concept for a novel AAV-based vector platform with high specificity towards CD4-positive cells. These nanobody-engineered AAVs further preserve all beneficial AAV vector characteristic. Adaptation to other serotypes and exchange of nanobodies is straightforward. In combination with Crispr/Cas modules or HIV-specific recombinases, we proposed CD4-AAV vectors as valuable tool for safe and efficient anti-HIV *in vivo* gene therapy approaches.

426 AN IMMUNOCYTOCHEMISTRY METHOD TO INVESTIGATE THE TRANSLATIONALLY ACTIVE HIV RESERVOIR

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Background: Despite the success of combination antiretroviral therapies (cART) to suppress HIV replication, HIV persists in a long-lived reservoir that can give rise to viral rebound upon cART cessation. The active reservoir consists of infected cells that continue to transcribe HIV and produce viral protein even in the presence of cART. These transcriptionally and translationally competent HIV-infected cells likely contribute to chronic immune activation in cART-suppressed, HIV-infected individuals and are implicated in rebound viremia upon cART cessation. Methodologies to quantify the active reservoir are needed.
Methods: We developed an automated immunocytochemistry (ICC) assay coupled with computational image analysis to detect and quantify intracellular Gag capsid protein (CA). For this purpose, we cytospinned fixed cells onto microscopy slides and used an automated stainer with antibodies against CA. Stained slides were digitized with a slide scanner, after which nuclear staining was used to enumerate total cells and chromogenic signal to quantify the percentage of CA-positive cells. We used qPCR, digital ELISA and flow cytometry to quantify plasma viral loads (pVL) and CA to validate CA-ICC with established assays.
Results: We determined the sensitivity of the CA-ICC assay using the MoltIIIB cell line spiked into uninfected Jurkat cells in limiting dilutions and assayed the specificity of the staining with peripheral blood mononuclear cells (PMBCs) from HIV-seronegative donors or after *in vitro* infection with an HIV laboratory strain. We then evaluated the application of this assay with mouse and non-human primate animal models to detect HIV-1 p24- or SIV p27-containing cells in PBMCs, respectively. The frequency of intracellular CA positive cells from both animal models' PBMCs corresponded with the pVL and cell-associated CA. We also quantified CA-positive cells in PBMCs obtained from donors living with HIV on cART and found specimens in resting condition with detectable CA-positive cells above the background determined by cells from HIV-seronegative donors. This CA-ICC method allowed us to quantify the activity of small molecule targeted activators of cell kill (TACK) in eliminating CA-expressing cells.
Conclusion: We developed and validated an ICC assay to investigate the active HIV-1 reservoir. Efforts are ongoing to multiplex markers to further characterize the active HIV-1 reservoir and provide a benchmark towards a functional HIV-1 cure.

427 DUAL ANTIRETROVIRAL-LOADED NANOPARTICLES FOR LONG-ACTING SUPPRESSIVE HIV THERAPY

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Background: Viral persistence in secondary lymphoid tissues (SLTs) of patients on cART has been linked to low SLT penetration of antiretrovirals (ARVs). Furthermore, suboptimal adherence to ARVs can lead to drug failure and rapid viral rebound from these SLTs. Therapeutic strategies that sustain ARV concentrations in SLTs are essential. Hence, we designed membrane-wrapped poly-lactic acid nanoparticles expressing the CD169-ligand GM3 (GM3+ NPs) and co-incorporating Rilpivirine (RPV) and Cabotegravir (CAB) to selectively target CD169+ macrophages in SLTs. We hypothesized that GM3+ NP retention within CD169+ CD81+ non-degradative compartments (NPCCs) in macrophages will lead to establishment of myeloid cell-associated ARV-depots for sustained viral suppression in SLTs.

Methods: GM3-NPs were formulated by one-step nanoprecipitation of lipids, poly-lactic acid, RPV and CAB. Intracellular ARV retention in monocyte-derived macrophages (MDMs) was quantified by high performance liquid chromatography (HPLC). Trafficking of NPs in MDMs was determined by quantifying co-localization of NPs with CD81+ NPCCs via confocal microscopy. Antiviral effect of NPs was assessed in CD169+ MDMs pre-treated with ARV loaded GM3(+/-) NPs or NP-free ARVs and infected weekly with luciferase expressing HIV-1 over 35 days. Dissemination of GM3(+/-) NPs *in vivo* was determined by IVIS and immunofluorescence microscopy upon single s.c. injection of fluorescently labelled NPs in BALB/c mice. Long-acting antiviral potency was assessed in HIV-1CH185-infected BLT humanized mice by weekly quantification of plasma viral RNA for 21 days, upon single injection of ARV-GM3(+/-) NPs or daily NP-free ARVs.

Results: Temporal HPLC analysis of MDM lysates revealed that GM3+ NPs maintained high intracellular ARV concentration for 28 days, which correlated with persistent localization of GM3+ NPs in CD81+ NPCCs. GM3+ NPs sustained antiviral effect in MDMs, with robust viral suppression for 35 days post NP addition. Furthermore, GM3+ NPs co-localized with CD169+ cells and were retained in SLTs for 21 days unlike GM3- NPs. Importantly, a single dose of ARV-GM3+ NPs suppressed viremia in HIV-infected BLT mice for 21 days to levels observed with daily NP-free RPV/CAB.

Conclusion: These results suggest that GM3+ NPs are an attractive long-acting delivery platform with the potential to enhance ARV pharmacokinetics and facilitate sustained inhibition of HIV-1 replication by establishing drug depots in CD169+ macrophages in SLTs.

428 REDUCTION IN HIV RESERVOIR MARKERS WITH GAG/POL/IL-12 DNA THERAPEUTIC VACCINATION

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Background: T cell-based therapeutic vaccination is a potential approach to achieving durable control of HIV. We previously reported immunogenicity data from a randomized clinical trial ("PENNVAX", NCT03606213) of Gag+Pol+IL-12 DNA (G/P), Gag+Pol+Env+IL-12 DNA (G/P/E), or placebo (PBO) vaccination in 45 participants with HIV on suppressive antiretroviral therapy, and found that vaccination induced de novo and boosted Gag-specific T-cell responses, with the most robust responses with G/P. We now present virologic outcomes from the trial.

Methods: Participants (median 8.4 years virologically suppressed) were vaccinated Weeks 0, 4, 8, and 12. The HIV-1 reservoir was assessed serially pre- and post-vaccination by LTR-gag HIV-1 DNA (total DNA), cell-associated LTR-gag RNA (caRNA) and intact proviral DNA assay (IPDA) on isolated CD4+ T cells from cryopreserved PBMCs, as well as plasma HIV-1 RNA (vRNA) by automated single-copy assay (SCA). Longitudinal changes from baseline to week 64 (W64) were compared between arms by linear mixed effects models, parametric model accommodating left censoring at limit of detection for change in SCA, and Fisher exact tests. Two participants with known ART interruptions were excluded from analyses.

Results: Across all reservoir measurements, G/P recipients had numerically greater reductions in total HIV-1 DNA, defective genomes, caRNA, and plasma vRNA and increases in the proportion who achieved an undetectable plasma vRNA over time, but no change in intact proviruses by IPDA (Table). The effects were modest and significant compared to placebo only for total DNA and quantitative plasma vRNA.

Conclusion: We found modest but consistent signals of reductions in reservoir markers with G/P vaccination, the arm that induced the greatest Gag-specific T-cell responses by IFNg ELISPOT. Further work to characterize correlates of favorable vaccine-elicited immunologic and virologic responses is ongoing, and may inform future therapeutic vaccine design.

Table. Change in reservoir measures from baseline to week 64 by treatment arm.

Assay	Change from baseline to Week 64			Between-arm p-value*		
	G/P total n=12	G/P/E total n=16	PBO total n=15	G/P vs PBO	G/P/E vs PBO	G/P vs G/P/E
Total HIV DNA, mean (SE) log10 change copies/10^6 CD4	-0.20 (0.10)	-0.07 (0.09)	0.08 (0.09)	**0.04**	0.25	0.33
Intact provirus, mean (SE) log10 change count/10^6 CD4	0.00 (0.10)	-0.11 (0.08)	0.02 (0.08)	0.88	0.23	0.35
Total (3'+5') defective provirus, mean (SE) log10 change count/10^6 CD4	-0.12 (0.06)	0.05 (0.05)	0.02 (0.06)	0.11	0.62	**0.03**
3' defective provirus, mean (SE) log10 change count/10^6 CD4	-0.12 (0.07)	-0.01 (0.06)	-0.02 (0.06)	0.09	0.26	0.22
5' defective provirus, mean (SE) log10 change count/10^6 CD4	-0.04 (0.10	0.17 (0.09)	0.05 (0.10)	0.52	0.34	0.11
caRNA, mean (SE) log10 change copies/10^6 CD4	-0.26 (0.13)	0.02 (0.11)	-0.10 (0.12)	0.34	0.46	0.09
caRNA/total DNA, mean (SE) change	-0.39 (1.11)	0.52 (0.99)	0.85 (0.99)	0.41	0.81	0.54
SCA, mean change (SE) log10 copies/mL	-0.30 (0.10)	0.05 (0.13)	0.17 (0.16)	**0.01**	0.58	**0.03**
SCA, change in proportion of participants with undetectable plasma RNA	+21% (29% baseline vs 50% W64)	-3% (28% baseline vs 25% W64)	+7% (33% baseline vs 40% W64)	N/A	N/A	N/A
SCA, n (%) not detected at Week 64 (of participants detectable at baseline)	5/8 (62.5%)	3/12 (25%)	1/8 (12.5%)	0.12		

G/P = gag/pol/IL-12, G/P/E = gag/pol/env/IL-12, PBO = placebo, SE = standard error, CI = confidence interval, caRNA = cell-associated RNA, SCA = single-copy assay, W64 = Week 64
*Linear mixed effects models with log10 transformation for all cellular reservoir comparisons, parametric model accommodating left censoring at limit of detection for change in SCA, and Fisher exact test for proportion undetectable by SCA. Statistically significant p-values in bold.

429 DOUBLING DOLUTEGRAVIR DOSAGE REDUCES HIV PERSISTENCE MARKERS IN ART-TREATED ADULTS

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Background: Whether ongoing viral replication occurs in people living with HIV (PLWH) despite antiretroviral therapy (ART) and leads to low-level residual viremia is still debated. Here we report on a study, in which we intensified the ART regimen by doubling dolutegravir (DTG) dosage. We investigated the impact of this strategy on HIV blood and tissue latent reservoirs, residual viremia, immune activation, and inflammation.

Methods: Twenty HIV-infected adults, who received a triple therapy consisting of DTG 50mg/ABC/3TC and were fully suppressed for at least 2 years, were enrolled in a phase 3 randomized clinical trial. Half of them received an additional 50 mg of DTG as treatment intensification. Peripheral blood mononuclear cells (PBMCs), plasma and rectal biopsies were collected at different time points over 3 months. We quantified total HIV DNA, intact HIV DNA (IPDA), cell-associated unspliced (US) HIV RNA in PBMCs and in tissue. Single copy assay was performed to determine ultrasensitive plasma viral load. Expression of immune activation (HLA-DR, CD38) and exhaustion (PD-1, TIGIT, LAG-3) markers on CD4+ and CD8+ T cells was evaluated. Inflammation was assessed by measuring the levels of several plasma biomarkers including sCD14, IL-4, IL-6, IP-10, usCRP, IFN gamma, and TNF alpha. Concentration of dolutegravir was measured in plasma and in tissue.

Results: There was no significant difference in total HIV DNA in PBMCs and in tissue between day 0 and day 84 in both groups. However, we observed a significant decrease in US HIV RNA in PBMCs (p=0.020) and in ultrasensitive plasma viral load (p=0.016) between day 0 and day 84 in the intensified group, whereas no such differences were observed in the control group. These results

suggest ongoing viral replication prior to intensification, even though we could not detect differences in immune activation or inflammation between the groups. These results should be confirmed in tissue where it would be even more relevant.

Conclusion: We observed a decrease in US RNA and ultrasensitive plasma viral load following DTG intensification, suggesting ongoing viral replication in some participants. However, it had no measurable impact on chronic inflammation or immune activation. If confirmed in larger clinical trials, these results could have an impact on the clinical management of PLWH.

430 RANDOMIZED CONTROLLED TRIAL OF VRC01 MONOCLONAL ANTIBODY DURING ACUTE HIV INFECTION

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RV398 Study Team
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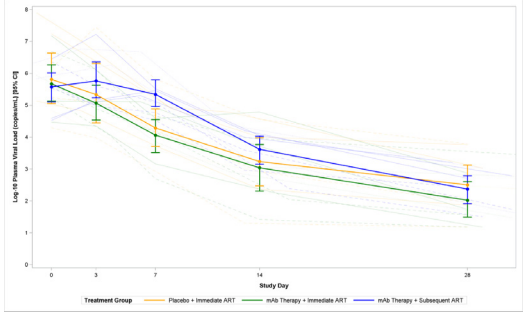
Background: The VRC01 broadly neutralizing monoclonal antibody (mAb), targeting the CD4 binding site of HIV-1, has been shown to decrease viremia and prevent infection with neutralization-sensitive strains. We investigated the impact of a single intravenous VRC01 infusion in acute HIV-1 infection in individuals who received antiretroviral therapy (ART) simultaneously or one week later.

Methods: RV398 (NCT02591420) was a randomized placebo-controlled trial of 24 adults enrolled with acute HIV-1 infection in Thailand, Kenya, Uganda, and Tanzania. Eight participants were randomized to each of the three arms: 1) placebo infusion + immediate ART, 2) VRC01 40mg/kg + immediate ART, or 3) VRC01 40mg/kg + subsequent ART initiated on day 7. Infusions in arms 1 and 2 were blinded; study duration was 24 weeks. Primary objectives were to assess mAb safety and the change in plasma viremia through day 7.

Results: Enrollment completed in September 2020 with 15 (63%) participants in Thailand and 9 (37%) in East Africa. Mean age (SD) was 23.4 (3.6) years; 14 participants (58%) were cis-men, 7 (29%) cis-women, and 3 (13%) transgender women. Twelve (50%) were recruited in Fiebig stages I-II, 6 (25%) in III, and 6 (25%) in IV-V. There was one grade 3 mAb-related transient AST elevation and no mAb-related serious adverse events (AEs). Solicited AEs were mild or moderate. We observed a significantly greater viral load reduction by day 7 in the immediate ART arms compared to the subsequent ART arm in pairwise comparisons (p=0.007 and 0.003, respectively) with the greatest (mean $\log_{10}$; CI) reduction in those receiving mAb + immediate ART (-1.61; -2.10,-1.07) followed by placebo + immediate ART (-1.52; -2.08,-1.04) and mAb + subsequent ART (-0.23; -0.82, 0.43). Median time to virologic suppression and mean area under the viral load curve followed the same arm ordering but were statistically similar across the three arms. Sequencing of HIV-1 genomes at baseline from 23/24 infections reflected the geographic diversity of the participants with env sequences corresponding to CRF01_AE (n=13) and subtypes A1 (6), B (2) and C (2).

Conclusion: Initial results demonstrate the safety of VRC01 with ART in acute HIV infection and the feasibility of studying mAb interventions during AHI across diverse subtypes and geographies. Further studies, including viral isolate mAb sensitivity, are ongoing to identify the determinants of the limited impact of VRC01 on acute HIV-1 viremia.

Figure 1: Plasma Viremia Through Day 28



431 BEAT2 PRIMARY TRIAL OUTCOMES: PEG-IFN-α2b +3BNC117 & 10-1074 IN CHRONIC HIV INFECTION

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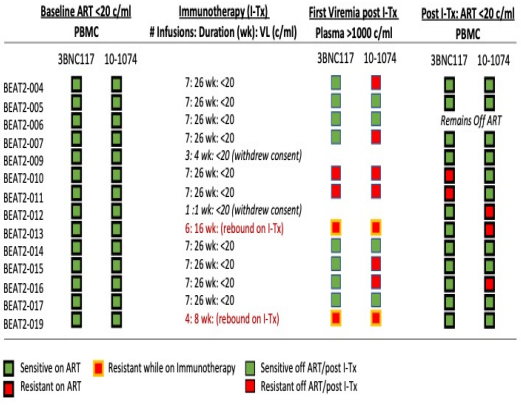
Background: BEAT2 (NCT03588715) is an open-label 50-week study in ART-suppressed PLWH undergoing ART substitution with 26 weeks of immunotherapy (IMM-Tx) [pegylated interferon alfa-2b (peg-IFN-α2b) and broadly neutralizing antibodies (bNABs) 3BNC117 and 10-1074], followed by an IMM-Tx free ATI up to 24 weeks. Primary results at week 38 are presented.

Methods: Participants had baseline HIV bNAb-sensitive virus on PBMC using the PhenoSense mAb Assay (Labcorp-Monogram Bio.) (IC_{90} < 2.0 µg/mL (3BNC117) and < 1.5 µg/mL (10-1074)). Participants received A) 29 weekly doses of peg-IFN-α2b (1.5µg/kg) (Step 2 = 4 wks on ART and Step 3 = 26 wks off ART), and B) seven IV infusions of the bNAbs combination (30 mg/kg of each) at weeks 0, 2, 4 ,8 ,12, 16, 20 of Step 3. Step 4 (ATI: IMM-Tx cessation) was initiated after Step 3; Step 5 (ART re-start) triggered by 6 consecutive weekly measurements HIV VL > 1,000 c/ml. We measured reservoir size (IPDA) during Step 3, and bNAbs PK during Step 3 and 4. The primary end-point was not meeting ART re-treatment criteria in more than 10% (one sided 5% alpha level) at week 38. bNAbs sensitivity was evaluated upon viremia (plasma) and after re-starting ART when the HIV VL was < 50 c/ml (PBMC).

Results: We enrolled 14 participants (12 males, 8 African American) (median CD4 count = 818 c/mm3 (IQR 739-1079); nadir CD4 > 200 c/mm3. Two participants voluntarily discontinued the study due to bNAbs infusion-related chills. IMM-Tx regimen was safe and well tolerated and maintained ART-free HIV suppression (< 20 c/mL) for 26 weeks in 80% (10/12) of participants. Primary endpoint: 4 of 14 participants (28.6%) did not meet ART re-treatment criteria at 12 weeks of IMM-Tx cessation, and 2 (14.3%) maintained < 50c/ml for > 50 weeks. This rate was greater than observed in non-intervention ATI historical controls (p< 0.05). Variants resistant to both bNAbs emerged in two participants (14.3 %) during IMM-Tx (Figure). BNAb escape was detected during viral rebound in step 4 in 6/10 (60%) after IMM-Tx stopped. Resistance to bNAbs was detected after ART re-suppression in 5/13 persons (38.4%). No change from baseline in IPDA was noted at end of IMM-Tx (26 wks of Step 3).

Conclusion: BNAbs and peg-IFN-α2b maintained 80% viral suppression for 26 weeks in the absence of ART, and results in subsequent improved viral control without effects on HIV reservoir. Selection of bNAb escape was observed in 75% of participants during IMM-Tx cessation.



432 LONG-TERM PROTECTION OF CD4+ T CELLS AGAINST HIV BY ONE-YEAR TREATMENT WITH PONATINIB

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Background: Tyrosine kinase inhibitors (TKIs) interfere with the formation and replenishment of HIV reservoir by preserving SAMHD1 antiviral activity in

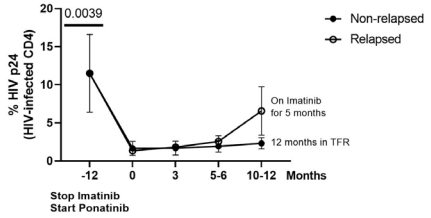
CD4 cells and impeding homeostatic proliferation. We evaluated the persistence of TKI-mediated protective activity against HIV in CD4 from individuals who received one-year treatment with ponatinib against chronic myeloid leukemia (CML).

Methods: Nine participants of Phase II clinical trial NCT04043676 were recruited. They achieved deep molecular response against CML after 14 (IQR 5.5-15.5) years of treatment with imatinib before interruption and then received one-year consolidation treatment with ponatinib 15 mg/day. Blood samples were taken before starting ponatinib (t=-12 months), after one year of treatment (t=0), and 3, 6 and 12 months after interruption. PBMCs were activated with PHA/IL-2 for 48h and then infected with NL4-3_wt for 72h. HIV p24, SAMHD1 phosphorylation at T592 (pSAMHD1), and distribution of CD4 memory subpopulations were analyzed by flow cytometry

Results: 1) 5 participants (55.5%) did not relapse from CML 12 months after ponatinib interruption (Non-relapsed), while 4 participants (44.4%) relapsed after 5,5 months (IQR 4,25-6,75) of ponatinib interruption (Relapsed). 2) CD4 were susceptible to HIV infection in all participants while they were treated with imatinib, but one-year treatment with ponatinib reduced 8.8-fold HIV infection in these cells (Figure). This protection was maintained after 12 months of treatment-free remission (TFR) in Non-relapsed (p=0.0039), in correlation with interference of pSAMHD1. 3) All CD4 memory subpopulations regained susceptibility to HIV infection after CML relapse and imatinib reintroduction. Therefore, p24 production was increased 6.1-(p=0.0159), 8.6-(p=0.0159), and 5.0-fold (p=0.0317) in CD4 naïve, TCM, and TEMRA cells of Relapsed, while CD4 of Non-relapsed were protected against HIV infection 12 months after ponatinib interruption. Increased p24 synthesis correlated with increased pSAMHD1 in CD4; pSAMHD1 levels were not significantly modified in CD8.

Conclusion: One-year treatment with ponatinib preserved SAMHD1 antiviral activity in CD4 by a potent sustained cytostatic effect, impeding HIV infection. The antiviral protection was maintained for 12 months during TFR in correlation with sustained antileukemic response. Transient use of TKIs may be applied to advance towards an HIV cure.

Figure



433 A PLACEBO-CONTROLLED RANDOMIZED TRIAL OF THE HTI IMMUNOGEN VACCINE AND VESATOLIMOD

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The AELIX-003 Study Team

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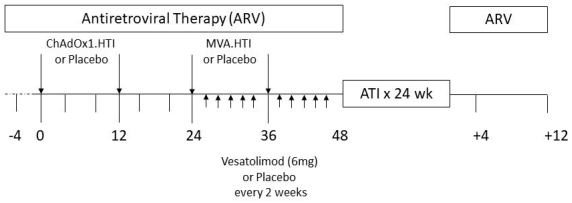
Background: In early-treated people with HIV (PWH), the HIV-specific T cell response induced by a combination of DNA.HTI (D), MVA.HTI (M) and ChAdOx1. HTI (C) vaccines was associated with longer time off antiretroviral therapy (ART) during analytical treatment interruption (ATI) (AELIX-002; Bailón L et al. Nat Med 2022). AELIX-003 (NCT04364035) was a double-blind, randomized (2:1), multi-center trial, to evaluate the safety, immunogenicity and efficacy of CCMM and the TLR7 agonist vesatolimod (VES) in early-treated PWH.

Methods: PWH who started ART within 6 months of infection and had been suppressed on ART for at least one year were randomized 2:1 to receive vaccines and 10 doses of oral vesatolimod 6 mg or placebo while continuing ART (Fig 1). During a 24-week ATI, ART was resumed if plasma viral load >100,000 c/mL, or >10,000 c/mL for 8 weeks, and/or CD4< 350 cells/µL. INFg ELISpot on cryopreserved PBMC, SIMOA, multiplex cytokine and intact proviral HIV DNA assays were used to evaluate immunogenicity, VES pharmacodynamic (PD) biomarkers and changes in viral reservoir, respectively.

Results: 50 participants were enrolled and 47 entered the ATI (CCMM+VES [n=30] or placebo [n=17]). The intervention was well-tolerated with 1 unrelated SAE. Currently available immune data from 31/47 (66%) participants demonstrated strong immunogenicity. The total peak HTI-specific T cell response increased from baseline in the active arm, with median (range) increase of 2474 spot-forming cells (SFC)/10^6 PMBC (635 to 9310) vs. 610 SFC/10^6 PMBC (50 to 3645) in the placebo arm, respectively (p=0.001). Compared to AELIX-002, where HTI vaccines were given alone as DDDMM followed by CCM, peak total HTI-specific responses in AELIX-003 were significantly higher (p=0.027). At time of ATI start, a median (range) of 52% (13% to 100%) of the total anti-HIV-1 T-cell response was HTI-specific in the active arm vs 19% (0% to 100%) in the placebo arm (p=0.01). VES increased the production of antiviral cytokines (IFN-a, IL1RA) and chemokines (ITAC) 24h post-dosing. Decay in total and intact HIV proviral DNA from baseline to ATI was similar between arms. Ten out of 30 (33%) participants in the active arm remained off ART for 24 weeks compared to 24% (4/17) in the placebo arm.

Conclusion: In early-treated PWH, HTI vaccines and VES were safe and induced stronger HTI responses than the more complex AELIX-002 vaccine regimen. Mechanism of action and viral outcome correlate analyses are ongoing.

Figure 1 AELIX-003 study design



434 HIV-1 VIRAL RESERVOIR REACTIVATION AFTER CCR5 DELTA 32/32 STEM CELL TRANSPLANTATION

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Background: To date, four persons living with HIV infection (PLWH) have achieved HIV cure through CCR5Δ32 homozygous allogeneic stem cell transplantation (SCT). Post-SCT events leading to remission in this setting are uncertain, and no detailed analyses of HIV reactivation have been reported. Here we conducted virologic and immunologic analyses of HIV reactivation after CCR5Δ32/Δ32 SCT.

Methods: The HEME-17 protocol evaluates HIV-1 persistence in PLWH pre and post allogeneic SCT utilizing CCR5Δ32/Δ32 donors. Plasma and peripheral blood mononuclear cells (PBMCs) samples were analyzed by single-copy quantification of CCR5/CCR5Δ32 (digital PCR, dPCR) and of HIV gag DNA and RNA (HMMC-gag), and by single-genome sequencing (SGS) of HIV env. Plasma antibodies to HIV Gag, Env, and Nef were quantified by a luciferase immunoprecipitation system.

Results: A 67 yo male PLWH with 100% R5-tropic HIV undergoing ART with HIV RNA < 50 copies/ml for 14 years developed acute myeloid leukemia. The patient underwent a reduced intensity allogeneic SCT with a 10/10 CCR5Δ32/Δ32 matched unrelated donor. By day 30, 100% engraftment was achieved. HIV was not detected in plasma (< 0.3 copies HIV-1 RNA/ml) or in PBMC (< 0.3 copy HIV RNA or DNA/million) at 3, 9, 12, and 15 months post SCT; no WT CCR5 was detected in the PBMC at 1 year by dPCR (Fig 1). Antiretroviral treatment interruption (ATI) was initiated 15 months post-SCT. At ATI, weekly HIV-1 qPCR demonstrated undetectable HIV-1, (< 20 copies/ml), until 8 weeks, when the plasma VL was detected at 780 copies/ml. A repeat VL, one week later, demonstrated a drop in the viral load to 300 copies/ml, when ART was re-initiated. Five (7) plasma HIV env sequences obtained at this time were genetically diverse and all had predicted R5 tropism. At viral rebound, HIV cell-associated DNA/RNA (< 0.14 copies/million) and wt CCR5 (< 20 copies/million)

were not detected. Three months after ART re-initiation, HIV was detected in plasma (0.39 copies/ml) but not in PBMC (< 0.14 c/million PBMC). Levels of anti-HIV antibodies remained lower than those detected in PLWH undergoing ART and were comparable to HIV-uninfected controls.

Conclusion: We report the first known case of HIV reactivation during ATI following CCR5Δ32/Δ32 SCT for AML. Our findings indicate that residual R5-tropic HIV can persist and potentially spread *in vivo* even >1 year after clinically successful CCR5d32/d32 allo-SCT.

Figure 1.

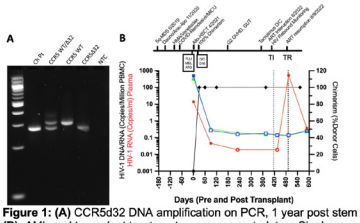

Figure 1: (A) CCR5d32 DNA amplification on PCR, 1 year post stem cell transplant compared to controls. **(B)** AML and transplant treatment course are noted, top. Single copy PCR (scPCR) of cell-associated HIV-1 DNA (■), RNA (▲), and plasma HIV-1 RNA(●) are noted with respect to days pre and post stem cell transplant. Open symbols represent below the limit of detection. Chimerism (♦) described as % donor cells is also noted over time pre and post-transplant.

435 REBOUND DYNAMICS FOLLOWING IMMUNOTHERAPY WITH AN HIV VACCINE, TLR9 AGONIST, AND bNAbs

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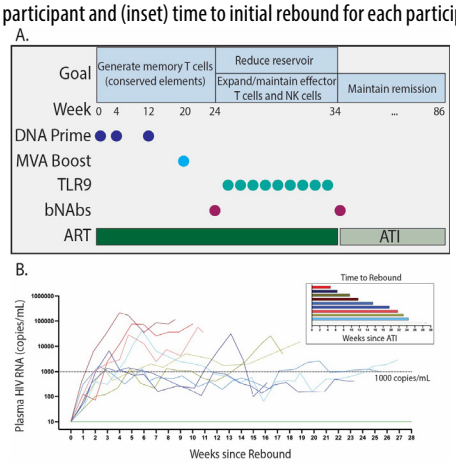
Background: Various anti-HIV immunotherapy strategies have been associated with ART-free control in non-human primates. We sought to determine whether a combination of such strategies could affect virologic control in people with HIV after ART discontinuation.

Methods: We performed a single-arm proof-of-concept study to evaluate the efficacy of a combination approach involving (1) Gag conserved element (CE)-targeted DNA+IL-12 prime/MVA boost vaccination, followed by (2) a combination of two broadly neutralizing antibodies (bNAbs; 10-1074, VRC07-523LS) and a TLR-9 agonist (lefitolimod) and then (3) two bNAbs given at the time of treatment interruption. Seven of the 10 participants (9 cisgender men, 1 transgender woman) had initiated ART within 6 months of HIV infection. We defined the set point as the median of all values off ART beginning 2 weeks after peak rebound. We measured bNAb sensitivity using the PhenoSense assay and T cell responses by intracellular cytokine staining.

Results: Viral rebound occurred on average 15 weeks after ART interruption and median ATI length was 37 weeks. Notably, 7/10 exhibited atypical rebound dynamics characterized by non-exponential growth and/or oscillations; 5/10 had set points < 1000 copies/mL and 7/10 < 5000 copies/mL. One individual has not experienced rebound as of 18 months off ART, with low levels of non-intact provirus in gut tissue and intermittent detection below the quantification limit of HIV DNA and RNA in PBMCs during the ATI. Higher bNAb exposure (AUC) was associated with a later time to rebound (p=0.054 and p=0.052 for VRC07-523LS and 10-1074, respectively), but bnAb levels at rebound were highly variable across participants (1.3-38.3 mcg/mL for 10-1074, 0.2-57.9 mcg/mL for VRC07-523LS). Phenotypic susceptibility to both 10-1074 and VRC07-523LS declined over time. The vaccine regimen increased the magnitude of IFNg+ CE-specific CD4+ and CD8+ T cell responses in all 10 participants between pre-vaccination and 2-weeks post-boost (median CD4: 0.03% vs 0.341% [p=0.002]; CD8: 0.026% vs 0.158% [p=0.002]). Neither antibody levels nor associated susceptibility could completely explain the variability in post-ART set points, suggesting the involvement of other factors.

Conclusion: The majority of individuals who received combination immunotherapy exhibited evidence of virologic control post-ART. Treatment-mediated virologic and immunologic factors may have contributed to this outcome.

A. Study schematic. B. Plasma HIV RNA during ATI timed from initial rebound in each participant and (inset) time to initial rebound for each participant.



436 HIV GAG X CD3 SOLUBLE TCR BISPECIFIC: SAFETY AND ACTIVITY IN A FIRST IN HUMAN TRIAL

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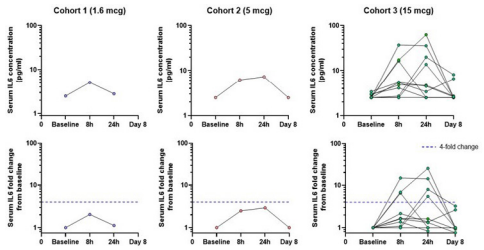
Background: A stable reservoir of replication-competent HIV proviruses that persist in CD4+ T cells is the main barrier to functional cure. Safe and effective strategies for immune clearance of the HIV reservoir are needed. Immune-mobilising monoclonal T cell receptors (TCR) against viruses (ImmTAV®) are unique bispecific soluble proteins comprising an affinity-enhanced TCR fused to an anti-CD3 scFv T cell activating moiety that redirects polyclonal T cells of any specificity to kill virus-infected cells. IMC-M113V is an HIV-specific ImmTAV® (GAGxCD3) that redirects effector T cells to eliminate HIV-infected cells presenting a specific HLA-bound Gag-derived peptide. Induction of systemic cytokines is an expected on-target pharmacodynamic (PD) effect, based on clinical studies with TCR bispecifics with a similar mechanism of action, against cancer and hepatitis B.

Methods: STRIVE (Soluble T cell Receptors In Virus Eradication) is an open-label Phase 1/2 study evaluating IMC-M113V in HLA-A*02:01 positive PLWH receiving suppressive antiretroviral therapy (ART) (EudraCT: 2021-002008-11). PLWH on ART for ≤7 years were enrolled in a single ascending dose study to identify a safe and biologically active dose. Secondary objectives were to characterize pharmacokinetic and PD profiles, including serum cytokines (IL2, IL6, IL8, IL10, IFNγ, TNFα, and IP10) pre- and ≤24 hours post-dosing. A ≥4-fold rise in IL6 was prespecified as indicative of PD activity.

Results: Three dose levels of IMC-M113V, given as a single IV infusion, were evaluated: a starting dose of 1.6 mcg, based on the minimum anticipated biological effect level (n=1), 5 mcg (n=1) and 15 mcg (n=10). Doses were well tolerated and were not associated with cytokine release syndrome or neurotoxicity of any grade. There were no serious adverse events, nor significant changes in hematology or chemistry. One subject reported moderate fatigue of < 24 hours' duration. Plasma viral load remained suppressed throughout dosing and follow-up. Transient, dose-dependent increases in serum IL6 occurred 8-24 hours post-infusion, with 5/10 subjects showing a >4-fold rise after receiving the 15 mcg dose. Further cytokine quantification is ongoing.

Conclusion: A single infusion of IMC-M113V was associated with biological activity consistent with the mechanism of action and was well tolerated at doses ≤15 mcg. This study provides the first human safety and PD impact of this novel agent to inform the design of a multiple ascending dose study.



437 VESATOLIMOD PHARMACODYNAMIC RESPONSE IS ASSOCIATED WITH TIME TO HIV REBOUND

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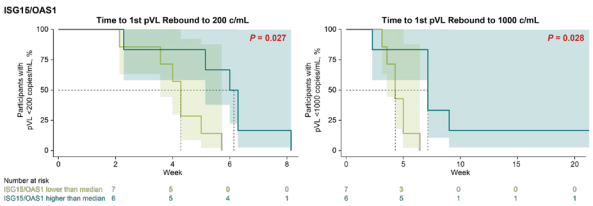
Background: Vesatolimod (VES) is a well-tolerated toll-like receptor 7 agonist that was associated with a modest delay in time-to-HIV-rebound (TTHR) during analytical treatment interruption (ATI) in HIV viremic controllers. This analysis evaluated VES exposure in relation to pharmacodynamic (PD) biomarkers and TTHR, as well as the associations among VES pharmacokinetics (PK)/PD, PD biomarkers and TTHR.

Methods: 25 HIV viremic controllers (pre-ART plasma viral load [pVL] 50-5000 copies/mL) on ART were randomized to receive VES (n=17) or placebo (n=8) biweekly for 20 weeks followed by ATI for up to 48 weeks. Whole blood samples were collected at pre-dose and 24h post first dose to evaluate interferon-stimulated genes (ISGs) with real-time QPCR method. Plasma samples were collected pre-dose* and at 0.5, 1, 2, 4*, 6*, 8, 10*, and 24*h after the first dose to evaluate VES PK and biomarkers*. Plasma protein levels were evaluated with multiplex or SIMOA method. Maximum fold change (FC_{max}) and area under the curve (AUC) of % baseline ($AUEC_{0-24h}$) were used to analyze plasma proteins including PD cytokines VES PK (peak concentration [C_{max}] or AUC_{0-24h}) and plasma protein (FC_{max} or $AUEC_{0-24h}$) correlations were analyzed using Spearman's correlation. The relationships of VES PK and biomarkers (ISGs or plasma proteins) with viral outcomes (1st time of viral rebound to ≥200 c/mL or 1000 c/mL, duration of VL < 400 c/mL during ATI, or change from baseline in intact proviral HIV DNA [IPDA]) were analyzed with Spearman's correlation and Cox proportional-hazards model.

Results: Significant increases in VES PD biomarkers and several plasma proteins were observed after the first VES dose and were significantly correlated with VES PK (adj.p < 0.05), including ISGs (ISG15, OAS1, MX1), IFNa, IL-1RA, IP-10, CCL4, CCL8, MCP-1, CXCL9, and IL-8. Increased ISGs and CCL4 were associated with longer TTHR. Additionally, Factor VII, MMP3, BDNF, IL-2, and MMP9 were also associated with TTHR. There was no significant association between PK and viral outcomes.

Conclusion: These data indicate that VES-mediated biological effects, particularly PD response, were associated with viral outcome in viremic controllers. Larger independent cohorts are needed to validate these findings and investigate the prognostic and functional significance of the biomarkers identified.

Figure 1. Higher Elevation in ISGs at 24h Post First VES Dose Was Associated with Longer Time-to-HIV-rebound



438 DIFFERENTIATION ENHANCES REACTIVATION OF HIV-1 IN CD4+ T CELLS AFTER LONG-TERM ART

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Background: Accurately quantifying the frequency of HIV-1 infected CD4+ T cells in people living with HIV (PLWH) on anti-retroviral therapy (ART) remains a significant barrier to evaluation of cure strategies. Molecular measurements cannot discriminate replication fitness of intact provirus, while the Quantitative Viral Outgrowth Assay (QVOA) has been shown to underestimate the viral reservoir frequency. We previously reported that *ex vivo* differentiation of resting CD4+ T cells to an effector memory phenotype in viral outgrowth assays significantly enhanced HIV-1 latency reversal and demonstrated the replication competent reservoir size was on average 18-fold higher than had been estimated. Here we used the differentiation QVOA (dQVOA) to further refine the relationship between CD4+ T cell differentiation, persistence of the replication competent reservoir and time on ART.

Methods: Resting CD4+ T cells were isolated from cryopreserved PBMCs from 32 ART-suppressed PLWH with short (1.8±0.8 years, n=9), intermediate (4.1±0.9 years, n=9), and long-term ART suppression (12.1±3.1 years, n=14). We assessed the frequency of cell-associated- (ca-) HIV RNA by real-time RT-PCR, ca-total and integrated HIV DNA by real-time PCR, and infectious units per million (IUPM) CD4+ T cells via both QVOA and dQVOA in parallel.

Results: Analysis of the 32 participant samples revealed a relatively stable frequency of cells carrying ca-HIV-1 RNA, ca-total or integrated HIV-1 DNA across the cohort. However, further analysis revealed divergent replication competent reservoir measurements across short, intermediate, and long-term ART suppression. Results from the standard QVOA conditions showed long-term ART suppression was consistent with low IUPM values. In contrast, dQVOA performed on the same pool of resting CD4+ T cells enriched from each participant revealed significantly higher IUPM values from individuals with intermediate (p=0.0056) or long (p< 0.0001) term ART suppression. This data suggests long-term ART may not result in a smaller reservoir size, but instead CD4+ T cells from long-term suppressed PLWH may require additional signaling for effective viral reactivation.

Conclusion: Together, these data provide insight into the biology of the CD4+ T cells that carry the replication competent reservoir and persist in therapy and suggest that more targeted approaches may be required to reactivate latent HIV after long-term viral suppression, providing crucial insights into designing and evaluating HIV curative approaches.

439 A NUCLEOSOMAL MODIFICATION COMPLEX FOR SILENCING HIV

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Background: Post-integration HIV latency is the major hurdle for a cure. To counter HIV latency, it is important to develop a better understanding of the full range of host factors promoting latency. Their identification could suggest new strategies to achieve a functional cure. We recently developed a genetic screening strategy termed "Reiterative Enrichment and Authentication of CRISPRi Targets" (REACT) and unambiguously identified several Silencing Promoting Agents (SPAs) even in the presence of high background "noise" produced by the stochastic nature of HIV reactivation.

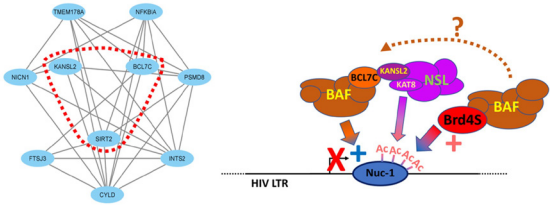
Methods: In the current study, we modified the REACT method to look for synergies between Silencing Promoting Agents (SPAs) across the human genome. As a proof-of-concept, we used 7 SPAs to conduct 7 parallel screen to look across the human genome for factors that synergize with them to block HIV reactivation.

Results: We identified thirty synergies among ten SPAs. Three of them (BCL7C, KANSL2, SIRT2) are previously unrecognized. Overexpression (OE) of BCL7C, KANSL2 and SIRT2 reduced spontaneous and PMA-induced HIV reactivation in J-Lat A2 cells, a Jurkat-based HIV latency model, as well as in CD4 T cells from people living with HIV. These factors inhibit HIV reactivation through different mechanisms: we found OE of BCL7C and KANSL2 increased histone acetylation on the HIV promoter (LTR) region on chromatin, and this in turn resulted in more Brd4S (an inhibitor for HIV transcription) binding to the HIV LTR. In contrast, OE of SIRT2 decreased histone acetylation on HIV LTR. BCL7C is part of the SWI/SNF nucleosomal remodeling complex, while KANSL2 is a regulatory subunit of the KAT8 (MOF) histone acetylation complex. Interestingly, our data demonstrate that BCL7C and KANSL2 are interacting with each other together with a set of proteins from the BAF and NSL subclasses of SWI/SNF and MOF respectively.

Conclusion: Our data indicate that a BAF-NSL super complex in the latently infected cells may hyper-acetylate the HIV promoter to recruit excessive Brd4S to inhibit HIV reactivation. Identification and mechanistic characterization of

this nucleosomal modification complex indicate that increasing the loading and function of this complex on HIV LTR might enhance HIV silencing.

A BAF-NSL super complex inhibiting HIV by Brd4S-BAF pathway identified through systematic mapping of genetic interaction networks for HIV latency



440 CCNT1 IS A NONESSENTIAL GENE IN JURKAT T CELLS REQUIRED FOR HIV RELEASE FROM LATENCY

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Background: A major barrier to HIV cure is the existence of the latent pool of virus that perdures in memory T cells which reactivates upon stopping antiretroviral treatment. We are examining pathways that would prevent reactivation of HIV from latently infected cells with a goal of permanently silencing the latent reservoir. Our hypothesis is that some of the host genes necessary for HIV replication could be non-essential for cell growth but may be key targets for preventing latency reactivation.

Methods: A CRISPR screening method previously developed in the lab called Latency HIV-CRISPR uses packaging of CRISPR guides into budding virions as a readout. We used a library of sgRNAs known as the dependency factor targeting 500 genes involved in HIV replication. Two latently infected Jurkat T Cell lines (Jlats) with integrated provirus were used in this study. Jlat cells were transduced with a lentiviral vector containing Cas9 and a library of guide RNAs targeting HIV dependency factors. Jlat cells were treated with latency reversal agents (LRAs) to stimulate transcription, and viral supernatant and gDNA were deep sequenced to look for guides that were depleted in the supernatant relative to gDNA. The most depleted genes in both cell lines were tested to validate whether they led to a decrease in proviral reactivation on treatment with LRAs.

Results: We find 47 genes from the HIV-DEP library that are depleted relative to gDNA knockout in both Jlat cell lines. The top hit was Cyclin T1 (CCNT1) – a gene known to be critical for HIV transcription. We knocked out CCNT1 with CRISPR and find that it is not essential for host cell growth. However, CCNT1 is essential for HIV transcription and release from latency using several different activators of proviral transcription – including CD3/CD28 and TNFα.

Conclusion: Several HIV dependency factors also play a role in promoting transcription in latently infected cells; thus HIV dependency factors can provide insight into genes that can be targeted to permanently silence the latent reservoir. We find that CCNT1 – a gene that plays both a key role in host and HIV proviral transcription, can be knocked out without dramatic effect on lethality on Jurkat T cells, but dramatic effects on release of HIV from latency. We hypothesize this may be due to the presence of a paralog of CCNT1 – CCNT2, which is involved in host transcription but not required for proviral transcription.

441 ncRNA PROFILE IN EXTRACELLULAR VESICLES REVEALS A POTENCIAL MECHANISM OF HIV-CONTROL

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Background: Recent findings have pointed out extracellular vesicles(EVs) as therapeutic tools against HIV infection given their capacity to transfer HIV restriction factors, including mRNAs and non-coding RNAs(ncRNAs), to nearby cells. However, HIV can also package its own material into EVs to enhance infection and pathogenesis. Herein, we analyzed coding and non coding HIV RNAs and human ncRNAs content carried by EVs from plasma of patients with different degrees of HIV virologic control

Methods: Three groups of HIV patients were included according to plasma viral load(pVL): 10 elite controllers(EC); 10 cART-treated patients(TT) and 10 cART-naive with detectable pVL(NT). Ten uninfected controls (UC) were included as reference. EVs, isolated from plasma by Size Exclusion Chromatography, were quantified and visualized by Nano Tracking Analysis and microscopy-TEM. Viral RNAs and human ncRNAs were evaluated by RNAseq in a Miseq System. Identification of RNAs sequences was carried out by mapping them to HXB2 sequence and to human ncRNA database. A differential enrichment analysis of the identified human ncRNAs was conducted with EdgeR, and then, target genes for the differently expressed ncRNAs were predicted with miRDB database

Results: Compared to EC and TT, Vif(p=0.03), Vpr(p=0.03), Pol(p=0.00) and Gag(p=0.01) mRNAs, and 3LTR-RNA(p=0.03) were more frequently carried in EVs of NT. A total of 109 human ncRNAs were differently expressed between UC and NT, mostly (89%) upregulated in NT. Also compared to UC, only 14 ncRNAs in EC and 9 ncRNAs in TT were differently expressed, mostly (80% in both cases) upregulated in patients.The comparison between EC and TT showed 28 ncRNAs differentially expressed:19 ncRNAs upregulated in EC and 9 ncRNAs upregulated in TT. Target prediction showed that ncRNAs upregulated in TT could inhibit expression of HIV restriction factors, whereas ncRNAs upregulated in EC could inhibit expression of cellular targets related to promotion of HIV infection and replication

Conclusion: Our results show that HIV replication induces the packing of different HIV RNAs in EVs and promotes deregulation in the human ncRNAs profile packed in the EVs, which could modify the expression of genes in recipient cells. Moreover, ncRNAs profile differs depending on the viral control (by cART or spontaneous). Of note, EC showed increased levels of ncRNAs that could inhibit HIV replication and enhance immune response against the virus, revealing the importance of EVs as a new mechanism of anti-HIV action

442 c-Myc AND NR4A REGULATE STOCHASTIC REACTIVATION OF LATENT HIV-1

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Background: The "shock and kill" approach to eliminate HIV-1 latent reservoirs uses Latency Reversing Agents (LRA) to activate the provirus. At present reactivation in 100% of the latent cells is not possible and one reason is the stochasticity or 'noise' in pro-viral transcriptional activation. Current strategies do not address stochasticity in reactivation during LRA treatment.

Methods: To test stochasticity in latent HIV-1 proviral reactivation, we adopted single molecule RNA fluorescence *in situ* hybridization (smRNA-FISH) combined with quantitation of single RNA molecules within cells using FISH-Quant. To facilitate the identification of rare, reactivated cells, we utilized a High Speed and High-Resolution-Scanning (HSHRS). To determine the "extrinsic factors" responsible for stochastic activation, we carried out a single-cell RNA-seq (scRNA-seq) analysis, using the 10x genomics. The findings were validated using qRT-PCR.

Results: Kinetic analysis using smRNA-FISH and FISH-Quant indicated that HIV-1 reactivation in latent T-cells is rapid (15-30 min) and that transcription proceeded in waves. There was a high degree of stochasticity and cell-to-cell variability in reactivation and the number of transcripts/cells varied from 0-1,000, at any given time. HSHRS analysis of a large pool of uninduced latent cells (>100,000 cells) indicated that ~1-10% of cells are active even in the absence of an inducer.

To determine factors responsible for stochastic reactivation, we used scRNA-seq analysis and identified differentially regulated cellular genes (DEGs) present selectively in reactivated cells within the pool of un-induced cells. The DEGs were validated using qRT-PCR. We found that c-MYC and NR4A (Orphan nuclear receptor 4A) are extrinsic factors that modulate reactivation in latent cell lines and in patient-derived latent cells. SN-38, an active metabolite of the topoisomerase-I inhibitor irinotecan (an FDA-approved drug) inhibits cMYC via activation of the NR4A pathway. We found that SN-38 reactivated the HIV-1 latent provirus in cell lines and patient samples, suggesting the significance of cMYC in regulating proviral reactivation.

Conclusion: We have identified NR4A and c-MYC as key extrinsic factors associated with stochastic HIV-1 reactivation. We demonstrated that SN-38 that inhibits cMYC via. NR4A can reactivate latent HIV-1 provirus in cell lines and in patient samples. SN-38 is a novel LRA that could potentially reduce stochasticity.

443 HIV TEM-SEQ: TARGETED ENZYMATIC METHYLATION SEQUENCING OF HIV-1 PROVIRUSES

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Background: DNA methylation is an epigenetic modification that mediates retroviral epigenetic silencing. However, the role of DNA methylation in HIV-1 proviruses remains controversial. Challenges in assessing DNA methylation in HIV proviruses have included large input DNA requirements due to harsh bisulfite conversion methods, low sampling of proviruses and viral regions due to bisulfite PCR sequencing, and problems of designing and optimizing bisulfite PCR primers accounting for HIV sequence diversity. Here, we address these challenges and develop a novel targeted enzymatic methylation sequencing approach termed HIV TEM-Seq to overcome limitations of prior assays in assessing HIV provirus methylation.
Methods: HIV TEM-Seq combines enzymatic methylation sequencing (EM-Seq) and target enrichment of full-length autologous proviral sequences. EM-Seq uses TET2 and T4-BGT to convert 5mc and 5hmc into products protected from deamination from APOBEC3A. Unmodified cytosines are converted to uracil enabling discrimination and quantification of DNA methylation at single nucleotide resolution. Autologous HIV sequences are utilized for custom capture probe design enriching for unmethylated and methylated proviral sequences spanning the entire provirus. Next generation DNA sequencing provides >30X coverage of all proviral methylation sites.
Results: HIV TEM-Seq captured DNA methylation states across the full-length of HIV proviruses in replication competent ACH-2 and U1 cell lines and confirmed increased CpG methylation at the LTR region of single copy integrated provirus in J-Lat 8.4 and 5A8 latent cell lines. Activation of J-Lat cells with anti-CD3/CD28 and PMA/ionomycin significantly decreased CpG methylation at the LTR region. In proviral DNA from blood and CD4 T cells of people living with HIV, we observed increased non-CpG methylation compared to CpG methylation in HIV proviruses. Confirming prior reports, HIV TEM-Seq did not detect CpG nor non-CpG methylation at LTR regions of *in vivo* proviruses, suggesting the lack of DNA methylation in the LTR likely promotes the presence of a high transcriptionally active reservoir and permissive latency.
Conclusion: HIV TEM-Seq will have future utility in assaying block-and-lock strategies that aim to deposit DNA methylation using epigenetic editing approaches and evaluating whether DNA methylation increases in proviruses of older people living with HIV on long term ART for decades.

444 EX-VIVO IMPACT OF LRAS AND SPECIFIC LIGANDS ON ESTROGEN RECEPTOR IN CD4+ T CELLS

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Background: Variations in estrogen concentration have been hypothesized to explain sex differences observed in HIV infection, clinical progression and reservoir size. Estrogen receptor alpha (ERα) is reported to directly influence HIV-latency and transcription. However, in contrast to the important role of ERα in breast cancer, the regulation of ERα in immune cells is less clear. Furthermore, in strategies to attack persistent HIV infection, the influence of latency reversal agents (LRAs) on ERα is unknown.
Methods: To obtain a better understanding of ERα regulation in CD4+ T cells, we evaluated nuclear localization of ERα and ERα protein degradation by Fulvestrant, a selective estrogen receptor degrader (SERD), or by ARV-471, a novel, potent, first-in-human PROteolysis TArgeting Chimera (PROTAC), specific ERα-protein degrader. We next assessed the impact of different LRA classes (HDAC and BET inhibitors, PKC and STING agonist, SMAC mimetic) on ERα at both mRNA and protein levels by WB and qPCR. The breast cancer cell line T-47D was used as control and all experiments were performed in hormone-free media.
Results: In contrast to T-47D breast cancer cells, in CD4+ T cells ERα is not primarily localized in the nucleus and β-estradiol (ER agonist) does not induce ERα nuclear translocation. Similarly, both Fulvestrant and ARV-471 do not induce degradation of ERα in CD4+ T cells. In both PBMC and CD4+ T cells, we observed a significant downregulation of ERα gene expression following 6-hour and/or 24-hour of treatment with all tested LRAs with downregulation with PMAi, PEP005 and romidepsin being the most pronounced (0.04- and 0.02-, 0.21-fold change; $P < 0.01$). ERα mRNA downregulation resulted in temporal decrease of ERα protein. Protein levels dropped significantly after 6-hour treatment with PMAi and after 24-hour treatment with PMAi, PEP005 and romidepsin (0.57-, 0.37-, 0.57- and 0.77-fold change; $P < 0.01$).
Conclusion: Our results suggest that ERα regulation in immune cells is different than what is previously demonstrated in breast cancer. We show for the first time that in CD4+ T cells canonical nuclear translocation of ERα does not occur after exposure to estrogen and that SERD and ERα PROTAC are ineffective at ERα degradation. However, the impact of LRAs on ERα protein levels does not exclude a role of ERα in HIV latency. Collectively, these results suggest that estrogen impact on HIV transcription is unlikely due to canonical ERα nuclear mechanisms of action and merits further investigations.

445 ENHANCED HIV-INDUCED LINEAGE TRACING REPORTER SYSTEM REVEALS EARLY LATENCY PHENOTYPE

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Background: Current Human Immunodeficiency Virus (HIV) treatments effectively suppress viral replication but fail to cure patients of infection due to the persistence of latently infected cells. Latently infected cells are nearly indistinguishable from uninfected cells and evade clearance by the host immune system. Current primary cell models of latency utilize *in vitro* infection often employ reporter genes that are carried by a replication incompetent HIV. A limitation of these models is that they are susceptible to integration site-specific silencing mechanisms and do not allow tracking of selective pressures of the reservoir driven by pathogenic or immunologic selective pressures.
Methods: We have designed an infectious model system that independently reports on a cell's HIV infection status and viral gene expression and used this model to study the kinetics of infection and early latency establishment. The system employs a cre-lox activated genetic switch, along with replication-competent HIV clone, HIV-miRFP670nano Cre (HIV-RC) that co-express cre-recombinase and miRFP670nano (nano) reporter gene for viral gene expression. This system, described as Enhanced HIV-Induced Lineage Tracing (EHILT), identifies cells with a "history" of HIV infection through an irreversible genetic marking system of HIV-infected cells. HIV infections were performed in T cell lines, primary CD4 T cells from healthy donors, and PBMC engrafted mice (HuPbl mice) with a replication competent HIV designed to express cre and nano as a reporter for viral gene transcription. The system efficiently distinguishes latently infected cells from infected cells with active viral transcription.
Results: Infected T cell lines and primary CD4+ T cells with a latent phenotype are established as early as 2 dpi, and with ongoing replication, latent cells accumulate over time. qRT-PCR and DNA qPCR confirmed low levels of viral mRNA expression in latent cells compared to actively infected cells and the presence viral DNA. Higher proviral copy numbers were observed in productively infected cells, while lower copy numbers were observed in surviving latent cells. HIV DNA or RNA was not detected in the unswitched uninfected cells. HuPbl mice infected with HIV-RC showed detectable levels of plasma viremia.
Conclusion: This model system enables single cell resolution transcriptomic and epigenomic analysis of productive infection verses latent infection in both *in vitro* and *in vivo* settings to probe the forces that shape the latent reservoir.

446 TARGETING 2 NEUTRAL SPHINGOMYELINASE 2 PROMOTES DEATH OF HIV-INFECTED CELLS

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Background: Eradication of HIV infected cells is a major goal of cure efforts. Antiretroviral (ARV) drugs suppress HIV, but viral replication rebounds when therapy is discontinued. Efforts to reverse latency are likewise limited by an effective means to kill cells with replicating HIV.
Methods: We identified the sphingomyelin hydrolase neutral sphingomyelinase 2 (nSMase2) as a critical component of the late stages of HIV assembly/maturation. We developed phenyl(R)-(1-(3-(3,4-dimethoxyphenyl)-2,6-dimethylimidazo[1,2-b] pyridazin-8-yl)pyrrolidin-3-yl) carbamate (PDDC), a small molecule inhibitor of nSMase2 that is potent (IC_{50}=300nM), selective, with favorable oral pharmacokinetics and safety

profile. PDDC was tested in two independent humanized mouse models and mechanisms of action explored in cell culture.
Results: The rate of reduction in plasma HIV loads in mice administered PDDC was similar to that achieved with ARVs. With untreated HIV infection the number of CD14+ and CD4+ cells declined as a function of time. ARVs preserved CD14+ and CD4+ cell counts, while PDDC further reduced CD14+ and CD4+ cell counts. CD45+, CD3+, and CD19+ cell counts were unaffected by PDDC. Following drug withdrawal mice administered ARVs exhibited viral rebound, while mice treated with PDDC that achieved plasma HIV below detectable limits (100 copies/mL) did not rebound. An inactive structural analog of PDDC (Cmpd5) had no effect on viral loads or immune cell counts. Results were similar in both models of mice tested.
HIV infection of cells increased nSMase2 expression and its metabolic product ceramide. PDDC or knock down of nSMase2 resulted in oddly shaped, immature, non-infectious HIV particles, enlarged/stressed lysosomes, caspase activation and cell death. The highest dose of PDDC did not reduce the survival of non-infected cells.
Conclusion: PDDC is a structurally novel inhibitor of nSMase2 that interferes with the late stages of HIV assembly/maturation. PDDC appears to selectively kill actively replicating HIV infected cells (sparing uninfected cells) resulting in no viral rebound if plasma HIV is reduced to below detectable limits.

447 DPP9 INHIBITION ENHANCES NNRTI-MEDIATED CLEARANCE OF HIV-1 LATENT RESERVOIRS

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Background: The inflammasome sensor CARD8 can sense intracellular HIV-1 protease activity which leads to targeted cell killing of HIV-1 infected cells which can be achieved using NNRTIs. Additionally, we recently reported that inhibition of DPP9, the negative regulator of CARD8, was able to enhance NNRTI mediated clearance of HIV-1 infected CD4+ T cells *in vitro* and in humanized mice. However, it's potential use on clinically relevant HIV-1 strains and its ability to clear latent HIV reservoirs had yet to be investigated. Here we discuss the clinical translatability of this approach for an HIV cure.
Methods: CD4+ T cells were isolated from PBMC of healthy donors, infected with a panel of clinical HIV-1 isolates and treated with NNRTIs with or without VbP/1g244 in the presence of T-20 and Raltegravir. Killing was assessed by intracellular HIV-1 p24 staining. To measure removal of HIV latent reservoirs, CD4+ T cells were isolated from people living with HIV (PLWH) under suppressive antiretroviral therapy. These cells were plated in limiting dilution for a quantitative viral outgrowth assay. Cells were treated with either NVP, EFV, or EFV with VbP in the presence of T-20 and Raltegravir. Reductions in the infectious units per million (IUPM) were calculated using the frequency of HIV p24 positive wells via ELISA.
Results: We first tested the ability of DPP9 inhibitors VbP and 1g244 to clear replication competent HIV-1 strains from a panel of clinical isolates. We show that both drugs can enhance NNRTI-mediated clearance of infected cells. We also note that 1g244 had lower levels of toxicity and greater activity at nanomolar concentrations than VbP. We also show that VbP was able to enhance clearance of HIV reservoirs as indicated by reductions in the IUPM of samples from PLWH. The median IUPM were 7.55 (NVP), 3.747 (EFV), and 1.886 (combination) indicating a rapid clearance of 50.4% and 75.0% of latent HIV reservoirs from EFV and combination respectively.
Conclusion: Our previous work on DPP9 inhibition which sensitizes the CARD8 inflammasome laid the foundation for an alternative strategy for eliminating HIV-1 reservoirs. This work expands upon this and shows that this strategy can enhance NNRTI clearance of clinical isolates and reduce viral reservoirs *ex vivo*. This proves the broad suitability of this method for the existing genetic variation seen in PLWH. We also note that other DPP9 inhibitors may be more potent with less off-target effects calling for the development of new DPP9 inhibitors.

448 INTERLEUKIN-2-INDUCIBLE T-CELL KINASE (ITK) INHIBITION PREVENTS HIV LATENCY REVERSAL

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Background: Inducible T-cell kinase (Itk) belongs to the Tec family of tyrosine kinases, and is expressed in mast cells and T lymphocytes. Itk functions downstream of the T-cell receptor (TCR) and regulates T-cell development, activation and differentiation. The role of ITK signaling in HIV persistence is as yet unknown. Here, we determined the impact of ITK on HIV latency and infected cell proliferation in primary CD4+ T cells and cell lines.
Methods: CPI-818, a small molecule inhibitor of ITK was used assess the impact of ITK inhibition on TCR signaling by measuring pERK (phosphorylated extracellular signal-regulated kinase) expression by flow cytometry in primary CD4+ T cells, Jurkat and J-Lat 5A8 cells (Jurkat cells latently infected with a GFP reporter virus). To determine impact on latency reversal, J-Lat cells were pretreated with 100 nM, 1 uM, or 10 uM of CPI-818 followed by CD3/CD28 stimulation, and percent GFP positive cells was assayed by flow cytometry. CD4+ T cells from PLWH (people living with HIV) were also used to assess effects on latency reversal. HIV transcripts were quantified using RT-qPCR of Tat/Rev trasncripts. The effect of CPI-818 on proliferation of HIV infected CD4+ T cells was assessed in an *in vitro* infection model by using eFluor670 dye to track cell division. The effect of ITK inhibition on establishment of latency in primary CD4+ T cells was studied in an *ex vivo* infection model using a dual reporter virus enabling isolation and enumeration of latently- and productively-infected cells.
Results: CPI-818 treatment resulted in a significant decrease in the mean fluorescence intensity of pERK in primary CD4+ T ($p=0.006$, t test) and Jurkat ($p=0.002$) cells. CPI-818 exhibited dose-dependent inhibition of CD3/CD28-mediated latency reversal in J-Lat cells ($p< 0.0001$). CPI-818 treatment resulted in a significant decrease in latency reversal in primary CD4+ T cells from PLWH ($p< 0.0001$). CPI-818 inhibited proliferation of HIV-infected cells more than uninfected cells ($p=0.052$). CPI-818 enhanced the initial establishment of latency in primary CD4+ T cells as compared to no-drug control ($p=0.0248$).
Conclusion: ITK inhibition blocks the reversal of latency upon CD3/CD28 stimulation by inhibiting the TCR signaling pathway. ITK inhibition also promotes the initial establishment of latency in primary CD4+ T cells and disproportionately suppresses the proliferation of HIV-infected cells. ITK inhibitors should be explored within antiproliferative and "block-and-lock" HIV cure strategies.

449 IN-DEPTH ASSESSMENT OF THE HIV-1 VIRAL RESERVOIR IN EARLY TREATED INDIVIDUALS

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Background: The integration site and intactness of proviral genomes remain poorly characterized in early treated individuals on antiretroviral therapy (ART). Moreover, the inducibility of the viral reservoir in these individuals is hampered by the lack of latency reversing agents (LRA) capable of inducing potent HIV reactivation. Here, we did an in-depth assessment of the total and inducible viral reservoir in early treated individuals.
Methods: We collected leukaphereses from 8 individuals treated during acute infection (Fiebig II-III: n=6; Fiebig IV: n=1; Fiebig V: n=1) who received ART for a median of 0.96 years (0.49-1.93 years). Total HIV DNA and intact HIV proviral DNA (IPDA) were assessed by multiplex digital PCR. Near full-length (NFL) proviral sequences and integration sites were obtained by matched integration site and proviral sequencing (MIP-Seq). Following a 24h-stimulation with a Tat mimetic (Tat#1) and PMA, the frequency of p24-expressing cells and their phenotype were assessed by HIV-Flow.
Results: In total, 252 integration sites and 64 proviral genomes were obtained. Clonally expanded cells were retrieved in only 4 out of 8 participants and accounted for 5% of total integration sites. NFL genome analyses revealed that 9% of the proviruses were intact (91% defects: 2% inversions, 53% large internal deletions, 17% hypermutations, 9% PSI/MSD defects, 9% premature stopcodon/frameshift). The analysis of a 4.5 kb region at the 3' end of the provirus (HXB2 positions 5089-9602, n=59) revealed that the intra-individual genetic diversity is limited (average genetic distance=1.9 bp). Following PMA/Tat#1 stimulation, the frequency of p24+ cells ranged between 0.4-20 per million CD4 T cells. p24-expressing cells were enriched in effector memory T cells ($p=0.06$). Interestingly, a significantly higher fraction of p24+ cells displayed a naïve phenotype in early treated individuals compared to chronically treated individuals ($p=0.03$).

Conclusion: Collectively, these data indicate that the contribution of clonal expansion to the persistence of the viral reservoir in early treated individuals is minimal after 1 year of treatment. We report a combination of LRAs that allows for the successful detection of the inducible reservoir in early treated individuals on ART. Single-cell assessment of the viral composition of the inducible reservoir should provide further insights into the persistence of those cells during ART.

450 HIV-1 RESERVOIRS IN YOUNG ADULTS AFTER LONG-TERM ART FOR CONGENITAL INFECTION

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Background: Prolonged durations of antiretroviral therapy may allow for immune-mediated selection of HIV-1 reservoir cells, specifically when initiated early after viral transmission. We conducted a deep analysis of the HIV-1 reservoir profile in 9 young adults (age range: 10-26) with congenital HIV-1 infection who started ART at a median of 3.9 months after birth (IQR: 2.3 – 5.8) and remained on antiretroviral therapy for a median of 19 years (range 9 – 26 years).

Methods: Full Length Individual Provirus sequencing (FLIP-seq) was used to interrogate the viral reservoir for the frequency of intact and defective proviruses in peripheral blood samples collected by leukapheresis. Quantitative viral outgrowth assays (QVOA) were used to assess replication competent proviruses. Proviral integration sites were analysed by matched integration site and proviral sequencing (MIP-Seq). Reservoir analyses in young adults were compared to a reference cohort of adults on long-term suppressive ART for a median of 9 years (n=41).

Results: The median number of total HIV-1 DNA copies/10^6 cells and intact HIV-1 sequences/10^6 cells for this cohort (n=9) were 2.96 and 0.02, respectively. In comparison, the median of total and intact proviruses in long-term ART-treated adults were 29.15/10^6 and 2.16/10^6 cells ($p< 0.0001$). In study subject 3, we identified no intact proviral sequences from 300 million PBMC; this result was validated by a QVOA that demonstrated absence of replication-competent virus across 1.5 billion PBMCs/300 million CD4+ cells. In study subject 8, 37 intact proviral sequences were detected across 51 million PBMCs; 19 out of 37 intact sequences were clonal, with an integration site located in the ZNF718 gene on Chr. 4. Subdominant clones of intact sequences were located in the ZNF813 gene on Chr. 19. In study subject 15, no genome-intact proviral sequences were detected across 289 million PBMCs.

Conclusion: In some long-term ART-treated young adults, we noted either complete absence of genome-intact and replication-competent viruses in large numbers of cells, or an integration site profile dominated by intact proviruses in heterochromatin locations. These data suggest that the paediatric immune system can exert effective selection pressure on viral reservoir cells.

451 CTL SELECTION ENRICHES FOR HIV INTEGRATION SITE FEATURES AND EXPANDED CLONES IN VIVO

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Background: In elite controllers (EC) and people on very long-term antiretroviral therapy (ART), the integration sites of intact HIV proviruses become skewed towards transcriptionally inactive genomic loci. Understanding the mechanisms that select for integration sites in gene-distal loci that are refractory to reactivation is key towards developing strategies for functional HIV cures. We devised a novel *in vivo* model to test whether sustained CD8 T cell pressure would be sufficient to recapitulate these integration site profiles.

Methods: NSG mice were engrafted with memory CD4 T cells from a human cisgender male HLA-B27+ controller with or without autologous CD8 T cells. Viral loads and flow cytometry were performed weekly including HLA-B27+ KK10 (Gag) tetramer staining. Eight weeks post infection with HIVJRCSF, human CD4 T cells were quantified in spleens by flow cytometry (Gag+) and the intact proviral DNA assay (IPDA). Proviral integration site isolation and sequencing was performed using ligation-mediated PCR. Integration sites were then identified using the AAvengeR software pipeline. We investigated the association of integration sites with various genomic features, including epigenetic marks, inferred nuclear localization markers, and catalogs of gene expression.

Results: KK10-specific cells expanded to >20% of CD8 T cells, driving sustained 2-3 log reductions in viral load without immune escape. The ratio of Gag protein-expressing to intact provirus-harboring cells was reduced in +CD8 mice compared to –CD8 mice – consistent with selection for latency ($p=0.027$). This was associated with a clear footprint on the proviral integration site landscape with enrichment of integrations: 1. Outside of genes ($p=0.018$), 2. Further away from genes ($p< 0.001$), 3. Closer to the nuclear periphery ($p=0.01$) and 4. With the provirus in opposite orientation relative to host gene transcription ($p=0.002$, odds ratio 0.64). The total diversity of integration sites was decimated in the presence of CD8 T cells leaving predominately expanded clones; 10 clones constituted 32-76% of infected cells. No significant differences were observed in the percentages of intact HIV proviruses between +CD8 and –CD8 mice (IPDA, $p=0.209$).

Conclusion: Our findings validate the idea that CD8 T cells can shape the integration site landscape by selecting for latent proviruses and describe a precise signature of this footprint. This mirrors features seen in ECs and provides guidance for interpreting the impacts of clinical interventions.

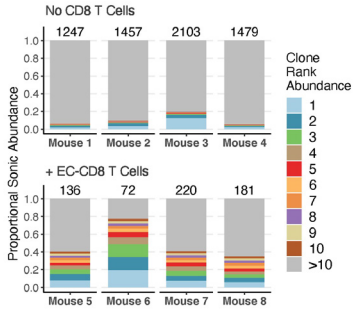

Figure 1: Relative abundances of top ten most abundant infected CD4 T cell clones. Stacked bar plots show the relative abundances of the ten most abundant cell clones, i.e. cells with a shared proviral integration site. The remaining cells (comprising unique as well as repeatedly detected integration sites) are combined into the gray "low abundance" bin. The total number of genomic fragments used to identify integration sites are listed atop of each plot.

452 IMPACT OF HIV RESERVOIR IN THE LOSS OF NATURAL ELITE CONTROL OF HIV-1 INFECTION

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Background: Approximately 25% of elite controllers (EC) eventually loss virological control. This has enabled to classify EC in two groups: i) "transient elite controllers" (TC), those who eventually lose viremia control and ii) "persistent controllers" (PC), those who maintain viremia control indefinitely overtime. It is important to identify the factors that lead to HIV disease progression to open new avenues in HIV cure strategies. Several studies have shown that PC and TC present different immunological, proteomic, metabolomic and miRNA profiles but in terms of virological factors, it is essential to deeply characterize the quality of HIV reservoirs to distinguish both phenotypes.

Methods: Genomic DNA, from 18 PC (viremia control for more than 23 years), 10 TC (sustained viral load above the detection limit, >40 HIV RNA copies/mL, during more than one year of follow-up) before losing the control (0.3-2 years) and 41 antiretroviral-treated individuals for a median of 9 years (2-19 years), was isolated from peripheral blood mononuclear cells (PBMCs). Subsequently, the characterization of HIV-1 reservoir was performed using next-generation sequencing techniques, such as full-length individual proviral sequencing (FLIP-seq) and matched integration site and proviral sequencing (MIP-seq).

Results: PC and TC presented significantly lower total, intact and defective proviruses compared to ART-treated individuals. Although no significant difference was found in total proviruses between PC and TC, a trend in TC to have higher defective provirus was observed ($p=0.072$). Interestingly, the

proportion of intact proviruses were significantly higher in TC compared to PC (p=0.005). Moreover, non-clonally expanded intact proviruses were found in TC, showing a higher viral diversity in comparison to PC. Regarding the integration sites, intact proviruses from TC and ART were located in permissive genic euchromatic positions in contrast to PC whose intact proviruses were located in centromeric satellite DNA or zinc-finger genes, both associated with heterochromatin features.
Conclusion: PC, TC and ART-treated individuals presented a distinct proviral reservoir landscape in PBMCs. The intact proviruses from TC and ART-treated individuals were located in genic regions in contrast to persistent controllers' intact proviruses that were preferentially integrated in non-genic or pseudogenic regions.

452 IMPACT OF HIV RESERVOIR IN THE LOSS OF NATURAL ELITE CONTROL OF HIV-1 INFECTION

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Background: Approximately 25% of elite controllers (EC) eventually loss virological control. This has enabled to classify EC in two groups: i) "transient elite controllers" (TC), those who eventually lose viremia control and ii) "persistent controllers" (PC), those who maintain viremia control indefinitely overtime. It is important to identify the factors that lead to HIV disease progression to open new avenues in HIV cure strategies. Several studies have shown that PC and TC present different immunological, proteomic, metabolomic and miRNA profiles but in terms of virological factors, it is essential to deeply characterize the quality of HIV reservoirs to distinguish both phenotypes.
Methods: Genomic DNA, from 18 PC (viremia control for more than 23 years), 10 TC (sustained viral load above the detection limit, >40 HIV RNA copies/mL, during more than one year of follow-up) before losing the control (0.3-2 years) and 41 antiretroviral-treated individuals for a median of 9 years (2-19 years), was isolated from peripheral blood mononuclear cells (PBMCs). Subsequently, the characterization of HIV-1 reservoir was performed using next-generation sequencing techniques, such as full-length individual proviral sequencing (FLIP-seq) and matched integration site and proviral sequencing (MIP-seq).
Results: PC and TC presented significantly lower total, intact and defective proviruses compared to ART-treated individuals. Although no significant difference was found in total proviruses between PC and TC, a trend in TC to have higher defective provirus was observed (p=0.072). Interestingly, the proportion of intact proviruses were significantly higher in TC compared to PC (p=0.005). Moreover, non-clonally expanded intact proviruses were found in TC, showing a higher viral diversity in comparison to PC. Regarding the integration sites, intact proviruses from TC and ART were located in permissive genic euchromatic positions in contrast to PC whose intact proviruses were located in centromeric satellite DNA or zinc-finger genes, both associated with heterochromatin features.
Conclusion: PC, TC and ART-treated individuals presented a distinct proviral reservoir landscape in PBMCs. The intact proviruses from TC and ART-treated individuals were located in genic regions in contrast to persistent controllers' intact proviruses that were preferentially integrated in non-genic or pseudogenic regions.

453 DISTINCT INTEGRATION SITES OF INTACT HIV-1 PROVIRUSES IN POST-TREATMENT CONTROLLERS

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Background: For people living with HIV-1, the cessation of combination antiretroviral therapy (cART) typically results in rapid viral rebound. However, a particular group of individuals termed post-treatment controllers (PTCs) are able to maintain undetectable or low viremia for months or years after discontinuation of cART. The mechanisms underlying this control, namely the proviral landscape of PTCs, remain largely unknown.
Methods: Samples were obtained longitudinally from 4 PTCs following the discontinuation of cART for up to 4.9 years. Samples were also obtained from 2 individuals who sustained viral rebound following cessation of cART. Genomic DNA was diluted to single-genome levels and then analyzed using full-length proviral sequencing (FLIP-Seq) and matched integration proviral sequencing (MIP-Seq).
Results: In total, 2959 proviral genomes were obtained and classified, with 191 found to be intact. Out of the 41 intact proviruses detected in the four PTCs prior to cART interruption, 80.5% were located in non-genic DNA, centromeric DNA or ZNF genes, all of which have been associated with heterochromatin features and "deep" proviral latency. The PTCs also had a relatively high prevalence of intact clonal sequences among total intact sequences (48.3%). Conversely, only a small minority of the n=12 intact proviruses detected in the two rebounders prior to antiretroviral treatment interruptions (ATI) were integrated in non-genic/satellite DNA or ZNF genes (8%, p< 0.0001 relative to PTC). Intact proviruses integrated in non-genic/satellite DNA or ZNF genes prior to ATI persisted at multiple follow-up time points off-therapy; in contrast, the small number of intact proviruses detected in genes prior to ATI were selectively eliminated over time.
Conclusion: This analysis suggests that an integration site profile dominated intact proviruses integrated in non-genic or heterochromatin regions of the human genome may facilitate drug-free control after ART discontinuation, presumably because intact proviruses integrated in these regions are in a deeper state of latency and less rebound-competent. We propose that the integration site profile of intact proviruses can serve as biomarker for identifying putative PTCs and for selecting candidates for future treatment interruption studies.

454 EFFECTS OF CHEMORADIATION ON EXPANDED PROVIRAL CLONES IN AN ELITE CONTROLLER

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Background: Clonal expansion of latently infected CD4+ T cells contributes to the latent reservoir. Disruption of this process may be needed for viral eradication to be achieved. Recent studies suggest that intact proviruses integrated in certain Zinc Finger (ZNF) genes have a survival advantage due to reduced viral expression caused by a repressive epigenetic environment. However, direct evidence of this mechanism is lacking.
Methods: We characterized HIV integration sites and used digital PCR assays to measure total, intact, and provirus-specific HIV DNA in an elite controller (EC) before and after he received antiretroviral therapy, chemoradiation, and immunotherapy for metastatic lung cancer. CD8-depleted PBMC were stimulated with overlapping Gag peptide for 10 days. Provirus expansion and virus production were used to establish epitope recognition.
Results: We detected a marked yet transient contraction in the number of expanded infected-clones after chemoradiation. In addition, there was a modest decline in both total and intact HIV DNA that returned to pre-treatment levels. Of note, his plasma HIV RNA remained undetectable (< 20 copies/ml) throughout the follow-up. We found that the proviral landscape at the end of treatment was dominated by two large clones with replication competent virus integrated into ZNF 721 and 470 genes. One clone, with a provirus integrated in ZNF470, was stable during treatment. In contrast the other clone, which has a provirus integrated in ZNF721 and recognizes the Gag peptide STLQEQIGWMTNNPP (241-255), underwent a 70-fold expansion after chemotherapy was completed. A third clone with a deletion in the primer binding site region and an unknown integration site recognized the overlapping Gag peptides EKAFSPEVIPMFSAL (162-176) and SPEVIPMFSALSEGA (166-180). Stimulation with Gag peptides *in vitro* resulted in virus production and cell proliferation. However, we observed an RNA to DNA ratio of 0.2 for the clone integrated in ZNF721, and 147 for the defective clone, suggesting that the lower inducibility of the intact provirus in the ZNF721 gene can favor its persistence.
Conclusion: Our results suggest that chemoradiation can transiently disrupt clonal expansion and can be used in conjunction with other interventions as part

of an HIV cure strategy. Despite the lower inducibility of the ZNF721 integrant, virus production can still occur, suggesting that strong CTL killing is required to maintain elite control of HIV replication.

455 EFFECT OF HIV-1 INFECTION AND VIRUS PRODUCTION ON CD4+ T CELL PROLIFERATION

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Background: The latent reservoir (LR) in resting CD4+ T cells is the major barrier to cure. In HIV-infected individuals on long-term ART, many CD4+ T cells in the LR are clonal and have arisen from proliferation. Consequently, clonal expansion is a major mechanism of HIV persistence. Stimulation of latently-infected CD4+ T cells results in the nuclear translocation of transcription factors that are required for both cellular activation and reactivation of the latent provirus. These two transcriptional programs can result in opposing cell fates, cell division and survival or virion production and cell death. We asked whether proviral intactness, viral particle production, and HIV-1 integration site affect the fate of an individual infected CD4+ T cell.

Methods: We validated a high-throughput assay to isolate individual latently-infected resting memory CD4+ T cells in a background of uninfected cells from peripheral blood of 10 PLWH suppressed on ART for >7 years. Cells were stimulated with anti-CD3/CD28 beads in the presence of IL-2 to mimic antigenic stimulation. ART was included in cell culture media to prevent reinfection. At the end of the culture, clonal expansion and viral particle production were quantified and proviral intactness and integration site were determined.

Results: Uninfected T cells and T cells with a defective HIV provirus proliferated ten and four times better, respectively, than T cells with an intact HIV provirus. HIV-1 integration into a cancer- or proliferation-associated gene endowed a proliferative advantage. Infected cell clones that produced >100,000 viral particles had a proliferative disadvantage. However, viral particle-positive clones did not display inferior proliferation overall compared with viral particle-negative clones. Moreover, >80% of infected cell clones produced no viral particles. Unexpectedly, viral particle production was not strongly correlated with poor infected cell proliferation.

Conclusion: These findings further our understanding of overall reservoir persistence and the fate of individual latently-infected T cells upon antigenic stimulation. Clinically, these experiments suggest that anti-proliferative agents may disproportionately affect uninfected T cells. Although there is no biomarker that distinguishes infected from uninfected T cells, we observed differences in proliferation in response to T cell activation. Future studies should investigate whether dividing infected T cells transiently express viral proteins, which may be targetable.

456 A NOT-SO-STABLE RESERVOIR: HIV DRIVES INFECTED CELLS TO DIE AND DIVIDE

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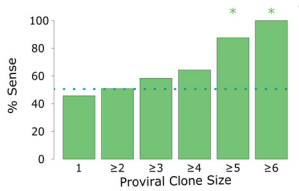
Background: There is emerging evidence that a significant fraction of HIV proviruses on ART are transcriptionally active resulting in positive and negative selection of infected cells. Evidence of negative selection includes faster decay of intact over defective proviruses while the presence of large proviral clones with integration sites in cancer-related genes is consistent with positive selection. Thus, we hypothesize that HIV drives cells to die and divide faster than their uninfected counterparts.

Methods: To assess the effects of proviral orientation on clone size, we obtained ~3000 integration sites in two chronic progessors at multiple, well distributed time points over 14 years. We used linear regression and exact binomial statistics to assess effects of proviral integration in the sense orientation. To estimate turnover, we measured clonal overlap between paired time points of proviral sequences by the Morisita index in four chronic progressors and two elite controllers.

Results: Among intronic integrations, proviral clones (size >1) in sense orientation increase over time more than clones in antisense ($p < 0.001$). We found small proviral clones favored the antisense orientation, but larger clones increasingly favored sense orientation especially when integrated in cancer-related genes (clone size >4: >80% sense, $p < 0.05$; Figure). We validated this finding with a larger publicly available data set (Coffin et al 2021). Since proviral expression not only increased cell death, but also appeared to increase division, we turned to study turnover. We found proviruses from distant time points had less clonal overlap ($p < 0.001$) consistent with a reservoir that is turning over. Intriguingly, there was minimal turnover in two elite controllers. Finally, we probed the mechanism behind HIV-host influence using 48 infected CEM-SS T-cell clones. Surprisingly, the majority of sense proviruses enhanced downstream gene expression by aberrant splicing (median 9-fold increase) while antisense proviruses had no effect.

Conclusion: While reservoir contraction occurs with expression of HIV proteins, expansion is only apparent in sense orientation and frequently results in enhanced downstream gene expression. Sense-oriented proviruses were associated with the largest clones. Intriguingly, proviral turnover appears faster in chronic progressors than elite controllers, consistent with their divergent proviral landscapes in which ECs lack proviruses in sense orientation of cancer-related genes.

Highly expanded proviral clones in cancer-related genes are usually in the sense orientation.



457 ACUTE/RECENT HIV INFECTION IN YOUTH: HIV RESERVOIRS AND ANTIBODY FOLLOWING EARLY ART

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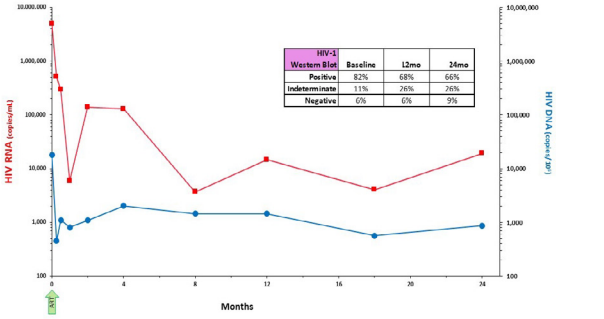
Background: Initiation of antiretrovirals (ART) during acute HIV infection reduces viral reservoirs with improved long term virologic control; there is limited data on youth. HIV reservoir decay in youth treated during acute HIV infection (A) may be greater than in those treated with non-acute infection (NA). ATN 147 identified A or NA HIV-infected youth (12-24 yr.) assessing HIV plasma RNA PCR, DNA digital drop (dd) PCR and HIV antibody from baseline (BL) to 24 mo.

Methods: Youth newly diagnosed with HIV infection initiated ART in Los Angeles and New Orleans. Acute infection was defined as Fiebig stage I-V on HIV Western blot (WB) at BL. Fiebig stage VI defined NA infection. Blood was collected over 24 mo. with viral suppression (VS) defined as plasma HIV RNA < 20 copies/ml. HIV DNA ddPCR on PBMC and WB were performed at BL, 12, 24 mo. Statistical comparisons at different timepoints/between groups used log-transformed DNA & RNA values in a mixed effect model.

Results: 103 youth enrolled with mean age of 20.8 yr. (range:16-24); 60% identified as black, 25% Latino, 8% white, 7% Asian/Native American; 90% identified as cis-male, 2% cis-female, 5% trans-female, 3% gender nonconforming; 95% reported same gender/bisexual orientation. ART was initiated within 24 hours in 78%, within 1 week in 88%. At BL, 36 (35%) were A and 67 (65%) NA. Median virus load (VL) at BL was 104,650 (A) and 32,334 cps/ml (NA), $p < 0.001$ & at 4mo. 30 (A) and 20 cps/ml (NA), $p = 0.815$. By 12 & 24 mo. both A and NA had median VL of 20 cps/ml, p=NS. At 4, 12, 24 mo., 50/82 (61%), 52/76 (68%), 41/57 (72%) youth achieved VS. Median ddPCR copies/million PBMCs for youth over time (BL,12,24 mo.) was 844, 192, 127, $p < 0.001$. For A vs. NA youth, BL,12,24 mo. ddPCR values were 1448 vs. 633, 188 vs. 192, 148 vs. 106, p=0.66. Median dd PCR for VS youth at 12 mo. was 115 vs. 485 in non-VS youth, $p < 0.001$; at 24 mo. 107 (VS) vs. 202 (non-VS), $p < 0.001$. Negative/indeterminate (NI) WB occurred in 32% of the cohort at 12 & 35% at 24 mo. NI WB was associated with A status at 12 & 24 mo. (OR 11.5; 95%CI:3.88-34.08). VL suppression at 12 & 24 mo. was not associated with NI WB (OR 2.96; 95% CI 0.91-9.66).

Conclusion: Early ART induced sustained VS in 68% of youth by 12 mo., significantly reducing HIV DNA and antibody levels. Within 4 mo. of ART, VS was similar in both A and NA youth. HIV DNA decay was similar in A and NA youth with VS. Acutely treated youth were less likely to maintain positive HIV WB.

Median HIV RNA, HIV DNA, and HIV Antibody Responses to Early ART Treatment



	B/L	4mo	12mo	18mo	24mo
n (RNA)	103	82	75	48	56
n (DNA)	101	86	73	20	54

458 LEUKAPHERESIS: A FEASIBLE TOOL TO INFORM ATI THROUGH HIV RESERVOIR STUDY IN CHILDREN

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Background: The unique features of the infant immune system at the time of reservoir establishment impact the characteristics of long-term virus persistence, susceptibility to immune-mediated clearance, and reactivation potential. These characteristics limit the size of the HIV reservoir which is further reduced over time by a suppressive antiretroviral treatment. These characteristics, coupled with paucity of sample which characterizes the pediatric setting makes the HIV reservoir analysis particularly difficult in perinatally HIV infected children treated early (ePHIV). We here aimed to define the safety of leukapheresis (LA) to deeply characterize the latent reservoir from a large amount of peripheral blood mononuclear cells (PBMCs) in ePHIV that may be considered as candidates for analytical treatment interruption (ATI). We further analyzed RNA seq and DNA methylation in proximity of the intact HIV DNA integration sites.

Methods: nine patients (age range 12-26y, mean age 18,6y), treated within the first year of life (age at ART start=range 0-336 dd, mean 118 dd) with a history of suppressive ART >2 years (range 2-14 years, mean 8,8y) and with a cumulative time on ART ranging from 11 to 25y (mean 17,7y) underwent a LA (avg duration 3,5h). Total CD4, collected from PBMCs collected (range 2,5-9,4 mean 5.06 billions) were analyzed for HIV DNA by Full Length Individual Provirus sequencing (FLIP-Seq) and matched integration and proviral Seq (MIP-Seq). RNA Seq from purified CD4 in unstimulated and stimulated samples (18h PMA and ionomycin) and DNA methylation was performed by Nanopore.

Results: LA was well tolerated in all patients with no adverse events reported. FLIP-Seq showed the total absence of intact provirus in 2 patients where a total of 1,2 billion PBMCs and 280 millions PBMCs were screened. Intact proviruses were detected in 2 patients. RNA Seq and DNA methylation analysis were focused aligning RNA-Seq and DNA methylation in proximity of the HIV proviruses integration sites. These data provided peculiar characteristics both in terms of gene expression after *in vitro* stimulation and in terms of CpG islands methylation.

Conclusion: This study suggests that LA procedure can be considered a safe procedure for ePHIV where the in depth analysis of HIV reservoir is needed in order to select potential candidates for ATI. The multi OMIC analysis within integration sites of intact HIV proviruses may provide crucial information regarding the reactivation potential of the viral reservoir in ePHIV.

459 SIV CLEARANCE FROM NEONATAL MACAQUES FOLLOWING TRANSIENT CCR5 DEPLETION

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Background: Treatment of people with HIV (PWH) with antiretroviral therapy (ART) results in sustained suppression of viremia, but due to virus that persists during ART, stopping treatment leads almost invariably to viral recrudescence and rebound viremia. This persistent virus, the "rebound competent viral reservoir" (RCVR), is the primary obstacle to more definitive treatment of HIV. The RCVR has been successfully depleted only in a handful of PWH following cytotoxic chemotherapy and bone marrow transplantation from donors with a mutation in CCR5 that provides resistance to HIV. We hypothesized that depletion of infected and infectable cells could permit SIV cure if accomplished soon after infection when the RCVR remains limited in extent and uniform in terms of associated surface markers.

Methods: Neonatal rhesus macaques were infected orally with virulent SIVmac251, then treated with ART beginning one week after infection, followed by treatment with either a CCR5/CD3-bispecific or a CD4-specific antibody.

Results: Both antibodies depleted target cells and increased the rate of plasma viremia decrease in subsequent weeks. Animals were maintained on ART until viremia could no longer be quantified. Upon subsequent cessation of ART, four of seven animals treated with CCR5/CD3-bispecific antibody did not rebound. Two of these four eventually rebounded three or six months after ART interruption. The remaining two remained aviremic and efforts to detect replication-competent virus were unsuccessful.

Conclusion: We found that long-term SIV remission and apparent cure can be achieved for infant macaques via targeted depletion of potential reservoir cells bearing the chemokine receptor, CCR5. Our results show that bispecific antibody treatment can achieve meaningful SIV reservoir depletion and suggest that functional HIV cure might be achievable for recently infected individuals having a restricted reservoir.

460 COGNITIVE TRAJECTORIES AMONG PEOPLE WITH HIV MODELED BEFORE AND AFTER SUSTAINED ART

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Background: The present analysis leveraged the longitudinal study design of the Sabes cohort to identify cognitive trajectory subgroups modeled before and 192 weeks after ART using a culturally validated cognitive assessment protocol.

Methods: Longitudinal cognitive data from the Sabes cohort. Study participants began ART immediately at diagnosis or deferred for 24 weeks and completed cognitive assessments at the time of HIV diagnosis with repeat evaluations conducted for 192 weeks. Measures of attention, information processing speed, executive function, language, learning and memory, and fine motor speed were administered. Performances were converted to z-scores using normative data from demographically similar Peruvian adults without HIV infection. Group-based trajectory analysis (GBTA) was implemented to identify individuals who followed similar cognitive trajectories. Group comparisons were then utilized to identify features (e.g., demographic, HIV disease severity) that differed between individuals in the specific clusters.

Results: The trajectory analysis identified three clusters (Figure 1). Cluster 1 (35% of the sample) included individuals with average to above average cognitive profiles across all study visits. Cluster 2 (49%) included individuals with average cognitive profiles across the study visits. Cluster 3 (16%) included individuals with below average cognitive performance at the time of ART initiation, with normal performance achieved on ART. All three clusters exhibited gains in cognitive performance after ART, regardless of whether ART initiation was immediate or deferred. All three subgroups achieved normal cognitive levels after sustained use of ART. Post-hoc analyses revealed that individuals in cluster 1 (above average) were younger at the time of diagnosis,

had shorter duration of time between EDDI and enrollment, and reported more years of education. Individuals in cluster 3 reported fewer years of education, had higher depression scores, and higher HIV viral load at the time of ART onset compared to the other trajectory clusters.

Conclusion: This is the first study to model cognitive trajectories before and after ART among PWH randomized to immediate vs. deferred treatment. Results identify a combination of demographic, psychosocial, and HIV disease variables that contribute to cognitive heterogeneity before ART. Importantly, a short delay in ART onset did not correspond to poor cognitive outcomes at week 192.

Cognitive performances for the three trajectory subgroups

Figure 1. Cognitive performances for the three trajectory subgroups.

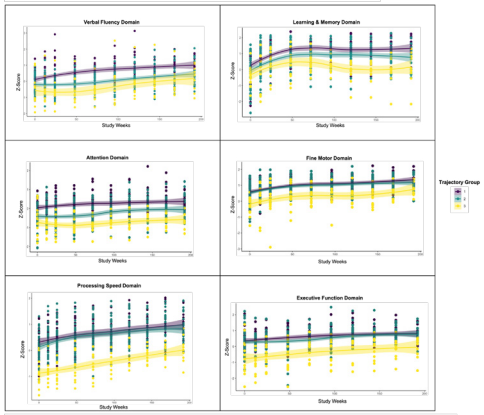

Fig 1. Latent class trajectories of neurocognitive functioning over 192 weeks per cognitive domain. Each cluster exhibited stable or increasing performance over the assessment period.

461 THE COURSE OF NEUROCOGNITIVE PERFORMANCE OVER FOUR YEARS IN WELL-TREATED PLWH

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Swiss HIV Cohort Study
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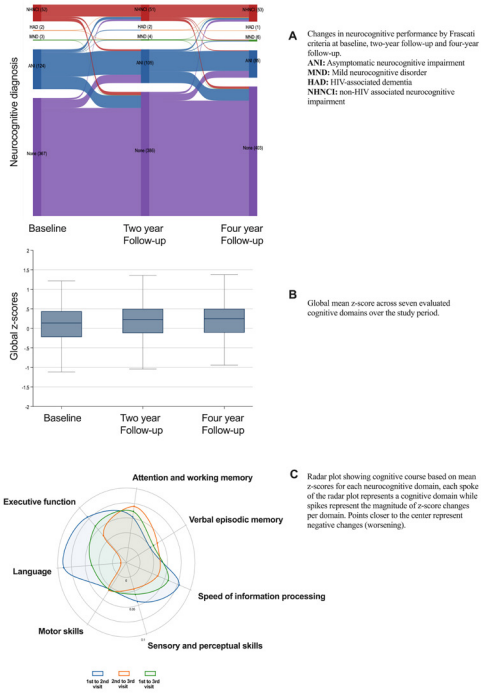
Background: Among people living with HIV (PLWH) enrolled in the Neurocognitive Assessment in the Metabolic and Aging Cohort (NAMACO) study, we have observed a neurocognitive impairment (NCI) prevalence of 40% by Frascati criteria. However, most patients have asymptomatic neurocognitive impairment (ANI), and analysed trajectories at two-years follow-up showed no signs of decline. In the current study, we examined neurocognitive performance (NP) after four years, and its associated characteristics.

Methods: The NAMACO study is an ongoing prospective, longitudinal, multicentre and multilingual (French, German, Italian) study embedded within the Swiss HIV Cohort Study. PLWH ≥ 45 years old were recruited and assessed with standardized neuropsychological tests performed by neuropsychologists at baseline (between 2013 and 2016) and then at two- and four-years follow-up. NP was described by Frascati criteria, and by global and per cognitive domains z-scores. To evaluate factors associated with changes in NP over time, we defined our outcome as mean yearly changes in global mean z-scores from baseline. Uni- and multivariable linear regression models were performed and subsequently weighted for the inverse probability of dropping out of the study. Probabilities of dropping out of the study were obtained by multivariable logistic regression adjusted for all baseline characteristics.

Results: At baseline, 981 participants were recruited. A total of 548 (55.9%) completed all three assessments (median age 53, male 80%, Caucasian 91%, MSM 56%, highly educated 88%, smoking 32%, severe alcohol consumption 18%, HIV viral loads ≤ 50 copies/mL 97%, and median CD4+ 618 cells/µl. PLWH lost to follow-up were more likely to have ANI at baseline, mild or severe depression, being smokers and to have a moderate or severe alcohol consumption. Neurocognitive trajectories over the study period are presented in Figure 1 (panel A to C). After adjusting for confounders, age over 65 years was the only factor associated with a decline in NP, measured by changes in z-score, after four years (Coeff. -0.03 95% CI -0.05 to -0.01, p-value = 0.005).

Conclusion: In a well-treated population of PLWH we observed stability or improvement of NP after four years of follow-up. Age remained the only factor associated with changes in NP.

Figure 1.



462 NEUROCOGNITIVE IMPAIRMENT NEGATIVELY AFFECTS VIRAL CONTROL IN ART-TREATED PWH

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Background: The clinical relevance of the highly prevalent asymptomatic neurocognitive impairment (ANI) among the spectrum of neurocognitive impairment (NCI) in people with HIV (PWH) is debated. NCI may affect treatment adherence, but very few data are available on whether it significantly affects viral control during antiretroviral therapy (ART).

Methods: Cross-sectional monocentric study enrolling (2010-2019) adult PWH on ART without neuropsychological confounding conditions that underwent a comprehensive battery (16 tests) to assess NCI. Demographics, clinical and immuno-virological data from the 2 years preceding and the 2 years following the neurocognitive assessment were collected to identify single (s) or persistent (p, if 2/more consecutive determinations) very low-level and low-level viremia (undetectability < VLLV < 50 cp/mL and 50 cp/mL ≤ LLV < 200cp/mL), high-level viremia (HLV) and viral failure (VF), when single or 2/more consecutive HIV-RNA > 200 cp/mL, respectively. Participants on ART since < 6 months before the first collected viremia were excluded. Frascati's criteria were used to classify NCI severity. Nonparametric tests and logistic regressions were used.

Results: We included 300 PWH: median age and time on ART were 52 and 10 years; 69% male, 96% Caucasian, 85% had undetectable serum HIV RNA at the neurocognitive evaluation; 43.7% and 10.3% were diagnosed with ANI and mild neurocognitive disorders/HIV-associated dementia (M/D). Compared to those without NCI, participants with ANI showed increased risk of pVLLV, sLLV and VF (OR 2.75 p=0.004; 2.31 p=0.041; and 5.34 p=0.003, respectively). The risk increased further for patients with M/D (OR pVLLV 3.08, p=0.024; pLLV 5.24, p=0.001; VF 6.44, p=0.008). Multivariate analysis showed an association between sVLLV and M/D (aOR 3.29 p=0.039), pVLLV and both ANI (aOR 2.87 p=0.030) and M/D (aOR 8.50 p=0.003), pLLV and M/D (6.40, p=0.016), and between VF and both ANI (7.46, p=0.008) and M/D (9.44, p=0.018), independently from ART type, age, sex, HIV acquisition route, CD4 nadir, calendar year, years on ART, number of plasma determinations and co-medications. PWH experiencing VLLV and LLV had worse scores in tests assessing memory and executive functions only, whereas those developing VF showed broader NCI in several domains.

Conclusion: The whole spectrum of NCI was associated with worse viral control in PWH with a further higher risk of persistent low-level viremia and viral failure in participants diagnosed with symptomatic NCI.

463 ASSOCIATIONS BETWEEN PLASMA BIOMARKERS AND CHANGES IN COGNITIVE FUNCTION OVER 2 YEARS

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Background: Chronic inflammation may be associated with the development of cognitive disorders. We examine the associations between changes in cognitive function (CF) scores and plasma biomarkers of neuronal injury, systemic inflammation and innate immune activation measured in people with HIV (PWH) and demographically-similar HIV-negative controls in the POPPY study.
Methods: At baseline and 2-year follow-up, participants completed a cognitive test battery assessing psychomotor function, visual learning, visual attention, working memory, verbal learning and executive function. T-scores were derived, with a Global T-score of overall CF obtained by averaging domain T-scores (higher T-score indicates better CF). We used a t-test to assess change in Global T-scores, and linear regression to explore associations between changes in Global T-scores and log-transformed plasma biomarkers (measured at/near follow-up) of neuronal injury (NFL, S100B), systemic inflammation (IL-2, IL-2, TNF-α) and innate immune activation (CD14, IL-10, MCP-1, CD163, MIP-1α) separately. We adjusted for HIV status, age, sex and education; and explored whether effects of biomarkers differed by HIV status using likelihood ratio tests.
Results: 350 participants were included (255 (73%) PWH, median [interquartile range, IQR] age 54 [50-60] years, 85% male, 94% white, and 77% men having sex with men). Among PWH, most (98%) were on antiretroviral therapy, 236 (93%) had HIV-RNA ≤50 copies/mL and median [IQR] CD4+ T-cell count was 629 [490, 794] cells/mm3. Mean (standard deviation (SD)) baseline Global T-score was 47.7 (5.9); after median [IQR] follow-up time of 26 [24-29] months, mean (SD) Global T-score was 48.9 (5.5) (p-value for within-individual change < .001). A reduction in CF (i.e. decline in Global T-scores) was associated with higher concentrations of MIP-1α (estimated mean change in Global T-scores: -0.38 [95% confidence interval: -0.61, -0.16] for a 10% increase in biomarker concentration) and CD14 (-0.16 [-0.30, -0.02]), though only MIP-1α (-0.46 [-0.68, -0.23]) remained significant after adjustment. There was some evidence that the effects of MIP-1α (p-interaction=.08) and IL-2 (p-interaction=.05) were stronger in PWH (Table).
Conclusion: Within an extensive panel of plasma biomarkers, we observed negative associations with plasma MIP-1α, CD14 and IL-2 suggesting innate immune activation and systemic inflammation may both be implicated in the pathogenesis of CF changes and these effects may differ in PWH.

Table. Results of unadjusted and adjusted linear regression analyses testing associations between changes in Global T-scores (outcome: change scores) and log-transformed biomarkers, Estimate* (95% confidence interval (CI))

	Unadjusted		Adjusted (HIV status, age, sex, race and education[†])		
Biomarker	**Estimate (95% CI)**	**p-value**	**Estimate (95% CI)**	**p-value****	**p-value (HIV Status:Biomarker interaction)**
Neuronal Injury					
S100B	0.02 (-0.10, 0.15)	0.70	0.03 (-0.10, 0.17)	0.66	0.29
NFL	-0.02 (-0.11, 0.06)	0.59	-0.05 (-0.14, 0.05)	0.32	0.91
Systemic Inflammation					
IL-6	-0.03 (-0.10, 0.05)	0.48	-0.03 (-0.11, 0.05)	0.50	0.19
IL-2	-0.04 (-0.08, 0.01)	0.10	-0.03 (-0.07, 0.01)	0.18	0.05
TNF-alpha	-0.01 (-0.10, 0.09)	0.92	0.02 (-0.08, 0.12)	0.67	0.30
Innate Immune Activation					
CD163	0.03 (-0.04, 0.10)	0.37	0.03 (-0.04, 0.10)	0.39	0.51
MIP-1α	-0.38 (-0.61, -0.16)	0.001	-0.46 (-0.68, -0.23)	<0.001	0.08
MCP-1	-0.07 (-0.20, 0.05)	0.24	-0.08 (-0.20, 0.05)	0.23	0.55
IL-10	-0.01 (-0.09, 0.06)	0.73	-0.003 (-0.08, 0.08)	0.94	0.68
CD14	-0.16 (-0.30, -0.02)	0.02	-0.13 (-0.28, 0.01)	0.07	0.37

[†]education was included as a binary variable: university degree or above is 1; otherwise 0.
*Note, coefficients have been scaled to represent the mean change in the Global T-score for every 10% change in the biomarker concentration, where an increase indicates "improved" cognitive function and a decrease indicates "reduced" cognitive function.
**p-value for the biomarker effect without an interaction with HIV status; thus, the Estimate (95% CI) is the estimated biomarker effect without an interaction with HIV status.

464 VASCULAR AGE AND COGNITIVE OUTCOMES IN AN ACUTE HIV COHORT AFTER 6 YEARS OF ART

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Background: Immune dysregulation persists in people with HIV (PWH) on antiretroviral therapy (ART) and may lead to accelerated vascular aging and cardiovascular (CV) disease. We evaluated relationships between HIV parameters, Framingham Risk Score (FRS)-based 10-year CV risk, vascular age and cognitive function 6 years after ART initiation during acute HIV infection (AHI).
Methods: RV254 Thai participants were enrolled during AHI, initiated ART within days and underwent regular follow-up. FRS-based CV risk at week 288 was calculated using age, sex, lipid profile, systolic blood pressure, smoking, diabetes and antihypertensive usage status. FRS-based vascular age was defined as age with the same predicted CV risk but optimally-controlled risk factors. Vascular age deviation (VAD) was vascular age minus actual age. Cognitive performance (NPZ-4) was determined by averaging z-scores of: Color Trails 1 & 2, non-dominant hand Grooved Pegboard (GPB), and Trails Making A. Linear regression model was used to assess factors associated with VAD.
Results: The study included 356 participants (98% male; 100% viral suppression) who completed week 288 visits between 5/2009 and 6/2022. CV risk factors are summarized in Table 1. At week 288, the actual and vascular ages were 32 (IQR 28,37) and 34 (IQR 30,40) years (p< 0.001). Vascular age was higher than actual age in 232 (65%) participants (VAD = 3(IQR -1,7) years). The 10-year CV risk was 2.3% (IQR 1.6,3.9, "low risk" ≤10%). Only one clinically-relevant CV adverse event occurred (embolic stroke) within the study period. In univariable analysis, higher week 288 CD4+ T-cell count was associated with increased VAD (b[95%CI]: 0.5 years [0.3-0.7] per 100 cell increase in CD4+ T-cell count, p< 0.001). Given a known association between smoking and CD4+ T-cell count in the literature, and that CD4+ T-cell count was 102 (95%CI 20-183) cells higher in smokers (p=0.015) in this study, stratification analysis was performed. CD4+ T-cell count remained independently associated with VAD regardless of smoking status (p< 0.05). Vascular age and VAD at week 288 were not associated with NPZ-4. There was an unexpected association between higher VAD and better z-GPB scores (b[95%CI]: 0.5 [0.01-1.02], p=0.045).
Conclusion: In young PWH after 6 years of ART initiated during AHI, 10-year CV risk was low and CV events were rare. Higher CD4 count was associated with higher VAD even after controlling for smoking. Vascular risk after 6 years on ART did not predict cognitive test performance.

Table 1. HIV serum parameters, cardiovascular comorbidities, and cognitive test scores at acute HIV (baseline) and week 288 follow-up

N=356	Baseline	Week 288
HIV parameters		
Age (year)	26 (23, 32)	32 (28, 37)
Sex, male, n (%)	347 (98)	-
CD4+ T-cell count (cells/mm^3)	369 (266, 493)	676 (564, 847)
CD8+ T-cell count (cells/mm^3)	515 (341,862)	630 (470,797)
CD4/CD8 ratio	0.71 (0.42, 1.00)	1.11 (0.91, 1.36)
Plasma HIV RNA (log_{10} cps/ml)	5.94 (5.33, 6.74)	-
Plasma HIV suppression, n (%)	0 (0)	356 (100)
Cardiovascular parameters		
Hypertension, n (%)	7 (2.0)	17 (4.8)
Diabetes Mellitus, n (%)	1 (0.3)	3 (0.8)
Hyperlipidemia, n (%)	4 (1.1)	40 (11.1)
Smoking, n (%)*	36 (17.1)	45 (12.6)
Total cholesterol (mg/dL)	172 (152, 196)	200 (175, 230)
High density lipoprotein (mg/dL)	38 (32, 45)	49 (42, 57)
Systolic Blood Pressure, mmHg	117 (108, 125)	122 (112, 130)
Diastolic Blood Pressure, mmHg	74 (67, 81)	76 (71, 83)
Framingham Risk Score	-	2 (0,5)
10-year Cardiovascular risk (%)	-	2.3 (1.6, 3.9)
Vascular age (year)	-	34 (30, 40)
Cognitive test scores		
NPZ-4 score[§]	-	0.92 (0.55, 1.32)
z-Color Trails 1	-	1.43 (0.98, 1.86)
z-Color Trails 2	-	1.02 (0.53, 1.43)
z-Grooved Pegboard	-	0.71 (0.08, 1.20)
z-Trails Making A	-	0.85 (0.19, 1.34)

Median (IQR) is reported unless specified. Cognitive test scores are standardized and corrected for age, sex, and education.
*week 0 n=211 due to missing baseline smoking status

465 NON-CLASSICAL MONOCYTES CORRELATE NEGATIVELY WITH HIV-ASSOCIATED COGNITIVE PERFORMANCE

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Background: Despite anti-retroviral treatment (ART), people living with HIV (PLWH) are more susceptible to cerebral small vessel disease (CSVD) and subsequent neurocognitive impairment. Altered blood brain barrier (BBB) and transmigration of inflammatory monocytes are risk factors for developing CSVD. Our group has shown that interaction with activated platelets, drives monocytes towards proinflammatory, promigratory phenotype *in vitro*. In this study we hypothesized that inflammatory monocytes exacerbate CSVD and cognitive impairment by affecting cerebrovascular permeability and reactivity, especially in older individuals.
Methods: 110 PLWH, on ART and 110 age, sex matched healthy control individuals were enrolled. Platelet-monocyte interaction, monocyte activation

and soluble markers of monocyte and endothelial activation were measured in whole blood. Neuropsychological testing and brain MRI imaging was also performed. Kruskal Wallis test followed by Dunn's multiple comparisons and Spearman Correlation were used for data analysis.

Results: There was higher prevalence of CSVD (as measured by the presence of white matter hyperintensities on MRI) and cognitive impairment in PLWH. Increased levels of platelet-monocyte complexes (PMCs) were found in PLWH in classical, intermediate and non-classical monocyte subsets. Increased levels of CCR2, CD40, PSGL-1, TNFR2 and TF were found on PMCs as compared to non-complexed monocytes. PLWH with CSVD had the highest circulating levels of non-classical monocytes as compared with healthy controls with and without CSVD. Percentages of non-classical monocytes correlated negatively with cognitive Z score only in PLWH (r=-0.2334, p=0.0021), with a much stronger negative correlation in PLWH with CSVD as compared to PLWH without CSVD (r=-0.3579, p=0.0032). Increased levels of ICAM were found in PLWH, especially those with CSVD and correlated negatively with cognitive Z score (r=-0.1792, p=0.0173).

Conclusion: This study, with a much larger group of study participants, reiterated our previous findings that increased interaction with platelets activates monocytes and drives their differentiation to inflammatory monocyte subset in PLWH. Most interestingly, increased levels of non-classical monocytes can be used as easily measurable predictors of CSVD and cognitive impairment during HIV infection, especially in resource limited settings where MRI imaging might not be available for CSVD diagnosis.

466 COCAINE USE INDEPENDENTLY PREDICTS WHITE MATTER LESION BURDEN IN HIV DISEASE

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Background: White matter hyperintensities (WMH), a marker of diffuse small vessel disease and predictor of cognitive decline, has been observed at higher rates in PWH. Aging and cardiovascular disease (CVD) are the main risk factors for developing WMH. The use of cocaine, a potent central nervous system stimulant, is disproportionately common in persons with HIV and may contribute to the development of WMH.

Methods: The sample includes 110 adults with chronic HIV disease who were on antiretroviral therapy and had persistent viral suppression. Fluid-attenuated inversion recovery (FLAIR) and T1-weighted anatomical MRI scans were collected, as well as comprehensive neuropsychological testing. FLAIR images were processed using the Lesion Segmentation Toolbox, with a subset of images manually segmented to optimize the threshold for the automatic segmentation. White matter lesion burden was calculated as total lesion volume / total intracranial volume. A CVD risk score for each participant was computed as the sum number of common risk factors: diabetes, current smoking, hyperlipidemia, hypertension, obesity, and prior cardiovascular disease, with scores ranging from 0-6. A hierarchical regression model was run to investigate predictors of WMH burden (block 1: demographics; block 2: CVD risk; block 3: lesion burden).

Results: The sample was 20% female, 79% African American, with a mean age of 45.37. Mean years since HIV diagnosis was 14.60, and median current CD4+ T-cell count was 750. Nearly a third of participants (29%) were classified as current regular cocaine users, with 23.75 (SD=20.95) days of use in the past 90 days and 18.28 (SD=10.70) years of regular use on average. In the hierarchical linear regression model, after accounting for age, sex, race, and CVD risk, cocaine use was a significant predictor of white matter lesion burden (β= .211, p= .036). CVD risk score also remained a significant predictor in the final model (β= .288, p= .003). Furthermore, in a partial regression accounting for age, white matter lesion burden was negatively correlated with global cognitive function (r= -.273, p= .004).

Conclusion: White matter lesion burden is associated with poorer cognitive performance in PWH. Cocaine use and CVD risk independently contribute to WMH, and addressing these conditions as part of HIV care may mitigate brain injury underlying neurocognitive impairment.

467 EXTRACELLULAR VESICLES IN ALWH PROMOTE CEREBRAL ENDOTHELIAL PROFILES LINKED TO STROKE

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Background: The incidence of ischemic stroke in adults living with HIV (ALWH) is three times higher than uninfected adults. Mechanisms underlying this heightened rate of ischemic stroke are poorly understood. Circulating endothelial cell-derived microvesicles (EMVs) have been linked to cerebrovascular events. We have previously reported that EMVs are elevated in ALWH; whether HIV associated EMVs promote endothelial abnormalities known to increase stroke risk is unknown. The experimental aim of this study was to determine the effect of EMVs isolated from ALWH on brain endothelial cell inflammation, nitric oxide (NO) and endothelin (ET)-1 production and fibrinolytic capacity.

Methods: Circulating EMVs (CD 144-PE) were isolated (flow cytometry) from 18 adults: 9 healthy (6M/3F; age 55±1 yr; BMI: 24.2±0.5 kg/m2) and 9 ALWH on stable antiretroviral therapy (6M/3F; 53±2 yr; 26.1±0.8 kg/m2). Human cerebral microvascular endothelial cells (hCMECs) were cultured and separately treated with EMVs from each subject.

Results: EMVs from ALWH induced significantly greater release of interleukin (IL)-6 (32.2±1.6 vs 23.4±1.2 pg/mL) and IL-8 (792.8±26.7 vs 661.3±36.4 pg/mL) vs EMVs from healthy adults. Concordantly, HIV-1-related EMVs induced higher (P< 0.05) expression of phosphorylated-NF-kB p65 (Ser536; active NF-kB) (14.9+0.6 vs 10.8+0.7 AU). Although total endothelial nitric oxide synthase (eNOS) expression was not significantly altered; active eNOS (pSer1177) (46.7+2.8 vs 57.2+2.1 AU) and, in turn, NO production (6.0+0.3 vs 7.7+0.3 mmol/L) was lower (P< 0.05) in cells treated with EMVs from ALWH. HIV-associated EMVs also significantly increased the expression of endothelin converting enzyme (39.2+1.3 vs 33.4+1.4 AU) and ET-1 production (35.6+0.9 vs 30.6+0.8 pg/mL), reduced tissue plasminogen activator (t-PA) (8.7+0.4 vs 10.8+0.6 AU) and increased plasminogen activator inhibitor (PAI)-1 (25.4+1.5 vs 18.1+ 1.0 AU) protein expression in hCMECs. The t-PA:PAI-1 protein ratio (2.9+0.1 vs 1.8+0.1 AU; P< 0.05) was higher in HIV-1 EMV treated cells, indicative of decreased fibrinolytic capacity.

Conclusion: EMV-induced increase in inflammation, reduction in NO bioavailability, increased ET-1 production and impairment in fibrinolytic capacity in brain endothelial cells may contribute to the heightened risk and accelerated rate of ischemic stroke with HIV-1. EMVs represent a potential therapeutic target for reducing cerebrovascular risk in ALWH.

468 NEUROFILAMENT LIGHT IS ASSOCIATED WITH CARDIORESPIRATORY AND METABOLIC HEALTH IN HIV

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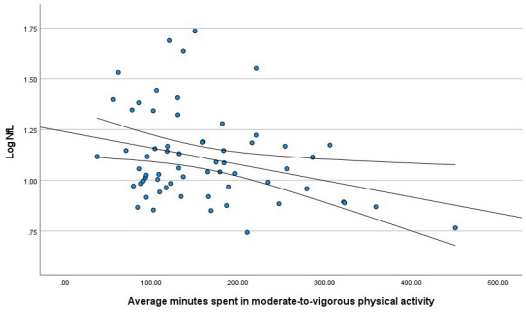
Background: Neurofilament light (NfL) has been identified as a potential biomarker of neuronal injury and cognitive impairment in people with HIV (PWH). In people without HIV (PWoH), NfL levels have been reported to correlate with lifestyle factors, such as exercise, and measures of metabolic health, such glucose and diabetes. These relationships have not yet been analyzed in PWH, who are often more sedentary and at a higher risk for diabetes or poorer metabolic health compared to PWoH.

Methods: 64 PWH (age ≥50 years; male n=51, female n=13; 16% diagnosed with diabetes) with undetectable viral load (< 50 copies/mL) completed cardiorespiratory and physical fitness testing, including a stationary bike graded exercise test to measure VO2 maximum (VO2 max; ml/kg/min), a six-minute walk test (SMWT), and wore a wrist Actigraph activity monitor for one week. Additionally, participants completed a comprehensive neuropsychological battery and a blood draw (NfL; glucose, HbA1c, triglycerides, cholesterols). Regression analyses (adjusted for sex) examined relationships between log-transformed plasma NfL and VO2 max, time to complete SMWT, average time spent in moderate-to-vigorous physical activity (MVPA), metabolic blood markers, cognitive domain Z-scores, or HIV variables (CD4 t-cell count, CD8 t-cell count, CD4:CD8 ratio).

Results: Lower concentrations of plasma NfL were significantly associated with a higher VO2 max (r=-0.34, p=.003), more time spent in MVPA (r=-0.30, p=.009; Figure 1), and greater distance walked during the SMWT (r=-0.30,

p=.01). Although diabetes diagnosis did not associate with NfL, lower NfL values significantly related to higher glucose (r=.21, p=.04), higher triglycerides (r=.21, p=.04), and higher HbA1c (r=0.26, p=.02) values. There were no significant relationships between plasma NfL and any cognitive or HIV variables.
Conclusion: Better cardiorespiratory, physical and metabolic health, but not markers of HIV disease, were linked to lower levels of a biomarker that may reflect neuronal damage (NfL) in older PWH. Longitudinal and interventional studies are needed to examine how changes to these factors may improve NfL levels and brain integrity in PWH.
Greater time spent in moderate-to-vigorous physical activity was associated with lower levels of NfL in older PWH.



469 EFFECT OF COMMON ANTIRETROVIRAL COMBINATIONS ON DEPRESSIVE SYMPTOMS IN WOMEN WITH HIV

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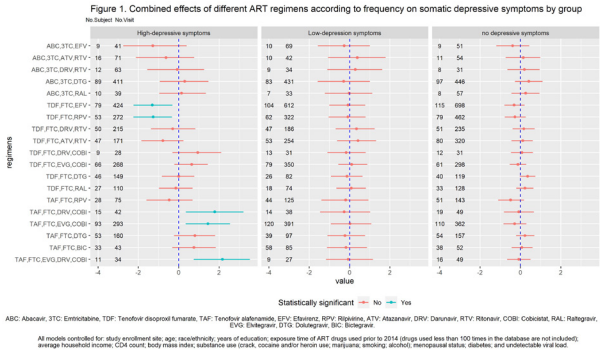
Background: While modern antiretroviral therapy (ART) effectively suppresses HIV replication, it has been associated with neuropsychiatric adverse events including depression. We examined the combined effect of ART regimens on somatic (e.g. sleep/appetite disturbances) and non-somatic (e.g. sadness) depressive symptoms in women with HIV.
Methods: Women's Interagency HIV Study (WIHS) participants with ≥2 study visits after January 1st, 2014, receiving common contemporary ART regimens were divided into three groups using longitudinal Center of Epidemiology Studies Depression (CES-D) scale scores: high (CES-D >16 on >50% of WIHS visits since study enrollment), low (CES-D >16 on < 50% of WIHS visits), and no (CES-D < 16 for all WIHS visits) depressive symptoms. Novel Bayesian machine learning methods building upon a subset-tree kernel approach were developed to estimate the combined effects of ART regimen on somatic and non-somatic depressive symptoms in each group after controlling for relevant covariates.
Results: Among 1,538 women who participated in 12,924 (mean 8.4) visits, the mean age was 49.9 years; 72.4% were Black, 14.3% were Hispanic, and 72.5% had HIV RNA < 50 copies/mL at study entry. Tenofovir disoproxil fumarate (TDF) (54%) followed by tenofovir alafenamide (TAF) (20%) were the most common ART agents used; 49% received integrase inhibitors (INSTI); 33% non-nucleoside reverse transcriptase inhibitors (NNRTI); and 31%, protease inhibitors (PI). In the high-depression group, the combination of TAF with either a cobicistat-boosted INSTI or PI was associated with greater somatic symptoms (worse concentration, sleep, and motivation) while no difference was observed with TDF in these combinations (Figure 1). Moreover, in the same group, TDF combined with an NNRTI was associated with fewer somatic symptoms. ART regimens were not associated with somatic symptoms in the low- or no-depression groups, and no relationship was found between ART and non-somatic symptoms in any group.
Conclusion: Somatic depressive symptoms were observed more frequently among women who received TAF with a cobicistat-boosted INSTI or PI, but no relationship was found between depressive symptoms and TDF or un-boosted INSTIs or PIs. Our findings suggest complex associations between ART and depression, such that ART combinations rather than individual agents are associated with depressive symptoms. Future studies should consider complete drug regimens when assessing the risk of long-term neuropsychiatric complications of ART.
Combined effects of different ART regimens according to frequency on somatic depressive symptoms by group



470 DTG IMPACTS ZEBRAFISH BEHAVIOUR THROUGH DOPAMINERGIC PATHWAYS: RESCUE BY FOLATE

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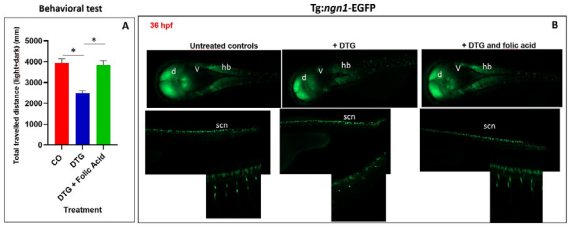
Background: Among patients who begin DTG treatment an increase in mild to severe anxiety, insomnia, depression has been observed. Little is known about the mechanisms involved in these symptoms. Zebrafish emerged as an important model for drug screening and neurological research, due to its high similarity with mammals in neuro-anatomical and behavioural features. We explored the locomotor behaviour of zebrafish embryos exposed to DTG and the possibility of a folate rescue.
Methods: Wild type and transgenic (tg:ngn1-EGFP) zebrafish embryos were exposed to 1 µM DTG with/without 5 µM folate from gastrula stage (4 hpf) up to 120 hpf. Locomotor activity was studied by analyzing wild-type larval swimming in a 2h trial period under dark/light cycling to analyze the embryos' ability to adapt to environmental stimuli. To understand the relationship between altered behaviour and CNS development, we used tg:ngn1-EGFP embryos, expressing the green fluorescent protein under the promoter regulation of ngn1, a transcription factor playing an important role in the development of dopaminergic neurons.
Results: Embryos treated with DTG had significantly reduced locomotor activity (50% reduction). Folate addition completely restored movement frequency. ngn1-driven fluorescence was evident in control embryos in CNS regions corresponding to the diencephalon (d), hindbrain (hb), ventricle (v) and the trunk region within spinal cord neurons (scn). In treated embryos, ngn1 expression was decreased and impaired in those brain areas particularly enriched with dopaminergic neurons, like (d), (v) and (h), while a consistent number of (scn)s, peripheral projections of central dopaminergic neurons, were missing, as evidenced by the fluorescence pattern. The addition of folate restored the normal phenotype.
Conclusion: The swimming behaviour of zebrafish embryos in light/dark stimuli is increasingly employed in studying neuroactive drugs. Locomotion in zebrafish is a complex behaviour produced by the activity of various neuronal pathways and its reduction upon the light/dark transition is interpreted as an anxiety state. Our results in the zebrafish embryo model show for the first time DTG effects on the dopaminergic pathways, characterized by a decrease in locomotor activity and an impaired expression of ngn1 in dopaminergic areas of the CNS and in the (scn)s of the trunk that can be rescued by folate co-administration.

Figure 1. Behavioral study and neuronal characterization in tg:ngn1-EGFP embryos.

A - Behavioral study. The graph shows mean ± SD (* $p < 0.05$) of the total distance travelled by control embryos (CO) and embryos treated with DTG 1 µM +/- 5 µM folate. The total distance, calculated during both light and dark stimuli, is expressed in mm.

B - Neuronal characterization in *tg:ngn1-EGFP* embryos. Representative images of control (CO) and treated embryos (DTG 1 µM +/- 5 µM folate) at 36 hpf. Main brain regions with dopaminergic neurons are labelled: diencephalon (d); hindbrain (hb), ventricle (v) and spinal cord neurons (scn).



471 DOLUTEGRAVIR IS ASSOCIATED WITH MORE DEPRESSIVE SYMPTOMS IN OLDER PEOPLE WITH HIV

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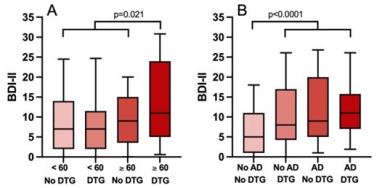
Background: Integrase strand transfer inhibitors (InSTIs) are first-line therapy in the U.S. and other countries. One InSTI drug, dolutegravir (DTG), has been linked to neuropsychiatric adverse events but few reports have used standardized assessments of depression or assessed the concomitant influence of age and antidepressant use. The aim of these analyses was to determine the relationships between InSTI use, aging, antidepressant use, and depressive symptoms in people with HIV (PWH).

Methods: All 280 participants were comprehensively assessed in the CHARTER Aging project; were taking ART; and had plasma HIV RNA ≤ 200 copies/mL. The project enrolled participants based on chronological age < or ≥ 60 years. The Beck Depression Inventory (BDI)-II and four subscales were compared to demographic characteristics, use of InSTIs and antidepressants, and clinical biomarkers in a cross-sectional design by multivariable linear regression, including backward selection by Akaike Information Criterion.

Results: Participant characteristics included median age 56 years (28.7% > 60), 18.3% female, 38.8% black, 71.7% AIDS, median CD4+ T-cells 625/µL, median duration of the current ART regimen 19.4 months, and 67.8% InSTI use. Overall, InSTI use was not associated with BDI-II but DTG use trended toward association with worse BDI-II scores (p=0.064). Multivariable analysis identified that non-black race (p=0.0033), DTG use (p=0.0042), female sex (p=0.011), antidepressant use (p=0.039), and age ≥ 60 (p=0.056) were associated with worse BDI-II scores. The effects of DTG were present in the Apathy (p=0.0027), Cognitive (p=0.019), and Somatic (p=0.020) BDI-II subscales. Interaction analyses identified that DTG was associated with worse BDI-II principally among those older than 60 years (interaction p=0.026, see Figure) and those who were not using antidepressants (interaction p=0.015).

Conclusion: DTG may increase depressive symptoms in older PWH and those who do not use an antidepressant. DTG did not worsen depressive symptoms in younger PWH or those who were taking an antidepressant. Others have reported neuropsychiatric adverse events associated with DTG but this is the first study to use a standardized depression assessment and to identify an interaction with antidepressants, which may provide mechanistic and clinical insights to improve the care of PWH.

Figure. A) DTG was associated with higher BDI-II values in people aged ≥ 60 years. B) People who did not use DTG or an antidepressant (AD) had lower BDI-II values



472 PSYCHIATRIC SYMPTOMS IN PLHIV: PREVALENCES, INTERACTIONS AND CONSEQUENCES

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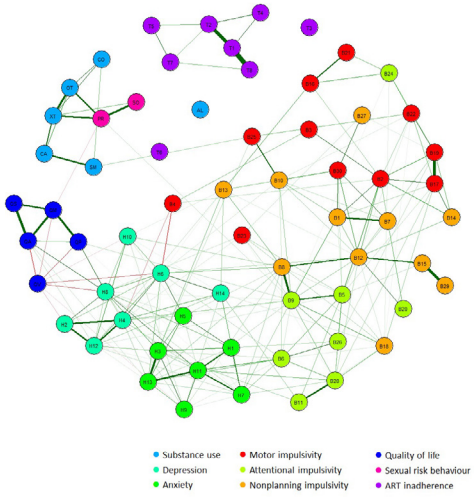
Background: Psychiatric symptoms are prevalent in PLHIV, especially depression, anxiety, impulsivity and substance use. The increased prevalence of psychiatric symptoms in PLHIV is thought to have important consequences for quality of life, sexual risk behaviour and antiretroviral treatment (ART) adherence. Both in PLHIV as well as in the general population, divergent psychiatric symptoms often co-occur, and influence one another. Network analysis allows a hypothesis-free assessment of the interrelatedness of psychiatric symptoms and their potential consequences.

Methods: Data from 1615 outpatient PLHIV using suppressive ART from the 2000HIV study (NCT03994835) were analysed. Participants reported on the severity of substance use (MATE-Q), depression and anxiety (HADS), impulsivity (BIS-11), quality of life (EQ-5D-5L), ART adherence (MASS-8) and sexual risk behaviour. For these variables, prevalence rates and mean scores were calculated. After binarizing the data, an Ising network model was constructed. Using this network, interrelations between psychiatric symptoms were assessed, the centrality of symptoms was estimated and connections with clinical consequences were explored.

Results: In our cohort of PLHIV, the increased prevalence of substance use was most pronounced, as shown by a prevalence rate of 28.7% for smoking, 13.6% for cannabis use, 11.1% for heavy alcohol drinking and 9.2% for ecstasy use in the past month. In addition, 6.1% suffered from symptoms of depression, 9.3% from anxiety, and 8.4% could be classified as highly impulsive. The network analysis revealed that symptoms of depression and anxiety were most strongly interrelated. The depressive symptom "feeling slowed down" was one of the most central symptoms, and was most strongly connected with quality of life. Substance use was associated with a higher occurrence of sexually transmitted diseases, and this relationship was mediated by a higher level of promiscuity. Notably, ART adherence did not display any connections with depression, anxiety, impulsivity or substance use.

Conclusion: The high occurrence of substance use and its link with sexual risk behaviour, emphasizes its role as an important target for prevention of HIV transmission. Contrary to general assumption, psychiatric symptoms were not associated with lower levels of ART adherence in our cohort. Treatment of depression in PLHIV might be improved by focussing on the symptom of feeling slowed down, since this symptom was most strongly connected with quality of life.

Network of symptoms of depression and anxiety (HADS), impulsivity (BIS-11), substance use (MATE-Q), quality of life (EQ-5D-5L), ART adherence (MASS-8) and sexual risk behaviour in the 2000HIV cohort.



473 SLEEP DISTURBANCES ARE ASSOCIATED WITH COGNITIVE FUNCTION IN WOMEN LIVING WITH HIV

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Background: Poor sleep quality and cognitive impairment are associated with HIV infection; however the relationship between sleep and cognition in women living with HIV (WLWH) remains underexplored. We examined associations between measures of sleep quality and domain-specific cognitive function in WLWH to identify potential modifiable factors.

Methods: In 2018 and 2019, 337 WLWH enrolled in the Women's Interagency HIV Study (WIHS) completed the Pittsburgh Sleep Quality Index [PSQI]) survey within 12 months of neuropsychological (NP) testing. Linear regression models were used to examine associations between overall sleep quality (total PSQI score 0-21; higher is worse) and NP performance stratified by study-derived cognitive impairment (global T-score < 40 vs. >40), as well as associations between specific potentially modifiable sleep disturbances (e.g., mid-sleep waking, pain, snoring), sleep duration, and sleep medication use, and NP performance. All models adjusted for enrollment site, age, education, race/ethnicity, smoking, drinking, and menopausal status; nadir CD4, log viral load, and body mass index.

Results: Poorer overall sleep quality was associated with worse NP performance among WLWH who had global NP impairment (n=102; Table 1) but not in those without impairment (n=235; P's >0.06). Among WLWH with NP impairment, poorer overall sleep quality was associated with poorer attention/working memory and processing speed; moreover, waking up mid-sleep was associated with poorer processing speed and executive function. Pain disturbing sleep was associated with poorer working memory; snoring was associated with poorer executive function; bad dreams were associated with poorer processing speed; and short (< 6 hours) and long (>8 hours) sleep duration was associated with both poorer attention and executive function.

Conclusion: We identified distinct measures of poor sleep associated with diminished working memory, attention, and executive function among WLWH demonstrating global cognitive impairment. Given that unimpaired cognition is essential for managing HIV and associated comorbidities, targeted interventions that improve these potentially modifiable aspects of sleep may prevent worsening of cognitive function as WLWH age. Larger longitudinal studies are needed to understand causal relationships and mechanisms between sleep and cognition within the context of HIV especially among women.

Results from the multivariable linear regression models examining associations between sleep and cognitive performance among cognitively impaired women living with HIV. Only neuropsychological (NP) test correlates of sleep are included.

Table 1. Results from the multivariable linear regression models examining associations between sleep and cognitive performance among cognitively impaired women living with HIV. Only neuropsychological (NP) test correlates of sleep are included.

	B (SE)									
Cognitive Domains	Fluency	Attention/Working Memory		Processing Speed			Executive Function			Motor
NP Measures	Animal Fluency	LNS Attention	LNS Working Memory	Stroop Trial 2	Trail Making Part A	SDMT	Stroop Trial 3	Trail Making Part B		Grooved Pegboard
Overall Sleep Quality	-0.0 (0.3)	**-0.6 (0.3)***	**-0.7 (0.3)***	-0.5 (0.3)	-0.2 (0.3)	**-0.5 (0.2)***	-0.5 (0.3)	-0.3 (0.3)		-0.1 (0.2)
Mid-sleep waking	-0.0 (2.2)	-0.7 (2.2)	-0.2 (2.3)	**-7.1 (2.4)****	**-4.1 (2.1)***	-2.3 (2.0)	-1.9 (2.3)	**-6.0 (2.3)***		1.5 (1.7)
Bathroom usage	0.6 (2.4)	-2.5 (2.2)	-3.8 (2.3)	-0.0 (2.7)	-1.5 (2.3)	-2.0 (2.1)	0.9 (2.5)	0.9 (2.5)		2.7 (1.8)
Trouble breathing	-1.9 (2.9)	0.7 (3.0)	-3.4 (3.0)	**-6.7 (3.2)***	0.0 (2.8)	-1.7 (2.6)	-5.9 (3.2)	-1.4 (3.2)		-0.2 (2.2)
Pain	-3.4 (2.7)	-2.2 (2. 6)	**-6.4 (2.6)***	-3.1 (3.1)	1.6 (2.6)	-2.5 (2.5)	-3.6 (2.9)	-3.9 (3.0)		-1.1 (2.1)
Snoring	0.2 (2.8)	-1.1 (2. 6)	-3.1 (2.7)	-3.5 (3.1)	0.5 (2.6)	-3.1 (2.5)	**-5.7 (2.8)***	-3.2 (2.7)		2.3 (2.1)
Feeling Cold	1.3 (3.0)	-1.8 (3.0)	-5.7 (3.1)	-3.5 (3.4)	-4.1 (2.8)	-4.3 (2.6)	-1.6 (3.1)	**-7.5 (2.9)***		1.2 (2.3)
Feeling Hot	-3.4 (2.4)	-3.5 (2.3)	-3.2 (2.5)	-1.4 (2.8)	-0.5 (2.3)	-3.2 (2.2)	-3.9 (2.5)	-2.8 (2.5)		0.6 (1.9)
Needs sleep medications										
Less than once a week	*Referent*									
Not during the past month	5.2 (3.9)	-5.1 (3.9)	5.6 (4.2)	**1.2 (4.5)***	2.8 (3.8)	**7.8 (3.7)***	-0.7 (4.7)	1.7 (4.4)		-2.2 (3.0)
Once or twice a week	**1.6 (4.9)****	0.3 (4.9)	7.2 (5.1)	**1.8 (5.6)****	7.9 (4.7)	8.2 (4.6)	3.8 (5.7)	4.4 (5.6)		-2.2 (4.0)
Three or more times a week	4.3 (4.4)	-4.3 (4.6)	3.8 (4.8)	7.1 (5.1)	-3.7 (4.3)	4.2 (4.2)	-1.8 (5.4)	-0.4 (5.0)		**-7.3 (3.6)***
Sleep Duration										
6-8 hours	*Referent*									
<6 hours	3.0 (2.7)	**-7.5 (2.3)****	-3.0 (2.6)	-0.6 (3.1)	-3.2 (2.5)	-0.8 (2.4)	-3.8 (2.7)	-0.3 (2.8)		-3.2 (2.0)
>8 hours	3.1 (3.6)	1.4 (3.1)	-4.4 (3.8)	-5.7 (4.1)	-6.6 (3.3)	-6.0 (3.2)	**-10 (3.7)****	-4.4 (4.2)		-3.5 (2.8)

Note. *p<0.05; **p<0.01; ***p<0.001; B=unstandardized beta coefficient; SE=standard error; LNS=Letter-Number Sequencing; SDMT=Symbol Digit Modalities

474 BIOPSYCHOSOCIAL PHENOTYPES IN PEOPLE WITH HIV IN THE CHARTER COHORT

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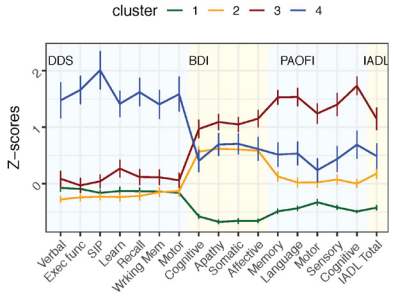
Background: Neuropsychiatric complications such as neurocognitive (NC) impairment (NCI) and depression are common in people with HIV (PWH) despite viral suppression on antiretroviral therapy (ART), but these conditions are heterogeneous in their clinical presentations and associated disability. Identifying novel biopsychosocial (BPS) phenotypes that account for NC performance, depressive symptoms, and daily functioning will promote better understanding of interplay between these conditions.

Methods: We classified 1,580 PWH based on 17 BPS features, including 7 cognitive domains (deficit scores, DDS), 4 subscales of the Beck Depression Inventory-II (BDI-II), 5 components of the Patient's Assessment of Own Functioning Inventory (PAOFI), and 1 total score of dependence in instrumental activities of daily living (IADLs). A two-stage clustering procedure composed of self-organizing maps (SOM) and k-means clustering algorithms was applied to cross-sectional data. Cluster stability was assessed with adjusted Rand index (ARI) and Cramer's V. Demographic and clinical characteristics were compared between the clusters using one-way ANOVA and chi-square test for continuous and categorical data respectively.

Results: Four distinct phenotypes were identified: 1) a healthy group (Cluster 1, n=831), 2) a group with mild-to-moderate depression (Cluster 2, n=443), 3) a group with mild cognitive impairment, moderate-to-severe depression, and very impaired daily functioning (Cluster 3, n=191), and 4) a very cognitively impaired group (Cluster 4, n=115) (see Figure 1). Compared to the healthy group (Cluster 1), Cluster 2 had higher proportions of lifetime cannabis and any substance use disorders (p=.008 and .003 respectively); Cluster 3 had a higher proportion of females (34.0% vs. 19.6%, p< .001); Cluster 4 had higher proportions of Hispanic and White people. In Cluster 1, depression was three times more common in participants with both NCI and self-reported cognitive symptoms than among in those without either NCI or symptoms (18.2% vs. 5.72%, p< .001). All participants in Cluster 4 had NCI, but those with self-reported symptoms had much higher proportion of depression than those without symptoms (80.6% vs. 31.8%, p< .001).

Conclusion: We found complex, multidimensional BPS profiles in PWH that were associated with different patterns of risk factors. Future longitudinal work should determine the stability of these phenotypes and consider factors that may influence PWH change from one phenotype to another.

Figure 1. Profile plot of clusters on the features. Error bars represent the 95% confidence interval at each feature.



475 SEX-SPECIFIC ASSOCIATION BETWEEN IL-6 AND DEPRESSION IN PERSONS WITH AND WITHOUT HIV

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Background: Persons with HIV (PWH) have elevated prevalence of depression compared to persons without HIV (PWoH), and elevated plasma inflammatory biomarkers. Inflammation and depressive symptoms are known to be linked, including in PWH; however, it is unclear whether these associations differ by HIV serostatus and biological sex.

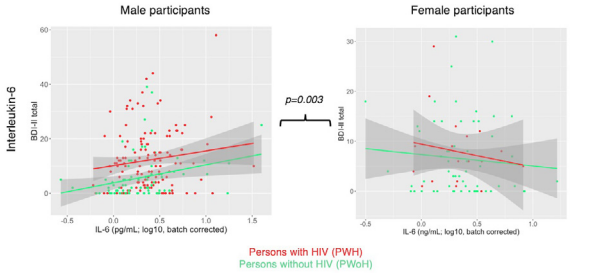
Methods: Six plasma inflammatory biomarkers were assessed using samples from PWH (n=150; age=48.4±13.0 yr.; 88% biologically male) and PWoH (n=138; age=47.8±13.8; 56% male) who participated in six NIH-funded studies through the UCSD HIV Neurobehavioral Research Program (HNRP) from 2011 to 2019. Factor analysis was performed to identify intercorrelated groups of biomarkers. Factors and their components were examined for relationships with Beck Depression Inventory-II (BDI-II) and modifying effects of sex or HIV

serostatus using multivariable linear regression, adjusting for demographics, substance use diagnoses, and relevant co-morbidities.

Results: BDI-II scores were elevated in PWH compared to PWoH (11.7±10.8 vs. 6.2±8.0; p< 0.0001). Two inflammatory factors were identified: Factor 1 loaded on interleukin-6 (IL-6), C-reactive protein (CRP), and D-dimer; Factor 2 loaded on IL-8, chemokine C-C ligand 2 (CCL2), and chemokine C-X-C ligand 10 (CXCL10). Sex modified the effect of Factor 1 on BDI-II, with a more positive association for men than women (p=0.041). No significant association between Factor 2 and BDI-II was found. Of the biomarkers in Factor 1, only IL-6 was significantly associated with BDI-II and was modified by sex (p=0.003). In sex-stratified analysis, a positive IL-6 vs. BDI-II association was found for men (β=5.42; 95% confidence interval=[1.32, 9.52]) but not women (β=-3.88; 95% C.I.=[-11.02, 3.26]). No HIV-related interactions were detected (see Figure).

Conclusion: We identified a depression-associated inflammatory factor present in both PWH and PWoH, consistent with smaller studies of PWH only. The association was driven by a correlation of IL-6 and depression exclusively in men, suggesting that the depression-inflammation link differs by sex. Although associations did not differ by HIV serostatus, PWH may nonetheless be at greater risk for depression in part due to elevated chronic inflammation.

Sex-stratified associations between interleukin-6 (IL-6) and Beck Depression Inventory-II total score, by HIV serostatus.



476 (NEURO)INFLAMMATORY BIOMARKERS MEDIATE THE ASSOCIATION BETWEEN HIV AND DEPRESSION

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COmorBidity in Relation to AIDS (COBRA) cohort
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Background: People with HIV are at increased risk for depression, though the underlying mechanisms for this are unclear. In the general population, depression is associated with peripheral and central inflammation. Since HIV infection may elicit (neuro)inflammation, we hypothesised that (neuro) inflammatory biomarkers would mediate the association between HIV and depression.

Methods: People with and without HIV in the COmorBidity in Relation to AIDS (COBRA) cohort were included. Using logistic regression, we investigated the possible mediating roles of (neuro)inflammatory biomarkers (neuroimaging, blood, and CSF) on the relationship between HIV status and Any Depression (Patient Health Questionnaire [PHQ-9] scores > 4). We considered changes in the Odds Ratio for Any Depression (OR, adjusted for age, sex, ethnicity, and years of education), before and after adjusting for each biomarker separately. All analyses accounted for varying sample sizes. Biomarkers resulting in >10% reduction in OR were considered potential mediators.

Results: We included 204 participants (125 with HIV, 79 without HIV, median [interquartile range (IQR)] age 57 years [51-62], 93% male, 92% White) with PHQ-9 score and at least one biomarker available. Both groups had similar baseline characteristics. All people with HIV were on antiretroviral therapy and had HIV-RNA viral load < 200 copies/mL. The prevalence of Any Depression was significantly higher amongst participants with HIV than those without HIV (26.4% vs 11.4%, p = 0.02). The OR (95% confidence interval) for Any Depression in the full sample (N = 204), adjusted for sociodemographic factors but before adjusting for biomarkers, was 3.27 (1.46, 8.09). Of the biomarkers analysed, plasma MIG (-15.0%), plasma TNF-α (-11.4%), CSF MIP1-α (-21.0%), and CSF IL-6 (-18.0%) met our criteria for >10% reduction in OR associated with HIV status for Any Depression.

Conclusion: In this sample, MIG and TNF-α in plasma, and MIP1-α and IL-6 in CSF mediated the association between HIV status and depression. As these biomarkers are hallmarks of inflammation (IL-6, TNF-α) and chemotaxis (MIP1-α, MIG), our results implicate different processes constituting (neuro) inflammation in the risk for depression in people with HIV. We did not observe notable attenuation by the neuroimaging biomarkers, suggesting that this mediation may be peripherally driven. Given the lack of gender and ethnic diversity in this cohort, larger and more diverse datasets are needed to extend these findings.

Table 1. OR (with 95% CI) for the association between HIV status and Any Depression, before and after adjustment for each biomarker fitted separately, and percentage change in OR from each model.

Biomarker	*N*	*N* Any Depression	Odds Ratio (95% CI) Adjusted for HIV status and sociodemographic factors: Before adjusting for biomarker	Adjusted for biomarker	% Change in OR
Neurometabolites*					
Myo-inositol					
White matter	161	29	2.96 (1.12, 9.13)	3.23 (1.19, 10.15)	9.1
Putamen	63	20	3.19 (1.32, 27.63)	3.35 (1.35, 30.35)	6.9
Choline-containing compounds					
White matter	184	36	2.75 (1.17, 7.20)	2.91 (1.21, 7.74)	5.8
Putamen	128	29	7.46 (2.26, 35.53)	8.54 (2.50, 41.47)	14.5
Circulating biomarkers *(measured in all participants, where possible)*					
Plasma					
CRP	204	42	3.27 (1.46, 8.09)	3.05 (1.34, 7.61)	-6.7
I-FABP	202	41	3.81 (1.65, 9.91)	3.98 (1.62, 10.86)	4.5
KynTrp	203	41	3.76 (1.63, 9.78)	3.63 (1.54, 9.39)	-3.5
Neopterin	203	41	3.76 (1.63, 9.78)	3.50 (1.44, 9.45)	-6.9
NFL	202	41	3.16 (1.41, 7.80)	2.94 (1.29, 7.31)	-7.0
sCD14	201	40	3.01 (1.34, 7.40)	3.22 (1.39, 8.20)	7.0
sCD16	202	42	3.36 (1.50, 8.30)	3.27 (1.44, 8.18)	-2.7
sCD163	204	42	3.27 (1.46, 8.09)	3.62 (1.59, 9.11)	10.7
CSF					
KynTrp	202	41	3.07 (1.37, 7.57)	3.04 (1.34, 7.62)	-1.0
Neopterin	202	41	3.07 (1.37, 7.57)	2.84 (1.25, 7.11)	-7.5
sCD14	202	41	3.08 (1.38, 7.62)	3.14 (1.39, 7.78)	1.9
sCD163	203	41	3.13 (1.40, 7.72)	3.28 (1.46, 8.13)	4.8
Circulating biomarkers *(measured in a subset of 78 participants)*					
Plasma					
IL-6	78	13	1.67 (0.46, 6.58)	1.51 (0.40, 6.01)	-9.6
IP-10 / CXCL10	78	13	1.67 (0.46, 6.58)	1.68 (0.45, 6.66)	0.6
MCP-1 / CCL2	78	13	1.67 (0.46, 6.58)	1.67 (0.46, 6.59)	0.0
MIG / CXCL9	78	13	1.67 (0.46, 6.58)	1.42 (0.38, 5.62)	-15.0
MIP1α / CCL3	78	13	1.67 (0.46, 6.58)	1.74 (0.47, 7.00)	4.2
RANTES / CCL5	78	13	1.67 (0.46, 6.58)	1.55 (0.41, 6.20)	-7.2
TNF-α	78	13	1.67 (0.46, 6.58)	1.48 (0.39, 5.98)	-11.4
CSF					
IL-6	78	13	1.67 (0.46, 6.58)	1.37 (0.35, 5.59)	-18.0
IP-10 / CXCL10	78	13	1.67 (0.46, 6.58)	1.75 (0.46, 7.16)	4.8
MCP-1 / CCL2	78	13	1.67 (0.46, 6.58)	1.67 (0.45, 6.58)	0.0
MIG / CXCL9	78	13	1.67 (0.46, 6.58)	1.66 (0.45, 6.58)	-0.6
MIP1α / CCL3	78	13	1.67 (0.46, 6.58)	1.32 (0.35, 5.26)	-21.0
RANTES / CCL5	78	13	1.67 (0.46, 6.58)	1.64 (0.45, 6.47)	-1.8
TNF-α	78	13	1.67 (0.46, 6.58)	1.83 (0.49, 7.31)	9.6

* Models involving neurometabolite measures were also corrected for scanner. All analyses accounted for varying sample sizes for each biomarker.

477 ESTABLISHMENT OF HIV LATENCY AND MICROGLIOSIS IN PRIMARY HUMAN MICROGLIA CELLS

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Background: In the brain, microglia are susceptible to HIV infection and can maintain the viral reservoir. Analysis of HIV latently infected microglia cells at a single-cell level is technically challenging and our understanding of the molecular mechanisms of latency establishment in microglia remains incomplete.

Methods: We used pMorpheus-EGFP, a dual-reporter HIV construct, to examine latency establishment in microglia cells isolated from eleven post-mortem human brains. pMorpheus-EGFP encodes reporters whose expression is either HIV LTR-dependent (i.e., HSA and Cherry) or independent (i.e., EGFP). Single cycle viruses were pseudotyped with a dual-tropic HIV Env or with VSV-G envelope. Infection of primary human microglia cells were monitored for up to 50 days. We determined the number of productively and latently infected cells by microscopy and by flow cytometry. Proximity extension assay by Olink was used to measure >90 distinct immune-modulatory protein markers in culture supernatants.

Results: In contrast to infection of CD4+ T-cells, we found that infection with pMorpheus-EGFP resulted in rapid and sustained proliferation of microglia cells (microgliosis). Our results indicate that LTR-silent and LTR-active cells are present from the beginning of the infection, with latently infected cells making up between 7% and 40% of all infected cells. Latently infected cells persisted for > 50 days while active infection was silenced within 30 days of infection. We identified growth factors, cytokines, and chemokines up-regulated upon infection providing information on the mechanism driving microgliosis.

Conclusion: Taken together, our findings indicate that infection of primary human microglial cells creates a reservoir of latently infected cells by driving cell proliferation. If confirmed within the CNS, this "self-renewing" viral reservoir

could contribute to HIV-associated Neurocognitive Disorder (HAND). Treatment would likely require interventions to curb infected cell expansion in addition to limiting productive infections using HAART.

478 REBOUND HIV-1 IN CSF AFTER TI IS DOMINATED BY CLONALLY AMPLIFIED T CELL-TROPIC VIRUS

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Background: HIV-1 persists during suppressive antiretroviral therapy (ART) as a latent reservoir but reappears with treatment interruption (TI). In the absence of ART most viral replication takes place within the lymphoid system, although HIV-1 can be detected in cerebrospinal fluid (CSF). Most of what is known about the latent reservoir is based on studies of cells from peripheral blood and less is known about reservoirs in the central nervous system (CNS).

Methods: In this study we compare rebound virus in archived blood and CSF longitudinally sampled from 11 participants after TI to look for evidence of a distinct reservoir within the CNS. Single genome amplification (SGA) and/or Illumina MiSeq deep sequencing with Primer ID were used to assess env diversity and drug resistance in pro-pol. Full-length env genes were cloned from the rebound virus of 4 participants and assessed for their ability to efficiently enter cells with a low surface density of CD4 (a proxy for macrophage tropism; M-tropism).

Results: TI occurred a median of 12 years after HIV diagnosis and participants had a median nadir CD4 count of 117 cells/ul. Five participants were suppressed in the blood plasma at the time of TI while 7 participants were viremic. Multiple viral lineages were present in the blood at all time points analyzed after TI. When the CSF lacked pleocytosis (≤5 WBC/ul), virus in the CSF and blood were genetically mixed and the CSF viral load (VL) was much lower than the plasma VL. At time points with CSF pleocytosis (>5 WBC/ul), CSF VL reached levels similar to the plasma VL and virus in the CSF was largely clonal. In all participants examined (N=4), CSF rebound virus was adapted to entering CD4+ T cells rather than macrophage (R5 T cell-tropic).

Conclusion: These results are consistent with a model in which the virus first released after TI in the blood and in the CSF comes from infected T cells. These latently infected T cells, either resident to the CNS or entering from the blood, can proliferate in the CNS and contribute to rebound virus in the compartment. We did not find evidence of M-tropic lineages emerging in the CNS during TI, even in one case where a M-tropic virus was present in the CNS pre-therapy.

479 IMPACT OF IL-15 NEUTRALIZATION ON CNS PATHOGENESIS IN ACUTE HIV/SIV INFECTION

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Background: Immune responses mounted in the CNS during acute HIV/SIV infection are insufficient to prevent viral seeding and reservoir establishment. The pleiotropic cytokine IL-15 plays a crucial role in anti-viral immune response by stimulating NK and CD8+ T cells to control HIV/SIV infection in blood and tissues. However, the effects of IL-15 on the CNS are largely unknown. Experimental neutralization of IL-15, leading to the depletion of NK and T cells, could significantly influence the viral pathogenesis in the brain, alter reservoir formation, and clarify the role of IL-15 in lentivirus disease. We comprehensively evaluated brain immune and inflammatory responses to acute SIV infection with and without IL-15 neutralization in an established nonhuman primate model.

Methods: Rhesus macaques(*Macaca mulatta*) were administered two doses of rhesusized monoclonal antibodies against IL-15(anti-mRh-IL-15) at days -21 and -7 prior to challenge with SIVmac239X(day 0) and necropsied at 7 and 14 days post-infection(dpi). A control group did not receive anti-mRh-IL-15. Peripheral and brain viral load were quantified by qPCR and RNAscope. Sequencing analysis of viral clones were obtained from several brain regions and compared to those in blood and peripheral lymph nodes. CNS histopathology were analyzed by immunohistochemistry in combination with *in situ* hybridization. Transcriptomic analyses were performed on brain tissue.

Results: While anti-mRh-IL-15 treatment depleted NK cells from blood and increased virus replication, there was no significant differences in the quantities of SIV RNA or DNA in the brain on either 7 and 14 dpi. Barcoded virus detected in the blood and brain showed clonal expansion restricted to anatomical brain regions. For brain resident cells, peripheral neutralization of IL-15 resulted in increased microglial activation with infection, but decreased the number of astrocytes. While blood T cells were unaltered with IL-15 neutralization, CD8+ T cells decreased in brain, which may have led to an altered balance of local pro- and anti-inflammatory responses, where significantly fewer microglia cells expressed the proinflammatory cytokine – IL-6, and higher numbers of macrophages expressed the anti-inflammatory cytokine- TGF-β.

Conclusion: IL-15 neutralization altered CNS immune and inflammatory responses to acute SIV infection by decreasing CD8+ T cells and resulting in a tissue environment favoring anti-inflammation, which could overall support the establishment of viral reservoir.

480 A FRESH SINGLE-CELL STUDY DETECTS MULTI-COMPARTMENT PERSISTENT HIV RNA DESPITE ART

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SEARCH013/RV304 study group

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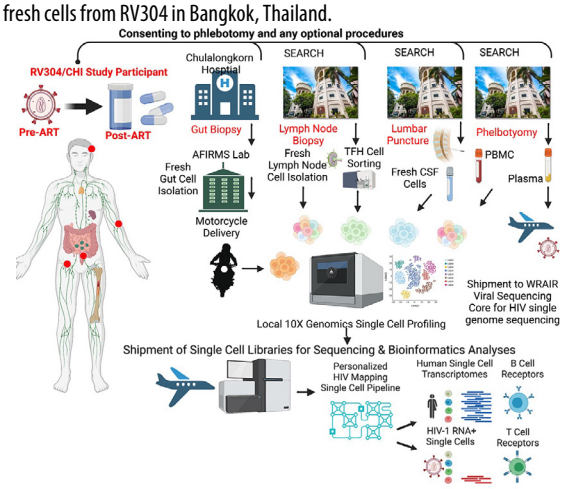
Background: Single cell methods enhance the resolution at which infected cells in blood and tissues can be studied in people with HIV (PWH). Capturing the native state of infected cells obtained from multiple tissue compartments, especially cells in the cerebrospinal fluid (CSF), while minimizing cell loss from cryopreservation remains a challenge, especially in resource limited settings.

Methods: Fresh blood, CSF, gut, lymph node (LN) and cell-sorted T follicular helper (TFH) cells were collected from participants enrolled in the RV304/SEARCH013 study enrolling people with chronic HIV (PWCH) in Bangkok, Thailand where uptake of optional procedures including leukapheresis, lumbar puncture (LP), gut biopsy, and lymph node (LN) biopsy is high. Longitudinal fresh samples from 4 compartments were collected from one PWH at baseline (ART naïve) and after 32 months of ART. An aliquot of baseline CSF cells were set aside and frozen for separate analysis. We used the 10X genomics platform locally to generate single cell RNA and T-cell/B-cell receptor data from fresh cells within hours of sampling and from frozen CSF cells.

Results: Single cell data were generated for 18,790 CSF cells, 18,341 gut cells, 37,055 LN cells, 11,561 TFH cells, and 23,349 blood cells. To enhance detection of HIV viral transcripts pre-ART, we generated autologous near full-length patched viral sequences from pre-ART plasma to align single cell sequencing reads and detected high and low HIV transcript containing cells in all compartments pre-ART. Despite 32 months of suppressive ART, transcriptionally active HIV-infected cells were present in all 4 compartments at single cell resolution, including the CNS, predominately in memory CD4 T cells. Notably, single cell comparisons of fresh (9,603 cells) versus frozen CSF cells (9,187 cells) revealed a significant loss of infected HIV cells in CSF after cryopreservation. T cell clonotypes were shared across CSF, gut, LN, and blood compartments; however, the observed HIV transcript containing cell clones were all unique pre-ART.

Conclusion: Longitudinal multi-compartment studies of fresh cells indicate presence of transcriptionally active HIV in several compartments. In CNS, sensitivity was markedly greater in fresh compared to cryopreserved cells. Future studies should evaluate whether HIV-infected cells from diverse tissue sites may be sensitive to cryopreservation, potentially leading to an inaccurate representation of the viral reservoir.

Logistics and workflow of longitudinal multi- compartment single cell study of fresh cells from RV304 in Bangkok, Thailand.



481 INTERACTIONS BETWEEN GUT MICROBIOTA SIGNATURES AND CNS STATUS IN A HIV CURE STRATEGY

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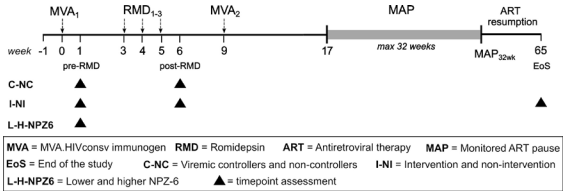
Background: The microbiome-gut-brain axis interplay is a major player in regulating the CNS status. In a substudy from the BCN02 trial, pro-inflammatory microbial signatures were identified as potential predictors of immune-mediated HIV-1 control in the absence of ART. Assessments from a BCN02 substudy investigating the CNS safety of using the histone deacetylase inhibitor romidepsin (RMD) showed no significant changes in neurocognitive and functional outcomes over the intervention. Here, we investigated possible interactions between the gut microbiota and CNS status in the BCN02 HIV vaccine strategy.

Methods: Associations between microbial abundance (shotgun metagenomics), global neurocognitive functioning (NPZ-6) and functional outcomes (CNS-related symptoms, emotional status, daily functioning, and quality of life) were assessed in 2 subgroups from the BCN02 trial (intervention scheme shown in Figure): (i) HIV-1 viremic controllers and non-controllers (C-NC, n=11) and (ii) intervention and non-intervention (I-NI, n=16) at different timepoints (Figure). Spearman's correlations and BH-adjusted p-values (≤0.05) were measured by R/rcorr. Gut microbiota profiling in subjects with lower (NPZ-6< -0.5; n=3) and higher (NPZ-6 >-0.5; n=15) global neurocognitive functioning at pre-RMD was performed using R/phyloseq.

Results: In the C-NC subgroup, Clostridiales, Methanosphaera stadtmanae and Methanobrevibacter unclassified positively correlated with NPZ-6. Such associations were also observed in the I-NI subgroup, in which methanogenic archaea (Methanosphaera and Methanobrevibacter) as well as short fatty acids (SCFAs)-producing bacterial genera (Megasphaera and Phascolarctobacterium) positively correlated with NPZ-6. Bacteria associated with CNS disorders in previous reports, including Sutterella and Desulfovibrio spp. positively correlated with emotional status (depression, anxiety and perceived stress) and negatively with quality of life and NPZ-6. No discernable longitudinal trends were observed in the 2 subgroups. The gut microbiota of subjects with lower NPZ-6 was enriched in brain disorder-associated bacteria and related functions such as S. wadsworthensis and D. desulfuricans (α< 0.05,LDA >2.0) and 1,2-propanediol degradation pathway.

Conclusion: Neurocognitive functioning positively associates with anti-inflammatory gut methanogenic archaea and SCFAs-producing bacteria in a HIV cure strategy. CNS disruption-associated bacteria are increased in individuals with lower global neurocognitive functioning.

BCN02 intervention scheme



482 ASTROCYTES-MICROGLIA CROSSTALK: HOMEOSTATIC MODULATION OF HIV EXPRESSION IN MICROGLIA

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Background: The brain cells crosstalk involves a wide range of signaling pathways that can affect gene transcription. We have previously shown that neurons-microglia crosstalk regulates HIV expression in microglia cells. Since the astrocytes are essential homeostatic and immune cells in the brain, we expanded our work to explore the astrocyte-microglia crosstalk in the context of HIV infection. We hypothesize that astrocytes-released factors can regulate microglia activation and therefore silence HIV in infected microglia.

Methods: We used Pluripotent Stem cells (iPSC) derived astrocytes (iA) and the HIV-latently infected microglia cell line HC69 to identify astrocytes soluble factors regulating HIV. This microglia cell line is an HIV-latently infected clone with a single round HIV-1 containing a short-lived GFP. Cell tracing marked HC69 cells were co-cultured with iA for 24 hours. GFP expression was determined by microscopy and cytometry analysis. HC69 were also treated with increasing concentration of possible iA-released factors (ATP, BDNF, GDNF, IL10). Coculture of iA and iPSC-microglia (iMG) was stablished to confirm the results obtained with HC69. iMG was also infected with the same HIV provirus expressing GFP. Triculture of iA, iPSC-neurons (iN) and iMG was used to confirm regulatory activity of brain cells over HIV-infected microglia.

Results: iA-microglia cocultures showed a significant reduction of HIV expression in microglia cells. We identified that astrocytes-released ATP as responsible for such reduction. Since astrocytes-released ATP can be catabolized to adenosine by CD73, we blocked the CD73 activity with a specific inhibitor (AB-680). The ATP regulatory effect on HIV expression was then diminished, suggesting the effect was indeed due to adenosine and not by ATP itself. Same effect was observed when AB-680 was added to the iA-microglia cocultures. We also observed that low concentrations of ATP (0.5 to 5 mM) would activate the virus. However, with concentrations higher than 10 mM a clear reduction of HIV expression was observed.

Conclusion: iA-iMG coculture and iA-iMG-iN triculture showed that there are in the brain regulatory/homeostatic mechanisms that could be explored to reduce inflammation and HIV expression in infected cells. As our data suggests, one of those mechanisms could be related to ATP/Adenosine. Finally, our results support the importance of studying the crosstalk among different brain cell types to identify possible therapeutic targets.

483 CSF COMPLEMENT IS CORRELATED TO IMMUNE ACTIVATION IN UNTREATED BUT NOT TREATED HIV

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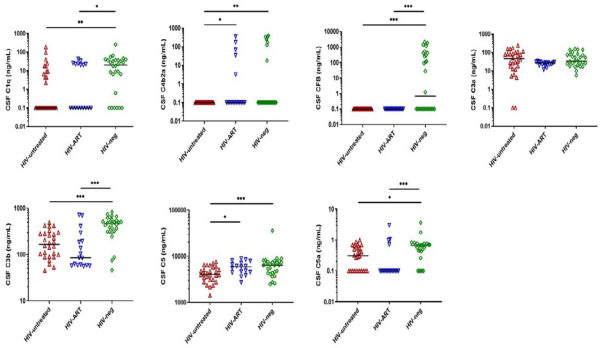
Background: Antiretroviral therapy (ART) has substantially reduced the risk for serious central nervous system (CNS) complications in chronic HIV infection, but milder forms of neurocognitive impairment have been described in people living with HIV (PLWH) using ART. Intrathecal immune activation is a key component in HIV-associated CNS injury in advanced untreated infection, while the importance of the residual, low grade CNS inflammation seen during ART is less clear. The immune activation is initiated by the virus, but secondary immunological mechanisms may contribute to the inflammatory process. The complement system is involved in the pathogenesis of other inflammatory CNS conditions, but the importance in HIV-associated CNS infection, as well as the potential impact of ART is less well characterized. The aim of this study was to explore evidence of complement activation in CSF in untreated HIV infection and in PLWH on ART.

Methods: Retrospective cross-sectional study including PLWH on (HIV-ART) or off (HIV-untreated) ART monitored in a standardized CSF sampling protocol, and 28 HIV-negative controls (no evidence of CNS infection in clinical lumbar puncture). Complement factor B (CFB), C1q, C3a, C4b2a, C5, C5a and C3b was analyzed by commercial ELISA (complement) or immunoassay (neopterin). CSF NfL was analyzed by in-house ELISA.

Results: Forty-five (26 male) PLWH (were included in the study; 17 (9 male) were on ART (plasma HIV-RNA < 20 copies/mL). Significant differences in CSF complement concentrations were seen between HIV-untreated and controls in C1q (p=.004), C4b2a (p=.003), CFB (p=< .001), C3b (p=< .001), C5 (p=.001) and C5a (p=.02), but not C3a (p=.3), between HIV-ART and controls for C1q (p=.05), CFB (p=< .001), C3b (p=< .001) and C5a (p=< .001), and between HIV-untreated and HIV-ART for C4b2a (p=.03), C5 (p=.02). CSF neopterin was significantly correlated to C1q (r=.63; p< .001), C3b (r=.47; p=.01) and C5 (r=.56; p=.002) in PLWH without, but not on, ART.

Conclusion: Different patterns were found in PLWH compared to controls in CSF complement activity in all activation pathways (classic, alternative, lectin) as well as the terminal cascade. Correlation to macrophage/microglial activation was seem only in untreated PLWH. ART appeared to reduce, but not eliminate, complement activity in CSF. Although the clinical significance of residual intrathecal immune activation needs further study, complement activity may potentially contribute to the CNS pathogenesis in HIV.

CSF complement factor concentrations



484 LONGITUDINAL ASSESSMENT OF GRAPH THEORY MEASURES IN EARLY HIV INFECTION

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Background: Advanced imaging techniques have shown that the brain is comprised of complex networks that work together to support function. Graph theory adapted for neuroscience allows researchers to quantitatively assess connectivity and derive biologically meaningful brain network metrics. In this study, we use resting state functional connectivity with graph theory to evaluate participants in early HIV infection to investigate network changes over the first two years.

Methods: Data from the Chicago Early HIV Infection study was used for this analysis. The cohort included 45 HIV+ (42M, 3F, mean age 32.9 +/- 10.6 years, 30 ART naïve, 26 on ART) and 17 seronegative controls (14M, 3F, mean age 31.2 +/- 8.5 years) at baseline. Follow-up data was collected 26.8 +/- 10 months later in 42 HIV+ and 15 seronegative controls. Resting state fMRI data was collected on a 3T Siemens Trio scanner (TR/TE/resolution = 2.5 s/20 ms/1.7x1.7x3 mm3, 235 volumes, 40 slices). After standard preprocessing using FMRIPREP and ICA-based AROMA, RS-FMRI data was spatially normalized to the ICBM 152 Nonlinear Asymmetrical template and smoothed by 4mm FWHM. Average signal from 116 regions of interest (ROI) of the AAL template were extracted and used to calculate graph theory metrics. Global network metrics were averaged over all 116 ROIs and compared between groups using t-tests at each timepoint.

Results: Table 1 shows the mean ± stdev of the global network metrics for the early HIV+ and control groups at baseline and follow-up. Path length for the HIV+ group was significantly longer than for the control group both at baseline and follow-up (* denotes p< 0.001). Other network metrics for the HIV+ group follow a similar finding of network disruption (e.g. decreased strength, global efficiency and clustering coefficient, increased modularity) compared to the control group.

Conclusion: We found significantly longer path length in HIV patients compared to healthy controls at both baseline and two-year follow-up. Path length, which represents the shortest distance between two nodes, is frequently used as a measure for network integration. Our results demonstrate that network efficiency is affected during the early period of HIV infection and that this continues to worsen with infection duration. These findings may provide insight into the development of HIV associated neurocognitive disorder in virally suppressed HIV patients.

Table 1: Global network metrics at baseline and follow-up for HIV and control groups. (mean +/- standard deviation. * denotes p<0.001)

Network Metric	Baseline		Follow-up	
	Control (n=17)	HIV (n=44)	Control (n=16)	HIV (n=41)
Clustering Coefficient	0.4510 ± 0.0519	0.4407 ± 0.0481	0.4143 ± 0.0529	0.4250 ± 0.0565
Path Length*	0.4286 ± 0.0010	0.4692 ± 3.9723e-04	0.4606 ± 6.2299e-04	0.5107 ± 2.4045e-04
Strength	55.28 ± 7.84	54.42 ± 7.19	51.75 ± 7.78	53.31 ± 8.20
Global Efficiency	0.0781 ± 0.1744	0.0579 ± 0.1014	0.0619 ± 0.1153	0.0289 ± 0.0681
Modularity	0.0933 ± 0.0558	0.0989 ± 0.0375	0.1127 ± 0.0531	0.1187 ± 0.0604
Assortativity	-0.0090 ± 0.0210	-0.0076 ± 0.0195	-0.0061 ± 0.0283	0.0028 ± 0.0559

485 SINGLE-COPY HIV AND NEURODEGENERATION, OXIDATIVE STRESS, AND NEUROINFLAMMATION

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Background: HIV is not eradicated by antiretroviral therapy (ART) and resides in multiple sanctuaries, including the central nervous system (CNS). Single copy assays (SCAs) detect HIV at very low levels, but the implications of full suppression by SCA are unclear. Prior research has shown that HIV RNA can be detected in cerebrospinal fluid (CSF) by SCA during suppressive ART.

Methods: Comprehensive evaluation of CHARTER Aging cohort participants included neuropsychiatric assessment and biospecimen collection. SCA was performed in those on ART with HIV RNA < 50 copies/mL in blood (n=69) and CSF (n=50). Neopterin, C-reactive protein (CRP), interleukin (IL)-6, CCL2, soluble tumor necrosis factor receptor (sTNFR)-II, neurofilament light chain (NFL), amyloid β1-42 (Aβ42), soluble amyloid precursor protein (sAPP), total Tau, 8-OH-deoxyguanosine(dG), D-dimer, and protein carbonyls were also measured. Backwards stepwise regression assessed relationships between single copy suppression (SCS+, denoting undetectable on SCA) and biomarkers, cognition, and depressive symptoms. Candidate covariables included age, sex, race, ethnicity, current CD4+ T-cells, estimated duration of HIV (eDoH), and ART drugs. The False Discovery Rate (FDR) method accounted for type I error.

Results: Participant characteristics: median age 56 years, 78%men, 36% black, median eDOH 24 years, and median CD4+ T-cell count 586/μL. 39% were SCS+ in plasma and 48% were SCS+ in CSF. There were no significant differences in biomarker results based on sex. Plasma and CSF SCS+ were each associated with lower Aβ42 (CSF and plasma), higher 8-OHdG (plasma and CSF), higher IL-6 (CSF), and higher total Tau (CSF), see table for CSF SCS results. Plasma SCS+ was also associated with higher plasma protein carbonyls, while CSF SCS+ was also associated with higher CSF sTNFR-II, lower CSF CCL2, and lower plasma D-dimer. CSF SCS+ was associated with more depressive symptoms (P=0.005), but there was no significant association between cognitive performance and SCS in either fluid. Use of tenofovir alafenamide (P=0.0031) or abacavir (P=0.0137) was associated with CSF SCS+.

Conclusion: Single-copy CSF HIV suppression is associated most strongly with biomarkers of neurodegeneration, oxidative stress, neuroinflammatory cytokines, and depressive symptoms. Certain ART drugs may better suppress HIV RNA in CSF. Longitudinal research in a larger sample should be performed to confirm these findings.

Table: Associations between biomarkers and CSF Single Copy Suppression				
Biomarker	Coefficient	Standardized Coefficient	P value	FDR P value
Plasma Aβ42	-15.29	-0.35	0.0061	0.0089*
Plasma 8-OHdG	43.09	0.53	<.0001	0.0001*
Plasma D-dimer	-71.55	-0.30	0.0322	0.0343*
CSF CCL2	-44.18	-0.30	0.0354	0.0354*
CSF sTNF-R II	49.49	0.26	0.0234	0.0267*
CSF IL-6	0.26	0.37	0.0080	0.0107*
CSF Aβ42	-652.50	-0.82	<.0001	<.0001*
CSF Total Tau	141.10	0.61	<.0001	<.0001*
CSF 8-OHdG	7.45	0.70	<.0001	<.0001*
AB42: amyloid beta; 8-OHdG: 8-hydroxy-2'-deoxyguanosine; sTNF-RII: soluble tumor necrosis factor alpha receptor II; IL: Interleukin, *<0.05				

486 CHARACTERIZING THE ROLE OF MONOCYTES IN HIV NEUROPATHOGENESIS

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Background: 15-40% of people with HIV (PWH) develop HIV associated Neurocognitive Impairment (HIV-NCI) despite viral suppression with ART. HIV-NCI is mediated, in part, by transmigration of infected $CD14^+CD16^+$ monocytes across the blood brain barrier (BBB), establishing a CNS viral reservoir. We showed that $CD14^+CD16^+$ monocytes from PBMC of PWH have increased transmigration across an in-vitro BBB model to CCL2, a chemokine elevated in the CNS of PWH. In a pilot study, we showed that CCR2, the receptor for CCL2, on $CD14^+CD16^+$ monocytes is associated with HIV-NCI. This study builds on these findings. Mechanisms by which $CD14^+CD16^+$ monocytes mediate HIV-NCI have not been characterized extensively or examined in detail longitudinally. During HIV infection some cells harbor viral DNA (HIV^+), and others do not, but are exposed to viral factors (HIV^{exp}). We hypothesize that transmigration of $CD14^+CD16^+$ monocytes, particularly HIV^+ $CD14^+CD16^+$ monocytes, across the BBB contributes HIV-NCI pathogenesis in PWH on ART.
Methods: In a longitudinal study, we examined the baseline visits of 54 participants. PWH on Tenofovir-Emtricitabine-based regimens for ≥ 3 mos were recruited by the Manhattan HIV Brain Bank to undergo ^{1}H-MRS and neurocognitive evaluation at 2 timepoints, 24 mos apart. PBMC were isolated from participants at both timepoints. PBMC were added to an in-vitro BBB model to analyze CCL2-induced transmigration of monocytes and of HIV^+ and HIV^{exp} PBMC. We measured associations between transmigration and HIV-NCI status using Frascati Criteria. We evaluated associations between CCR2 on $CD14^+CD16^+$ monocytes and HIV-NCI. Cross-sectional data from the first timepoint are presented. We are not powered to stratify by sex. Statistical comparisons were done by Wilcoxon Rank Sum Test.
Results: We showed that $CD14^+CD16^+$ monocytes from PWH with HIV-NCI transmigrated more than those from PWH with normal cognition at time 1 ($p < 0.05$). Transmigration was also higher in those with impairment in speed of information processing ($p < 0.05$) and working memory ($p < 0.01$). CCR2 was higher on $CD14^+CD16^+$ monocytes in those with HIV-NCI at time 1 ($p < 0.05$). These results will also be correlated with indices of neuronal health cross-sectionally and longitudinally. We will assess whether HIV^+ PBMC transmigrate more than HIV^{exp} cells and determine an association with HIV-NCI.
Conclusion: Peripheral circulating $CD14^+CD16^+$ monocytes and their CCR2 expression are indicators of CNS dysfunction, even with successful viral suppression.

487 PLASMA Aβ42/Aβ40 RATIOS ARE NOT REDUCED IN OLDER PERSONS WITH HIV

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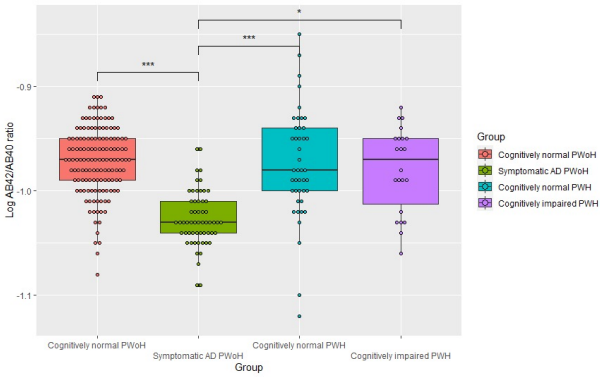
Background: As people with HIV (PWH) continue to age, it remains unclear whether they are at higher risk for age-related neurodegenerative disorders e.g. Alzheimer disease (AD), and how to differentiate HIV-related neurocognitive impairment from AD. This study used a novel blood-based AD biomarker,plasma Aβ42/Aβ40 ratio and the Amyloid Probability Score (APS), in cognitively normal (CN) or cognitively impaired (CI) PWH compared to people without HIV (PWoH) who were CN or had symptomatic AD.
Methods: 66 PWH (age >40 years old) with undetectable viral load (< 50 copies/mL) and 195 PWoH completed a blood draw, magnetic resonance imaging (MRI), and a comprehensive neuropsychological battery or structured clinical interview (Clinical Dementia Rating scale [CDR]). Participants were categorized by degree of cognitive impairment (PWH_CN n=43; PWH_CI n=23; PWoH_CN n=138; PWoH_AD n=57). Plasma Aβ42/Aβ40 ratios were obtained using a liquid chromatography tandem mass spectrometry method. APS, which incorporates Aβ42/Aβ40 ratio, ApoE proteotype and age and indicates the likelihood of brain amyloidosis, was also calculated. Log-transformed plasma Aβ42/Aβ40 ratios and the APS were compared among groups. Regression analyses assessed relationships between Aβ42/Aβ40 or APS and hippocampus volume for each group, and between Aβ42/Aβ40 or APS and cognitive domain scores or HIV clinical characteristics (CD4 and CD8 t-cell count, CD4:CD8 ratio, duration of infection) within PWH.
Results: PWoH_AD (mean log Aβ42/Aβ40=-1.03, SD=0.03; mean APS=41.2, SD=28.9) exhibited significantly reduced plasma Aβ42/Aβ40 ratio ($p < .001$; Figure 1) and higher APS ($p < .001$) compared to PWoH_CN (mean log Aβ42/Aβ40 = -0.97, SD=0.03; mean APS=4.73, SD=11.3), PWH_CN (mean log Aβ42/Aβ40 = -0.98, SD=0.05; mean APS=6.63, SD=13.6), and PWH_CI (mean log Aβ42/Aβ40 = -0.99, SD=0.06; mean APS=10.2, SD=17.7). There were no differences observed among other groups. Lower Aβ42/Aβ40 ratio and higher APS was associated with smaller hippocampal volume only within the PWoH_AD group. Within the PWH group, neither Aβ42/Aβ40 ratios nor APS were significantly associated with cognitive domain scores, global cognition, or any HIV clinical characteristics (CD4 and CD8 t-cell count, CD4:CD8 ratio, or duration of HIV infection) (p -values >.05).
Conclusion: Plasma Aβ42/Aβ40 ratio and APS may serve as a screening tool for AD and help differentiate cognitive impairment due to AD from HIV-related cognitive impairment in older PWH.

Log-transformed Aβ42/Aβ40 ratios by group. People without HIV (PWoH) with symptomatic Alzheimer disease (PWoH_AD) exhibited significantly reduced ratios compared to the other three groups. People with HIV (PWH) did not have lower ratios compared to cognitively normal PWoH (PWoH_CN), regardless of cognitive impairment status.



488 THE CEREBROSPINAL FLUID VIROME IN VIRALLY SUPPRESSED PEOPLE LIVING WITH HIV

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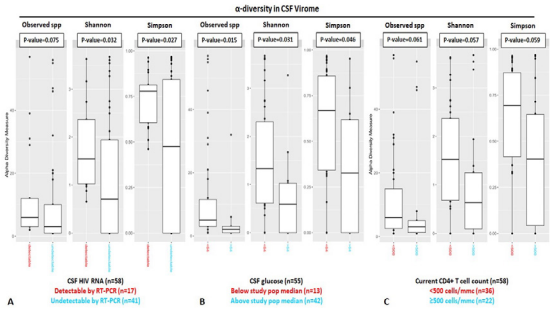
Background: A relevant proportion of central nervous system (CNS) inflammation and disorders in people with HIV (PWH) remains unexplained despite effective viral control. We aim at describing the cerebrospinal fluid virome (CSFV) of PWH on antiretroviral therapy (ART) and its association with neuroinflammation and CNS outcomes.
Methods: Eighty one CSFVs of adult PWH on three drug regimen ART with plasma HIV RNA< 200 cp/mL and no active CNS infections/disorders were analyzed. Prokaryotic and eukaryotic viruses (DNA+RNA) were enriched and sequenced following a modified version of QIAseq® Single Cell RNA Library Kit. After host decontamination and background removal, taxonomy and species abundance were estimated by Kraken2 v2.1.2 and Bracken v2.7. The α (Observed, Shannon, Simpson) and β (Bray-Curtis, Jaccard) diversities and PcoA analysis were performed by phyloseq v1.40.0 and Vegan v2.6.2 R packages. CSFV composition was compared by the following participants' features (PFs): demographics, viroimmunological status, mood/neurocognition (Beck Depression Inventory II and 13 neurocognitive tests) and CSF biomarkers (tau, p-tau, neopterin, S100β, Amyloidβ 1-42, intrathecal synthesis, blood-brain

barrier integrity, cells, proteins, glucose) by Spearman correlations and Mann-Whitney test.

Results: Among the 81 participants (71.6% male, median age and CD4+ T cells of 49 years and 455 cell/µL), 25.9% had CSF HIV RNA >20 cp/mL (median [IQR] 46 [30-58] cp/mL). CSFV was not detected in 23 samples, while a median of 305 (122-1035) viral reads was observed in 58 (71.6%) samples. All CSFV+ presented bacteriophages (mostly *Siphoviridae*, *Myoviridae*, *Podoviridae*; 231 [110-1,057] reads), and 7.4% also eukaryotic viruses (EBV, HCV, HHV6, TTV, HPV-96/-201; 122 [79-303] reads). Among all the assessed PFs, CSFV α-diversity was more pronounced in HIV-1 CSF positive compared to HIV-1 CSF negative samples (Fig.A). Higher CSFV α-diversity was also observed in patients with lower CSF glucose and CD4+ T cells (Fig.B-C). All these associations were confirmed by correlations (ρ=+0.264; -0.444; -0.223, respectively; p< 0.05 for all). No other significant difference in α- and none in β-diversity was observed for any other PFs.

Conclusion: Both prokaryotic and eukaryotic viruses were found in the CSF of ART-treated PWH. Our results suggest that worse viroimmunological profiles may correlate with higher CSFV diversity. Further insights are needed to confirm these findings and address the interplay among HIV, CSFV and neuroinflammation.

Alpha diversity of CSF Virome according to CSF HIV RNA, CSF glucose and current CD4+ T cells count



489 DIVERGENT NEUROIMMUNE SIGNATURES AND HIV-ASSOCIATED CRYPTOCOCCAL MENINGITIS SURVIVAL

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Background: HIV-associated cryptococcal meningitis caused by *Cryptococcus neoformans* causes 15-19% of HIV-related deaths globally. Underlying immune modulated mechanisms to be advanced to improve host survival on antifungal treatment was the challenge. We hypothesized that host immune response at diagnosis predicts host survival on antifungal treatment.

Methods: In a cohort of HIV+ adults with cryptococcal meningitis, we interrogated B cells compartment in blood and CSF, CSF white cells, and representative CSF type-1 T helper response (Th1), Th2, Th17, and T follicular helper cell (Tfh) cytokines, chemokines, and immune checkpoint responses. We used principal component analysis (PCA) to compare baseline responses between those who died (cases) versus survived (controls) at 18 weeks.

Results: Survival was lower among women at 47% compared to men at 60%, hazard ratio, HR=1.4, 95% CI: 1.0 to 1.9; p=0.023. PCA demonstrated the downregulation of immune responses typical of severe immune senescence/exhaustion was associated with higher quantitative CSF *Cryptococcus* culture burden (CFU/mL) and a higher hazard of death. For example, low levels of IL-17A among women were highly predictive of death C-statistic=0.672, 95% CI, 0.585 to 0.758, p< 0.001. Elevation in CSF IL-10 and PD-L1/B7-H1 distinguished evoked immune regulated response, especially by biological sex-specific survival. Overall, better survival was associated with increase expression of blood PD-1 plasmablasts/plasma cells (>20%), CSF white cell pleocytosis of >50 cells/µL, Th1 interferon-gamma >9 pg/mL, pro-inflammatory tumor necrosis factor (TNF)-alpha >85 pg/mL, Th17 interleukin (IL)-17 >4 pg/mL, anti-inflammatory IL-10 >300 pg/mL, immune checkpoint PD-L/B7-H1 >150 pg/mL, chemokine CXCL10 >2507 pg/mL, and CCL11/Eotaxin >15 pg/mL, and lower quantitative CSF culture < 10,000 *Cryptococcus* CFU/mL.

Conclusion: In theory, survival among patients with HIV-associated cryptococcal meningitis depends on an evoked elevation of immune-regulated responses typical of a functional immune system. Elevations of a cluster of chemokines, cytokines, and immune checkpoint responses correlated with lower CSF cryptococcal fungal burden and better host survival. Hence, severe immune exhaustion typical of immune senescence/hijacked immune response presented the greatest risk of death. Immune modulation could be a customized therapeutic strategy to improve the survival of persons with cryptococcal meningitis.

Survival in men and women over time of HIV-associated cryptococcal meningitis.

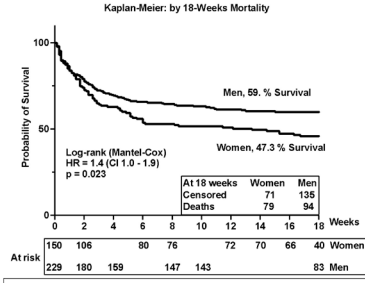

Figure 1. Survival in men and women over time of HIV-associated cryptococcal meningitis. Legend: p-value < 0.05 is statistically different. We will plan to present the cytokine and chemokine data associated with the distinctive gender-specific difference in survival and the underpinning mechanisms elucidated during the course of the Ph.D. research. The findings are novel, and the manuscript is in the pipeline for peer review and journal online publications.

490 CLINICAL AND LABORATORY OUTCOMES OF HEPATITIS C TREATMENT IN AN ACUTE HIV COHORT

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Background: HIV/HCV co-infection is associated with impaired immune recovery and cognitive impairment. This study compared the clinical and neuropsychiatric parameters before and after direct-acting antiviral (DAA) therapy with sustained virologic response (SVR) in people with HIV (PWH) on stable antiretroviral therapy (ART).

Methods: RV254 cohort participants were enrolled during acute HIV (AHI/baseline, Fiebig I-V) and initiated ART within days. They underwent assessments at pre-ART baseline, weeks 24 and 96, and every 48 weeks afterwards, including blood tests (complete blood count, liver enzymes, CD4+ & CD8+ T-cell counts, HIV RNA, lipid profile and HCV screening), neurological examination, depressive and stress symptoms assessment by Patient Health Questionnaire-9 (PHQ-9, score 0-27) and Distress Thermometer (DT, score 0-10), and a 4-test neuropsychiatric (NP) battery. The battery included Color Trails 1 (CT1) & 2 (CT2), non-dominant hand Grooved Pegboard (GPB), and Trails Making A (TMA). An NPZ-4 score was generated by averaging the z-scores of the 4 tests. To control ART effects, only participants on ≥24 weeks of ART with plasma HIV suppression (HIV RNA < 50 cps/ml) were included. Parameters before and after SVR were compared by Wilcoxon signed-rank test or McNemar's test.

Results: Between May 2009 and July 2022, 79 of 688 participants with at least week 24 visit became HCV seropositive; 50 had sustained HCV viremia and received DAA with SVR. All were male with a median age of 30 years [IQR 26-35]; 33 (66%) were diagnosed with other sexually transmitted infections within 6 months of HCV seroconversion; 31 (62%) denied any past intravenous methamphetamine use. The durations between AHI and HCV seroconversion and between HCV seroconversion and DAA initiation were 192 [IQR 96-312] and 58 [IQR 27-70] weeks. AST and ALT declined (p< 0.001), and total cholesterol, LDL-C, and triglycerides increased (all p< 0.01) after SVR (Table 1). CD4+ and CD8+ T-cell counts did not change significantly, but CD4/CD8 ratio increased after achieving SVR (p=0.012). The frequency of peripheral neuropathy and PHQ-9 scores remained unchanged, but stress scores by DT increased after DAA

(p=0.045). NPZ-4 (p=0.004) and z-TMA (p=0.028) improved significantly post-DAA. Of note, no improvements in CD4/CD8 ratio and NP battery were observed between HCV seroconversion and DAA initiation.

Conclusion: In PWH on stable ART with HCV co-infection, CD4/CD8 ratio and cognitive test performance improved after DAA therapy with SVR.

Laboratory and clinical outcomes of participants who achieved sustained virologic response (SVR) after DAA therapy (N=50)

Parameters	Before Treatment[1]	After Treatment[2]	P-value
Biochemistry and hematologic			
ALT, U/L	98.5 (49, 179)	18.5 (13, 26)	**<0.001**
AST[3], U/L	56 (36, 100)	20 (16, 25)	**<0.001**
Plasma HCV RNA, log_{10} cps/mL	6.35 (5.33, 6.91)	1.08 (1.08, 1.08)	**<0.001**
Total white blood cell count, 10^9/L	5.99 (4.86, 6.94)	5.8 (4.92, 6.88)	0.964
Platelet count, 10^9/L	269 (246, 298)	277 (246, 304)	0.567
Hemoglobin, g/dL	15.1 (14.3, 15.5)	14.85 (13.7, 15.6)	0.153
Total cholesterol, mg/dL	183.5 (159, 210)	200.5 (174, 225)	**<0.001**
Low density lipoprotein (LDL), mg/dL	112.5 (94, 138)	135.5 (111, 160)	**<0.001**
Triglycerides, mg/dL	87 (72, 119)	111.5 (82, 161)	**0.003**
Immunologic and Virologic			
CD4+ T-cell count, cells/mm^3	687 (571, 813)	660 (513, 925)	0.994
CD8+ T-cell count, cells/mm^3	776 (588, 909)	736 (542, 863)	0.170
CD4/CD8 ratio	0.91 (0.73, 1.1)	0.97 (0.76, 1.29)	**0.012**
Plasma HIV RNA, log_{10} cps/ml	1.3 (1.3, 1.3)	1.3 (1.3, 1.3)	1.000
Cognitive tests			
NPZ-4 score	0.75 (0.42, 1.02)	0.91 (0.55, 1.31)	**0.004**
z-Color Trails 1	1.23 (0.74, 1.65)	1.29 (0.84, 1.73)	0.287
z-Color Trails 2	0.78 (0.21, 1.46)	0.92 (0.44, 1.26)	0.515
z-Grooved Pegboard	0.43 (-0.49, 1.19)	0.79 (-0.05, 1.38)	0.076
z-Trails Making A	0.6 (0.17, 1.32)	0.91 (0.4, 1.4)	**0.028**
Mood assessment scores			
PHQ-9 (range 0-27)	6 (2, 8)	4 (2, 8)	0.723
PHQ-9 >= 10, n (%)	11 (22.0%)	9 (18.0%)	0.727
PHQ-9 >= 15, n (%)	4 (8.0%)	3 (6.0%)	1
Distress Thermometer (range 0-10)	1.7 (1, 4.2)	2.7 (1.1, 5)	**0.045**
Peripheral neuropathy, n (%)	2 (4%)	1 (2%)	1.00

Median and IQR are shown unless specified.
[1]Median of 103 days (IQR 61.25, 201) before treatment
[2]Median of 190 days (IQR 142.5, 267.25) after treatment
[3]N=34 participants with pre- and post-treatment AST measurements

491 CMV, SEX, AND COGNITION IN PEOPLE WITH HIV (PWH)

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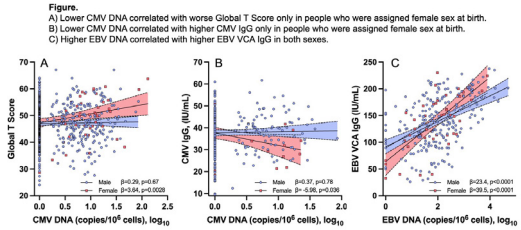
Background: Interactions between chronic co-infections, HIV persistence, and immune response have been implicated in persistent inflammation and cognitive disorders in people with HIV (PWH), but findings have been inconsistent. Most data are based on serology and have not examined sex effects. We aimed to assess the relationships among viral DNA, IgG, and cognition and whether they are influenced by assigned sex at birth.

Methods: Participants included 486 PWH (81 female) who had prior comprehensive cognitive testing, HIV RNA< 200 copies/mL on antiretroviral therapy and stored blood. Digital droplet PCR quantified CMV, EBV, and total HIV DNA in peripheral blood mononuclear cells. EBV VCA IgG and CMV IgG were measured in plasma by commercial immunoassays in a subset (N=267 and 300, respectively). Using linear regression, we tested the association of viral DNA and IgG on cognition and whether associations were affected by sex. Analyses were adjusted for age, race, ethnicity, estimated duration of HIV infection (EDI), current CD4+ T-cells, and AIDS diagnosis.

Results: Cohort characteristics: Median age 55 years, 17% female, 55% white, median CD4+ T-cells 629/µL, EDI 21 years, and 65% with AIDS diagnosis. CMV DNA was detected in 45.4% and EBV DNA in 95.5% of samples. Overall, lower levels of CMV DNA tended to associate with worse Global cognitive T score (p=0.095). Sex and CMV DNA interacted (p=0.004) in relation to Global T score: lower CMV DNA was associated with worse Global T score only in women (p < 0.0001). Among women, lower CMV DNA correlated with worse processing speed (p=0.0017), executive functioning (p=0.002), working memory (p=0.025), learning (p=0.026) and recall (p=0.018). In unadjusted analyses, lower CMV DNA also correlated with higher CMV IgG only in women (p=0.036, interaction p=0.05). CMV IgG, EBV VCA IgG, EBV DNA, and HIV DNA levels did not significantly correlate with global T scores. Higher EBV DNA correlated significantly with higher EBV VCA IgG in both sexes (p< 0.001) with trend toward sex interaction (p=0.06).

Conclusion: In PWH, lower CMV DNA levels were associated with higher CMV IgG and worse cognitive performance only in women. These sex-specific effects emphasize the complex interactions between co-infections, host immune factors, and cognition. Further research is needed to confirm our findings in an independent cohort that includes more women with and without HIV and to identify specific immune mechanisms, which might be targeted to improve or prevent cognitive decline.

Associations Between Viral DNA, Antibody Titers and Cognition (unadjusted linear regression)



492 POST-COVID COGNITIVE IMPAIRMENT MRI BRAIN SCAN ABNORMALITIES: A POTENTIAL BIOMARKER

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Background: Post-acute sequelae of SARS-COV-2 infection (PASC) is associated with cognitive impairment (CI) with unclear pathogenesis though blood brain barrier (BBB) impairment and excitotoxic injury appear significant.

Post-acute sequelae of SARS-COV-2 infection (PASC) is associated with cognitive impairment (CI) with unclear pathogenesis though blood brain barrier (BBB) impairment and excitotoxic injury appear significant.

We hypothesized that PASC CI patients would have brain inflammation and BBB disruption using advanced MR imaging.

Methods: In this prospective longitudinal study, 14 patients with PASC CI (mild and non-hospitalised) were enrolled (mean age of 45; 10 F and 4 M) and 10 sex and age matched healthy controls. 13 had a follow up MR at 9-12 months (mean 10 months). All participants underwent DCE perfusion (an index of BBB integrity with Ktrans as the measurement), Diffusion Tensor Imaging (DTI) and single voxel MR spectroscopy (MRS) of the frontal cortex/white matter and the brainstem in addition to brain anatomical MRI. Between group analyses were used to determine which MRI outcomes were significantly different from controls in patients with PASC CI.

Results: The PASCI CI group showed significantly increased (ie BBB impairment) Ktrans, and increased region (Frontal white matter and Brain Stem)-specific areas in the brain (p=< 0.005), reduction in NAA (ie neuronal injury) and mild reduction of Glx (ie excitotoxicity) in the frontal white matter and brain stem (p=0.004), and reduction in white matter integrity (increased diffusivity - greater radial and mean diffusivity). Increased Ktrans was correlated with increased both radial and mean diffusivity (r=0.9) in all tested brain regions. Ktrans significantly improved in the follow up MR (p= 002596 Z=-2.794872) with no difference between subjects and controls indicating BBB normalisation (p= 0.442418, z= -0.144841). White matter integrity also improved especially in the fractional anisotropy values in the executive networks (p=< 0.00045). MRS showed significant improvement in the NAA in the frontal white matter but Glx remain high as compared to the controls (p=0.0006).

Conclusion: PASC CI was characterised by reversible diffuse BBB impairment, neuronal/axonal and excitotoxic injury. BBB impairment was associated with white matter disruption. These are suggestive biomarkers for the presence, severity and prognosis of PASC CI. Such biomarkers could underpin appropriate trial design and timing of intervention.

493 COGNITIVE, MOTOR, & NEGATIVE VALENCE SYSTEMS IN NEUROLOGIC PASC: A PRELIMINARY STUDY

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The COVID Mind Study
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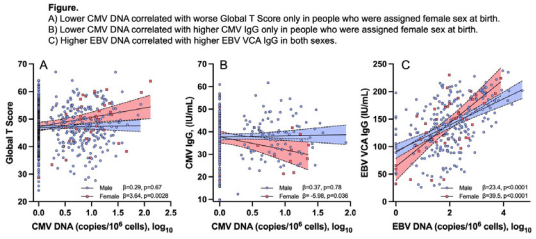
Background: Nervous system post-acute sequelae of COVID-19 (NS-PASC) include cognitive and mental health symptoms. To further define these, we applied a Research Domain Criteria (RDoC) approach to examine motor, positive valence (PV) and negative valence (NV) systems, and social processing data in The COVID Mind Study of NS-PASC.

Methods: NS-PASC participants (>3 months after COVID-19) referred from a NeuroCOVID Clinic and non-COVID controls from New Haven, CT and Baltimore, MD completed an RDoC test battery for cognition (language, declarative and working memory, cognitive control, perception), motor, PV, NV, and social processes. To date, 3T MRI with diffusion tensor imaging was performed in 11 NS-PASC to assess white matter integrity (global white matter fractional anisotropy [FA]) as a contributor to alterations identified on the RDoC tests. Analysis of Covariance examined group differences after adjusting for sex, race, ethnicity, age, and years of education.

Results: 25 NS-PASC participants (age 43.4±11.3 yrs, 76% female, 402 days after COVID-19 symptom onset) and 29 controls (age 46.2.6±13.1 yrs, 66% female) completed the battery. Controls were more racially diverse and less educated than NS-PASC (43% vs. 12% Black, $p=0.005$; 14.5 vs. 16.1 yrs of education, $p<0.05$). Means and statistics for RDoC between NS-PASC and controls are shown in Table. NS-PASC performed worse in language, verbal working and declarative memory, and perception and reported greater cognitive control difficulties (e.g., behavioral inhibition, set shifting) without issues on performance-based metrics (Stroop, Trail Making Test-Part B), and had slower motor function. NS-PASC reported more NV issues including greater symptoms of depression, rumination in response to depressive mood, apathy, childhood trauma, anxiety, and perceived stress. There were no differences in PV and social processing. In a subset of NS-PASC participants who underwent MRI, there was a dynamic range of FA values with a mean of 0.509 (IQR 0.481 – 0.536).

Conclusion: Our findings extend previous PASC studies characterizing cognitive and mental health alterations, indicating that additional RDoC assessments warrant focus, including alterations in motor and the negative valence system. In future analyses, we will examine white matter integrity as a pathophysiologic contributor to these RDoC systems.

Figure 1



494 CHARACTERISTICS AND OUTCOMES OF COVID-19 IN AN EARLY-TREATED HIV COHORT IN THAILAND

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Background: Emerging data indicate that people with HIV (PWH) are at risk of more severe outcomes from COVID-19. We described the clinical course and laboratory parameters pre- and post-COVID-19 in an early-treated HIV cohort in Thailand.

Methods: RV254 cohort participants were enrolled during Fiebig I-V acute HIV and initiated antiretroviral therapy (ART) within days. They underwent regular blood tests (CD4+ & CD8+ T-cell counts, HIV RNA), neuropsychiatric (NP) assessment (Color Trails 1 & 2, non-dominant hand Grooved Pegboard, Trails Making A), and mood questionnaires (Patient Health Questionnaire-9, Distress Thermometer) post-enrollment longitudinally. Their assessment outcomes pre- and post-COVID-19 were compared using Generalized Estimating Equations (GEE) with a normal distribution and identity link (CD4+, CD8+ T-cell counts, NP parameters) or binomial distribution with log link (HIV RNA), and autoregressive correlation structure.

Results: Between 4/2021 and 9/2022, 295 participants on ART (98% male, median age 32 [IQR 28-37] were diagnosed with COVID-19. Of these, 16(5%), 38(13%) and 241(82%) were infected with α, δ and o variants, determined by the predominant strain circulating in Thailand at the time of infection; 238(81%) received ≥2 doses of COVID-19 vaccines prior to diagnosis; 121(41%) received favipiravir. While 106 (36%) were managed in hospital or 'hospitel', including one intensive care unit admission, only 4(1.4%) received supplemental oxygen and none required mechanical ventilation (mean length of stay: 12 days). The participants were followed a median of 8 [IQR 5–15] weeks post-COVID. Comparing the outcomes pre- and post-COVID, plasma HIV suppression rate remained stable (98% vs. 96%, p=0.212). CD4+ (782 [IQR 708-856] vs. 823 [IQR 748-899], p=0.018) and CD8+ (622 [IQR 563-681] vs. 667 [IQR 605-728], p=0.023) T-cell counts were higher at follow-up after adjusting for age, sex, and duration between COVID-19 diagnosis and follow-up. The increasing trends of CD4+ and CD8+ T-cell were sustained on subsequent visits. Mood scores and NP performance (n=217) were stable at follow-up.

Conclusion: In this cohort of young PWH on stable ART, we did not observe major clinical adverse events after COVID-19. Increases of CD4+ and CD8+ T-cell counts were observed while mood and NP parameters remained stable. More extensive NP assessment with incorporation of multimodal imaging outcomes and longer follow-up are needed to determine the long-term sequelae of COVID-19 in PWH.

Laboratory and clinical outcomes of RV254 participants who had COVID-19 between April 2021 & September 2022

Table 1 Laboratory and clinical outcomes of RV254 participants who had COVID-19 between April 2021 & September 2022

Parameters	Before COVID-19	After COVID-19	P-value
IMMUNOLOGIC& VIROLOGIC[1]			
CD4 T-cell count (cells/mm³)			
First post-COVID measure			
Unadjusted	738.5 (710.9-766.1)	752.1 (723.5-780.8)	0.188
Age, sex, and week adjusted	781.7 (707.8-855.6)	823.3 (747.5-899.0)	**0.018**
All available post-COVID measures			
Unadjusted	735.3 (706.8-763.7)	748.1 (720.3-775.9)	0.199
Age, sex, and week adjusted	800.2 (730.6-869.8)	824.5 (754.7-894.2)	**0.054**
CD8+ count (cells/mm³)			
First post-COVID measure			
Unadjusted	678.5 (650.6-706.5)	708.5 (676.0-741.1)	**0.007**
Age, sex, and week adjusted	622.0 (563.3-680.6)	666.6 (605.3-728.0)	**0.023**
All available post-COVID measures			
Unadjusted	672.6 (644.6-700.5)	700.9 (669.8-732.1)	**0.009**
Age, sex, and week adjusted	627.9 (566.8-689.1)	667.6 (607.0-728.2)	**0.003**
CD4/CD8 ratio			
First post-COVID measure			
Unadjusted	1.173 (1.126-1.219)	1.157 (1.110-1.205)	0.195
Age, sex, and week adjusted	1.340 (1.204-1.476)	1.335 (1.200-1.471)	0.830
All available post-COVID measures			
Unadjusted	1.177 (1.130-1.224)	1.162 (1.115-1.209)	0.203
Age, sex, and week adjusted	1.354 (1.229-1.479)	1.336 (1.211-1.462)	0.239
Detectable Viral load, %(n)[2]			
First post-COVID measure	2.4% (7)	3.9% (11)	
Unadjusted OR (95%CI)	1.66 (0.75-3.68)		0.212
Age-adjusted OR (95% CI)	1.66 (0.73-3.83)		0.231
All available post-COVID measures	2.4% (7)	6.8% (20)	
Unadjusted OR (95% CI)	1.41 (0.60-3.29)		0.431
Age-adjusted OR (95% CI)	1.48 (0.65-3.39)		0.356
COGNITIVE[3]			
NPZ-4 score	0.917 (0.845-0.988)	0.868 (0.779-0.957)	0.161
Color Trails 1 (CT1) z-score	1.321 (1.236-1.406)	1.324 (1.227-1.421)	0.952
Color Trails 2 (CT2) z-score	0.967 (0.878-1.056)	1.013 (0.915-1.112)	0.283
Grooved Pegboard (GPB) z-score	0.607 (0.471-0.742)	0.490 (0.341-0.640)	0.075
Trails making A (TMA) z-score	0.773 (0.60-0.865)	0.636 (0.443-0.828)	0.125
MOOD[3]			
PHQ-9 score			
Unadjusted	5.304 (4.896-6.134)	5.304 (4.777-6.134)	0.397
Age, sex, and week adjusted	4.177 (3.361-4.994)	4.582 (3.683-5.481)	0.224
DT			
Unadjusted	2.789 (2.508-3.063)	2.906 (2.588-3.225)	0.402
Age, sex, and week adjusted	2.449 (1.752-3.145)	2.509 (1.773-3.245)	0.771

[1]Values presented are mean and 95% confidence intervals, unless otherwise specified. Virologic parameters were assessed after a median of 8 weeks [IQR 5.0 – 14.5] from COVID-19 diagnosis.
[2]Models presented include unadjusted and age-adjusted.
[3]Values presented are mean and 95% confidence intervals, unless otherwise specified. Cognitive and mood (n=218) and distress (n=217) parameters were assessed after a median of 17.1 weeks [IQR 7.1-27.4] from COVID diagnosis

495 TRAJECTORY OF POST-COVID NEUROCOGNITIVE RECOVERY IN PEOPLE LIVING WITH AND WITHOUT HIV

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Background: Neurocognitive dysfunction is common in long COVID and in people living with HIV (PWH). It is unknown whether PWH experience different disturbances in neurocognitive function following COVID-19 compared to HIV-seronegative people.

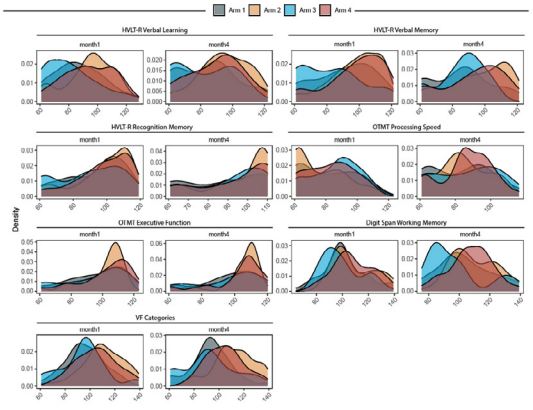
Methods: The amfAR-Johns Hopkins University COVID Recovery Study is a prospective observational cohort study consisting of four groups: participants who had SARS-CoV-2 infection for the first time within 30 days prior to enrollment with HIV (PWH, arm 1) and without HIV (arm 2); participants with no history of SARS-CoV-2 infection with HIV (arm 3) and without HIV (arm 4). 93.5% of the cohort had received a COVID-19 vaccine prior to enrollment. Cognitive tests were administered at 1- and 4-months post symptom onset (arms 1-2) or post-enrollment (arms 3-4) in seven domains. Age standardized scores (all tests) and age-sex-and education-standardized scores (verbal fluency) were obtained. Standardized scores were compared using the Mann-Whitney U Test and the Kruskal-Wallis test.

Results: PWH scored lower than HIV-seronegative participants at 1 and 4 months post-COVID on three tests: the Hopkins Verbal Learning Test-Revised (HVLT-R) learning (M1, p=0.011, M4, p=0.015), HVLT-R memory (M1, p=0.029,

M4, p=0.007), and category-cued verbal fluency (VF; M1&4, p< 0.001). For the majority of timepoints, PWH who were post-COVID produced equivalent scores as PWH who never had COVID (p-levels > 0.05). Comparing post-COVID HIV-seronegative people to those who never had COVID, post-COVID participants scored lower than never-COVID participants on the Oral Trail Making Test part A (OTMT) test of processing speed at month 1 (p=0.033). Between month 1 and 4, HIV- seronegative people who were post-COVID showed improvements in HVLT-R Recognition (p=0.039), OTMT A (p=0.003), and OTMT B test of executive function (p=0.032).

Conclusion: Neurocognitive scores in PWH were independent of COVID status, suggesting that higher frequencies of post-COVID neurocognitive dysfunction in PWH compared to HIV-seronegative people are due to HIV-associated factors more so than COVID. HIV-seronegative, post-COVID people demonstrate diminished recognition memory, processing speed, and executive function at 1 month post-COVID that improves by 4 months. Post-COVID neurocognitive dysfunction is present, if temporary, even in a highly vaccinated cohort of people.

Distribution of Standardized Neurocognitive Test Scores by Month.



496 INFLAMMATORY AND BLOOD-BRAIN BARRIER MARKERS AFTER COVID-19 AMONG PEOPLE WITH HIV

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Background: COVID-19, the disease caused by SARS-CoV-2, has resulted in devastating morbidity and mortality worldwide. Alarming evidence indicates that long-term adverse outcomes of COVID-19 can affect all major systems of the body, including the immune, respiratory, cardiovascular, and neurological systems. While acute COVID-19 pathology does not appear to be markedly different by HIV status, long-term outcomes of COVID-19 in People with HIV (PWH) are unknown and require further investigation. This study evaluates the inflammatory profile longitudinally up to three months after COVID-19. In addition, markers of the blood-brain barrier (BBB) integrity and vascular dysfunction were also evaluated.

Methods: Plasma samples were collected from 15 males and 6 females with COVID-19 and HIV infection (COVID+/HIV+) and 9 males and 14 females with COVID-19 without HIV infection (COVID+/HIV-) between March 2020 and March 2021. Baseline samples were obtained approx. 10 days after COVID-19 diagnosis (T=0) and three months after (T=3). Mean age group for COVID+/HIV- was 45.4±17.8 years for males and 39.7±15.3 for females and for COVID+/HIV+ was 52.1±12.3 for males and 48.7±1 for females (N=15 and 6, respectively). 27 inflammatory molecules were measured by Bio-Plex Multiplex Immunoassay (Bio-Rad) and two markers of BBB and vascular dysfunction (soluble ICAM1 and S100β) by ELISA.

Results: Out of 27 inflammatory analytes, 20 had detectable signals. Eotaxin (CCL11) and G-CSF levels were differentially upregulated in the COVID+/HIV+ group as compared to the COVID+/HIV- group in both time point studied (Table 1). IFN-g showed sustained increased levels at T=3 in the COVID+/HIV+ group, whereas there was a significant reduction over time in the COVID+/HIV- group. At T3, inflammatory markers (IL-4, IL-8, IL-13, basic FGF, TNF-α, MIP-1α, and CCL2) either decreased or remained unchanged in both groups. In contrast, the markers of the BBB disruption and vascular dysfunction, such as S100β and soluble ICAM-1 increased in the COVID+/HIV+ group, suggesting long-term progressive BBB and vascular alterations.

Conclusion: HIV-1 may potentiate long COVID-19-induced neuropathology, with progressive BBB breakdown and sustained increase in eotaxin-1 and G-CSF.

Plasma inflammatory markers in COVID-19 patients with or without HIV-1 co-infection

Table 1. Plasma inflammatory markers in COVID-19 patients with or without HIV-1 co-infection.

Group	IL-4	IL-8	IL-13	IFN-γ	TNF-α	CCL2 (MCP-1)	CCL3 (MIP-1α)	CCL4 (MIP-1β)	CCL11 (Eotaxin)	FGF2	G-CSF	S100β	sICAM-1
COVID+ /HIV- T=0	2.1±0.5	4.0±1.3	4.4±3.8	2.0±1.8	95.1±10	7.6±3.6	1.7±0.3	76.4±7.1	25.0±7.1	5.69±3.4	34.8±12.8	211.0±198.9	197.7±79.9
COVID+ /HIV- T=3	**1.6±0.6****	**2.9±1.4** **	**2.6±1.5** **	**1.0±0.7***	**86.8±11.5** *	**5.4±1.9***	**1.4±0.4****	73.0±5.2	24.2±7.4	**3.54±1.9****	26.1±11.4	**1,222.3±175.5** ****	**517.1±96.7****
COVID+ /HIV+ T=0	2.3±0.6	4.8±2.2	4.8±2.7	1.7±.14	98.2±17	8.8±3.9	1.9±0.6	76.0±9.6	**34.1±13.1††**	6.57±4.2	**46.5±20.2†**	318.6±668.0	202.94±95.8
COVID+ /HIV+ T=3	**1.8±0.6****	**2.8±1.1** ****	**2.8±1.0** **	1.1±0.8	**85.4±12.3** ***	**6.2±4****	**1.6±0.6****	**70.3±9.1***	**32.5±10.2†**	**3.2±2.2****	**39.0±18.3†**	**1,311.3±554.2** ****	**609.0±214.9****

Values in pg/ml ± standard deviation. sICAM-1 values in ng/ml.

*: p<0.05; **: p<0.01, ***: p<0.001; ****: p<0.0001; T=3 compared to T=0, Two-Way ANOVA with Bonferroni post-test

†: p<0.05, ††: p<0.01; COVID+/HIV+ compared to COVID+/HIV- at respective time point, Two-Way ANOVA with Bonferroni post-test

497 MODELING TO OPTIMIZE ISLATRAVIR QW DOSE IN HIV VIROLOGICALLY SUPRESSED PWH

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Background: Islatravir (ISL) is a nucleoside reverse transcriptase translocation inhibitor (NRTTI) being studied for HIV-1 treatment and prevention. Exposure-related decreases in total lymphocytes and CD4+ T-cell counts were observed across ISL clinical trials, with higher frequencies and magnitude of changes observed in ISL higher-dose regimens [20 mg once weekly (QW); 60 and 120 mg once monthly]. Data from Phase 2 and 3 ISL treatment and PrEP trials were used to develop models that describe the changes in lymphocytes and CD4+ T-cells in relationship to intracellular ISL-TP concentrations. Optimized doses were identified to achieve efficacy thresholds and similar CD4+ Tcell and lymphocyte dynamics compared to standard antiretroviral therapy (ART).

Methods: An ISL popPK model was developed incorporating ISL PK data from once daily (QD) and QW doses. Subsequently an ISL popPKPD model was developed incorporating longitudinal CD4+ T-cell and lymphocyte data from long-term ISL studies. Additionally, CD4+ T-cell changes were summarized across approved ART regimens for the virologically suppressed population to compare to PK/PD model predictions. Revised ISL QW doses were selected based on simulated doses providing ISL exposures ensuring coverage for WT and M184V variants as well as CD4 and Lymph counts changes comparable to standard ART in switch population.

Results: The ISL population PK model was updated with additional phase 1 studies and the Phase 3 QD HIV trials and captures both plasma ISL and intracellular ISL-TP dynamics across regimens. The CD4+ T cell and lymphocyte models were developed and captures the changes for treatment naïve, virologically suppressed, and prevention populations on standard therapy. The CD4+ T cell model captured the ISL changes ISL in the daily treatment Phase 2 and 3 studies and the lymphocyte model additionally captured the ISL changes for the Phase 2 PrEP trial. The summary of switch trials show that the majority of trials have CD4+ T cell changes that fall between -5 and +10% changes over the course of the trials and allowed for benchmarking of the CD4+ T cell model simulations. Simulations of the models were conducted for ISL 0.5-20 mg QW predicting ISL-TP exposures and CD4+ T cell and lymphocyte changes.

Conclusion: ISL 2 mg QW is predicted to rapidly achieve efficacious exposures for wild-type and M184I/V HIV variants and have similar CD4+ T cell and lymphocyte changes as standard ART for virologically suppressed PWH.

498 ESTRADIOL CONCENTRATIONS IN TRANS WOMEN ON InSTIs COMPARED TO THOSE WITHOUT HIV

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Background: Accessing feminizing hormone therapy (FHT) is essential to trans women. Concern of negative drug interactions between their FHT and antiretroviral therapy (ART) can be a barrier to acceptance of ART in trans

women with HIV. In this study, we measured serum estradiol concentrations in trans women with HIV taking FHT and integrase strand transfer inhibitor (INSTI)-based ART versus trans women without HIV taking FHT.

Methods: This was a single-center, parallel group, clinical cross-sectional study of trans women with and without HIV, 18 years or older, and taking at least 2 mg/day of oral 17-beta estradiol plus a form of anti-androgen therapy, with no medication changes for at least one month prior to inclusion. Women with HIV were to be on suppressive ART. Blood was collected prior to ART and estradiol dosing and then at 2, 4, 6, and 8 hours post-dose and estradiol concentrations were measured from serum using CMIA (LifeLabs). Median estradiol concentrations at each time point, estradiol C_{max}, and T_{max} were calculated and compared between groups using Wilcoxon rank-sum tests.

Results: Participants (n=15) were enrolled March to August 2022 and had a median age of 32 (IQR: 28, 39); 8 participants with HIV had a median age of 36 (IQR: 32, 48.75) years compared to 30 (IQR: 27.25, 41.75) years for 7 participants without HIV (p=0.042). Among trans women with HIV, the median duration of HIV was 9.5 years (IQR: 5.0, 23.0); 6 were taking bictegravir/emtricitabine/tenofovir alafenamide and 2 were taking dolutegravir/abacavir/lamivudine. Among all participants (n=15), the median oral estradiol dose was 4 mg (range 2-6 mg). Anti-androgen therapy (some on multiple) included spironolactone (n=8), orchidectomy (n=6), central hypogonadism (n=1), and cyproterone (n=1). Three participants were taking progesterone. Participants had been taking FHT for a median of 4 years (IQR: 2, 8). Eleven (73%) participants had ideal estradiol concentrations of 200 to 735 pmol/L at C4h (75% among women with HIV and 71% among those without HIV). Table 1 summarizes oral estradiol concentrations overall and by HIV status. No statistically significant differences were identified by HIV status.

Conclusion: In trans women on FHT, estradiol concentrations were similar between trans women on ART and trans women without HIV with a slightly higher C_{max} among those with HIV. This suggests a low probability of clinically relevant drug-drug interactions between FHT and INSTI-based ART.

Table 1: Summary of oral estradiol concentrations overall and by HIV status

	Median (Q1, Q3)			
	Overall sample (n=15)	HIV positive (n=8)	HIV negative (n=7)	P value*
Age	32 (28, 39)	36 (32, 48.75)	30 (27.25, 41.75)	0.042
Estradiol dose	4 (4, 4)	4 (2.5, 4)	4 (4, 4)	0.677
C_{0h}	230 (153, 366)	226 (84, 439.5)	230 (190, 273)	0.728
C_{2h}	331 (213, 586)	476 (232, 847.75)	225 (213, 351)	0.165
C_{4h}	268 (203, 554)	420.5 (207.25, 634.25)	265 (184, 369)	0.298
C_{6h}	256 (160, 360)	266.5 (122.25, 478.25)	233 (175, 360)	0.908
C_{8h}	240 (171, 372)	235 (139.5, 559.5)	240 (187, 358)	0.908
C_{max}	369 (208, 668)	560 (249.5, 850.75)	265 (208, 369)	0.105
T_{max}	4 (4, 4)	4 (4, 4)	4 (4, 4)	0.333

*Medians of HIV positive and HIV negative groups compared using Wilcoxon rank-sum tests with no statistically significant differences identified.

499 N6LS WITH rHuPH20 ENABLES SAFE HIGH-DOSE MONOCLONAL ANTIBODY SUBCUTAENOUS DELIVERY

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VRC 609 Study Team

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Background: Immunization with a broadly neutralizing monoclonal antibody (bnMAb) is a potential strategy for the prevention and treatment of HIV-1 infection. N6 is a human bnMAb that was derived from a patient who was HIV infected for 21 years without antiretroviral treatment. An LS mutation was introduced to extend serum half-life. N6LS is a member of the VRC01 class of antibodies that targets the CD4-binding site of the HIV-1 envelope glycoprotein. Its neutralizing abilities are broader and more potent than VRC01, neutralizing up to 98% of viral strains on a 181 pseudovirus panel.

Methods: In this first-in-human phase 1 clinical trial (NCT03538626), we assessed the safety and pharmacokinetics (PK) of N6LS administered to healthy adults either by intravenous (IV) or subcutaneous (SC) routes. Additional participants received SC administrations with recombinant human hyaluronidase PH20 (rHuPH20, 2000 U/mL), for rapid high dose/volume drug delivery. Previously N6LS was demonstrated to be safe and well tolerated when administered by IV or SC routes (5, 20 or 40 mg/kg IV or 5 mg/kg SC) to 22 participants with a serum half-life of over 40 days. Ten additional participants were enrolled and received 5 or 20 mg/kg N6LS SC co-administered with rHuPH20.

Results: Infusion site erythema was reported in all 10 newly enrolled participants and five participants met grade 3 severity criteria based off erythema dimensions. Participants tolerated the post-infusion period well, without concomitant systemic reactions or complications. The erythema was self-limiting with most cases resolving within days. Systemic reactogenicity was mild. No serious adverse events, dose-limiting toxicities or infusion reactions occurred. PK following N6LS 5 mg/kg SC was similar with and without rHuPH20. N6LS demonstrated broad and potent neutralization following administration, and there was no evidence of development of anti-drug antibodies to N6LS.

Conclusion: In summary, N6LS was safe and well tolerated when administered with or without rHuPH20. Given its broad and potent neutralization of circulating HIV-1 clades, N6LS remains a promising candidate for HIV-1 prevention and therapy. As demonstrated in this trial, the ability to safely administer higher doses/volumes of N6LS subcutaneously opens new potential avenues for prophylactic and therapeutic self-administration of bnMAbs.

Serum Concentrations of N6LS

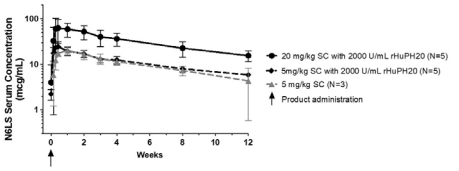

Figure 1. Serum Concentrations of N6LS. Geometric mean serum concentrations with standard deviation (indicated by bars) are displayed for each study group after a single administration of N6LS with or without rHuPH20 on Day 0. The dose and route of administration for each group is specified in the key. SC denotes subcutaneous route of N6LS administration.

500 TFV-DP & FTC-TP IN BLOOD CELL SUBSETS OF PERSONS WITH HIV

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Background: Nucleos(t)ide reverse transcriptase inhibitors (N(t)RTIs) are anabolized to their active forms within multiple cell types, but data have been primarily focused on red blood cells, dried blood spots (DBS) and peripheral blood mononuclear cells (PBMCs) to date. Understanding the extent to which N(t)RTIs accumulate in other major blood cells may inform clinicians' understanding of ART efficacy and toxicity, such as cardiometabolic effects. We examined the cell pharmacology and platelet effects of abacavir (ABC)/lamivudine (3TC) and tenofovir alafenamide (TAF)/emtricitabine (FTC) in persons with HIV (PWH). Here, we aimed to establish TFV-diphosphate (DP) and FTC-triphosphate (TP) concentrations in different cell types and compare them with historical data in persons without HIV (PWOH).

Methods: PWH receiving TAF 25mg/FTC 200mg as part of clinical care with HIV VL < 200 c/mL for ≥6 months prior to entry were eligible (NCT04301661). Adherence was confirmed using video directly observed therapy (vDOT) for 28±3 days prior to PK sample collection (2±1 hrs post-dose). Whole blood was processed into DBS, PBMCs, platelets, and neutrophils. LC-MS/MS methods were used to quantify TFV-DP and FTC-TP across all cell types in addition to the mono (MP)- and DP fractions in platelets. Data in PWOH originated from TAF-DBS (NCT02962739). Cellular concentrations by HIV status were compared using linear regression models.

Results: 13 PWH were enrolled in the TAF/FTC cohort (12 male; 8 white, 2 black, 3 other; 4 Hispanic/Latino; median (range) age and weight of 42 (26-64) years and 74.2 (58.3-116.7) kg). Median (range) 4-week vDOT adherence was 96% (76-100%). Historical data were available in 31 PWOH (median [range] age 29 [18-41] years and weight 76.3 [56.7-118.2] kg). Cellular concentrations by cell type are summarized in the table. Within platelets, TFV-DP >TFV >TFV-MP and FTC-TP >FTC-DP >FTC-MP. TFV-DP in DBS and platelets were 73% higher and 61% higher, respectively, and FTC-TP in platelets were 71% higher in PWH vs. PWOH. No other differences were identified.

Conclusion: Higher TFV-DP in DBS is consistent with previous studies in PWH, but higher TFV-DP and FTC-TP concentrations in platelets suggests an undescribed difference in cell-specific physiology in PWH. The mechanism behind this differential accumulation warrants further investigation. Cellular data with ABC/3TC and comparisons of metabolic effects in platelets may help provide further insight into intracellular processes.

TAF-FTC Anabolites by Cell Type in PWH & comparisons to PWOH

Cell Type	TFV-DP (fmol)		FTC-TP (pmol)	
	PWH (n=13)[a]	Percent Difference (95% CI)[a]	PWH (n=13)[a]	Percent Difference (95% CI)[a]
DBS (per 2x7mm punch)	2963 (1826-4767)	73.0% (29.6%, 131%)*	4.84 (2.1-7.96)	4.61% (-25.7%, 47.4%)
PBMC (per 10^6 cells)	619 (397-1193)	-2.76% (-26.8%, 29.1%)	6.72 (4.46-13.1)	-15.6% (-39.5%, 17.9%)
Neutrophils (per 10^6 cells)	334 (121-880)	25.3% (-28.3%, 119%)	5.37 (1.54-10.9)	35.1% (-32.6%, 171%)
Platelets (per 10^6 cells)				
MP fraction	7.37 (3.93-11.6)	--	0.059 (0.035-0.13)	--
DP fraction	2.55 (1.26-5.21)	--	0.077 (0.045-0.12)	--
TP fraction	10.0 (6.31-17.4)	61% (4.9%, 147%)**	0.15 (0.059-0.22)	71.4% (28.9%, 128%)*

[a]Data presented as geometric mean (range) [b]PWH compared to PWOH; point estimates reflect those after controlling for adherence and time since last dose *p<0.001 **p<0.05

501 IN SILICO PHARMACOKINETICS EVALUATION OF FORGIVENESS FOR DORAVIRINE & RILPIVIRINE

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Background: ANRS 170 QUATUOR findings showed the non-inferiority of some intermittent maintenance treatment strategies, but treatment failures related to emerging disease-resistant mutations with rilpivirine as third therapeutic agent have been observed. The consequences of the 3-days-off strategy on non-nucleoside reverse transcriptase inhibitors (NNTI) concentrations are not known. The aim of this study was to evaluate in silico, using simulation from population pharmacokinetics models, the concentrations of rilpivirine (RLP) after 3 days off, with doravirine (DOR) as a comparator.

Methods: Previously published population pharmacokinetic models for DOR (Yee et al, Antimicrob Agents Chemother. 2019) and for RLP (Aouri et al, Antimicrob Agents Chemother. 2016) were implemented in the mrgsolve R package. 10000 Monte Carlo simulations at steady state for typical dose of 25 mg/day for RLP and 100mg/day for DOR were drawn for two scenario: without drug cessation and after 3 days off. Filters were applied on simulated trough concentration (C24h) to keep the 2.5 to 97.5 simulated profiles. The validation of the implementation was performed based on the comparison of the median C24h to the one observed in the literature. The proportion of simulated patient with C24h and C72h after 3 day off (C72h/3do) higher than IC_{50} (5.2 µg/L (DOR) ; 20.5 µg/L (RLP)) and IQ (6 X IC_{50} (DOR); 4.5 X IC_{50} (RLP)) were calculated for both drugs. Finally, nomograms to estimate probability of having a concentration > IC_{50} after 72h of drug cessation for different range of C24h were built.

Results: Simulated C24h median [range] for RLP were 62.8 [23-142] µg/L and for DOR 400 [209-603] µg/L. The proportion of patient with C24h >IC_{50}, C72h/3do >IC_{50} and C72h/3do >IQ were 100%, 36.6% and 0% for RLP and 100%, 89.4% and 74.3% for DOR. The nomogram for probability of target attainment at 72h as function of C24 range is presented in Table 1.

Conclusion: Based on these findings, treating with DOR would be more forgiving than with RLP since the former drug exhibits a larger proportion of patients with effective drug exposure. The main limit of this work is that we only evaluated the drug concentrations that cannot be a perfect surrogate of the drug effect. However, DOR is a promising third therapeutic agent suitable for an intermittent maintenance treatment strategy. Further studies are needed to confirm this assumption and evaluate the developed nomograms.

Table 1 Probability of effective concentration after 72h of forgiveness based on C_{trough} at 24h.

Doravirine			Rilpivirine		
Residual concentration interval at 24h (µg/l)	Probability Ctrough >C150 at 72h (%)	Probability Ctrough >C150x6 at 72h (%)	Residual concentration interval at 24h (µg/l)	Probability Ctrough >C150 at 72h (%)	Probability Ctrough >C150x6 at 72h (%)
209-287	63.5	31.4	23-35	0	0
287-325	74.8	45.4	35-43	0	0
325-354	81.7	56.2	43-50	0	0
354-377	90	69.4	50-56	0	0
377-401	92.2	77.3	56-63	3.16	0
401-424	96.3	84.8	63-70	62.0	0
424-450	97.7	88.5	70-77	99.7	0
450-479	99.1	94.3	77-88	100	0
479-519	99.5	98	88-104	100	0
519-603	100	99.7	104-142	100	0

502 SCREENING APPROACHES AND CLINICAL DESCRIPTION OF THE ANTICHOLINERGIC BURDEN IN PWH

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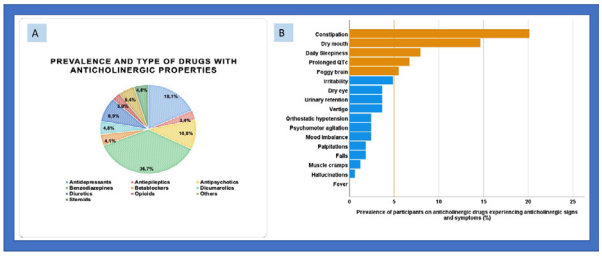
Background: Clinical impact of anticholinergic (AC) burden in people with HIV (PWH) and how to routinely detect it in clinical practice have been poorly investigated. We assessed the screening effectiveness of 3 AC scales in detecting AC symptoms and their clinical correlates in our cohort.

Methods: This cross-sectional analysis enrolled adult PWH who attended the Infectious Disease Unit of Padua Hospital (Italy) for their clinical checks (November 2021-March 2022). The AC burden scale (ABS), AC risk score (ARS), and AC drug score (ADS) were calculated. We recorded clinical data, comedications and the presence of 17 AC signs/symptoms over the last 3 month. High AC risk was defined by validated cut-offs: ABS score≥2, ARS, and ADS score≥3. Nonparametric tests and logistic regression were used; screening effectiveness of the three AC scales was assessed by the Area Under the Receiver Operating Characteristic curve (AUROC).

Results: We included 721 participants (median age 53 years, 72.0% males). Polypharmacy was present in 21.1% and 164 PWH (22.7%) were at least on 1 drug with AC properties (drug prevalence/type in Fig.1A). 4.4% PWH were classified as high AC risk by at least 1 scale (1.1%, 3.5% and 3.1% according to ARS, ABS, and ADS, respectively). Agreement between ARS and the other scales was poor (Cohen's k 0.33 and 0.22) and moderate between ABS and ADS (k 0.60). Among PWH on AC drugs, 28.6% experienced at least 1 AC sign/symptom (prevalence/type in Fig.1B). After adjusting for univariate significant variables, factors independently associated with AC signs/symptoms were the type of antiretroviral regimen (aOR 15.2 and 32.0 for triple INSTI- and NN-based regimen vs. dual therapy, p=0.024 and 0.009; aOR 82.6 for triple protease inhibitors-based vs. dual therapy, p=0.082) and the overall number of AC drugs (aOR 9.7, p< 0.001). AUROC of ARS, ABS and ADS were 0.73 [0.63-0.82], 0.85 [0.78-0.92], and 0.84 [0.75-0.92], respectively (p< 0.001 for all). Nevertheless, at the cut-offs established for the general population the correct classification rate (78.0%, 82.9% and 84.8%) was affected by low sensitivity (34.0%, 46.8% and 46.8%).

Conclusion: AC drug use affected almost 1 out of 4 PWH in our cohort and the risk of developing AC manifestations was correlated both with the type of antiretroviral regimen and the number of drugs with AC properties. Current scales for screening AC risk in the general population showed promising use even in PWH but may require a tailored reassessment of the best cut-off.

Figure 1. Prevalence of drugs with AC properties and signs/symptoms detected in our population.



503 PHARMACOKINETICS & SAFETY OF SUSTAINED-RELEASE FLUCYTOSINE PELLET FORMULATION

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Background: WHO recommends flucytosine (5FC) as an essential component of cryptococcal meningitis (CM) treatment regimens. The currently available formulation, an immediate release (IR) tablet, needs to be administered four times a day and is sub optimal for administration via naso-gastric tube. This

study evaluated the pharmacokinetics and safety of a sustained release 5FC (SR) pellet formulation suitable for twice-daily oral or naso-gastric administration in resource limited settings.

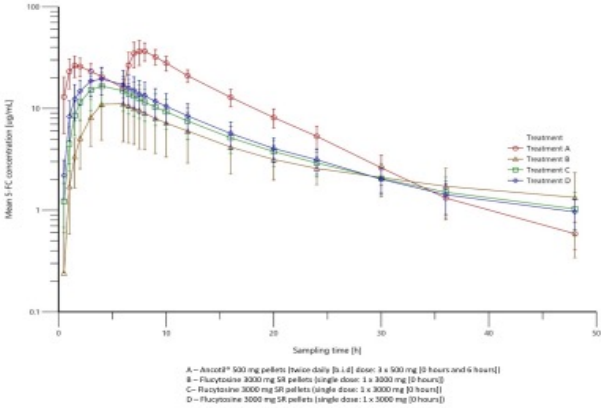
Methods: Phase I open-label, randomized, single dose, four-period crossover, comparative bioavailability study of 5FC commercial IR tablets and SR pellets in healthy male and female participants at a single site in South Africa. The primary objective was to assess for relative bioavailability of three prototype (B, C, D) SR pellets (single dose: 1 x 3000 mg at 0 hours) relative to the reference product (A) IR Ancotil® tablets (3 x 500 mg at 0 and 6 hours after first dosing) under fasting conditions. The primary end points were plasma C_{max} and AUC_{0-t}. Physiologically based pharmacokinetic modelling (PBPK) was performed.

Results: Between Jan and April 2022, 35/42 randomised participants completed the four study treatment periods; 7 dropped out. Following administration of Ancotil (A) and 5FC SR prototypes B, C and D, AUC0-t (ug*h/mL) of 471.8±72.1, 179.4±68.6, 227.8±61.2 and 258.3±64.6, and C_{max} (ug/mL) of 40.9± 8.3, 12.1±6.5, 17.3±5.8 and 20.5±5.9 for 5-FC, respectively were observed (Figure 1). The relative bioavailability of selected prototype D was calculated at 0.62, indicating a need for an increase in nominal dose to achieve the same exposures as Ancotil. PBPK modelling indicates that a double dose (2x3000 mg) of 5FC SR prototype D is needed to achieve target 5FC exposure (20-100mg/L) in fasting conditions.

No severe or serious adverse events (AEs) were reported. 36 AEs were reported in 20 participants, of which 9 (mild to moderate severity) were related to treatment. Treatment was discontinued for safety reasons in one participant due to isolated transaminase elevation (AST, 3.5xULN, prototype C), without other associated liver abnormalities.

Conclusion: A promising SR pellet formulation was selected for development. Single dose fasted administration of 5FC in healthy participants demonstrated no new safety concerns. Further studies with the selected prototype need to be conducted with the higher dose to compare the bioavailability of IR and SR 5FC in fed conditions and in people with HIV-associated CM.

Mean (SD) concentrations of 5-FC by treatment in the PK population semi-log scale



504 POPULATION PK ANALYSIS TO GUIDE DOSING WINDOW FOLLOWING LENACAPAVIR SC ADMINISTRATION

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Background: Lenacapavir (LEN) is a potent first-in-class capsid inhibitor in development for the treatment and prevention of HIV-1 infection. Current data indicates that LEN exhibits near maximal antiviral activity when the lower bound of the 90% confidence interval (CI) of mean C_{trough} is maintained above inhibitory quotient 4 (IQ4) (at least 4-fold greater than the *in vitro* protein adjusted 95% effective concentration). In ongoing Phase 2/3 studies, people with HIV-1 (PWH) received 2 weeks of oral LEN loading prior to starting every 6 month (q6m) subcutaneous (SC) dosing on Day 15. The objective of this analysis was to simulate scenarios to assess the impact of potential shifts (advancement or delays) in q6m dosing on C_{trough} to allow flexibility in dosing window for LEN SC injection.

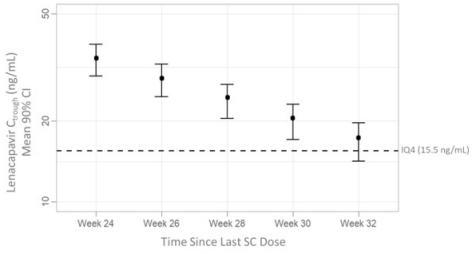
Methods: A previously developed 2-compartment LEN PopPK model with first-order absorption and linear elimination based on data from Phase 1-3 studies was utilized to simulate LEN concentrations. Various scenarios for second SC dose were simulated to evaluate the forgiveness window.

Results: Following oral lead-in and SC maintenance, simulated LEN concentrations at 26 weeks after last SC injection were 29.2 ng/mL corresponding to a mean IQ of 7.5 with 90% CI of IQ 6.3-8.4. Similarly, at 24 weeks after last SC dose LEN concentrations were 34.6 ng/mL (mean IQ of 8.9 with 90% CI 7.5-9.9) and at 28 weeks after last SC dose, LEN concentrations were 24.5 ng/mL (mean IQ of 6.3 with 90% CI 5.2-7.0) as shown in Figure 1. If the maintenance SC dose is administered 2 weeks earlier than the planned 26-week dosing interval (i.e., Week 24), LEN concentrations (upper bound of 90% CI was 38.5 ng/mL) are predicted to remain within a range that can be supported with existing safety data. If SC dose is administered 2 weeks later (i.e., Week 28), LEN concentration (lower bound 90% CI was 20.4 ng/mL) were above IQ 5.2, providing a dosing window of ±2 weeks after last SC dose. For participants who cannot receive SC LEN within this window, i.e., participants whose dosing falls beyond the 28-week window, restart of oral LEN loading followed by SC LEN is recommended.

Conclusion: In administering SC LEN every 6 months, a 4-week dosing window (±2 weeks around the scheduled injection) is adequate to maintain safe and efficacious exposure.

Simulated Lenacapavir C_{trough} on Weeks 24 to 32 in Adult People With HIV Who Received the Phase 2/3 Dosing Regimen

Figure 1: Simulated Lenacapavir C_{trough} on Weeks 24 to 32 in Adult People With HIV Who Received the Phase 2/3 Dosing Regimen



505 GENETICS OF HIV AND TB DRUG INTERACTIONS WITH LEVONORGESTREL EMERGENCY CONTRACEPTION

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AIDS Clinical Trials Group A5375 Study Team

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Background: Levonorgestrel (LNG) is primarily metabolized by CYP3A4. Efavirenz (EFV) and rifampin (RIF) induce, while isoniazid (INH) inhibits CYP3A4. ACTG A5375, a pharmacokinetic (PK) trial of LNG emergency contraception (EC), showed that double-dose LNG (3mg vs 1.5mg) offsets the effects of EFV and RIF on LNG PK over the first 8 hours after a single dose for EC. We characterized the pharmacogenetics of these drug interactions.

Methods: A5375 enrolled participants in Africa, Asia, South America and the US into four groups: women living with HIV (WLH) on EFV-based ART were randomized 1:2 to LNG 1.5mg (Group A) or 3mg (Group B); WLH on dolutegravir (DTG)-based ART were assigned to 1.5mg (Group C; control group); Women treated for TB with INH/RIF were assigned to 3mg (Group D). On day 0, women received a single dose of LNG EC. Intensive PK sampling was done pre-dose and 0.5, 1, 1.5, 2, 3, 4, 6, 8, 24 and 48 hours post-dose. AUC_{0-8h} was the primary outcome. Genotyping defined *CYP2B6* metabolizer and *NAT2* acetylator status (associated with plasma EFV and INH exposure, respectively). Linear regression models adjusted for BMI and age, and used log-transformed PK parameters.

Results: Of 122 cisgender women, 118 (97%) were evaluable for genetic associations: 73 (62%) identified as Black, 33 (28%) Asian, and 10 (8%) Latina. In the combined EFV Groups A/B, 8 (15%) of 52 were *CYP2B6* poor metabolizers. In Group D, 15 (44%) of 34 were NAT2 slow acetylators. Within Groups A/B, *CYP2B6*

genotypes that increase plasma EFV exposure had more rapid LNG clearance (β=0.29, p=0.025). In CYP2B6 poor metabolizers in Group B, LNG $AUC_{0\text{-}8h}$ was lower than Group C (GMR=0.60; 90% CI 0.44, 0.82; Figure); LNG C_{max} was not significantly lower (GMR=0.77; 90% CI 0.55, 1.06). Within Group D, *NAT2* genotypes that increase plasma INH exposure had slower LNG clearance (β=-0.31, p=0.022). *In NAT2* slow acetylators in Group D, LNG $AUC_{0\text{-}8h}$ was greater than Group C (GMR=1.36; 90% CI 1.08, 1.71; Figure). BMI was independently associated with LNG $AUC_{0\text{-}8h}$ in each analysis.

Conclusion: Pharmacogenetics of ART and TB drugs affect interactions with LNG EC. *CYP2B6* slow metabolizer genotypes worsen the EFV-LNG interaction, likely by increased *CYP3A* induction with higher EFV exposure, making this interaction more difficult to overcome. *NAT2* slow acetylator genotypes attenuate the RIF-LNG interaction, likely by increased CYP3A inhibition with higher INH exposure.

Relationships between genetics and plasma LNG exposure.

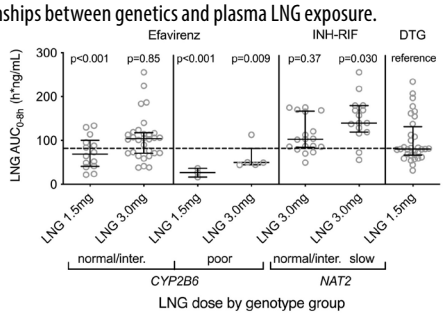

Figure: Relationships between genetics and LNG $AUC_{0\text{-}8h}$. Left section: *CYP2B6* normal/intermediate metabolizer WLH on EFV. Second section from left: *CYP2B6* poor metabolizer WLH on EFV. Second section from right. *NAT2* genotype in women with TB on INH-RIF. Right section: WLH on DTG. LNG mg doses are shown. Error bars indicate median and IQR. Horizontal dashed line indicates median $AUC_{0\text{-}8h}$ in DTG control group. Individual markers are unadjusted for BMI or sex. P-values are from linear regression models with log LNG $AUC_{0\text{-}8h}$, adjusted for BMI and age, in comparison with the DTG group.

506 IMPACT OF OBESITY ON THE DRUG-DRUG INTERACTION BETWEEN DOLUTEGRAVIR AND RIFAMPICIN

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Background: Obesity is increasing globally and has also become more prevalent among people living with HIV. We previously demonstrated that obesity may lower the exposure of drugs and consequently could impact drug-drug interactions (DDIs). Obese individuals are often underrepresented in clinical trials therefore the combined effect of obesity and drug induction has not yet been evaluated. This study aimed to compare the magnitude of the DDI between dolutegravir (DTG) and the strong inducer rifampicin (RIF) in obese and non-obese individuals using physiologically based pharmacokinetic (PBPK) modelling.

Methods: The in-house whole-body PBPK model, built in Matlab® R2020a was implemented with the recently published repository describing physiological changes of a White obese population. The ability of the model to predict the DDI between DTG (50 mg q.d.) and RIF (600 mg q.d.) and the dose adjustment scenario (DTG 50 mg b.i.d. plus RIF 600 mg q.d.) in non-obese (BMI 18.5-30 kg/m^2) was verified using published clinical data. The verified PBPK model was then used to simulate the dose adjustment scenario in obese (BMI 30-40 kg/m^2 and 40-50 kg/m^2).

Results: The predicted pharmacokinetic parameters in non-obese individuals for both clinical scenarios were within the 2-fold error margin apart the trough concentration (C_τ) of DTG q.d. with RIF q.d. which was slightly underpredicted, nonetheless all clinical observed data were within the 90% normal range of the predicted data. The simulated vs observed $AUC_{0\text{-}\tau}$ and C_τ were 53281 vs 52101 ng*h/mL and 1085 vs 1061 ng for DTG q.d. alone and were 17712 vs 22750 ng*h/mL and 59 vs 156 ng when in combination with RIF in non-obese. The DDI-ratios for the dose adjustment scenario are shown in Table 1. The induction potential of RIF was comparable across the three populations tested. However, when comparing the ratio between DTG with RIF in obese vs DTG without RIF in the non-obese, an increase in the DDI magnitude was observed and explained by the combined effect of induction and obesity. Nonetheless, none of the obese individuals were predicted to have DTG C_τ lower than PA-IC_{90} (64 ng/mL) suggesting that doubling DTG dose is sufficient to overcome the DDI with strong inducers in obese with a BMI up to 50 kg/m^2.

Conclusion: Obesity is predicted to impact the DDI between DTG and RIF by further lowering the exposure and C_τ of DTG. However, the recommendation to double DTG dose is still sufficient to overcome the DDI with rifampicin in obese individuals.

Table 1: Observed vs predicted DDI-ratios for dolutegravir 50 mg b.i.d given with rifampicin 600 mg q.d. compared to dolutegravir 50 mg b.i.d. alone in non-obese and obese individuals.

	Non-obese (BMI 18.5-30 kg/m^2)		Obese (BMI 30-40 kg/m^2)	Obese (BMI 40-50 kg/m^2)	DDI-ratio obese with RIF/non-obese without RIF	
Dolutegravir	DDI-ratio observed	DDI-ratio predicted	DDI-ratio predicted	DDI-ratio predicted	DDI-ratio predicted (obese BMI 30-40 kg/m^2)	DDI-ratio predicted (obese BMI 40-50 kg/m^2)
C_{max} (ng/mL)	0.56	0.45	0.47	0.47	0.37	0.29
C_τ (ng/mL)	0.28	0.17	0.20	0.21	0.17	0.15
AUC_τ (ng*h/mL)	0.46	0.32	0.35	0.35	0.28	0.23

507 PHARMACOKINETICS OF STANDARD VS DOUBLE-DOSE DOLUTEGRAVIR AFTER SWITCH FROM EFAVIRENZ

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Background: Dolutegravir (DTG) is the preferred second-line antiretroviral backbone agent for people living with HIV (PLWH) failing a first-line efavirenz (EFV)-based regimen. EFV induces genes associated with the metabolism and transport of DTG. The resulting drug-drug interaction between EFV and DTG significantly reduces DTG's exposure for up to 14 days when switching from an EFV-based regimen. Exposure to sub-therapeutic DTG concentrations in PLWH failing EFV-based first-line ART could select for DTG resistance mutations. We conducted a pharmacokinetic study to evaluate DTG trough concentrations after switching from a failing first-line EFV-based regimen to assess the need for a lead-in supplemental dose of DTG.

Methods: We conducted a pharmacokinetic sub-study nested within a phase 2b trial (the ARTIST study) that randomised participants failing a first-line EFV-based regimen to supplemental DTG 50mg or placebo for 14 days post-switch to tenofovir/lamivudine/DTG (TLD). We obtained EFV (baseline and days 3, 7, and 14) and DTG trough plasma concentrations (days 3, 7, 14, and 28). Dose-to-sampling time was assessed using electronic medication dispensing devices. *CYP2B6* metaboliser genotype was determined as this affects the extent of induction by EFV.

Results: We enrolled 36 participants: 11 in the placebo arm and 25 in the supplemental arm. One participant in the supplemental arm had undetectable baseline EFV and was excluded. The median age was 36 years (IQR 30–42), 77% female, baseline CD4 254 cells/mm^3 (IQR 158–441), and HIV-RNA log 4.0 copies/mL (IQR 3.3–4.4). One participant in the supplemental DTG arm and none in the placebo arm had a DTG trough concentration below the PA-IC_{90} (0.064 µg/mL) at day 3. DTG trough concentrations per arm are presented in **Table 1**. The difference in day 28 trough concentrations between the supplemental and placebo DTG arms was explained by *CYP2B6* metaboliser genotypes: there were no slow metabolisers in the placebo arm and 5 in the supplemental arm, and DTG concentrations in normal and intermediate *CYP2B6* metabolisers were similar between arms (P-values = 0.088 and 0.223, respectively).

Conclusion: No participants in the placebo arm had DTG trough concentrations below the PA-IC_{90}. Prolonged EFV induction effect in *CYP2B6* slow metabolisers contributed to lower DTG trough concentrations at day 28 in the supplemental arm. Our findings do not support the need for a supplemental DTG dose when switching from a failing first-line EFV-based regimen.

Table 1: Geometric mean and geometric mean ratios of DTG trough concentration exposure when administered as standard vs double dose (N=35)

	Geometric Mean (90% CI) (µg/mL)				Geometric Mean Ratio (90% CI)		
Dosing arm	**Day 3**	**Day 7**	**Day 14**	**Day 28**	**Day 3/Day28**	**Day 7/Day 28**	**Day 14/Day 28**
DTG standard dose (n=11)	0.35 (0.21 to 0.56)	0.39 (0.24 to 0.61)	0.69 (0.49 to 0.97)	1.09 (0.72 to 1.63)	0.32* (0.17 to 0.60)	0.35 (0.19 to 0.66)	0.63 (0.37 to 1.08)
DTG double dose (n=24)	1.10 (0.73 to 1.67)	1.37 (0.92 to 2.03)	1.88 (1.53 to 2.31)	0.45 (0.31 to 0.66)	2.45 (1.40 to 4.31)	3.04* (1.76 to 5.25)	4.17** (2.71 to 6.42)

* p-value <0.01
** p-value <0.001

508 INTRAMUSCULAR CABOTEGRAVIR/RILPIVIRINE CONCENTRATIONS AFTER SWITCHING FROM EFAVIRENZ

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Background: Intramuscular cabotegravir and rilpivirine (IM CAB/RPV) are used once viral load suppression is achieved on another antiretroviral regimen. While CAB/RPV are substrates of UGT1A1/CYP3A4, efavirenz induces these enzymes therefore switching from an efavirenz containing regimen to IM CAB/RPV could possibly result in a time window with suboptimal drug levels. The aim of this study was to simulate the initial IM CAB/RPV concentrations after stopping efavirenz using physiologically based pharmacokinetic (PBPK) modelling.

Methods: The in-house PBPK model implemented with a mechanistic intramuscular framework was validated against observed clinical data. Prior to simulate IM CAB/RPV concentrations after switching from efavirenz, we firstly verified the models for CAB, RPV, and efavirenz separately. Secondly, we simulated the switch from efavirenz to oral RPV and dolutegravir (another UGT1A1 substrate). The model was considered validated when the predictions were within 2-fold of clinical data. A cohort of 100 virtual individuals (20-50 years old, 50% female, 18-30 kg/m^2) was generated to simulate IM CAB/RPV concentrations over time when administering CAB/RPV (600/900 mg) 12 hours after the last oral dose of efavirenz (600 mg). IM CAB/RPV concentrations during the switch period were compared to those in absence of residual efavirenz concentrations.

Results: The model was successfully verified as all predictions were within 2-fold of observed clinical data. Initiating IM CAB/RPV 12 hours after the last dose of efavirenz was predicted to have a minimal effect as IM CAB concentrations (C_τ) were reduced by 11%, 13% and 8% at days 1, 7 and 14 after discontinuing efavirenz (Table 1). For all time points, CAB C_τ was above the 4-fold PA-IC_{90}. Similarly, efavirenz was predicted to have a modest effect on IM RPV concentrations with the lowest reduction being 10% and occurring 7 days after the last dose of efavirenz. Residual efavirenz concentrations were predicted to have a less pronounced effect on IM RPV compared to the observed switch data with oral RPV (e.g., IM RPV reduced by 8% vs 28% for oral RPV at day 14 post efavirenz) (Crauwels et al. Antiviral Therapy 2012).

Conclusion: The PBPK model demonstrates that switching from an efavirenz-containing regimen to IM CAB/RPV does not put at risk of having a time window with suboptimal drug levels.

Table 1: Predictions of IM cabotegravir and rilpivirine concentrations at days 1, 7, 14, and 28 after stopping efavirenz.

	C_τ [ng/mL] absence of efavirenz	C_τ [ng/mL] after stopping efavirenz	C_τ ratio
Intramuscular cabotegravir			
Day 1	421 (20)	373 (22)	0.89
Day 7	1362 (41)	1180 (40)	0.87
Day 14	1251 (55)	1153 (50)	0.92
Day 28	962 (59)	939 (54)	0.98
Intramuscular rilpivirine			
Day 1	45 (17)	42 (16)	0.94
Day 7	79 (24)	71 (21)	0.90
Day 14	45 (35)	41 (29)	0.92
Day 28	31 (35)	30 (30)	0.98

Table legend: the results are expressed as geometric mean (CV)

509 SWITCHING OFF EFAVIRENZ TO NON-EFAVIRENZ ART LOWERS NICOTINE METABOLITE RATIO IN PWH

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Background: Cigarette smoking in people with HIV (PWH) is 2-3x that of people without HIV, over 40% in some US groups, and causes more morbidity than HIV itself in smokers with viral control. Nicotine is metabolized by CYP2A6, measured by nicotine metabolite ratio (NMR; 3-hydroxy cotinine/cotinine) and higher NMR is associated with lower quit rates. In trials, PWH have lower quit rates than expected from studies in people without HIV. Efavirenz, still a mainstay antiretroviral therapy (ART) drug in lower income countries, upregulates its own metabolism. We hypothesized that efavirenz increases NMR compared with non-efavirenz ART.

Methods: We compared NMR from plasma during and post-efavirenz use among current cigarette smokers with HIV in the CNICS cohort. Eligibility included having stored plasma at two time points when smoking cigarettes and HIV RNA < 400 copies/ml: 1) on efavirenz and 2) after switching to non-efavirenz ART. Cotinine and 3-hydroxycotinine were measured in plasma using liquid chromatography-tandem mass spectrometry. We used signed rank tests to compare NMR on and off efavirenz. We targeted enrolling at least 71 pairs for 80% power to detect a clinically meaningful 0.1 unit increase in NMR with p=0.05.

Results: We analyzed samples between January 2010 and November 2019 in 72 PWH, 63 (88%) men, 34 (47%) Black, median age 51 years (range: 21-66) with 53 (74%) switching to integrase inhibitor-based and 19 (26%) switching to non-nucleoside analog based ART. Specimens were a median of 629 days apart (range 133, 3157 days) with median plasma cotinine on efavirenz of 164 ng/ml (IQR: 128, 218) and median plasma cotinine of 180 ng/ml (IQR: 138, 332) on non-efavirenz ART. The median NMR on efavirenz was 0.73 (IQR: 0.52, 0.98) and on non-efavirenz ART was 0.46 (IQR: 0.29, 0.67) with a median difference of 0.26 decrease (IQR: -0.41, -0.007, p< 0.001) with 44 (61%) having NMR decrease by at least 0.1. The findings were not changed when stratified by age, race, sex assigned at birth, or non-efavirenz ART regimen type.

Conclusion: Switching off efavirenz resulted in substantial decreases in the NMR. Our findings suggest that previously observed higher NMR among PWH may be due to direct pharmacologic effects of individual ART drugs. If subsequent studies show higher quit rates in those on non-efavirenz than efavirenz-based ART, assessing each ART drug's effect on NMR may inform ART choice in HIV+ smokers away from nicotine metabolism inducers to potentially increase smoking cessation rates in PWH.

510 IMMUNE-VIRAL DYNAMICS MODELING OF THE BASIS FOR INDIVIDUAL VARIATION IN COVID-19

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Background: Viral dynamics models provide mechanistic insights into viral disease and therapeutic interventions. A detailed, mechanistic model of COVID-19 was developed and fit to data from molnupiravir (MOV) trials to characterize the SARS-CoV-2 viral dynamics in MOV-treated and untreated participants and describe the basis for variation across individuals.

Methods: An Immune-Viral Dynamics Model (IVDM) incorporating mechanisms of viral infection, viral replication, and induced innate and adaptive immune response described the dynamics of viral load (VL) from pooled data from MOV Phase 2 and 3 trials (N=1958). Population approaches were incorporated to estimate variation across individuals and to conduct an extensive covariate analysis. Nineteen parameters in a system of five differential equations described SARS-CoV-2 viral dynamics in humans. Six population parameters were successfully informed through fitting to observed trial data while the remaining parameters were fixed based on literature values or calibrated via sensitivity analysis.

Results: Final viral dynamics and immune response parameters were all estimated with high certainty and reasonable inter-individual variabilities. The model captured the viral load profiles across a wide range of subpopulations and predicted lymphocyte dynamics without using this data to inform the parameters, suggesting inferred immune response curves from this model were accurate. This mechanistic representation of COVID-19 disease indicated that the processes of cellular infection, viral production, and immune response are in a time-varying, non-equilibrium state throughout the course of infection. MOV mechanism of action was best described as an inhibitory process on the infectivity term with estimated AUC50 of 10.5 µM*hr. Covariates identified included baseline viral load on infectivity and age, baseline disease severity, viral clade, baseline viral load, and diabetes on immune response parameters. Greater variation was identified for immune parameters than viral kinetic parameters.

Conclusion: These findings show that the variation in the human response (e.g., immune response) is more influential in COVID-19 disease than variations

in the virus kinetics. The model indicates that immunocompromised patients (due to HIV, organ transplant, active cancer, immunosuppressive therapies) develop an immune response to SARS-CoV-2, albeit more slowly than in immunocompetent, and MOV is effective in further reducing viral loads in the immunocompromised.

511 FACTORS INFLUENCING COVID-19 RISK: INSIGHTS FROM MOLNUPIRAVIR EXPOSURE-RESPONSE

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Background: Exposure-response (E-R) models were developed for the primary endpoint of hospitalization or death in COVID-19 patients from the Phase 3 portion of the MOVe-OUT study (Clinicaltrials.gov NCT04577797). Beyond dose, these models can identify other determinants of response, highlight the relationship of virologic response with clinical outcomes, and provide a basis for differential efficacy across trials.
Methods: Logistic regression models were constructed using a multi-step process with influential covariates identified first using placebo arm data only. Subsequently the assessment of drug effect based on drug exposure was determined using placebo and molnupiravir (MOV) arm data. To validate the models, the rate of hospitalization/death was predicted for published studies of COVID-19 treatment. All work was performed using R Version 3.0 or later.
Results: A total of 1313 participants were included in the E-R analysis, including subjects having received MOV (N=630) and placebo (N=683). Participants with missing baseline RNA or PK were excluded (79 from MOV and 16 from placebo arms). The covariates shown to be significant determinants of response were baseline viral load, baseline disease severity, age, weight, viral clade, and co-morbidities of active cancer and diabetes. Day 5 and Day 10 viral load were identified as strong on-treatment predictors of hospitalization/death, pointing to sustained high viral load as driving negative outcomes. Estimated AUC50 was 19900 nM*hr with bootstrapped 95% C.I. of (9270, 32700). In an external validation exercise based on baseline characteristics, the E-R model predicted the mean (95% CI) placebo hospitalization rates across trials of 9.3% (7.6%, 11.7%) for MOVe-OUT, 7.2% (5.3%, 9.8%) for the nirmatrelvir/ritonavir EPIC-HR trial, and 3.2% (1.9%, 5.5%) for generic MOV trials by Aurobindo and Hetero, consistent with the differing observed placebo rates in these trials. The relative reduction in hospitalization/death rate predicted with MOV treatment (relative to placebo) also varied with the above patient populations.
Conclusion: Overall, the exposure-response results support the MOV dose of 800 mg Q12H for treatment of COVID-19. The results further support that many clinical characteristics impacted hospitalization rate beyond drug exposures which can vary widely across studies. These characteristics also influenced the magnitude of relative risk reduction achieved by MOV in the MOVe-OUT study.

512 NO DOSE ADJUSTMENTS FOR CYP3A4 SUBSTRATES WHEN COADMINISTERED WITH BEMNIFOSBUVIR

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Background: Bemnifosbuvir (BEM, AT-527) is a guanosine nucleotide prodrug in development for the treatment of COVID-19 and chronic HCV. BEM was identified *in vitro* as an inhibitor [competitive and time-dependent inhibition (TDI)] and inducer of CYP3A4, prompting evaluation of the clinical relevance of these results in a Ph 1 drug-drug interaction (DDI) study in healthy participants using midazolam (MDZ), a sensitive CYP3A4 substrate as an index drug.
Methods: Two groups of 12 healthy participants were enrolled and received a single dose of 2mg MDZ alone on Day 1. Between Days 3 and 7 inclusive, all participants received oral BEM 550mg twice daily (BID). On day 3 and day 7, Group A received a single dose of 2mg MDZ simultaneously with BEM; Group B on these two days received 2mg MDZ 2h after BEM. Serial plasma samples were obtained and measured for MDZ and 1-OH-MDZ levels.
Results: A single dose (simultaneous or staggered) of BEM slightly increased the plasma exposure of MDZ (↑14%-26%). Staggered BEM had less impact (↑8%-17%) on 1-OH- MDZ than simultaneous dosing (↑22%-31%). Inhibitory effect of BEM was more pronounced with repeat dosing, consistent with *in vitro* data showing TDI on CYP3A4. After repeat dosing, simultaneously administered BEM increased plasma MDZ exposure by 83%-98%, without affecting the exposure of 1-OH-MDZ. With repeat dosing, staggered BEM showed less effect on both MDZ and 1-OH-MDZ. There was no effect on vital signs, ECG, and no SAEs or drug discontinuations.
Conclusion: BEM is a weak inhibitor (ratio between 1.25 and 2) of CYP3A4. No dose adjustment is needed for drugs that are substrates of CYP3A4 when co-administered with BEM.

513 BEMNIFOSBUVIR HAS LOW POTENTIAL TO INHIBIT P-gp, BCRP, AND OATP1B1 MEDIATED TRANSPORT

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Background: Bemnifosbuvir (BEM, AT-527) is a guanosine nucleotide prodrug candidate for the treatment of COVID-19 and chronic HCV. BEM was identified *in vitro* as an inhibitor of drug transporters P-glycoprotein, breast cancer resistant protein (BCRP) and organic anion transporting polypeptide 1B1 (OATP1B1). Ph 1 studies in healthy participants were conducted to assess the clinical implications of these results using digoxin (DIG) and rosuvastatin (ROSU) as P-gp and BCRP/OATP1B1 index drugs, respectively.
Methods: Both studies employed a similar design with 2 groups of 14 healthy participants: Day 1/period 1, all participants received a single dose of DIG 0.25mg or ROSU 10mg alone. In period 2, participants received DIG 0.25mg or ROSU 10mg with BEM 1100mg, simultaneously (n=14) or staggered by 2h (n=14). Serial plasma samples were collected and quantitated for DIG or ROSU concentrations.
Results: A single dose of BEM 1100mg simultaneously administered slightly increased the C_{max} of DIG (↑78%), yet had no effect on its AUC, consistent with the transient nature of BEM plasma PK. When dosed staggered, BEM did not affect the PK of DIG. A single dose (simultaneous or staggered) of BEM 1100mg slightly increased the plasma exposure of ROSU (↑20%-40%). There was no effect on vital signs, ECG, and no SAEs or drug discontinuations.
Conclusion: A single high dose of BEM 1100mg only slightly increased the plasma exposure of the P-gp and BCRP/OATP1B1 index drugs DIG and ROSU. BEM has low potential to exhibit clinical meaningful inhibition of these transporters. No dose adjustment will be needed for drugs that are sensitive substrates of P-gp or BCRP/OAT1B1 when co-administered with BEM, staggered dosing may lessen any DDI risk.

514 PHARMACOKINETICS INFORMS REMDESIVIR DOSING FOR PATIENTS WITH SEVERE RENAL IMPAIRMENT

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Background: Despite renal impairment (RI) being a risk factor for severe COVID-19, there are no approved antiviral treatment options for patients with severely impaired kidney function (eGFR less than 30 mL/min/1.73 m^2 or kidney failure) in the US. At the time remdesivir (RDV) was initially approved for the treatment of COVID-19, the impact of renal impairment (RI) on pharmacokinetics (PK) of RDV, its metabolites, and the excipient, sulfobutylether β-cyclodextrin sodium (SBECD), was not known.
Methods: Here, we report the PK data supporting dosing of RDV in COVID-19 patients with severely impaired kidney function. PK samples for RDV and metabolites (GS-704277, GS-441524) were collected in the Phase 3 REDPINE study in hospitalized COVID-19 patients with severely impaired kidney function. Participants in this double-blind study were randomized 2:1 to intravenous (IV) remdesivir (200 mg on Day 1, then 100 mg daily up to Day 5) or IV saline as placebo-to-match. SBECD PK was analyzed in a phase 1 study in non-COVID-19 participants with normal kidney function, mild and moderate RI who received 100 mg dose of remdesivir (containing 3000 mg SBECD). The population PK analysis included observations from healthy and COVID-19 patients with full range of renal function across all adult studies.
Results: Geometric mean exposures (AUC_{tau}) observed in REDPINE Study as compared to PINETREE Study increased up to 553% for the GS-441524 metabolite (dependent on renal elimination) and to a lesser degree GS-704277 (294%, minor renal elimination) and RDV (78.9%; an increase explained by factors other than renal function, namely, hospitalization and body weight)

(Table 1). The increased PK exposures were not associated with new safety signals in this study (n=163 remdesivir, n=80 placebo). Population PK analysis identified baseline eGFR as a significant covariate for GS-704277 and GS-441524 clearance, but not for RDV itself. SBECD PK was characterized by short half-life ($t_{1/2}$) (1.6 hours in normal renal function to 3.8 hours in moderate RI) and fast plasma clearance (7.9 L/h in normal renal function). Analysis of SBECD in severe RI (REDPINE) is ongoing, but accumulation is not expected based on its observed short plasma $t_{1/2}$.

Conclusion: Given the observed PK and the absence of any new safety signals associated with increased metabolite levels in patients with severely impaired kidney function, no dose adjustment is recommended for RDV in COVID-19 patients with eGFR < 30 mL/min/1.73 m^2, regardless of the need for dialysis.

Table 1: Estimated Multiple Dose exposure metrics[a] of RDV and Metabolites (GS-704277 and GS-441524) in REDPINE Study Participants (hospitalized) and Statistical Comparison to PINETREE (non-hospitalized, eGFR≥30 ml/min/1.73 m^2) and REMDACTA (hospitalized) Study Participants

Characteristics	REDPINE Study (test) GM (%CV)	PINETREE Study (reference) GM (%CV)	REMDACTA Study (reference) GM(%CV)	GMR (90% CI) REDPINE vs PINETREE	GMR (90% CI) REDPINE vs REMDACTA
Number of participants eGFR (mL/min/1.73m^2) median [min, max]	90[b] [severe RI; kidney failure] 14.7 [2.54,41.7[c]]	148 85.7 [34.2,146]	289 81.0 [6.30[e],251]		
Body Weight (kg)	79.0 [43.0,148][d]	87.1 [46.3,173][d]	90.0 [49.9,280][d]		
RDV AUC_{tau} (h•ng/mL)	2950 (63.1%) [3250 (68.5%); 2670 (56.8%)]	1650 (51.2%)	1790 (44.4%)	179 (159, 201)	165 (150, 182)
RDV C_{max} (ng/mL)	3850 (56.3%) [4170 (58.9%); 3570 (53.8%)]	2770 (44.2%)	3110 (39.5%)	139 (125, 154)	124 (114, 135)
GS-704277 AUC_{tau} (h•ng/mL)	1550 (57.5%) [1480 (55.1%); 1660 (55.6%)]	392 (54.4%)	754 (54.9%)	394 (350, 443)	205 (184, 228)
GS-704277 C_{max} (ng/mL)	378 (67%) [397 (73.3%); 370 (59.2%)]	205 (50%)	258 (60.3%)	184 (164, 208)	146 (130, 165)
GS-441524 AUC_{tau} (h•ng/mL)	15,400 (44.6%) [11,600 (38.3%); 20,200 (28%)]	2360 (35.5%)	3170 (56.2%)	653 (599, 711)	495 (446, 548)
GS-441524 C_{max} (ng/mL)	703 (41.5%) [548 (36.7%); 893 (28.1%)]	142 (31.4%)	170 (49.4%)	495 (457, 535)	414 (377, 454)
GS-441524 C_{tau} (ng/mL)	377 (40.3%) [321 (38.7%); 440 (35.3%)]	65 (52%)	88 (52.7%)	582 (525, 645)	431 (391, 475)

%CV = percentage coefficient of variation of the geometric mean; CI = confidence interval; Mean. = geometric mean; GM= Geometric Mean; GMR = geometric mean ratio expressed as percent (%); IV = intravenous; PK = pharmacokinetic(s); RDV = remdesivir
a: Population PK estimates for 30-minute IV infusion of remdesivir for 5 days (REDPINE, REMDACTA) and 3 days (PINETREE). All study participants received remdesivir 200 mg on Day 1 followed by 100 mg once daily maintenance doses. **b**: Among REDPINE participants with PK data available 47.8% (43/90) had severe RI (eGFR 15 to 29 ml/min and 51.1% (46/90) had kidney failure (eGFR <15 ml/min); 45.6% (41/90) needed renal replacement therapy; 5/90 received intermittent hemodialysis. **c**: Protocol enrollment criteria was baseline eGFR<30 ml/min for REDPINE and eGFR≥30 ml/min for REMDACTA; a few subjects had eGFR value reported outside of the range. **d**: body weight distribution is different among studies influencing the mean observed RDV exposures (e.g. more heavier patients in REMDACTA result in lower exposure than patients in REDPINE Study); similarly, body weight distribution affects RDV exposures observed in REMDACTA as compared to PINETREE (e.g. considering hospitalization is significant covariate for RDV resulting in ~30% higher exposures, if exposures were corrected for body weight distribution, non-hospitalized patients have lower RDV exposures).

515 GLOBAL COLLABORATION TO PROVIDE DRUG INTERACTION GUIDANCE FOR NIRMATRELVIR/RITONAVIR

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Background: Nirmatrelvir/ritonavir (NMV/r), a preferred antiviral for high-risk outpatients with COVID-19, is associated with major drug-drug interactions (DDIs). Given the lack of DDI data with short course ritonavir (RTV), initial NMV/r product information was extrapolated from chronic, full dose RTV use. In Jan 2022, DDI experts from the University of Liverpool (UoL), NIH COVID-19 Guidelines Panel, and Ontario Science Table (OST) contributors established a global collaboration to address DDI challenges limiting NMV/r use in real-life settings. We report how safe, pragmatic, and consistent resources were developed to support NMV/r prescribing, and the utilization of these resources globally.

Methods: The 3 teams met monthly to discuss DDIs, review NMV/r DDI literature, and achieve consensus on recommendations. Additional experts were invited as needed. Metrics from the UoL DDI checker guided review of most searched DDIs overall and by severity. 2022 usage metrics for each DDI guide were collected. Differences in recommendations between initial DDI guides and product information were compared.

Results: In 2022, 12 meetings were convened. Each team's DDI guide was revised and expanded (Table 1). To factor in the lower RTV dose and shorter treatment duration, some recommendations differed from product information. Drug categories that required the most discussion and revision included: anticoagulants (ACs), immunosuppressants, calcium channel blockers. NMV/r accounted for 85% of queries on the UoL site. NMV/r DDI guidance was the most viewed page of the NIH guidelines and among the OST ID/clinical care Science Briefs. Top searched drugs on the UoL site with serious DDIs were certain ACs and statins. Utilization of DDI guides was not limited to in-country resources: 51% and 7% of UoL queries came from the USA and Canada, respectively. NIH users followed links to the UoL and OST sites 161,478 and 37,619 times, respectively.

Conclusion: Significant efforts have been made by the 3 teams to provide up-to-date, complementary DDI guidance. Usage metrics confirm the demand for DDI guidance during the pandemic. Cross-utilization of the DDI guides confirms the need for consistency. DDI recommendations were more permissive than initial product information, expanding clinicians' ability to prescribe NMV/r. DDI guidance for ACs and immunosuppressants was particularly challenging. During drug development, complex interactions likely to be encountered in target populations should be addressed.

Table 1. Description and 2022 Metrics for NMV/r DDI Guides

	University of Liverpool	NIH Guidelines	Ontario Science Table
Description	• Web-based, interactive DDI checker	• Webpage/PDF	▲ Webpage/PDF (DDI table and DOAC algorithm)
No. of drugs in DDI guide vs product information, at initial versions[1]	558 UoL 137 EMA product label/ FDA EUA FS	68 NIH 100 FDA EUA FS	133 OST 120 Health Canada monograph
% of recommendations different between DDI guide and product information, at initial versions[1]	27%	33%	61%
No. of drugs included in DDI guide, first version/end of 2022	558/880	68/214	133/139
No. of revisions to drug entries in 2022[2]	143	37	20
No. of revisions resulting in upgrades or downgrades in severity of DDI	6 upgrades 44 downgrades	3 upgrades 23 downgrades	1 upgrade 1 downgrade
NMV/r DDI Usage Metrics for 2022	• Total NMV/r queries: • 7,026,530 (85% of all DDI queries) • NMV/r DDI queries by country[3]: • USA: 3,271,973 (51%) • Canada: 459,234 (7%) • UK: 320,050 (5%)	• Total DDI pageviews: • 1,618,633 (11% of all views on NIH guidelines website) • Most viewed page in 2022 • No. of referrals to other DDI resources: • UoL: 161,478 • FDA: 47,045 • OST: 37,618	• Total DDI pageviews: • 244,695 (43% of all views on OST website) • Most viewed page in 2022

Key: DOAC = direct oral anticoagulant; DDI = drug-drug interaction; EMA = European Medicines Agency; EUA FS = Emergency Use Authorization Fact Sheet for Healthcare Providers; FDA = Food and Drug Administration; NMV/r = nirmatrelvir/ritonavir; OST = Ontario Science Table; University of Liverpool (UoL)
[1] Product information refers to the product labeling, fact sheet, or monograph authorized by the relevant regulatory agency for each region or country. Product information was not uniformly consistent between regions or countries (e.g., the number of drugs addressed and/or certain DDI interpretations).
[2] Includes revisions that did not lead to changes in DDI recommendations, such as updates to evidence summaries or comments.
[3] NMV/r nomenclature changed over the year. NMV/r DDI queries by country could only be extracted for the predominant nomenclature so that the total number of queries is 6,433,077 (denominator for queries by country).

516 PREDICTORS OF POST SWITCH VIREMIA IN PATIENTS ON INJECTABLE CABOTEGRAVIR/RILPIVIRINE

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Background: Data are lacking evaluating predictors of varying levels of on-treatment elevations in viral load in patients receiving long-acting cabotegravir plus rilpivirine (CAB/RPV) for people with HIV (PWH). Study objectives were to I) quantify the occurrence of detectable viremia on CAB/RPV and II) determine if HIVRNA values in the preceding year predicted virologic outcomes.

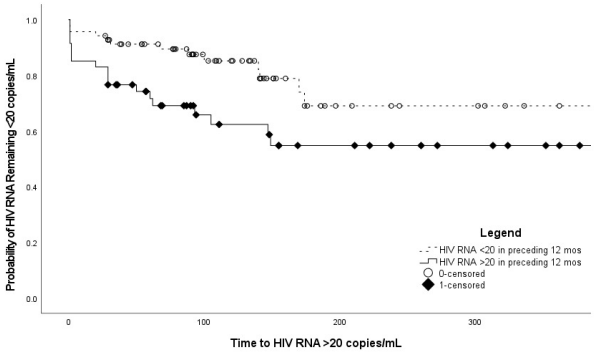
Methods: A retrospective cohort study was performed among those receiving care at the University of California San Diego Owen Clinic. Inclusion criteria included treatment with CAB/RPV for at least three months, availability of both pre- and on-treatment HIVRNA values, and at least one on-treatment HIVRNA collected >21 days after start of CAB/RPV. Demographic and laboratory data were extracted from the electronic medical record. Outcomes of interest were incidence of on-treatment HIVRNA values ≥20, ≥50 and ≥200 copies/mL (cpm).

Results: Among 144 PWH the median duration of follow up was 131 days. The most frequent (58.3%) regimen prior to CAB/RPV was a second-generation integrase inhibitor plus two NRTIs. In PWH with a baseline HIVRNA < 20 cpm (N=116, 80.6%) at time of switch to injectable CAB/RPV, the occurrences of HIVRNA ≥20, ≥50 and ≥200 cpm after switch were 27.6%, 10.3%, and 1.7% respectively. Patients with at least one HIVRNA value ≥20 cpm in the 12 months preceding initiation of CAB/RPV were significantly more likely to have an HIVRNA ≥20 cpm while on CAB/RPV compared to those with no HIVRNA values ≥20 cpm (19/47, 40.4% versus 13/69, 18.8%, p=0.01). Time to event analyses comparing these groups corroborated this relationship (Figure 1, log-rank p=0.02). Multiple consecutive HIVRNA values ≥20 cpm in the preceding year was also associated with increased probability of on-treatment HIVRNA ≥20 cpm (10/21, 47.6% versus 22/95, 23.2%, p=0.02). An HIVRNA value ≥20 in preceding year did not significantly predict the other two virologic outcomes (HIVRNA ≥50 or ≥200).

Conclusion: Despite virologic suppression at time of switch to CAB/RPV, over 25% of patients experienced at least one HIVRNA >20 cpm with incidence highest among patients with at least one HIVRNA >20 cpm in the preceding year. While the impact of low-level increases in viral load is not entirely clear,

initiating CAB/RPV in patients with multiple HIVRNA values >20 cpm in the preceding year should be done cautiously.

Time to Event Analyses Comparing Probability of HIVRNA Remaining <20 copies/mL



517 PROJECTED BENEFITS OF LONG-ACTING ART IN PWH WITH VIREMIA DESPITE PRESCRIBED ORAL ART

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Background: Long-acting injectable antiretroviral therapy (LA-ART) with cabotegravir-rilpivirine (CAB-RPV) is approved for PWH with viral suppression on oral ART. A recent pilot project showed that monthly CAB-RPV with wrap-around social services (WS) resulted in viral suppression in most PWH who had remained viremic despite prescribed oral ART. We projected the clinical impact of providing LA-ART with WS compared with oral ART with or without WS for PWH failing to suppress on oral ART.

Methods: Using the CEPAC microsimulation model, we compared 3 strategies: 1) Standard of care using oral INSTI-based ART (*SOC*), 2) SOC with WS (*SOC/WS*), and 3) LA-ART with WS (*LA-ART/WS*). WS consisted of community-based supports (e.g., case managers, home- and street-based nursing services). Model outcomes included viral suppression, changes in CD4, retention in care at 2y, life expectancy (life years, LYs), and transitions to PI-based regimens for failure with INSTI resistance. Base case cohort characteristics were from published data: mean age 40y; 87% male; mean (SD) CD4 100 (50)/μl. Viral suppression at 6m was 25% (*SOC*) and 49% (*SOC/WS*) from published data, and 72% (*LA-ART/WS*; assumption). Mean (SD) loss to follow-up rates were 29.0 (10.3)/100PY *SOC* and 22.4 (12.2)/100PY *SOC/WS* and *LA-ART/WS*. In sensitivity analysis, we varied all key parameters.

Results: Viral suppression at 2y varied widely: 22% SOC, 45% SOC/WS, and 63% LA-ART/WS (Table). Projected life expectancy was 10.22 LY SOC, 13.53 LY SOC/WS, and 17.09 LY LA-ART/WS. Of those initiating LA-ART, 58% experienced virologic failure on LA-ART over their lifetime and transitioned to a PI-based regimen. Projected clinical benefits were greater in PWH with lower CD4 counts but remained substantial in PWH with higher CD4 counts. For PWH with lower ART adherence and engagement in care, LA-ART/WS still resulted in substantial gains in life expectancy (+5.4y compared with *SOC/WS*, Table). Even if LA-ART efficacy was as low as 20% at 3 months and WS improved care retention by only 5% at 2y, *LA-ART/WS* would still result in greater viral suppression and major increases in life expectancy (+1.4y compared with *SOC/WS*).

Conclusion: For PWH with persistent viremia despite prescribed oral ART, LA-ART with CAB-RPV and wraparound services is likely to substantially increase viral suppression and improve survival for this difficult-to-treat population. A clinical trial to provide further supportive evidence is urgently needed.

Table. Results of a simulation model of LA-ART with wrap-around services in PWH with persistent viremia despite being prescribed oral ART.

	2y viral suppression, %	2y retention, %	2y CD4 increase, /μL	2y survival, %	Life expectancy, life years (LYs)
Base case cohort					
SOC	22	56	78	81	10.2
SOC/WS	45	72	182	87	13.5
LA-ART/WS	63	75	258	92	17.1
Lower engagement cohort*					
SOC	7	47	51	74	6.1
SOC/WS	20	59	120	80	8.1
LA-ART/WS	46	63	255	88	13.5

LA-ART: long-acting antiretroviral therapy, **PWH:** people with HIV, **SD:** standard deviation, **SOC:** standard of care, **WS:** wrap-around services. *Compared with the base case, the lower engagement cohort is less likely to attain virologic suppression or engage in care. Viral suppression at 6m were 8% *SOC*, 22% *SOC/WS*, and 59% *LA-ART/WS*. Rates of LTFU were 34.1 (6.2)/100PY *SOC* and 30.3 (9.6)/100PY *SOC/WS* or *LA-ART/WS*.

518 HIGH VIROLOGIC SUPPRESSION RATES ON LONG-ACTING ART IN A SAFETY-NET CLINIC POPULATION

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Background: Long-acting antiretroviral therapy (LA-ART) with cabotegravir (CAB) and rilpivirine (RPV) was recently approved in the U.S., but real-world data from demonstration projects are lacking. LA-ART was approved for treatment naïve or experienced patients with virologic suppression (VS) on oral ART for at least 5 months prior to switching to injectables. However, patients with adherence challenges unable to achieve or maintain VS with oral medications may also benefit.

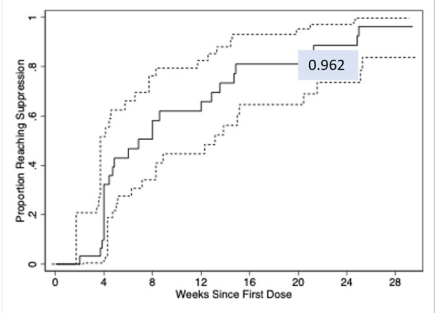
Methods: The Ward 86 HIV Clinic is a safety-net clinic in San Francisco serving publicly-insured patients. The overall rate of VS in the clinic (n=2600) is 88%. To maximize potential benefit of LA-ART, we offered direct-to-inject LA-ART for persons with and without VS. Eligibility required willingness to receive LA-ART every 4 weeks; a history of resistance mutations to RPV or >1 mutation to CAB were exclusion criteria. Injections were given in clinic with drop-in access with rare injections provided in the community via street medicine. We present descriptive statistics and a Kaplan Meier (KM) curve to estimate time to VS (< 30 copies/mL) for those without VS.

Results: From November 2020-August 2022, we started 94 patients on LA-ART: median age 44 (range 28-69) years; 85% male, 10% female, 5% transgender/non-binary; 40% White, 13% Black, 36% Hispanic, 11% Other. Of the 94, 31% were homeless, 68% reported active substance use, and 45% had a major mental illness. In the study population, 47 had initial VS on oral ART; 43 were viremic [HIV RNA median 4.5 log, IQR: 2.8 to 5.1], with only 7 having a prior history of VS on oral ART; and 4 did not have a recent viral load; 67/94 patients had on-time injections throughout; 24 had 1 and 3 had ≥2 late injections; 4 received out-of-clinic injections. All 47 patients with VS stayed suppressed on LA ART. All patients without initial VS achieved viral loads (VL) < 30; median weeks to VS was 6.9 (95% CI 4 to 12.9). KM analysis estimates a probability of 0.962 of reaching VS by 28 weeks (**Figure**). By 42 weeks, 100% had reached VS with one patient exhibiting low-level viremia until undetectable.

Conclusion: We report a demonstration project of using LA-ART on a population of PLWH inclusive of those without virologic suppression with high rates of substance use, homelessness, and mental illness. LA-ART led to VS in all patients not initially suppressed. LA-ART may be indicated for patients with adherence challenges unable to achieve or maintain viral suppression on oral ART to extend its benefits.

KM curve of reaching virologic suppression for non-virologically suppressed patients on long-acting ART

Figure: Kaplan Meier curve of probability of reaching virologic suppression (VL <30) on LA ART (n=43; dotted lines 95% CI)



519 THIGH INJECTIONS OF CABOTEGRAVIR+RILPIVIRINE IN VIRALLY SUPPRESSED ADULTS WITH HIV-1

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Background: Cabotegravir (CAB) + rilpivirine (RPV) long-acting (LA) administered via gluteal intramuscular (IM) injections is recommended by treatment guidelines for maintaining HIV-1 virologic suppression. Previous data in healthy participants receiving single CAB+RPV LA IM injections to the *vastus lateralis* (thigh muscle) were supportive of further evaluation. Here we present the results of a substudy evaluating the pharmacokinetics (PK), safety, tolerability, and efficacy of CAB+RPV LA following short-term repeat IM thigh administration in adults with HIV-1 who had received ≥3 years of gluteal injections while participating in the ongoing Phase 3b ATLAS 2M study.

Methods: ATLAS-2M participants volunteered and reconsented for the substudy, which included a screening phase, thigh injection phase [Day 1–Week (W) 16], and return to gluteal injection phase (W16–24). The substudy injection schedule was unchanged from the main study [every 8 week arm (Q8W) arm, CAB 600 mg + RPV 900 mg; every 4 week (Q4W) arm, CAB 400 mg + RPV 600 mg]. CAB and RPV PK parameters following the last thigh gluteal injections and first and last thigh injections were determined by noncompartmental analysis and compared by mixed-effects modeling. Safety, tolerability, participant-reported outcomes, and efficacy were assessed.

Results: 118 participants (Q8W, n=54; Q4W, n=64) enrolled; median (range) age was 48 years (24–71), 38% were female sex at birth, 82% were White. In the Q8W arm, first CAB thigh injection $AUC_{(0-t)}$ and C_{max}, first RPV thigh injection C_{max}, and all last RPV thigh injection parameters were statistically higher vs. gluteal injections. No statistically significant differences occurred in the Q4W arm (**Table**). No participants had HIV-1 RNA ≥50 c/mL during the substudy; 3 per arm withdrew for non-virologic reasons. Across 210 Q8W and 494 Q4W thigh injections, 132 and 195 injection site reactions (ISRs) occurred, respectively; most were Grade 1 (55–76%) or 2 (19–38%), with 4–7% Grade 3. The median duration of ISRs was 3–3.5 days. One Grade 2 ISR led to withdrawal. Overall, 28–33% preferred thigh injections, largely due to ease of access.

Conclusion: CAB and RPV parameters following 16 weeks of thigh injections were similar to gluteal administration, with no clinically significant differences observed. These results support rotational/short-term CAB+RPV LA IM lateral thigh administration within an established gluteal regimen. Additional analyses will assess the potential for early or chronic thigh administration.

Table. Geometric Least Squares Mean Ratios and 90% Confidence Intervals for CAB and RPV Parameters Following Thigh (Test) and Gluteal (Reference) Administration by Injection Interval and Treatment Arm (Paired Data)

Analyte	Parameter	Q8W		Q4W	
		First thigh injection:Gluteal	Last thigh injection:Gluteal	First thigh injection:Gluteal	Last thigh injection:Gluteal
CAB	$AUC_{(0-\tau)}$	**1.21** (1.13, 1.30) (n=41)	1.09 (1.00, 1.20) (n=32)	1.13 (1.08, 1.19) (n=48)	1.04 (0.97, 1.11) (n=50)
	C_{max}	**1.35** (1.22, 1.49) (n=54)	1.10 (0.975, 1.24) (n=50)	1.18 (1.11, 1.25) (n=60)	1.06 (0.989, 1.14) (n=59)
	C_{τ}	0.926 (0.831, 1.03) (n=30)	0.929 (0.816, 1.06) (n=26)	1.16 (1.08, 1.25) (n=44)	0.983 (0.890, 1.09) (n=43)
RPV	$AUC_{(0-\tau)}$	1.15 (1.07, 1.23) (n=41)	**1.29** (1.20, 1.38) (n=33)	1.06 (1.02, 1.11) (n=49)	1.06 (1.01, 1.11) (n=50)
	C_{max}	**1.26** (1.12, 1.40) (n=54)	**1.18** (1.09, 1.28) (n=51)	1.08 (1.03, 1.12) (n=61)	1.04 (0.997, 1.08) (n=59)
	C_{τ}	1.06 (0.966, 1.17) (n=30)	**1.18** (1.07, 1.29) (n=26)	1.06 (0.991, 1.13) (n=44)	1.04 (0.974, 1.12) (n=43)

Bolded numbers are statistically significant. Statistical significance was determined when the 90% CIs of the GMR fall outside of the 0.8–1.25 range.
$AUC_{(0-\tau)}$, area under the plasma concentration–time curve from time 0 to the end of the dosing interval; CAB, cabotegravir; CI, confidence interval; C_{max}, maximum plasma concentration post intramuscular injection; C_{τ}, plasma concentration at end of dosing interval; GMR, geometric least squares mean ratio; Q4W, every 4 weeks; Q8W, every 8 weeks; RPV, rilpivirine.

520 IMPACT OF BASELINE FACTORS ON VIROLOGIC RESPONSE TO bNAb VH3810109 (N6LS) IN BANNER

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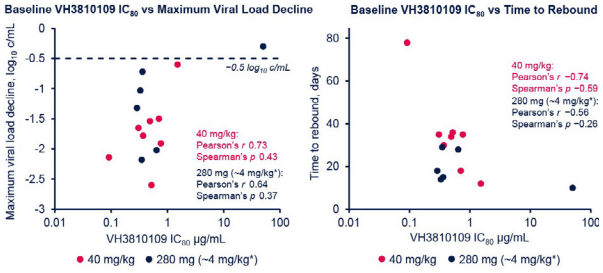
Background: Broadly neutralizing antibodies (bNAbs) are being developed for long-acting HIV-1 therapy. VH3810109 (N6LS) is a CD4-bs antibody with broad and potent neutralization activity *in vitro*, which is currently being evaluated in the Phase 2a BANNER study.

Methods: BANNER is a randomized, open-label, 2-part, multicenter study in treatment-naive viremic (viral load [VL] ≥5000 c/mL) adults to evaluate safety, pharmacokinetics, and antiviral activity of VH3810109. In part 1, VH3810109 was evaluated during monotherapy after a single IV infusion of 40mg/kg or 280mg (~4mg/kg) followed by 48 weeks of standard-of-care ART. Monotherapy duration was determined by either virologic non-response (VL < 0.5 log_{10} by Day 11) or rebound (VL ≥1.0 log_{10} over nadir or < 0.5 log_{10} from baseline [BL]). Antibody sensitivity of pre-dose and rebound viruses was determined retrospectively, using the PhenoSense mAb assay. Here we report the impact of BL viral and participant factors, on maximum VL decline (VLD) and time to virologic rebound following infusion of VH3810109.

Results: Fourteen participants enrolled, 13 were male, median (range) BL VL was 4.31 (3.13-5.24) log_{10} c/mL and median (range) BL CD4+ count was 369 (190-700) cells/mm^3. Virologic response was observed in 13 participants; median (range) viral nadir from BL was 1.72 (0.60-2.60) and 1.18 (0.30-2.18) log_{10} c/mL for 40mg/kg and 280mg, respectively. In a post hoc analysis, BL VH3810109 IC_{80} and CD4+ cell count were moderately correlated with maximum VLD and time to viral rebound in both treatment arms. The 2 participants with the highest BL IC_{80}s (1.512 and >50 µg/mL) had the smallest VLD (0.60 and 0.30 log_{10} c/mL) and the shortest time to rebound (12 days and virologic non-response). The longest time to rebound (78 days) was observed in the participant with the lowest IC_{80} (0.091 µg/mL). A weak correlation between lower BL log_{10} HIV-1 RNA and virologic response was apparent only in the 280mg dose group.

Conclusion: In BANNER part 1, a single IV infusion of VH3810109 was well tolerated, with few drug-related AEs and robust antiviral efficacy at both doses studied. In this small study, viral sensitivity to VH3810109 and BL CD4+ cell count correlated with magnitude and duration of antiviral response. However, other factors may impact virologic outcome, including pre-treatment VL, serum antibody concentration, and an individual's inherent control of viral replication. BANNER part 2 is ongoing to evaluate alternate dosing options and modalities for VH3810109.

FIgure. Viral Responses and Baseline Antibody Sensitivity of Plasma Viruses



Viral dynamic measures, N=14	40 mg/kg n=8	280 mg (~4 mg/kg*) n=6
Median VH3810109 IC_{80} of pre-dose virus, µg/mL	0.505 (0.091-1.512)	0.355 (0.288-50)
Median VH3810109 IC_{80} of rebound virus, µg/mL	3.166 (1.731-7.267) [n=7]	1.208 (0.807-50)
Median viral nadir from BL, log_{10} c/mL	1.72 (0.6-2.60)	1.18 (0.30-2.18)
Median time to viral nadir, days	16 (5-21)	9 (7-16)
Maximum viral nadir from BL, log_{10} c/mL	2.60	2.18
Median time to viral rebound among responders, days	35 (12-78) [n=8]	18 (14-29) [n=5]

*mg/kg dose assuming a body weight of ~70 kg.
IC_{80} value of 50 µg/mL represents the highest concentration tested in the PhenoSense mAb assay.

521 RAPID ART INITIATION USING BIC/FTC/TAF AND TDF+3TC+EFV IN PEOPLE WITH HIV IN CHINA

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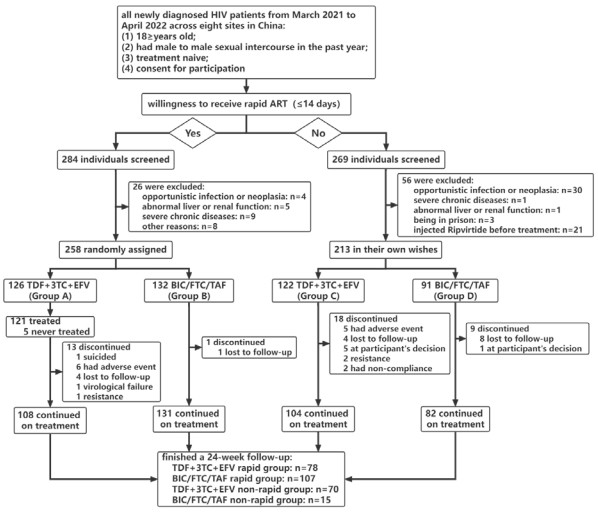
Background: The benefits of antiretroviral therapy (rapid ART) has been widely proven among people with HIV, but related data are still limited in China. This study examined virological outcomes and the treatment retention rate at 24 weeks after rapid versus non-rapid ART initiation, and analyzed the efficacy of Efavirenz 400 mg + Lamivudine 300 mg + Tenofovir disoproxil fumarate 300 mg (EFV+3TC+TDF) and Bictegravir 50mg/Emtricitabine 200mg/Tenofovir Alafenamide 25mg (BIC/FTC/TAF) for rapid ART.

Methods: This was a national, open lable, pragmatic randomized controlled trial. We enrolled all the HIV-1 infected adult (age ≥18 years) men who have sex with men (MSM) diagnosed from March 2021 to April 2022 across eight sites in China.The participants chose to start ART within 14 days after HIV diagnosis were randomly assigned (1:1) to the EFV group (A) and BIC group (B); those who denied rapid ART used EFV (C) or BIC (D) voluntarily. The primary endpoint was the percentage of viral suppression (<50 copies/mL) after 24 weeks.

Results: A total of 495 participants were enrolled, including 126, 132, 122 and 91 participants in A, B, C, D group respectively. In the rapid (group A and B) and non-rapid ART (group C and D) groups, 92.6% and 86.9% (P=0.053) participants retained in care (Figure 1). Viral suppression rate was higher in group B than in group A (93.5% vs 74.7%, p< 0.001) but similar between group A and group C (74.7% vs 76.1%, p=0.16) per FDA snapshot. In group B, 33.3% patients changed from underweight (BMI < 18.5) at baseline to normal weight (18.5≤BMI<25) after 24 weeks,10% patients and 18.0% patients changed from normal weight to overweight (25≤BMI< 30) in group A and B, 5.3% patient in group A and 8.1% patients in group B changed from overweight to obese (BMI≥30) respectively. Total serum cholesterol levels increased in both groups (+0.03 VS +0.47 mmol/L, P=0.001). The level of LDL was reduced in group A, while increased in group B after 24 weeks compared to baseline (-0.22 VS +0.27 mmol/L, P< 0.001). Changes of HDL (+0.10 VS +0.12 mmol/L, P=0.135), triglycerides(+0.04 VS +0.09mmol/L, P=0.881) and cholesterol/HDL(-0.24 VS -0.15, P=0.147) between the two groups were not statistically significant.

Conclusion: Rapid ART was associated with a good retention rate of care, BIC/FTC/TAF was effective for rapid ART.

Fig.1 Study flowchart



522 LONG-ACTING LENACAPAVIR IN A COMBINATION REGIMEN FOR TREATMENT-NAIVE PWH: WEEK 80

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Background: Lenacapavir (LEN), a potent first-in-class long-acting HIV-1 capsid inhibitor, is in development for treatment and prevention of HIV-1. CALIBRATE is an ongoing Phase 2 open-label active-controlled study evaluating subcutaneous (SC) and oral LEN, in combination with other antiretrovirals, in people with HIV-1 (PWH) who are initiating treatment. At the Week 54 (W54) primary endpoint, SC LEN every 6 months or oral LEN daily (QD) in combination with tenofovir alafenamide (TAF), bictegravir (BIC; B), or emtricitabine (F)/TAF, maintained high rates of virologic suppression (90%, 85%, 85%, respectively) and was generally well tolerated.

Methods: Participants were randomized (2:2:2:1) to 1 of 4 treatment groups (TG). TG1 and TG2 both received SC LEN + oral QD F/TAF for 28 weeks, after which virologically suppressed participants continued a 2-drug maintenance regimen: SC LEN with QD TAF (TG1) or QD BIC (TG2). TG3 received oral QD LEN + F/TAF, and TG4 received oral QD B/F/TAF throughout. We report the secondary efficacy endpoint by FDA Snapshot algorithm and safety at W80. The study did not have prespecified formal statistical comparisons between TGs.

Results: 182 participants (7% female, 52% Black) were randomized and dosed (n=52, 53, 52, 25 in TG1 to TG4). Median age was 29 years; 15% had viral load (VL) >100,000 c/mL. At W28, 94%, 92%, 94%, and 100% had VL < 50 c/mL. At W80, 87%, 76%, 87%, and 92% had VL < 50 c/mL; most remaining participants had discontinued study drug for reasons other than efficacy or safety (e.g. lost to follow up, participant decision, investigator decision: TG1 [n=6, 11%], TG2 [n=9, 17%], TG3 [n=6, 11%]). By missing=excluded analysis, 98%, 100%, 98% and 96% had VL < 50 c/mL. For participants in TG1 to TG3, CD4 count increased by a median of 249 cells/μL (IQR 122, 384) at W80 (223 [92, 350] in TG4). No participant experienced a study drug-related serious adverse event (SAE). No participants discontinued LEN due to AEs after W54. In TG1 to TG3, the most frequent non-injection site reaction (ISR) AEs were headache (16%) and nausea (13%). LEN-related ISRs were mostly mild to moderate.

Conclusion: LEN, given SC or orally in combination with TAF, BIC, or F/TAF, maintained high rates of virologic suppression through W80 and was well tolerated. These results support ongoing evaluation and further development of LEN in combination with other long-acting partner agents for the treatment of HIV-1 infection and support Gilead's long-acting oral and injectable development program.

523 WEEK 52 SUBGROUP EFFICACY OF LENACAPAVIR IN HEAVILY TREATMENT-EXPERIENCED PWH

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Background: Lenacapavir (LEN), a potent first-in-class long-acting inhibitor of HIV-1 capsid function, is in development for treatment and prevention of HIV-1. CAPELLA is an ongoing Phase 2/3 study in people with HIV-1 (PWH) who are heavily treatment-experienced (HTE) and who are viremic on their current regimen with multidrug resistance (MDR). At Week 52, LEN in combination with an optimized background regimen (OBR) led to high rates of virologic suppression (78%, 56/72) and CD4 increase (median 84 cells/μL). We report subgroup analyses of Week 52 efficacy by baseline HIV-1 RNA, CD4, INSTI resistance, and OBR in both cohorts.

Methods: The study included randomized and nonrandomized cohorts. In the randomized cohort, participants were randomized (2:1) to add oral LEN (600 mg on Days 1 and 2, 300 mg on Day 8) or placebo to their failing regimen. At

Day 15 (D15), those on oral LEN received subcutaneous (SC) LEN 927 mg every 6 months (Q6M); those on placebo started the oral lead-in, followed by SC Q6M. Randomized participants discontinued the failing regimen and initiated an investigator-selected OBR at D15. In the nonrandomized cohort, participants initiated OBR concurrent with LEN (OBR concurrent with LEN oral lead-in). Week 52 efficacy was assessed in both cohorts using FDA snapshot algorithm.

Results: 72 participants enrolled (36 in each cohort). 46% (33/72) had 4-class resistance (NRTI, NNRTI, PI, and INSTI); 17% (12/72) had no fully active agents in the OBR. High rates of virologic suppression were achieved among participants who had baseline high HIV-1 RNA, low CD4, INSTI resistance, suboptimal OBR, and regardless of use of DTG and DRV in the OBR (Table).

Conclusion: In this population of PWH who were heavily treatment-experienced with limited treatment options due to MDR HIV, LEN in combination with OBR led to high rates of virologic suppression, regardless of baseline HIV-1 RNA, CD4 count, INSTI resistance, and number of fully active OBR agents.

Table: HIV-1 RNA < 50 copies/mL at Week 52 (Snapshot Algorithm) by Subgroup

Table: HIV-1 RNA < 50 copies/mL at Week 52 (Snapshot Algorithm) by Subgroup

Subgroups	Randomized and nonrandomized cohorts (n=72)
Overall	78% (56/72)
Baseline CD4 < 200 cells/μL	72% (33/46)
Baseline CD4 ≥ 200 cells/μL	88% (23/26)
Baseline HIV-1 RNA < 100,000 copies/mL	81% (47/58)
Baseline HIV-1 RNA > 100,000 copies/mL	64% (9/14)
With INSTI Resistance	78% (39/50)
Without INSTI Resistance	75% (15/20)
0 fully active agents in OBR	75% (9/12)
1 fully active agent in OBR	77% (20/26)
≥ 2 fully active agents in OBR	79% (27/34)
With dolutegravir	67% (24/36)
Without dolutegravir	89% (32/36)

524 BASELINE nRTI HIV DRUG RESISTANCE AND EFFECT ON RECYCLED nRTIs: THE VISEND TRIAL

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VISEND TRIAL GROUP

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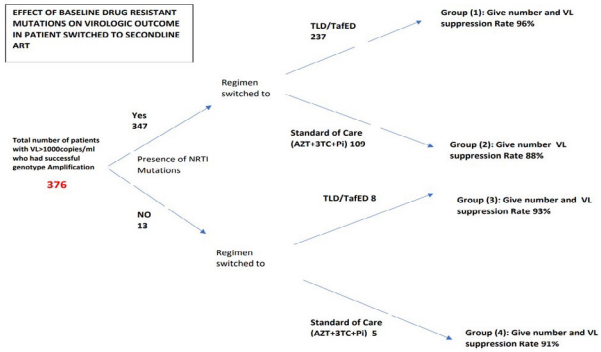
Background: The World Health Organisation approved Dolutegravir (DTG) with Zidovudine (ZDV) and Lamivudine (3TC) for second-line antiretroviral therapy. However, ZDV has been associated with adverse events which lead to treatment interruptions. There is evidence on efficacy of recycling failing NRTI backbone [tenofovir disoproxil fumarate (TDF) or tenofovir alafenamide (TAF), lamivudine (3TC) or emtricitabine (FTC) but this is seldom linked to baseline drug resistant mutations (bDRM) at the time of switch. We here analyzed the effect bDRM to NRTI on virologic outcome in patients switched from TDF, 3TC, Efavirenz (EFV) or Nevirapine (NVP) to DTG combined with either TDF,3TC [TLD] or TAF,FTC [TAFED], or ZDV, 3TC with a boosted protease inhibitor (bPI) of either lopinavir/ritonavir or atazanavir/ritonavir in the VISEND trial, an ongoing, 144-week randomised, open-label, noninferiority trial done at the University Teaching Hospital in Zambia.

Methods: We evaluated virological outcomes at 96 week post-transition among individuals with a baseline HIV RNA >1000 copies/mL and HIVDR switched to either TLD/TAFED or ZDV,3TC,bPI. HIVDR testing was done using an Applied Biosystems Genetic Analyzer model 3500XL. Genotyping encompassed protease and codons 1–230 of reverse-transcriptase genes. Sequences were assembled and manually edited using Sequencer version 4.5 software. Descriptive statistics were computed using STATA version 13. Viral suppression rates and Multivariate logistic regressions for common factors associated with treatment failure were computed.

Results: 783 patients with VL >1000 copies/ml were enrolled of which 62% were females and mean age was 41. 640 patients had samples taken for genotype of which 376 had successful amplification with 347 participants having NRTI associated mutations of which 191 had K65R. 39 participants had >=2 Thymidine analogue mutation (TAMS). There was no difference in virological suppression among those switched to TLD/TAFED with or without NRTI mutations (95.8% vs 93%: p=0.14). in those with NRTI mutation, those on TLD/TAFED were more like to have VLS compared to those switched to ZDV,3TC,bPI (95.8 v 88% : p = < 0.001) . K65R mutation was not associated with viral suppression.

Conclusion: This study demonstrated that recycling the NRTI backbone maybe efficacious in the presence of DTG despite NRTI mutations. Long time point assessment for the efficacy is required.

Effect of baseline HIVDR on Virologic outcomes in participants switched to second-line ART



525 INITIAL SUPPLEMENTAL DOLUTEGRAVIR DOSE IN SECOND-LINE ART: A PHASE 2 RANDOMISED TRIAL

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Background: Dolutegravir concentrations are reduced by the induction effect of efavirenz, necessitating twice daily dolutegravir dosing when co-administered. Efavirenz induction persists for several weeks after stopping, which could select for resistance if switching occurred with unsuppressed HIV-1 RNA levels. We evaluated the need for a lead-in supplemental dolutegravir dose in adults failing first-line antiretroviral therapy (ART) with tenofovir-emtricitabine-efavirenz (TEE) switching to tenofovir-lamivudine-dolutegravir (TLD).

Methods: We conducted a randomised, double-blind, placebo-controlled, phase 2 trial in Khayelitsha, Cape Town, South Africa. Eligible patients had virologic failure (defined as two consecutive plasma HIV-1 RNA ≥1000 copies/mL) on first-line TEE. Participants were randomly assigned (1:1) to switch to TLD with a supplemental 50 mg dolutegravir dose or placebo taken 12 hours later for the first 14 days. The primary outcome was the proportion of participants with plasma HIV-1 RNA < 50 copies/mL at week 24. This study was not powered to formally compare arms.

Results: 130 participants were randomly assigned to receive TLD with supplemental dolutegravir (n = 65) or placebo (n = 65). Median age was 38 years (IQR 32 – 45), 69% female, and participants had a median of 85 months of experience with ART (IQR 50 – 119). The median baseline HIV-1 RNA was 4.0 $\log_{10}$ copies/mL (IQR 3.5 – 4.7) and 76% had baseline resistance to both tenofovir and lamivudine. Baseline characteristics were similar between arms. By week 24, one participant died and two were lost to follow-up. Proportions with virologic suppression at weeks 12 and 24 were similar between arms (**Table 1**). In the subgroup of participants with baseline resistance to both tenofovir and lamivudine, 76 (84%, 95% CI, 75 – 91%) of 90 participants had HIV-1 RNA < 50 copies/mL at week 24. There were 19 participants with HIV-1 RNA ≥50 copies/mL at week 24; 15/19 (79%) participants re-suppressed HIV-1 RNA < 50 copies/mL with enhanced adherence counselling. Grade 3 or 4 adverse events were similar in frequency between arms. None of the six participants (3 in each arm) meeting criteria for resistance testing developed dolutegravir resistance.

Conclusion: TLD in second-line ART was effective and well tolerated in both arms. Our findings do not support the need for initial dolutegravir dose adjustment in patients switching to TLD who failed first-line TEE.

Table 1: Summary of primary and certain secondary efficacy outcomes

	TLD + Dolutegravir (n = 65)	TLD + Placebo (n = 65)
HIV-1 RNA <50 copies/mL, n (% [95% CI])		
Week 24		
mITT analysis*	55/64 (86% [75-93])	53/65 (82% [70-90])
Week 12		
mITT analysis	53/64 (83% [71-91])	55/65 (85% [74-92])
HIV-1 RNA <400 copies/mL, n (% [95% CI])		
Week 24		
mITT analysis	63/64 (98% [92-100])	59/65 (91% [81-97])
Week 12		
mITT analysis	61/64 (95% [87-99])	59/65 (91% [81-97])

TLD = tenofovir-lamivudine-dolutegravir, mITT = modified intention-to-treat

* Primary endpoint analysis

526 DORAVIRINE: SAFETY, TOLERABILITY & EFFICACY IN SOUTH AFRICAN WOMEN ON CONTRACEPTION

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Background: Prior to local scale-up of new antiretroviral therapy (ART) for HIV treatment, exploring drug-drug interactions between ART and contraception is crucial. We are conducting EPIC (Evaluation of Pharmacokinetic drug-drug Interactions between Contraceptives and doravirine-containing ART), a parallel group pharmacokinetic study to examine interactions with doravirine (DOR)-containing ART (DOR+3TC+TDF) among women of reproductive potential living with HIV in Johannesburg, South Africa.

Methods: EPIC began in November 2021 and is ongoing. A ≥6-week lead-in period with oral DOR was required after aviraemic participants switched from their existing ART. Participants in the 3 intervention groups on DOR-containing ART concomitantly self-selected contraception: intramuscular depomedroxyprogesterone acetate (DMPA; Group 1), etonogestrel implant (ETG; Group 2), or copper intrauterine device (IUD; Group 3). ETG & IUD groups were compared to historical control groups using the same contraceptive method but on dolutegravir-containing ART, plus a fourth group to compare DMPA-users (dolutegravir + DMPA; Group 4). Participants were followed up for 12 (Groups 1 & 4) or 24 weeks (Groups 2 & 3). Early safety (measured by number & severity of adverse events (AE)), tolerability (measured by patient satisfaction & drug adherence), and efficacy (HIV aviraemia as ≤40 copies/mL) are reported.

Results: Of 155 women screened, 87 have been enrolled: Group 1 (n=21), Group 2 (n=24), Group 3 (n=21) & Group 4 (n=21). The most common reasons for ineligibility were lack of HIV aviraemia (n=43, 74%) and/or haemoglobin abnormality of grade 2 or higher (n=13; 22%) at screening. Of all AEs reported to date (n=162), 13 (8%) were attributable to DOR, of which headaches (n=4, 2%) or nausea (n=2, 1%) were most frequent. All AEs were reported at grade 1, except for one AE of diarrhoea in Group 2 at grade 2. Among the DOR groups, only 1 participant reported dissatisfaction with this ART, 99% were happy to continue it, and adherence by pill count was 96% for >76% adherence. All but 2 participants (7%) in the DOR groups maintained viral suppression at study exit.

Conclusion: Switching from first-line regimens to DOR-containing ART appears to be safe, tolerable, and efficacious in maintaining viral suppression in South African women concomitantly using hormonal contraceptives. These data support the viability of this option for those living in resource-limited settings who are intolerant of or unable to take dolutegravir-containing ART.

Table 1. Safety, tolerability, and efficacy of doravirine-containing ART when concomitantly used with hormonal contraceptive methods, EPIC study, November 2022 to September 2023
(max 8 columns and 12 rows, not counted towards character count)

	Group 1 (DOR + ETG)	Group 2 (DOR + DMPA)	Group 3 (DOR + IUD)	Group 4 (DTG + DMPA)
Total number of participants enrolled	21	24	21	21
Total number of adverse events reported	52	43	27	40
Total number of participants with an adverse event reported	19	16	16	18
Grading of adverse events				
Grade 1:	39	36	18	26
Grade 2:	13	7	8	14
Grade 3 or higher:	0	0	1	0
Total adverse events attributable to DOR, and total at Grade 2 (proportion %)[1]	0	1	0	0
ART satisfaction				
Very satisfied	58	60	56	37
Satisfied	63	73	36	61
Not satisfied	1	0	0	0
Happy with continuing ART				
YES	119	131	91	95
NO	2	2	1	3
Adherence %				
0-25%	1	0	0	0
26-50%	1	1	0	0
51-75%	12	9	2	1
76-100%	55	43	33	0
>100%	175	214	134	200
Number (proportion %) with HIV viral suppression at study exit	5	15	6	16
<40 copies/ml	0	1	0	2
≥40 copies/ml	1	0	0	0
≥1000 copies/ml				

527 PLASMA AND URINE PK OF DOLUTEGRAVIR AND TENOFOVIR TO AID POINT-OF-CARE TESTING

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Background: Poor adherence to antiretroviral therapy and PrEP can significantly impact patient and public health. Point-of-care testing (POCT) may aid monitoring and improvement of adherence. We report the PK of dolutegravir (DTG) and tenofovir (TFV) [dosed as disoproxil fumarate (TDF)] in plasma and urine following drug cessation to evaluate missed dosing (non-adherence) and potential targets in urine for POCT.

Methods: Healthy volunteers were randomised (1:1) to receive DTG/FTC/TAF (Arm 1) or DTG/3TC/TDF (Arm 2) for 15 days. Plasma and urine were collected prior to dosing and up to 14 days (0, 1, 4, 24, 48, 72, 96, 168, 336 hours) post drug cessation. Concentrations in plasma and urine were quantified using validated LC-MS methods and nonlinear mixed effects (NONMEM v.7.4) applied to determine drug disposition between matrices and relationship with potential thresholds [DTG time above protein-adjusted (PA) IC_{90} (64 ng/mL) and recommended minimum effective concentration (MEC; 324 ng/mL), and concentration of TFV in urine indicative of more than 1 missed dose (1500 ng/mL, TDF)].

Results: Of 30 individuals enrolled, 29 were included (15 Arm 1, 14 Arm 2; 72% female at birth, 90% Caucasian). Plasma DTG and TFV (TDF, Arm 2) were described by 2-compartment models and concentrations in urine were modelled as a proportion of plasma using an accumulation ratio as a proportionality constant (AR_U). AR_U (RSE%) was 0.086 (0.2%) for DTG and 244 (16%) for TFV, with interindividual variabilities (RSE%) of 47.4% (0.2%) and 53.3% (53%), respectively. Median (range) predicted time to plasma DTG PA-IC_{90} and MEC was 83.5 hours (41.0-152) and 49.0 hours (23.7-78.9), corresponding to geometric mean (90%) urine concentrations of 5.42 ng/mL (4.37-6.46) and 27.4 ng/mL (22.1-32.7), respectively. TFV (TDF) in urine reached the threshold of 1500 ng/mL by 101 hours (58.6-205) [4.2 days (2.4-8.50)] with an equivalent plasma concentration of 6.20 ng/mL (4.21-8.18). Predicted concentrations following 1-3 missed doses are summarised (Table 1).

Conclusion: Given the low concentrations of DTG in urine, utility of a urine-based POCT would be limited to a readout of recent drug intake within 24 hours (i.e. 1 missed dose). By contrast, due to the persistence of TFV in urine, these data validate use of a urinary TFV threshold concentration of < 1500 ng/mL (for TDF-based regimens) as a marker of 1-3 missed doses, for a POCT platform.

Table 1. Predicted geometric mean (90% CI) dolutegravir and tenofovir (from TDF) concentrations in plasma and urine in healthy volunteers following drug intake cessation (1-3 missed doses).

	Number of missed doses (hours post-intake cessation)		
DTG	**1 (48 h)**	**2 (72 h)**	**3 (96 h)**
Plasma, ng/mL	348 (248, 449)	104 (60.8, 146)	34.1 (14.1, 54.2)
Urine, ng/mL	29.5 (5.50, 53.5)	8.77 (-2.73, 20.3)	2.89 (-2.68, 8.46)
TFV (TDF)	**1 (48 h)**	**2 (72 h)**	**3 (96 h)**
Plasma, ng/mL	26.6 (23.1-30.1)	11.8 (9.84-7.80)	6.46 (5.12-7.80)
Urine, ng/mL	6441 (4340-8542)	2859 (1850-3868)	1565 (975-2155)

528 HIGH SUPPRESSION AMONG PLHIV ON DOLUTEGRAVIR WITH VIROLOGICAL FAILURE IN UGANDA

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Background: In 2019, WHO recommended dolutegravir (DTG) for first- and second-line antiretroviral therapy (ART) regimens for people living with HIV (PLHIV). Per Uganda treatment guidelines, patients with virologic non-suppression (≥1,000 copies/mL) should receive intensive adherence counseling (IAC) with repeat VL within 6 months. This evaluation analyzed prevalence and factors contributing to suppression following programmatic routine IAC among PLHIV on DTG based regimens with virologic failure in Uganda.

Methods: We conducted a retrospective analysis on virologic non-suppressed (≥1,000 copies/mL) PLHIV on DBRs during October 2019–September 2020 who had a follow up VL test result, presumably following routine programmatic IAC. Data were abstracted from the Central Public Health Laboratory (CPHL), including patient demographics and test results. Suppression was defined as a VL test result of < 1,000 copies/mL at follow up given a previous result of ≥1,000 copies/mL. We characterized PLHIV on DBRs and used logistic regression models to assess factors (e.g., sex, age) associated with suppression.

Results: We analyzed 521 PLHIV on DBRs with virologic non-suppression who had a follow up VL test. Of these, 220 (42.2%) were children < 15 years and 231 (44.3%) were female. Median age was 28 years (interquartile range [IQR]: 12–43 years), and median duration on DBRs was 12 months (IQR: 6–15 months). Overall, 80.8% (421/521) PLHIV suppressed at the follow up VL test (children = 74.5% [164/220]; adults = 85.4% [257/301]). Compared to adults, children < 15 years were less likely to achieve suppression (Odds Ratio [OR]: 0.5; 95% Confidence Interval [CI]: 0.32–0.78, p=0.002). PLHIV with initial VL results ≥5,000 copies/mL were less likely to achieve virologic suppression at follow up testing compared to those with < 5000 copies/mL. (OR: 0.44; 95% CI: 0.29–0.84, p< 0.001).

Conclusion: Majority of adults and children with virologic failure achieved viral suppression following routine programmatic IAC as per the national treatment guidelines. Additional specialized support is needed for younger age groups and those with high VL results at first test.

529 EARLY VIROLOGICAL OUTCOME OF DTG-BASED REGIMEN IN ADULT ARV-NAIVE PLHIV IN RWANDA

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Background: In 2018, the Rwanda introduced DTG in the national HIV treatment guideline as the first-line regimen option for newly diagnosed HIV+ patients. The efficacy of DTG in the antiretroviral therapy (ART)-naïve population has been widely demonstrated in randomized clinical trials, showing superiority compared to both non-nucleoside reverse transcriptase inhibitors and protease inhibitors-based regimens. The aim of this study was to compare the early virological outcome of dolutegravir-based regimens with other regimens in adult (≥15 years) ART-naive people living with HIV (PLHIV) in Rwanda.

Methods: We performed a cross-sectional study; including all adult ART naïve patients initiated on ART from January 2018 to December 2020. The data was collected from the viral load sample management system (VL SMS) database and analyzed using Stata v.16. We evaluated the viral load suppression after 6 months on ART. All Adult clients initiated on ART during the study period and who have targeted viral load results were included in the data analysis. Proportions and frequencies were used to describe the study population. Logistic regression was used to assess the relationship between HIV viral load suppression (< 1000 copies/mL) and ART regimens. A p-value < 0.05 was considered significant.

Results: A total of 16,636 HIV viral load results were analyzed. Initiation on ART with DGT-based regimens increase from 29.8% in 2019 to 54.9% in 2020 (p >0.001). Highest in the City of Kigali (55.7%) followed by Western (47.3%), Northern (46.7%), Southern (44.8%), and Eastern (42.3%) provinces. The proportion of patients with 'target not detected' (TND) outcome was higher in the DTG group compared to the non-DTG group (61.5% vs 58.7%, p< 0.001). Unsuppressed VL was significantly lower in the DGT group (2.6% vs 4.7%, p< 0.001) with an adjusted odd ratio (aOR) = 0.499 (95%CI: 0.406 – 0.613) after adjusting for differences in age, sex, adherence, and province.

Conclusion: PLHIV initiated on DTG-based ART regimens have better virology outcomes than those initiated on on-DTG-based ART regimens. This is reassuring, since DTG has already been introduced in the national HIV treatment guideline as the first-line regimen option for newly diagnosed HIV+ clients.

530 VIROLOGIC FAILURE AFTER ROUTINE SWITCHING TO DTG-BASED FIRST-LINE ART

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Background: WHO recommends Dolutegravir (DTG) as the third drug in first-line antiretroviral therapy (ART) for people living with HIV (PLWH). Some pre-existing NRTI resistance mutations could lead to "functional" DTG monotherapy and thus increase the risk of DTG resistance. As resistance testing at the time of the switch is generally unavailable, there are concerns that PLWH who switch to a DTG-based regimen with HIV replication could develop resistance to DTG. We report early viral load (VL) results from DTG SWITCH study in Malawi and Zambia, two ART programs with different switching policies.

Methods: DTG SWITCH monitors virologic and drug resistance outcomes among adult PLWH routinely switched to DTG-based first-line ART in two ART programs in Malawi (Lighthouse Trust, Lilongwe) and Zambia (Centre for Infectious Disease Research in Zambia). According to national guidelines, PLWH in Malawi are switched irrespective of their VL, while in Zambia, only patients with the last routine VL < 1000 copies/mL are switched. PLWH with VL measurements between -90 to +7 days around the switching date (baseline) were eligible. We present proportions of patients with virologic failure (VF; VL >400 copies/ml) 1 year after switching (+/-90 days), by country and VL suppression status at baseline. We calculated relative risks (RR) of VF by VL suppression at baseline, with 95% confidence intervals (CI) and P values.

Results: In Malawi, 1121/1388 (81%) of eligible participants had a VL measurement also at 1 year and were included in the analysis (Table). Among those, 1114/1121 (99%) were women, the median age was 35.5 (IQR 30.4-40) years, and the median time on ART was 6.0 (IQR 3.8-8.9) years. At 1 year, the proportion with VF was 2.7% among those with suppressed baseline VL and 23.2% among those with unsuppressed baseline VL, for a RR of 8.6 (95% CI 4.7 to 15.5). In Zambia: 1321/1411 (94%) participants had 1-year VL, of whom 1102/1321 (83%) were women, the median age was 39.6 (IQR 33.2-45.2) years, and the median time on ART was 5.8 (IQR 3.3-8.4) years. At 1 year, the proportion with VF was 1.9% among those with suppressed baseline VL and 2.6% with unsuppressed VL, for a RR of 1.4 (95% CI 0.19 to 9.9).

Conclusion: The Malawi data indicate that PLWH switching with unsuppressed VL have a substantially higher risk of unsuppressed VL at 1 year than PLWH with suppressed VL at the time of the switch. The Zambian policy of only switching patients who were virologically suppressed at the last routine VL may reduce this risk.

Table: Virologic outcomes of PLWH at 1 year after routine switching to DTG-based first-line ART by viral load at switch, at two ART programmes in Malawi and Zambia.

	VL available at 1Y		VL missing at 1Y[b]	
	VL < 400 copies/ml N	VL ≥ 400 copies/ml N (%)[a]	N (%)[b]	Total N
Malawi (N=1388)				
VL < 400 at BL	1036	29 (2.7%)	247 (18.8%)	1312
VL ≥ 400 at BL	43	13 (23.2%)	20 (26.3%)	76
RR (95% CI)	8.6 (4.7 to 15.5)			
P	<0.0001			
Zambia (N=1411)				
VL < 400 at BL	1258	24 (1.9%)	87 (6.4%)	1369
VL ≥ 400 at BL	38	1 (2.6%)	3 (7.1%)	42
RR (95% CI)	1.4 (0.19 to 9.9)			
P	0.75			

VL, viral load; BL, baseline; 1Y, 1-year follow-up; RR, relative risk; CI, confidence interval; P, P-value
a; denominator is the number of patients with VL measurement at 1Y.
b; denominator is the number of patients with VL measurement at BL (Total N).

531 TRENDS IN TDR TO FIRST-LINE ANTIRETROVIRALS IN SPAIN: 2007-2021

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Background: Treatment guidelines currently recommend resistance testing in the RT and protease of HIV as a part of the initial evaluation of HIV infected patients. Thus, it is of interest to evaluate the prevalence of drug resistance mutations (DRM) and, also of clinically relevant resistance. Here, we present data on trends in DRM and clinically relevant transmitted drug resistance to ARVs recommended for first-line treatment in Spain

Methods: We analysed 7948 RT & Pro Fasta sequences from CoRIS (2007-2021). As Integrase resistance is not part of routine testing in naïve patients in Spain, we analysed 1975 integrase sequences. We evaluated the prevalence of RT/Pro and INSTI SDRMs using the CPR tools from Stanford. Clinically relevant resistance was evaluated using the Stanford Algorithm v9.1. We analysed periods for which significant changes in first line regimens recommended by the Spanish treatment guidelines (GESIDA) were provided.

Results: During the period 2007-2019, the prevalence of SDRMs were 3.5% NRTI, 4.3% NNRTI, 2.0% PIs, and 2.7% INI); in the last two years (2020-2021) we observed a similar trend for NNRTIs and NRTIs SDRM (3.8% NRTIs, 6.5% NNRTIs), and a decrease in TDR to PIs (1%) and to INSTIs (0%). Clinically Relevant resistance to recommended GESIDA's first line regimens showed no trend from 2007-2012 (always close to 9%), peaked in 2013-2014 due to the inclusion of Rilpivirine for 1st line in the Spanish recommendations, and lowered to below 3% for the years 2015-2019. For years 2020-2021, clinically relevant resistance to first line antiretrovirals in Spain was 0% to Dolutegravir, Bictegravir and Darunavir, 0.5% for 3TC/FTC; 1,2% for TDF/TAF, 1.7% for Abacavir, and 2.4% for Raltegravir.

Conclusion: While NNRTIs and NRTIs SDRM prevalence remained stable in Spain through 2007-2021, we observed a trend to a decrease in the levels of PIs and INIs SDRMs. Clinically relevant TDR to approved first line regimens is at low levels since 2016 to 2021. These findings support GESIDA's recommendations on baseline resistance testing and test and treat strategies.

532 WHAT INFLUENCES SWITCHING TO DTG/3TC VS B/F/TAF IN CLINICAL PRACTICE?

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Background: Both B/F/TAF and DTG/3TC are recommended in treatment guidelines for both initial and switch therapy in people with HIV (PWH). Understanding clinical and socio-demographic drivers of switching to DTG/3TC or B/F/TAF and how PWH vary by regimen is critical when comparing outcomes.

Methods: Retrospective study with Trio Health HIV Network EMR data. Eligibility: ≥18 yrs, switched to B/F/TAF or DTG/3TC after DTG/3TC approval (4/2019-6/2022). Baseline (BL) characteristics were compared (X-square, t-test). Logistic regression (LR) predicted probability of prescribing/dispensing DTG/3TC (propensity scores; PS) given BL characteristics. Classification regression trees (CRT) and LR identified primary predictors of prescribing/dispensing DTG/3TC. All shown comparisons were significant ($p < .05$).

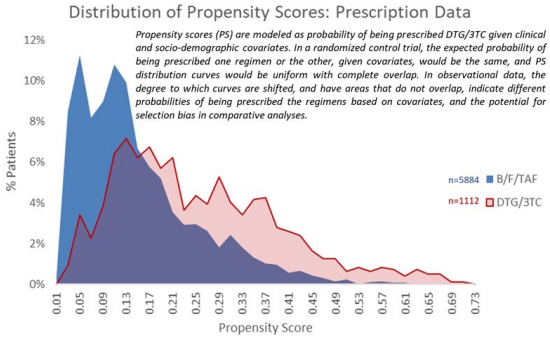
Results: Of 6996 PWH, 1112 (16%) were prescribed DTG/3TC. PWH prescribed DTG/3TC differed in key characteristics: age ≥50 yrs (49 vs 38% B/F/TAF), commercial payer (57 vs 45%), BL viral suppression (VS < 200 copies/ml; 94 vs 92%), CD4 >200 cells/mm^3 (84 vs 66%), eGFR < 60 mL/min/1.73m^2 (15 vs 6%), prior INSTI use (59 vs 36%), obese (BMI > 30 kg/m^2; 32 vs 26%), hyperlipidemia (32 vs 28%), hypertension (34 vs 25%), osteoporosis (4 vs 2%), renal disease (10 vs 3%), alcohol (4 vs 6%), or substance use (5 vs 10%). Similar results were observed in the subset with dispensing data (n=3946; 13% DTG/3TC).

The PS distribution [Fig.] for DTG/3TC was shifted right, with distinct tails for DTG/3TC (right) and B/F/TAF (left), where the probability of the alternate regimen was lower based on BL characteristics.

For DTG/3TC (vs B/F/TAF), CRT and LR identified primary prescribing predictors: prior INSTI (odds ratio [OR]=2.4), CD4 >200 (OR=2.7), eGFR< 60 (OR=2.2), no substance use (OR=2.8), payer (Commercial vs Medicare OR=1.4). Payer was the primary predictor of DTG/3TC dispensing (followed by hyperlipidemia, CD4, prior INSTI).

Conclusion: Baseline characteristics of PWH switching to DTG/3TC vs B/F/TAF were significantly different. B/F/TAF prescription was associated with factors that reflect HIV clinical parameters and adherence (e.g., VS, CD4< 200, substance use). By contrast, prescribing DTG/3TC was associated with renal toxicity and obesity. The results argue that although they are both guideline-recommended regimens, clinicians do not perceive them as equally appropriate for all patients. Accounting for channeling bias in observational studies evaluating outcomes is essential for interpreting differences between regimens.

Figure. Distribution of Propensity Scores.



533 ASSOCIATION OF WEIGHT GAIN ON DOLUTEGRAVIR WITH CHANGES IN ADHERENCE AND VIRAL LOAD

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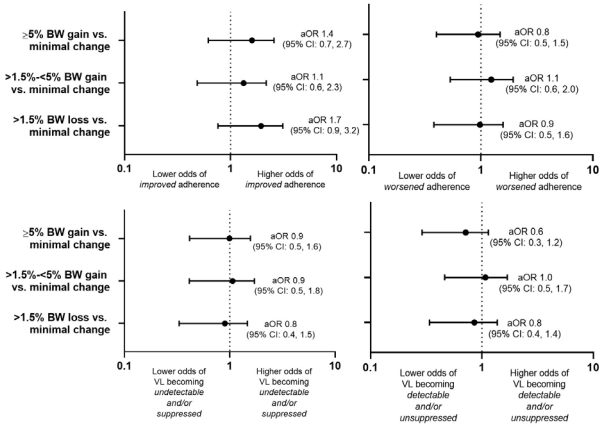
Background: Excess weight gain has been associated with dolutegravir-containing antiretroviral therapy (ART), especially among people living with HIV (PLWH) of female sex and Black African origin. If undesired, weight gain after initiating dolutegravir might impact adherence, with potential downstream effects on viral suppression. We sought to examine the relationship between changes in body weight (BW) and changes in adherence and viral load (VL) among PLWH switching to tenofovir disoproxil fumarate/lamivudine/dolutegravir (TLD).

Methods: The longitudinal African Cohort Study (AFRICOS) enrolls PLWH engaged in routine care at 12 PEPFAR-supported facilities in Kenya, Nigeria, Tanzania, and Uganda. We included participants who initiated TLD and had been on ART for ≥6 months prior and had visits both within 12 months before and 6-18 months after starting TLD, and were not pregnant. Pre/post-TLD initiation, we examined percent change in BW (≤1.5% [minimal change], >1.5% loss, >1.5%-< 5% gain, ≥5% gain [clinically significant]), change in self-reported antiretroviral adherence (0, 1-2, ≥3 doses missed in past 30 days), and change in HIV-1 RNA VL category (< 50 c/mL [undetectable], 50-999 c/mL [suppressed], ≥1000 c/mL). The association of percent BW change with change in adherence and VL was examined using multivariable multinomial logistic regression models using no change in either outcome as the reference value.

Results: Among 1507 participants who started TLD from 10/2018-11/2021, median time from starting TLD to follow-up visit was 9 months (IQR: 7, 11). Pre/post-TLD, the prevalence of overweight/obesity increased from 33% to 38%, with 29% of all participants having a ≥5% BW gain. There were statistically significant (p=0.01) differences by sex in percent BW change, with largest differences for a ≥5% gain (females: 32%, males: 25%) and a >1.5% loss (females: 21%, males: 25%; 23% overall). Compared with a BW change ≤1.5%, BW changes ≥1.5%, including a ≥5% BW gain, were not significantly associated with changes in adherence or VL (figure). Results were similar when limiting to participants who were not underweight at baseline.

Conclusion: Clinically significant weight gain after switching to TLD may not be a major threat to short-term adherence or viral suppression among ART experienced PLWH in sub-Saharan Africa. Although this finding is reassuring, increasing cardiometabolic risk in the TLD era needs to be urgently addressed while simultaneously optimizing HIV treatment outcomes.

Associations* of changes in body weight with changes in adherence and viral load before and after starting TLD



*Models were adjusted for age, sex, baseline BMI, year of starting ART, time since starting TLD, and program.

534 PREDICTIVE VALIDITY OF A MEASURE OF BARRIERS TO ART ADHERENCE FOR HIV CARE (I-SCORE)

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Background: It is recommended to identify and address adherence barriers to antiretroviral therapy (ART) in routine HIV care. From a conceptual framework, we created a 7-item patient-reported measure (Interference-Score) to evaluate seven barrier domains (i.e. Thoughts/Feelings, Habits/Activities, Social situation, Economic status, Medication, Care, and Health). Both English and French versions were produced with stakeholder engagement and cognitive testing. Here, we assess the measure's construct validity.

Methods: Recruited January to August 2022, people with HIV (PHIV) on ART in Canada and France completed the 7-item I-Score with 4 dependent variables at baseline (Time 1) and 4 weeks later (Time 2): dichotomized self-reported measures of adherence (past 7 days, past 30 days), intention to adhere, and HIV viral load. We conducted 3 types of analyses: 1) inter-item correlations (Spearman's coefficients) to assess item redundancy at Time 1; 2) logistic regressions with all 7 items (covariates), with one model for each dependent variable, to assess each item's significance; and 3) Receiver operating characteristic (ROC) curve analyses and appropriate reference values, to evaluate the 7-item models' predictive capacity. Analyses 2) and 3) were performed using I-Score Time 1 items to predict the dependent variables at Time 1 and Time 2, respectively. Areas under the curve are reported with 95% bootstrap confidence intervals.

Results: Analyses included 265 PHIV at Time 1 and 154 at Time 2. Correlation coefficients ranged from 0.33 to 0.68; hence, no item was considered for elimination. Table 1 shows all other statistical analyses. The items (covariates) of "Thoughts", "Habits", "Health" and "Economic status" were significantly and independently associated with from 1 to 3 dependent variables. The ROC analyses showed the 7-item models' predictive capacity to be "excellent" to "outstanding" for viral load, correctly classifying over 80% of respondents. The models were also "acceptable" for Adherence in the past 30 days and past 7 days, correctly classifying at least 72% of respondents.

Conclusion: While there was sample attrition from Time 1 to Time 2, no negative impact on the models' predictive capacity was observed. The 7-item I-Score is a promising, simple, valid, and comprehensive tool to evaluate ART adherence barriers in care. Its items show limited redundancy, and the analyses provide strong evidence of concurrent and predictive validity for viral load.

Table 1. Results of the eight logistic regressions and ROC curve analyses for the 7-item I-Score.

Dependent variable	Dependent variable timing	Significant covariate	Area under ROC curve	Predictive capacity
Adherence past 30 days (≥95%, 0-94%)	Time 1	Thoughts (p=0.03) Habits (p=0.003)	0.72 (0.64-0.80)	Acceptable
	Time 2	Thoughts (p=0.04) Habits (p=0.02)	0.74 (0.63-0.83)	Acceptable
Adherence past 7 days (All pills taken, ≥1 missed pill)	Time 1	Habits (p<0.001)	0.78 (0.69-0.86)	Acceptable
	Time 2	Habits (p=0.02) Thoughts (p=0.01) Health (p=0.01)	0.78 (0.64-0.85)	Acceptable
Intention to adhere (M=5 Strongly agree, M<5)	Time 1	Economic (p=0.04)	0.68 (0.60-0.74)	Poor
	Time 2	Thoughts (p=0.003) Economic (p=0.02)	0.76 (0.68-0.84)	Acceptable
Viral load (Detectable, Undetectable)	Time 1	Habits (p<0.001) Health (p=0.002)	0.82 (0.71-0.89)	Excellent
	Time 2	Health (p=0.004)	0.96 (0.88-1.00)	Outstanding

535 US PATIENT PREFERENCES FOR LONG-ACTING HIV TREATMENT: A DISCRETE CHOICE EXPERIMENT

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Background: Recent advances in long-acting antiretroviral therapy (LA-ART) could provide new options for HIV treatment and reduce adherence barriers, if regimens are acceptable to patients. We elicited preferences for key attributes of potential LA-ART regimens among people with HIV (PWH) in the United States, focusing on four different treatment modalities (oral tablets, subcutaneous and

intramuscular injections, and implants), product characteristics, and location of administration.

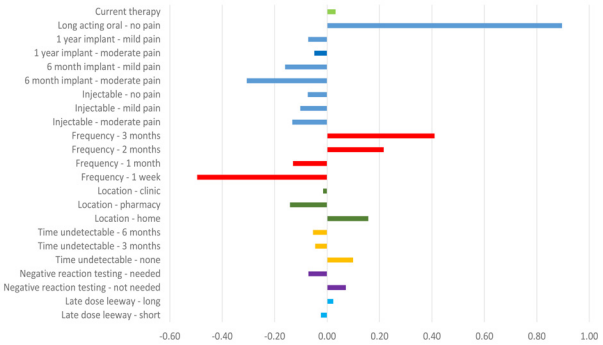
Methods: A discrete choice experiment was conducted among PWH aged ≥18 years recruited from HIV clinics in western Washington State and Atlanta, Georgia from 3/2021 to 6/2022. Participants responded to 17 choice scenarios, each with three options: two systematically generated hypothetical LA-ART regimens and a constant opt-out (their current daily oral treatment). LA-ART regimen descriptions included delivery mode, pain, dosing frequency, location, pre-treatment time undetectable, pre-treatment negative reaction testing, and late-dose leeway (i.e., flexibility in timing next dose). Implant frequency was constrained to be every 6 or 12 months, with mild or moderate pain. We used conditional logistic regression, with an interaction between delivery mode and pain, to estimate preference weights for all attribute levels.

Results: Seven hundred participants (350 at each site) enrolled, with median age 51 years (range 23-70); 70% identified as male, 24% as female, and 6% as non-binary/missing. Preference weights for each attribute level were summarized (Figure), with more preferred characteristics having higher preference weights. Across all participants, LA oral tablets were the only modality preferred over current daily oral treatment, with annual implants and injections the next most preferred. Longer time between doses was preferred, and administration at home was preferred to clinics, which were preferred to pharmacies. Attributes that impacted preferences less included oral lead-in treatment to achieve viral suppression or test for negative reactions and late-dose leeway around the prescribed dosing interval.

Conclusion: PWH in the United States may soon have several options for LA-ART. Our results suggest that LA oral tablets will be preferred by many patients over their current treatment, while implants and injections with longer duration may be acceptable to some patients. Future research should investigate sources of preference heterogeneity and actual uptake of and retention on products, when available.

Figure: Long-acting antiretroviral treatment preference weights from conditional logistic regression.

Figure: Long-acting antiretroviral treatment preference weights from conditional logistic regression. Mean preference-weight estimates for each attribute relative to the mean attribute effect are presented, normalized around zero. Positive weights indicate lower preference relative to the other levels evaluated. The overall relative importance of an attribute overall is the difference between the largest and the smallest preference weights of that attribute.



536 ANTIRETROVIRAL THERAPY CONCEALMENT, ADHERENCE, AND PREFERENCES IN PEOPLE WITH HIV

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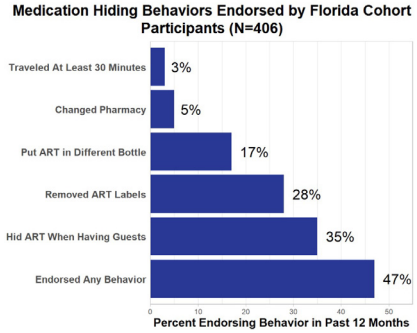
Background: It is unknown if antiretroviral therapy (ART) concealment to prevent inadvertent disclosure of one's HIV status impacts ART adherence. Our aims are to describe ART concealment behaviors and associated factors among a cohort of PWH and assess whether ART concealment is associated with ART adherence or interest in long-acting injectable (LAI) ART.

Methods: The Florida Cohort Study has been enrolling adult PWH around the state since October 2020. Participants were asked about ART adherence (optimal ≥85%) in the preceding 30 days, engagement in at least one of five ART concealment behaviors to hide their HIV status in the past year (hiding ART bottles, removing prescription labels, moving ART to another bottle, changing their pharmacy, and traveling ≥30 miles to obtain ART), and preferences for ART formulations (strong preference for LAI or not). Disclosure of HIV status to social network was categorized as having no social network to disclose to, incomplete disclosure of status to social network, and complete disclosure (reference). Simple and, if significant, multivariable (adjusting for age, alcohol use, injection drug use, depression, and anxiety) logistic regression models were used to discern differences between those with and without ART concealment and associations with ART adherence and LAI preference.

Results: Of 406 participants between 2020-2022 (62% aged 50+, 60% male, 42% non-Hispanic Black), 47% reported at least one ART concealment behavior, 6% reported < 85% adherence, and 64% of the 308 participants who responded preferred LAI. ART concealment was associated with at-risk drinking (aOR 2.5 95% CI 1.4, 4.6), depression symptoms (aOR 2.2 95% CI 1.1, 4.2), incomplete disclosure to their close social network (aOR 3.1 95% CI 1.9, 5.0) or reporting not having a social network (aOR 3.3 95% CI 1.4, 7.8), and ≥85% ART adherence (aOR 0.3 95% CI 0.1, 0.9). ART concealment was not significantly associated with LAI preference in simple regression (OR 1.3 95% CI 0.8, 2.3).

Conclusion: Concealing ART to hide one's HIV status was common and was associated with at-risk drinking, depression, incomplete disclosure to or lack of close social network, and reduced likelihood of optimal adherence. These findings show PWH may prefer receiving ART through mechanisms that ensure privacy. Future research can examine the impact of ART concealment on HIV outcomes like viral suppression and improve adherence among PWH concerned with disclosure of their HIV status.



537 HIV-1 RNA DECAY IN SEMEN AND RECTUM AFTER INITIATING THERAPY WITH DTG PLUS 3TC

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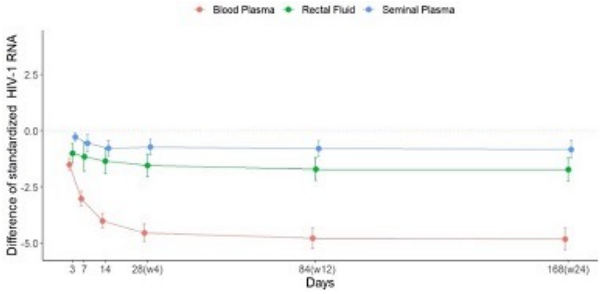
Background: The study of HIV decay in genital fluids and rectum is important to assess the potential risk of sexual transmission after initiating ART. We observed similar HIV-1 RNA decay patterns in seminal plasma (SP) and rectal fluid (RF) with DTG+3TC and BIC/FTC/TAF (Imaz et al. CROI 2022). The present study aims to evaluate differences in HIV-1 RNA decay in SP, RF, and blood plasma (BP) with the dual combination DTG+3TC.

Methods: This is a sub-study of a randomized pilot trial. Inclusion criteria were ART–naive male, BP HIV-1 RNA < 500,000 copies(c)/mL, CD4 count >200 cells/µL, HBV negative and no resistance to the study drugs. Participants were randomized (2:1) to DTG + 3TC 300 or BIC/F/TAF. HIV-1 RNA was measured in BP, SP and RF at baseline (BL), days 3, 7, 14 and 28, weeks 12 and 24 (LOQ: 20 c/mL or swab). This analysis is focused on the DTG+3TC group. HIV-1 RNA decline from BL at each timepoint was compared between compartments using the Friedman test. Linear mixed effects models were used to assess factors related with HIV-1 RNA decline.

Results: Of 24 participants, 16 received DTG+3TC. Median [range] age was 31 [22;60] years and CD4 392[331;463] cells/µL. Median BL HIV-1 RNA was 4.56 [4.22;4.86] $\log_{10}$ c/mL in BP; 2.38[1.30;2.95]$\log_{10}$ c/mL in SP; and 2.92[2.36;3.73] $\log_{10}$ c/swab in RF. In 6/16 and 1/16 individuals BL HIV-1 RNA was < 20 c/mL in SP and RF, respectively.

The HIV-1 RNA decline from BL was significantly more pronounced in BP at all timepoints in comparison with SP, and from Day 7 through W24 in comparison with RF. HIV-1 RNA reduction was greater in RF compared with SP at day 3 and from Day 28 to W24 while no significant differences were observed at Days 7

and 14. Figure 1 shows the median[IQR] reduction of standardized HIV-1 RNA by study timepoint and compartment.
The linear mixed effects models showed a significant interaction between the compartment and the magnitude of HIV-1 RNA decline when SP and RF were compared to BP.
The median time to achieve HIV-1 RNA < 20 c/mL was shorter in SP (7 days [0;8.75]) and RF (10 days [3;17.5]) than in BP (28 days [14;84]) (p< 0.001). In 1 individual HIV-1 RNA < 20c/mL was not achieved in SP (32 c/mL at W24) despite suppression in BP and RF.
Conclusion: Different HIV-1 RNA decay patterns were observed in SP and RF compared to BP in PLWH treated with DTG+3TC. Despite a more pronounced decline in BP, a rapid HIV-1 RNA suppression was observed in SP and RF due to a lower BL viral load in these compartments.
Differences of standardizes HIV-1 RNA between compartments



538 ANTIVIRAL ACTIVITY OF LENACAPAVIR AGAINST HIV-2 ISOLATES

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Background: Lenacapavir (LEN) is a first-in-class, multistage inhibitor of HIV-1 capsid function in clinical development that was recently approved in the European Union for use in adults with multidrug-resistant HIV-1 infection. LEN is highly potent against HIV-1 *in vitro* and maintains wild-type activity across HIV-1 isolates with resistance to all existing drug classes. In clinical trials, LEN has shown high levels of efficacy in people with HIV-1 who are treatment-naïve or treatment-experienced. However, a comprehensive characterization of the antiviral activity of LEN against HIV-2 is lacking. Herein, we studied the activity of LEN against a panel of HIV-2 isolates with or without resistance to existing drug classes.
Methods: The activity of LEN against HIV-1 and HIV-2 isolates from antiretroviral-naïve individuals was directly compared in two different assays: single-cycle infections of MAGIC-5A indicator cells and multicycle infections of an immortalized T cell line (CEM-NKR-CCR5-Luc). Drug-resistant HIV-2 variants with mutations in reverse transcriptase (RT) and integrase (IN) were tested for resistance to LEN in the single-cycle assay.
Results: In the single-cycle assay, LEN inhibited HIV-1 with a mean 50% inhibitory concentration (IC_{50}) of 210 pM (range = 140–310 pM; n = 10 isolates). In comparison, the mean IC_{50} value for HIV-2 was 2.3 nM (range = 1.1–3.2 nM; n = 12 isolates), indicating an 11-fold decrease in the activity of LEN against HIV-2 compared with HIV-1. In the multicycle assay, a comparable difference in LEN activity between HIV-1 and HIV-2 was also noted, with mean IC_{50} values of 110 pM for HIV-1 (range = 67–196 pM; n = 4 isolates) and 1.8 nM for HIV-2 (range = 1.0–3.2 nM; n = 6 isolates). The presence of drug resistance mutations in HIV-2 RT and IN had no effect on LEN activity (fold-change in LEN IC_{50} = 0.73–1.2 relative to wild-type HIV-2ROD9).
Conclusion: In our study, LEN was active against HIV-2 isolates with low-nanomolar activity, but was 11- to 16-fold less potent against HIV-2 in comparison to HIV-1, regardless of the presence of drug resistance mutations in HIV-2 RT or IN. As a result of this difference in potency, treating people with HIV-2 with a LEN-based regimen would require careful monitoring to assess virologic and immunologic responsiveness. These data provide information on the potential clinical utility of LEN in people with HIV-2 for whom treatment options are limited.

539 IMMUNO-VIROLOGICAL AND CLINICAL FOLLOW-UP OF HIV-2 PATIENTS RECEIVING BIC/FTC/TAF

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Background: HIV-2 infection remains a significant health problem in West Africa. Choices of antiretroviral drugs (ARVs) are limited but HIV-2 is fully susceptible to all nucleoside inhibitors (NRTIs) and integrase inhibitors (INSTIs). Bictegravir is active *in vitro* but no clinical data are available.
Methods: A retrospective study of patients (Pts) followed for HIV-2 infection in the Infectious Diseases Unit at Bichat Hospital, Paris, France and treated with BIC/FTC/TAF. Data were obtained from flow charts after patients' written informed consent and were censored at September 1st 2022.
Results: Twenty-four Pts living with HIV-2 (PLHIV-2) received BIC/FTC/TAF, 14 women and 10 men. Median age was 56 yrs [IQR 50.2-60.2], median time since HIV-2 infection diagnosis was 19 yrs [IQR 8-23] and median nadir CD4 cell count 319/mm3 [IQR 174-432]. Zenith viral load was below 100 c/mL in 13 Pts and detectable in 11 Pts with a median value of 597 c/mL [IQR 513-567]. Five Pts were treatment-naive and 19 were receiving ARVs with a median of 2 [IQR 1-3] previous regimens. ARVs preceding switch to BIC/FTC/TAF was a backbone of 2 NRTIs combined with darunavir/r in 5 Pts, raltegravir in 10 Pts, and dolutegravir in 4. Eight of these 19 pretreated patients had an history of treatment failure.
At time of BIC/FTC/TAF initiation, median CD4 cell count was 580/mm3 [IQR 380-697]. Three Pts only, all naïve, had detectable viral load (57, 94 et 130 c/mL) with a viral load assay threshold of 40 c/mL
At time of evaluation, the median duration of BIC/FTC/TAF treatment was 21.7 months IQR [12.9-30.4]. No Pt discontinued treatment. Viral load was < 40 c/mL in all Pts. Median CD4 cell count was 655/mm3 [IQR 495-800], p = 0.06 by Wilcoxon signed rank test when compared with CD4 count at time of BIC/FTC/TAF initiation.
Conclusion: In this observational study of PLHIV-2, BIC/FTC/TAF was well tolerated and efficient to achieve or maintain suppression of HIV-2 replication in all Pts. These results suggest that this BIC/FTC/TAF single-tablet-regimen is a valuable treatment option in PLHIV-2.
Furthermore, TAF has a reduced risk of renal toxicity compared to TDF and is active against B hepatitis virus infection, that is frequent in Africa and overlaps with HIV-2 epidemics. More data in ARV-naive PLHIV-2 with detectable viral load at time of ARVs initiation should now be obtained to confirm the value of this combination in the treatment of HIV-2 infection.

540 ULTRA-LONG-ACTING BICTEGRAVIR NANOFORMULATIONS

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Background: Antiretroviral therapy (ART) halts viral replication leading to reduced morbidity, mortality, and transmission of infection in people living with or at risk for HIV infection. However, therapeutic limitations remain. These include suboptimal adherence, adverse events, regimen tolerability, and viral resistance. To these ends, the need for ultra-long-acting (ULA) antiretroviral (ARV) formulations with extended duration of action cannot be overstated. Herein, we report the transformation of bictegravir (BIC) into prodrug formulations with apparent half-life extensions. The BIC prodrugs and corresponding nanocrystals were tested for their physicochemical and pharmacokinetic (PK) properties. The overarching goal was to create ULA BIC prodrug formulations with limited injection volumes and a shorter terminal phase PK tail.
Methods: Dimeric (DiBIC) and monomeric (MBIC, M2BIC, M3BIC) BIC prodrugs were synthesized by one-step dimerization and mono-esterification reactions. The synthesized prodrugs were nanoformulated by high-pressure homogenization. The formed aqueous solid drug nanocrystals were stabilized by non-ionic surfactants. Prodrug stability, particle size, homogeneity, and surface charge were assessed. Cellular uptake and retention, antiretroviral efficacy, and cytotoxicity were tested in primary human monocyte-derived macrophages (MDM). Following a single intramuscular (IM) injection, PK and biodistribution (BD) profiles were evaluated in Balb/cJ mice, SD rats, and rhesus macaques.

Results: The lead nanoformulated DiBIC (NDiBIC) and M2BIC (NM2BIC) were stable for at least six months and demonstrated drug loadings and encapsulation efficiencies of >75%, 230-450 nm size, and PDIs of 0.2-0.3. A single treatment of MDM with 25 µM of either NDiBIC or NM2BIC led to sustained intracellular drug l that led to protection against HIV-1ADA for up to 30 days. Importantly, PK testing of NDiBIC after a single IM injection of rodents at 45 mg BIC eq./kg dose produced plasma BIC concentrations at or above the protein-adjusted (PA) 95% inhibitory concentration (PA-IC_{95}) for >7 months. The profiles demonstrated a shorter terminal phase PK tail. NM2BIC demonstrated plasma BIC concentrations at or above the PA-$IC_{95}$for >11 months in rodents. Ongoing evaluation of NM2BIC in rhesus macaques demonstrates BIC plasma levels remain above the PA-IC_{95} at three months (**Figure 1**)

Conclusion: The lead NDiBIC and NM2BIC prodrug formulations demonstrate the potential for beyond every six-month dosing interval of BIC.

PK testing of a single dose of BIC prodrug formulations (NMBIC, NM2BIC, NM3BIC or NDiBIC)

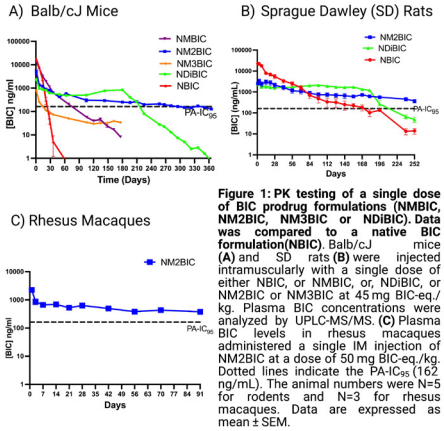

Figure 1: PK testing of a single dose of BIC prodrug formulations (NMBIC, NM2BIC, NM3BIC or NDiBIC). Data was compared to a native BIC formulation(NBIC). Balb/cJ mice **(A)** and SD rats **(B)** were injected intramuscularly with a single dose of either NBIC, or NMBIC, or, NDiBIC, or NM2BIC or NM3BIC at 45 mg BIC-eq./kg. Plasma BIC concentrations were analyzed by UPLC-MS/MS. **(C)** Plasma BIC levels in rhesus macaques administered a single IM injection of NM2BIC at a dose of 50 mg BIC-eq./kg. Dotted lines indicate the PA-IC_{95} (162 ng/mL). The animal numbers were N=5 for rodents and N=3 for rhesus macaques. Data are expressed as mean ± SEM.

542 ZINC ADJUVANT TREATMENT IN SARS-CoV-2: A RANDOMIZED CLINICAL TRIAL

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Background: The immune system is highly susceptible to changes of zinc levels and this might imply a different response against infection. Prior evidence suggests some benefit on viral infection prognosis after zinc supplementation. We aim to study the efficacy of zinc supplementation in SARS-CoV-2 infection outcomes.

Methods: This is an unicenter prospective, randomized cliinical trial where unvaccinated individuals with moderate SARS-CoV-2 infection without end-organ failure were randomized to standard of care+oral zinc for 15 days (three times per day a tablet of 83mg of Zn acetate equals to 75 mg of Zn element) (zSoC) (n =37) or standard of care alone (SoC) (n = 34). The primary combined outcome was death due to SARS-CoV-2 or intensive care unit (ICU) admission. Secondary outcomes included length of hospital stay (LoS) and time to clinical stability (defined as: oxygen saturation >94% [FiO2 21%], normalized level of consciousness [baseline], HR < 100rpm, systolic BP >90mm Hg,Temperature < 37.2ºC). Wilcoxon–Mann–Whitney test generalized Odds ratio (ORs) and 95% confidence intervals (CIs) for differences in outcomes between SoC and zSoC. A logistic regression model was fitted adjusted by age, sex, severity and comorbidity to compare the primary outcome between SoC and zSoC.

Results: Seventy-one participants were recruited. No significant differences in terms of age, gender and comorbidities nor in SoC were found between groups (Table 1). 14-day Mortality was 2.90 % (2 participants) in the SoC group and none in zSoC. ICU admission rates were, respectively, 8 (23%) and 1 (2.7%) (OR: .098; 95% CI .013–.766). The principal combined outcome occurred in 8 participants (23%) in SoC and in 2 (5.4%) in zSoC (OR: 0.18; 95% CI .03–.946). In a logistic regression model adjusting by age, sex, comorbidity and severity the OR for the combined outcome in those in zSoC was 0.091 (95% CI: 0.007-0.913; p=0.045). LoS was shorter in zSoC (6.9 days (SD 6.1) vs 12.7 (SD 11.6);p=0.013) respectively. Time to clinical stability was significantly shorter in zSoC (5 days (SD 6.1)) compared to SoC (11.9(SD 9.1)); p=0.005. No significant differences in changes in inflammatory markers were found among groups. No severe adverse events were observed during the study.

Conclusion: Daily zinc supplementation with 240 mg of zinc acetate for 14 days during the acute phase of SARS-CoV-2 infection resulted in lower rates of severity (less death and ICU admission) and faster clinical recovery along with shorter hospital stay.

Table 1. Population Characteristics at inclusion

Table 1. Population Characteristics at inclusion

	Zinc	SoC
Age median (IQR)	52 (43-58)	53 (36-66)
Male gender, n (%)	22 (61%)	20 (59%)
Active smoking, n (%)	6 (16%)	4 (12%)
High Blood Pressure, n (%)	13 (35%)	9 (26%)
Type 2 Diabetes Mellitus, n (%)	5 (13%)	6 (17%)
COPD, n(%)	1 (2.7%)	1 (2.9%)
Charlson comorbidity Index		
No comorbidity (0-1) n,(%)	30 (81%)	26 (76%)
Mild Comorbidities (2-3),n(%)	4 (11%)	6 (16%)
Highly comorbid (>3), n(%)	3 (8%)	2 (5%)
Blood parameters		
C-Reactive Protein mg/dl, median (IQR)	5.7 (1.1-9.7)	5.4 (1.3-5.8)
IL-6 , median (IQR)	8 (2.1-22.5)	12 (4-50)
D-Dimer UI/l , median (IQR)	410 (345-690)	470 (350-800)
Zinc mg/dl, median (IQR)	83 (72-95)	89 (70-102)
PaO2/FiO2	291 (235-302)	257 (233-313)
MEWS-Severity score, median (IQR)	4 (3-5)	3 (2-4)
Treatments		
Dexamethasone, n (%)	37 (100%)	34 (100%)
Tocilizumab, n (%)	6 (16%)	7 (20%)
Low-Weight Heparin, n (%)	33 (89%)	31 (91%)

543 RETHINKING REMDESIVIR: ENHANCING ANTI-SARS-CoV-2 ACTIVITY OF ORAL LIPID RVn PRODRUGS

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Background: SARS-CoV-2 evolution has contributed to successive waves of infections and severely compromised the efficacy of available SARS-CoV-2 monoclonal antibodies. Decaying vaccine-induced immunity, vaccine hesitancy, and limited vaccine protection in older and immunocompromised populations further compromises vaccine efficacy at the population level. Early antiviral treatments, including intravenous remdesivir (RDV), reduce hospitalization and severe disease due to COVID-19. An orally bioavailable RDV analog could facilitate earlier widespread administration to non-hospitalized COVID-19 patients.

Methods: We synthesized monoalkyl glyceryl ether phosphodiesters of GS-441524 (RVn), lysophospholipid analogs which allow for oral bioavailability and stability in plasma. We evaluated the *in vivo* efficacy of our lead compound, 1-O-octadecyl-2-O-benzyl-*sn*-glyceryl-3-phospho-RVn (V2043), in an oral treatment model of murine SARS-CoV-2 infection. We then synthesized numerous phospholipid analogs of RVn and determined which modifications enhanced *in vitro* antiviral activity and selectivity. The most effective compounds against SARS-CoV-2 were then evaluated for antiviral activity against other RNA viruses.

Results: Oral treatment of SARS-CoV-2 infected BALB/c mice with V2043 (60 mg/kg once daily for 5 days, starting 12 hrs after infection) reduced lung viral load by more than 100-fold versus vehicle at day 2 and to below the LOD at day 5. V2043 inhibited previous and contemporary SARS-CoV-2 Variants of concern to a similar degree, as measured by the half maximal effective concentration (EC_{50}) in a human lung epithelial cell line (Calu-3). Evaluation of multiple RVn analogs with hydrophobic esters at the sn-2 of glycerol revealed that *in vitro* antiviral activity was improved by the introduction of a 3-fluoro-4-methoxy-substituted benzyl or a 3- or 4-cyano-substituted benzyl. These compounds showed a 2- to 6-fold improvement in antiviral activity compared to analogs having an unsubstituted benzyl, such as V2043, and were more active than RDV.

These compounds also showed enhanced antiviral activity against multiple contemporary and emerging RNA viruses.
Conclusion: Collectively, our data support the development of RVn phospholipid prodrugs as oral antiviral agents for prevention and treatment of SARS-CoV-2 infections and as preparation for future outbreaks of pandemic RNA viruses.

544 SARS-CoV-2 ANTIVIRAL ACTIVITY OF ZOTATIFIN, A HOST-TARGETING eIF4A INHIBITOR

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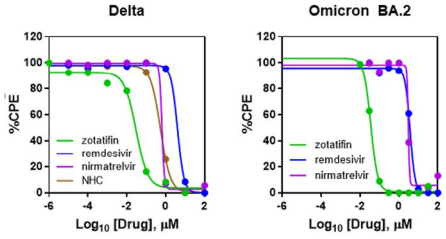
Background: Zotatifin (eFT226) is a potent and selective inhibitor of eukaryotic initiation factor 4A (eIF4A), a host RNA helicase required for SARS-CoV-2 replication. Zotatifin selectively inhibits translation of ribonucleic acids (RNAs) containing specific short polypurine motifs in their 5-prime (5′) regions. Two such highly conserved motifs are found in the SARS-CoV-2 genome. Zotatifin is currently being evaluated in a Phase 1b dose escalation study in 36 patients with mild to moderate COVID disease. In this *in vitro* study, we evaluated the selectivity of zotatifin's inhibition of SARS-CoV-2 translation, the antiviral activity of zotatifin alone against different human coronaviruses and the antiviral activity of zotatifin in combination with other antivirals against SARS-CoV-2.
Methods: The selectivity of zotatifin for viral translation was evaluated in a cell-based reporter assay wherein luciferase translation was driven by 5′-sequences from SARS-CoV-2 or tubulin, a housekeeping gene. The antiviral activity of zotatifin was evaluated against SARS-CoV-1, SARS-CoV-2 variants (Wash/1/2020 (ancestral), delta, omicron BA.2), MERS-CoV and HCoV-299E in primary or established cell lines using cytopathic effect or infectious virus as endpoints. The antiviral activity of zotatifin in combination with remdesivir, N-hydroxycytidine (NHC; active nucleoside analogue metabolite of molnupiravir), nirmatrelvir, baricitinib or sotrovimab was evaluated against SARS-CoV-2 and analyzed by the method of Pritchard and Shipman.
Results: Zotatifin inhibited the translation of the SARS-CoV-2 luciferase reporter construct with a mean IC_{50} of 3 nM and was ~14-fold less potent in inhibiting the tubulin reporter construct. Zotatifin potently inhibited the replication of all human coronaviruses tested with 50% effective concentrations (EC_{50}s) ranging from 0.016 to 37.3 nM. The 50% cytotoxic concentration (CC_{50}) value for zotatifin was 250 to >100,000 nM, yielding selectivity indices of 7 to >6250. Zotatifin was ~20 to >100-fold more potent than remdesivir, nirmatrelvir or NHC (figure) and demonstrated additive interactions when combined with remdesivir, NHC, nirmatrelvir, baricitinib or sotrovimab *in vitro*.
Conclusion: The potent broad-spectrum activity of zotatifin against a variety of human coronaviruses and additive activity when combined with different anti-SARS-CoV-2 antivirals highlight the advantages of eIF4A as a target and warrant further evaluation in human clinical trials.
Cytopathic effect (CPE) inhibition assay in Vero E6 cells infected with SARS-CoV-2 variants (delta or omicron BA.2)



545 A PHASE 1B STUDY OF ZOTATIFIN FOR THE TREATMENT OF MILD TO MODERATE COVID (PROpel)

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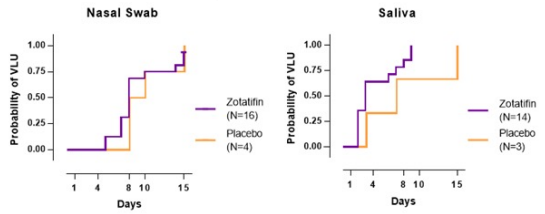
Background: Zotatifin (eFT226) is a potent and selective inhibitor of eukaryotic initiation factor 4A (eIF4A), a host RNA helicase required for SARS-CoV-2 replication. *In vitro*, zotatifin demonstrates broad spectrum antiviral activity against all human coronaviruses tested. Zotatifin has physicochemical and pharmacokinetic (PK) properties suitable for convenient, single subcutaneous (sc) injection. This study assessed the safety, antiviral activity, and PK of zotatifin in non-hospitalized patients (pts) with mild/moderate COVID.
Methods: PROPEL is a randomized, placebo-controlled, double-blind study in non-hospitalized pts with mild/moderate COVID. At randomization, pts must have had a SARS-CoV-2 positive test within 7 days and at least 1 COVID symptom. Pts were randomized (3:1) to zotatifin or placebo sc in 3 cohorts of 12 pts each. Cohort 1, 2 and 3 received a single dose (SD) of zotatifin of 0.01. 0.02 and 0.035 mg/kg or matching placebo. Safety (adverse event (AE) and laboratory tests), antiviral activity (mid-turbinate nasal swabs and saliva), and plasma PK were collected over 30 days. The primary endpoint was safety; key secondary endpoints included SARS-CoV-2 viral load (VL) and PK. The study was not powered for statistical inferential testing.
Results: 36 pts were enrolled across all three cohorts and completed a 30-day follow up. Data is currently available for pts in cohorts 1 and 2, 18 and 6 of whom received zotatifin and placebo, respectively. Baseline characteristics were comparable between groups. The most common AE was erythema at injection site in cohort 1 (44%) and cohort 2 (89%), vs. 0% in the zotatifin and pooled placebo groups, respectively. Other AE frequencies were comparable between zotatifin and placebo and no serious AEs were reported. The concentration-time profile of zotatifin from cohorts 1 and 2 following sc administration was similar to that reported previously following IV administration, demonstrated a terminal elimination half-life ($t_{1/2}$) of ~ 4 days, high steady-state volume of distribution (V_{ss}) of 31 L/kg, and low plasma clearance (Cl) of 3.9 mL/min/kg. A faster time to viral RNA undetectability was observed with zotatifin vs. placebo (see Fig 1. Not statistically significant).
Conclusion: Zotatifin was safe, well tolerated and demonstrated a trend in clinical antiviral activity in patients with mild to moderate COVID which supports further clinical development. Zotatifin sc route of administration supports a point of care treatment for COVID.
Time to Viral Load Undectability (VLU)



546 WITHDRAWN

547 SMALL MOLECULE INHIBITOR FOR BLOCKING SARS-CoV-2 ENTRY

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Background: Severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) is a novel and highly pathogenic coronavirus and is the causative agent of COVID-19, an ongoing pandemic that has posed a serious threat to public health and global economy. Thus, there is a pressing need for therapeutic interventions that target essential viral proteins and regulate virus spread and replication. To invade the host cell, the receptor-binding domain (RBD) of SARS-CoV-2 Spike protein binds to the host cell's ACE2 receptor, followed by cleavage events that allow the Spike protein to fuse with the host cell membrane. Thus, the essential role of Spike protein in ACE2 receptor binding and viral fusion makes it a prime target for therapeutic interventions.
Methods: We performed molecular docking and molecular dynamics (MD) simulation-based virtual screening against SARS-CoV-2 RBD/ACE2 interface using a commercial library of 93,835 drug-like compounds. Compounds with promising docking poses and scores were selected for further MD simulation refinement, from which ten lead compounds were identified. Antiviral potencies of ten lead compounds were evaluated against lentiviral vectors pseudotyped with SARS-CoV-2 Spike to down select to a single lead compound, "SAI4". ELISA-based assays were employed to determine the binding affinities of SAI4 to recombinant SARS-CoV-2 RBD. Antiviral potential of SAI4 was validated against genuine SARS-CoV-2 in a BSL3 setting.
Results: We identified SAI4 as a candidate small molecule, which inhibited SARS-CoV-2 pseudovirus entry with IC_{50} value of ~18 μM. We determined that SAI4 binds RDB with a Kd of ~20 μM. Using cells engineered to express ACE2 and cells that express physiological levels of ACE2, we found that SAI4 inhibited SARS-CoV-2 pseudovirus entry at both engineered and physiological ACE2 levels. We validated the antiviral potential of SAI4 against genuine SARS-CoV-2 and HCoV-NL63. Lastly, we demonstrated antiviral potential of SAI4 against four SARS-CoV-2 variants of concern (α, β, γ, and δ).
Conclusion: Using virtual screening, we identified SAI4 as the promising hit compound which displayed inhibitory activities against SARS-CoV-2 entry and its four variants of concern. Thus, our study will pave the way for further development of small molecules for therapeutic targeting of SARS-CoV-2 entry to combat the COVID-19 pandemic.

548 PLITIDEPSIN IS A BROAD-SPECTRUM ANTIVIRAL SHAPING THE CELL PROTEOSTATIC BALANCE

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Background: Different viruses employ similar pathways for replication, revealing key intracellular hotspots to target with host-directed therapies and achieve a broad-spectrum antiviral activity. Plitidepsin is a clinically approved antitumoral agent that blocks the elongation factor eEF1A required for protein translation. This drug counteracts SARS-CoV-2 replication and shows a favorable safety profile in COVID-19 patients. Yet, the precise antiviral mechanism of action of plitidepsin remains unknown.
Methods: Here we used a deep quantitative proteomic analysis to measure the impact of plitidepsin on the proteome of SARS-CoV-2-infected Vero E6 cells. This was complemented with transmission electron microscopy assays, which unraveled the subcellular and morphological changes associated to plitidepsin treatment. In addition, we performed functional *in vitro* assays to dissect the antiviral activity of plitidepsin against SARS-CoV-2 and other viruses.
Results: We found that this drug inhibited the synthesis of all SARS-CoV-2 proteins in a dose-dependent manner. These included the R1AB polyproteins, which facilitate the synthesis of non-structural proteins involved in the formation of double membrane vesicles (DMV) required for viral replication. Plitidepsin reduced DMV formation and the morphogenesis of new viruses, having a greater impact on viral than on host proteins. Less than 14% of the cellular proteome was significantly affected by plitidepsin, inducing the up-regulation of key molecules associated with protein biosynthesis, such as the translation initiation factors eIF4A2 and eIF2S3. Therefore, plitidepsin induced a compensatory state that rescued protein translation. This proteostatic response explains how cells preserve the cellular proteome after treatment with a translation inhibitor such as plitidepsin. In addition, it suggests that plitidepsin could inhibit other RNA-dependent and non-integrated DNA viruses, as we confirmed *in vitro* using Zika virus, Hepatitis C virus replicon and Herpes simplex virus. However, the compensatory proteostasis induced by plitidespin also explains why this drug failed to inhibit the replication of integrated DNA proviruses such as HIV-1.
Conclusion: Unraveling the mechanism of action of host-directed therapies like plitidepsin is imperative to define the indications and antiviral profile of these compounds. This knowledge will be key to develop broad-spectrum treatments and have them ready to deploy when future pandemic viruses break through.

549 TARGETING THE HOST-VIRUS INTERFACE TO BLOCK SARS-CoV-2 ASSEMBLY IN AIRWAY CELLS

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Background: The rapid emergence of the SARS-CoV-2 Omicron variant that evades many therapies illustrates the need for antiviral treatments with high genetic barriers to resistance. The small molecule PAV-104, identified through a moderate-throughput screen involving cell-free protein synthesis, was recently shown to target a subset of host protein assembly machinery in a manner specific to viral assembly with minimal host toxicity. The chemotype shows broad activity against respiratory viral pathogens, including Orthomyxoviridae, Paramyxoviridae, Adenoviridae, Herpesviridae, and Picornaviridae, with low susceptibility to evolutionary escape. Here, we investigated the capacity of PAV-104 to inhibit SARS-CoV-2 replication in human airway epithelial cells (AECs).
Methods: Dose-dependent cytotoxicity of PAV-104 in Calu-3 cells was determined by MTT assay. Calu-3 cells were infected with SARS-CoV-2 isolate USA-WA1/2020 (MOI=0.01). Primary AECs were isolated from healthy donor lung transplant tissue, cultured at air liquid interface (ALI), and infected with SARS-CoV-2 Gamma, Delta, and Omicron variants (MOI=0.1). SARS-CoV-2 replication was assessed by RT-PCR quantitation of the N gene, immunofluorescence assay (IFA) of nucleocapsid (N) protein, and titration of supernatant ($TCID_{50}$). Transient co-expression of four SARS-CoV-2 structural proteins (N, M, S, E) to produce virus-like particles (VLPs) was used to study the effect of PAV-104 on viral assembly. Drug resin affinity chromatography was performed to study the interaction between PAV-104 and N. Glycerol gradient sedimentation was used to assess N oligomerization. Total RNA-seq and the REACTOME database were used to evaluate PAV-104 effects on the host transcriptome.
Results: PAV-104 reached 50% cytotoxicity in Calu-3 cells at 3732 nM (Fig.1A). 50 nM PAV-104 inhibited >99% of SARS-CoV-2 infection in Calu-3 cells ($p < 0.01$) and in primary AECs ($p < 0.01$) (Fig.1B-E). PAV-104 specifically inhibited SARS-CoV-2 post entry, and suppressed production of SARS-CoV-2 VLPs without affecting viral protein synthesis. PAV-104 interacted with SARS-CoV-2 N and

interfered with N oligomerization. Transcriptome analysis revealed that PAV-104 treatment reversed SARS-CoV-2 induction of the interferon and "maturation of nucleoprotein" signaling pathways.

Conclusion: PAV-104 is a pan-respiratory virus small molecule inhibitor with promising activity against SARS-CoV-2 in human airway epithelial cells that should be explored in animal models and clinical studies.

Figure 1. PAV-104 decreases SARS-CoV-2 replication in airway epithelial cells.

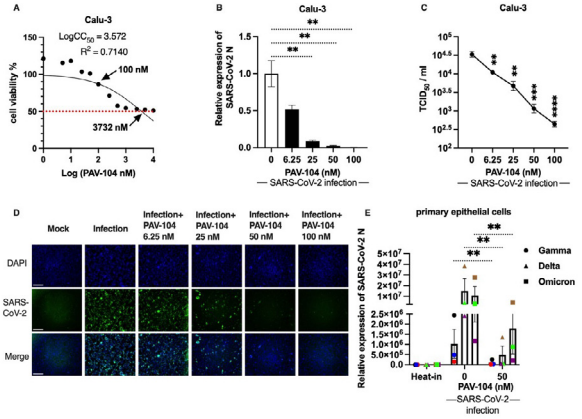

Figure 1. PAV-104 decreases SARS-CoV-2 replication in airway epithelial cells.
A. Cellular toxicity was examined in Calu-3 cells using MTT assay and was expressed as relative cell viability normalized to DMSO control.
B. SARS-CoV-2 *N* gene expression was measured by qRT-PCR in Calu-3 cells in the presence of PAV-104 treatment at specified concentrations. Results were normalized to RNaseP and are shown as the fold change compared to DMSO control.
C. Viral titer (TCID50/ml) of supernatants collected after SARS-CoV-2 infection in the presence of PAV-104 at the indicated concentrations.
D. Calu-3 cells were stained with DAPI nuclear marker (blue) and anti-SARS-CoV-2 N protein antibody (with FITC-conjugated secondary antibody) to measure SARS-CoV-2 infection (green) and PAV-104 effects.
E. qRT-PCR analysis of SARS-CoV-2 *N* gene from ALI-cultured primary airway epithelial cells with or without PAV-104 treatment in six different donors. Each color represents data from a single donor. Results were normalized to RNaseP and are shown as the fold change compared to heat-inactivated control (Heat-in). Statistical analysis was performed by Student's *t*-test or paired *t*-tests. Bar = mean ± SEM. *, $P < 0.05$, **, $P < 0.01$, ***, $P < 0.001$, ****, $P < 0.0001$.

550 SAFETY AND PHARMACOKINETICS OF A NOVEL DOUBLE PRODRUG ASC10 IN HEALTHY SUBJECTS

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Background: ASC10 is an oral double prodrug of the active antiviral ribonucleoside analog, ASC10-A (also known as β-d-N^4-hydroxycytidine), which is a potent inhibitor of SARS-CoV-2. ASC10 is rapidly metabolized into ASC10-A *in vivo* after oral dosing. Here, we report the results of the first-in-human, phase 1 study to determine the safety, tolerability, and pharmacokinetics (PK) of ASC10 in healthy subjects, and to assess the food effect on the pharmacokinetics.

Methods: This study included 2 parts. Part 1 (multiple-ascending-dose) consisted of 6 cohorts (8 or 12 subjects per cohort). Eligible subjects were randomized in a 3:1 ratio to receive either twice-daily (BID) doses of 50 to 800 mg ASC10 or placebo for 5.5 days, and were then followed for 7 days for safety. In Part 2 (food effect), 12 subjects were randomized in a 1:1 ratio to either 800 mg ASC10 in the fed state followed by 800 mg in the fasted state, or vice versa, with a 7-day washout period between doses. PK blood samples were collected and measured for ASC10-A along with ASC10 and molnupiravir. Safety assessments included monitoring of adverse events (AEs), measurement of vital signs, clinical laboratory tests, and physical examinations.

Results: ASC10-A was the major circulating metabolite (>99.94%) in subjects after oral dosing of ASC10. ASC10-A appeared rapidly in plasma, with a median T_{max} of 1.00 to 2.00 h, and declined with a geometric $t_{1/2}$ of approximately 1.10 to 3.04 h. After multiple dosing for 5.5 days, both C_{max} and AUC of ASC10-A increased in a dose-proportional manner from doses of 50 to 800 mg BID without accumulation. of ASC10-A in the fed state occurred slightly later, with a median of 3.99 h postdose versus 2.00 h (fasted state). However, C_{max} and AUC were very similar or the same between fed and fasted states. Thus, administration of ASC10 with food is unlikely to have an effect on exposure. The incidence of AEs was similar between subjects receiving ASC10 or placebo (both 66.7%) and 95.0% of AEs were mild. There were no serious adverse events as well as no clinically significant findings in clinical laboratory, vital signs, or electrocardiography.

Conclusion: Results of this study showed that ASC10 was well tolerated, and the increase in plasma exposure of ASC10-A was dose proportional across the range of doses tested with no accumulation and no food effect. 800 mg ASC10 BID is selected for further studies in patients infected with SARS-CoV-2.

551 MECHANISM AND RESISTANCE STUDIES OF SARS-CoV-2 MPRO INHIBITOR POMOTRELVIR (PBI-0451)

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Background: The unprecedented scale of the COVID-19 pandemic and rapid evolution of SARS-CoV-2 variants underscores the need for broadly active inhibitors with a high barrier to resistance. The coronavirus main protease (Mpro) is an essential viral enzyme required for viral polyprotein processing and is highly conserved across human coronaviruses. Pomotrelvir (PBI-0451) is a novel Mpro inhibitor currently completing phase 2 clinical trial. Here we describe the mechanism of action, broad activity against SARS-CoV-2 clinical isolates, combination studies with other SARS-CoV-2 inhibitors and favorable resistance profile of pomotrelvir.

Methods: The kinetic parameters of pomotrelvir M^{pro} inhibition and its interaction with nirmaltrevir were determined in a kinetic protease assay. The IC_{50}s of pomotrelvir on mutant Mpro proteins were measured in an endpoint M^{pro} assay. Combination studies of pomotrelvir with remdesivir and molnupiravir were carried out in A549-hACE2 cells infected with SARS-CoV-2 NLuc virus. Activity against SARS-CoV-2 clinical variants was assessed by infection of A549-ACE2-TMPRSS2 cells followed by immunostaining of the viral nucleocapsid protein.

Results: Pomotrelvir is a potent competitive inhibitor of SARS-CoV-2 M^{pro} (Ki =2.7 nM). Binding of pomotrelvir and the M^{pro} inhibitor nirmatrelvir to the active site is mutually exclusive. In the SARS-CoV-2 NLuc assay, pomotrelvir is additive when combined with remdesivir or molnupiravir, two nucleoside analogs targeting viral RNA synthesis. When the effect of M^{pro} substitutions previously selected in a resistance study of pomotrelvir were analyzed in an enzyme assay, only Mpro_N133H showed a significant increase in IC_{50} (45-fold). The catalytic efficiency of M^{pro}_N133H is reduced by 10-fold and the recombinant virus SARS-CoV-2 (WA1)_N133H is not viable, suggesting that N133H has lower replicative fitness. Lastly, pomotrelvir exhibits broad activity against all SARS-CoV-2 clinical isolates tested to date, including five omicron variants.

Conclusion: PBI-0451 is a potent competitive inhibitor of SARS-CoV-2 M^{pro} and is broadly active against SARS-CoV-2 clinical isolates including omicron variants. Results from inhibitor interaction studies support the potential combination of pomotrelvir with remdesivir and molnupiravir but not nirmatrelvir. Enzymatic characterization of *in vitro* selected pomotrelvir resistant variants indicates they either confer no resistance or have reduced fitness.

552 SARS-CoV-2 E-PROTEIN VIROPORIN INHIBITOR BIT225 ACTIVE IN hACE2 TRANSGENIC MICE

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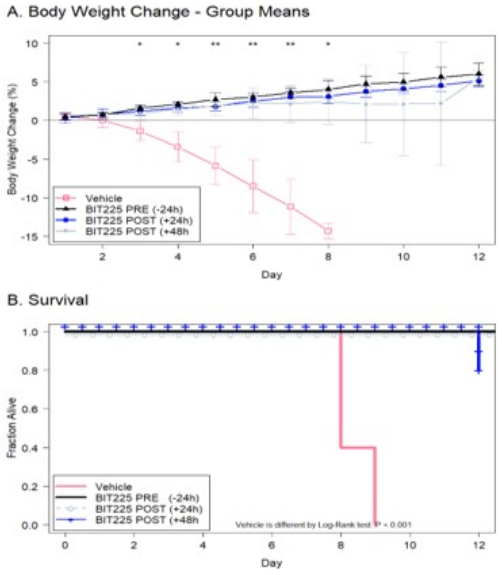
Background: The CoV-2 envelope (E) protein plays an important role in virus assembly, budding, immunopathogenesis and disease severity. E protein has ion channel activity, is located in Golgi and ER membranes of infected cells and is associated with inflammasome activation and immune dysregulation. Here we report that BIT225, an investigational HIV clinical compound, inhibits E ion channel activity and prevents body weight loss and mortality and reduces inflammation in lethally infected K18-hACE2 transgenic mice. BIT225 efficacy was observed when dosing was initiated before or 24 h or 48 h after infection.

Methods: SARS-CoV-2 E protein ion channel activity and Xenopus TMEM16A were measured in Xenopus oocytes. K18-hACE2 transgenic mice were infected intranasally with 10^4 pfu SARS CoV 2 (US-WA1/2020) and dosed orally twice daily with BIT225 for up to 12 Days. Dosing was initiated 12 h pre-infection or 24 h or 48 h post-infection. Disease parameters measured were survival, body weight, viral RNA by qPCR and infectious virus titre (plaque assay) in lung tissue homogenates and serum. In addition, levels of pro-inflammatory cytokines (IL-6, IL-1α, IL-1β, TNFα & TGFβ, MCP-1) were measured in lung and serum samples.

Results: BIT225 inhibited ion channel activity of E-protein, but not that of TMEM16A in Xenopus oocytes. BIT225 dosed at 300mg/kg BID for 12 days starting 12 h pre-infection completely prevented body weight loss and

mortality in SARS-CoV-2 infected K18 mice (n=12), while all vehicle-dosed animals reached a mortality endpoint by day 9 across two studies (n=12). Figure 1 shows results from a time of addition study: When treatment with BIT225 started at 24 h post-infection, body weight loss and mortality was also prevented (100% survival, n=5). In the group of mice where treatment started at 48 h after infection, body weight loss and mortality were prevented in 4 of 5 mice. Treatment efficacy was associated with significant reduction in lung viral load (3.5 log_{10}), virus titer (4000 pfu/ml) and lung and serum cytokine levels.
Conclusion: BIT225 is an inhibitor of SARS-CoV-2 E-protein viroporin activity. In the K18 model BIT225 protected mice from weight loss and death, inhibited virus replication and reduced inflammation. These effects were noted when treatment with BIT225 was initiated before or 24-48 hours after infection and validate viroporin E as a viable antiviral target and support the clinical study of BIT225 in treatment of SARS-CoV-2.
FIGURE 1: BIT225 Time of Addition Study: Time courses for (A) body weight and (B) mortality in SARS-2 infected K18-hACE2 mice (n=5 per group).



553 NAFAMOSTAT AS NASAL CHEMOPROPHYLAXIS FOR SARS-CoV-2 IN HAMSTERS

Megan Neary[1], Joanne Sharp[1], Eduardo Gallardo-Toledo[1], Joanne Herriott[1], Edyta Kijak[1], Chloe Bramwell[1], Helen Cox[1], Lee Tatham[1], Paul Curley[1], James Hobson[1], Steve Rannard[1], Anja Kipar[2], James Stewart[1], Andrew Owen[1]
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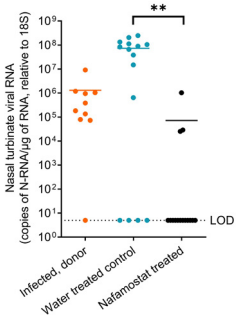
Background: Chemoprophylaxis is a critical tool for many infectious diseases, and in COVID-19 may have particular benefit for vulnerable patients that do not maximally benefit from vaccination. Nafamostat inhibits TMPRSS2, which catalyses a critical cell entry pathway for SARS-CoV-2. This study sought to assess efficacy of intranasal nafamostat against airborne transmission of SARS-CoV-2 in Syrian Golden hamsters.
Methods: Male hamsters were intranasally administered water or 5 mg/kg nafamostat in water twice daily for 5 days (sentinels). One day after treatment initiation, sentinels were co-housed with an untreated hamster that was intranasally inoculated with 1 x 10^4 PFU of Wuhan SARS-CoV-2 (donor). Sentinels were separated from the donor by a perforated divider, allowing airflow between zones but not contact. Hamsters were weighed and throat-swabbed throughout. At day 4, all animals were culled, and lung and nasal turbinates were harvested. N-RNA was quantified relative to 18S-RNA by qPCR. A 2-way ANOVA with Bonferroni correction was applied to compare weight changes in the nafamostat group to those in controls. An unpaired t-test was used to compare viral RNA in lung and nasal turbinate between groups.
Results: SARS-CoV-2 viral RNA was significantly lower in the nasal turbinates of nafamostat-treated hamsters compared to water-treated controls ($P = 0.012$; Figure 1). Within the lung, SARS-CoV-2 RNA was undetectable in the nafamostat-treated hamsters, but was detectable in the water-treated controls. Viral RNA was undetectable in the swabs of the nafamostat-treated hamsters at all timepoints, but was quantifiable in the water-treated control group from day 3. Body weight of the nafamostat-treated hamsters was significantly lower ($P < 0.001$) than in the water-treated animals throughout. SARS-CoV-2 viral RNA was detectable in the donor hamsters lung, nasal turbinate and swab samples confirming validity of the experiment.
Conclusion: This study demonstrated a protective effect of intranasal nafamostat against airborne SARS-CoV-2 transmission in Syrian golden hamsters. A phase IIa study of intravenously administered nafamostat yielded no evidence of clinical efficacy in hospitalised patients, but further investigation of intranasally administered nafamostat in a prophylactic setting may be warranted.
Figure 1: SARS-CoV-2 viral RNA concentration quantified from the nasal turbinates of the donor, nafamostat or water treated hamsters.



554 PHASE 1 CLINICAL TRIALS OF A Q-GRIFFITHSIN NASAL SPRAY FOR SARS-CoV-2 PROPHYLAXIS

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Background: The currently approved vaccines do not induce sterilizing immunity against SAR-CoV-2 infection, and immunity wanes over time. A robust broad spectrum topical prophylaxis strategy could protect vulnerable populations in the face of continuous evolution of SARS-CoV-2. The algal antiviral lectin Griffithsin (GRFT), and an engineered oxidation-resistant variant Q-GRFT have robust entry inhibitory activity against SARS-CoV variants of concern, in addition to other respiratory viruses with pandemic potential. We designed a nasal spray to deliver Q-GRFT to the upper respiratory tract mucosa for on-demand use as a broad-spectrum prophylactic. Two clinical trials (Phase 1a and 1b) were conducted to assess safety, tolerability, and pharmacokinetics of Q-GRFT nasal spray in healthy adults.
Methods: Healthy adult volunteers were enrolled in a Phase 1a double blinded, randomized study to receive a single dose of either intranasal Q-GRFT (3.0 mg, 2 sprays per nostril) or placebo at 2:1 ratio. Following a safety review, the Phase 1b study was initiated. Eleven volunteers in Group 1 received 3.0 mg dose once daily, for 7 days. After a safety review, 11 volunteers in Group 2 received a total of 6.0 mg Q-GRFT (3.0 mg twice daily for 7 days). Topical Q-GRFT concentrations were measured by ELISA in collected nasal and nasopharyngeal fluids. Drug levels in plasma were assayed to determine systemic exposure. Viral microneutralization cytopathic effect (CPE) assays were performed against SARS-CoV-2 Omicron BA-5 and MERS-CoV.
Results: Eighteen adults (24-54 years; Males 58.3%, Females 41.7%; 12 Q-GRFT, 6 Placebo), and 22 adults (aged 23-59 years; Males 52.4%, Females 47.6%) were enrolled in Phase 1a and 1b, respectively. In Phase 1a, a single dose of Q-GRFT maintained quantifiable levels in nasal passages and nasopharynx for up to 24 hours. Similarly, Q-GRFT was quantifiable in nasal and nasopharyngeal regions in the Phase 1b study. No dose accumulation effect or systemic exposure was observed. Nasal and nasopharyngeal swab eluates inhibited SARS-CoV-2 Omicron BA.5 and MERS-CoV in CPE assays. Q-GRFT did not modify olfactory sensation. No severe adverse events were reported. Thus, the nasal spray was deemed safe.

Conclusion: Intranasal Q-GRFT was safe and enhanced mucosal SARS-CoV-2 inhibitory activity in human volunteers. The results support further development of Q-GRFT as a broad-spectrum prophylactic against coronaviruses to curb ongoing infections, and for future pandemic preparedness.

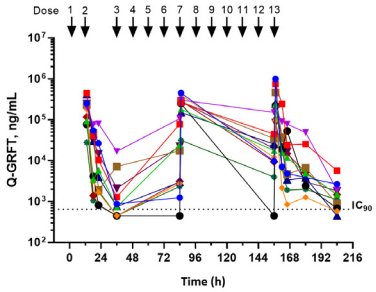

FIG 1. Q-GRFT detection in nasopharyngeal fluids among Phase 1b Group 2 volunteers. N=11 volunteers received intranasal Q-GRFT 3.0 mg twice daily for 7 days. Each curve represents data from one volunteer obtained over the period of the study. Nasopharyngeal fluids were eluted from swabs collected at predetermined timepoints: these were 1, 6, 10, 24 hours post second dose; predose and 1 hour post seventh dose; and predose, 1, 6, 10, 24, 48 hours post 13th dose. Q-GRFT levels were determined by ELISA. The concentration of Q-GRFT that inhibits 90% (IC_{90}) SARS-CoV-2 BA5 replication is 645.2 ng/ml.

555 NIRMATRELVIR AND MOLNUPIRAVIR COADMINISTRATION MODIFIES PRECLINICAL VIRAL EXPOSURE

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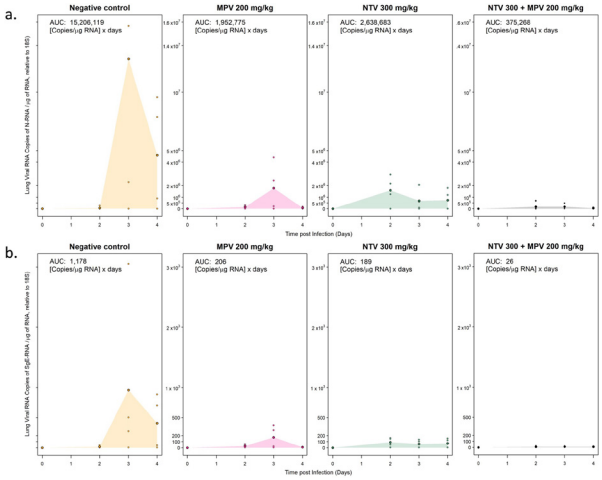
Background: Implementation of vaccination programmes has had a transformational impact on control of the SARS-CoV-2 pandemic, but the need for effective antiviral drugs remains. Molnupiravir (MPV) targets viral RNA polymerase inhibiting replication via lethal mutagenesis and nirmatrelvir (NTV) is a protease inhibitor boosted with ritonavir when given clinically. This study aimed to assess the virological efficacy of NTV and MPV individually and in combination against the SARS-CoV-2 BA.1 Omicron variant in a K18-hACE2 mouse model.

Methods: K18-hACE2 mice were inoculated intranasally with 10^3 PFU of SARS-CoV-2 BA.1 Omicron (B.1.1.529). After 24 hours, mice were orally dosed q12H, as outlined in Figure 1. At 2, 3, and 4-days post infection mice were sacrificed, and lung samples harvested. Animals were weighed and monitored daily throughout. Subsequently, viral replication in the lung was quantified using qRT-PCR to measure total (N-gene) and sub-genomic (E-gene) viral RNA. Data were normalized to 18S for quantitation. Viral exposures expressed as Areas Under viral load Curves (AUCs) were calculated by the trapezoidal method using mean values at each timepoint. Separate studies in Syrian golden hamsters using individual drugs were also conducted, and total serum IgG was measured by ELISA at 4-days post infection.

Results: Mice gained weight in all groups post-treatment, with no significant difference between groups. A reduction in lung viral exposure was evident in all treatment groups compared to the vehicle control dosed mice (Figure 1). Coadministration of NTV with MPV displayed a trend towards lower lung viral exposure compared to the vehicle control with ~40- and ~45-fold reduction in AUC for N- and SgE-gene assays, respectively. Dosed individually, NTV and MPV reduced viral exposure 5.7- and 7.7-fold for the N-gene assay, respectively. Differences in total serum IgG concentrations were evident between vehicle and NTV- (34-fold reduction, P=0.018), and MPV- (4.2-fold reduction, P=0.053) treated hamsters.

Conclusion: These data show virological efficacy of NTV and MPV against the SARS-CoV-2 BA.1 Omicron variant. The combination of NTV and MPV demonstrated a lower viral RNA exposure in the lung than either drug alone, albeit not statistically significant. Initial data indicate potential immune alterations in NTV and MPV dosed hamsters. Studies to clarify the utility of NTV/MPV combinations and further characterize the impact of antiviral therapy on IgG are warranted.

Figure 1. Viral exposures in K18-hACE2 mice infected with SARS-CoV-2 BA.1 Omicron (B.1.1.529), treated with NTV and MPV individually or in combination (a) N-gene, (b) SgE-gene. n=4 per group, per time-point.



556 REMDESIVIR REDUCES MORTALITY IN HOSPITALIZED COVID-19 PATIENTS ACROSS VARIANT ERAS

Essy Mozaffari[1], Aastha Chandak[2], Robert L. Gottlieb[3], Chidinma Chima-Melton[4], Stephanie H. Read[5], Heng Jiang[6], Celine Der-Torossian[1], Eunyoung Lee[1], Lauren Dau[1], Mark Thrun[1], Mark Berry[1], Richard Haubrich[1], Andre C. Kalil[7]
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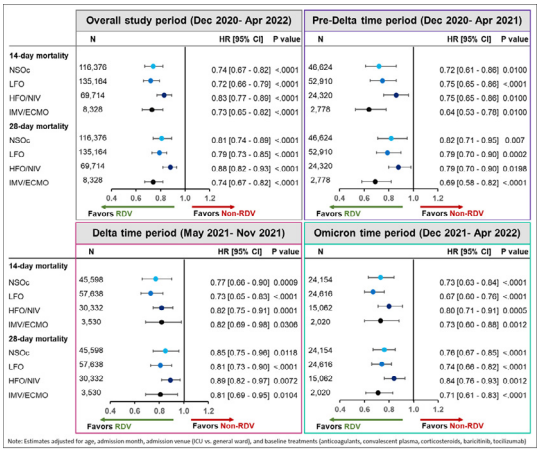
Background: Clinical management of COVID-19 based on oxygenation requirements continues to change over time as variants of concern (VOC) evolve. We examine hospital all-cause mortality for early hospital RDV use vs. no RDV use across dominant VOC periods: pre-Delta (Dec'20-Apr'21), Delta (May-Nov'21) and Omicron (Dec'21-Apr'22).

Methods: We examined adults with a primary discharge diagnosis of COVID-19 (ICD-10: U07.1) using the Premier Healthcare Database. Patients treated with RDV in the first 2 days of admission vs. those not treated with RDV during the hospitalization were matched using a 1:1 preferential within-hospital propensity matching with replacement. Patients were excluded if discharged within 3 days of RDV initiation. Time to mortality at 14- and 28-days was examined for patients with no supplemental oxygen charges (NSOc), low-flow oxygen (LFO), high-flow oxygen/non-invasive ventilation (HFO/NIV) and invasive mechanical ventilation/ECMO (IMV/ECMO) at baseline. Baseline was defined as first 2 days of hospitalization.

Results: 164,791 RDV-treated patients were matched to 48,473 unique non-RDV patients. Post-matching balance was achieved across groups with different baseline oxygenation levels and VOC periods. In the matched weighted cohort, 35% required NSOc, 41% LFO, 21% HFO/NIV and 3% IMV/ECMO.
During the overall study period (Dec'20-Apr'22), unadjusted mortality rate was significantly lower for RDV patients across all oxygenation levels at 14 days (NSOc: 5.4% vs. 7.3%, LFO: 6.4% vs. 8.8%, HFO/NIV: 16.8% vs. 19.4%, IMV/ECMO: 27.8% vs. 35.3%) and 28 days (NSOc: 8.0% vs. 9.8%, LFO: 9.8% vs. 12.3%, HFO/NIV: 25.8% vs. 28.3%, IMV/ECMO: 41.4% vs. 50.6%).
After adjusting for baseline and clinical covariates, 14-day mortality results showed that RDV significantly lower risk compared to non-RDV across all oxygenation levels at baseline [NSO (26%), LFO (28%), HFO/NIV (17%), IMV/ECMO (27%)]. Similarly, 28-day mortality results showed that RDV significantly lower risk compared to non-RDV across all oxygenation levels at baseline [NSO (19%), LFO (21%), HFO/NIV (12%), IMV/ECMO (26%)].
This lower mortality risk associated with RDV was consistently observed across all variant periods (Figure).

Conclusion: Timely initiation of RDV within first two days of hospital admission demonstrated significant mortality reduction in patients hospitalized for a primary diagnosis of COVID-19 across all oxygenation levels. Remdesivir demonstrated consistent benefit across all variant periods of the pandemic to-date.

Figure: Time to 14- and 28- day mortality across the COVID-19 variant periods (adjusted Cox Proportional Hazards model)



557 REMDESIVIR REDUCES MORTALITY IN IMMUNOCOMPROMISED PATIENTS HOSPITALIZED FOR COVID-19

Essy Mozaffari[1], Aastha Chandak[2], Robert L. Gottlieb[3], Andre C. Kalil[4], Stephanie H. Read[5], Heng Jiang[6], Mel Chiang[7], Eunyoung Lee[1], Rikisha Gupta[1], Mark Thrun[1], Chidinma Chima-Melton[8]

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Background: There is limited information on effectiveness of COVID-19 therapies in immunocompromised patients, who are at higher risk of hospitalizations, complications, and mortality due to COVID-19. We examined hospital all-cause mortality for early RDV use vs. no RDV use among immunocompromised COVID-19 patients across several distinct dominant variants of concern (VOC) periods: pre-Delta (Dec'20-Apr'21), Delta (May-Nov'21) and Omicron (Dec'21-Apr'22).

Methods: Using the Premier Healthcare Database, we identified adults with an immunocompromised condition (cancer, solid organ and hematopoietic stem cell transplant, hematologic malignancies, primary immunodeficiencies, asplenia, bone marrow failure/aplastic anemia, severe combined immunodeficiencies or HIV), hospitalized with a primary diagnosis of COVID-19. Patients treated with RDV in first 2 days of admission vs. those not treated with RDV during the hospitalization were matched using 1:1 preferential within-hospital propensity matching with replacement. Patients were excluded if discharged within 3 days of RDV initiation. Cox Proportional Hazards Model was used to examine time to 14- and 28-day mortality.

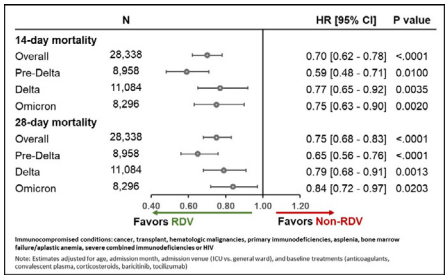
Results: Overall (Dec'20-Apr'22), 14,169 RDV-treated patients were matched to 5,341 unique non-RDV patients. Post-matching balance was achieved with 59% being 65+ years, 40.5% with no supplementary oxygen charges, 39% received low-flow oxygen, 19% on high-flow oxygen/non-invasive ventilation and 1.5% on invasive mechanical ventilation/ECMO at baseline.

During the study period, unadjusted mortality rate was significantly lower for RDV patients at 14 days (11% [95% CI: 11%-12%] vs 15% [15%-16%];p< .0001) and 28 days (18% [17%-18%];p< .0001 vs 22% [22%-23%];p< .0001) as compared to patients that did not receive RDV.

After adjusting for baseline and clinical covariates, 14-day results showed that RDV had significantly lower mortality risk compared to non-RDV across all VOC periods [overall (30% lower risk), pre-delta (41%), Delta (23%), Omicron (25%)]. Similarly, 28-day results showed that RDV had significantly lower mortality risk compared to non-RDV across all VOC periods [overall (25%), pre-delta (35%), Delta (21%), Omicron (16%)] (Fig).

Conclusion: Timely initiation of RDV in first two days of hospital admission demonstrated significant mortality reduction in immunocompromised patients hospitalized with primary diagnosis of COVID-19. RDV demonstrated consistent benefit in an immunocompromised cohort across all variant periods of the pandemic.

Figure: Time to 14- and 28- day mortality in immunocompromised patients across the COVID-19 variant periods (adjusted Cox Proportional Hazards model)



558 REMDESIVIR IS ASSOCIATED WITH REDUCED READMISSION AFTER COVID-19 HOSPITALIZATION

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Background: There is limited data on the association between COVID-19 therapy and hospital readmissions, including during evolution of the pandemic over time. We examine all cause 30-day readmissions after a COVID-19 hospitalization among remdesivir (RDV)-treated vs non-RDV treated patients across different dominant variants of concern (VOC) periods: pre-Delta (May'20-Apr'21), Delta (May-Nov'21) and Omicron (Dec'21-Apr'22).

Methods: Using the Premier Healthcare Database, we examined adults hospitalized with a primary diagnosis of COVID-19 (ICD-10:U07.1) who were discharged alive from the COVID-19 hospitalization. All-cause readmission to the same hospital was examined using multivariate logistic regression. The model adjusted for: age, corticosteroids use, VOC period, Charlson comorbidity index, maximum oxygenation requirements and ICU admission during COVID-19 hospitalization.

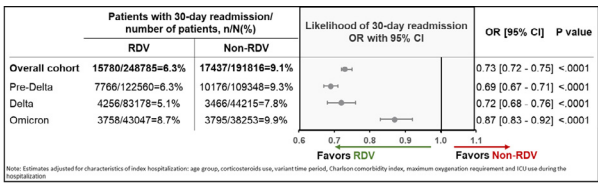
Results: In the study period (May'20-Apr'22), 440,601 patients with a primary diagnosis of COVID-19 were discharged alive, of which 53% received RDV. As compared to non-RDV, RDV patients were younger (median[IQR]: 62[51–73] vs 64[52–76]), with a lower proportion with no supplementary oxygen charges (30% vs 52%), a higher proportion with low-flow oxygen (46% vs 36%), high-flow oxygen/non-invasive ventilation (20% vs 10%), and invasive mechanical ventilation/ECMO (4% vs 2%).

Among RDV-treated, the all-cause 30-day readmission was 6.3% compared to 9.1% (p< .0001) in non-RDV treated. Lower readmission for RDV vs non-RDV was seen in Pre-delta (6.3% vs 9.3%; p< .0001), Delta (5.1% vs 7.8%; p< .0001), and Omicron (8.7% vs 9.9%; p< .0001) (Fig).

After adjusting for age and characteristics at index hospitalization including corticosteroid, RDV patients had significantly lower likelihood of all-cause 30-day readmission (OR[95% CI]:0.73[0.72-0.75]) as compared to non-RDV. Significantly Lower odds of 30-day readmission for RDV vs non-RDV patients were observed in Pre-delta (0.69[0.67-0.71]), Delta (0.72[0.68-0.76]) and Omicron- (0.87[0.83-0.92]) (Fig). Similarly, RDV-related reduction in readmissions was also seen for COVID-19 related readmissions.

Conclusion: RDV use during the COVID-19 hospitalization was associated with significantly lower likelihood of all-cause 30-day readmission across the VOC periods of the pandemic May 2020 till April 2022. The lower rate of hospital re-admission for RDV-treated patients was observed despite the RDV group having higher supplemental oxygen requirement during their index COVID-19 hospitalization.

Figure: 30-day all-cause readmission among hospitalized COVID-19 patients across the variant periods



559 RISK OF DEATH IN REMDESIVIR TREATED AND UNTREATED PATIENTS WITH COVID-19 INFECTION

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Background: The role of remdesivir in hospitalized patients with COVID-19 is not clear. Some studies have demonstrated improved clinical outcomes and reduced mortality, while others have failed to show a benefit.

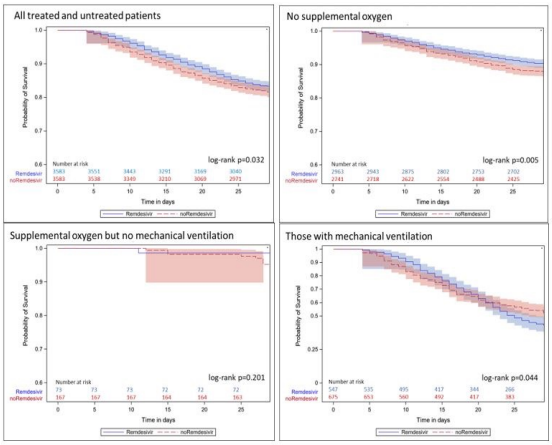
Methods: We used the Department of Veterans Affairs' (VA) national COVID-19 Shared Data Resource database to identify confirmed SARS-CoV-2 infected Veterans between July 1, 2020 and December 31, 2021 who were hospitalized and received remdesivir and propensity-score matched controls who had not received remdesivir. Variables for propensity-score matching included demographics, comorbidities, time and location of diagnosis/admission, severity of illness, and use of other potential COVID-19 therapeutics. Primary outcome of interest was 28-day mortality in the entire matched cohort, and among subgroups stratified by use of supplemental oxygen.

Results: Among 238,298 SARS-CoV-2 infected Veterans, 31,632 were hospitalized, and 13,147 received remdesivir. Our final dataset included 3,583 remdesivir recipients and 3,583 propensity-score matched controls. Probability of survival at 28 days overall was higher in those who had received remdesivir (P=0.032). Remdesivir recipients had better survival among the group who received supplemental oxygen but did not require mechanical ventilation (P=0.005).

Conclusion: Remdesivir demonstrated a survival benefit among hospitalized patients with COVID-19 which was limited to those who received supplemental oxygen but did not require mechanical ventilation.

PROBABILITY OF EVENT-FREE SURVIVAL AMONG REMDESIVIR TREATED PERSONS (N=3,583) AND PROPENSITY-SCORE MATCHED UNTREATED PERSONS (N=3,583), OVERALL AND STRATIFIED BY OXYGEN REQUIREMENT AT ADMISSION.

Figure. Probability of event-free survival among Remdesivir treated persons (N=3,583) and propensity-score matched untreated persons (N=3,583), overall and stratified by oxygen requirement at admission.



560 REMDESIVIR IN HOSPITALIZED COVID-19 PATIENTS: INDIVIDUAL PATIENT DATA META-ANALYSIS

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Background: The interpretation of the evidence from randomized clinical trials (RCTs) on remdesivir for hospitalized patients with coronavirus disease 2019 (COVID-19) is conflicting. We conducted a systematic review and individual patient data meta-analysis (IPDMA) of RCTs to assess the benefit and harm of remdesivir compared to placebo or usual care in hospitalized patients and whether treatment effects differed between prespecified subgroups.

Methods: We systematically searched electronic databases and registries through April 11th 2022 and contacted authors of eligible trials to share individual patient data. The primary outcome was all-cause mortality at day 28. We used multivariable hierarchical regression adjusting for respiratory support, age, and enrollment period to investigate effect modifiers. The study was registered in PROSPERO (CRD42021257134).

Results: Out of nine eligible RCTs, eight provided individual data for 10480 hospitalized COVID-19 patients (99% of global IPD) recruited between February 2020 and April 2021. Within 28 days of randomization, 662 of 5317 patients (12.5%) assigned to remdesivir and 706 of 5005 (14.1%) assigned to no remdesivir died (adjusted odds ratio [aOR] 0.88; 95% confidence interval [CI], 0.78-1.00; p=0.045). We found evidence for a credible subgroup effect according to respiratory support at baseline (interaction p=0.019). Of those ventilated including high-flow oxygen, 253/844 (30.0%) assigned to remdesivir died versus 241/846 (28.5%) assigned to no remdesivir (aOR 1.10 [0.88-1.38]; low certainty evidence). Of those receiving no or low flow oxygen, 409/4473 (9.1%) assigned to remdesivir died versus 465/4159 (11.2%) assigned to no remdesivir (aOR 0.80 [0.70-0.93]; high certainty evidence). There was no credible subgroup effect with respect to time to start of remdesivir after symptom onset, age, presence of comorbidities, enrollment period or corticosteroid use. Remdesivir did not increase the frequency of severe or serious adverse events. Table 1 summarizes the findings according to GRADE (Grading of Recommendations, Assessment, Development and Evaluations).

Conclusion: This IPDMA, summarizing the evidence of 99% patients ever randomized on the topic, demonstrated that remdesivir reduced mortality in hospitalized COVID-19 patients requiring no or conventional oxygen support, but patients requiring more respiratory support may not benefit. These findings may inform clinical guidelines, especially due to increasing resistance to current monoclonal antibodies.

Table 1: Summary of findings and certainty of evidence, by respiratory support

Table 1: Summary of findings and certainty of evidence, by respiratory support

Outcome	Study Results and Measurements	Absolute Effect Estimates*		Certainty in Effect Estimates (Quality of Evidence)	Summary
		Remdesivir	No Remdesivir		
For patients receiving no or only low-flow oxygen at treatment start					
All-cause mortality at day 28	aOR 0.80 (0.70-0.93) Based on data from 8632 patients from 8 trials	92 per 1000	112 per 1000	High	Remdesivir reduces 28-day mortality in this patient subgroup
		Absolute Difference: 20 fewer per 1000 (95% CI, 31 fewer to 7 fewer); *NNT 50 / If ACR* 2.5%: NNT 205*			
New mechanical ventilation or death at day 28	aOR 0.78 (0.69-0.87) Based on data from 8662 patients from 8 trials	155 per 1000	190 per 1000	High	Remdesivir reduces progression to mechanical ventilation or death
		Absolute Difference: 35 fewer per 1000 (95% CI, 51 fewer to 21 fewer)			
Days until discharge/ reaching discharge criteria up to day 28	aHR 1.02 (0.98-1.07) Based on data from 8737 patients from 8 trials	7 (median)	7 (median)	Moderate†	Remdesivir probably has little or no effect on days until hospital discharge
		Absolute Difference: 0 day less (95% CI, 0 to 1 day more)‡			
Adverse event grade 3 or 4 or serious adverse event within 28 days	aOR 0.82 (0.68-0.99) Based on data from 2810 patients from 6 trials	214 per 1000	249 per 1000	Moderate§	Remdesivir probably reduces the risk of severe and serious adverse events
		Absolute Difference: 35 fewer per 1000 (95% CI, 65 fewer to 2 fewer)			
For patients receiving high-flow oxygen, non-invasive ventilation, mechanical ventilation or ECMO at treatment start					
All-cause mortality at day 28	aOR 1.10 (0.88-1.38) Based on data from 1690 patients from 8 trials	305 per 1000	285 per 1000	Low¶	Remdesivir may have little or no effect on 28-day mortality
		Absolute Difference: 20 more per 1000 (95% CI, 26 fewer to 70 more) *NNH: 51 / If ACR* 2.5%: NNH 412*			
New mechanical ventilation or death at day 28	aOR 0.91 (0.74-1.11) Based on data from 1718 patients from 8 trials	365 per 1000	387 per 1000	Moderate‖	Remdesivir probably has little or no effect on progression to mechanical ventilation or death
		Absolute Difference: 22 fewer per 1000 (95% CI, 69 fewer to 25 more)			
Days until discharge/ reaching discharge criteria up to day 28	aHR 0.97 (0.84-1.12) Based on data from 1729 patients from 8 trials	13 (median)	13 (median)	Low**	Remdesivir may have little or no effect on time to hospital discharge
		Absolute Difference: 0 day less (95% CI, 1 day less to 2 days more)‡			
Adverse event grade 3 or 4 or serious adverse event within 28 days	aOR 0.96 (0.76-1.21) Based on data from 1281 patients from 6 trials	463 per 1000	473 per 1000	Low††	Remdesivir may have little or no effect on severe and serious adverse events
		Absolute Difference: 10 fewer per 1000 (95% CI, 68 fewer to 48 more)			

Abbreviations: aOR, adjusted Odds Ratio; aHR, adjusted Hazard Ratio; ECMO, Extracorporeal membrane oxygenation; NNH, number needed to harm; NNT, number needed to treat; ACR, assumed control risk
*Assumed control risks (ACR): weighted mean baseline risk across all trials (events in control / observations in control). Alternative ACR for in-hospital mortality (2.5%) based on recent data (May 2022) from CDC
†Outcome was rated down for risk of bias
‡Median (event-free) survival time, i.e. median hospitalization time, converted according to GRADE guidelines[24]
§Outcome was rated down for inconsistency
¶Outcome was rated down twice for imprecision
‖Outcome was rated down for imprecision
**Outcome was rated down for imprecision and risk of bias
††Outcome was rated down for imprecision and inconsistency

561 REMDESIVIR RESISTANCE ANALYSES FROM THE PINETREE STUDY IN OUTPATIENTS WITH COVID-19

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Background: Remdesivir (RDV) is a broad-spectrum nucleotide analog antiviral approved for the treatment of COVID-19 in patients who are hospitalized or non-hospitalized and at risk of progressing to severe disease. Here we present SARS-CoV-2 resistance analyses from the Phase 3 PINETREE trial.

Methods: PINETREE was a double-blind, placebo-controlled trial of non-hospitalized participants (N=562) with COVID-19 and ≥1 risk factor for disease progression, randomized to receive RDV or placebo once-daily for 3 days. The whole genome of SARS-CoV-2 was sequenced from nasopharyngeal swabs collected at days 1 (baseline), 2, 3, 7, and 14 using next-generation sequencing. Emergent amino acid substitutions in SARS-CoV-2 from participants treated

with RDV were tested in a replicon system to determine if they alter sensitivity to RDV.

Results: Resistance analysis criteria included all participants in the RDV group and 50% in the placebo group with viral load above the lower limit of detection for the viral load assay. Of 281 participants who met these criteria, baseline and postbaseline sequencing data were available for 115/130 (88.5%) participants in the RDV group and 129/151 (85.4%) participants in the placebo group (**Table 1**). Among these, emergent substitutions in Nsp12 were observed in 8/115 (7.0%) in the RDV group and 7/129 (5.4%) in the placebo group. A total of 7 emergent amino acid substitutions in Nsp12 were observed in the RDV group, but not in the placebo group. Among these, only one substitution from one participant (A376V; first detected at day 14), showed reduced *in vitro* susceptibility to RDV, with a half-maximal effective concentration (EC_{50}) fold-change of 12.6 compared with a wildtype reference. The participant achieved clinical recovery by day 14. None of the other substitutions impacted RDV susceptibility (EC_{50} fold-change ≤1.4). Emergent substitutions in Nsp8, Nsp10, Nsp13, or Nsp14 were detected in 10/115 (8.7%) of participants in the RDV group and 10/129 (7.8%) in the placebo group, with substitutions in the RDV group showing similar susceptibility to RDV as the wildtype reference (EC_{50} fold-change ≤2.3).

Conclusion: Overall, emergent substitutions in the SARS-CoV-2 replication complex including Nsp12 were observed with similar frequency in the RDV and placebo groups, with only one participant developing a substitution associated with reduced *in vitro* RDV susceptibility, indicating a high barrier to the development of RDV resistance in COVID-19 patients.

Table 1. PINETREE Sequencing Data

	Number of Participants	
	RDV	Placebo
Treated population	279	283
Met resistance analysis criteria and sequencing attempted	130/279 (46.6%)	151/283 (53.4%)
Sequencing data available		
Baseline	119/130 (91.5%)	138/151 (91.4%)
Postbaseline	122/130 (93.8%)	137/151 (90.7%)
Baseline + postbaseline	115/130 (88.5%)	129/151 (85.4%)
Participants with emergent Nsp12 substitutions	8/115 (7.0%)	7/129 (5.4%)
Participants with Nsp12 substitutions affecting RDV in vitro activity	1/115 (0.9%)	N/A

RDV, remdesivir.

562 REMDESIVIR RETAINS POTENT ACTIVITY AGAINST SARS-CoV-2 VARIANTS OF CONCERN

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Background: Recent SARS-CoV-2 variants of concern (VOCs) have shown a progressive loss of sensitivity to monoclonal antibody therapeutics. Remdesivir (RDV) is a nucleotide analog prodrug that targets the viral RNA-dependent RNA polymerase (RdRp) Nsp12 and is approved to treat COVID-19 in hospitalized and non-hospitalized patients. Nsp12 is highly conserved across VOCs to date and RDV antiviral activity against previous VOCs (Alpha to Omicron BA.1) has been maintained. Here, we conduct a structural analysis of Nsp12 substitutions observed in recent Omicron subvariants (BA.2, BA.2.12.1, BA.4, BA.5 and BA.2.75) and assess RDV antiviral activity against clinical isolates and site-directed mutants (SDMs) in a replicon system.

Methods: The prevalence of Nsp12 substitutions in Omicron subvariants was evaluated by analysis of sequences from the *Global Initiative on Sharing Avian Influenza Data* (GISAID) EpiCoV database. Structural analysis of identified substitutions was conducted on a prior cryo-electron microscopy-based model of the replication-transcription complex. Antiviral activity against subvariant clinical isolates was assessed by nucleoprotein ELISA in A549-hACE2-TMPRSS2 cells and by SDMs in the replicon system.

Results: Genomic analysis of >1.4 million Omicron subvariant sequences revealed unique substitutions in Nsp12 compared to the ancestral WA1 strain. Besides P323L, present in all subvariants, G671S was observed in 95.9% of BA.2.75 sequences, F694Y was observed in ≤1.9% of BA.4, BA.5 and BA.2.75 sequences, and Y521C was observed in 1.7% of BA.5 sequences. As anticipated, structural analysis of these substitutions showed no direct interaction with the incoming RDV nucleotide triphosphate or the viral RNA. Phenotyping of clinical isolates of Omicron subvariants BA.2, BA.2.12.1, BA.4, BA.5, and BA.2.75 consistently resulted in mean RDV EC_{50} values of 24.5 nM (BA.2) to 106.0 nM (BA.5). This represented 0.15- to 0.66-fold changes compared to WA1, indicating no loss of *in vitro* RDV antiviral activity against these VOCs. P323L, G671S, and F694Y were shown previously to have no impact on RDV antiviral activity. Similarly, the individual substitution Y521C showed no change in RDV susceptibility in the SARS-CoV-2 replicon system.

Conclusion: RDV retained potent *in vitro* antiviral activity against all tested Omicron VOCs with potencies comparable to the WA1 isolate. These data support the continued use of RDV in patients infected with Omicron subvariants.

563 SARS-CoV-2 VIRAL LOAD CHANGE IN A RANDOMIZED TRIAL ON THREE DIFFERENT EARLY THERAPIES

Valentina Mazzotta, **Simone Lanini**, Giulia Matusali, Francesca Colavita, Alessandra Vergori, Emanuela Giombini, Silvia Rosati, Sabrina Minicucci, Martina Reuca, Francesca Gavaruzzi, Enrico Girardi, Emanuele Nicastri, Francesco Vaia, Fabrizio Maggi, Andrea Antinori

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Background: SARS-CoV-2 Omicron sublineages exhibit evolving escape to *in vitro* neutralization by monoclonal antibodies (mAbs), with an unclear impact on *in vivo* treatment response.

Our aim is to assess the impact of SARS-Cov-2 variants on the decline of viral load (VL) after treatment with 3 different drugs approved in EU for the early treatment of patients with mild-moderate COVID-19.

Methods: Post-hoc analysis from MONET (EudraCT: 2021-004188-28), phase 4 open-label RCT to assess efficacy of 500 mg intravenous sotrovimab (SOT), 600 mg intramuscular tixagevimab/cilgavimab (TIX/CIL) and oral 5-days course of NMV/r 300/100 mg BID, in non-hospitalized high-risk patients (pts) with early COVID-19. Pts' features were analyzed as binary variables by Chi-squared test. SARS-Cov-2 VL in nasopharyngeal swabs was carried out at randomization (1d) and at day 7 (7d) by cycle threshold value (Ct). Variant sequencing was performed at 1d. Ct variation was assessed by mixed effect log-linear model including random intercept at pts' level, log of Ct as independent variable, time, arm, viral variant as dependent variables, and interaction between time and arm. Multiple comparisons were adjusted by Bonferroni.

Results: Among the 320 pts included between 4 Mar and 16 Nov, 2022, 108 (33.75%) received NMV/r, 103 (32.19%) TIX/CIL, and 109 (34.06%) SOT. Main characteristics were balanced across arms.

Most of the pts were infected either with BA.2 (N=194; 60.63%) or BA.4/BA.5 (N=100; 31.25%) (Fig1A). VL at 1d was similar across the arms. In contrast, mean 7d VL was significantly lower in pts receiving NMV/r than in those receiving TIX/CIL or SOT (P< 0.001) No significant VL variation was observed between the mAb arms (Fig1B). The analysis of the impact of viral variants suggests that while VL was significantly affected by variants (P=0.034), the superior effect of NMV/r over mAbs was homogeneous across all variant groups (P=0.290 for interaction) (Fig1C).

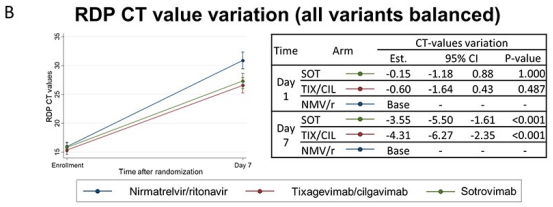
Conclusion: Our study provides for the first time strong *in vivo* evidence that, when used against Omicron lineages, NMV/r exerts a stronger antiviral effect than mAbs. These results confirm previous *in vitro* evidence suggesting that mAbs may not retain neutralizing activity against all Omicron sublineages and provide preliminary information on how to use VL variation as a surrogate marker of efficacy. Further studies are needed to investigate whether the superior virologic activity of NMV/r over mAbs is confirmed for newly emerging variants, including BQ.1.1 or XBB.

Figure 1. A. Main patients' characteristics and SARS-CoV-2 variant distribution across the 3 arms; B. Mixed log-linear model to compare the VL variation between enrollment and day 7 in the 3 arm (VL difference are reported in table as mean Ct-difference); C. SARS-CoV-2 variant effect on RNA RPD Ct values by arms. SOT=sotrovimab; TIX/CIL=tixagevimab/cilgavimab; NMV/r=nirmatrelvir/ritonavir; COPD=chronic obstructive pulmonary disease; CVD=cardiovascular disease

A

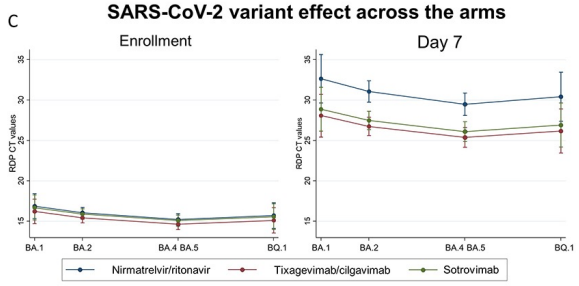
Patient's features (N=320)		Arms						P-value
		SOT(N=109)		TIX/CIL (N=103)		NMV/r (N=108)		
		N	%	N	%	N	%	
Variant	BA.1	4	3.67%	4	3.88%	6	5.56%	0.749
	BA.2	67	61.47%	67	65.05%	60	55.56%	
	BA.4 & BA.5	34	31.19%	30	29.13%	36	33.33%	
	BQ	4	3.67%	2	1.94%	6	5.56%	
Epidemiological features	Male gender	61	55.96%	46	44.66%	52	48.15%	0.239
	Caucasian	105	96.33%	101	98.06%	105	97.22%	0.749
	Simptoms onset ≤2 days	32	29.36%	32	31.07%	33	30.56%	0.962
	People age > 65	54	49.54%	44	42.72%	52	48.15%	0.578
	BMI > 30	19	17.43%	20	19.42%	15	13.89%	0.553
	Diabetes	18	16.51%	11	10.68%	12	11.11%	0.361
	CV disease	46	42.20%	41	39.81%	48	44.44%	0.793
	COPD	19	17.43%	28	27.18%	18	16.67%	0.108
	Renal failure	5	4.59%	4	3.88%	4	3.70%	0.941
	Leukemia/lymphoma	24	22.02%	29	28.16%	22	20.37%	0.374
	Immunodeficiency	21	19.27%	14	13.59%	15	13.89%	0.435
	Neurological disease	3	2.75%	5	4.85%	5	4.63%	0.692
	Vaccination ≥ 2 doses	103	94.50%	94	91.26%	103	95.37%	0.433
	Other	4	3.67%	7	6.80%	6	5.56%	na

B



Time	Arm	CT-values variation			
		Est.	95% CI		P-value
Day 1	SOT	-0.15	-1.18	0.88	1.000
	TIX/CIL	-0.60	-1.64	0.43	0.487
	NMV/r	Base	-	-	-
Day 7	SOT	-3.55	-5.50	-1.61	<0.001
	TIX/CIL	-4.31	-6.27	-2.35	<0.001
	NMV/r	Base	-	-	-

C



564 A RANDOMIZED TRIAL ON EARLY THERAPY IN COVID-19 HIGH-RISK OUTPATIENTS IN OMICRON ERA

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Background: Antivirals and monoclonal antibodies (mAbs) were approved for early treatment of COVID-19 based on data from trials conducted in unvaccinated people before the Omicron era. The comparative effectiveness of different treatments is unknown. We present the results of the interim analysis of MONET trial (EudraCT: 2021-004188-28).

Methods: In this ongoing multicenter, open-label, phase 4 trial, we randomly assigned, in a 1:1:1 ratio, non-hospitalized patients with early symptomatic Covid-19 (≤5 days after symptoms onset) and >=1 risk factor for disease progression, to receive 500 mg of intravenous sotrovimab (SOT) or 600 mg of intramuscular tixagevimab/cilgavimab (TIX/CIL) or oral 5-days course of NMV/r 300/100 mg BID. Primary outcome was hospitalization or death for any cause within 29 days after randomization, reported as cumulative incidence per 100 (95% CI), and P-value calculated by Fisher's exact test. Inflammatory marker (CRP, d-dimer, and neutrophils-to-lymphocytes ratio) and antibody level (serum anti-S IgG and anti-N IgG) analysed by mixed linear regression with random intercept and P-values for time trend calculated by ANOVA-style test with Bonferroni correction.

Results: Prespecified interim analysis, including 400 patients (SOT =133, TIX/CIL=130, NMV/r=137) enrolled from Mar 4 to Nov 16, 2022 (Fig.1A). Overall, 5 pts (3/5 immunosuppressed) had disease progression leading to hospitalization [1.25% (95% CI 0.4%-2.89%)], 1 in SOT (0.75%, 95% CI 0.01%- 4.1%), 4 in TIX/CIL (3.08%, 95% CI 0.84%-7.69%) and none in NMV/r arm (P=0.030). No deaths or ICU admissions were observed. Among the hospitalized pts, 3 were infected with BA.2 (1 SOT, 2 TIX/CIL), one with BA.4/5, and one BQ.1.1 (both TIX/CIL). No serious adverse events and no kidney or liver toxicity were reported. Temporal trend of inflammation markers was similar in the three arms, and their estimates are shown in Fig.1B. Kinetics of antibody was reported in Fig.1C. The plot shows a rapid increase of anti-S in both mAb arm and a linear increase of IgG in the NMV/r arm. Anti-N IgG kinetics was similar in the three arms.

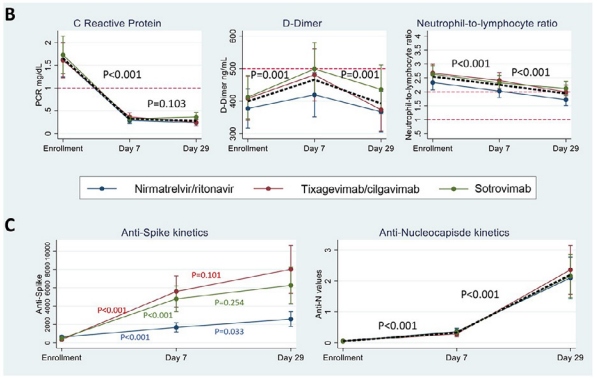
Conclusion: By these data the overall cumulative risk of clinical failure in mild Covid-19 occurring in the Omicron era is low. The hypothesis that differences in clinical progression among the three arms could be related to different activity against the Omicron subvariant observed *in vitro* should be further investigated. Type of treatment does not seem to influence the development of the natural antibody response.

Figure 1. A. Main patients' characteristics across the 3 randomized arms; B. Inflammatory marker (CRP, d-dimer, and neutrophils-to-lymphocytes ratio) and C. antibody level (serum anti-S IgG and serum anti-N IgG) analysed by mixed linear regression model with random intercept and P-values for time trend calculated by ANOVA-style test with Bonferroni correction. SOT=sotrovimab; TIX/CIL=tixagevimab/cilgavimab; NMV/r=nirmatrelvir/ritonavir; COPD=chronic obstructive pulmonary disease; CV=cardiovascular; CRP= c reactive protein.

A

Patient's features (N=400)		Arms						P-value
		SOT (N=133)		TIX/CIL (N=130)		NMV/r (N=137)		
		N	%	N	%	N	%	
Epidemiological features	Male gender	72	54.1	59	45.3	66	48.1	0.348
	Caucasian	129	96.9	126	96.9	133	97.1	0.997
	Simptoms onset ≤2 days	40	30.1	37	28.5	42	30.7	0.921
	People age > 65	65	48.8	52	40.0	61	44.5	0.351
	BMI > 30	24	18.0	25	19.2	21	15.3	0.689
	Diabetes	22	16.5	13	10.0	18	13.1	0.294
	CV disease	59	44.3	47	36.1	54	39.4	0.392
	COPD	21	15.7	36	27.7	21	15.3	0.016
	Renal failure	8	6.0	4	3.1	8	5.8	0.471
	Liver disease	1	0.75	2	1.5	0	0.0	0.346
	Leukemia/lymphoma	28	21.0	34	26.1	28	20.4	0.475
	Immunodeficiency	22	16.5	23	17.7	19	13.9	0.681
	Neurological disease	5	3.75	6	4.6	6	4.4	0.938
	Vaccina ≥ 2 doses	127	95.5	120	92.3	127	92.7	0.519

B



C

565 SARS-CoV-2 OMICRON VIRAL LOAD DECREASE AFTER MONOCLONAL ANTIBODIES OR ANTIVIRALS

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Background: Omicron subvariants questioned the efficacy of the approved therapies for the early COVID-19. *In vitro* data show that remdesivir (RDV), molnupiravir (MLN), and nirmatrelvir/ritonavir (NMV/r) all retained activity against all sub-lineages, while poor neutralizing activity was observed for Sotrovimab (SOT) and Tixagevimab/cilgavimab (TIX/CIL). No data about the risk of clinical failure or even *in vivo* antiviral activity are available.

Methods: Single-center observational comparison study enrolling all consecutive patients (pts) seen for care with a confirmed SARS-CoV-2 Omicron diagnosis and who met the AIFA criteria for eligibility for treatment with RDV, MLN, NMV/r, TIX/CIL, or SOT. Treatment allocation was subject to drug availability, time from symptoms onset, and comorbidities. Nasopharyngeal

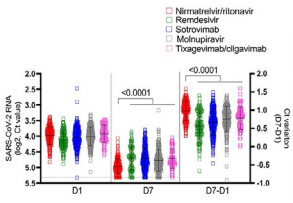
swab (NPS) VL was measured on day 1 (D1) and D7 and was expressed by log_2 cycle threshold (CT) scale. Comparisons between treatment groups were made by Chi-square, and Wilcoxon paired tests. Primary endpoint was D1-D7 VL variation. Potential decrease in VL and average treatment effect (ATE) were calculated from fitting marginal linear regression models weighted for calendar month of drug initiation, duration of symptoms, and immunodeficiency using NMV/r as the comparator trial arm.

Results: A total of 971 pts received treatments (SOT 321, MLN 231, NMV/r 211, TIX/CIL 70, and RDV 138): female 457 (47%), median age 67 yrs (IQR 56-78), 93% vaccinated; 12% with negative baseline serology. At D1, median time from symptoms onset was 3 days (IQR 2,4). 379 (39%) pts were infected with BA.1, 215 (22%) with BA.2, 372 with BA.4/5 (38%), and 5 with BQ.1 (0,5%). D1 mean viral load was 4.02 log_2. Adjusted analysis (ATE) showed that NMV/r significantly reduced VL compared to all the other drugs in pts infected with all sublineages, (Fig.1A-B) while less evidence for a difference vs. TIX/CIL was seen in those infected with BA.2 (p=0.05) (Fig.1 C-D).

Conclusion: In this analysis of *in vivo* early VL reductions, NMV/r appears to be the drug showing the greatest antiviral activity, regardless of the underlying subvariant, perhaps with the exception of TIX/CIL in people infected with BA.2 for which there was less evidence for a difference. In the Omicron era, due to the high prevalence of vaccinated people and in absence of clinical events, VL is one of the possible alternative endpoints which guarantees adequate statistical power.

Fig 1 SARS-CoV-2 RNA levels at D1 and D7 in patients treated with Nirmatrelvir/ritonavir, Sotrovimab, Molnupiravir, Remdesivir, and Tixagevimab/cilgavimab. Dot-plots showing the comparison of viral loads detected at D1 and D7 and the variation of RNA levels observed between the two time-points by intervention in (A) all patients treated with Nirmatrelvir/ritonavir (n=211), Sotrovimab (n=321), or Molnupiravir (n=231), or Remdesivir (n=138), or Tixagevimab/cilgavimab (n=136); (C) patients with Omicron BA.2 infection treated with Nirmatrelvir/ritonavir (n=58), Sotrovimab (n=81), or Molnupiravir (n=21), or Remdesivir (n=37), or Tixagevimab/cilgavimab (n=18); (D) patients with Omicron BA.4/5 infection treated with Nirmatrelvir/ritonavir (n=102), Sotrovimab (n=92), or Molnupiravir (n=110), or Remdesivir (n=16), or Tixagevimab/cilgavimab (n=52). Viral RNA levels are expressed as log_2 CT values. The horizontal dashed line represents the limit of detection (CT: 40.0), values ≥40 are considered negative. Mean of log_2 CT values, and SD are shown in the graph. Statistical analysis of the differences in viral loads by intervention as compared to Nirmatrelvir/ritonavir was performed by Mann-Whitney test. Potential decrease in VL and average treatment effect (ATE) were calculated from fitting marginal linear regression models weighted for calendar month of drug initiation, duration of symptoms, and immunodeficiency using NMV/r as the comparator trial arm. Results are shown (B) for patients infected with all Omicron sublineages and (D) for those infected with Omicron BA.2 sublineage.

(A)



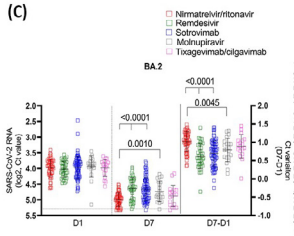
(B)

Potential Day 7 decrease in CT from baseline and ATE[a] from fitting a linear regression model (log2 scale)

	Decrease (log2) in intervention (95% CI)	Decrease (log2) in control (95% CI)	ATE* (95% CI)	p-value
Tixagevimab/cilgavimab vs. Nirmatrelvir/r				
IPWs	0.79 (0.71, 0.87)	0.98 (0.95, 1.02)	-0.19 (-0.28, -0.10)	<.001
Double Robust	0.82 (0.73, 0.92)	0.98 (0.95, 1.02)	-0.16 (-0.26, -0.06)	<.001
Regression adjustment	0.82 (0.82, 1.01)	0.98 (0.95, 1.02)	-0.16 (-0.36, 0.03)	0.100
Truncated			-0.20 (-0.28, -0.12)	<.001
Molnupiravir vs. Nirmatrelvir/r				
IPWs	0.75 (0.70, 0.81)	0.96 (0.93, 1.00)	-0.21 (-0.28, -0.14)	<.001
Double Robust	0.76 (0.69, 0.82)	0.96 (0.93, 1.00)	-0.21 (-0.28, -0.13)	<.001
Regression adjustment	0.76 (0.71, 0.82)	0.91 (0.88, 0.95)	-0.15 (-0.22, 0.08)	<.001
Truncated			-0.32 (-0.41, -0.24)	<.001
Remdesivir vs. Nirmatrelvir/r				
IPWs	0.64 (0.58, 0.71)	0.97 (0.94, 1.01)	-0.33 (-0.40, -0.26)	<.001
Double Robust	0.64 (0.58, 0.70)	0.95 (0.91, 1.00)	-0.31 (-0.39, -0.24)	<.001
Regression adjustment	0.64 (0.58, 0.70)	0.91 (0.87, 0.95)	-0.27 (-0.34, -0.20)	<.001
Truncated			-0.57 (-0.70, -0.45)	<.001
Sotrovimab vs. Nirmatrelvir/r				
IPWs	0.70 (0.66, 0.75)	0.95 (0.91, 0.99)	-0.25 (-0.30, -0.19)	<.001
Double Robust	0.70 (0.66, 0.74)	0.95 (0.91, 0.99)	-0.25 (-0.31, -0.20)	<.001
Regression adjustment	0.70 (0.66, 0.74)	0.92 (0.88, 0.95)	-0.22 (-0.27, -0.16)	<.001
Truncated			-0.41 (-0.49, -0.33	<.001

*Average Treatment Effect; †weighted for month of infusion, duration of symptoms and immunodeficiency

(C)



(D)

Potential Day 7 decrease in CT from baseline and ATE[a] from fitting a linear regression model (log2 scale)

	Decrease (log2) in intervention (95% CI)	Decrease (log2) in control (95% CI)	ATE* (95% CI)	p-value
Tixagevimab/cilgavimab vs. Nirmatrelvir/r				
IPWs	0.94 (0.80, 1.07)	1.02 (0.96, 1.08)	-0.09 (-0.23, 0.06)	0.255
Double Robust	0.93 (0.75, 1.12)	1.02 (0.96, 1.09)	-0.09 (-0.28, 0.10)	0.050
Regression adjustment	0.94 (0.78, 1.11)	1.02 (0.96, 1.09)	-0.08 (-0.26, 0.09)	0.351
Truncated			-0.12 (-0.31, 0.06)	0.187
Molnupiravir vs. Nirmatrelvir/r				
IPWs	0.81 (0.69, 0.94)	1.01 (0.95, 1.08)	-0.20 (-0.36, -0.04)	0.013
Double Robust	0.77 (0.64, 0.91)	1.02 (0.94, 1.09)	-0.24 (-0.41, -0.08)	<.001
Regression adjustment	0.77 (0.63, 0.90)	1.02 (0.94, 1.09)	-0.25 (-0.41, -0.09)	0.002
Truncated			-0.30 (-0.45, -0.14)	<.001
Remdesivir vs. Nirmatrelvir/r				
IPWs	0.45 (0.35, 0.56)	0.98 (0.91, 1.04)	-0.53 (-0.65, -0.40)	<.001
Double Robust	0.63 (0.54, 0.72)	1.00 (0.93, 1.08)	-0.37 (-0.49, -0.26)	<.001
Regression adjustment	0.61 (0.51, 0.70)	1.00 (0.93, 1.08)	-0.40 (-0.52, -0.28)	<.001
Truncated			-0.44 (-0.58, -0.29)	<.001
Sotrovimab vs. Nirmatrelvir/r				
IPWs	0.74 (0.66, 0.83)	0.98 (0.90, 1.06)	-0.24 (-0.35, -0.13)	<.001
Double Robust	0.72 (0.64, 0.81)	0.97 (0.87, 1.06)	-0.25 (-0.37, -0.12)	<.001
Regression adjustment	0.72 (0.64, 0.80)	0.97 (0.89, 1.06)	-0.25 (-0.36, -0.14)	<.001
Truncated			-0.40 (-0.53, -0.27)	<.001

*weighted for month of infusion, duration of symptoms and immunodeficiency; &Average Treatment Effect

566 INCIDENCE AND PREDICTORS OF CLINICAL PROGRESSION IN AN EARLY TREATED COVID-19 COHORT

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Background: Early treatment for preventing severe outcome of COVID-19 in high-risk not-hospitalized patients (pts) by monoclonal antibodies or antivirals represented a high-priority approach. Real-world evidence (RWE) from observational studies could give information on clinical effectiveness and predictors of treatment failure.

Methods: Single-center observational study on SARS-CoV-2 pts, not requiring hospital admission but having high-risk of severe outcome from COVID-19. All were selected for early treatment with monoclonal antibodies or antivirals from March 2021 to November 2022. Participants were classified according to whether they were hospitalized due to severe COVID-19 or died by day 30 from starting treatment in the outpatient setting (baseline). We conducted a logistic regression analysis with this binary endpoint and 4 main exposures of interest measured at baseline: i) age (>75 years old) ii) vaccination status iii) VoC, and iv) immunosuppression or having received immunosuppressive therapy. We built a separate model for each of these exposures, which included a specific set of potential confounders.

Results: 3,491 pts, female 48.6%, median age 67 yrs (IQR 55-77), fully vaccinated 83.7%; previous infection 4.6%; CVD 52.2%; cancer 24.6%; immunodeficiency 40.6%. Prevalence of SARS-CoV-2 VoC: delta 8.7%, BA.1 16.9%, BA.2 6.8%, BA.4/5 12.2, BQ 0.1%, other 3.0% (Tab.1A). Treatment exposure was BAM/ETE 569 (16.5%), CAS/IMD 262 (7.6%), SOT 935 (27.1%), TIX/CIL 79 (2.3%), NMV/r 555 (16.1%), MLP 684 (19.8%), RDV 356 (10.3%). Primary endpoint occurred in 80/3,491 pts with a day-30 incident risk of 2.3% (95%CI 1.8-2.9). Tab.1B shows the unadjusted and adjusted odds ratios (OR) of hospitalization due to COVID-19 or death by day 30. After controlling for potential confounders, higher risk was observed for the unvaccinated (OR 1.95;95%CI 1.03-3.71) and for those affected by immunodeficiency [1.73; 1.04-2.89). Having delta as reference variant, an increased risk was observed for BA.2 [2.08; 1.00-2.34]. No evidence for a difference was seen by age or other comorbidities.

Conclusion: In this RWE study, largely represented by vaccinated people and prevalently observed in the Omicron era, the estimated risk of clinical failure of early treatment was slightly higher than that recorded in the experimental arms of randomized studies. The analysis confirms that among those eligible for early treatment, the unvaccinated and those with severe immunodeficiency are at higher risk of developing severe COVID-19.

Table 1 - A. Main characteristics of 3,491 not-hospitalized people with mild-to-moderate COVID-19 at high risk of severe disease observed between March 2021 to November 2022 according to reaching (n=80) or not reaching (3,411) primary clinical endpoint. B. Odds ratios (OR) of having a COVID-19-related hospitalization or death by different exposure factors.

1A)

	Population characteristic according to clinical outcome			
	Progressing to COVID hospitalization/death	Non progressing	p-value*	Total
	N= 80	N= 3411		N= 3491
Characteristics				
Gender, n(%)			0.183	
Female	33 (41.3%)	1664 (48.8%)		1697 (48.6%)
Age, years			0.649	
Median (IQR)	68 (56, 78)	67 (55, 77)		67 (55, 77)
Older than 75, n(%)	27 (33.8%)	1113 (32.6%)	0.833	1140 (32.7%)
Natural infection, n(%)			0.877	
Yes	4 (5.0%)	158 (4.6%)		162 (4.6%)
Vaccination, n(%)			<.001	
None or incomplete	29 (36.3%)	541 (15.9%)		570 (16.3%)
Full, not recent	32 (40.0%)	1911 (56.0%)		1943 (55.7%)
Full, recent	19 (23.8%)	959 (28.1%)		978 (28.0%)
Comorbidities, n(%)				
CVD	33 (41.3%)	1791 (52.5%)	0.046	1824 (52.2%)
Hepatic Disease	1 (1.3%)	56 (1.6%)	0.384	57 (1.6%)
Cancer	23 (28.8%)	836 (24.5%)	0.226	859 (24.6%)
Primary/secondary immunodeficiency	24 (30.0%)	823 (24.1%)	0.785	847 (24.3%)
General immunodeficiency	36 (45.0%)	1380 (40.5%)	0.413	1416 (40.6%)
Year of enrolment, n(%)			<.001	
2022	43 (53.8%)	2643 (77.5%)		2686 (76.9%)
VoC, n(%)			<.001	
Delta	11 (13.8%)	293 (8.6%)		304 (8.7%)
BA.1	9 (11.3%)	582 (17.1%)		591 (16.9%)
BA.2	9 (11.3%)	228 (6.7%)		237 (6.8%)
BA.4/5	9 (11.3%)	413 (12.1%)		422 (12.1%)
BQ.1	0 (0.0%)	5 (0.1%)		5 (0.1%)
Other	15 (18.8%)	89 (2.6%)		104 (3.0%)
Not sequenced	27 (33.8%)	1801 (52.8%)		1828 (52.4%)

*Chi2 and Mann-Whitney test

1B)

	OR of COVID hospitalization or death					
	Unadjusted OR (95% CI)	p-value	Adjusted1* OR (95% CI)	p-value	Adjusted2§ OR (95% CI)	p-va
Age						
>75 vs. <=75	1.05 (0.66, 1.68)	0.833				
Vaccination						
None or incomplete	2.71 (1.50, 4.87)	<.001	2.81 (1.55, 5.08)	<.001	1.95 (1.03, 3.71)	0.0
Full, not recent[a]	0.85 (0.48, 1.50)	0.565	0.85 (0.48, 1.50)	0.566	0.83 (0.46, 1.47)	0.5
Full recent[b]	1		1		1	
VoC						
Delta	1		1		1	
BA.1	0.64 (0.31, 1.30)	0.217	0.64 (0.31, 1.30)	0.213	0.81 (0.39, 1.67)	0.5
BA.2	1.63 (0.79, 3.35)	0.183	1.62 (0.79, 3.33)	0.190	2.08 (1.00, 4.34)	0.0
BA.4/5	0.90 (0.44, 1.84)	0.772	0.89 (0.43, 1.81)	0.742	1.01 (0.49, 2.08)	0.9
Immunodeficiency[c]						
Yes vs No	1.35 (0.83, 2.19)	0.227	1.44 (0.87, 2.40)	0.154	1.73 (1.04, 2.89)	0.0

*adjusted for gender and age

§separate adjustments for each exposure

a) Vaccination - for age, natural infection, immunodeficiency and calendar year

b) VoC - for natural infection and vaccination

c) Immunosuppression - for age, vaccination and calendar year

[c]Immunosuppressed or treated with immunosuppressed agents

[a]last dose older than 120 days

[b]last dose less than 120 days ago

567 NIRMATRELVIR/RITONAVIR UPTAKE AMONG ADULTS WITH COVID-19, DECEMBER 2021-OCTOBER 2022

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CHASING COVID Cohort Study Team

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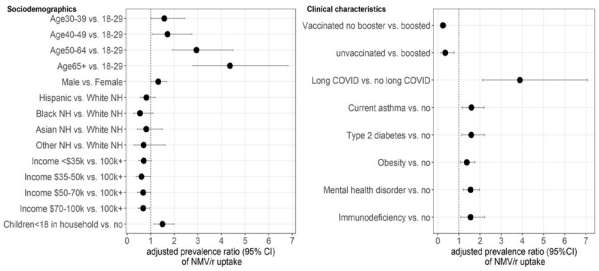
Background: COVID-19 vaccine booster uptake remains low and preventable COVID-19 deaths continue to occur, making access to oral antivirals for those most at risk of severe COVID-19 outcomes essential.

Methods: We estimated age and gender adjusted prevalence ratios of oral nirmatrelvir-ritonavir (NMV/r) uptake by sociodemographics, clinical characteristics, and prescription eligibility (based on age, underlying medical conditions, body mass index, physical inactivity, pregnancy, or smokers), among participants in a large U.S. national prospective cohort who were infected with SARS-CoV-2 between December 2021 and October 2022. Among participants who reported NMV/r uptake, we also described the proportion who reported (1) taking NMV/r as directed and (2) NMV/r was helpful for reducing COVID-19 symptoms.

Results: Among 1,594 participants with a SARS-CoV-2 infection as of October 2022, 1,356 were eligible for NMV/r prescription; of whom 209 (15.4% [95%CI:13.5–17.3]) reported receiving NMV/r. NMV/r uptake increased from 2.2% (95%CI:1.0–3.4) between December 2021 and March 2022 to 16.5% (95% CI:13.0–20.0) between April and July 2022 and 28.6% (95%CI:24.4–32.8) between August and October 2022, respectively. Participants ≥65 years of age reported the highest uptake of NMV/r (30.2% [95%CI:22.2–38.2]). Black non-Hispanic participants (7.2% [95%CI:2.4–12.0]) and those in the lowest income group (10.6% [95%CI:7.3–13.8]) had lower uptake than white non-Hispanic (15.8% [95%CI:13.6–18.0]) and high-income individuals (18.4% [95%CI:15.2–21.7]), respectively. Participants with type 2 diabetes had greater uptake (28.8% [95%CI:20.4–37.3]), compared to those without it (12.4% [95%CI:4.8-20.0]). Among a subset of 278 participants who had a prior SARS-CoV-2 infection, those who had a history of long COVID reported greater uptake (22.0% [95%CI:13.9–30.1]) for a subsequent SARS-CoV-2 infection than those without a history of long COVID (7.9% [95%CI:3.9–11.8]). Among all participants who were prescribed NMV/r (N=216), 89% (95%CI:85–93) reported that they took NMV/r as directed and 63% (95%CI:57–70) stated NMV/r was helpful for reducing COVID-19 symptoms.

Conclusion: Uptake of NMV/r increased over time coinciding with national efforts to increase awareness and access. However, most individuals who were eligible for NMV/r did not receive it. Lower NMV/r uptake among racial/ethnic minorities and individuals with lower household income suggests a need to improve awareness and address barriers to uptake in these populations.



Adjusted Prevalence Ratios of Nirmatrelvir-Ritonavir (NMV/r) Uptake by Sociodemographic and Clinical Factors – United States CHASING COVID Cohort Study Participants with SARS-CoV-2 Infection, December 2021-October 2022

568 VIRAL DYNAMIC MODELS PROVIDE AN EXPLANATION FOR SARS-CoV-2 REBOUND AFTER NIRMATRELVIR

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Background: A 5-day course of nirmatrelvir-ritonavir (N/R) can significantly reduce the hospitalization and death rates and the duration of infectiousness in high-risk SARS-CoV-2 patients. However, in a fraction of treated individuals virus rebounds following an initial recovery after treatment. The mechanism driving rebound is not well understood. We hypothesize that treatment with N/R near the time of symptom onset halts the depletion of target cells, but does not fully eliminate the virus, and thus can lead to viral rebound.

Methods: Previously, we and others have developed viral dynamic models and successfully used them to fit data on SARS-CoV-2 infection. Here we expand these models and incorporate N/R pharmacokinetic and pharmacodynamic effects and an adaptive immune response.

Results: We fit this model to the data presented in Charness et al., NEJM (2022) where longitudinal quantitative PCR data is available for 3 individuals who experienced viral rebounds after taking N/R. We found that the model fit the data well. By varying model parameters from their best-fit values, we show the occurrence of viral rebound is sensitive to model parameters, and the time treatment is initiated, which may explain why only a fraction of individuals rebound. Finally, the model with its best-fit parameter values was used to test the therapeutic effects of treatment extended to 10 days or a second 5-day course of N/R initiated one day after symptoms reoccur.

Conclusion: Our model fits predicted that virus is not fully eliminated during N/R treatment and supported our initial hypothesis that at the end of treatment target cells are available to allow viral resurgence. Simulating the effect of starting treatment later, we find the probability of viral rebound occurring decreases, suggesting that delaying treatment may be a strategy to reduce viral rebound. However, N/R treatment accelerates viral clearance and hence potentially can reduce viral transmission. Thus, delaying treatment may have a detrimental effect on public health and could also have impact on the severity of disease in the high-risk patients for whom N/R is recommended. Increasing treatment from 5 to 10 days continues to preserve target cells and thus may still allow viral rebound if viable virus is present at the end of treatment and sufficient adaptive immunity has not developed. Simulating giving a second course of treatment one day after symptoms reappear, did not prevent rebound.

569 NIRMATRELVIR USE AND HOSPITALIZATIONS OR DEATH IN INDIVIDUALS WITH COVID-19

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Background: Nirmatrelvir/ritonavir (NMV/r) was granted Emergency Use Authorization in December 2021 for treatment of early symptomatic patients with mild to moderate COVID-19 at high risk of progression. However, its benefit is specific population subgroups remains unclear.

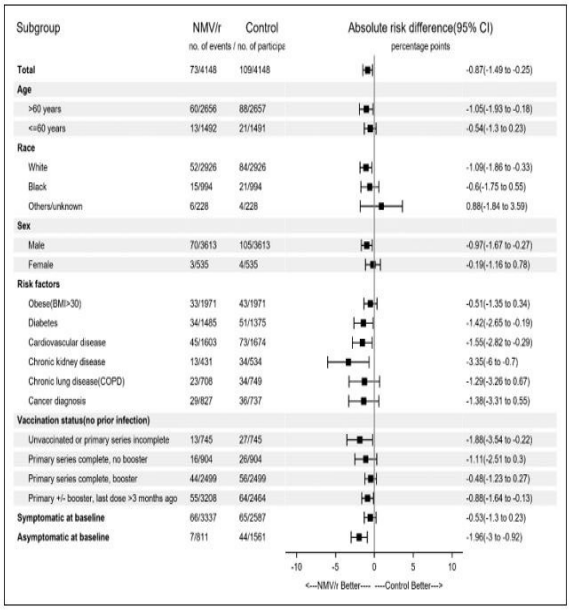
Methods: We used a matched cohort design to emulate a target trial within the VA COVID-19 Shared Data Resource database. Eligible individuals were those with at least two episodes of care in the VA in the last 2 years, who had a first confirmed SARS-CoV-2 infection between January 1 and August 31, 2022 and were free of hospitalization or death within 3 days of testing positive. Those hospitalized in the previous 60-days and those who received Molnupiravir after diagnosis were ineligible. Among the eligible individuals, we matched those prescribed NMV/r with those not prescribed NMV/r within 3 days of diagnosis. Controls were matched 1:1 on age (5-year blocks), race, sex, body mass index, Charlson Comorbidity Index, VA facility where NMV/r was prescribed, and

vaccination status. Our primary outcome measure was hospitalization or death within 30 days of the index COVID-19 diagnosis date.

Results: Among 90,432 persons with a confirmed first SARS-CoV-2 positive test, 68,236 persons met the eligibility criteria. Of those, 4,886 were prescribed NMV/r. Final primary analysis dataset included 4,148 matched pairs of NMV/r treated cases and controls. The incidence of hospitalization or death was significantly lower among those who were prescribed NMV/r overall (73 vs. 109 events; ARD [95% CI] -0.87 [-1.49 to -0.25]), for those older than 60 years (60 vs. 88 events; ARD [95% CI] -1.05 [-1.93 to -0.18]), for unvaccinated/incomplete primary series (ARD -1.88 [-3.54 to -0.22]), and those asymptomatic at baseline (ARD -1.96 [-3.00 to -0.92]). Those who were <60 years old, vaccinated with or without a booster, and those symptomatic at baseline did not experience a significant benefit.

Conclusion: NMV/r use is associated with a modest but statistically significant reduction in hospitalization or death among previously uninfected, non-hospitalized population with COVID-19 who are at a high risk of progression to severe disease. The benefit is evident in older, unvaccinated, asymptomatic persons and those with certain comorbidities. But not in younger, vaccinated, and symptomatic persons.

ABSOLUTE RISK DIFFERENCE IN INCIDENCE OF HOSPITALIZATION OR DEATH WITHIN 30 DAYS AMONG PATIENTS WHO RECEIVED NIRMATRELVIR/RITONAVIR AND MATCHED CONTROLS WHO DID NOT RECEIVE NIRMATLEVIR/RITONAVIR BEFORE MATCHING.



NMV/r, Nirmatrelvir/ritonavir; COPD, chronic obstructive pulmonary disease.

570 MOLNUPAVIR IN PREVIOUSLY UNINFECTED NONHOSPITALIZED PERSONS WITH COVID-19

Adeel Butt[1], Peng Yan[2], Obaid Shaikh[2], Saad Omer[3], Florian G. Mayr[4], Victor Talisa[4]

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Background: Clinical benefit of Molnupiravir (MPV) in COVID-19 infected sub-populations is unclear.

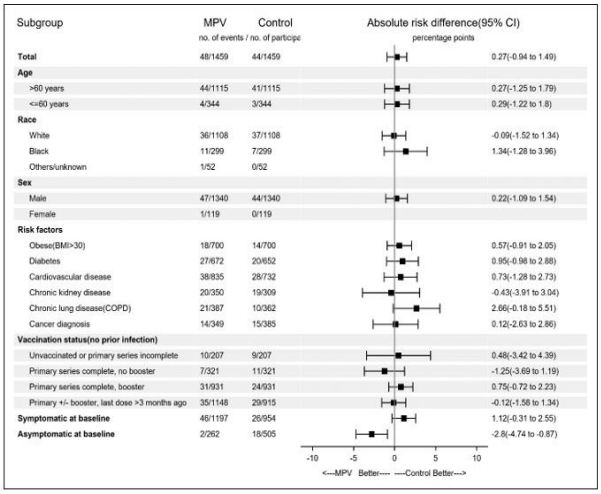
Methods: We used a matched cohort design emulating a target trial to analyze the VA COVID-19 Shared Resource database to determine the association of MPV with hospitalization or death within 30 days compared with untreated controls in previously uninfected non-hospitalized persons. Incidence of hospitalization/death and absolute risk difference (ARD) with 95% confidence intervals were calculated for the treated and untreated groups.

Results: Among 1,459 matched pairs, the incidence of hospitalization/death was not different among MPV treated vs. untreated controls (48 vs. 44 cases; ARD [95% CI] 0.27 [-0.94,1.49]). No benefit was observed among those >60 or <60 years old (ARD 0.27 [-1.25,1.79] vs. -0.29 [-1.22,1.80]), those with specific comorbidities, or by vaccination status. A significant benefit was observed in asymptomatic but not in symptomatic persons (ARD -2.80 [-4.74,-0.87] vs. 1.12 [-0.31,2.55]). Kaplan-Meier curves did not show a significant reduction in proportion of persons who were hospitalized or died among those treated with MPV compared with untreated controls (logrank P=0.7).

Conclusion: MPV was not associated with a significant reduction in hospitalization or death within 30 days of COVID-19 diagnosis overall. A subgroup of patients presenting without symptoms experienced a benefit.

INCIDENCE OF HOSPITALIZATION OR DEATH WITHIN 30 DAYS AND ABSOLUTE RISK DIFFERENCE AMONG PATIENTS WHO RECEIVED MOLNUPIRAVIR AND CONTROLS. RESULTS FOR THE MATCHED GROUPS.

Figure. Incidence of hospitalization or death within 30 days and absolute risk difference among patients who received Molnupiravir and controls. Results for the matched groups.



MPV, Molnupiravir; COPD, chronic obstructive pulmonary disease.

571 TIXAGEVIMAB/CILGAVIMAB IM AND IV FOR COVID-19: A RANDOMIZED CONTROLLED ACTIV-2 TRIAL

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ACTIV-2/A5401 Study Team

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Background: Within the ACTIV-2/A5401 platform (NCT04518410), the safety and efficacy of tixagevimab/cilgavimab (T/C), an anti-SARS-CoV-2 monoclonal antibody combination, was studied in outpatients with COVID-19. Intravenous (IV) and intramuscular (IM) administration of T/C were assessed.

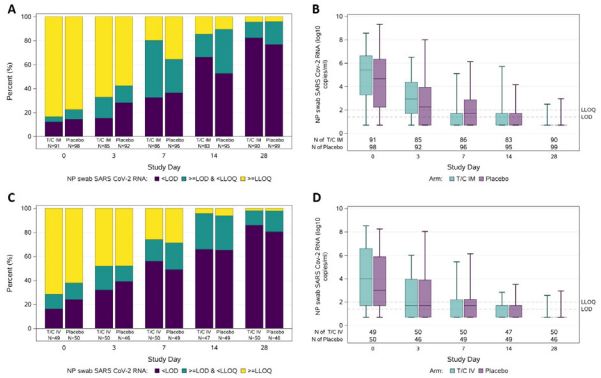
Methods: Non-hospitalized adults ≥18 years enrolled within 10 days of positive SARS-CoV-2 test and symptom onset. Participants at higher risk of disease progression were eligible for IV T/C 300mg (150mg each component) or placebo; all were eligible for IM T/C 600mg (300mg each) administered to the lateral thigh or placebo. Co-primary outcomes were: time to symptom improvement through day 28; nasopharyngeal (NP) SARS-CoV-2 RNA below lower limit of quantification (LLoQ) on days 3, 7 or 14; and treatment emergent Grade ≥3 adverse events.

Results: Between February and May 2021, 223 participants (106 T/C, 117 placebo) initiated study intervention and were included in the IM analysis and 114 participants (58 T/C, 56 placebo) in the IV analysis; the IV study was stopped early for administrative reasons. Both studies enrolled 45% Latinx; the IM and IV populations included 12% and 19% Black participants, 49% and 59% female sex at birth, and median age was 39 and 44 years, respectively, all of which were balanced between active vs placebo for each. Median (IQR) days from symptom onset at enrollment was 6 (4, 7). There were no differences in time to symptom improvement comparing IM T/C to placebo (median 8 (IQR 7, 12) vs 10 (8, 13) days; p=0.35) or IV T/C to placebo (11 (9, 15) vs 10 (7, 15) days; p=0.71). A significantly greater proportion (80%) in the IM T/C arm had NP SARS-CoV-2 RNA below LLoQ at day 7 compared to placebo (65%), but not days

3 or 14, overall p=0.003 across visits. Secondary and post-hoc analyses revealed antiviral effects within the smaller IV study. There was no difference in Grade ≥3 AEs with either administration route. Fewer participants were hospitalized who received T/C vs placebo (4 vs 7 in IM group; 0 vs 4 in IV group), neither group reaching statistical significance.

Conclusion: Tixagevimab/cilgavimab administered IM or IV was well-tolerated and demonstrated antiviral activity and a trend towards fewer hospitalizations, but did not change time to symptom improvement in mild-to-moderate COVID-19 compared to placebo. Monoclonal antibodies administered intramuscularly to the thigh may present a valuable alternative for early SARS-CoV-2 infection.

Virologic Outcomes of Tixagevimab/Cilgavimab treatment 600mg IM (panels A and B) or 300mg IV (panels C and D) versus placebo.



572 A RANDOMIZED TRIAL OF IVERMECTIN 600 MCG/KG VS PLACEBO IN MILD/MODERATE COVID-19

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Accelerating Covid-19 Therapeutic Interventions and Vaccines (ACTIV)-6 Study Group and Investigators

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Background: Whether ivermectin, with a maximum targeted dose of 600 µg/kg, shortens symptom duration or prevents hospitalization among outpatients with mild to moderate coronavirus disease 2019 (COVID-19) remains unknown. Our objective was to evaluate the effectiveness of ivermectin, maximum targeted dose of 600 µg/kg, daily for 6 days compared with placebo for the treatment of early mild to moderate COVID-19.

Methods: ACTIV-6, an ongoing, decentralized, randomized, double-blind, placebo-controlled, platform trial, was designed to evaluate repurposed therapies in outpatients with mild to moderate COVID-19. A total of 1206 participants age ≥30 years with confirmed COVID-19, experiencing ≥2 symptoms of acute infection for ≤7 days, were enrolled from February 16, 2022, through July 22, 2022, with follow-up data through November 10, 2022, at 93 sites in the US. Participants were randomized to receive ivermectin, with a maximum targeted dose of 600 µg/kg (n=602), daily vs placebo daily (n=604) for 6 days. The primary outcome was time to sustained recovery, defined as at least 3 consecutive days without symptoms. The 7 secondary outcomes included a composite of hospitalization, death, or urgent/emergent care utilization by day 28.

Results: Among 1206 randomized participants who received study medication or placebo, median (interquartile range) age was 48 (38–58) years; 713 (59%) were women; and 1008 (84%) reported ≥2 SARS-CoV-2 vaccine doses. Median time to recovery was 11 (11–12) days in the ivermectin group and 11 (11–12) days in the placebo group. The hazard ratio (HR) (95% credible interval [CrI], posterior probability of benefit) for improvement in time to recovery was 1.02 (0.92–1.13; P[HR >1]=0.68). In those receiving ivermectin, 34 (5.7%) were hospitalized, died, or had urgent or emergency care visits compared with 36 (6.0%) receiving placebo (HR 1.0, 0.6–1.5; P[HR< 1]=0.53). In the ivermectin group, 1 participant died and 4 were hospitalized (0.8%); 2 participants (0.3%) were hospitalized in the placebo group and there were no deaths. Adverse events were uncommon in both groups.

Conclusion: Among outpatients with mild to moderate COVID-19, treatment with ivermectin, with a maximum targeted dose of 600 µg/kg daily for 6 days, compared with placebo did not improve time to recovery. These findings do not support the use of ivermectin in patients with mild to moderate COVID-19.

Primary and secondary outcomes

Table. Primary and secondary outcomes

Endpoint	Ivermectin 600 (n=602)	Placebo (n=604)	Adjusted estimate (95% CrI)[a]	Posterior P(efficacy)
Primary endpoint, time to recovery[b]				
Skeptical prior (primary analysis)			HR, 1.02 (0.92 to 1.13)	0.68
Skeptical prior (matched/unmatched placebos)			HR, 1.03 (0.93 to 1.14)	0.70
Non-informative prior (sensitivity analysis)			HR, 1.03 (0.91 to 1.17)	0.69
No prior (sensitivity analysis)			HR, 1.03 (0.91 to 1.17)	NE[c]
Secondary endpoints				
Mortality at day 28	1 (0.17)	0 (0.00)		
Hospitalization or death through day 28	5 (0.83)	2 (0.33)	HR, 2.51 (0.49 to 12.96)[c]	
Hospitalization, urgent care, ED visit, or death through day 28	34 (5.65)	36 (5.96)	HR, 1.0 (0.6 to 1.5)	0.527
Clinical progression ordinal outcome scale[d]				
Day 7			OR: 1.61 (0.87 to 2.46)	0.044
No.			1206	
Day 14			OR: 2.14 (0.87 to 3.77)	0.029
No.			1175	
Day 28			OR: 2.61 (0.77 to 4.80)	0.019
No.			1206	
Time unwell, mean (95% CrI), d[e]	11.21 (11.01 to 11.41)	11.35 (11.16 to 11.54)	Δ: -0.14 (-0.51 to 0.24)	0.772
Days benefit, mean (95%CrI), d	3.42 (3.18 to 3.64)	3.26 (3.03 to 3.48)	Δ: 0.16 (-0.28 to 0.61)	0.772

Abbreviations: ED, emergency department; HR, hazard ratio; OR, odds ratio; NE, not estimated
[a]Unless otherwise noted, a highest-density credible interval. Adjustment variables for time to recovery, mortality, composite clinical endpoints, and clinical progression in addition to randomization assignment: age (as restricted cubic spline), sex, duration of symptoms prior to receipt of study drug, calendar time (as restricted cubic spline), vaccination status, geographic region (Northeast, Midwest, South, West), call center indicator, and baseline symptom severity. For time to recovery, HR > 1 is favorable for faster recovery for ivermectin compared with placebo. For the secondary endpoints, HR < 1, OR < 1, and Δ < 0 is favorable for ivermectin.
[b]Time to recovery is from receipt of study drug to achieving the third of 3 days of recovery. HR >1.0 is favorable for faster recovery for ivermectin compared with placebo
[c]Confidence interval, low event rate precluded covariate adjustment
[d]The description of the 8 levels of the clinical progression ordinal outcome scale is reported in the supplement. Proportional odds was not evaluated as the vast majority of participants were either at home with limitations or at home without limitations, resulting in a model that is approximately a logistic regression.
[e]Adjustment variables for mean time unwell in addition to randomization assignment: age and calendar time.

573 FACTORS ASSOCIATED WITH HIV-1 RESISTANCE TO INTEGRASE STRAND TRANSFER INHIBITORS

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Background: Integrase strand transfer inhibitor (INSTI)-containing regimens in HIV-1-infected patients have experienced a global increase. Recently, WHO has emphasized the need to fast-track the transition to dolutegravir (DTG)-based antiretroviral (ARV) treatments. However, continued surveillance of INSTI resistance is recommended. In this study, clinical, epidemiological, and virological features associated with INSTI resistance in HIV-1-infected patients attended in Spanish clinical centers were analyzed.

Methods: Samples collected between 2008 and 2021 from HIV-1-infected patients attended in clinical centers from 10 Spanish regions were analyzed in integrase, protease, and reverse transcriptase using Sanger population sequencing. ARV drug resistance was evaluated with the Stanford University HIVdb program.

Results: Among 2,696 patients, 174 (6.5%) had INSTI resistance, all of them to first-generation INSTIs, and 71 (2.6%) had also resistance to second-generation INSTIs. Of these, only 5 individuals were exposed to DTG as the only INSTI, in whom resistance development was associated with poor treatment adherence and/or resistance to other ARV classes. Of newly HIV-1-diagnosed individuals, 0.92% carried INSTI-resistant viruses, with low prevalences maintained along time, and only one had low-level resistance to DTG. Persons who inject drugs, age over 39 years, resistance to other ARV classes, and longer time from diagnosis were associated with INSTI resistance (p< 0.001). Non-subtype B viruses (representing 25% of total and 24% of INSTI-resistant viruses) lacked the Q148H+G140S resistance pathway and showed lower INSTI resistance levels compared to subtype B viruses.

Conclusion: INSTI resistance is uncommon and associated with long-term infections, older age and additional resistance to other ARV drug classes, and is rare in newly diagnosed HIV-1 infections. Lower INSTI resistance levels were observed in non-subtype B than in subtype B viruses. Our results also support the preferential use of DTG-containing regimens in first-line treatments, although surveillance of INSTI resistance is encouraged.

574 EFFICACY OF 3TC+DTG VS 3-DRUG REGIMENS IN VIROLOGICALLY-SUPPRESSED PLWH

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Background: In people living with HIV (PLWH) lamivudine (3TC)+dolutegravir (DTG) maintenance dual therapy (DT) could be less effective than three-drug therapies (TT) with 2NRTIs+DTG in the context of both resistance-associated mutations (RAMs) and lower time of virological suppression (VS). However, data have shown that PLWH who switch to DT usually have longer time of VS than PLWH switching to TT, leading to an immortal-time bias when analyzing observational data. To overcome this issue, we emulated a trial-study design by querying the Italian "ARCA" database.

Methods: PLWH on a TT with PI or a NNRTI, switching to a DTG-based TT or to DT with 3TC+DTG were followed from the first HIV-RNA< 50 cps/mL (baseline, BL) up to virological failure (VF) (i.e., 2 consecutive HIV-RNA≥50 cps/ml or one HIV-RNA^{3}200 cp/mL). After choosing a grace period of 3 years (i.e., the maximum time of VS after which we supposed an advantage in terms of virologic success for PLWH on DT, based on literature data) we assigned PLWH switching to DT within 3 years to the "treatment"-arm, and PLWH switching to 2NRTIs+DTG (or to DT after 3 years) to the "control"-arm. By using a cloning technique, each participant was also assigned the opposite strategy and censored at the time of deviation from that strategy. By estimating the inverse-probability of censoring weight (IPCW) for each participant, we accounted for the informative censoring triggered by cloning. A Cox regression model was then performed to obtain an unbiased estimate of the effect of DT over TT on VF.

Results: A cohort of 626 PLWH (204 on DT, 422 on TT; 73% men, mean age 44 years) was eligible for analysis (table 1 summarizes characteristics of study population). The mean time of VS was 5 and 4 years before switch to DT and DTG-based TT, respectively. Overall, 41 VF (10 with DT, 31 with TT) occurred after a mean time of 2.2 and 1.6 years with DT and TT, respectively. A higher crude risk of VF was shown for TT (7.6% versus 4.5% at 2 years; p=0.055). Conversely, the inverse probability weighted-Cox model indicated a similar risk of VF between DT and TT when no RAMs were present (DT versus TT aHR: 0.88, 95% CI 0.45-1.72; p=0.713) but a higher risk of VF for DT in the presence of M184V/I (versus TT and no RAMs: aHR 4.24, 95% CI 1.29-13.93; p=0.017). No difference in VF risk among TT with and without previous RAMs was detected.

Conclusion: Previous detection of M184V/I could affect the efficacy of 3TC+DTG as a maintenance strategy.

Table 1. Characteristics of study population at baseline.

Variables	Triple therapy arm (n=422)	Dual therapy arm (n=204)	p-value
Age, median (IQR)	45 (44-46)	44 (42-45)	0.299
Male sex, n (%)	297 (70.4)	160 (78.4)	0.033
Risk factor for HIV infection (%):			<0.001
- Heterosexual	176 (41.7)	88 (43.1)	
- MSM	140 (33.2)	90 (44.1)	
- PWID	64 (15.1)	23 (11.3)	
- Other/unknown	42 (10.0)	3 (1.5)	
Caucasian ethnicity, n (%)	333 (78.9)	159 (77.9)	0.965
Years since HIV diagnosis, median (IQR)	5 (1-13)	3 (1-9)	0.002
Years of antiretrovirals exposure, median (IQR)	2 (1-10)	1 (0-5)	<0.001
Zenith HIV-RNA (log_{10} copies/mL), median (IQR)	4.57 (4.44-4.70)	4.73 (4.58-4.88)	0.136
Nadir CD4 count (cells/μL), median (IQR)	217 (200-234)	267 (246-289)	0.001
Previous virological failure (at least one), n (%)	47 (11.1)	22 (10.8)	0.895
CDC stage C, n (%)	53 (12.6)	14 (6.7)	0.031
Anti-HCV positive serostatus, n (%)	74 (17.5)	21 (10.3)	0.018
RAMs to study drugs at historical genotype (at least one), n (%)	87 (20.6)	18 (8.8)	<0.001
B viral subtype, n (%)	346 (82.0)	156 (76.5)	0.010

Abbreviation: MSM: Men who have sex with men; PWID: People Who Inject Drugs (PWID); RAMs Resistance-associated mutations.

575 INFREQUENT DETECTION OF EMERGENT HIV DRUG RESISTANCE IN LOW VIRAL LOAD SPECIMENS

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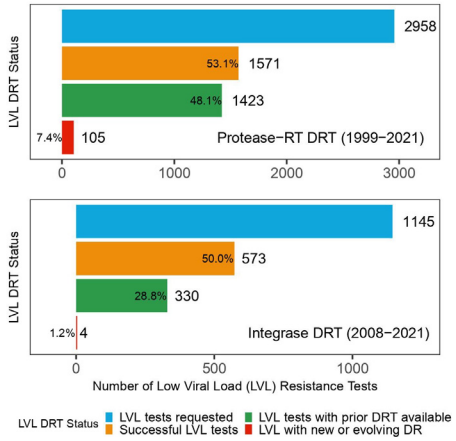
Background: Treatment guidelines recommend genotypic HIV drug resistance testing (DRT) prior to treatment initiation and at virologic failure. While many DR assays are validated for samples with plasma viral loads (VL) >1000 HIV RNA c/mL, the BC Centre for Excellence in HIV/AIDS (BC-CfE) is accredited to test samples with VL >250 c/mL; low viral load (LVL) samples with VL of 50–250 c/mL are tested under a research-use-only protocol. As LVL DRT is resource-intensive and the clinical relevance of results is unclear, we investigated the frequency of emergent DR in LVL samples and the clinical factors associated with newly detected resistance.

Methods: A retrospective analysis of physician-requested LVL DRT from the BC-CfE's Drug Treatment Program database was performed. HIV Protease-RT and IN sequences from LVL samples were compared against all prior resistance genotypes from the same participants to identify newly emergent or evolving resistance. DR was interpreted using Stanford HIVdb v9.0. Associations between emergent resistance and clinical factors were investigated using the Mann-Whitney U test or Fisher's Exact Test.

Results: A total of 44,301 Protease-RT DRTs were performed in 1999-2021, of which 2958 (6.7%) were on LVL samples. Testing was successful for 1571 (53.1%) LVL samples compared to 81.4% and 94.4% of samples with VL 250-999 and VL ≥1000 c/mL, respectively (p< 0.001). Of the LVL DR tests, 1423 (48.1%) were from participants with prior DRT (median 4, Q1-Q3 2–7 samples/participant), where the LVL samples were collected a median 417 days (Q1-Q3 113-1502) after the previous test. A total of 105 (7.4%) cases of new or evolving DR were identified, of which 49.5%, 42.9% and 22.9% exhibited new NRTI, NNRTI and PI resistance, respectively. LVL samples with new resistance were collected a median of 2.6 years (Q1-Q3 0.65-6.7) after the prior test vs. 1.1 years (Q1-Q3 0.28-3.9) in samples without resistance (p< 0.001). New resistance was not observed more frequently during persistent low-level viremia versus virological blips (p=0.14). Of 9309 Integrase DR tests performed in 2008-2021, 1145 (12.3%) were LVL. Of 330 (28.8 %) successful LVL DR tests from participants with prior DRT, only 4 (1.2%) new or evolving integrase DR cases were found.

Conclusion: DRT of samples with VL of 50–250 c/mL infrequently identifies new or evolving DR not captured by prior testing. LVL DRT may be useful in specific clinical scenarios; however, given its resource-intensive nature, it may not be generally warranted.

Low Viral Load HIV Resistance Testing Volumes in British Columbia, Canada



576 DRUG RESISTANCE IN PEOPLE FAILING DOLUTEGRAVIR-BASED ART: HIV COHORT COLLABORATION

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Background: In 2019, the World Health Organization (WHO) recommended dolutegravir (DTG) as the preferred drug for first- and second-line antiretroviral therapy (ART) among all people with HIV (PWH), including pregnant women and those of childbearing age. DTG has a high genetic barrier to resistance, but PWH with resistance to nucleoside reverse-transcriptase inhibitors (NRTIs)

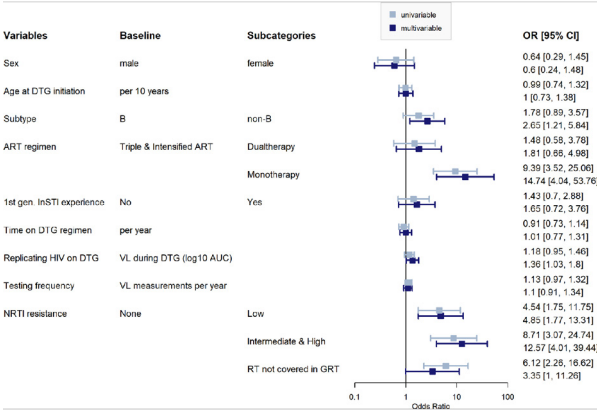
who are on (functional) DTG dual- or mono-therapy, and those experiencing challenges adhering to ART, may be at particular risk of DTG resistance.

Methods: We pooled data from six European (ATHENA, The Netherlands; Aquitaine cohort, France; Cologne Cohort, Germany; ICONA, Italy; SHCS, Switzerland; UK CHIC, UK), one North American (S Alberta HIV Clinic , Canada) and one South African (AID for Aids) cohort to identify PWH who underwent genotypic resistance testing (GRT) while on DTG-based ART. Drug resistance levels and drug resistance mutations (DRMs) were identified using the Stanford algorithm. We assessed associations with DTG resistance using uni- and multivariable ordinal logistic regression, including covariables age, sex, HIV subtype, ART regimen, time on DTG, exposure to integrase strand transfer inhibitors (INSTIs), area under the viral load curve (AUC) and testing frequency, and resistance to RTIs.

Results: Among 728 eligible PWH most were from European cohorts (628, 86.3%), men (534, 69.8%) and had HIV subtype B (456, 59.6%). Median time on DTG-based ART was 1.7 years (IQR 0.7 – 3.2); 284 (39.0%) had resistance to RTIs. Ninety-eight (13.5%) had INSTI DRMs with: 8 potential low; 6 low; 19 intermediate; and 6 high resistance levels. DTG monotherapy and NRTI resistance were strongly associated with DTG resistance (Figure). There was some evidence that non-B subtype might be associated with DTG resistance.

Conclusion: DTG resistance is rare in PWH failing on a DTG-based ART regimen. It might become a problem with the global scale-up of DTG, particularly in low- and middle-income countries where pre-existing drug resistance is more common, and where individuals remain longer on failing regimens and are switched to DTG without viral load or resistance testing. Global surveillance of DTG resistance is essential. The mutational pathways require further investigation.

Uni- and multivariable ordinal logistic regression models for genotypic DTG resistance levels in PLHIV on DTG-based ART. PLHIV with more than one year of clinical data available prior to the GRT were included (N = 653).



577 LOW-FREQUENCY NNRTI MUTATIONS CORRELATE WITH HIV ART FAILURE IN PREGNANT WOMEN

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Background: High frequency HIV drug resistance mutations (DRMs) are known risk factors for treatment failure (TF), but the association between low frequency DRMs and TF is controversial. We explore this association using deep sequencing methods that accurately sample low frequency DRMs.

Methods: We enrolled pregnant women with HIV in Malawi who were either ART naïve (A), had ART failure (B), or defaulted on ART and were resuming (C). At entry, A & C began a TDF/3TC/EFV regimen and B started TDF/3TC/ATZ/r. TF was defined as either undetectable viremia followed by rebound, or failure to suppress by 6 months. We used Primer ID MiSeq to sequence partial *pol* gene to identify regimen-relevant DRMs in entry & TF plasma samples. This approach labels each RNA genome with a unique molecular identifier to correct sequencing errors & define sampling depth. We used a Cox proportional hazards model to calculate hazard ratios (HRs) for high/low frequency entry DRMs and TF. Low frequency DRMs were defined as DRMs present at ≤ 20%.

Results: A total of 428 participants were selected for sequencing from 1,881 enrolled women. We successfully sequenced 340 participants, of which 193 were from cohort A, 74 from cohort B and 73 from cohort C. At entry, 28.5% of participants had the K103N DRM, 8.8% had K65R, and 11.8% had M184V; cohorts B & C had significantly more DRMs than cohort A. PI DRMs were rarely seen except for M46I/L at low frequency. Cohort B & C participants were more likely to have TF than those in cohort A (Fig. 1A), at TF rates of 26% (A), 41% (B), and 44% (C) (p< 0.001). Presence of K103N at entry significantly increased TF risk among participants on an EFV-based regimen at both high & low frequency, with HR of 3.26 [1.52-6.98, CI 95%] and 2.53 [1.00-6.37, CI 95%] respectively in multivariable analysis stratified by entry viral load (Fig. 1B). For all other DRMs at low frequency we found no significant association with TF. At TF, we observed the selection of DRMs in 45% of participants, while remaining participants lacked selection pressure from ART. Only one participant who received a PI-based regimen failed with new PI DRMs. Overall, DRMs to INSTIs were rare, but 1.5% of participants had Q148R at entry despite never taking INSTI drugs.

Conclusion: Previous ART experience was associated with increased TF rates, as was K103N at both high & low frequencies for people on NNRTIs. High background of NNRTI DRMs provides additional evidence supporting the transition to INSTI based regimens adopted by Malawi.

DRMs and previous ART experience impact treatment failure

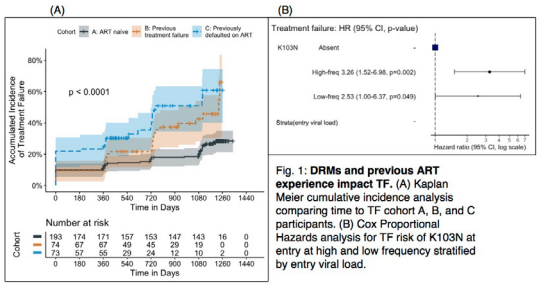

Fig. 1: **DRMs and previous ART experience impact TF.** (A) Kaplan Meier cumulative incidence analysis comparing time to TF cohort A, B, and C participants. (B) Cox Proportional Hazards analysis for TF risk of K103N at entry at high and low frequency stratified by entry viral load.

578 EMERGING INTEGRASE INHIBITOR HIV DRUG RESISTANCE MUTATIONS: TANZANIAN NATIONAL SURVEY

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Background: In 2019, a potent integrase strand transfer inhibitor (INSTI), dolutegravir (DTG) was made available for public use in Tanzania. However, the switching was conducted without confirmation of the virological suppression, hence the treatment success has not been fully appreciated. HIV drug resistance (HIVDR) including against DTG could be implicated in the notable suboptimal viral load suppression among people living with HIV (PLHIV) in Tanzania. Therefore, we aimed to determine the prevalence and patterns of acquired drug resistance mutations among children and adult populations on antiretroviral therapy (ART) in Tanzania.

Methods: We conducted a national cross-sectional HIVDR survey among PLHIV, 866 children (< 15 years) on ART for 12(±3) months and ≥ 36 months; and 1173 adults (≥ 15 years) on ART for 12(±3) months and ≥ 48 months. HIV viral load was estimated using Cobas® 8800 System (Roche Molecular System, Inc. South Branchburg, New Jersey USA). Genotyping was done on DBS and/or plasma of participants with high HIV viremia (VL ≥ 1000 copies/ml). HIV genes (reverse transcriptase, protease, and integrase) were amplified by Polymerase Chain Reaction (PCR) and directly sequenced using Applied Biosystems 3730XL DNA Analyser. The Stanford HIVDR database was used for HIVDR assignment and prediction of phenotypic susceptibility to ART drugs.

Results: A total of 137 participants samples (92 children and 45 adults) with VL≥ 1000 copies/ml, underwent HIVDR genotyping. The overall prevalence of HIV drug resistance mutations was 71.5% where 78.3% of children and 57.8% of adults had drug resistance mutations. Notably, 5.8% of participants had INSTI drug resistance mutations including major drug resistance mutations; Q148K, E138K, G118R, G140A, T66A, and R263K. Non-nucleoside reverse transcriptase inhibitors (NNRTI), nucleoside/nucleotide reverse transcriptase inhibitors (NRTI),

and protease inhibitor (PI) drug resistance mutations were also detected in 62.8%, 44.5%, and 8% of the participants, respectively. In addition, we observed that all the participants with major INSTI drug resistance mutations harbored drug resistance mutations targeting NRTI backbone drugs used in our setting.
Conclusion: Taken together, the findings from this survey have revealed that more than 7 out of 10 patients with high HIV viremia in Tanzania have drug resistance mutations. The early emergence of DTG resistance is of concern to the efficacy of the Tanzanian ART program and other similar settings in Sub-Saharan Africa.

579 INCIDENCE OF ACQUIRED INTEGRASE RESISTANCE AFTER TRANSITION TO DOLUTEGRAVIR IN UGANDA

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Background: Millions of people with HIV in sub-Saharan Africa have been switched from non-nucleoside reverse transcriptase inhibitor (NNRTI)-based antiretroviral therapy (ART) to tenofovir-lamivudine-dolutegravir (TLD) since 2018. Whereas clinical trials have rarely documented resistance to TLD after switch, limited programmatic data are available to estimate the incidence of acquired drug resistance on TLD in the region.
Methods: We conducted a longitudinal cohort study of adults with HIV age >18 years in Uganda who were programmatically switched from NNRTI-based ART to TLD. We measured plasma HIV-1 RNA viral load (VL) using the Cepheid GeneXpert platform on the day of switch to TLD and at 24- and 48-weeks post-switch. We conducted Sanger sequencing of reverse transcriptase and integrase regions of the pol gene on any plasma specimen with a VL >500 copies/mL.
Results: We enrolled 500 participants with a median age of 47 years (IQR 40 – 53); 41% were women. Sequencing was performed on specimens from 19 participants (Table) with a detectable VL at any of the three study visits. Sequenced participants had a median age of 40 years (IQR 32 – 52), and 16% were women. At the time of switch to TLD, five participants (1%) had a VL >500 copies/mL, and four of these were sequenced. None had integrase inhibitor mutations prior to switch to TLD. All had NNRTI mutations and three had nucleoside reverse transcriptase inhibitor mutations; yet all were suppressed by 24 or 48 weeks. In follow-up, 1% (n=5/448) and 2% (n=9/483) of participants who completed study visits at 24 and 48 weeks after switch to TLD, respectively, had a VL >500 copies/mL. Although two participants failed with M184V and five participants failed with NNRTI mutations, we did not observe K65R or integrase inhibitor mutations in any individuals after TLD transition. The one individual with M184V alone at 24 weeks resuppressed by 48 weeks. Thus, incidence of acquired integrase resistance in this cohort was 0% (95% CI 0 – 0.008%) by 48 weeks.
Conclusion: No treatment-emergent resistance to dolutegravir was observed after 48-weeks in this large cohort study of ART-experienced adults transitioning to TLD in the Ugandan public sector. Furthermore, two individuals achieved viral suppression despite high-level resistance to both tenofovir and lamivudine at the time of switch from NNRTI-based therapy. These data are reassuring and affirm World Health Organization guidelines for the use of TLD as the preferred ART regimen in resource-limited settings.

HIV Drug Resistance Outcomes in the DISCO Cohort Study

Participant	Week 0 VL (copies/mL)	Week 0 HIVDR			Week 24 VL (copies/mL)	Week 24 HIVDR			Week 48 VL (copies/mL)	Week 48 HIVDR		
		NRTI Mutations	NNRTI Mutations	INSTI Mutations		NRTI Mutations	NNRTI Mutations	INSTI Mutations		NRTI Mutations	NNRTI Mutations	INSTI Mutations
A	2,860	E44D, K65R, M184V, K219Q	K103N,Y181C	None	<40	NA	NA	NA	<40	NA	NA	NA
B	5,860	K65R, D67G, M184MV, K219E	V106A,G190V	None	<40	NA	NA	NA	<40	NA	NA	NA
C	10,700	None	F130A	None	<40	NA	NA	NA	320	NA	NA	NA
D	2,900	Failed RT sequencing	Failed RT sequencing	None	*	*	*	*	<40	NA	NA	NA
E	6,840	M184V	K103N,V108I	None	*	*	*	*	<40	NA	NA	NA
F	<40	NA	NA	NA	19,100	None	E138EA	None	<40	NA	NA	NA
G	<40	NA	NA	NA	1,440	None	None	None	<40	NA	NA	NA
H	<40	NA	NA	NA	12,200	None	None	None	<40	NA	NA	NA
I	56	NA	NA	NA	640	Failed RT sequencing	Failed RT sequencing K103KN, V179I/AIT, G190GRS	None	<40	NA	NA	NA
J	<40	NA	NA	NA	6,700	M184MV		None	<40	NA	NA	NA
K	<40	NA	NA	NA	<40	NA	NA	NA	78,200	None	None	None
L	<40	NA	NA	NA	*	*	*	*	500,000	None	None	None
M	<40	NA	NA	NA	*	*	*	*	105,000	None	K103N	None
N	<40	NA	NA	NA	<40	NA	NA	NA	14,800	None	None	None
O	<40	NA	NA	NA	<40	NA	NA	NA	510	None	K103N	None
P	<40	NA	NA	NA	*	*	*	*	258,000	None	None	None
Q	<40	NA	NA	NA	<40	NA	NA	NA	1,580,000	None	None	None
R	<40	NA	NA	NA	<40	NA	NA	NA	298,000	None	None	None
S	<40	NA	NA	NA	*	*	*	*	11,000	K70E, M184V, K219R	A98G, K103N, P225H, F227L	None

VL = HIV-1 RNA viral load, HIVDR = HIV drug resistance, RT = reverse transcriptase, NA = not applicable * Missed week 24 visit

580 SUSCEPTIBILITY SCREENING TO bNAbs GS-5423 AND GS-2872 IN ART-SUPPRESSED PARTICIPANTS

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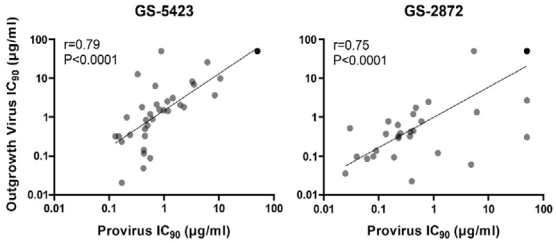
Background: Broadly neutralizing antibodies (bNAbs) display strong antiviral activity by targeting HIV Envelope (Env) with high potency and breadth. However, Env diversity can lead to natural resistance, creating challenges for the use of bNAbs as antiviral therapies, and posing the need to screen participants for susceptibility to bNAbs. We compared genotypic and phenotypic analyses to determine participant susceptibility to GS-5423 (3BNC117-LS) and GS-2872 (10-1074-LS) prior to enrollment into a Phase 1b study evaluating their safety, tolerability, and efficacy in combination with the HIV capsid inhibitor lenacapavir dosed every 6 months in ART-suppressed people with HIV (PWH).
Methods: PBMCs from 124 participants obtained at screening were used to assess susceptibility to GS-5423 and GS-2872 using 3 different methods. Phenotypic analysis of proviral DNA from PBMCs was performed using the PhenoSense mAb DNA assay (Monogram), with susceptibility defined as $IC_{90} \leq 2$ µg/mL. Viral outgrowth in combination with the PhenoSense mAb RNA assay (Monogram) was performed on available PBMCs from 92 participants. The HIV Env gene from proviral DNA in PBMCs was genotyped using deep sequencing (Seq-IT) and susceptibility to bNAbs predicted using previously described Env amino acid signatures (Moldt, B. et al. 2021).
Results: PhenoSense mAb DNA assay results were obtained for 109 of 124 participants (15 assay failures). 75% of participants were susceptible to GS-5423, 65% to GS-2872, and 50% to both bNAbs. Viral outgrowth >1,000 copies/ml was observed for 48 of 92 samples. Phenotypic susceptibility was obtained for 35 of those samples, with 49% susceptible to GS-5423, 69% to GS-2872, and 31% to both bNAbs. Phenotypic susceptibilities determined for outgrowth virus and proviruses were correlated (Fig. 1) (GS-5423 r=0.79, P< 0.0001; GS-2872 r=0.75, P< 0.0001). Genotypic susceptibility to GS-5423 and GS-2872 was determined for 59 of 109 proviral sequences with phenotypic data. Proviral genotypic signatures predicted phenotypic susceptibility of proviruses and outgrowth virus with high specificity (93-100% GS-5423, 71-96% GS-2872), but low sensitivity (24-11% GS-5423, 76-8% GS-2872).
Conclusion: We compared 3 different methods to determine susceptibility to GS-5423 and GS-2872 in ART-suppressed participants. These data demonstrate that the susceptibility to bNAbs is correlated between all 3 assay types and may be useful in further refining the criteria for selecting PWH who could be eligible for bNAbs studies.

Fig. 1: Correlation of neutralization IC_{90} values between outgrowth viruses and proviruses



581 PHENOTYPIC SUSCEPTIBILITY TO VRC07-523LS AND ITS CORRELATES IN THE ACTG A5357 STUDY

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Background: VRC07-523LS is a broadly neutralizing anti-HIV-1 envelope monoclonal antibody under investigation in combination with LA-cabotegravir for maintenance of HIV-1 suppression in the AIDS Clinical Trials Group (ACTG)

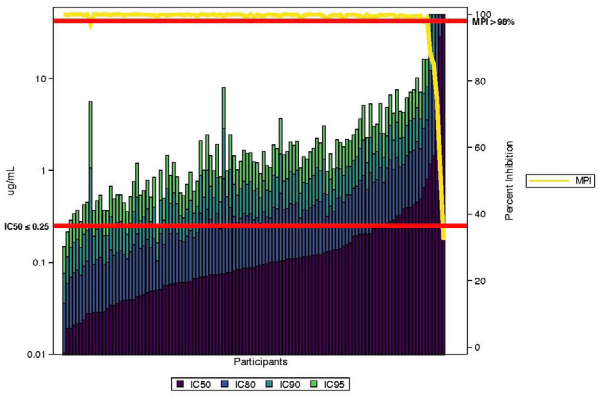
A5357 study. Eligibility for A5357 required susceptibility to VRC07-523LS, defined as half-maximal inhibitory concentration (IC_{50}) ≤ 0.25 µg/mL and a maximum percent inhibition (MPI) > 98% on the Monogram PhenoSense mAb Assay (Labcorp-Monogram Biosciences) using PBMCs collected at screening. The predictors and correlates of VRC07-523LS susceptibility have not been established; thus, we conducted this exploratory analysis to evaluate the range of PhenoSense mAb assay results and correlations with demographic and clinical variables.

Methods: All participants screened for A5357 who had at least one PhenoSense mAb assay result were included in the analysis. Correlations between VRC07-523LS and the covariates were explored using Chi-Square tests (sex, race/ethnicity), Wilcoxon rank-sum rests (age, nadir CD4, and years since HIV diagnosis), and logistic regression. All analyses were exploratory with no adjustments for multiple testing.

Results: We included 137 participants: 21% female, 1% transgender female, median age 52 years, 43% White, 38% Black, 15% Hispanic. Median nadir CD4 count was 305 cells/mm3 with a median of 15 years post HIV diagnosis. Based on the first Phenosense assay, 67% were reported as susceptible to VRC07-523LS and 14% as not susceptible; 19% were non-reportable. There were no significant differences in demographic characteristics between those with reported and non-reportable assay results. Nine of 26 participants with non-reportable results were rescreened using new PBMC aliquots, of which 4/9 (44%) were successfully assayed, all reported as VRC07 susceptible. Neutralization measurements showed correlation between IC_{50}, IC_{80} and IC_{95} (r values 0.88-0.99). There was moderate negative correlation between years since HIV diagnosis and IC_{50} values (r=-0.20, p=0.034). We found no associations between the neutralization measures and the other variables considered.

Conclusion: A5357 has conducted the highest number of baseline susceptibility assays for VRC07-523LS clinical trials to date. Approximately 70% of participants screened and tested met protocol-specified definition of VRC07-523LS susceptibility. A trend towards higher IC_{50} values for individuals who were more recently diagnosed was observed, which requires further evaluation.

Bar Chart of Neutralization Measurements



582 HIGH PREDICTED bNAb RESISTANCE AMONG ADULTS WITH HIV-1 SEROCONVERSION IN BOTSWANA

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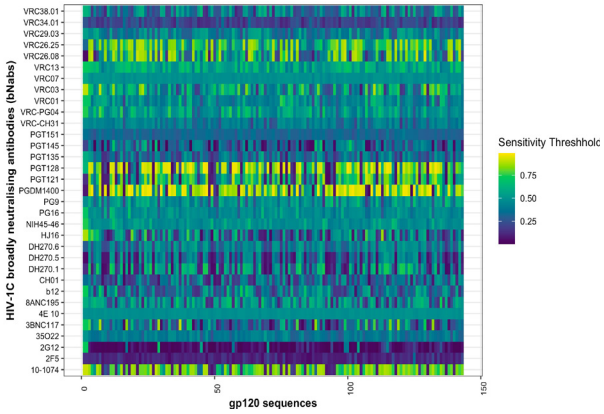
Background: We used proviral HIV-1C sequences from adults with documented HIV-1 seroconversion in Botswana, to determine HIV drug resistance mutations and predict (in silico) resistance to 33 known broadly neutralizing antibodies (bNAbs).

Methods: We analyzed proviral sequences from adults with documented HIV-1 seroconversion (N=140) from a population-based household study (Botswana Combination Prevention Project, 2013-2018). HIV-1C near-full length proviral sequences were generated and adjusted for hypermutations using Hypermut. Surveillance drug resistance mutations (SDRMs) associated with protease inhibitors (PI), integrase strand transfer inhibitors (INSTI), nucleoside reverse transcriptase inhibitors (NRTI) and non-nucleoside reverse transcriptase inhibitors (NNRTI) were analyzed according to Stanford Calculated Population Resistance program. HIV gp120 region was used to predict sensitivity of contact sites to 33 known bNAbs using the bNAb-ReP algorithm (https://github.com/RedaRawi/bNAb-ReP). A cutoff of 0.5 probability value was used to classify sensitivity (>0.5) or resistance (< 0.5). All gp120 alignments were also used to determine the number of potential N-linked glycosylation sites (PNGS) and compared among bNAb resistant and sensitive strains.

Results: One-hundred-and six (76%) adults with documented seroconversion were ART-naïve at the time of sample collection, with a median viral load of 3.9 (Q1, Q3: 3.2,4.4) log_{10} copies/mL. Median age was 27 years (Q1, Q3: 22,33) and most (79%) were female. The overall prevalence of any SDRMs at baseline was 6.6%. We found PI-, NRTI-, NNRTI- and INSTI-associated SDRMs in 1.9% (95%CI 0.2–6.6), 3.8% (95%CI 1.0–9.4), 1.9% (95%CI 0.2–6.6), 1.9% (95%CI 0.2–6.6), respectively. Prevalence of predicted resistance to 1 or more bNAbs was high among seroconverters (Fig 1); 100% of sequences showed resistance to 2F5, PG16, PGT151 and VRC34.01. In contrast, most sequences (>60%) were likely susceptible to 10-1074, PGDM1400, PCT128, VRC13 and VRC25.25. No difference was observed in the frequency of PNGS compared to bNAb resistance/sensitivity.

Conclusion: We report low levels of transmitted HIV drug resistance mutations but high prevalence of predicted bNAb resistance in adults with HIV-1 seroconversion in Botswana.

Fig 1. Predicted bNAb resistance based on in silico models using HIV proviral sequences from seroconverters in Botswana



583 STATEWIDE TRENDS OF ACQUIRED HIV-1 DRUG RESISTANCE IN RHODE ISLAND: 2004-2021

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Background: HIV-1 acquired drug resistance (ADR) may compromise sustainable antiretroviral therapy (ART) effectiveness and efforts toward ending the HIV epidemic. However, comprehensive and longitudinal data on ADR, and its current extent and impact on ART options and newer medications are limited and can inform care.

Methods: We aggregated all available HIV-1 protease-reverse-transcriptase-integrase sequences from ART- experienced persons in care in Rhode Island (RI), reviewed their detailed ART histories, and evaluated statewide ADR extent, trends and impact. Drug resistance was evaluated with Stanford Database tools, trends were measured with Mann-Kendall statistic, and multivariable regression analyses were used to evaluate sociodemographic, clinical and ART predictors of impactful resistance.

Results: A total of 1,035 (44% of those with HIV in RI) ART experienced persons (34% female, 42% non-white,64% men who have sex with men (MSM); mean 6.8 years on ART, exposed to 5.8 drugs and 3.4 regimens; CD4 355 cells/µL) had available sequences in 2004-2021, at least 30 days after ART initiation. Statewide ADR to any drug decreased from 72% to 49% during 2004-2021 (-0.59 Mann-Kendall statistic), with trends mostly driven by NNRTI- (52% to 39%) and NRTI- (58% to 23%), and less by PI- (25% to 6%) associated mutations during those years; with INSTI-associated mutations decreasing from 13% in 2017 to 10% in 2021; all corresponding to ART used in those years. Multiclass

(≥2, ≥3, 4) resistance changed from 50%, 12% and 0% in 2004 to 15%, 4% and 1% in 2021 respectively. In 2021, 97.8% of individuals had a three-drug one-pill-once-a-day (OPOD) option, and 93% had a 2-drug OPOD option, with no obvious trends over time for both. People with HIV-1 subtype B were more likely, whileMSM and people with longer time on ART were less likely to have ≥2 multiclass resistance. People exposed to a larger number of antiretrovirals and those with HIV-1 subtype B were less likely to have 3- drug OPOD options.
Conclusion: In a unique statewide analysis of longitudinal ADR trends within a densely-sampled HIV epidemic over 2004-2021, we found extensive but decreasing ADR. Lower observed ADR to high-resistance-barrier medications and sustained rates of OPOD eligibility are reassuring; however, continued ADR monitoring is important to maintain ART success, particularly with rising INSTI use in all lines of therapy and 2-drug regimen options.

584 FOSTEMSAVIR RESISTANCE-ASSOCIATED MUTATIONS IN HIV-1C STRAINS FROM BOTSWANA

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Background: There is limited data on the prevalence of fostemsavir (FTR)-associated drug resistance mutations in people with HIV (PWH) in Botswana. Botswana is currently experiencing increased cases of patients with MDR HIV strains, which may limit future antiretroviral therapy (ART) options. We here use a large set of HIV-1 C sequences from across Botswana to determine the possibility of the use of FTR-containing regimens by exploring the prevalence of FTR-associated resistance mutations among ART-naïve and -experienced individuals in Botswana.
Methods: Previously reported FTR-associated drug resistance mutations (DRMs) were surveyed from 6,030 HIV-1 near full-length sequences generated from participants of the Botswana Combination Prevention Project (BCPP) (2013-2018). Both antiretroviral (ART)-naïve and experienced were included. ART experienced individuals were further classified into suppressed (VL≤400 copies/mL) and virologic failure ((VF) (VL >400 copies/mL)).
Results: Among 6,030 HIV-1 gp120 sequences, 1,282 (21.3%) were ART naïve participants while 4748 (78.7%) were on ART at study enrolment. VL data was available for 4,739 (99.8%) among ART experienced, of whom 4526 (95.5%) were suppressed and 213 (4.5%) had VL >400 copies/mL (VF). The overall prevalence of FTR resistance was 13.3% (CI 11.6-15.1). Stratifying the prevalence by ART status, 13.6%(29/213) was reported among ART experienced with VF and 13.3% (170/1282) in ART naïve individuals (p-value=0.9) . The most predominant mutations were M434I and M475I reported among 60.3% and 36.2% individuals, respectively. Mutation M434V was higher at ART experienced (10.3%) compared to 1.2% among ART-naïve individuals (p > 0.01).
Conclusion: The overall prevalence of FTR DRM was similar in ART naïve and ART experienced individuals in a setting with no prior FTR exposure. We recommend periodic surveillance of FTR-associated drug resistance mutations in order to guide its clinical use in people living with HIV.

585 NO ANTAGONISM OR CROSS-RESISTANCE OBSERVED BETWEEN ISLATRAVIR AND LENACAPAVIR

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Background: Islatravir (ISL) is a deoxyadenosine analog that inhibits HIV-1 reverse transcription by multiple mechanisms, including inhibition of translocation and delayed chain termination. Lenacapavir (LEN) is a novel capsid (CA) inhibitor that inhibits HIV at multiple points in the viral cycle. Here several *in vitro* studies are described which support the combination of ISL and LEN for the treatment of HIV-1 infection.
Methods: All assays were conducted *in vitro* in MT4 cells, which express green fluorescent protein upon infection (MT4-GFP cells) . To assess the potential for synergy or antagonism, ISL and LEN were tested for combinatorial antiviral activity and cytotoxicity and data were analyzed using MacSynergy™. Antiviral activity of ISL against wild-type (WT) HIV-1 and known LEN resistance-associated mutant viruses was determined. Static resistance selection experiments were conducted *in vitro* with ISL and LEN alone and in combination with either subtype B (R8) wild-type (WT) virus or virus containing M184I reverse transcriptase (RT) to further assess their barrier to resistance. Antiviral activity of ISL and LEN against emergent resistance-associated mutations in both CA and RT were measured.
Results: ISL with LEN demonstrated additive inhibition of HIV-1 replication, with no evidence of antagonism and no significant synergistic or antagonistic effects on cytotoxicity across the range of concentrations tested. ISL exhibited potent (nM) antiviral activity against known LEN resistance-associated variants and addition of M184V did not alter the antiviral activity of LEN against LEN resistance-associated variants. The combination of reported LEN resistance-associated mutations and M184V did not confer additional potency reductions to ISL beyond M184V alone. In resistance selection experiments, the ISL/LEN combination more effectively suppressed viral breakthrough at lower multiples of the compounds' IC_{50} values and fewer mutations emerged with the combination compared to either compound on its own. The resistance pathways for ISL and LEN were not altered, and no novel mutations emerged that substantially altered the potency of LEN or ISL.
Conclusion: A lack of antagonism and cross-resistance suggest that ISL and LEN can make an effective 2-drug combination for the treatment of HIV.

586 KINETICS OF HBV RNA AND CORE-RELATED ANTIGEN LEVELS IN PLWH WITH FUNCTIONAL HBV CURE

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Swiss HIV Cohort Study
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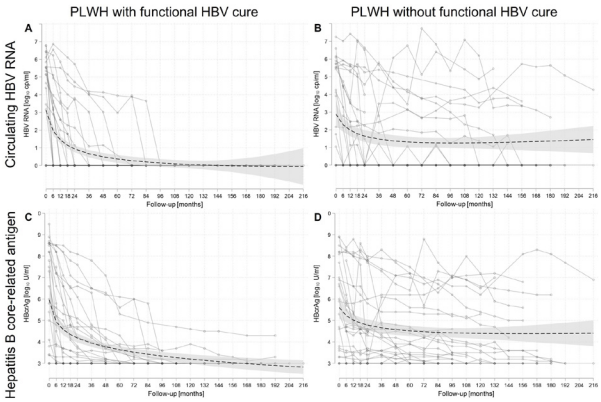
Background: The determinants of functional cure of hepatitis B virus (HBV) infection during antiviral therapy are poorly understood. Hepatitis B core-related antigen (HBcrAg) and circulating HBV RNA correlate with intrahepatic covalently closed circular DNA (cccDNA) levels and cccDNA transcriptional activity. Both markers may help identify persons who eventually experience functional HBV cure on therapy. We aimed to compare long-term kinetics of circulating HBV RNA and HBcrAg levels among persons living with HIV (PLWH) and HBV treated with tenofovir in the Swiss HIV Cohort Study.
Methods: We matched 29 participants with to 29 participants without functional HBV cure based on age, sex, pre-treatment with lamivudine and CD4+ T-cell count. We modeled HBV RNA and HBcrAg levels over time using linear regression with time as a function of fractional polynomials, and compared HBV RNA and HBcrAg levels during tenofovir therapy in participants with and without functional HBV cure. We defined functional HBV cure as the first occurrence of a quantitative hepatitis B surface antigen < 0.05 IU/ml.
Results: Median follow-up time was 12 years (interquartile range [IQR] 8-14) with functional HBV cure occurring after a median of 4 years (range 0.5-14). At start of tenofovir, 23/58 (40%) participants had undetectable HBV RNA and 11/58 (19%) had HBcrAg below cut-off. Median levels of HBV RNA and HBcrAg at tenofovir start were similar in those with and without functional HBV cure (HBV RNA: 5.5 [IQR 4.9-6.3] vs. 5.5 $\log_{10}$ cp/ml [IQR 4.0-6.0], p=0.57; HBcrAg: 7.5 [IQR 5.4-8.6] vs. 6.6 $\log_{10}$ U/ml [IQR 4.6-8.1], p=0.22). Among those with detectable HBV RNA at tenofovir start, 14/17 (82%) with functional HBV cure compared to 10/18 (56%) without cure had an HBV RNA decline of ≥1 $\log_{10}$ cp/ml after one year on tenofovir (p=0.15, Figure 1). In participants with HBcrAg above cut-off at tenofovir start, 14/22 (64%) with functional HBV cure compared to 8/25 (32%) without cure had an HBcrAg decline of ≥1 $\log_{10}$ U/ml (p=0.04) after one year. Five years after tenofovir start, HBV RNA was undetectable among 26/28 (93%) participants with functional HBV cure compared to 17/26 (65%) without cure (p=0.02), and 18/28 (64%) with cure had HBcrAg below cut-off compared to 6/26 (23%) without cure (p=0.003).
Conclusion: A decline in circulating HBV RNA and HBcrAg levels during tenofovir therapy is more likely in PLWH with functional HBV cure than in those without cure. HBV RNA and HBcrAg may be promising predictive markers of functional HBV cure.

Kinetics of circulating HBV RNA levels in participants with (A) and without (B) functional HBV cure and kinetics of HBcrAg levels in participants with (C) and without (D) functional HBV cure during treatment with tenofovir. Mean levels of HBV RNA and HBcrAg were modeled as fractional polynomials of time (dashed line) with 95% confidence intervals (shaded area) and individual changes of HBV

RNA and HBcrAg (circles with connecting solid lines). Cut-off was 10 cp/ml for HBV RNA and 3 log_{10} U/ml for HBcrAg.



587 LONG-TERM HEPATITIS B OUTCOMES IN ZAMBIA WITH TENOFOVIR-TREATED HBV/HIV COINFECTION

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Background: Where HBV/HIV coinfection is most common – sub-Saharan Africa – long-term outcomes have rarely been documented. We evaluated long-term hepatitis B viral, serological, and liver outcomes of tenofovir-based ART in Zambia.
Methods: Adults (18+ years) who were dually HIV antibody and hepatitis B surface antigen (HBsAg) positive were prospectively enrolled at the start of ART (EFV+TDF+3TC and DTG+TDF+3TC after 2019). Labs for HBV (hepatitis B e antigen [HBeAg], HBsAg, HBV DNA, liver transaminases) and HIV (CD4 count, HIV RNA), and transient elastography, were performed at enrollment and at least yearly thereafter. HBV DNA non-suppression (beyond 2 years on ART) and e and s antigen seroclearance were ascertained. Predictors of DNA non-suppression and HBsAg seroclearance were analyzed with multivariable regression. Normalization of ALT elevation and progression of liver fibrosis and cirrhosis, based on TE, were described. In subgroup analysis, we examined the outcomes of patients who were HBeAg-negative, had DNA < 2,000 IU/ml, and no-minimal fibrosis at ART start.
Results: Among 291 analyzed (median follow-up of 4.9 years), median age was 33 years, 40.9% were women, and 54.3% reported current alcohol use. At enrollment, median CD4 count was 192 cells/mm^3, 41.2% were HBeAg-positive, 46.4% had DNA >2,000 IU/ml, 17.7% had significant fibrosis and 6.2% had cirrhosis. DNA non-suppression occurred in 13.5% and was associated with pre-ART WHO stage 3/4 and high DNA and reduced adherence during ART. ALT normalized in two-thirds of patients; however, ALT elevation was present at 20-30% of visits beyond 2 years and associated with alcohol use. HBeAg seroclearance was 26.6% at 2 and 34.2% at 5 years. HBsAg seroclearance was 9.2% at 2 and 16.5% at 5 years. No demographic, HBV, HIV, or liver factor examined was associated with HBsAg seroclearance. Regression of fibrosis (80.4%) and cirrhosis (93.8%) were common, progression to fibrosis was rare (2%); none progressed to cirrhosis. In those with markers of inactive HBV and liver disease, both ALT normalization and HBsAg loss occurred on ART
Conclusion: In Zambia, Tenofovir-based ART effectively controlled HBV in PLWH with higher than expected HBsAg seroclearance. Even those with minimal apparent need for HBV control experienced desired end points with ART. Behavioral interventions for medication adherence and unhealthy alcohol use may be needed to optimize the long-term outcomes of HBV/HIV coinfection.

588 "MICRO-INFECTION" OF HBV CAN OCCUR IN MSM WITH VACCINATION OR TENOFOVIR-BASED PrEP

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Background: HBV vaccination and tenofovir-based PrEP prevent acute HBV hepatitis. However, there is little data on prophylactic effect of these HBV prophylaxes against asymptomatic HBV infection. We investigated acute HBV infection and its serological characteristics according to the HBV prophylaxes among an HIV-negative MSM cohort, at sexual health clinic (SHC) in Tokyo, Japan.
Methods: HIV-negative MSM aged 16 years and older were included in SHC. Participants were examined with HBs antigen (HBsAg)/antibody and HBc antibody (HBcAb), HIV infection, syphilis, *Chlamydia trachomatis* and *Neisseria gonorrhoeae* infections every 3 months. Those who were diagnosed with acute HBV infection between January 2018 and March 2022 in SHC were subjects for this study. The definition of acute HBV infection was as followed; 1) for those with positive HBsAg at the enrollment of SHC, clearance of HBsAg within 6 months from the first HBsAg positivity, and 2) for those with HBsAg and HBc Ab negativity at the enrollment of SHC, HBsAg or HBcAb seroconversion during the study period. The cases of acute HBV infection were categorized into A) positive HBsAg, B) negative HBsAg and continuous HBcAb positivity, and C) negative HBsAg and transient HBcAb positivity. B) and C) were analyzed by HBV prophylaxes including prior HBV vaccination and tenofovir-based PrEP with t-test or chi-square test. HBV DNA was measured among C) if available serum samples were stocked.
Results: A total of 1972 MSM were included in SHC as of March 2022. Among them, 48 (mean age 31 years) were diagnosed with acute HBV infection. As shown in the table, MSM with transient HBcAb positivity were significantly more likely to have HBV prophylaxes, while MSM with symptomatic hepatitis and HBsAg positivity were not observed among those who had HBV prophylaxes. MSM with transient HBcAb positivity was older than MSM with continuous HBcAb positivity, which may be reflected by the fact that MSM with the HBV prophylaxes were significantly older (39.3 vs 28.3 years, p< 0.001). Of 11 MSM with transient HBcAb positivity, 3 cases were tested for HBV DNA and it was detected in one case. The average time to disappearance of HBcAb was 174 days.
Conclusion: While HBV prophylaxes prevented symptomatic hepatitis, the infection without serological trace occurred. Clinical significance of this "micro-infection" should be investigated in further studies.

Detail of acute HBV infection according to serology and prophylaxes

	All acute HBV infection (n=48)	By Serology				By Symptom
		HBsAg+ (n=24)	HBsAg- (24)			Symptomatic hepatitis (n=19)
			Continuous HBcAb+ (n=13)	Transient HBcAb+ (n=11)	p value (continuous vs transient)	
Age, year (SD)	31 (8.1)	29 (5.7)	29.5 (6.9)	37.2 (11.1)	0.049	28.6 (5.6)
Prophylaxes+	12 (25%)	0	3 (23.1%)	9 (81.8%)	0.006	0
Vaccination	11 (22.9%)	0	3 (23.1%)	8 (72.7%)	0.0038	0
PrEP	6 (12.5%)	0	1 (7.7%)	5 (45.5%)	0.061	0
Both	5 (10.4%)	0	1 (7.7%)	4 (36.4%)	0.142	0

589 BULEVIRTIDE +/- PEG-IFN IN HIV/HBV/HDV COINFECTED PATIENTS IN REAL-LIFE SETTINGS

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Background: Bulevirtide (BLV) is a lipopeptide inhibiting the HBV/HDV entry into the hepatocytes. Significant HDV RNA decline was observed in HBV/HDV patients who received 48 weeks of BLV in monotherapy or in combination with PEG-interferon α 2a (PEG-IFNα). Until now, no data has been presented in HIV/HBV/HDV co-infected patients treated with BLV. The aim of this analysis was to evaluate the efficacy and safety of BLV 2mg daily with or without PEG-IFNa 2a

for 12 months in HIV co-infected patients treated in the French BLV early access program.

Methods: 21 HIV patients (male 71%, mean age 48 years, cirrhosis 52%, median HDV-RNA 6.09 log_{10} IU/mL, median HIV-RNA 0 cp/mL (three patients had detectable HIV-RNA at day 0, all < 100 cp/mL), median CD4 558/mm^3) with chronic HIV/HBV/HDV infection, with compensated cirrhosis/severe fibrosis or moderate fibrosis with elevated ALT levels, were included in the French early access program. Patients received BLV 2mg QD SC alone (N=13) or in combination with PEG-IFNα once weekly (N=8) according to physician's choice. HIV drugs regimen (DR) were TAF/FTC (in 100% of patients), and either NRTI, INI, PI, ISTI, or NNRTI.

Results: No specific adverse events were reported and no HIV drug modification was needed (median CD4 at M12: 540/mm^3). Only one patient had detectable HIV-RNA at M12 (31 cp/mL at baseline and 54 cp/mL at M12). Early discontinuation (before M12) was observed in 8 (38%) patients: 2 adverse events (variceal bleeding, rectal cancer), 3 lost to follow-up or patient decision, 3 other reason). From baseline, HDV RNA (log_{10} IU/mL) declined overtime: M3 -2.25, M6 -4.09, M9 –3.37, and M12 -4.19. Main results at M12 are indicated in Table.

Conclusion: In this first real-world cohort of HIV/HBV/HDV patients, daily administration of BLV 2 mg for 12 months was safe and well tolerated with no impact on CD4 and HIV viral suppression. Strong HDV antiviral and biochemical responses were observed in real-life irrespective of the BLV regimen administered.

Virological and Biochemical response at Month12

Results at M12	BLV monotherapy	BLV + PEG-IFN
Normal ALT level (< 40 IU/L)	5/8 (62.5%)	3/7 (42.9%)
2 log decrease from baseline or undetectable HDV-RNA (%)	7/9 (77.7%)	5/7 (71.4%)
Undetectable HDV-RNA (%)	6/9 (66.7%)	5/7 (71.4%)

590 HCV INCIDENCE AMONG MSM ON PrEP AND MSM WITH HIV IN NEW YORK CITY OVER 2 DECADES

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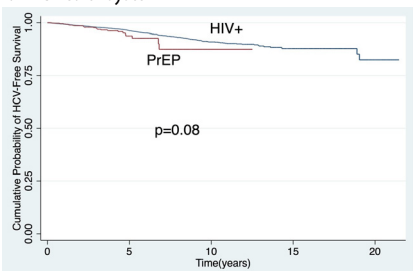
Background: Despite HCV elimination efforts, transmission among MSM with HIV has continued at a high rate in most locales. Recently, MSM on PrEP have emerged as a risk group, significantly expanding those at risk for sexual acquisition of HCV. New York City (NYC) has been an epicenter of this HCV epidemic, but there are no data quantifying the extent of this epidemic in the US.

Methods: We performed a retrospective analysis of the electronic health records from across the Mount Sinai Health System for incident HCV infections among MSM (2000-2022). The primary comparison was MSM with HIV and MSM on PrEP. Incident HCV infection was defined as a positive HCV Antibody test after a negative Ab test. Incidence rates were calculated using the time between the initial negative Ab test and either a positive Ab test or the last negative Ab test. Kaplan-Meier (KM) analysis was used to compare cumulative probability of incident HCV infection.

Results: Records were available for 20,844 MSM. Among those with a baseline HCV Ab test and at least one follow-up Ab test >30 days later, 6443 were MSM with HIV, 1728 were MSM on PrEP, and 503 were MSM not on PrEP. Among MSM with HIV, there were 271 incident HCV infections over 32,693 years of follow up [mean 5.1 (SD 3.9) years]. Among MSM on PrEP there were 43 incident HCV infections over 4540 years of follow up [mean 2.6 (SD 1.9) years]. There was no difference between the HCV incidence rates for these groups [0.83 (95% CI 0.73, 0.93)/100 PY; 0.95 (95% CI 0.69, 1.28)/100 PY, respectively, p=0.32]. Similarly, KM analysis showed no difference in cumulative probability of HCV infection between MSM with HIV (blue) and MSM on PrEP (red) (p=0.08) (Figure). Time trend analysis suggested no declines in incidence rates during the study period for either group. There were just three incident HCV infections among MSM not on PrEP [incidence rate 0.12 (95% CI 0.03, 0.35)/100 PY], significantly lower than for MSM on PrEP.

Conclusion: Less than a decade after the FDA approval of PrEP, and despite the availability of curative all-oral HCV treatment, touted as the tool sufficient to eliminate HCV among MSM, the incidence rate of HCV infection among MSM on PrEP in NYC is equivalent to that of MSM with HIV. Our data indicate that active HCV surveillance is needed for MSM on PrEP, and the CDC PrEP guidelines, which do not adequately address HCV testing, should be updated. Most importantly, further HCV risk reduction and prevention efforts are needed for both MSM on PrEP and MSM with HIV.

Kaplan-Meier Curve of Incident HCV Infections among MSM on PrEP and MSM with HIV in a NYC Health System



591 HEPATITIS C BURDEN IN GREECE, ITALY, PORTUGAL, AND SPAIN: 2000-2019

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Background: Viral Hepatitis remains a health priority. We performed a comprehensive evaluation of epidemiological HCV estimates in Southern countries of Western Europe and assessed the impact of the 2008 economic crisis on HCV burden.

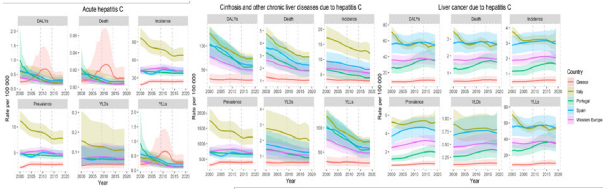
Methods: We analyzed data of the Global Burden of Diseases to describe the patterns of six measures of HCV burden [prevalence, incidence, mortality, years lived with disability (YLDs), years of life lost (YLLs), disability adjusted life years (DALYs)] in Greece, Italy, Portugal, Spain. We assessed age-standardized rates (per 100,000 population) between 2000-2019, disaggregated by sex and age, and compared the annualized age-standardized rate of change (ARC%) in 2000-2010 (pre-austerity) and 2010-2019 (post-austerity).

Results: Prevalence, incidence and YLDs rates of acute HCV showed a general stable trend in Western Europe (WE), globally and in the four studied countries except Italy, where, despite a marked decline (ARC: 1.4% in 2010-2019), the 2019 estimates [7.8 (95% UI 6.6-9.2)] were still 1.7-fold higher than in WE. Mortality, YLLs and DALYs associated with acute HCV decreased in the analyzed countries and peaked in Greece post-austerity. Globally and in Greece, mortality rate was higher in females than in males (1.3-times and 1.5-times in 2019, respectively). Mortality caused by chronic liver diseases including cirrhosis decreased globally, in WE and in all countries albeit at a lower rate in the post-austerity period (decrease in ARC for WE: 2.5% in 2000-2010; 1.6 in 2010-2019).

Liver cancer prevalence due to HCV increased in WE (ARC: 2.1%) and in the analyzed countries mainly in the pre-austerity period except for Italy. However, despite having the highest prevalence rate in both sexes, Italy showed major decreases in all six-disease metrics. HCV liver cancer mortality declined significantly only in Italy (ARC: 2.6%) and globally (ARC: 2.1%) especially in the pre-austerity period, while Portugal experienced a major increase post-austerity. Overall, males and people over 70 years old are at greater risk of developing chronic liver diseases due to HCV infection.

Conclusion: The economic crisis of 2008 negatively impacted hepatitis C related liver cancer mortality rates in Greece, Italy, Portugal and Spain. Despite the observed recovery in recent years, elimination of HCV infection by 2030 will be a major challenge in these countries and the COVID-19 pandemic and the current grim economic context are expected to compromise even further hepatitis C elimination.

Figure 1 - Acute and chronic HCV age-standardized rates from 2000 to 2019.



592 USABILITY AND ACCEPTABILITY OF HCV SELF-TESTING IN THE GENERAL POPULATION FROM BRAZIL

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Background: Hepatitis C virus self-testing (HCVST) has been recommended by the World Health Organization (WHO). However, data on the feasibility of HCVST in Latin America remain scarce. Therefore, we aimed to assess the usability and acceptability of HCVST among the general population in the Primary Health Care (PHC) in Rio de Janeiro (Brazil).
Methods: This cross-sectional study was conducted in a Basic Health Unit in Rio de Janeiro from 04-Jul-2022 to 13-Sep-2022. Participants had access to written instructions for use and a video with a step-by-step oral fluid HCVST kit [OraQuick® HCV Self-Test]. A trained healthcare worker (HCW) observed the participant performing the test. After HCVST, the HCW performed a second HCV testing using the same kit. Usability was assessed by observing errors made and difficulties faced by participants. A post-testing questionnaire assessed the acceptability of HCV self-testing. Inter-reader (re-reading) and inter-operator (re-testing) concordance were assessed.
Results: A total of 553 participants [75% female; median age=52 (IQR,39-61) years, 51.7% with schooling ≤ 10 years; 16.8% with diabetes] were included. People correctly opened the kit package, inserted the tube in the tube support, and collected oral-fluid samples in 95.1%, 90.2%, and 69.3%, respectively. After sample collection, correct insertion of the flat pad in the tube and correct timekeeping for result interpretation were observed in 86.8% and 93.5% of cases, respectively. A total of 62.2 % (n=344) of participants completed the HCVST process without assistance from an HCW. Inter-reader agreement of HCVST results was 94.4%, with a Cohen's kappa of 0.52 (n=550) (Table). The agreement between participant-reported HCVST results and HCW-administered oral fluid HCV rapid test results was 99.6%, with a Cohen's kappa of 0.67 (excluding invalid tests, n=500) (Table). A total of 91.5% felt safe performing HCVST. Most participants rated the HCVST process as easy (74.1%) or very easy (23.3%), 98.7% reported that they would be willing to use HCVST again, and 99.6% would recommend HCVST to their family, sexual partners, or friends. A total of 70.7% would prefer to perform HCVST in a health unit, and few people would like remote/digital (14.8%) or presential (28.6%) assistance by an HCW for HCVST.
Conclusion: We demonstrated high usability and acceptability of oral fluid HCVST in a large sample of the population in a PHC in Rio de Janeiro.

Table. Inter-reader (re-reading) and inter-operator (re-testing) concordance of HCVST stratified by age and schooling (n=553)

			Agreement	Cohen's kappa
Inter-reader concordance (re-reading) §	**Overall**	**All (n=550)**	**94.4%**	**0.52**
	Stratified by age	< 60 years (n=386)	94.8%	0.52
		≥ 60 years (n=164)	93.3%	0.50
	Stratified by schooling	< 10 years (n=285)	94.7%	0.49
		≥ 10 years (n=265)	93.9%	0.53
			Agreement	**Cohen's kappa**
Inter-operator concordance (re-testing)* §	**Overall**	**All (n=500)**	**99.6%**	**0.67**
	Stratified by age	< 60 years (n=351)	No discordance	
		≥ 60 years (n=149)	98.7%	0.66
	Stratified by schooling	< 10 years (n=262)	99.2%	0.50
		≥ 10 years (n=238)	99.1%	0.50

N=553
Re-testing: HCVST result informed by participants compared to administered by HCW
§ three participants refused to inform HCVST result
* excluding invalid tests informed by participants (n=44) or by HCW (n=3); three participants refused to be tested by HCW

593 UPTAKE AND LINKAGE TO CARE FOR HCV SELF-TESTING: RESULTS FROM A MULTI-COUNTRY RCT

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Background: Globally, of the estimated 58 million people living with the hepatitis C virus (HCV), only 21% know their status. Scale-up of HCV testing is needed to close this diagnostic gap and aid in the achievement of the WHO 2030 elimination goals. There are currently no data on the real-world impact of HCVST. We evaluated the impact on uptake of HCVST compared to standard of care in 3 different HCVST models in Georgia, Malaysia, and Pakistan.
Methods: Multiple modalities of HCVST were evaluated across the project countries. This included: 1) in Georgia: courier delivery of HCVST (for men who have sex with men [MSM]), peer delivery of HCVST (for MSM and people who inject drugs [PWID]), and the standard of care- referral to HCV-testing facility; 2) in Malaysia (for those who self-identify as a key population): courier delivery of HCVST, and standard care -referral to HCV-testing facility; 3) in Pakistan (general population): home distribution of HCVST or standard care of hospital-based HCV screening. To understand the relative impact in the different modalities of HCVST in HCV diagnosis, we evaluated the HCV care cascade for each subgroup in each modality of care compared to the standard of care.
Results: In all 3 countries across all subpopulations, uptake of HCV Ab testing was higher in the HCVST groups compared to the control group (Table 1). Linkage to care was better in the HCVST arms as compared to the standard of care in Malaysia and Georgia for all sub populations and self-test modalities. In Pakistan, while the linkage to care was technically lower for self-test compared to standard of care, the total number of people successfully diagnosed was more than 10-fold greater. Results on uptake and linkage for HCVST compared to standard care did not differ significantly by sex.
Conclusion: Across all HCVST modalities in all three countries, HCV testing uptake was greater with self-testing modalities as compared to the standard of care. Further to that, linkage to care was high across HCVST modalities. Careful consideration is needed for further scale-up of HCVST including; expected HCV Ab prevalence among target groups (affecting underlying cost-effectiveness of HCVST modalities), provision of tools to ensure testers are able to perform and interpret the test correctly, and mechanisms to facilitate psychosocial support and linkage to care.

Table 1: preliminary results across Georgia, Malaysia, Pakistan

Model of care (n)	Completed survey (if conducted the HCV Ab test or not)	Of those who returned results, completed HCV Ab test (uptake)	HCV Ab+ result reported	Of those who reported HCV Ab+ results, number who had RNA test done (linkage to care)
Georgia MSM (n=497)				
Courier delivery (n=163)	77 (47%)	70 (91%)	1 (1%)	0 (0%)
Peer delivery (n=153)	108 (71%)	101 (94%)	1 (1%)	1 (100%)
SOC (n=181)	105 (58%)	76 (72%)	2 (3%)	0 (0%)
Georgia PWID (n=510)				
Peer delivery (n=262)	224 (85%)	212 (95%)	6 (3%)	5 (83%)
SOC (n=248)	216 (87%)	164 (76%)	10 (6%)	4 (50%)
Malaysia (n=750)				
Courier delivery (n=499)	364 (72%)	358 (n=98%)	3 (1%)	2 (67%)
SOC (n=251)	107 (43%)	55 (51%)	0 (0%)	NA
Pakistan (n=2185)				
Home delivery (n=1184)	1026 (87%)	1026 (100%)	168 (68%)	115 (68%)
SOC (n=1001)	224 (22%)	224 (100%)	15 (7%)	14 (93%)

HCV Ab: hepatitis C virus antibody, RNA: ribonucleic acid, MSM: men who have sex with men, SOC: standard of care

594 MOBILIZING PRIMARY CARE PROVIDERS TO TREAT HEPATITIS C IN RURAL WEST VIRGINIA

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Background: WV has ranked 1st or 2nd for acute HCV incidence for over a decade but has few specialists and severe transportation challenges, contributing to

inequitable access to HCV care. Most clinicians trained before 2016 are unaware that HCV is readily curable.

Methods: We developed the WV Hepatitis Mentoring Partnership (WVHAMP) to empower primary care providers (PCPs) to manage HCV by training and mentoring them through the cascade of care. WVHAMP supports health equity in under-resourced areas while also meeting Medicaid's initial requirement for treatment under specialist guidance. PCPs engage with HCV experts via web-based training combined with a customized, HIPAA-compliant, web-based data system for case-based bidirectional communication. Using an informatics platform available to all partners supports shared decision-making, fostering a learning network for HCV care and increasing self-efficacy and efficiency while enabling patients to receive care in the community from clinicians they know and trust.

Results: Since 3/2020, WVHAMP has trained 150 providers and responded to 761 consults. Of the 261 patients who have reached the SVR12 timepoint, 257 (98.5%) have been cured by PCPs who have never previously treated HCV, a rate similar to that of specialists (95-99%).

Conclusion: WVHAMP Scholars, who have achieved an SVR12 rate comparable to experts, are contributing to HCV microelimination in underserved rural communities. This model can be readily expanded to HCV care in underserved urban areas as well.

595 OPTIMAL FREQUENCY OF HCV RNA TESTING FOR PLWH AT RISK FOR ACUTE HCV INFECTION

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Background: Timely diagnosis of acute HCV infection with subsequent treatment with direct-acting antivirals among at-risk populations is the most effective and feasible way to cease HCV transmission. However, the optimal frequency of HCV RNA testing has rarely been assessed among people living with HIV (PLWH).

Methods: In this multi-center study involving 11 hospitals designated for HIV care around Taiwan, we conducted 3-stage pooled-plasma HCV RNA testing every 3 months among PLWH who were at high risk for acute HCV viremia, including PLWH recently diagnosed with sexually transmitted diseases (STDs), those with HCV clearance spontaneously or with antiviral therapy, and those with elevated aminotransferases. Repeat enrollment was allowed. We estimated the incidence rates of HCV viremia during the 1-year follow-up and examined the proportions of delayed detection of HCV viremia if the testing frequency had been changed from every 3 months to every 6 or 12 months.

Results: A total of 1,875 PLWH were enrolled between June 2019 and August 2022; 99.9% were men and 98.3% were men who have sex with men (Table). At enrollment, 74.7% of the participants were included because of recent STDs, 25.2% and 3.8% because of HCV viral clearance by antiviral therapy and spontaneously, respectively, and 15.4% because of elevated aminotransferases. A total of 108 cases of HCV viremia were detected during the study period, with 63 cases (58.3%) detected at enrollment and the remaining 45 cases (41.7%) detected during 1,208.11 person-years of follow-up (PYFU), which led to an incidence rate of HCV viremia of 37.25 cases per 1000 PYFU. The mean HCV RNA load of the 45 incident cases was 5.41 (range, 1.30-7.77) $\log_{10}$ IU/mL. If the testing frequency had been changed to every 6 or 12 months, the incidence rates would have decreased to 37.05 and 36.66 per 1000 PYFU, respectively. However, the diagnosis of 62.2% (28/45) cases of acute HCV viremia (mean HCV RNA load, 6.10; range, 2.48-7.77 $\log_{10}$ IU/mL) and 91.1% (41/45) (mean HCV RNA load, 5.53; range 1.30-7.77 $\log_{10}$ IU/mL) would have been delayed, respectively, before their HCV viremia could have been detected at months 6 and 12, respectively.

Conclusion: With HCV RNA testing performed every 6 or 12 months among high-risk PLWH, the detection of a large proportion (62.2-91.1%) of PLWH who recently acquired HCV would be delayed, which may contribute to onward HCV transmission with longer durations.

Characteristics of the enrolled 1,875 PLWH

	Case number
Male gender, n (%)	1874 (99.9)
Risk group of HIV transmission	
MSM	1844 (98.3)
Heterosexuals	11 (0.6)
IDUs	16 (0.9)
Criteria of enrollment, n (%)	
STDs	1368/1832 (74.7)
SVR12	462/1832 (25.2)
Spontaneous HCV clearance	69/1832 (3.8)
Elevated aminotransferases	280/1824 (15.4)
Status of HIV infection at enrollment	
CD4 count >200 cells/mm^3	1761/1823 (96.6)
Plasma HIV RNA load <50 copies/mL	1680/1732 (97.0)
Use of ART	1875 (100)
Time point of the last follow-up as of 31 August, 2022, n (%)	
Day 1	324 (17.3)
Unscheduled date	1 (0.1)
Month 3	273 (14.6)
Month 6	290 (15.5)
Month 9	170 (9.1)
Month 12	817 (43.6)
Time point of cases of HCV viremia detected, n (%)	
Overall	108 (100)
Day 1	63 (58.3)
Unscheduled date	1 (0.9)
Month 3	14 (13.0)
Month 6	13 (12.0)
Month 9	13 (12.0)
Month 12	4 (3.7)

Abbreviations: ART, antiretroviral therapy; HCV, hepatitis C virus; IDUs, injecting drug users; MSM, men who have sex with men; STDs, sexually transmitted diseases; SVR12, sustained virologic response 12 weeks off-therapy

596 SVR12 OUTCOMES FOR NOVEL HCV GENOTYPE/SUBTYPES WITH SOF/VEL IN MINMON STUDY

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Background: The characterization of response to direct antiviral agents for rare or novel HCV subtypes is important for global elimination strategies. Genotypes (GT) 1, 2, 3, 4 and 6 are comprised of multiple subtypes and display a high degree of genetic variability. Here, we describe the identification of novel GT-4 subtypes and a GT-7 HCV isolate distinct from 7a and 7b and their sustained virologic response (SVR) outcomes.

Methods: ACTG study A5360 [MINMON] was a phase 4 open-label study of minimal monitoring with 12 weeks of sofosbuvir/velpatasvir for treatment-naive HCV infection. Four hundred participants were enrolled across 38 sites in Brazil (n=131), South Africa (n=12), Thailand (n=110), Uganda (n=15) and the USA (n=132). Amplicon-based deep sequencing analyses of NS3, NS5A and/or NS5B were conducted for all baseline samples. HCV full genome using random primer Nugen amplification followed by Illumina MiSeq sequencing was performed on plasma samples which failed standard amplification. Nucleotide Blast analysis followed by phylogenetic analyses was used to confirm HCV subtype.

Results: In MINMON study, SVR12 was achieved in 96% (379/399) of participants treatment. For most participants enrolled, a specific HCV subtype was assigned based on a close genetic relationship to previously described subtypes. However, for 1 patient from Uganda, sequences obtained from plasma HCV RNA showed < 85% sequence homology to all known HCV subtype reference strains. Blast analyses of publicly available datasets revealed close homology to a provisional GT-7c HCV isolate also originating from Uganda (KU861171). In addition, there were N=5 patients from Uganda and South Africa with GT-4 HCV that showed < 85% amplicon homology to all known GT-4 subtypes. Presence of NS3, NS5A and NS5B resistance associated polymorphisms in GT-4 with novel subtypes and GT-7 HCV isolates are summarized in Table 1. All participants with novel subtypes of GT-4 and GT7 HCV treated with sofosbuvir/velpatasvir achieved SVR12 despite the presence of NS5A RAVs and NS5B nucleos(t)ide RAVs (100% SVR12).

Conclusion: A new strain of HCV subtype 7c and novel subtypes of GT-4 were identified. Sofosbuvir/velpatasvir treatment for 12 weeks was efficacious against these novel strains of HCV. These findings highlight even greater genetic diversity of HCV subtypes than previously recognized. Global HCV elimination strategies need to account for a growing understanding of HCV diversity.

Table 1. NS3, NS5A and NS5B Resistance Associated Polymorphisms in novel genotype 4 subtypes and genotype 7 HCV isolates.

					Resistance Associated Polymorphisms		
Sequence ID (Study)	GT	Treatment	SVR12 (Yes/No)	Country of Origin	NS3	NS5A	NS5B
EF108306	7a	NA	NA	Canada (via DRC)	V36L T54G V55P Q80D D168Q	M28L Q30S H58P A92S Y93H	E237S C289M
L89915 (Astral study)	7b	SOF/VEL 12 weeks	Yes	Belgium (via DRC)	V36L V55A Q80D D168Q	M28L Q30L H58P Y93H	E237C C289F
KU861171	7c	NA	NA	Uganda	V36L Q80E D168Q	Q30S H58G Y93H	E237N C289M
1241918 (A5360 study)	7c	SOF/VEL 12 weeks	Yes	Uganda	No Coverage	No Coverage	No Coverage
1241903 (A5360 study)	4	SOF/VEL 12 weeks	Yes	Uganda	V36L	M28L, Q30R, H58L	C289F
1241909 (A5360 study)	4	SOF/VEL 12 weeks	Yes	Uganda	No Coverage	M28L, Q30R, L31M, H58P	C289F
1241910 (A5360 study)	4	SOF/VEL 12 weeks	Yes	Uganda	V36L	Q30R, L31M, H58P	None
892840 (A5360 study)	4	SOF/VEL 12 weeks	Yes	South Africa	V36L	M28L, Q30L L31M, H58P	C289F
1112511 (A5360 study)	4	SOF/VEL 12 weeks	Yes	South Africa	No Coverage	Q30C, L31M, H58P	No Coverage
1241901 (A5360 study)	4	SOF/VEL 12 weeks	Yes	Uganda	No Coverage	Q30C, L31M, H58P	No Coverage

597 SOFOSBUVIR/VELPATASVIR PHARMACOKINETICS IN PREGNANT WOMEN WITH HEPATITIS C VIRUS

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Background: Treatment of hepatitis C virus (HCV) with direct acting antivirals during pregnancy could cure maternal HCV during antenatal care engagement and prevent perinatal HCV transmission. A study of ledipasvir/sofosbuvir in pregnancy (NCT02683005) showed good efficacy and favorable pharmacokinetics (PK), but a pan-genotypic regimen was needed. Our objectives were to compare the PK parameters of sofosbuvir/velpatasvir (SOF/VEL) in pregnant versus nonpregnant women, and to assess delivery outcomes and viral response.

Methods: In this open-label, phase 1 study, HIV-negative pregnant women with chronic HCV infection were enrolled between 23-25 weeks' gestation. At entry, participants began SOF-400mg/VEL-100mg daily for 12 weeks. Twenty-four-hour intensive PK visits were performed at 3 and 9 weeks of treatment. VEL, SOF and GS-331007 (the inactive metabolite of SOF) in plasma were measured using validated UPLC-MS/MS assays. PK parameters were determined using non-compartmental methods (Phoenix v8.3) and geometric mean ratios and 90% CI compared to historical intensive PK data in non-pregnant women from registrational trials. Maternal adverse events, delivery outcomes, and the sustained virologic response 12 weeks after therapy (SVR12) were also determined.

Results: Fourteen participants were screened, 3 were excluded due to declining participation, having a fetal anomaly and spontaneous HCV clearance, and 11 participants enrolled. One participant discontinued treatment after two doses due to worsening of hyperemesis. VEL exposures and SOF maximum concentration (C_{max}) were similar to historic data, but SOF area under the curve (AUC) was 38% higher and GS-331007 AUC and C_{max} were 38% and 43% lower, respectively (Table). All 10 participants that completed treatment had undetectable HCV RNA at delivery. All participants that completed the SVR12 visit were cured (n=7) and all the infants that followed up had an undetectable HCV RNA (n=7). Nine maternal participants experienced adverse events related to SOF/VEL; however, only one was greater than grade 2 (vomiting) and resulted in discontinuation of SOF/VEL. Two infants delivered preterm at 35- and 36-weeks' gestation.

Conclusion: SOF/VEL exposures were not clinically different in pregnancy. Consistent with SOF/ledipasvir in pregnant women, lower GS-331007 exposures were observed and possibly due to increased glomerular filtration rate during pregnancy. A multicenter study to evaluate SOF/VEL safety and efficacy in pregnancy is underway (NCT05140941).

SOF/VEL PK parameters during pregnancy compared to non-pregnant women

PK Parameter Geomean (%CV)		Pregnant Women (N=10)[a]	Non-Pregnant Women in Registrational Trials (N=25)[b]	%GMR (90%CI)
SOF	AUC_{tau} (hr*ng/mL)	2039.62 (29.75)	1483.83 (66.43)	1.38 (1.06, 1.78)
	C_{max} (ng/mL)	1455.09 (43.92)	1226.16 (59.46)	1.19 (0.88, 1.60)
GS-331007	AUC_{tau} (hr*ng/mL)	9588.94 (18.75)	15361.31 (22.35)	0.62 (0.55, 0.71)
	C_{max} (ng/mL)	752.66 (21.85)	1312.17 (32.55)	0.57 (0.49, 0.67)
VEL	AUC_{tau} (hr*ng/mL)	3244.45 (39.89)	3570.65 (72.04)	0.91 (0.67, 1.23)
	C_{max} (ng/mL)	381.93 (38.35)	449.39 (77.12)	0.85 (0.63, 1.15)
	C_{tau} (ng/mL)	40.56 (49.00)	49.77 (66.37)	0.82 (0.59, 1.13)

All data are presented to 2 significant digits. Abbreviations: AUC_{tau}, area under the concentration-time curve of the dosing interval; C_{max}, maximum concentration, C_{tau}, concentration at the end of the dosing interval; CI, confidence interval; CV, coefficient of variation; GMR, geometric mean ratio
a Geometric mean of individual participants PK parameters from 2 PK visits were used for summarization.
b Subset of non-pregnant women from registrational trials administered SOF/VEL with intensive PK assessments

598 HBV TRANSMISSION IN HOUSEHOLDS OF WOMEN ENGAGED IN DR CONGO'S HIV PMTCT PROGRAM

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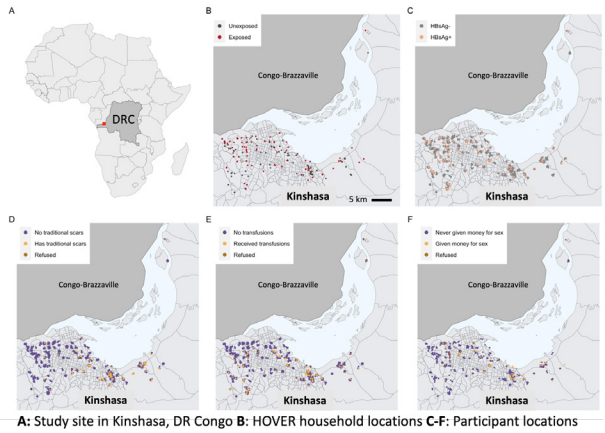
Background: Hepatitis B virus (HBV) remains endemic in Africa despite effective vaccines. Limited studies suggest horizontal modes of transmission within households or communities may be driving continued endemicity in the region. The relative impact of horizontal versus vertical transmission is unknown.

Methods: We conducted the Horizontal and Vertical Transmission of Hepatitis B in the Democratic Republic of Congo (DRC) study (HOVER-HBV), a prospective, cross-sectional study to determine HBV prevalence within households and characterize transmission in Kinshasa, one of Africa's largest cities. We recruited households of index mothers with ("exposed") and without ("unexposed") HBV through HBV surface antigen (HBsAg) screening during routine antenatal care at two large maternity centers. Enrolled household members underwent HBsAg testing, dried blood spot sampling, and an epidemiological survey. We used logistic regression and Moran's I to evaluate HBV risk factors.

Results: Among 200 households, we enrolled 1006 participants; 475 (47%) were direct offspring of index mothers. Clusters of ≥2 (range 2-6) infections were observed in 13 (8 exposed, 5 unexposed) households. Household members with HBV were more common in exposed than unexposed households (19 [5%] versus 8 [2%]), with 2.49 (95% CI: 1.65, 11.55) greater odds of being HBsAg+ after adjusting for household clustering. In exposed households, direct offspring of index mothers had similar odds (odds ratio [OR] 0.95 [95% CI: 0.37, 2.52]) of being HBsAg+ compared with other household members; while direct offspring in unexposed households had lower odds (OR 0.42 [95% CI: 0.09, 1.73]) compared to other household members. Of 22 who self-reported a past positive HIV test, 15 were HBsAg+, 14 of whom reported being on HIV treatment. Preliminary results indicate no spatial autocorrelation of household prevalence (Moran's I: 0.14, p=0.59), but notable spatial variation in HBV exposures (e.g., scarification, past transfusions, and transactional sex; Figure 1). Shared razors and premastication of food were also more frequently reported by exposed participants with HBV. Phylogenetic analyses to characterize transmission patterns are ongoing.

Conclusion: Vertical and horizontal HBV transmission is occurring in Kinshasa households despite infant vaccinations. Prevalence was highest among offspring and household members of women with HBV. Our findings reveal opportunities for expanded prevention efforts and integration of HBV in existing HIV programs.

Figure 1. Spatial variation in HBsAg positivity and potential community HBV exposures across Kinshasa, DR Congo



A: Study site in Kinshasa, DR Congo **B:** HOVER household locations **C-F:** Participant locations by HBsAg status (C), scarification practices (D), past transfusions (E), and transactional sex (F)

599 PREVALENCE AND EVALUATION OF HEPATITIS B VIRAL REPLICATION IN PREGNANT WOMEN IN MALI

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Background: Pregnant women with a high Hepatitis B Virus (HBV) DNA viral load (VL) can still transmit HBV to the fetus or newborn, despite receiving hepatitis B immunoglobulin (HBIg) and vaccination of the newborn at birth. Although HBV infection is common in sub-Saharan Africa, data on maternal virological outcomes are limited.

Methods: In this longitufinal study, we assessed the sero-prevalence of hepatitis B surface antigen (HBsAg) from pregnant womens' samples obtained during antenatal visits between January and May 2022 at a public health clinic in Bamako, Mali. HBsAg postitive samples were then tested for HBV VL, with a high VL defined as >2000 IU/mL.

Results: Of the 998 pregnant women included, 84 (8.4%) had a positive HBsAg. Of these 84, median age was 27 yrs (interquartile range [IQR], 23-32); most were married (98%) and homemarkers (73%); and 18% were primiparous, however, only 10% knew their HBV serological status before the current pregnancy. Alanine aminotransferase (ALT) level was < 35 IU/L in 92% of cases and 26 (34.6%) had a VL > 2000 IU/mL, including 5.3% with a VL > 200 000 IU/mL. Three (3.5%) were HIV co-infected of which two had a detectable HIV VL >40 and one had HBV DNA at 1500 IU/ML. There was no statistically significant relationship between age, parity, and VL (□2 test, respectively, p=0.67; p=0.76). At present, 32/84 women have delivered at term and 31/32 received the first vaccine dose within 24 hours of delivery. However, HBV immunoglobulin must be purchased by the patient and only 23/32 received immunoglobulin.

Conclusion: This study characterizes HBV infection among pregnant women in Mali. HBsAg seropositivity is high and a third of women had HBV VL >2000 where antiviral treatment would be indicated to prevent mother to child transmission of HBV. These data confirm the need for hepatitis B vaccination and treatment programs for women of child bearing age in sub-Saharan countries like Mali, as well as, routine HBs Ag screening of pregnant women.

600 EVOLUTIONARY HISTORY OF HEPATITIS B VIRUS SUB-GENOTYPE D3 IN BOTSWANA

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Background: Botswana has an intermediate Hepatitis B virus (HBV) prevalence of 2–7%. To date, three HBV genotypes (A, D and E) have been reported in Botswana at the prevalence rates 80%, 18.6%, and 1.4%, respectively. However, the evolutionary history of all the identified genotypes within the population of Botswana remains unexplored. Such evolutionary analysis of HBV/D3 within Botswana population help in tracking disease evolution over time hence aiding in theoretical HBV prevention and management strategies. Our study first describes the origins, introductions (Time to Most Common Recent Ancestor (tMRCA), and evolutionary patterns of HBV sub-genotype D3 circulating in Botswana. Furthermore, we investigate the pairwise diversity on this sub-genotype and its spread within the population.

Methods: Analysis was carried out using 69 available, HBV/D3 near-full-length sequences retrieved from the NCBI database of which 24 were from Botswana. Population dynamic analysis of the HBV/D3 (HBV/D3) sequences amongst people with HIV (PWH) was performed using the Bayesian coalescent model as implemented in BEAST2 software. The temporal signal was estimated through the root-to-tip method using node density in tempEst v1.5.3 and the correlation coefficient was used to indicate the amount of variation in genetic distance explained by sampling time. Skyline plots were used to estimate the effective HBV/D3 infections in Botswana population over time. Diversity analysis of Botswana sequences was done based on pairwise distances analysis implemented in MEGA v.7.0.1 software. Botswana sequences were partitioned into 7 HBV open reading frames (ORFs) and used to calculate nucleotide diversity.

Results: HBV/D3 tMRCA amongst PLWH in Botswana dated back to 1964 (1839–1989), 95% Highest Posterior Density (HPD). Skyline plot showed a sharp increase in the number of HBV/D3 infections around the years 1999 and 2000 which is over the last approximately 22-23 years ago. The PreCore region had the highest median diversity of 0.02652 (IQR, 0.0115–0.05) and the surface (S) region was relatively conserved with median diversity of 0.0074 (IQR, 0.004–0.0134) p < 0.01.

Conclusion: The study provides the first insights of HBV/D3 phylodynamic information in Botswana by predicting its tMRCA, origin and diversity thereby revealing the evolutionary dynamics of the HBV genotype. Diversity analysis showed that Core region was the most diverse region and confirmed that the surface region was the most conserved region.

601 HEPATITIS C TREATMENT OUTCOMES AMONG PEOPLE WHO INJECT DRUGS IN KENYA

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Background: Hepatitis C virus (HCV) is a growing public health concern with approximately 1.5 million infections occurring annually globally. Direct-acting-antivirals (DAAs) are highly efficacious in treating HCV and strategies tailored for disproportionally affected groups such as people who inject drugs (PWID) are needed for early identification and treatment of infected individuals.

Methods: We assessed factors associated with HCV treatment success among PWID receiving ledipasvir-sofosbuvir at needle syringe programs (NSP) and methadone clinics in 3 Kenyan counties. An observational cohort study investigated whether treatment success, measured by sustained viral response 12 weeks after treatment completion (SVR12), differed between daily directly observed therapy (DOT) delivered at NSPs versus methadone clinics. Negative binomial regression was used to compare the proportion of clients who were treated and achieved a SVR12 between NSPs and methadone programs. Multivariate models assessed factors associated with treatment completion and achieving SVR12.

Results: A total of 142 clients with confirmed genotype 1 or 4 HCV infection were screened for eligibility and 86.6% (123/142) were initiated on treatment; 2 (1.4%) were ineligible for treatment due to evidence of advanced liver disease (n=1) or the need for tuberculosis treatment prior the HCV treatment (n=1), and an additional 17 (12.0%) declined to start treatment. Of those treated, 37.6% were treated at NSP sites and 63.4% at methadone clinics. The median age was 38 years (IQR: 31 to 44), 101 (84.9%) were men, and median duration of injection drug use was 7 years (IQR: 5 to 13). SVR12 testing was conducted on 109 (88.6%) clients, including 98 (94.2%) of 104 who completed treatment and 11 (57.9%) of 19 who did not complete treatment. Among all treated clients, achieving a documented SVR12 was significantly more likely among those treated at methadone clinics (80.8%) versus NSP sites (60.0%) (aRR=1.48; p=0.006). Longer travel time to reach the treatment site (21-30 minutes and >45 minutes) was associated with a lower likelihood of SVR12 compared to traveling ≤20 minutes (aRR=0.65, p=0.004, and aRR=0.66, p=0.027, respectively).

Conclusion: HCV treatment for PWID using a DOT model resulted in a high proportion achieving SVR12, with best outcomes among those treated at methadone clinics and those with shorter travel times to treatment sites. Future studies will explore barriers and facilitators of HCV treatment delivery at NSPs and methadone clinics.

602 HEPATOCELLULAR CARCINOMA SCREENING AMONG HIV/HBV-COINFECTED INDIVIDUALS IN ZAMBIA

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Background: Chronic hepatitis B virus (HBV) infection is the most common cause of hepatocellular carcinoma (HCC) in sub-Saharan Africa (SSA). Guidelines recommend 6-monthly abdominal ultrasound (AUS) screening for adults of African origin living with chronic HBV, but few screening programs exist in SSA. We evaluated the uptake and outcomes of HCC screening in a cohort of people

living with HIV and HBV on tenofovir-containing antiretroviral therapy (ART) in Lusaka, Zambia.

Methods: All participants were eligible for 6-monthly AUS, with results collected in a standardized format. A 4-phase CT scan was performed in participants with a liver lesion >1 cm. All patients had yearly liver stiffness measurements (Fibroscan 402®), HBV viral load, HBV serology, and alcohol consumption assessments using the Alcohol Use Disorders Identification Test-Consumption (AUDIT-C). We analyzed the uptake of AUS and described abnormalities seen.

Results: Of 303 eligible individuals, 281 (92.7%) had at least one AUS. Their median age was 34 years (interquartile range [IQR] 27-38), 115 (40.9%) were female, the median CD4 count at ART start was 233 cells/µl (IQR 93-338), and 98 (36.2%) had WHO clinical stage 3/4. At ART start, 132 (55.5%) participants had HBV DNA levels >2000 IU/mL, 133 (54.7%) elevated ALT levels and 94 (40.3%) were HBeAg-positive. Thirty-nine (15.4%) had significant liver fibrosis, 25 (9.8%) cirrhosis. Overall, 123 (46.2%) participants reported unhealthy alcohol use and 36 (12.8%) were overweight/obese. At the first AUS examination, 96 (34.2%) had hepatomegaly, and 30 (12.1%) periportal fibrosis compatible with schistosomiasis. Over a median follow-up of 49 months (IQR 24-71), the median number of AUS was 6.4 per person (IQR 3-10), or 1.7 per person-year (py, IQR 1-2). A liver lesion >1cm was seen in five (1.8%) participants at the first AUS and in 18 (6.4%) in the later AUS. Among these 23 participants, 14 underwent a confirmation 4-phase CT scan and 9 had a repeat AUS instead. Of 13 confirmed lesions, 8 were haemangiomas, 2 liver cysts, and 3 regenerative liver nodules. None of the liver lesions showed features of a HCC.

Conclusion: During the first four years of HCC screening, the uptake of 6-monthly AUS was satisfactory, and CT scan confirmation was done in two-thirds of participants with eligible lesions. Over 1,075 py, no incident cases of HCC were diagnosed. Future studies should examine the cost-effectiveness of HCC screening for people with HIV/HBV in the era of universal ART.

603 RISK BEHAVIOUR TRAJECTORIES AMONG PEOPLE TREATED FOR RECENT HCV INFECTION

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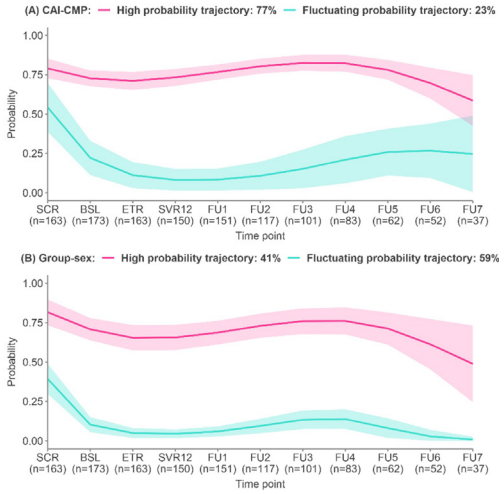
Background: There has been limited exploration of sexual and drug use behaviours following treatment for recent hepatitis C virus (HCV) infection (duration of infection < 12-months). This analysis modelled behavioural trajectories following treatment for recent HCV infection and assessed HCV reinfection and sexually transmitted infection (STI) incidence.

Methods: Participants treated for recent HCV in the Recently Acquired HCV Infection Trial (REACT) were followed at 3-monthly intervals for up to 2-years to assess longitudinal drug use and sexual behaviours. Population averaged behavioural changes were estimated using generalized estimating equations. Distinct behavioural trajectories within the population were identified using group-based trajectory modelling; this method models a variable of interest throughout time and identifies groups of individuals with similar behavioural profiles or patterns. HCV reinfection and STI rates were calculated using person-years (PY) of observation.

Results: During follow-up of 212 participants (median age 43 years; 96% male; 84% gay and bisexual men [GBM]; 69% HIV; 26% injecting drug use [IDU] in the past month), behavioural trajectories for IDU in the past month and stimulant use did not change. Population averaged decreases in the likelihood of daily IDU (adjusted odds ratio [AOR] 0.83; 95% CI 0.72, 0.95) and opioid use (AOR 0.84; 95% CI 0.75, 0.93) were observed. Among GBM, behavioural trajectories for chemsex (sexualised drug use) did not change; 41% had sustained high probability of chemsex throughout the study. Population averaged decreases in condomless anal intercourse with casual male partners (CAI-CMP; AOR 0.95; 95%CI 0.90, 0.99) and group-sex (AOR 0.86; 95%CI 0.80, 0.93) were observed, but masked distinct trajectories of behaviour. While a proportion of the population showed decreased probability of CAI-CMP and group-sex during treatment, a substantial proportion retained high probability of these behaviours (**Figure**). HCV reinfection incidence was highest for those with sustained high IDU (33.0/100 PY; 95%CI 17.7, 61.3) and chemsex behaviours (23.3/100 PY; 95%CI 14.5, 37.5). STI incidence was highest for those with sustained high group-sex behaviour (161.1/100 PY; 95%CI 136.4, 190.2).

Conclusion: Limited behavioural change was observed following treatment for recent HCV infection. Findings support regular reinfection surveillance and rapid access to retreatment.

Figure. Group based trajectory modelling of sexual behavioural outcomes among gay and bisexual men. Behavioural trajectories for (A) condomless anal intercourse with casual male partners, and (B) group-sex, during, and following treatment for recent HCV infection. The legend includes the proportion of the population assigned to each trajectory. Abbreviations: CAI-CMP, condomless anal intercourse with casual male partner; SCR, screening; BSL, baseline; ETR, end or treatment; SVR12, sustained virological response testing 12-weeks post treatment; FU, follow-up



604 BEHAVIORAL RISK FOLLOWING HCV TREATMENT AMONG MEN WHO HAVE SEX WITH MEN WITH HIV

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Background: With the introduction of direct-acting antivirals (DAAs), most individuals with hepatitis C virus (HCV) can be cured with well-tolerated regimens. Given more simplified treatments with higher cure rates compared to interferon (IFN)-based therapy, men who have sex with men (MSM) may be less prone to behavioral changes following HCV treatment.

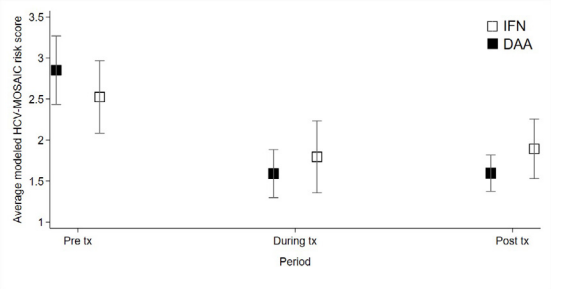
Methods: Data from the Dutch observational MOSAIC study between 2009 and 2017 were used. We included MSM with HIV aged ≥18 years who received any HCV treatment. We evaluated risk behavior through a validated HCV risk score (HCV-MOSAIC score=0-7) and individual risk behaviors included in this score (i.e., condomless receptive anal intercourse, sharing sex toys, sharing straws, unprotected fisting, injecting drug use (IDU) and ulcerative STI). Levels of risk behavior before, during and after HCV treatment were stratified by treatment type and modeled using linear/logistic regression with Generalized Estimating Equations. Changes in behavior post treatment were investigated in a separate model, while comparing treatment regimens.

Results: Of 143 study participants, 131 MSM were included with 157 infections. Median total follow-up was 29 months (IQR=10-54). Median age at first visit was 45 years (IQR=40-50); 78.6% were born in the Netherlands. For MSM treated with IFN-based treatment, the average risk score decreased from 2.9 (95%CI=2.4-3.3) pre-treatment to 1.6 (95%CI=1.3-1.9) during treatment and remained stable afterwards (1.6, 95%CI=1.4-1.8). For MSM treated with DAAs, the average risk score decreased from 2.5 (95%CI=2.1-2.9) pre-treatment to 1.8 (95%CI=1.3-2.2) during treatment and 1.9 (95%CI=1.5-2.2) post-treatment (Figure 1). There was no evidence of overall differences in risk scores between

treatment regimen across timepoints (p>0.05). For individual risk behaviors, the proportion of IDU differed significantly between treatment regimen across timepoints (p=0.03). There were no changes in risk scores or proportion of individuals engaging in individual risk behavior post treatment for either treated regimen (p >0.05)

Conclusion: In MSM with HIV-HCV, we found no difference in behavioral patterns, either from the HCV-MOSAIC score or for most individual behaviors, between IFN and DAA regimens. Nevertheless, a large proportion of individuals treated with DAAs are at risk of HCV reinfection (i.e., score ≥2.0) post-treatment, underscoring the need for ongoing HCV testing and behavioral interventions.

Average modeled HCV risk score pre-, during and post-treatment among MSM treated with IFN and DAAs



605 LONG-TERM LIVER EVENTS IN PATIENTS WITH HCV CHRONIC INFECTION AFTER SVR

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GEHEP-011
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Background: Despite achieving sustained viral response (SVR) with direct-acting antivirals (DAA), some individuals with HCV chronic infection remains at risk of developing liver complications. After SVR, there is a temporal pattern of appearance of liver complications depending on the type of event. Thus, ascites and hepatic encephalopathy (HE) usually present earlier after HCV cure. In contrast, hepatocellular carcinoma (HCC) and portal hypertensive gastrointestinal bleeding (PHGB) tend to manifest more continuously during follow-up. However, information on the long-term incidence and distribution of these liver events is limited.

Methods: Multicenter cohort study involving 17 hospitals in Spain. HCV-monoinfected and HIV/HCV-coinfected individuals from the GEHEP-011 cohort which inclusion criteria are: 1) Liver stiffness (LS) prior to treatment ≥ 9.5 kPa; 2) Achieved SVR with DAA-based therapy; 3) Available LS measurement at SVR. The main outcome was the appearance of a liver complication after SVR. Overall accumulated incidence of liver complications was estimated, so as by type of complication. The median time (Q1-Q3) to the emergence of a liver event was assessed.

Results: One thousand one hundred and eleven patients were included. Six hundred and sixty-seven (61%) individuals lived with HIV and 675 (61%) had compensated cirrhosis before treatment. After a median (Q1-Q3) follow-up time of 58 months (42-69), 69 (6.2%) patients developed hepatic events. The most frequent events were: 31 (2.8%) HCC, 21 (1.9%) ascites, 11 (1.0%) PHGB and 6 (0.5%) HE. The median (Q1-Q3) time to development of each event was: 31 (12 – 40) months for HCC, 16 (7 – 31) months for ascites, 25 (19 – 39) months for PHGB and 12 (9 – 40) months for HE. Two ascites events emerged 60 and 72 months after SVR. In these cases, patients reported a harmful alcohol intake during follow-up.

Conclusion: Liver complications continued to occur after long-term SVR, although the overall incidence is low. HCC remained the most frequent event. Three years after SVR, HCC and PHGB developed more frequently, while cases of ascites and EH emerged as a consequence of other toxic and/or metabolic causes. To identify patients who would benefit from long-term HCC and PHGB screening and thus design cost-effective surveillance programs for liver events is a high priority.

606 PREDICTION OF HEPATIC DECOMPENSATION AFTER SVR IN PATIENTS WITH HCV CHRONIC INFECTION

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GEHEP-011
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Background: In patients with HCV chronic infection, strategies based on liver stiffness (LS) identify patients at low risk of developing liver decompensation (LD) after SVR. Recently, it has been proposed that in individuals with compensated cirrhosis who have favorable Baveno VII criteria (HR < 12 KPa and platelet count >150,000 x10^6/mL) after SVR, portal hypertension (PHT)-related LD surveillance measures could be discontinued in the absence of other causes of liver disease. However, these criteria have not been validated in HCV/HIV coinfected individuals.

Methods: Multicenter prospective cohort study. Patients in the GEHEP-011 cohort who: 1) pre-treatment HR ≥14 KPa; 2) non-LD prior to SVR. We assessed the diagnostic accuracy of LS< 14 kPa and Baveno VII criteria (favorable status HR< 12 KPa and platelets >150,000/mL) at the time of SVR for predicting PHT-related LD. Non-predicted LD, negative predictive values (NPV) and the number of patients in whom screening for such LD (liver elastography and upper GI endoscopy) would be discontinued were specifically evaluated.

Results: Six hundred and eight patients were included, 374 (62%) were living with HIV. Twenty-seven (4.4%) individuals developed a LD after SVR: 14 (2.3%) hydropic decompensation, 8 (1.3%) gastrointestinal bleeding, 4 (0.7%) hepatic encephalopathy and 1 (0.2%) hepatorenal syndrome. The new Baveno VII criterion and LS< 14 KPa at the time of SVR achieved NPVs of 100% (96.5%-100%) and 100% (98.4%-100%), avoiding 17% and 38% of LD surveillance measures, respectively. Tacking into account HIV coinfection, the performance of the two criteria was similar. In HCV monoinfected patients, Baveno VII and RH< 14 KPa criteria maintained NPV at 100%. Among HIV/HCV-coinfected individuals, the NPV for these events were also 100% (94.0%-100%) and 100% (907.5%-100%) for Baveno VII and RH < 14 KPa, respectively. In both settings, their use resulted in 16% and 39% of LD surveillance measures being avoided.

Conclusion: Among HIV/HCV coinfected individuals, Baveno VII criterion also identifies patients at low risk of developing LD after SVR. The RH≤14 KPa criterion presents a better diagnostic performance than BAVENO VII, as it identifies a larger number of patients unlikely to develop LD. If this criterion were considered, LD surveillance measures could be spared in more than one third of cirrhotic patients with SVR, without failures in the prediction of these events.

607 LONG-TERM CHANGES IN LIVER STIFFNESS POST-SVR IN PATIENTS WITH HCV CHRONIC INFECTION

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Background: In patients with HCV chronic infection, the achievement of sustained viral response (SVR) is related to a marked reduction in liver stiffness (LS), which is associated with a decrease in the incidence of liver events. During HCV active infection, LS correlates with the severity of liver damage and adds prognostic information. After SVR, LS also identifies individuals with no risk of developing liver complications in the short term. However, Information on long-term changes in LS in this subset is scarce.
Methods: Multicenter ambispective cohort study (17 hospitals in Spain). HCV-monoinfected and HIV/HCV-coinfected individuals from the GEHEP-011 cohort [inclusion criteria: 1) LS prior to treatment≥9.5 kPa; 2) SVR with DAA-based therapy; 3) Available LS measurement at SVR]. LS was evaluated pre-treatment, at RVS and then annually until 60 months. The following LS categories were considered: ≤7.2 kPa; 7.3-9.4 kPa; 9.5-13.9 kPa; 14-20.9 kPa; and ≥ 21 kPa. LS normalization was defined as attaining LS values ≤ 7.2 kPa after SVR.
Results: 1116 patients were included. 677 (61%) lived with HIV. 675 (61%) had LS≥ 14 kPa prior to treatment, 422 (62%) HIV/HCV-coinfected and 253 (58%) HCV-monoinfected individuals (p=0.116). At SVR time-point, 468 (42%) patients showed LS≥ 14 kPa [HIV/HCV 289 (43%) vs. 179 (41%), p=0.527]. Median (Q1-Q3) LS at each time point was: pre-treatment 16.7 (11.8-26.6) kPa, SVR 11.9 (7.9-20.2) kPa, 12 months post-SVR 10.3 (7.0-17.1) kPa, 24 months post-SVR 9.4 (6.6-16, 4) kPa, 36 months post-RVS 9.7 (6.7-15.4) kPa, 48 months post-RVS 10.4 (7.0-16.5) and 60 months post-RVS 10.0 (7.0-16.8) kPa (p< 0.001). Median (Q1-Q3) time between first and last LS measurement was 29 (13-48) months. Taking into account the first and the last LS measurement, 789 (71%) individuals improved from 1 or more lower LS categories, in 288 (26%) there was no change, and 39 (3%) worsened. More specifically, 317 (27%) achieved LS normalization, 178 (26%) HIV/HCV-coinfected patients vs. 139 (32%) HCV-monoinfected individuals (p=0.052).
Conclusion: After SVR, LS decreases significantly. This reduction is quantitatively greater at the time of SVR and the following year. In a large majority of patients, this improvement also leads to a shift to lower LS categories. Specifically, more than a quarter of individuals achieved LS normalization during the follow-up. However, in one third of patients, LS does not change or even increases.

608 METABOLOMIC PROFILE ASSOCIATED WITH HVPG CHANGE AFTER DAAs IN HCV PTs WITH CIRRHOSIS

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*Presented at CROI by a nonauthor colleague

Background: Hepatic venous pressure gradient (HVPG) is currently the best available predictor of liver-related outcomes in cirrhotic patients. In response to direct-acting antivirals (DAAs) therapy, patients who experience a decrease in HVPG considerably reduce liver complications and higher survival. This study aimed to assess the metabolomic changes associated with the variation in HVPG from the start of DAA therapy until 48 weeks after effective DAAs therapy in patients with advanced HCV-related cirrhosis.
Methods: We performed a multicenter prospective study in 31 patients with advanced cirrhosis and clinically significant portal hypertension (HVPG≥10 mmHg) (8 HCV-monoinfected and 23 HIV/HCV-coinfected). Patients were assessed at baseline and 48 weeks after DAAs therapy completion. Metabolomics analysis was carried out by gas chromatography-mass spectrometry (GC-MS) and liquid chromatography-mass spectrometry (LC-MS). Inflammatory plasma biomarkers were analyzed by ProcartaPlex Immunoassays. The statistical analysis was performed by partial least squares discriminant analysis (PLS-DA) and generalized linear mixed-effects models, correcting for multiple testing.
Results: The PLS-DA analysis showed that the two sample sets, baseline and 48 weeks after DAA therapy, clearly separated according to the metabolomic profiles for GC-MS and LC-MS (permutation < 0.05). Thirty compounds in GC-MS and 64 in LC-MS had a VIP score ≥1. Of them, we found a direct association between the change in plasma levels of 2, 3-butanediol (AMR=1.15; p≤0.001; q=0.010), taurocholic acid (AMR=1.20; p≤0.001; q≤0.001) and N-gamma-glutamyl-S-allylcysteine (AMR=1.01; p=0.019; q=0.090) and the HVPG change. On the contrary, an indirect association was observed between the plasmatic levels of tartaric acid and the variation of HVPG (AMR=0.96; p=0.020; q=0.091). Finally, we found direct association between changes in taurocholic acid and inflammatory plasma biomarkers (IL6, IL8, IL1RA, IP10 and sICAM1).
Conclusion: Plasma metabolomic profile changed along with the HVPG from baseline to 48 weeks after completing DAAs therapy in patients with advanced HCV-related cirrhosis. Specifically, increased plasma levels of tartaric acid and decreased of 2,3-butanediol, taurocholic acid, and N-gamma-glutamyl-S-allylcysteine were associated with decreases in HVPG. In addition, the change in plasma taurocholic acid level was directly associated with inflammatory plasma biomarkers.

609 PREVALENCE AND FACTORS ASSOCIATED WITH NAFLD IN PEOPLE WITH HIV

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Background: Non-alcoholic fatty liver disease (NAFLD) in people living with HIV (PLHIV) may be more common than in the general population. Screening recommendations for NAFLD in PLHIV are based on guidelines for the general population, not considering HIV-specific factors contributing to NAFLD. In this study, we assessed the prevalence of liver steatosis and fibrosis in PLHIV and explored associations with demographic-, metabolic-, environmental-, and HIV-specific factors, including antiretroviral therapy (ART).
Methods: In the 2000HIV-study (clinicaltrials NTC03994835), 1895 virally suppressed PLHIV were included in 4 Dutch HIV treatment centers. Transient elastography was performed for the assessment of liver steatosis (controlled attenuation parameter, CAP) and fibrosis (liver stiffness measurement, LSM). Demographics, metabolic comorbidities, laboratory assessments including lipid profile and liver function tests, HIV-characteristics, and current and cumulative exposure to ART regimens, were tested in univariable (demographic factors) and multivariable (other factors) logistic regression models for association with steatosis and fibrosis.
Results: Data from 1075 PLHIV showed steatosis in 47.5% [95% CI: 44.4 – 50.6] and fibrosis in 8.8% [7.1 – 10.6]. Age (per decade, odds ratio (OR) 1.49, 95% CI [1.33-1.66], P-value < 0.001, and OR 1.12 [0.93-1.34], P-value = 0.356, respectively) and subcutaneous fat layer thickness (£ 25 mm^2 vs > 25 mm^2., OR 5.16 [3.90-6.83], P-value < 0.001, and OR 2.72 [1.69-4.39], P-value < 0.001, respectively) were significantly associated with steatosis or fibrosis and included in subsequent regression models as covariates. Traditional metabolic risk factors, e.g. diabetes mellitus type 2 (adjusted OR (aOR) 1.95 [1.02-3.71], P-value = 0.043, and aOR 3.29 [1.64-6.62], P-value = 0.001, respectively), were most strongly associated with both steatosis and fibrosis. In addition, steatosis was associated with current CD4+ and CD8+ T cell counts, cumulative exposure to integrase strand transfer inhibitors (INSTI) in general and raltegravir specifically, and to the nucleoside analogue stavudine.
Conclusion: Liver steatosis and fibrosis affect nearly one in two and one in ten PLHIV in this cohort, respectively. NAFLD was most strongly associated with traditional NAFLD risk factors. Of HIV-specific factors, only exposure to

stavudine, INSTI, and current CD4+ and CD8+ T cell counts were associated to steatosis.

610 LIVER STEATOSIS AND FIBROSIS IN WOMEN WITH HIV BY INTEGRASE INHIBITOR USE

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Background: Nonalcoholic fatty liver disease is prevalent in persons with HIV and can lead to hepatic fibrosis. Integrase strand-transfer inhibitors (INSTIs), first-line agents in antiretroviral therapy (ART), are associated with increased body mass index (BMI), particularly in women with HIV (WWH). We evaluated hepatic steatosis and fibrosis in WWH who did and did not switch to INSTIs.

Methods: We used clinical and FibroScan data collected between 2014-2018 in virally-suppressed WWH enrolled in the Liver Disease and Reproductive Aging substudy of the Women's Interagency HIV Study. WWH who switched to or added an INSTI to ART were included if they had clinical data and a FibroScan obtained post-switch and compared to women on non-INSTI ART (Control). Follow-up time was defined as time since switch visit (or comparable visit in Controls). Outcomes included differences between INSTI and Control group estimates of hepatic steatosis via controlled attenuation parameter (CAP≥248 dB/m), fibrosis via liver stiffness (LS≥7.1 kPa), and steatohepatitis with significant disease activity and fibrosis via FibroScan-aspartate aminotransferase scores (FAST ≥0.67). Adjusted regression and mixed-effects models compared each outcome by group.

Results: 257 WWH (123 INSTI, 134 Control) were included. Overall, mean age was 50 years (SD 8), 74% were Non-Hispanic Black, BMI was 32 (8) kg/m^2, CD4 count was 796 (305) cells/mm^3. WWH who switched to INSTIs had a 3.7 greater odds of having hepatic steatosis within 1 year compared to non-INSTI Controls (**Table 1**), but this difference was not seen at later periods of follow up. The model-adjusted difference between WWH switching to INSTIs vs Controls within 1 year was +1.62 KPa (95% CI 0.24, 2.99) for LS and +0.07 (0.01, 0.13) for FAST scores. However, there was little difference between groups in the odds of having fibrosis and only 4(1.6%) WWH had steatohepatitis by FAST score at any time-point.

Conclusion: WWH switching to INSTIs had a greater odds of having hepatic steatosis but not fibrosis within the 1st year of follow-up compared to women on non-INSTI ART, possibly reflecting early BMI gain with INSTIs. LS and FAST scores in WWH switching to INSTIs were minimally higher at 1 year, but the clinical significance is unclear. A larger study with longitudinal assessments of hepatic steatosis and fibrosis measures is warranted. Patients starting INSTIs need close monitoring of metabolic changes and low thresholds to pursue noninvasive liver fibrosis testing.

Adjusted model estimates of hepatic steatosis and fibrosis differences between groups

Table 1. Adjusted model estimates of hepatic steatosis and fibrosis differences between groups

	Continuous outcomes Quantitative Score			Categorical outcomes Odds Ratio	
Difference between INSTI and Controls at follow up time since switch visit (95% CI)	CAP, dB/m	LS, kPa	FAST	CAP ≥ 248 dB/m	LS ≥7.1 kPa
< 1 year	24.26 (-0.48, 49.00)	1.62 (0.24, 2.99)	0.07 (0.01, 0.13)	3.70 (1.22, 11.19)	1.56 (0.53, 4.57)
≥ 1 year to < 2 years	5.07 (-22.02, 32.16)	-0.14 (-1.68, 1.39)	0.01 (-0.06, 0.08)	1.56 (0.48, 5.03)	1.59 (0.55, 4.61)
≥ 2 years to < 6 years	17.78 (-7.40,42.95)	-0.42 (-1.88, 1.04)	-0.01 (-0.07, 0.05)	0.94 (0.33, 2.66)	1.31 (0.43, 3.97)

INSTI=integrase strand transfer inhibitor; CI=confidence interval; CAP=controlled attenuation parameter; LS=liver stiffness; FAST=FibroScan-aspartate aminotransferase score.
Mixed-effects models were created for continuous outcomes and logistic regression models for categorical outcomes; n=257 participants for LS models, n=253 for CAP models, and n=247 for FAST model. LS models were adjusted for age, CD4 lymphocyte percentage, and body mass index (BMI); CAP and FAST models were adjusted for age, CD4 lymphocyte percentage, BMI, tenofovir alafenamide use, tenofovir disoproxil fumarate use, and alcohol use. Categorical models for FAST were unable to be created due to low distribution of outcomes.

611 SEX DIFFERENCES IN THE ASSOCIATION OF HIV WITH METABOLIC-FATTY LIVER DISEASE

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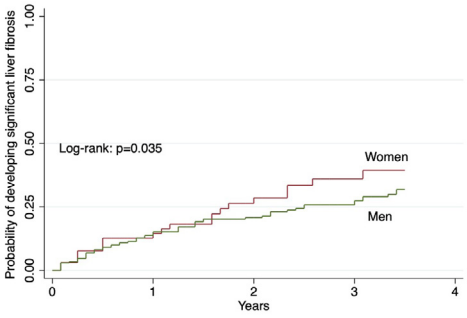
Background: People with HIV (PWH) are at high risk for metabolic-dysfunction associated fatty liver disease (MAFLD). In the general population, sex differences seem to exist in frequency and severity of MAFLD, with higher prevalence of MAFLD in men, but higher incidence of liver fibrosis in women. Less is known about sex differences in MAFLD and liver fibrosis in the setting of HIV infection.

Methods: This was a multicenter cohort study including consecutive PWH who underwent screening for MAFLD and liver fibrosis by liver stiffness measurement (LSM) with associated controlled attenuation parameter (CAP). MAFLD was defined as the presence of hepatic steatosis, diagnosed as CAP>270 dB/m, plus any among type 2 diabetes, overweight (BMI >25 Kg/m^2) or two other metabolic abnormalities. Significant liver fibrosis was diagnosed as LSM>8 kPa. Incidence of MAFLD and significant liver fibrosis was assessed through survival analysis.

Results: 1359 PWH (25% females, 70% HIV mono-infected) were included. Prevalence of MAFLD at baseline was lower in women than in men with HIV (17.7% vs. 24.3%, p=0.013). Conversely, there was no difference in prevalence of liver fibrosis (10.7% vs. 13.4%). Women with MAFLD were more frequently of black ethnicity (48% vs. 14%, p< 0.001), had lower ALT (26.4+20.4 vs. 33.4+22.5; p=0.035), higher HDL cholesterol (1.46+0.57 vs. 1.11+0.33; p< 0.001), lower triglycerides (1.69+0.96 vs. 2.47+2.63; p=0.035) compared to men with MAFLD. 485 of these PWH were followed for a median of 3.5 years. Incidence of MAFLD was similar between women and men with HIV. However, incidence of liver fibrosis was higher in women compared to men with HIV (7.0 per 100 person-years [PY] vs. 5.9 per 100 PY; p=0.035) (Figure 1). The higher incidence of significant liver fibrosis occurred particularly after the age of 50 years. On multivariable Cox regression analysis and after adjusting for age, presence of MAFLD (adjusted hazard ratio [aHR] 3.3, 95% CI 2.0-5.6) and female sex (aHR 2.2, 95% CI 1.3-3.5) were independent predictors of developing significant liver fibrosis while CD4 cell count was protective (aHR 0.99, 95% CI 0.99-0.99).

Conclusion: MAFLD seems a sexual dimorphic disease in PWH. Despite having lower rates of MAFLD, women with HIV have higher incidence of significant liver fibrosis compared to men, especially after 50 years of age. Future studies should target adequate consideration of sex differences in clinical investigation of MAFLD to fill current gaps and implement precision medicine for PWH.

Table 1 – Development of significant liver fibrosis by biological sex category.



612 NAFLD AND ITS COMBINATION WITH NASH PREDICT DM DEVELOPMENT IN PEOPLE WITH HIV

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Background: We investigated the association of non-alcoholic fatty liver disease (NAFLD) plus or minus a concurrent diagnosis of non-alcoholic steato-hepatitis (NASH) with incident diabetes mellitus (DM) among Thai people living with HIV (PLWH).

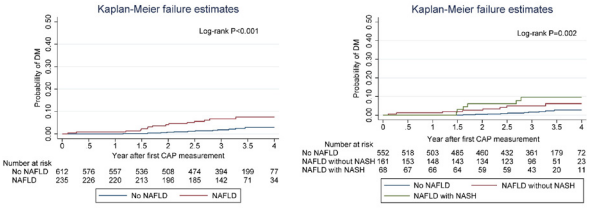
Methods: This prospective study analysed PLWH aged ≥18 years, on stable antiretroviral therapy (ART), in a long-term cohort in Bangkok, Thailand. Liver

stiffness (LS) and controlled attenuated parameter (CAP) values were collected from FibroScan. NAFLD was defined as CAP >248 dB/m, whereas NASH was defined as FibroScan-AST (FAST) score >0.67. Baseline was defined as the first FibroScan date. PLWH with hepatitis B or C virus infection, those with excessive alcohol consumption or with DM diagnosed prior to baseline were excluded. Cox proportional hazard models were used to investigate the association of NAFLD and NASH with incident DM. We also investigated the association of NAFLD with DM at baseline with incident NASH.

Results: Among 847 eligible PLWH, the median age at baseline was 46 (IQR 39-52) years (43% female). Median baseline CD4 was 588 (IQR 443-759) cells/mm^3 and 90% had HIV-1 RNA < 50 copies/mL. Median CAP value and FAST score was 215 (IQR 184-254) dB/m and 0.22 (IQR 0.12-0.43) respectively. 28% (235/847) and 15% (116/781) had NAFLD and NASH at baseline, respectively. During a median follow-up time of 3.3 (IQR 2.7-3.6) years, 28 developed DM (incidence rate=11.0 [95%CI 7.6-15.9] per 1000 person-years). Baseline NAFLD was associated with an increased risk of incident DM (hazard ratio[HR]: 2.8, 95%CI 1.3-6.4) after adjusting for age, sex, family history of DM, ART duration ART, and didanosine exposure, and time-updated BMI, hypertension and dyslipidemia. Combined NAFLD and NASH at baseline increased the risk of incident DM (HR: 3.1, 95%CI 1.1-9.3). **Figure 1A** and **1B** show the probability of incident DM stratified by NAFLD and NASH status at baseline. Baseline NASH alone showed a non-significant but elevated risk of incident DM (HR:1.8, 0.7-4.4). In a separate analysis including DM at baseline (but excluding NASH at baseline), NAFLD with DM at baseline was associated with incident NASH (HR: 2.5, 95%CI 1.1-6.0).

Conclusion: NAFLD alone or combined with NASH strongly predicts DM development in PLWH, highlighting the need for DM risk assessment and management in PLWH with NAFLD. Further mechanistic studies investigating the underlying metabolic associations of NAFLD or NASH and DM development in PLWH are warranted.

Figure 1A. Probability of DM development by baseline NAFLD status (N=847); Figure 1B. Probability of DM development by baseline NAFLD with NASH status among PLWH with FAST score (N=781)



613 AUTOMATED LIVER ATTENUATION ASSESSMENT FOR STEATOSIS IN CLINICAL IMAGES BY HIV STATUS

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Veterans Aging Cohort Study
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Background: The study of hepatic steatosis in HIV has been limited due to lack of direct diagnostic evaluations in real-world cohorts. Artificial intelligence offers tools to automate identification of hepatic steatosis within radiographic images for use in epidemiologic studies that examine associations with important risk factors and outcomes. We applied the Automatic Liver Attenuation Region-of-Interest-based Measurement (ALARM) deep learning tool for hepatic steatosis to persons with HIV (PWH) and people without HIV (PWoH) who underwent noncontrast abdominal computed tomography (CT) scans as part of routine clinical care.

Methods: We performed a cross-sectional study to evaluate the performance of ALARM within a sample of persons in the Veterans Aging Cohort Study, an electronic health record-based cohort of PWH and PWoH. We evaluated the ability of ALARM to identify moderate-to-severe hepatic steatosis, defined by mean absolute liver attenuation < 40 Hounsfield units (HU), compared to manual radiologist assessment

Results: Among 120 patients (51 PWH) who underwent noncontrast abdominal CT, moderate-to-severe hepatic steatosis was identified in 15 (12.5%) persons via ALARM and 12 (10%) by radiologist assessment. Overall, percent agreement between ALARM and radiologist assessment of absolute liver attenuation at the 40 HU threshold was 95.8% and Kappa was 0.79. Sensitivity, specificity, positive predictive value and negative predictive value of ALARM were 91.7%, 96.3%, 73.3%, and 99.0%, respectively. Among the five disagreements, absolute liver attenuation measurements were all near the 40 HU threshold, ranging between 36.6-41.8 HU and 39.0-44.3 HU for ALARM and radiologist assessment, respectively. No appreciable differences in performance were observed by HIV status with 96.1% and 95.7% percent agreement and Kappa of 0.84 and 0.75 for PWH and PWoH, respectively. Moderate-to-severe steatosis was identified in 8 (15.7%) PWH and 7 (10.1%) PWoH by ALARM and 6 (11.8%) PWH and 6 (8.7%) PWoH by radiologist assessment.

Conclusion: The ALARM deep learning tool demonstrated excellent accuracy for identification of moderate-to-severe hepatic steatosis within noncontrast abdominal CT scans, regardless of HIV status. Application of ALARM to large radiographic repositories could facilitate large-scale, real-world studies to define the risk factors and outcomes of hepatic steatosis by HIV status.

Table: Performance characteristics of the Automatic Liver Attenuation Region-Of-Interest-based Measurement (ALARM) for identification of moderate-to-severe hepatic steatosis in noncontrast abdominal computed tomography scans compared to radiologist review, by HIV status.

	Overall		PWH		PWoH	
	Radiologist Review		Radiologist Review		Radiologist Review	
ALARM	<40 HU	≥40 HU	<40 HU	≥40 HU	<40 HU	≥40 HU
<40 HU	11	4	6	2	5	2
≥40 HU	1	104	0	43	1	61
Sensitivity	91.7% (95% CI: 61.5-99.8%)		100% (95% CI: 91.8-100%)		83.3% (95% CI: 35.9-99.6%)	
Specificity	96.3% (95% CI: 90.8-99.0%)		95.5% (95% CI: 84.8-99.4%)		96.8% (95% CI: 89.0-99.6%)	
Positive Predictive Value	73.3% (95% CI: 44.9-92.2%)		75.0% (95% CI: 34.9-96.8%)		71.4% (95% CI: 29.0-96.3%)	
Negative Predictive Value	99.0% (95% CI: 94.8-100.0%)		100% (95% CI: 91.8-100%)		98.4% (95% CI: 91.3-99.9%)	

Abbreviations: CI, confidence interval; HU, Hounsfield units; PWH; people with HIV; PWoH; people without HIV

614 CONTROLLED ATTENUATION PARAMETER IS A VISCERAL ADIPOSITY MARKER IN HIV-RELATED NAFLD

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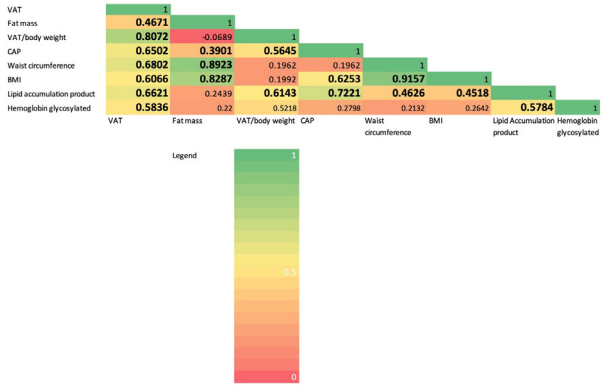
Background: Fat alterations are frequent in people with HIV (PWH) and predict worse cardiometabolic outcomes. Visceral adipose tissue (VAT) is a hormonally active tissue critically contributing to obesity-related disorders and associated with ectopic fat accumulation in the liver. We aimed to investigate HIV-associated nonalcoholic fatty liver disease (NAFLD) diagnosed by controlled attenuation parameter (CAP) as a marker of visceral adiposity.

Methods: We conducted a prospective pilot study (ClinicalTrials.gov NCT05359471) of HIV mono-infected patients undergoing metabolic characterization and paired CAP by transient elastography with dual-energy X-ray absorptiometry (DEXA) scan. NAFLD was defined as CAP ≥285 dB/m, in absence of alcohol abuse. Excess visceral adiposity was defined as VAT >1.32 Kg. Pairwise correlation, area under the curve (AUC) and logistic regression analysis were employed to study the association between VAT and CAP.

Results: 30 patients (90% male, mean age 49, mean BMI 30, mean waist circumference 101, 50% with NAFLD) were included. When compared to those without excess VAT, PWH with excess VAT were older, had longer duration of HIV infection, had higher BMI and waist circumference. They also had more history of cardiovascular events, higher triglycerides and LDL cholesterol. CAP was higher in PWH with excess VAT (319 vs. 213 dB/m, p< 0.001). CAP positively correlated with all visceral fat measurements by DEXA, including VAT (r=0.650, p< 0.001), VAT/body weight ratio (r=0.565, p=0.001) and fat mass (r=0.390, p=0.033). Both BMI and waist circumference showed correlation with VAT and fat mass, but not with VAT/body weight ratio (see Figure). After adjusting for duration of HIV infection (aOR 1.01 per year, 95% CI 0.91-1.12; p=0.921), BMI (aOR 1.77, 95% CI 0.74-4.23; p=0.202) and waist circumference (aOR 0.91 per cm, 95% 0.68-1.21; p=0.509), CAP remained the only independent predictor of excess VAT (aOR 1.05 per dB/m, 95% CI 1.01-1.10; p=0.036). The AUC analysis determined CAP had excellent performance to diagnose excess VAT (AUC 0.92, 95% CI 0.81-1.00), higher than BMI (AUC 0.83, 95% CI 0.68-0.99) and waist circumference (AUC 0.81, 95% CI 0.65-0.97). The optimized CAP cut-off to diagnose excess VAT was 266 dB/m, with a sensitivity of 88.3% and a specificity of 84.6%.

Conclusion: NAFLD diagnosed by CAP is associated with VAT in PWH independently of anthropometric measures of obesity. CAP could be used as a diagnostic marker of visceral adiposity in the practice of HIV medicine.

Correlation matrix with heatmap based on correlation coefficient analysis. Significant values (p<0.05) are bolded.



615 CAP AND METABOLIC PROFILE WORSENING POST-SVR IN HCV-HIV PEOPLE AS A SIGN OF STEATOSIS

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Background: The aim of this study is to investigate trajectories of controlled attenuation parameter (CAP), as indicator of steatosis, and of metabolic parameters after sustained virological response (SVR) post-DAAs in HIV/HCV people. We also explored the risk of developing diabetes mellitus (DM).

Methods: Observational study including HIV/HCV people, followed at San Raffaele Hospital, Italy, without diabetes, who achieved SVR. CAP data and those of metabolic parameters (weight, BMI, glucose, total (TC), HDL, LDL-cholesterol, triglycerides) were collected since DAAs start (baseline, BL) until the last available visit. Mean annual percent changes (trajectories) were estimated by uni- and multivariable linear mixed model with random intercept and slope for all the considered parameters in the overall sample and according to HCV genotype.

Results: Overall, 598 individuals included: at BL, median age 53 (IQR 49-56), 441 (74%) males, treated with ART since 18.3 (IQR 11-22) years, 49% on INSTI and 25% with TAF. The most common DAAs regimens were SOF/VEL (48%) and G/P (20%). HCV genotype (GT) were so distributed: GT1a (47%), GT3 (22%), GT4 (20%), GT1b (7%), GT2 (4%). BL and follow-up CAP values were available in 225 people while BL and follow-up (FU) metabolic parameters were available in 598 people. During a median FU of 3.3 (IQR 1.8-4.2) years (mean number of CAP values = 2.5, range 2-6), a significant increase of CAP was estimated in the overall sample (OS) and in GT4, GT1a, GT1b (Table 1). Overall, a significant increase was observed for TC, HDL, triglycerides, glucose, weight and BMI, while stiffness significantly decreased; different trajectories among HCV genotypes were found for LDL (p 0.041, Table 1). At multivariable analysis, dyslipidemia significantly influenced CAP trajectories (Yes: +2.6 (95%CI:1.2-3.9), p=0.0002; No: +3.3 (95%CI: 1.8-4.7), p< 0.0001) after adjustment for years of ART, HCV genotype, current ART type and TAF, current HIV-RNA, CD4 and BMI. During FU, 20/598 (3.3%) new diagnosis of DM were observed; 7 (3.1%) new DM diagnoses occurred among 225 people with CAP data. Median CAP trajectories among people who developed DM was 7.3 (IQR 4.9-11.2) vs 3.3 (IQR 0.06-5.8) among people without DM; CAP trajectories showed a marginal effect on the risk of DM (OR 1.08 (95%CI 0.97-1.18), p 0.095).

Conclusion: In HIV-HCV people, a significant worsening of CAP and metabolic profile was observed post SVR. We found a modest increase in risk of DM among people with a greater increase in CAP.

Mean annual percent changes (95% Confidential Interval) of CAP and metabolic parameters

Table 1: Mean annual percent changes (95% Confidence Interval) of CAP and metabolic parameters

Parameter	Overall	GT1a	GT1b	GT2	GT3	GT4	Pvalue difference between groups
Total Cholesterol	1.0180 (0.5629;1.4731) pvalue=< .0001 N=540	0.79 (0.12;1.46) pvalue=0.0203 N=253	1.46 (-0.13;3.05) pvalue=0.0728 N=40	0.59 (-1.67;2.86) pvalue=0.6085 N=21	1.9 (0.96;2.84) pvalue=< .0001 N=120	0.75 (-0.3;1.81) pvalue=0.1606 N=106	0.3533
LDL	-0.2604 (-1.341;0.8203) pvalue=0.6360 N=376	-1.5 (-3.04;0.03) pvalue=0.0547 N=181	0.86 (-1.35;4.06) pvalue=0.8503 N=25	-0.55 (-5.6;4.51) pvalue=0.8327 N=15	2.84 (0.59;5.1) pvalue=0.0136 N=86	0.47 (-2.16;3.1) pvalue=0.7252 N=69	0.0408
HDL	1.0004 (0.3938;1.6070) pvalue=0.0013 N=397	0.51 (-0.38;1.39) pvalue=0.2603 N=189	2.02 (0.03;4) pvalue=0.0467 N=28	1.75 (-1.22;4.73) pvalue=0.2482 N=15	1.9 (0.64;3.16) pvalue=0.0031 N=90	0.53 (-0.89;1.95) pvalue=0.4650 N=75	0.3076
Triglycerides	3.0519 (1.8669;4.2370) pvalue=< .0001 N=537	2.79 (1.03;4.54) pvalue=0.0019 N=250	4.87 (0.91;8.84) pvalue=0.0160 N=40	2.07 (-3.59;7.73) pvalue=0.4731 N=21	1.88 (-0.5;4.28) pvalue=0.1238 N=120	4.41 (1.63;7.19) pvalue=0.0019 N=106	0.5852
Weight	0.7883 (0.5895;0.9871) pvalue=< .0001 N=545	1.01 (0.72;1.29) pvalue=< .0001 N=255	0.73 (-0.01;1.47) pvalue=0.0529 N=39	0.09 (-0.83;1.02) pvalue=0.8414 N=22	0.43 (0.02;0.84) pvalue=0.0406 N=118	0.88 (0.42;1.33) pvalue=0.0002 N=111	0.1137
Stiffness	-4.2850 (-7.1623;-1.4077) pvalue=0.0036 N=287	-6.91 (-11.19;-2.62) pvalue=0.0017 N=126	-2.01 (-13.22;9.19) pvalue=0.7236 N=19	-2.25 (-15.49;11) pvalue=0.7384 N=10	0.67 (-5.09;6.42) pvalue=0.8197 N=70	-5.5 (-11.95;0.95) pvalue=0.0940 N=62	0.3203
BMI	0.8239 (0.6126;1.0353) pvalue=< .0001 N=541	1.02 (0.71;1.32) pvalue=< .0001 N=252	0.72 (-0.07;1.5) pvalue=0.0739 N=39	0.09 (-0.89;1.08) pvalue=0.8518 N=22	0.49 (0.05;0.93) pvalue=0.0280 N=117	0.97 (0.48;1.45) pvalue=< .0001 N=111	0.1816
Glucose	3.4023 (3.0413;3.7632) pvalue=< .0001 N=574	3.36 (2.83;3.88) pvalue=< .0001 N=268	4.14 (2.92;5.36) pvalue=< .0001 N=42	1.38 (0.35;3.10) pvalue=0.1181 N=23	3.43 (2.69;4.18) pvalue=< .0001 N=126	3.62 (2.77;4.48) pvalue=< .0001 N=115	0.1381
CAP	2.8606 (1.7580;3.9632) pvalue=< .0001 N=725	2.15 (0.52;3.77) pvalue=0.0101 N=100	5.27 (0.62;9.92) pvalue=0.0265 N=12	1.49 (-3.54;6.52) pvalue=0.5576 N=7	1.84 (-0.8;4) pvalue=0.0956 N=53	5.22 (2.85;7.59) pvalue=< .0001 N=53	0.1509

616 PERFORMANCE OF SEROLOGICAL SCORES FOR LIVER STEATOSIS AMONG PEOPLE LIVING WITH HIV

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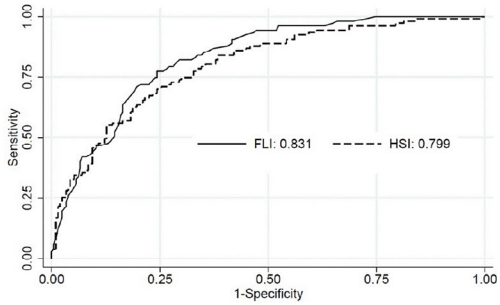
Background: Simple serological scores, such as the hepatic steatosis index (HSI) and fatty liver index (FLI), have been proposed for the detection of liver steatosis, but their prognostic value in people living with HIV (PLWH) remains ill-defined. We assessed their diagnostic performance in patients on antiretroviral therapy (ART) in the Swiss HIV Cohort Study (SHCS).

Methods: We included consecutive participants at Bern University Hospital with available transient elastography (TE) and parameters for the calculation of both scores between November 2019 and August 2021. Individuals with active or past viral hepatitis co-infection and pregnant women were excluded. We defined severe hepatic steatosis (S3) as controlled attenuation parameter (CAP) ≥280dB/m using TE. HSI (gender, BMI, AST, ALT and diabetes) and FLI (waist circumference, BMI, triglycerides and GGT) were calculated and validated diagnostic thresholds for steatosis were considered (HSI ≥36 and FLI ≥60). We calculated sensitivity, specificity and the area under the receiver operating curve (AUROC) of both biomarkers for diagnosing severe liver steatosis.

Results: Of 418 eligible individuals, 321 (76.8%) had measured biomarkers and a reliable TE measurement. Their median age was 51.4 years (interquartile range [IQR] 42-59), their median CD4+ count 757 cells/µl (IQR 546-933), 91 (28.4%) were female, 230 (71.7%) Caucasian, and 164 (51.1%) overweight (BMI ≥25kg/m^2). At time of TE, participants had been on ART for a median of 12.3 (IQR 6-19) years, 225 (70.1%) had been exposed to integrase strand inhibitors (InSTI) and 184 (57.3%) to tenofovir alafenamide (TAF). Overall, 107 (33.3%) participants had severe steatosis based on TE, 128 (39.9%) had a HSI ≥36 and 125 (38.9%) FLI ≥60. The AUROC for severe steatosis was 0.80 (95% confidence interval [CI] 0.75-0.85) using HSI, and 0.83 (95% CI 0.79-0.88) with FLI. HSI and FLI showed similar sensitivity (HSI: 70.1 vs. FLI: 72.0%) and specificity (HSI: 75.2 vs. FLI: 77.6) to detect severe steatosis in the whole study population. AUROC was highest for the diagnosis of severe steatosis among patients < 50 years (HSI: 0.86, 95% CI 0.79-0.93; FLI: 0.88, 95% CI 0.82-0.94), and lower for those ≥50 years (HSI: 0.79, 95% CI 0.72-0.85; FLI: 0.79, 95%CI 0.73-0.86).

Conclusion: HSI and FLI can be used as simple diagnostic tools to detect liver steatosis in PLWH, with a higher accuracy in patients aged < 50 years.

Figure. 1 Receiver operator characteristic (ROC) curve for Fatty Liver Index (FLI, solid line) and Hepatic Steatosis Index (HSI, dashed line) for the detection of severe liver steatosis (S3) in the whole study population. Numbers represent the area under the curve (AUC) measures for steatosis classification.



617 RISK FACTORS FOR LIVER FIBROSIS PROGRESSION IN HIV: A MULTI-CENTER LONGITUDINAL STUDY

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Background: People with HIV (PWH) are at high risk for metabolic dysfunction-associated fatty liver disease (MAFLD). Liver fibrosis (LF) is the most significant predictor of liver disease progression and mortality. We aimed to investigate the effect of MAFLD and antiretroviral exposure on LF progression in PWH.

Methods: This was a longitudinal study of three large prospective cohorts of PWH in Italy, Germany and Canada. Patients with at least two transient elastography with controlled attenuation parameters (CAP) exams were included. LF progression was defined as development of significant LF (defined as liver stiffness >8 kPa), or transition to cirrhosis (defined as liver stiffness >13 kPa for those with liver stiffness >8 but < 13 kPa at baseline). MAFLD was defined according to Eslam criteria: presence of hepatic steatosis (CAP>248 dB/m), plus any among type 2 diabetes, overweight (BMI >25 Kg/m^2) or two other metabolic abnormalities. Other longitudinal predictors included co-infection with HBV or HCV, weight gain (WG), defined as a 5% BMI increase in two consecutive visits, and current exposure to ART classes. A multi-state Markov model was used to describe the process in which PWH moved through the next LF state. Cox regression model was used to identify predictors for LF progression event.

Results: A total of 1183 PWH were included (median age 52.9 years, 77% males, median duration since HIV diagnosis 18 years). Prevalence of MAFLD was 46.8%. Coinfections with HBV and HCV were present in 3.6% and 21%, respectively. At baseline, liver stiffness was < 8 kPa in 85.6%, 8-12.9 kPa in 8.6%, and >13 kPa in 5.7% of PWH. During a median follow-up period of 2.5 years, a minimum of two and maximum of six yearly LF assessments were performed.

In Markov model, WG was positively associated with progression of LF (OR=3.107, 95% CI 1.588, 6.078) while it prevented LF regression (OR=0.304, 95% CI 0.037, 2.514).

The incidence rate of LF progression was 3.4 per 100 persons-year. Comparing 128 (9,6%) LF progressors with 1212 (90,4%) of non LF progressors, significant differences included mean BMI (26.3 vs 24.5), duration of HIV (16.7 vs 18.6 yrs), MAFLD (66.7 vs 48.3), HBV co-infection (7.8 vs 3.5%), ALT (36 vs. 25 UI) and WG (32.4 vs 21.9%). On multivariable analysis, predictors of LF progression were WG and MAFLD (see Table).

Conclusion: LF progression occurs in a significant proportion of PWH. Its main drivers include metabolic health variables, while ART exposure does not seem to impact LF progression.

Cox regression analysis of the liver fibrosis progression

	Cox regression analysis of the liver fibrosis progression		
Predictors	***Estimates***	***CI***	***p***
Current exposure to INSTI	1.47	0.61 – 3.52	0.389
Current exposure to TAF	0.85	0.39 – 1.87	0.683
Current exposure to NNRTI	0.83	0.32 – 2.18	0.704
Current exposure to PI	1.53	0.64 – 3.63	0.340
Male sex	1.08	0.43 – 2.71	0.863
Age at baseline	0.99	0.95 – 1.04	0.690
Nadir CD4 <200	0.56	0.27 – 1.17	0.120
Years since HIV diagnosis	1.05	1.00 – 1.10	0.064
Chronic hepatitis B virus infection	2.08	0.56 – 7.69	0.272
Chronic hepatitis C virus infection	1.08	0.45 – 2.57	0.868
MAFLD	2.50	1.06 – 5.89	**0.036**
BMI gain > 5%	2.64	1.32 – 5.26	**0.006**

618 INCIDENCE OF NON-HEPATIC CANCERS IN HBV, HCV, AND HBV/HCV COINFECTED PERSONS

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ERCHIVES (Electronically Retrieved Cohort of HCV Infected Veterans)

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Background: Viral hepatitis B and C (HBV, HCV) are among the leading causes of hepatocellular carcinoma (HCC) worldwide. Emerging data suggest that they may also be associated with hepatic and non-hepatic cancers. Co-infection may confer a higher risk than monoinfection with either virus. We sought to determine the incidence rate of Intrahepatic Cholangiocarcinoma (IHC), Non-Hodgkins lymphoma (NHL), Pancreatic cancer (PC), Colo-rectal cancer (CRC), and Gastric cancer (GC) among Veterans with these infections in ERCHIVES, a national cohort of HCV infected Veterans and matched HCV-uninfected controls.

Methods: Among the participants of ERCHIVES, we first identified Veterans with HBV and HCV monoinfection and HBV/HCV coinfection. We excluded those with a history of any of cancer of interest, those with missing data to calculate FIB-4 score, and those with HIV coinfection. We then propensity-score matched each HBV infected person with an HCV and a HBV/HCV coinfected person (1:1:1 matching). We calculated the incidence rate per 1,000 person-years of follow-up for IHC, NHL, PC, CRC, and GC overall, and stratified by presence of cirrhosis at baseline. Cancer diagnoses were based on presence of respective ICD-9/ICD-10 (clinical modification) codes.

Results: Among 818,318 participants of ERCHIVES, we identified 1,525 HBV monoinfected, 181,620 HCV monoinfected, and 1,380 HBV/HCV coinfected persons. The final propensity-score matched dataset included 990 HBV monoinfected, 1,374 HCV monoinfected, and 1,375 HBV/HCV coinfected persons. The incidence rates per 100-persons years were numerically highest for the cancers of interest among HBV monoinfected persons. However, the rates were not statistically significantly different among any of the comparison groups except for a higher incidence of PC among HBV monoinfected compared with HCV monoinfected persons.

Conclusion: HBV infection is associated with a numerically higher incidence rates for IHC, NHL, PC, CRC, and GC. However, among the demographically and clinically matched HBV, HCV, and HBV/HCV coinfected persons, the rates are not statistically significantly different except higher PC rate HBV compared with HCV monoinfected persons.

Table. Incidence rate per 1,000 person-years of follow-up of selected cancers by infection status.

Table. Incidence rate per 1,000 person-years of follow-up of selected cancers by infection status.

	INCIDENCE RATE PER 1,000 PERSON-YEARS (95% CI)			P-VALUE		
	HBV only (Group A; N=990)	HCV Only (Group B; N=1,374)	HBV/HCV (Group C; N=1,375)	A vs. B	A vs. C	B vs. C
Intrahepatic Cholangiocarcinoma	0.267 (0.086,0.826)	0.205 (0.066,0.635)	0.14 (0.035,0.559)	0.747	0.480	0.676
Non-Hodgkins lymphoma	1.244 (0.737,2.1)	0.614 (0.32,1.181)	0.699 (0.376,1.299)	0.099	0.164	0.778
Pancreatic cancer	0.977 (0.541,1.765)	0.205 (0.066,0.635)	0.489 (0.233,1.026)	0.016	0.152	0.207
Colo-rectal cancer	1.333 (0.803,2.21)	1.092 (0.669,1.783)	0.699 (0.376,1.299)	0.580	0.114	0.268
Gastric cancer	0.178 (0.044,0.71)	0.341 (0.142,0.82)	0.14 (0.035,0.559)	0.435	0.811	0.286

619 CONTRIBUTION OF ALCOHOL USE IN HIV/HCV CO-INFECTION TO ALL-CAUSE MORTALITY

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Antiretroviral Therapy Cohort Collaboration (ART-CC)

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Background: Among persons with HIV (PWH), both alcohol use and having hepatitis C virus (HCV) are separately associated with increased morbidity and mortality. We aimed to investigate whether the association between alcohol use and mortality among PWH is modified by having HCV.

Methods: Data were combined from European and North American cohorts contributing to the Antiretroviral Therapy Cohort Collaboration (ART-CC) of adult PWH who started antiretroviral therapy (ART) between 2001-2017. Baseline was date of ART initiation and PWH were followed for mortality. Self-reported current alcohol use data, collected in diverse ways between cohorts, were harmonised to give a value of grams alcohol/day. HCV antibody and/

or HCV RNA tests when available were used to define HCV status at baseline. Effect modification by baseline alcohol use (0, 0.1-20.0, >20.0 grams/day) and HCV status was assessed using interaction terms in multivariable Cox models, adjusted for ART start year category, HIV acquisition group, gender, prior AIDS status, age, CD4 count cells/μL, and log HIV-1 RNA copies/mL.

Results: Of 58,769 PWH, 21% were women and the median age at ART initiation was 40 years (interquartile range: 32-49). 29,711 (51%) self-reported alcohol use of 0g/day, 23,974 (41%) 0.1-20.0g/day, and 5,084 (9%) >20.0g/day, and 4,799 (8%) had HCV at baseline. The mortality rate per 1000 person-years was higher among PWH with HCV (21.6) than without HCV (6.2). Among PWH without HCV, there was a J-shaped relationship between mortality and alcohol use with adjusted hazard ratios (aHRs) of 1.21 (95%CI: 1.11-1.32) for 0.0g/day and 1.87 (1.65-2.12) for >20.0g/day compared with 0.1-20.0g/day (see table). The J-shaped pattern was not seen for those with HCV (interaction p-value< 0.001), with aHRs 0.99 (0.85-1.15) for 0.0g/day and 1.71 (1.39-2.10) for >20.0g/day compared with 0.1-20.0g/day.

Conclusion: Among PWH without HCV, mortality was higher in both persons who reported not drinking and persons who reported drinking heavily compared with persons who reported drinking moderately. Among PWH with HCV, mortality was higher only in persons who reported drinking heavily, potentially due to differing reasons for not drinking between PWH with and without HCV (e.g. illness).

Adjusted mortality hazard ratios (with 95% confidence intervals) for alcohol use categories, stratified by HCV RNA status.

	All patients		HCV negative		HCV positive	
Alcohol use (grams per day)	n (deaths)	HR (95% CI)	n (deaths)	HR (95% CI)	n (deaths)	HR (95%CI)
Adjusted						
0.0g	29711 (1789)	1.19 (1.11-1.29)	27202 (1356)	1.21 (1.11-1.32)	2509 (433)	0.99 (0.85-1.15)
0.1-20.0g	23974 (1302)	1	22336 (1003)	1	1638 (299)	1
>20.0g	5084 (508)	1.92 (1.72-2.14)	4432 (364)	1.87 (1.65-2.12)	652 (144)	1.71 (1.39-2.10)

620 SYNDEMIC OF CHRONIC VIRAL INFECTIONS ON THE RISK OF END-STAGE RENAL DISEASE

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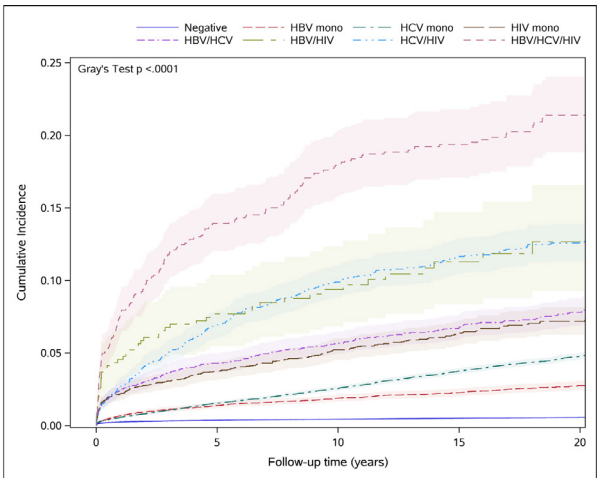
Background: Thanks to modern HIV therapy, people living with HIV now have a far longer lifespan; however, people aging with HIV are more likely to develop chronic diseases. Syndemic of viral infections is also associated with increased risk of end-stage renal disease (ESRD). Additionally, hypertension and diabetes are important risk factors for ESRD. We assessed the impact of HBV, HCV and HIV mono-, co- and triple infections on incident ESRD, in people with and without hypertension or diabetes.

Methods: All people who were tested in British Columbia (BC) between 1990 and 2015 for HBV, HCV, and HIV are included in the BC Hepatitis Testers Cohort and linked to administrative health databases. Individuals tested for all three infections were followed from the date of their last test until 1) incident ESRD 2) death or 3) 2021/03/31. We adjusted for sex, birth year, ethnicity, material/social deprivation, alcohol use, drug dependence, major mental illness, opioid agonist therapy and injection drug use, and estimated subdistributional hazard ratios (sHRs) for incident ESRD with Fine-Gray competing risk models. The impact of infections on ESRD by baseline hypertension or diabetes status was examined.

Results: The study included 690,873 people after excluding those with prevalent ESRD. There were 5,552 incident ESRD (0.8%) and 49,752 deaths (7.2%) during a median follow-up of 6.3 years. The highest ESRD incidence rate (per 1,000 person-years) was in persons with triple HBV/HCV/HIV infection (23.23), followed by HBV/HIV (11.39), HCV/HIV (10.32), HBV/HCV (5.8) coinfections, and HIV (4.75), HCV (2.83) and HBV (1.58) monoinfections. In multivariable analysis, compared to those with no infection, people with triple infection had the greatest ESRD risk (asHR 16.9, 95%CI 14.4-19.9). In people with no baseline diabetes or hypertension, those with triple infection had the highest asHRs for ESRD (22.5, 95%CI 19.0-26.5, and 30.5, 95%CI 25.6-36.3, respectively). Among those with diabetes or hypertension, people with HBV/HIV coinfection had the highest asHRs (39.9, 95%CI 20.8-76.9, and 41.3, 95%CI 22.9-74.5, respectively), though 95% CIs overlapped with asHRs for those with triple infection (27.7, 95%CI 16.1-47.9, and 36.8, 95%CI 23.9-56.6, respectively).

Conclusion: Syndemic of HBV, HCV and HIV infections and chronic comorbidities significantly increased the risk of ESRD. Prevention and surveillance for ESRD is crucial for the aging population with viral infections, especially among those with hypertension or diabetes.

Figure: Cumulative incidence curves of incident ESRD among individuals with viral infections; table shows ESRD incidence rates per 1,000 person-years (95% confidence interval)



Negative	HBV mono	HCV mono	HIV mono	HBV/HCV	HBV/HIV	HCV/HIV	HBV/HCV/HIV
0.55 (0.53-0.57)	1.58 (1.42-1.76)	2.83 (2.7-2.97)	4.75 (4.18-5.41)	5.8 (5.14-6.54)	11.39 (8.59-15.12)	10.32 (9.28-11.47)	23.23 (20.4-26.46)

621 LIVER NEUTROPHILS EXPRESS STRONGER PD-L1 SIGNALING IN HIV/HBV COMPARED TO HBV ALONE

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Background: HIV coinfection accelerates the natural history of hepatitis B infection (HBV); however, precise mechanisms for this are not fully understood, in part because the site of infection – the liver – is difficult to access. Further, patients with HIV/HBV coinfection may experience robust anti-HBV immune responses when starting antiretroviral therapy. In Zambia, where HIV/HBV coinfection is common, we established capacity for liver fine needle aspiration (FNA), a less invasive approach than core biopsy, which is more acceptable to patients for longitudinal sampling. Our aim is to understand how immune cells are modulated in the setting of HIV/HBV coinfection and mechanisms for HBV functional cure in coinfection.

Methods: Treatment-naïve adults with either HIV/HBV coinfection or treatment-eligible chronic HBV monoinfection were enrolled and underwent liver FNA at University Teaching Hospital in Lusaka. Liver cells were captured and analyzed using the HIVE single cell RNA sequencing approach (Honeycomb Biotechnologies). This analysis included liver FNAs from 12 patients (6 each) with HBV monoinfection and HIV/HBV coinfection.

Results: The median age of analyzed patients was 31 years (range: 20-45) and 4 were female (2 in each group). Coinfected patients had median peripheral CD4 count of 225 cells/mm^3 (range: 69-999). Across the patients, transcriptome profiling of a total of 8,785 immune cells from FNA samples showed significant differences in gene expression by HIV status across a range of immune cell types. HIV/HBV coinfection was associated with increased expression of interferon-stimulated genes (ISG). Notably, neutrophils captured in the sample overexpressed PD-L1 compared to other immune cells, and this correlated with increased expression of PD-1 in CD8+ T cells. Clustering of neutrophils revealed 3 subclusters, including one that strongly expressed both PD-L1 and ISGs. In HIV/HBV coinfection, neutrophil PD-1/PD-L1 signaling was significantly stronger compared to HBV monoinfection.

Conclusion: These data support neutrophil participation in the exhaustion and suppression of antiviral immune responses, a phenotype that is exacerbated in the setting of chronic HIV/HBV coinfection. This could represent a potential mechanism for T cell exhaustion and increased HBV chronicity in persons living with HIV.

622 YAP-MEDIATED HEPATOCYTE DAMAGE CONTRIBUTES TO LIVER FIBROSIS WITH HIV-RELATED INJURY

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*Presented at CROI by a nonauthor colleague

Background: HIV infection is known to accelerate the progression of liver fibrosis. In addition, Yes-associated protein (YAP) is a key regulator of cell proliferation and organ size. Recent work has shown that both the YAP and PI3K/AKT pathways are critical to hepatic fibrogenesis. Lysophosphatidic acid (LPA) and LPAR1 is involved in the fibrotic pathogenesis of hepatocellular carcinoma. However, their contribution to these processes during and after HIV-induced liver injury has not been fully explored. In this study, we sought to determine the role of YAP in modulating liver injury and recovery in the context of HIV infection.
Methods: We utilized liver specimens derived from an HIV-infected humanized murine model with and without antiretroviral therapy (ART). Further, a spheroid system and other coculture techniques allowed for further analysis of liver cell lines, primary human hepatocytes (pHHs), and primary hepatic stellate cells (pHSCs) exposed to HIV. Serum samples from HIV patients before and after antiretroviral treatment (ART) were also analyzed via ELISA.
Results: The YAP pathway components CYR61 and CTGF were increased within the livers of a humanized mouse model which demonstrated histologically worsened fibrosis after HIV infection. ART was effective partially abrogating these effects. *In vitro* analysis confirmed that YAP-related and profibrotic genes were upregulated within pHSCs and Huh7 cells exposed to HIV. An HIV-activated profibrotic program was dependent on hepatocyte-derived YAP within both Huh7s and pHSCs. Treatment of Huh7s and HSCs with verteporfin significantly abrogated the effects of HIV on both cell types. Moreover, when multiple HIV proteins were used as exposure agents among Huh7 cells, only GP120 was found to be responsible for activating this profibrotic program. Additionally, serum samples from treatment-naïve patients were analyzed via ELISA and demonstrated elevated levels of circulating YAP-related proteins in the context of HIV infection compared to uninfected controls. This elevation, while diminished, persisted even after 6 months of ART. Lastly, experiments utilizing siRNAs, overexpression of LPAR1, and small molecule inhibitors implicated PI3K and AKT as critical contributors to a profibrotic mechanism linking HIV infection to YAP activation.
Conclusion: This work suggests that HIV-related liver fibrosis and repair depends on hepatocyte injury and hepatic stellate cell activation via the YAP/LPAR/PI3K/AKT pathway.

623 CHRONIC LIVER IMFLAMMATION AND USE OF CONTEMPORARY ART AMONG PERSONS LIVING WITH HIV

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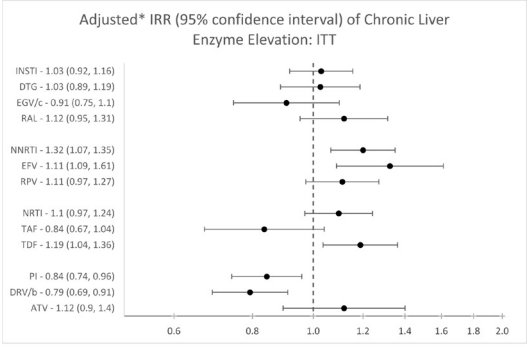
Background: Whilst use of some older antiretroviral drugs (ARVs) are associated with chronic liver enzyme elevation (cLEE), the impact of newer ARVs remain unknown.
Methods: Using RESPOND data, we included individuals who started an ARV to which they had not been previously exposed after the 2012 study baseline. ARVs considered were INSTIs: DTG, EVG/c, RAL, BIC; NNRTIs: RVP and EFV; NRTIs: TAF and TDF; PIs: DRV/b, ATV (see figure for abbreviations). Eligible Individuals had an HIV-RNA, CD4, and all alanine transaminase (ALT) measurements normal one year before baseline. The primary outcome was first cLEE: ALT elevations > than the upper limit of normal (males >50 IU/L; females >35 IU/L) at ≥2 visits over ≥6 months and < 2 years. In an intention to treat analysis (ITT), all were censored at cLEE, last visit, death or Dec 31 2020. Incidence rates (IR) (events/1000 person-years) were calculated for each ARV overall and by ARV exposure (6-12 months, 1-2 years, and 2+ years) to investigate cumulative effects. Poisson regression was used to estimate the incidence rate ratio (IRR) of cLEE and its association with individual ARVs and ARV class.
Results: Of 14,481 individuals included contributing 59,798 person years of follow-up, 1427 experienced cLEE [IR (95%CI) = 23.8 (22.7,22.1)]. Overall at baseline, 32% were ART naïve, 76% male, median (IQR) age was 47 (38,55), ALT was 23 (18, 30), CD4 was 541 (358,744) cells, 63% were virally suppressed, and 15% +HCV, 4% +HBV. Median (IQR) follow-up time was 4.1(2.3,5.8) years. There was no evidence of a cumulative ARV effect on cLEE incidence. cLEE was highest in the first 6-12 months post new ARV and declined thereafter; IR = 49.2 (44.3, 54.8) 6-12 months, 34.6 (31.5, 38.1) 1-2 years, and 23.9 (22.7, 25.1) 2+ years. Any use (vs. no prior use) of EFV and TDF were independently associated with an increased IRR of cLEE, and DRV was associated with a decreased risk of cLEE, Figure. INSTI were not associated with cLEE, Figure.
Conclusion: This is the first large study systematically looking at contemporary ARVs and cLEE. cLEE is not uncommon and more frequent during the first year after initiating new ARVs. With 4 years median follow-up, we found no short term liver safety concerns with the use of INSTIs. Use of EFV and TDF are associated with an increased cLEE risk, while TAF and DRV are associated with lower risks, although TAF not statistically significant.
Adjusted' IRR (95% confidence interval) of Chronic Liver Enzyme Elevation: ITT



The reference group for each model is no previous exposure to that drug. BIC, any ATV, and doravirine did not have enough events/follow-up to analyze individually. All models adjusted for viral hepatitis status, nadir CD4 at baseline (<350, 350-500, ≥500 cells/mm^3), HIV-RNA at baseline (<200, ≥ 200 copies/ml) , HIV transmission risk group (men who have sex with men, injection drug use, heterosexual, other, unknown), region of care (Western, Southern, Northern, Eastern Europe), dyslipidemia (random total cholesterol more than 240 mg/dl, HDL less than 35 mg/dl, triglyceride more than 200 mg/dl, or initiation of lipid-lowering therapy), diabetes mellitus, and BMI (<25, ≥25, missing). ARV Abbreviations: INSTI - Integrase strand transfer inhibitors; DTG – Dolutegravir; EGV/c – Elvitegravir; RAL – Raltegravir; BIC - Bictegravir; NNRTI - Non-nucleoside reverse transcriptase inhibitors; EFV – Efavirenz; RPV – Rilpivirine; NRTI - Nucleoside reverse transcriptase inhibitors; TAF – Tenofovir; TDF - Tenofovir disoproxil fumarate; PI - Protease inhibitors; DRV/b – Darunavir; ATV – Atazanavir.

624 COVID-19 OUTCOME IN PATIENTS WITH AND WITHOUT CIRRHOSIS

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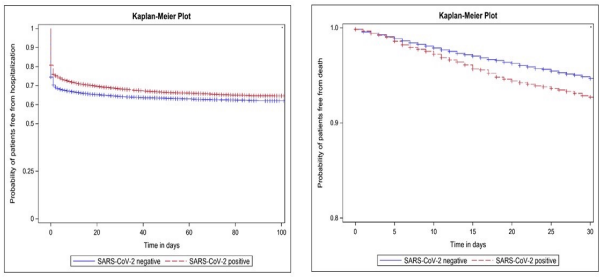
Background: Severe outcomes of COVID-19 are associated with advancing age, and multiple medical comorbidities. The impact of COVID-19 on the clinical course of patients with cirrhosis has not been well studied. We determined the effect of SARS-CoV-2 infection on the hospitalization and survival rates of patients with cirrhosis.
Methods: Using ICD-10-CM codes, we identified all Veterans with a diagnosis of cirrhosis in the VA Corporate Data Warehouse and COVID-19 Shared Data Resource. Study cohort included Veterans who were tested for SARS-CoV-2 and had no history of organ transplantation or malignancies. Each SARS-CoV-2 positive case was propensity-score matched by demographics and comorbidities with up to two SARS-CoV-2 negative controls. The primary endpoints were acute care hospitalization, admission to intensive care, respiratory support, or death.
Results: Of 1,115,037 individuals tested for SARS-CoV-2, 31,680 were noted to have cirrhosis and among them 5,047 (16%) were SARS-CoV-2 positive. After exclusions and propensity-score matching, 5,047 SARS-CoV-2 positive and 9,913 propensity score matched SARS-CoV-2 negative individuals were included in the analysis cohort. Median age was 67 years, 95% were men and 25% were of black race. Median BMI was 30 and history of hypertension, diabetes, cardiovascular and chronic pulmonary disease was noted among 81%, 54%, 56% and 32% respectively. Among all cirrhotic individuals, SARS-CoV-2 positive individuals less frequently progressed to hepatic decompensation (3.1% vs 4.8%, P< 0.0001) or hospitalization (35.7% vs 38.2%, P=0.002), but more frequently required ICU admission 15% vs 12.2%, P< 0.0001) or respiratory support (7.3% vs 8.4%, P=0.01). Among those admitted, length of hospital stay was

longer among SARS-CoV-2 positive individuals (7 vs 4 days, P< 0.0001). In Cox regression analysis, SARS-CoV-2 positivity was associated with a higher risk of all-cause mortality (HR 1.37, 95% CI 1.19,1.56).

Conclusion: Although patients with cirrhosis and COVID-19 were less often hospitalized, they had longer duration of hospitalization and were at higher risk of severe or critical illness and death.

KAPLAN-MEIER CURVES TO DEMONSTRATE EVENT-FREE SURVIVAL AMONG SARS-COV-2 POSITIVE AND NEGATIVE INDIVIDUALS.

Figure. Kaplan-Meier curves to demonstrate event-free survival among SARS-CoV-2 positive and negative individuals.
Panel A Panel B



625 ASSOCIATION OF HIV CONTROL AND IMMUNOSUPPRESSION WITH NADC RISK AMONG PATIENTS ON ART

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Background: Since inception of highly active antiretroviral therapy in 1996, AIDS-related mortality has decreased, and life expectancy among people with HIV (PHIV) has increased. This has translated into an increased prevalence of age-related conditions including non-AIDS defining cancers (NADCs). Our study investigated the association of measures of immunosuppression and HIV control with NADCs with viral or non-viral etiology among PHIV on antiretroviral therapy (ART) in the US.

Methods: Patients who sought care at clinics within the CFAR Network of Integrated Clinical Systems (CNICS) between 1996-2016 were assessed for development of a primary NADC. Follow-up started at CNICS enrollment and ended at first NADC diagnosis, death, last CNICS visit, or last date of cancer verification (12/31/2016). To assess immune function and HIV control, we utilized three parameterizations of CD4 count and HIV-RNA viral load (VL): (1) CD4 or VL at ART initiation; (2) change in CD4 or VL following ART initiation; and (3) proportion of follow-up time at CD4 >500 cells/ul or VL< 50 copies/ml. To ascertain the association of these measures with risk of a viral NADC (anal, Hodgkin lymphoma, liver, oropharyngeal, penile, vulva, vaginal) or non-viral NADC (all other sites), Cox models adjusted for age, race/ethnicity, sex, year of ART start, prior HBV and HCV diagnoses (viral only), and tobacco (non-viral only) were used.

Results: Among 29,568 patients on ART, there were 410 non-viral NADCs and 213 viral NADCs. PHIV with a CD4 < 200 cells/ul at ART initiation had an 80% elevated risk for developing a viral NADC (aHR: 1.80; 95% CI: 1.12-2.87). Each increase of 100 cells/ul in CD4 after ART initiation decreased risk 14% (aHR: 0.86; 95% CI: 0.77-0.95), and 10% more follow-up time spent with a CD4 >500 cells/ul was associated with decreased risk (aHR: 0.82; 95% CI:0.78-0.86), even after accounting for CD4 at ART initiation. Risk of non-viral NADCs was also lower for those with 10% more time spent with CD4 >500 (aHR: 0.88; 95% CI: 0.86-91). When examining HIV control only, 10% more time with VL < 50 copies/ml was significantly associated with decreased viral (aHR: 0.85; 95% CI: 0.82-0.89) and non-viral NADC risk (aHR: 0.88; 95% CI: 0.85-0.90).

Conclusion: This study demonstrates that even for PHIV on ART therapy, maintaining HIV control is associated with lower risk of both viral and non-viral NADCs.

626 HIV-ASSOCIATED DIFFERENCES IN THE TUMOR IMMUNE MICROENVIRNMENT OF NADCs

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Background: Antiretroviral therapy has translated into increased life expectancy for people living with HIV (PWH), resulting in a growing number of patients surviving to older ages when non-AIDS-defining cancer (NADC) are more common. Our prior work has demonstrated that patients with HIV have higher cancer-specific mortality compared to patients without HIV. A novel approach to identify factors that drive poor cancer outcomes in PWH is needed; one compelling hypothesis is that HIV influences the molecular profile of cancers that develop in PWH.

Methods: Tissue microarrays (TMAs) from PWH diagnosed with either prostate or anal cancer were obtained from the AIDS Cancer Specimen Resource. Comparison TMAs were created from HIV-uninfected prostate and anal cancer patients selected from the biorepositories at Moffitt Cancer Center and Huntsman Cancer Institute. In addition, one TMA was created at Moffitt to include tumors from PWH diagnosed with a range of NADCs and matched tumors from HIV-uninfected patients diagnosed with the same cancer type. Slides were stained using the Akoya Biosciences' OPAL™ 7-Color Automation IHC kit on the BOND RX autostainer (Leica Biosystems). After staining, slides were imaged using the Vectra®3 Automated Quantitative Pathology Imaging System, and multi-layer images were exported to the HALO Image Analysis Platform. We compared marker positivity by HIV status, adjusted for tumor site and patient age and race, using beta-binomial regression models.

Results: Multiplex immunofluorescence staining of tissues from 45 PWH (prostate cancer=22; anal cancer=14; other=9) and 238 HIV-uninfected patients (prostate cancer=216; anal cancer=5; other=17) demonstrated HIV-related differences in the tumor immune microenvironment. We stained for 15 different markers, and the abundance of six of these markers was significantly (P< 0.05) higher in tumors from PWH compared to tumors from patients without HIV, after adjustment for age, race, and tumor site. This included differences in infiltration of T-cells (CD8+ [OR=1.50] and delta-gamma [OR=1.81]), B-cells (CD20+ OR=1.67), and macrophages (CD163+ OR=1.98), as well as differences in expression of clinically targetable immune checkpoint molecules (PD-L1 [OR=3.83] and TIM3 [OR=1.76]). The T-regulatory cell phenotype (CD3+CD8+FOXP3+) was also statistically significantly more abundant in tumors from PWH (OR=2.19).

Conclusion: Our data indicate that NADCs developing in the setting of HIV are immunologically distinct.

627 SPECIFIC EXOSOMAL PROTEOMIC PROFILE ASSOCIATED TO PLWH PRESENTING NADCs

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Background: People living with HIV have an increased risk of developing different types of cancers (NADC:Non-Aids Defining Cancers).However, it is poorly understood the underlying mechanisms that link up HIV infection with the development and progression of these cancers. Previous *in vitro* studies have suggested that exosomes derived from HIV infected cells can promote and enhance cancer.Herein, we have analyzed the proteomic profile of exosomes from HIV patients with active NADC to identify biomarkers associated to this condition

Methods: Forty-five HIV patients were included:15 on cART (HIV^+NADCs^-),15 on cART with NADC (HIV^+NADCs^+) and 15 HIV-uninfected with NADCs (HIV^-NADCs^+). Fifteen healthy volunteers (HC) were included as reference.Size Exclusion Chromatography was employed to isolate plasma exosomes and Nanoparticle Tracking Analysis and microscopy-TEM to quantify and validate them.Proteins were extracted from exosomes,digested with trypsin and the resulting peptides were analyzed by liquid chromatography coupled with mass spectrometry. Proteins identification was carried out using the Mascot search engine through the Protein Discoverer software.Differential abundance of proteins between study groups was considered when the ratio of abundance was >2 or <0.5

Results: Respect to HC, there were 74, 77 and 72 differentially expressed proteins in HIV$^-$NADCs$^+$, HIV$^+$NADCs$^-$ and NADCs$^+$HIV$^+$ groups, respectively. Eighteen proteins were exclusive of NADC$^+$HIV$^+$ vs HC comparison, of which 11 were increased.Among these 11 proteins, 5 are related to cancer development and progression: hQSOX, Proprotein convertase 9, Complement component C9, Beta ig-h3 and C1r-LP.In contrast, one of the proteins diminished in NADC$^+$HIV$^+$ (GPx-3) is considered as anti-oncogenic factor, and curiously, its mRNA expression is downregulated by HIV-Tat. Moreover, there were 7 proteins exclusive of the comparison between HIV$^+$NADCs$^+$and HIV$^+$NADCs$^-$; among them two proteins associated to cancer development and metastasis were increased in NADC$^+$HIV$^+$: SAA1 and Thrombospondin 1.Interestingly, mRNA expression of SAA1 is upregulated by HIV-gp120

Conclusion: Our results show the existence of a specific exosomal proteomic profile associated to concomitant HIV infection and NADCs, characterized by increased levels of proteins related to cancer promotion and decreased levels of anti-oncogenic factors.Of note, some of these proteins are considered targets regulated by HIV,supporting the contribution of the virus to the development and progression of cancers

628 RISK FACTORS FOR 5-YEAR MORTALITY IN PEOPLE WITH HIV AFTER CANCER DIAGNOSIS

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North American AIDS Cohort Collaboration on Research and Design (NA-ACCORD) of IeDEA

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Background: Racial disparities in cancer outcomes among people with HIV (PWH) have not been extensively explored in the context of HIV-specific clinical factors such as HIV viral load and immune status. We estimated 5-year survival and risk factors for 5-year mortality among PWH diagnosed with cancer in North America from 2000-2017.

Methods: We included PWH, ≥18 years old, participating in the North American AIDS Cohort Collaboration on Research and Design, diagnosed with validated cancer between 2000-2017, with ICD-O-3 site/histology data. Patients were followed from age at cancer diagnosis to the earliest of: death, administrative censoring, loss-to-follow-up, or 5 years of follow-up. Cancers were categorized as AIDS-defining (ADC), virally-associated non-AIDS-defining (VAC), or non-AIDS-defining cancer (NADC). Patients could contribute multiple cancers. With age as the timescale, we estimated 5-year survival by cancer type (Kaplan-Meier). We assessed mortality risk factors at cancer diagnosis by cancer type using Cox proportional hazards models including race/ethnicity, viral suppression, CD4 count, AIDS-defining illness (ADI) prior to cancer, and calendar year of cancer diagnosis.

Results: There were 4556 cancer diagnoses (827 ADC, 2832 NADC, 897 VAC) among 4103 patients contributing 12185 person-years. Five-year survival was 50.1% (46.2%, 53.8%) for ADCs, 38.5% (36.4, 40.6%) for NADCs, and 32.9% (29.1%, 36.7%) for VACs. Viral suppression and high CD4 count (≥350 cells/mm3) were inversely associated with 5-year mortality. Age was an independent predictor of mortality for all cancers. For ADCs and NADCs, ADI history was associated with increased mortality risk. Mortality following ADCs and VACs was higher in Black patients; and mortality following NADC was lower for Hispanic compared to white patients.

Conclusion: Viral suppression and CD4 count were predictive of 5-year mortality following cancer diagnosis across cancer types. Inconsistent racial mortality disparities by cancer type merit further research. Future work will incorporate cancer treatment, screening, stage, and longitudinal HIV viremia/immune status to comprehensively characterize this association. Associations with HIV-specific factors and NADCs/VACs underscore the importance of maintaining suppression and high CD4 count following cancer diagnosis and exploring the etiologic role of these factors in cancer progression.

Table 1. Risk factors for 5-year mortality following cancer diagnosis in the NA-ACCORD 2000-2017

Table 1. Risk factors for 5-year mortality following cancer diagnosis in the NA-ACCORD 2000-2017

	ADC (N=827)		NADC (N=2832)		VAC* (N=897)	
Risk factor	aHR	95% CI	aHR	95% CI	aHR	95% CI
Race/ethnicity						
non-Hispanic white	ref	ref	ref	ref	ref	ref
non-Hispanic Black	**1.30**	**1.04, 1.63**	0.94	0.84, 1.04	**1.37**	**1.13, 1.66**
Hispanic	0.83	0.58, 1.20	**0.73**	**0.58, 0.92**	1.04	0.76, 1.44
Other	0.51	0.19, 1.39	1.30	0.76, 2.21	0.62	0.20, 1.97
Calendar year (per 1-year ↑)	**0.94**	**0.91, 0.96**	**0.96**	**0.94, 0.97**	**0.94**	**0.91, 0.96**
Sex (female vs. male)	0.82	0.48, 1.41	**1.49**	**1.12, 1.98**	1.81	0.96, 3.41
Age (per 5-year ↑)	**1.13**	**1.07, 1.19**	**1.13**	**1.10, 1.16**	**1.27**	**1.21, 1.35**
CD4 count (cells/mm³)						
<200	ref	ref	ref	ref	ref	ref
200- <350	**0.68**	**0.51, 0.90**	**0.70**	**0.61, 0.81**	0.85	0.67, 1.07
≥350	**0.52**	**0.39, 0.68**	**0.53**	**0.47, 0.60**	**0.71**	**0.56, 0.88**
ADI prior to diagnosis	**1.31**	**1.06, 1.62**	**1.28**	**1.14, 1.44**	0.91	0.74, 1.11
Viral suppression (<200 copies/mL)	**0.64**	**0.49, 0.83**	**0.74**	**0.66, 0.83**	**0.75**	**0.61, 0.91**

Statistically significant estimates are bolded
Abbreviations: aHR: adjusted hazard ratio; CI: confidence interval; ADC: AIDS-defining cancer; NADC: non-AIDS-defining cancer; VAC: virally-associated non-AIDS-defining cancer; ADI: AIDS-defining illness
*VACs include certain oral cavity/pharyngeal cancers, hepatocellular carcinoma, vulvar, penile, vaginal, and anal squamous cell carcinoma, and Hodgkin's Lymphoma, based on ICD O 3 site/histology (classification used in prior observational studies of PWH).

629 MARKERS OF IMMUNOSUPPRESSION AND MORTALITY AMONG CANCER PATIENTS WITH HIV

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Background: People with HIV who develop cancer have a higher risk of dying from their cancer compared with immunocompetent cancer patients in the general population. However, no prior study has assessed HIV disease markers in relation to cancer-specific mortality among cancer patients with HIV.

Methods: We used data from the HIV/AIDS Cancer Match Study, a linkage of US state HIV and cancer registries. We selected individuals with HIV who developed 3 common cancers during 2005-2018: anal cancer (N=765), lung cancer (N=682), or non-Hodgkin lymphoma (NHL, N=1173). We identified the most recent CD4 count and HIV viral load (VL) within the 6 months after cancer diagnosis. Deaths from these cancers were identified from death certificates. We used Cox proportional hazards models to assess adjusted associations of CD4 count and HIV VL with cancer-specific mortality (see Table).

Results: Among individuals with HIV diagnosed with anal cancer, lung cancer, or NHL, a total of 134, 334, and 171 patients, respectively, died from their cancer. For anal cancer and lung cancer, individuals with CD4 counts below 200 cells/mm^3 had significantly increased cancer-specific mortality (adjusted hazard ratio [HR] 2.00, 95%CI 1.14-3.51, and 2.05, 1.49-2.82, respectively, compared to individuals with CD4 350+ cells/mm3; Table). For anal cancer, patients with detectable HIV VL also had elevated cancer-specific mortality (adjusted HR 1.73, 95%CI 1.13-2.64). The association between CD4 and cancer-specific mortality was borderline for NHL (adjusted HR 1.52, 95%CI 0.98-2.35 for CD4 counts 0-199 vs. 350+ cells/mm^3; Table).

Conclusion: Among patients with anal cancer, lung cancer, or NHL living with HIV, a low CD4 count at the time of diagnosis was associated with an increased risk of individuals subsequently dying from their cancer. These results are preliminary, and additional analyses need to be performed that further adjust for cancer stage at diagnosis and cancer treatment. Nonetheless, our findings support that immunity plays a crucial role in the control of certain malignancies and preventing relapse and death. Optimizing antiretroviral therapy to suppress HIV replication and restore immune function should be an important component of cancer treatment.

Table: Associations of CD4 count and HIV viral load with cancer-specific mortality among cancer patients with HIV

	Anal cancer Adj HR (95%CI)	Lung cancer Adj HR (95%CI)	Non-Hodgkin lymphoma Adj HR (95%CI)
CD4 count, cells/mm^3			
0-199	2.00 (1.14-3.51)	2.05 (1.49-2.82)	1.52 (0.98-2.35)
200-349	1.01 (0.45-2.28)	1.60 (1.12-2.30)	0.73 (0.40-1.33)
350+	Reference	Reference	Reference
Missing	1.22 (0.62-2.41)	1.71 (1.22-2.39)	0.78 (0.44-1.40)
HIV viral load			
Detectable	1.73 (1.13-2.64)	1.04 (0.76-1.41)	1.10 (0.78-1.57)
Undetectable	Reference	Reference	Reference
Missing	1.19 (0.73-1.94)	0.91 (0.68-1.22)	1.16 (0.73-1.86)

Abbreviation: Adj HR= adjusted hazard ratio
Hazard ratios for CD4 count and HIV viral load are mutually adjusted for each other, and additionally adjusted for sex, HIV risk group, age, race/ethnicity, and calendar year of diagnosis.

630 RATIONALE FOR THE USE OF PACRITINIB IN KSHV-MULTICENTRIC CASTLEMAN DISEASE

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Background: The interleukin-6 (IL-6)/JAK/STAT3 pathway is hyperactive in primary effusion lymphoma (PEL) and important in Kaposi sarcoma herpesvirus (KSHV)-associated multicentric Castleman's disease (MCD), which is driven by

KSHV-infected B cell plasmablasts. Inhibition of STAT3 can induce apoptosis in PEL cells (Aoki Y. et al., *Blood*, 2003 101:1535), and signaling by KSHV-encoded viral IL-6 through STAT3 is believed to be important in KSHV-MCD pathogenesis. We explored the potential of JAK inhibitors for use in PEL and KSHV-MCD.
Methods: JAK Inhibitors (ruxolitinib, AZD1480, baricitinib, peficitinib, and pacritinib) and other kinase inhibitors were purchased from commercial sources; pacritinib was also provided by CTI BioPharma. PEL cell lines (JSC-1 and BCBL-1) were treated with the inhibitors, and their viability assessed using the CellTiter-Glo® Luminescent Cell Viability Assay and flow cytometry. To assess effects on cellular gene expression, mRNA sequencing was applied, and key results were verified using real-time (RT) PCR.
Results: As shown by flow cytometry and trypan blue counting, 1 μM pacritinib efficiently inhibited cell growth and induced apoptosis of PEL cell lines and was superior to the other JAK inhibitors tested. In addition to JAK2, pacritinib targets FLT3 and IRAK1; the possibility that these might contribute to the effect in PEL using small molecule inhibitors was explored. Several FLT3 inhibitors also inhibited growth of PEL cells *in vitro*, suggesting that FLT3, which is involved in B cell development, may play a role in pacritinib's growth inhibition of PEL. mRNA sequencing and RT-PCR showed that several key host genes including several cyclins and IL-6 were downregulated by pacritinib. Finally, pacritinib suppressed KSHV viral-IL6(vIL-6)-induced IL-6 production by peripheral blood mononuclear cells, which may model an important step the pathogenesis of KSHV-MCD.
Conclusion: : Pacritinib inhibited cell growth in PEL lines. It also downregulated a number of cellular genes believed to be important for PEL growth and for KSHV-MCD pathogenesis. These effects may stem from its simultaneous inhibition of multiple kinases including JAK2, IRAK1, and FLT3. These results suggest that pacritinib warrants testing for the treatment of KSHV-MCD and PEL.

631 IFNγ-IL18 AXIS CYTOKINES DISCERN MYCOBACTERIAL AND KSHV INFLAMMATORY SYNDROMES IN PWH

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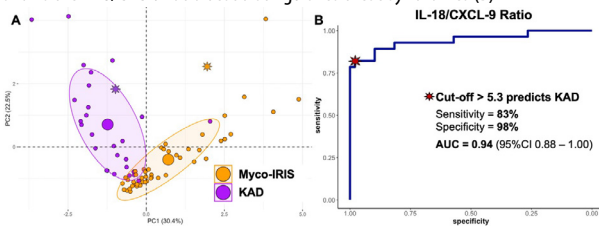
Background: Mycobacterial immune reconstitution inflammatory syndrome (myco-IRIS) occurs in people with HIV (PWH) who are also at risk of Kaposi sarcoma herpesvirus (KSHV)-associated inflammatory diseases (KAD) which are associated with elevated IL-6 and clinically resemble myco-IRIS. Differentiating these syndromes is essential as treatments vary markedly. IFNγ-IL18 axis biomarkers can distinguish pediatric hyperinflammatory syndromes and have been implicated in both myco-IRIS and KAD pathogenesis. We evaluated clinical and immune biomarkers in patients with myco-IRIS or KAD to identify markers that could differentiate these syndromes.
Methods: Plasma samples were obtained from PWH on antiretroviral therapy with active myco-IRIS or inflammatory KAD (multicentric Castleman disease, primary effusion lymphoma, KSHV inflammatory cytokine syndrome). All participants were enrolled in NIH IRB-approved protocols. We measured clinical labs and immune markers (IL6, IL10, IL18, IL18BP, IFNγ, CXCL9, sCD163, CRP, ferritin) and performed Wilcoxon test, principal component (PCA), and receiver operating curve analyses.
Results: Overall, 77-PWH were included (median age 39yrs [IQR 33-45]) with 59 (77%) cis-men. Fifty had myco-IRIS (tuberculosis, n=21; nontuberculous, n=29), and 27 had KAD. Two with myco-IRIS also had detectable KSHV PCR. There was no difference in CRP, IL6, ferritin, CD4 T-cells, or HIV viral load between the two groups. PCA incorporating all biomarkers revealed distinct clustering of the two inflammatory syndromes (Fig1A). The 2 patients with myco-IRIS and possible KAD mapped to separate inflammatory clusters (stars) suggesting unique pathophysiology in each. There were higher IFNγ and CXCL9 levels (T-cell activation) in myco-IRIS (IFNγ 135pg/mL [IQR 35.8-353]; CXCL9 786pg/mL [IQR 429-1863]) vs KADs (IFNγ 25.4pg/mL [IQR 19.4-37.6]; CXCL9 272pg/mL [IQR 171-437]) (p< 0.001). IL18 (inflammasome activation) was increased in KAD (IL18 4202pg/mL [IQR 2042-5923]) compared to myco-IRIS (IL18 1018pg/mL [IQR 670-1705]) (p< 0.001). The IL18/CXCL9 ratio showed the greatest discrimination capacity for KAD (Fig1B).
Conclusion: Although clinically indistinguishable, myco-IRIS and inflammatory KAD demonstrate unique immune profiles involving the IFNγ-IL18 axis suggesting different pathogenesis. These biomarkers, after validation, may help risk stratification and diagnosis of patients even in resource-limited settings, but also highlight possible therapeutic targets of these distinct hyperinflammatory syndromes.
Comparison of immune profiles between mycobacterial-IRIS and KSHV inflammatory syndromes by principal component analysis (A), ROC analysis shows the IL18/CXCL9 ratio best distinguishes these syndromes (B)



632 STUDY OF CHARACTERISTICS AND OUTCOMES OF KSHV INFLAMMATORY CYTOKINE SYNDROME (KICS)

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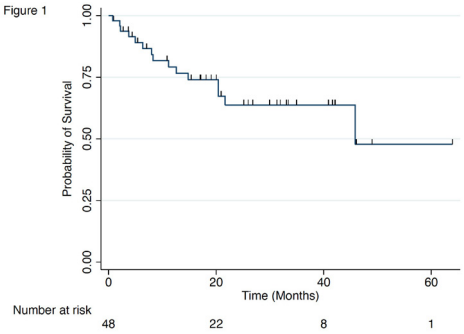
Background: KSHV inflammatory cytokine syndrome (KICS), caused by Kaposi sarcoma herpesvirus (KSHV), is characterized by severe inflammatory signs (elevated C-reactive protein, elevated KSHV viral load) and symptoms without evidence of multicentric Castleman disease (MCD). KICS, predominantly occurs among people with HIV (PWH) and Kaposi sarcoma (KS), and has overlapping clinical features of MCD and primary effusion lymphoma (PEL). We present findings from the largest prospective study of KICS.
Methods: The primary objective was to evaluate KICS natural history. There were broad eligibility criteria to allow thorough diagnostic evaluation for KICS and exclusion of other inflammatory disorders. Participants (pts) with confirmed KICS (without PEL, MCD or other causes of inflammation) were assigned to either an observation arm to treat KS with standard therapy or to a KICS treatment arm to receive rituximab-based regimens, high-dose zidovudine and valganciclovir (AZT/VGC) or other rational therapies, such as tocilizumab.
Results: Seventy-six pts were enrolled from 2011 to 2022. Twenty-eight pts did not meet further KICS criteria, as inflammatory symptoms were associated with PEL (20 pts), MCD (2 pts), HIV infection alone (5 pts), or paraganglioma (1 pt). Therefore, following initial evaluation, 48 pts (47 PWH) had confirmed KICS, and all but 1 had concurrent KS. In 47 pts with confirmed KICS and HIV infection, 43 pts (91%) were on antiretroviral therapy at baseline, median duration of HIV infection was 8.1 years (interquartile range (IQR): 0.7-15.8), median HIV viral load was 76 copies/mL (IQR: 23-4631), and median CD4+ T cell count was 86 cells/μL (IQR: 32-155). Among all pts with confirmed KICS, 27 pts (56%) received KS-focused therapy alone, 18 pts (35%) received rituximab-based therapy [with liposomal doxorubicin (15 pts) or paclitaxel (2 pts) or without chemotherapy (1 pt)], 1 pt received AZT/VGC, 1 pt received tocilizumab. Ten of 18 pts (55%) who received rituximab-based therapies had clinical benefit with improvement of KICS signs and symptoms within 8 weeks of treatment. For pts with confirmed KICS, the median overall survival was 45.8 months (95% confidence interval: 20.3 – not reached) (Figure 1).
Conclusion: KICS is a distinct diagnosis of exclusion that often occurs with KS and carries a relatively poor survival. Pts should have MCD and PEL ruled out prior to KICS diagnosis. Rituximab-based therapies may have a role in treatment of a subset of pts with KICS.

Figure 1: Kaplan-Meier curve of overall survival in 48 participants with confirmed KICS



633 KAPOSI SARCOMA IN ART-TREATED PLWH: DISTINCT VIRAL AND IMMUNE CHARACTERISTICS

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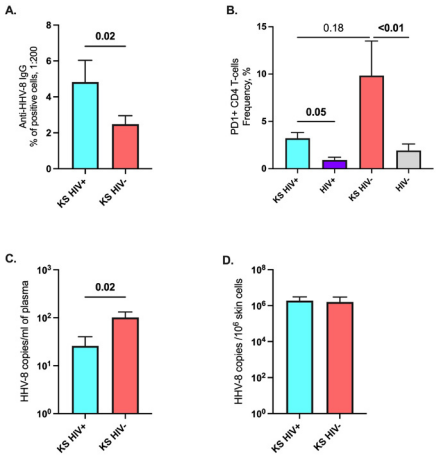
Background: Recent reports describe the reemergence of HHV8-induced Kaposi sarcoma (KS) in people living with HIV (PLWH) despite efficient antiretroviral therapy (ART). We aimed to assess the influence of immunological and virological factors in the development of KS in ART-treated PLWH compared to HIV-uninfected people with classic KS.

Methods: 4 groups of 11 participants were compared: 1. ART-treated PLWH with KS (KS HIV+), 2. Age-matched ART-treated PLWH without KS (HIV+), 3. HIV-uninfected patients with classic KS (KS HIV-), 4. Age-matched HIV-uninfected people without KS. We assessed CD4/CD8 ratios, circulating cytokines by ELISA multiplex, anti-HHV-8 IgG levels with an in-house cell-based assay, anti-HHV-8 specific T-cells by ELISPOT, and circulating and skin T-cells phenotypes by flow cytometry. HHV-8 viral loads (VL) were quantified by digital-droplet PCR and next-generation sequencing was performed.

Results: All KS participants presented with limited skin disease. KS HIV+ were younger than KS HIV- (53 vs 75yo, $p< 0.01$). CD4/CD8 ratios were lower in KS HIV+ compared to KS HIV- ($p=0.01$) and to HIV+ ($p< 0.05$). In KS HIV+, anti-HHV-8 IgG levels were higher compared to KS HIV- ($p=0.02$, Figure 1) and frequency of specific T-cells was low but similar. Circulating and tissular CD4 T-cells of both KS HIV+ and KS HIV- expressed a similarly high frequency of senescence markers (CD57+/CD28-) and PD1, higher than their own control group. Among cytokines, IL-10 levels were higher only in KS HIV- ($p=0.02$). HHV-8 VL were lower in KS HIV+ than in KS HIV- in plasma ($p=0.02$) and PBMCs ($p=0.04$), but were similar in skin biopsies. HHV-8 genetic subtypes A and C were similarly isolated in both KS groups, and a newly identified variant was found in two KS HIV- Inuit patients from Northern Canada.

Conclusion: Compared to age-matched PLWH, ART-treated PLWH with KS exhibited features of early immune senescence, with a lower CD4/CD8 ratio and increased frequency of CD57+/CD28- T-cells. Despite the younger age, senescent T-cells frequency was similar among KS HIV+ and KS HIV-. However, anti-HHV8 IgG levels were higher in KS HIV+ compared to KS HIV-, which was associated with lower circulating HHV-8 DNA and IL-10 levels. Although HHV-8 strains did not significantly differ between groups, we could isolate a new HHV-8 variant. Altogether, early immune senescence/exhaustion seems involved in the development of KS in ART-treated PLWH. Such insights will help developing therapeutical strategies to reduce KS-induced stigma.

Figure 1



634 IMPLICATIONS OF CERVICAL CANCER SCREENING AND TREATMENT PROGRAM ROLL OUT IN UGANDA

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Background: At 54.8 cases per 100,000 women, Uganda is one of the highest cervical cancer (CxCa) burdened countries in the world. Women living with HIV (WLHIV) are 6 times greater risk of developing CxCa, compared to women without HIV. To reduce the occurrence of CxCa among WLHIV, the Uganda Ministry of Health (MOH), with support from the US President's Emergency Plan for AIDS Relief (PEPFAR) through the PEPFAR agencies (CDC, USAID, DOD) and Implementing Partners, began a CxCa screening and treatment of pre-cancerous lesions program in October 2020. Here, we describe initial program performance and implications for national scale-up.

Methods: We supported the design, development and printing of standards, guidelines and monitoring and evaluation tools for the program; we also trained national, regional and health facility managers to support the roll-out of the program. MOH procured and distributed commodities required for CxCa screening and treatment of pre-cancerous lesions. To assess performance, we performed a retrospective analysis of CxCa screening and care cascade data from October 2020 through March 2022. We extracted data from the PEPFAR DATIM reporting system. We calculated the proportions of eligible WLHIV on antiretroviral therapy (ART) who were screened, those who screened positive (positivity rate), and those who received treatment for pre-cancerous lesions among those screened positive (treatment rate).

Results: Overall, 543,639 WLHIV on ART aged 25–49 years were eligible for screening during October 2020–October 2022. By March 2022, 47% (n=255,451) of eligible WLHIV were screened, with a positivity rate of 6% (n=14,378) and treatment rate of 64% (n=9,329). Percentage of WLHIV screened increased over time, with 27% (146,033/543639) screened during October 2021-March 2022 compared to 20% (109,418/543,639) screened in a whole year period (October 2020-September 2021). Treatment rates increased over time, with 75% (5,695/7,623) treated during October 2021–March 2022 compared to 54% (3,634/6,755) during October 2020–September 2021.

Conclusion: Improvements in proportion screened and treatment rate were due to consistent commodity distribution, enhanced technical support, and implementation of quality improvement innovations. Additional efforts are needed to ensure all WLHIV who are screened positive receive treatment, including barriers to timely referrals.

635 INTEGRATING POINT-OF-CARE HPV TESTING INTO HIV CARE FOR KENYAN WOMEN LIVING WITH HIV

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Background: Current cervical cancer screening methods for women living with HIV (WLHIV) in Kenya are underutilized, including visual inspection of the cervix with acetic acid (VIA) and/or of Lugol's iodine (VILI). Identifying WLHIV at the

highest risk for cervical cancer could motivate VIA/VILI screening and improve uptake. We integrated Xpert HPV testing for high-risk human papillomavirus (HR-HPV) within routine HIV care with the aim of increasing the overall uptake of cervical cancer screening among WLHIV enrolled in HIV care at Kenya's national referral hospital.

Methods: WLHIV aged ≥18 years enrolled in HIV care at Kenyatta National Hospital (KNH) HIV clinics were eligible and approached for participation during their routine HIV clinic visits between September 2021 and February 2022. We extracted medical records among consenting WLHIV to establish baseline VIA/VILI uptake. Participants were offered Xpert HPV testing if they had not previously received VIA in the last 12 months. Cervical smears were collected among consenting WLHIV by study nurses and analyzed on the Gene Xpert platform in the HIV care clinic molecular laboratory. Results were provided during that same HIV care visit and women with HR-HPV were referred for VIA/VILI in the HIV clinic.

Results: Overall, 691 WLHIV were enrolled. The median age was 42 years (IQR 37-48) and 72% of participants had secondary education or above. Forty-six percent of participants were married, 63% had a regular source of income, and 47% had a partner known to be living with HIV. Only 25% of participants were previously screened for cervical cancer. Among those not previously screened (n=518), most (95%) accepted Xpert HPV. Prevalence of HR-HPV was 35% (232/656); 10 % HR-HPV-16, 8% HR-HPV-18/ and 45, and 82% for other 11 HR-HPVs not individually genotyped by Xpert HPV. The median time to return Xpert HPV results was 60 minutes (IQR 60-80). All the results were available in the same HIV clinic visit. Overall, 96% of WLHIV with positive Xpert HPV results subsequently accepted and received VIA/VILLI assessment; of those, 26% had results predicting cervical abnormalities.

Conclusion: In this study among Kenyan WLHIV, integrating Xpert HPV into HIV care was feasible with high uptake and prevalence of HR-HPV. WLHIV with HR-HPV almost universally completed referrals for VIA/VILLI which frequently detected cervical abnormalities. Xpert HPV could potentially enhance cervical cancer screening programs for WLHIV in high-burden settings.

636 PROGRESS TOWARDS THE ELIMINATION OF CERVICAL CANCER AMONG WOMEN LIVING WITH HIV

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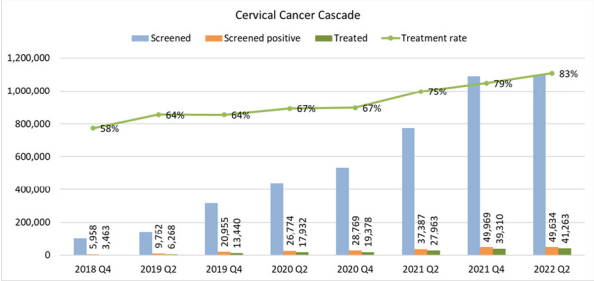
Background: Acquisition and persistence of carcinogenic human papillomavirus (HPV) infections and the incidence of precancerous lesions and invasive cervical cancers are all increased for women living with HIV (WLHIV) compared with their HIV-negative peers. To reduce new cervical cancer cases among WLHIV, the U.S. President's Emergency Plan for AIDS Relief (PEPFAR) supports regular cervical cancer screening, precancerous lesion treatment, and referral for treatment of invasive cervical cancers for women accessing routine HIV services. We describe cervical cancer screening and treatment results among WLHIV in PEPFAR-supported programs.

Methods: PEPFAR programs in 14 countries reported data semiannually at the end of March (Quarter 2) and September (Q4), 2018 to 2022. We report the absolute and relative number of WLHIV screened for cervical cancer for their first lifetime screen, routine follow up after prior negative screens, and after precancerous lesion treatment. Screen results are reported as negative, positive for precancerous lesions, and positive for suspected invasive cervical cancer. We describe the number and proportion of precancers treated with ablative and excisional therapies.

Results: Between April 2018 and March 2022, 4.5 million cervical cancer screenings were completed; 3.7 million (82.4%) were first time screens. Screen positivity for precancerous lesions was 5.1% (229,208 positive screens), and 0.9% (40,152 women) were referred to a higher level of care for suspected cancers. A total of 169,017 precancerous lesions were treated; 19.7% (33,289) with excisional, and the remainder with ablative therapies. The proportion of ablative treatments done with cryotherapy declined by 21.0%, while the proportion using thermal ablation increased by 26.1%, when comparing 2022 to 2018 semiannual rates. The precancerous lesion treatment rate increased from 58.1% in 2018 to 83.1% in 2022.

Conclusion: Offering cervical cancer screening services within ART clinics reached 4.5 million WLHIV at risk for cervical cancer—a significant contribution to the ongoing global effort to eliminate cervical cancer. PEPFAR programs should continue to optimize cervical cancer treatment modalities best suited to each location and to further increase the rising precancerous lesion treatment rates, to ensure that women have access to excellent cervical cancer screening and appropriate precancer treatments.



637 HUMAN PAPILLOMA VIRUS INFECTION PREVALENCE AMONG WOMEN LIVING WITH HIV IN ETHIOPIA

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*Presented at CROI by a nonauthor colleague

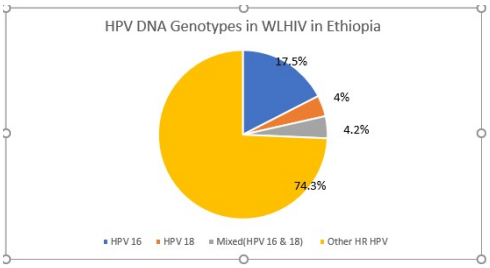
Background: Cervical cancer is the second most reported cancer (13%) among women aged 15-49 years old in Ethiopia. Human papilloma virus (HPV) types 16 and 18 are associated with about 70% of cervical cancer worldwide and HPV 16 alone is associated with 60% of cervical cancer. Women living with HIV (WLHIV) have an increased risk of acquiring HPV infection, more rapid progression to cervical cancer, and higher rates of recurrence following treatment. As part of the cervical cancer screening service scale-up efforts for WLHIV, CDC Ethiopia introduced WHO's 'screen, triage and treat' approach using HPV DNA testing followed by visual inspection of the cervix with acetic acid (VIA) in 2021.

Methods: HPV testing was introduced at 70 public health facilities providing ART services in five PEPFAR-supported regions in collaboration with the Regional Health Bureaus, Ethiopian Public Health Institute (EPHI), and the Ministry of Health (MoH) of Ethiopia. HPV testing was done in fifteen laboratories using the already existing molecular platforms (nine Abbott and six Roche). WLHIV between the ages 15-49 were targeted for HPV testing. HPV DNA test results were analyzed and reported by genotypes. All HPV positive WLHIV were contacted and advised to have VIA testing. We summarized these programmatic reports from these regional labs during April 2021-April 2022.

Results: Out of the total 13,374 WLHIV tested, 3798 (28%) were HPV DNA positive for high risk (HR) types. Out of those with HPV positive result, we retrieved 3324 results with HPV DNA genotypes reported. The prevalence of HPV 16 only infections was 580 (17.5%) and that of HPV 18 only was 134 (4%) from total positives. In addition, the prevalence of mixed HPV 16 and 18 types was 140 (4.2%) and that of other HR non-HPV 16 or 18 infection among WLHIV that were tested positive was 2470 (74.3%) (Figure). Of those who had VIA (3032), 639 (21%) were VIA positive and 95% were treated.

Conclusion: Over one-quarter of WLHIV in Ethiopia were infected with HR HPV and over 20% of those had a positive VIA increasing their risk of development of cervical cancer. Therefore, the implementation of strong cervical cancer screening program for early identification and treatment of high risk WLHIV is warranted.

HPV DNA Genotypes in WLHIV in Ethiopia



638 WITHDRAWN

641 ASSESSING PERSPECTIVES AMONG PEOPLE WITH HIV WHO HAVE HAD HIGH RESOLUTION ANOSCOPY

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Background: There is a rising prevalence of anal cancer in people with HIV (PWH) with recent evidence showing efficacy of screening procedures in preventing progression to anal cancer. A recent retrospective cohort study in our Ryan White HIV/AIDS Program (RWHAP) clinic evaluating engagement and retention in anal cancer screening services identified a significant gap in engagement in care among those eligible. This highlighted a need to identify and address barriers to engagement in screening services.

Methods: Semi-structured qualitative interviews were performed on people who were receiving care in the high resolution anoscopy (HRA) clinic at the University of Virginia. Participants were at least 35 years old, receiving HIV care in the clinic and had at least one HRA performed in the clinic. Recruitment was carried out by convenience sampling via internal clinic advertising and a tailored mobile app. Interviews were constructed using the health belief model and themes explored included perceived risks, benefits, and barriers to screening, as well as self-efficacy and cues to action.

Results: Prominent barriers to engaging in high resolution anoscopy (HRA) services included pain, prior sexual trauma, prolonged recovery after biopsy, and fear of new cancer diagnosis. Notable motivators to engaging in HRA services were increased perceived risk of cancer, sedation with anxiolytics, desire to maintain health as well as trust in RWHAP clinic providers and staff.

Conclusion: Our findings highlight the importance of eliciting patient perspectives as a powerful tool when evaluating and improving on a screening program's performance. There is a desire to meet the needs of those receiving HRAs and adapt practices when it comes to those who have experienced prior sexual trauma. There is also a need to promote awareness of anal cancer screening services to PWH and provide anticipatory guidance when counseling people on the HRA procedure.

642 RISK FACTORS FOR ANAL DYSPLASIA AND LINKAGE TO HRA IN TRANSGENDER WOMEN

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Background: Studies estimate that transgender women (TGW) have a high prevalence of high-risk HPV (HR-HPV) and anal intraepithelial lesions (1), and early intervention improves outcomes (2). We examined risk factors associated with anal dysplasia (AD) and linkage to high resolution anoscopy (HRA) in a sample of TGW with and without HIV.

Methods: We recruited a convenience sample of TGW in DC from 4/2021–9/2022. Data collected included: demographics; serum samples; anal swabs for cytology and HPV genotyping. We defined AD as a cytology diagnosis of atypical squamous cells of undetermined significance, low-grade or high-grade intraepithelial lesions (HSIL). Current use of gender affirming hormones (GAH) was defined as self-report of use, or serum estradiol level higher than 60 pg/mL (estrogen) and a testosterone level below 264 ng/dL (androgen blocker). Participants with AD were scheduled for off-site HRA. We used chi-square tests to compare differences between AD risk factors.

Results: Of 62 TGW with adequate anal cytology samples, most were black (87%), stably housed (55%), engaged in anal receptive sex within 12 months (77%), and on GAH (56%). Only 12 (19%) recalled receiving an HPV vaccine. Of 43 (69%) patients with HIV, 15 (35%) had HIV viral load >200 copies/mL, median CD4 count was 619, and 22 (47%) had previous anal cancer screening.

AD was found in 29 (47%), while 45 (74%) tested positive for HR-HPV. AD was associated with the presence of HR-HPV (p=0.04), and with black race (p=0.03), but was not significantly associated with current GAH use or HIV status (Table 1). In TGW with HIV, HIV viremia was not associated with a higher risk of AD: 10 (44%) AD with viremia and 13 (56%) AD in those without (p=0.2).

Of all TGW with AD, 23 (79%) had HRA scheduled, but only 6 (26%) attended, with HSIL found in 2 patients. A year after initial screening, 16 TGW had repeat anal samples collected. On repeat, 4 (25%) cleared anal HR-HPV, and 4 (25%) no longer had AD, including one with known HSIL on HRA.

Conclusion: Our findings highlight the high prevalence of HR- HPV and AD in TGW regardless of HIV status, HIV suppression, age or use of GAH. In this high-risk population, we found low rates of prior HPV vaccination, and limited HRA attendance despite facilitated linkage. Future studies should identify longitudinal risk factors for persistence of HR-HPV or AD, and strategies for enhancing HPV vaccination, anal cancer screening, and linkage to HRA in TGW.

Table 1: Association of risk factors with abnormal anal cytology.

Risk Factor		Anal Cytology		p-value	HPV Status		p-value
		Abnormal n(%)	Normal n(%)		Positive n(%)	Negative n(%)	
Age	21-34	9 (31)	16 (49)	0.16	18 (40)	7 (44)	0.79
	35 or older	20 (69)	17 (51)		27 (60)	9 (56)	
Current estrogen use	Yes	15 (52)	19 (58)	0.64	27 (60)	7 (44)	0.26
	No	14 (48)	14 (42)		18 (40)	9 (56)	
HIV	Positive	23 (79)	20 (61)	0.11	33 (73)	9 (56)	0.2
	Negative	6 (21)	13 (39)		12 (27)	7 (44)	
High risk HPV	Positive	24 (83)	19 (59)	0.04	NA	NA	
	Negative	5 (17)	13 (41)		NA	NA	
Race	Black	28 (97)	26 (79)	0.03	39 (87)	53 (88)	0.97
	Non-Black	1 (3)	7 (21)		6 (13)	8 (12)	

643 IMMUNOLOGICAL BIOMARKERS ASSOCIATED WITH ANAL DYSPLASIA IN PEOPLE LIVING WITH HIV

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Background: Early detection of squamous intraepithelial lesion (SIL) is essential to limit anal cancer development and progression. Men who have sex with men (MSM) living with HIV are at high risk for SIL and therefore, anal cancer. Here, we aimed to identify the local immunological mechanisms involved in the development of anal dysplasia that could be critical for prevention, diagnosis and development of novel treatments.
Methods: A cross-sectional study of 54 anal biopsies obtained from 47 MSM living with HIV who participated in an anal screening program was performed. In these samples, we assessed multiple lymphocyte and myeloid immunological subsets by flow cytometry, in addition to histological examination. Selected potential biomarkers were further assessed by immunohistochemistry.
Results: Resident Memory T cells expressing CD103 were less frequent in pathological biopsies (Low/High-grade-SIL (LSIL/HSIL)), with a more pronounced effect on the CD4+T cell subset (p=0.024). Increases in the frequency of Natural Killer cells (NK) expressing CD16 (p=0.030) and overall NK activation measured by HLA-DR (p=0.018), were also associated with pathological samples. Furthermore, potentially immune suppressive subsets, including CD15+CD16+ neutrophils, gradually increased as the anal lesion progressed (p=0.012). Staining of CD15 by immunohistochemistry confirmed the association between the presence of this biomarker in the epithelium and SIL, with a sensitivity of 80% and specificity of 71% (AUC 0.762) for the correlation with HSIL.
Conclusion: Immunological tissue analyses revealed a complex immunological environment where the balance between resident effectors and immune suppressive subsets was tilted towards the second in pathological samples. Neutrophil infiltration determined by CD15 staining, may represent a valuable biomarker associated to the grade of dysplasia.

644 NADIR CD4 AND ANAL CYTOLOGY PREDICT DEVELOPMENT OF INVASIVE ANAL CANCER

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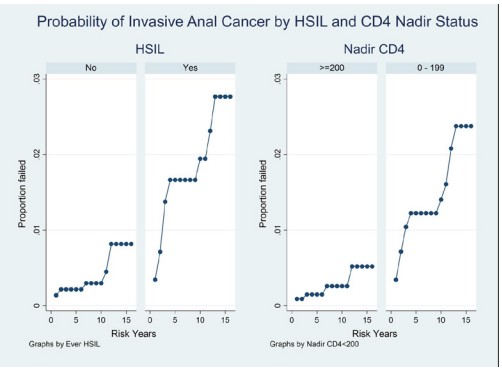
Background: The long-term natural history of anal high-grade squamous intraepithelial lesions (HSIL) is incompletely characterized. We aimed to evaluate the effects of readily available patient characteristics on the risk of developing IAC in a longitudinal cohort of people with HIV (PWH)
Methods: Retrospective inception cohort analysis of PWH between 2006-2021. Patients were eligible if they were at least 18 years of age, underwent ≥ 1 anal cytology screening as part of routine care, and provided informed consent. Validation of IAC was conducted through review of surgical pathology reports. We estimated the risk of developing IAC using Kaplan-Meier analysis and inverse probability of screening weighted (ipw) Cox proportional hazards modeling. Covariates included sociodemographics, HIV risk factors, smoking, antiretrovirals (ART), anal cytology, CD4 and HIV viral load (VL) results. Time-at-risk began on the date of the initial anal cytology and was censored on the date of initial diagnosis of IAC, the last clinic visit, or the end of the study period (31 Dec 2021), whichever occurred first
Results: The cohort included 3,967 PWH followed for a median of 5.5 years (up to 13.8 years), and 26 developed incident IAC during follow-up. PWH had a median of 2 anal cytologies. Patient characteristics included: median age 44, 10% females, 36% non-white, 78% men who had sex with men and 33% smokers. Most were on ART (91%). Those with VL < 400 copies/ml at the beginning and end of follow-up were 68% and 89%, respectively. PWH had a median nadir CD4 count of 267 cells/mm3 (IQR: 102, 454) and 39% had a CD4 count nadir < 200. At the first cytology test, 12 % had HSIL, while cumulatively 23% developed HSIL during follow-up. In weighted Cox models, independent predictors of developing IAC were having ever HSIL (HR:3.92, 95% CI:1.76-8.75, P=0.001) and nadir CD4 < 200 (HR:4.56, 95% CI: 1.54-12.8145, p=0.004). Neither age, sex, race, smoking status, VL or HIV risk factor predicted the IAC development, Harrell's C = 0.77. Comparing those with HSIL to those with less than HSIL, 5-year predicted probabilities of IAC were 1.67% and 0.22%, respectively. Comparing those with nadir CD4< 200 to those ≥200, 5-year IAC probabilities were 1.23% and 0.15% (Figure)
Conclusion: In this 15-year longitudinal cohort, HSIL and nadir CD4 count were independent predictors of IAC. Unbiased estimates of the natural history of IAC observed in inception cohorts should inform shared decision-making discussions regarding anal cancer screening

PREDICTED PROBABILITY OF INVASIVE ANAL CANCER BY HSIL AND NADIR CD4 CELL COUNT STATUS



645 TISSUE-RESIDENT T CELL RESPONSES IN HIV+ PATIENTS WITH HPV-DRIVEN ANAL DYSPLASIA

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Background: Men who have sex with men (MSM) and people living with HIV (PLHIV) have up to 150x increased risk of developing human papillomavirus (HPV)-driven anal cancer compared to the general population. Despite receiving antiretroviral therapy (ART), PLHIV can have poor HPV clearance resulting in high-grade squamous intraepithelial lesions (HSIL), an anal cancer precursor. High $CD103^+CD8^+$ tissue-resident memory T cell ($CD8^+$ T_{RM}) numbers are associated with improved survival in HPV^+ oropharyngeal and cervical cancer. Their role in anal cancer has not been investigated. We aim to delineate mucosal immunity responses in MSM (including PLHIV) that result in HPV clearance.
Methods: Anal biopsies from 67 MSM in the Study of the Prevention of Anal Cancer were studied. Multispectral microscopy was used to determine the effects of HIV co-infection with high-risk HPV16 on local T cell profile. Mann-Whitney t-tests and Spearman correlation were performed. Whole transcriptomic differences between the dysplastic lesion (DL) and peri-lesion (PL) areas were assessed in HSIL regression (R; n=2) or non-regressive disease (NR; n=2) (NanoString GeoMx Digital Spatial Profiler). gProfiler identified key signalling pathways in R versus NR.
Results: Higher numbers of total $CD4^+$ T cells were evident in MSM with HIV compared to those without (Fig. 1A). While total $CD8^+$ T cells were similar in both cohorts, $CD8^+$ T_{RMs} were lower in MSM with HIV (Fig. 1 B-C). In $HPV16^+$ HSIL, "classical" $CD103^-CD4^+$ T cells and $CD4^+$ T_{RM} numbers were lower in MSM with HIV compared to those without (Fig. 1 D-E). In both cohorts, total CD8+ T cell counts positively correlated with $CD4^+$ T cells (HIV^+: r=0.504, p< 0.01; HIV^-: r=0.617, p< 0.001) and $CD8^+$ T_{RMs} (HIV^+: r=0.779, p< 0.0001; HIV-: r=0.747, p< 0.0001). Only in MSM with HIV did $CD4^+$ T_{RM} numbers positively correlate with $CD8^+$ T_{RM} numbers (r=0.450, p=0.0059). In PL, 144 (NR) and 218 (R) genes, and in DL 140 (NR) and 73 (R) genes, were upregulated. Investigation of canonical gene sets found immune response and regulation to tumour cell signals in the R cohort compared to MHC regulation and viral gene expression signals in NR.

Conclusion: HIV infection is characterized by low $CD8^+$ T_{RMs} and $CD4^+$ T_{RMs}, and classical $CD4^+$ T cell numbers. Low $CD8^+$ T_{RM} numbers may be associated with $CD4^+$ T cell tissue lymphopenia resulting in poor HPV clearance. Even in the ART era, the immune response signals in R but not NR suggest differential cellular and molecular signals in response to HPV infection.

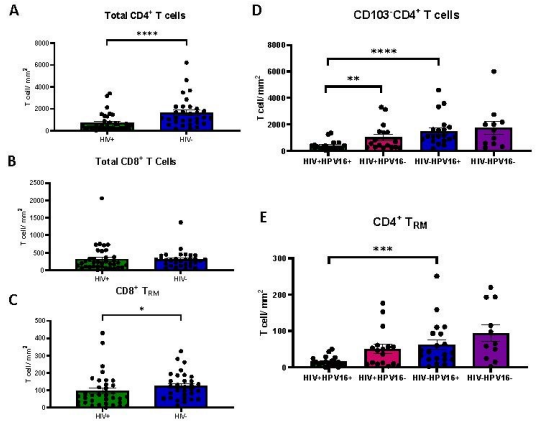

Figure 1. T cell subset numbers in HIV+ and HIV- HSILs: Proportions (cell/mm ^{2}) of (A) Total CD4+ T cells (B) Total $CD8^+$ T cells C) $CD8^+$ T_{RM} cells in HIV+ (n=36; green) and HIV- (n=31; blue) cohorts. The proportions (cell/mm ^{2}) of T cells D) CD103-$CD4^+$ classical T cells E) $CD4^+$ T_{RMs} are plotted within four main cohorts: HIV^+HPV16^+: n=19 (green), HIV^+HPV16^-: n=17 (pink), HIV^-HPV16^+: n=20 (blue); HIV^-HPV16^-: n=11 (purple). Mann-Whitney t-test was performed among different cohorts. *p<0.05, **p<0.005,***p<0.0005,****p<0.0001.

646 CORONARY ARTERY PLAQUE COMPOSITION AND SEVERITY RELATE TO THE INFLAMMASOME IN HIV

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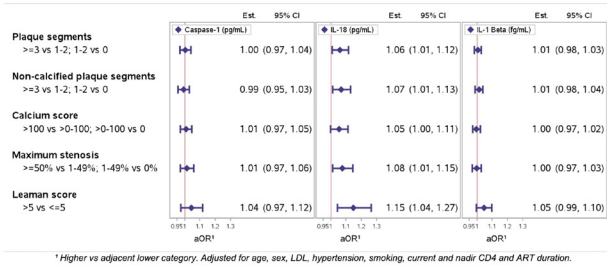
Background: The inflammasome, an innate immune system component that regulates the secretion of powerful proinflammatory cytokines, has increased activity in people with HIV (PWH) despite antiretroviral therapy (ART). However, the relationship between the inflammasome and coronary artery plaque composition and severity is unknown.

Methods: The Randomized Trial to Prevent Vascular Events in HIV (REPRIEVE) enrolled PWH aged 40-75 on stable ART with low-moderate ASCVD risk. In a subset of participants, cross-sectional relationships between inflammasome activation products and coronary plaque indices by coronary computed tomography angiography were explored. The relationships of caspase-1, IL-1ß, and IL-18 to five qualitative measures of plaque burden and composition were assessed via binary (Leaman score) or ordinal logistic regression, adjusted for age, natal sex, LDL, hypertension, smoking, current and nadir CD4, and ART duration. Ordinal models assumed proportional adjacent category odds.

Results: Among 752 participants, median age was 50, 18% were women, and median ASCVD risk score was 4.5%. Median current CD4 was 601, 51% had a nadir CD4 < 200, and 98% had a HIV viral load < 400. Caspase-1 and IL-18 were 12-16% lower in women vs men (P< 0.05 for both). IL-18 was 51% higher in those with VL >400 vs undetectable (P=0.001). No evidence of association was seen between inflammasome biomarkers and age, BMI, and current and nadir CD4. After adjustment, each 25% higher IL-18 was associated with greater odds of worse plaque (6%), non-calcified plaque (7%), and degree of stenosis (8%) (P≤0.03 for all; Figure). Each 25% higher IL-18 was associated with 15% higher odds of Leaman score >5 vs ≤5 (P=0.006). A 25% higher IL-1ß was associated with 5% greater odds of having a Leaman score >5 (vs ≤5), but this did not reach statistical significance (P=0.08).

Conclusion: Among treated PWH at low-to-moderate ASCVD risk, higher inflammasome activation markers were seen in men and those with persistent viremia. Higher IL-18 was consistently associated with multiple measures of calcified and non-calcified plaque as well as Leaman score, which integrates degree of stenosis and plaque location and composition into a single index. Given this and Leaman score's (>5) known association with increased major adverse cardiovascular events (MACE) in the general population, future research is needed to determine whether anti-inflammasome therapeutics may mitigate the progression of atherosclerotic plaque or MACE in PWH.

Adjusted Odds Ratios per 25% Higher Caspase-1, IL-18, and IL-1B



¹ Higher vs adjacent lower category. Adjusted for age, sex, LDL, hypertension, smoking, current and nadir CD4 and ART duration.

647 BURDEN OF CORONARY DISEASE IN TRANSGENDER WOMEN WITH AND WITHOUT HIV

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Background: Cardiovascular disease (CVD) burden in transgender women (TW) may be affected by gender-affirming hormonal therapies (GAHT), HIV and antiretroviral therapy (ART), but few data exist comparing TW on contemporary GAHT and ART to well-matched controls. We compared CVD burden and sex hormone profiles between TW and matched cisgender men (CM).

Methods: Adult TW on GAHT (n=31) were recruited from Houston, TX and Baltimore, MD for a cross-sectional study (2018-2020). CM (n=60) from the Multicenter AIDS Cohort Study were matched (2:1) to TW on HIV serostatus, age ±5 years, race/ethnicity, BMI category and ART type. All HIV+ persons had HIV-1 RNA < 50 copies/ml on ART. Subclinical coronary atherosclerosis was measured by computed tomography (CT) angiography. Serum was collected concurrent to CTs; sex hormone concentrations were measured centrally. Student's t, Kruskal-Wallis or Chi-square tests compared groups; correlations were determined using Pearson or Spearman testing.

Results: Overall, median age was 53 years and BMI 29 kg/m^2; 73% were non-white and 75% HIV+. Only 31% of TW had testosterone suppression (< 50 ng/dl, TW-S). Traditional CVD risk factors were similar, except that the subset of TW-S had higher BMI (34 kg/m^2) than TW with detectable testosterone (TW-T) and CM. Compared to CM and TW-T, TW-S with and without HIV had similar prevalences of calcified and mixed plaque, but none had non-calcified plaque or stenosis >50% (Table). Estradiol but not T correlated with mixed plaque (r=0.27, p< 0.01) and total plaque and total stenosis (both r=-0.21, p=0.05).

Conclusion: In older TW with suppressed total testosterone on GAHT, no non-calcified coronary plaque or advanced stenosis was observed, while CM and TW with detectable testosterone had equivalent subclinical CVD burden. Observations occurred independent of HIV serostatus and despite similar traditional CVD risk factor profiles to CM and more obesity among TW with suppressed testosterone. Longitudinal studies to understand relationships between GAHT and CVD risk in TW are needed.

Coronary plaque and stenosis burden and sex hormone concentrations.

	CM (n=60)	TW-T (n=21)	TW-S (n=10)
Any coronary plaque	68%	58%	44%
Non-calcified plaque*	47%	43%	0%
Mixed plaque	35%	11%	22%
Calcified plaque	45%	42%	44%
Any stenosis >50%	20%	16%	0%
Estradiol (pg/ml)*	22.4 (17.9, 28.6)	75.0 (30.8, 120.0)	96.1 (62.5, 308.2)
Total testosterone (ng/dl)*	440 (347, 570)	532 (310, 764)	13 (11, 16)
Free testosterone (ng/dl)*	12.8 (10.0, 15.8)	13.2 (6.9, 17.7)	0.6 (0.5, 0.6)

Frequency or median and interquartile range presented
*=p<0.05 between CM and TW-S
CM=cisgender men, TW-T=transgender women with detectable total testosterone (≥50 ng/dl), TW-S= transgender women with undetectable total testosterone

648 MUSCLE QUALITY IS ASSOCIATED WITH CORONARY ARTERY PLAQUE & PHYSICAL FUNCTION IN PWH

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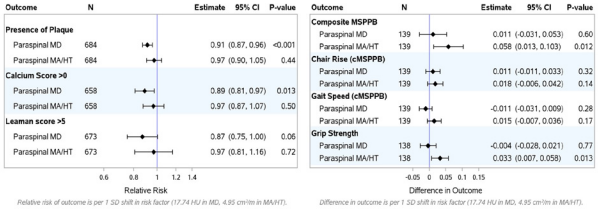
Background: Skeletal muscle quality and mass are critically important for maintaining physical function during advancing age. We leveraged baseline data from REPRIEVE to evaluate whether paraspinal muscle density (MD) and muscle area (MA) are associated with cardiac or physical function outcomes in people with HIV (PWH).
Methods: REPRIEVE is a double-blind randomized trial evaluating the effect of pitavastatin for primary prevention of coronary artery disease (CAD) in PWH. This cross-sectional analysis focuses on participants who underwent coronary CT at baseline. Lower thoracic paraspinal MD (Hounsfeld units, HU) and MA (cm^2) were assessed on non-contrast CT image. MA was divided by height to allow examination of associations across various body sizes (MA/HT). Physical function was standardized by maximum performance. Associations between muscle measures (risk factors) and baseline coronary CT and physical function measures (outcomes) were evaluated using log-binomial regression and linear regression models adjusted for age, sex, and body mass index (physical function only).
Results: Of 805 PWH, 708 had paraspinal measurements. Median age was 51 (Q1, Q3: 46, 55) years; 17% were natal female, 53% White, 36% Black, and 25% Hispanic. The median MD was 41 (31, 49) HU in males and 30 (16, 39) HU in females, and MA/HT 13.2 (9.4, 16.3) cm^2/m in males and 9.9 (7.5, 13.2) cm^2/m in females. In adjusted analyses, higher MD (less fat) was associated with lower prevalence of coronary artery plaque, lower prevalence of coronary artery calcium score >0, and lower prevalence of high plaque burden (Leaman score >5; p=0.06), while MA/HT was not associated with cardiac measures (Figure panel a). Among the 139 with baseline physical function measures, greater MA/HT was associated with better performance on a short physical performance battery and grip strength, while no associations between MD and physical function measures were apparent (Figure panel b).
Conclusion: Higher MD (less fat) was associated with lower prevalence of CAD, while higher MA was associated with better physical performance in PWH. Whether changes in muscle fat or area (especially if associated with pitavastatin) are associated with changes in CAD or improved physical performance will be evaluated as part of the REPRIEVE longitudinal analyses.

Figure: Associations of Paraspinal Muscle Measures with Coronary Artery Plaque and Physical Function



649 PERICORONARY ADIPOSE TISSUE DENSITY AND SUBCLINICAL CORONARY ARTERY DISEASE IN HIV

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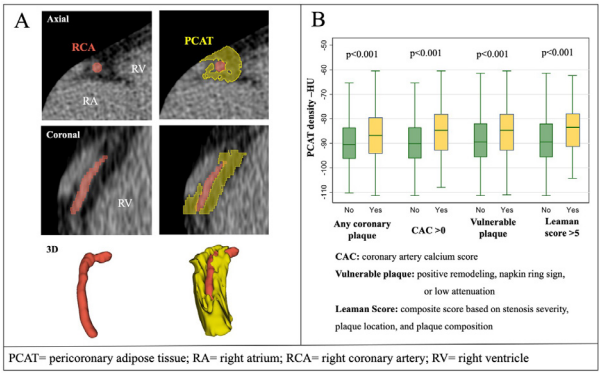
Background: HIV infection is associated with increased immune activation and inflammation, higher coronary artery disease (CAD) prevalence, and adverse cardiovascular outcomes.
Here, we relate pericoronary adipose tissue (PCAT) density, an index of pericoronary inflammation, to the presence and extent of CAD in people with HIV (PWH) and non-HIV controls.
Methods: In this baseline analysis of the Mechanistic Substudy of the Randomized Trial to Prevent Vascular Events in HIV (REPRIEVE) and non-HIV controls from the Framingham Heart Study (FHS), we related CT-derived PCAT density (**Fig. 1A**) to presence and extent (Leaman score) of CAD, coronary artery calcium (CAC) score, and vulnerable plaque (VP) features in PWH using multivariable logistic regression analysis. In addition, we compared the PCAT density between PWH in REPRIEVE (n=727) and age, sex, body mass index (BMI), and CAC score-matched non-HIV controls (N=590) from the FHS by t test and random effects modeling, further adjusting for additional clinical covariates.
Results: The REPRIEVE analytic cohort included 608 males and 119 females (median age 51 years). In REPRIEVE, PCAT density was higher in those with coronary plaque, CAC score >0, vulnerable plaque, and high CAD burden (Leaman >5) (p< 0.001 for all; **Fig. 1B**). In a multivariable analysis, PCAT density was related to prevalent CAD on coronary CTA (aOR [per 10 HU])= 1.51; 95% CI: 1.26–1.80; p< 0.001), adjusted for clinical cardiovascular risk factors, BMI, systemic immune/inflammatory biomarkers, and HIV-specific parameters including CD4, viral load, and ART duration. Similar results were found for the other CT indices of CAD (CAC: aOR= 1.72; 95%CI: 1.42–2.08; p< 0.001; VP: aOR=1.34; 95%CI: 1.10–1.63; p=0.003; Leaman score >5 aOR: 2.0; 95%CI: 1.56–2.57; p< 0.001). PCAT density was increased among REPRIEVE participants compared to FHS controls (-87.9±10.2 vs. -90.8±9.1 HU; p< 0.001) and remained significant in least squares random effects modeling (p=0.01).
Conclusion: Among PWH in REPRIEVE, a large primary CVD prevention cohort, increased PCAT density is independently associated with prevalence and severity of CAD. Moreover, PCAT density was higher among PWH in REPRIEVE than non-HIV controls. These data provide novel evidence linking increased pericoronary inflammation to CAD in PWH. Understanding the mechanisms and longer-term consequences of increased pericoronary inflammation may help guide preventive strategies for improved cardiovascular health in PWH.

Pericoronary Adipose Tissue Density in REPRIEVE



PCAT= pericoronary adipose tissue; RA= right atrium; RCA= right coronary artery; RV= right ventricle

650 SPATIAL PROFILING OF CORONARY PLAQUE SUGGESTS UNIQUE IMMUNE PATHWAYS IN HIV

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Background: Persons with HIV (PWH) have twice the risk of developing cardiovascular disease (CVD) and a greater burden of non-calcified coronary plaque, which is more likely to rupture. Although higher levels of systemic and local inflammation may contribute to altered plaque formation, there are few studies on coronary plaque content in PWH versus HIV-negative controls. We hypothesized that HIV alters the local inflammatory response within coronary plaques, thus contributing to the increased risk of CVD.

Methods: We obtained coronary arteries with varying stages of atheroma from deceased PWH (n=13) and matched HIV-negative donors (n=15). We measured virus copies within coronary arteries using droplet digital polymerase chain reaction (ddPCR) for HIV, cytomegalovirus (CMV), and human endogenous retrovirus (HERV K). We performed an unbiased analysis with a spatial whole transcriptomic approach (n=7 per group) and defined specific immune markers by targeted spatial transcriptomics, proteomics, and immunohistochemistry. Comparisons of immunohistochemistry results used Mann-Whitney U tests, and comparisons of multiple regions of interest used linear models for microarray data (LIMMA) with Benjamini Hochberg correction.
Results: Among coronary arteries matched by plaque type (pathological intimal thickening, early and late atheroma), plaque area, and stenosis (**Figure 1A-B**), we detected viral RNA sequences for HIV in 77% (10/13) of coronary arteries from PWH, while CMV was detected in 46% (6/13) of PWH and 53% (8/15) of controls. Coronary arteries from all donors had detectable HERV-K. The RNA transcriptomes differed by HIV status with enrichment of genes in several inflammatory pathways including the interferon signaling and nonsense-mediated decay pathway in PWH (**Figure 1C**). Partial Spearman rank correlation adjusted for plaque type in the PWH showed a significant relationship between HIV copies with STING, CD3, and VCAM1 protein expression.
Conclusion: The presence of HIV within the coronary arteries alters the immune environment with stimulation of several pathways such as interferon-gamma and the non-sense mediated decay pathway. Notably, the presence of other chronic viruses such as CMV or HERV K does not appear to differ by HIV status. HIV may be an important accelerator of atherosclerosis and increased CVD risk in PWH. Further studies are underway to establish whether intact virus, viral sequences or modified host DNA stimulate inflammation within coronary plaques.

Characterization of coronary plaques

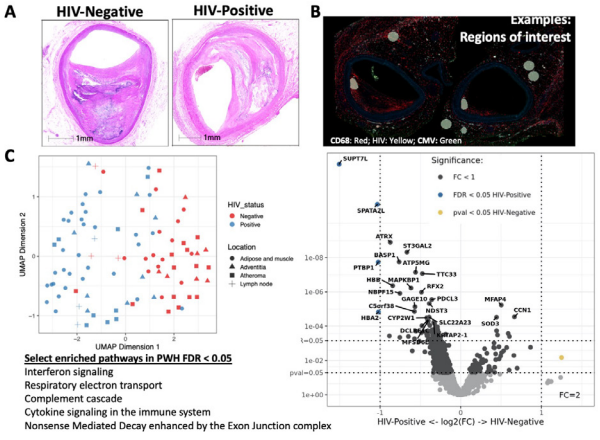

Figure 1. Characterization of coronary plaques. (A) Representative coronary plaques from HIV-positive and HIV-negative individuals were stained with H&E stain. (B) Representative image showing regions of interest selected for spatial transcriptomics, and (C) UMAP showing regions of interest clustered by HIV status, with differential gene expression and select pathways highlighted.

651 HIGH PLASMA APOE IN PEOPLE WITH HIV COMPARED WITH UNINFECTED CONTROLS

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Background: High levels of apolipoprotein E (apoE) in plasma are associated with increased risk of cardiovascular disease and all-cause mortality in the general population. *APOE* gene polymorphism accounts for 15-25% of variability in plasma apoE, but plasma apoE still vary between individuals with the same APOE genotype. Our aims were to assess if HIV is an independent risk factor for high plasma apoE and to determine HIV related risk factors for high plasma apoE.
Methods: We included 661 people with HIV (PWH) frequency matched 1:1 on age and sex with uninfected controls from the general population. Only people of Danish ancestry were included to minimize differences in APOE genotypes. Both PWH and controls underwent physical examination, filled out extensive questionnaires and had blood samples drawn according to the same study protocol.
High plasma apoE was defined as apoE levels above the 9th decile. The association between plasma apoE and HIV status was explored using both linear and logistic regression models adjusted for age, sex, body mass index, hypertension, diabetes, smoking, alcohol and plasma lipids. In PWH linear and logistic regression models were used to determine HIV-specific risk factors for high plasma apoE.
Results: Mean age was 52 years and 11% were female in both groups. Median plasma apoE was 49.0 mg/L in PWH and 43.3 mg/L in controls. High apoE was defined as above 66.2 mg/L.
In adjusted linear models PWH had 6.6 mg/L higher plasma apoE compared with controls [95%CI: 5.1 to 8.1 mg/L], p< 0.001. PWH also had higher odds of high plasma apoE with adjusted odds ratio (OR) of 2.55 [1.63, 3.99], p< 0.001. In age-adjusted analyses stratified by sex the estimated ORs for each sex were similar (OR 2.03 [1.35, 3.04], p< 0.001 for males and OR 2.02 [0.69, 5.89], p=0.20 for females).
In PWH, previous AIDS defining disease was associated with 4.50 mg/L higher plasma apoE [1.52, 7.48 mg/L], p=0.003 in sex- and age-adjusted analysis. Previous AIDS was also associated with higher odds of high apoE (OR 1.78 [1.03, 3.06], p=0.04) in unadjusted analysis, but not in adjusted models. CD4 nadir, detectable viral load, and exposure to old generation anti-retroviral therapy was not associated with plasma apoE levels.
Conclusion: PWH had higher concentrations of plasma apoE compared with uninfected controls even after adjusting for plasma lipids. Previous AIDS defining disease was associated with higher plasma apoE. Further studies are needed to elucidate the clinical impact of high plasma apoE in PWH.

652 PERFORMANCE OF LDL CHOLESTEROL POLYGENIC RISK SCORE IN INDIVIDUALS WITH HIV INFECTION

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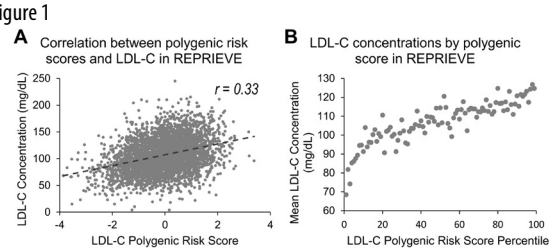
Background: Coronary artery disease (CAD) is a leading cause of death among the 37 million people with HIV (PWH) globally. Available cardiovascular disease (CVD) risk predictors underperform in this population. While alleles that influence LDL-C concentration summed as a polygenic risk score (PRS) predict LDL-C and CAD in the general population, their influence among PWH is not well understood.
Methods: A new PRS for LDL-C was constructed using PRS-CS, incorporating the weighted effects of over 1 million single nucleotide polymorphisms associated with LDL-C from over 1.9 million individuals without HIV from the Global Lipids Genetics Consortium, European Network for Genetic and Genomic Epidemiology, Biobank Japan, Genes and Health Study, and Million Veterans Program. Scores were trained in the UK Biobank then calculated using TOPMed-imputed genotypes from a global cohort of ART-treated PWH with low-to-moderate CVD risk enrolled in Randomized Trial to Prevent Vascular Events in HIV (REPRIEVE). Genotyping was performed on Illumina Infinium HTS. Linear and logistic regressions were performed to predict baseline lipid profiles in 4177 genotyped participants and markers of subclinical CAD including presence of plaque, calcification, or stenosis in a subset of 639 participants who received coronary computed tomography angiography (CT sub-study).
Results: Among a cohort of 4177 REPRIEVE participants (mean [SD] age 49.8 [6.3] years, 36.1% female; 56.5% African, 12.6% East Asian, 21.2% European, 9.6% South Asian ancestries), LDL-C PRS was correlated with fasting LDL-C (r = 0.33, p < 1E-97; Figure 1A), total cholesterol (r = 0.29, p < 1E-72), and oxidized LDL-C (r = 0.15, p < 1E-3). The mean [SD] LDL-C was 107.2 [30.7] mg/dL. Each standard deviation of the LDL-C PRS was associated with a 10.2 (95% CI 9.3 – 11.1, p< 0.001) mg/dL increase in LDL-C. The difference in LDL-C between the top and bottom one percentiles of the LDL-C PRS in REPRIEVE was 56.2 mg/dL (Figure 1B). Similar association results were identified in subgroups stratified by

self-reported ancestry and sex. Among 639 participants in the CT sub-study, we did not detect an association between LDL-C PRS and markers of subclinical CAD.
Conclusion: Among ART-treated PWH in REPRIEVE, a newly developed PRS for LDL-C was associated with levels of LDL-C, total cholesterol, and oxidized LDL-C, but not with subclinical CAD. Future analyses within REPRIEVE will assess whether LDL-C PRS predicts major adverse cardiovascular events in this at-risk population.

Figure 1



653 CHOLESTEROL EFFLUX IS REDUCED IN ART TREATED PWH BUT ASSOCIATED WITH SUBCLINICAL CAD

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Background: Impaired cholesterol efflux (MCE) from monocytes may lead to formation of lipid-laden 'foam cells' which are implicated in atherosclerotic coronary artery disease (CAD). Monocyte cholesterol efflux (MCE) may be impaired in people with HIV (PWH) with evidence of persistent abnormalities after antiretroviral therapy (ART) initiation, however, it is unclear whether this is associated with subclinical CAD.
Methods: We examined MCE *ex vivo* in monocytes isolated from PWH, virally suppressed on ART and propensity score (incorporating traditional CAD risk factors) matched uninfected controls. We measured total MCE as well as ABCA1-dependent MCE by exposing isolated monocytes, pre-incubated with LDL cholesterol, to Apolipoprotein A1 at 6 and 24 hours incubation, with MCE calculated as the ratio of measured intracellular and extracellular cholesterol at each time-point. Associations with MCE and coronary plaque phenotypes, as measured by coronary computer tomographic angiography (CCTA), were assessed using logistic regression. Data are median unless stated otherwise.
Results: Ninety five participants [age 50 (46, 56) years, 72% male, 76% Caucasian, 47 (49.5%) PWH] were included. Risk factors for CAD were evenly distributed across groups with the exception of HDL cholesterol concentration [PWH: 1.3 (1.0, 1.3); controls:1.4 (1.1, 1.7) mmol/l, p= 0.02], and statin use [PWH: 24 (51.1%); controls: 6 (12.5%), p< 0.001]. PWH had significantly less ABCA1-dependent MCE at 6 (T6a) hours [PWH 0.75 (0.6,1.0); controls 1.04 (0.7,1.33), p=0.01], which did not persist to 24 hours [PWH 1.23 (0.8, 1.6), controls: 1.39 (1.0, 1.8), P=0.24]. We did not observe differences in other MCE measures. 33 (35%) participants had evidence of subclinical CAD on CCTA. MCE (T6a) was significantly associated with non-calcified plaque on univariate analysis [Odds ratio 2.4 (95% confidence interval 1.0, 5.78), p=0.05], an association which persisted on adjustment for HIV status, HDL cholesterol, statin use and demographics [Odds ratio 3.4, (95% Confidence interval 0.8, 14.1) p=0.09; figure 1(b)].
Conclusion: PWH on long term ART had reduced ABCA1 dependent MCE compared to CAD risk matched controls. That MCE (T6A) was associated with non-calcified plaque gives further insights into the role of Monocyte/macrophages in CAD pathogenesis and warrants further investigation into potential mechanisms underlying the increased risk of CAD in PWH.

Figure 1: (a) Monocyte Cholesterol Effflux at 6 hours incubation with and without ApoA1 and (b) associations with subclinical CAD

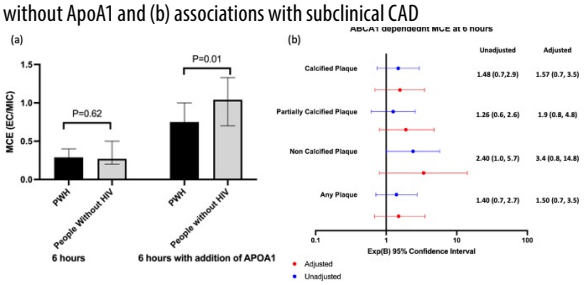

Figure 1: (a) Monocyte Cholesterol Effflux at 6 hours incubation with and without ApoA1 and (b) associations with subclinical CAD
MCE, Monocyte Cholesterol Efflux; EC, extracellular cholesterol; MIC, monocyte intracellular cholesterol; ApoA1, Apolipoprotein A1;
(a) Data reported as median with interquartile range; (b) logistic regression analysis, data reported as odds ratio (95% confidence interval), Adjusted for Demographics, HIV status, HDL cholesterol concentration and statin therapy

654 SMOKING CESSATION AND SHORT-TERM VASCULAR IMPROVEMENT IN A COHORT OF PEOPLE WITH HIV

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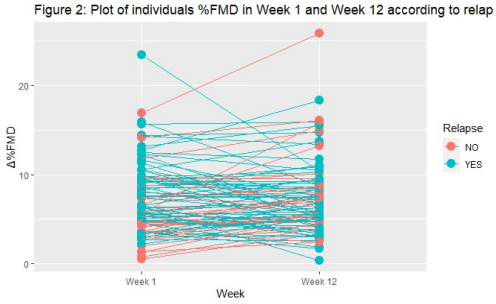
Background: Smoking is highly prevalent in people living with HIV/AIDS (PLHA) producing detrimental effects in different organs and leading to illness. There is limited evidence about pharmacological interventions for treating nicotine dependence in PLHA. We examined if Nicotine replacement therapy (NRT) is an option for smoking cessation and ameliorates vascular health in this specific population
Methods: From December 2019 to April 2022, we prospectively enrolled PLHA who were actively smoking in our center. The primary outcome of interest was to assess the effect of NRT plus counseling on smoking cessation and endothelial function measured by brachial artery flow-mediated dilatation (FMD). Statistical analysis evaluated the change in %FMD (Δ%FMD= %FMD at week12-%FMD at baseline) to test the hypothesis that Δ%FMD would improve among participants who quit smoking compared to those who relapse. To confirm the results, we have run multiple linear regression to account for classical cardiovascular (CV) confounders. Results are presented in medians (interquartile ranges) and percentages
Results: We included 117 participants with median age of 45.5 years (IQR= 36.4-54.8); 29 (25.4%) had hypertension, 10 (8.8%) had diabetes and 33 (28.4%) had dyslipidemia, almost half were smoking 20+ cigarettes/day (41.4%). Individuals were living with HIV for a median of 10.9 years (5.6-17.6) and were on antiretroviral therapy for 8.6 years (3.7-13.6) with median Nadir of CD4 of 307 (153-490.5). Baseline of median brachial artery diameter was 3.6 mm (IQR= 3.2-4.1). Unadjusted analysis showed that years of smoking, younger age and white race were associated with poor %FMD (75th per centile). After 12 weeks 44.4% participants quit smoking. Comparison of Δ%FMF change from baseline to week 12 showed that among participants adherent to therapy, there has been an increase in Δ%FMD when compared to those who relapsed (1.17% [0.29-2.98] vs -0.19% [-1.9-0.91], p< 0.001). After adjustment for CV factors, multiple linear regression showed that participants who quit smoking present a mean of 2.54 (p=0.001) points increase in Δ%FMD in comparison to those who continued to smoke.
Conclusion: This study provides evidence that a strategy of NRT and counseling is effective for smoking cessation in PLHA leading to an improved vascular health in a short period of time. This reinforces the importance of the widespread anti-tobacco programs in HIV clinics and the expected impact lowering the incidence of future cardiovascular events

Figure 2: Plot of individuals %FMD in Week 1 and Week 12 according to relap



655 AORTIC ANEURYSMS AND MARKERS OF ENDOTHELIAL AND PLATELET ACTIVATION IN PLWH

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COCOMO study
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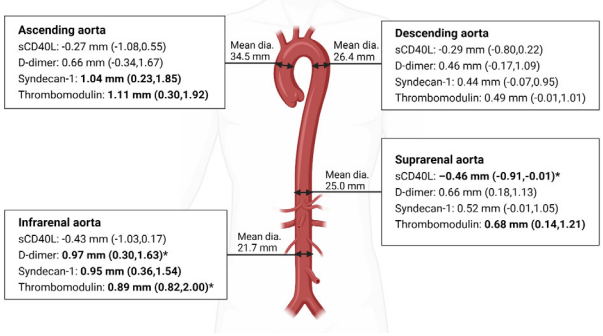
Background: People living with HIV (PLWH) have more than four times higher odds of aortic aneurysms (AA) compared with the uninfected population. There are currently no studies of biomarkers of AA in PLWH. We aimed to investigate if sCD40L, D-dimer, syndecan-1, and thrombomodulin were associated with AA in PLWH.

Methods: From the Copenhagen Comorbidity in HIV Infection (COCOMO) study, PLWH ≥40 years of age with an available contrast-enhanced CT scan and available biomarker analyses were included. AA was defined according to guidelines. The biomarkers were analysed on thawed plasma using Luminex®, a multiplex custom-designed assay. For each biomarker, levels in the upper quartile were defined as "high concentration". For D-dimer, the cut-off was defined as the lower limit of detection. Using adjusted logistic and linear regression models, we analysed associations between AA and sCD40L, D-dimer, syndecan-1, and thrombomodulin, respectively, in PLWH.

Results: We included 571 PLWH in whom 43 AA were found in 39 (6.8%) individuals. The median (IQR) age was 52 years (47-60), 88% were male, median (IQR) time since HIV diagnosis was 15 years (8-23), and 565 (99%) were currently on antiretroviral treatment. High concentration of sCD40L was associated with lower odds of AA (adjusted odds ratio, aOR: 0.23 (95% CI 0.07-0.78; P=.019)), and high concentration of D-dimer was associated with higher odds of AA (aOR: 2.22 (95% CI 1.02-4.85; P=.045)). Syndecan-1 and thrombomodulin were not associated with AA (P=.52 and P=.47, respectively). In linear regression, high concentration of sCD40L was associated with 0.46 mm (95% CI: 0.01 to 0.91) mm smaller suprarenal aorta; high D-dimer was associated with 0.97mm (0.30 to 1.63) larger infrarenal aorta; high concentration of syndecan-1 was associated with 1.04 mm (0.23 to 1.85) larger ascending aorta and 0.95 mm (0.36 to 1.54) larger infrarenal aorta; and high concentration of thrombomodulin was associated with 1.11mm (0.30 to 1.92) larger ascending aorta, 0.68mm (0.14 to 1.21) larger suprarenal aorta and with 0.89mm (0.82 to 2.00) larger infrarenal aorta.

Conclusion: Prevalence of AA is high in PLWH. sCD40L was associated with lower odds of AA and D-dimer was associated with higher odds of AA in PLWH calling for further investigations into specific biomarkers to aid early diagnosis of AA in PLWH.

Aortic diametres and markers of endothelial and platelet activation, and haemostasis in PLWH



656 BMI MEDIATES THE LINK BETWEEN HIV-RELATED FACTORS AND HYPERTENSION BUT NOT DIABETES

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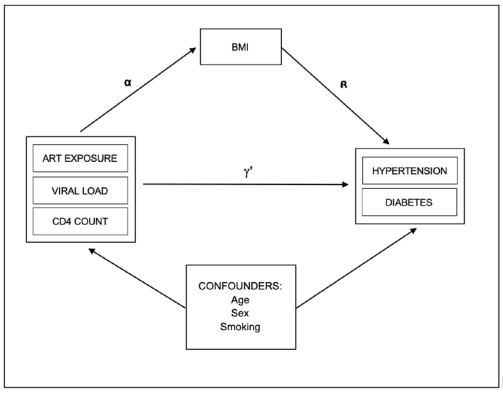
Background: HIV infection has been associated with an increased cardiometabolic risk profile, due to the HIV virus and the effects of ART. However, the nature of the causal pathway is unclear. This study aims to assess the mediating effect of body mass index on the association between HIV-related factors (ART exposure, CD4 count and viral load) and hypertension and diabetes mellitus (hereinafter referred to as diabetes) among people living with HIV/AIDS in a Sub-Saharan Africa setting.

Methods: This cross-sectional study included 14,119 consenting adults enrolled in the International Epidemiology Databases to Evaluate AIDS (IeDEA) in Cameroon, between 2016 and 2021. Hypertension was defined as Systolic BP (SBP) ≥140/90 mmHg and/or current use of antihypertensive medication while diabetes was defined as an elevated Fasting Blood Sugar (FBS) ≥126 mg/dL or use of antidiabetic medications. We conducted a causal mediation analysis through a nonparametric bootstrapped method using the "mediation" package for causal mediation analysis in R. The exposures were ART exposure (binary), viral load (continuous) and CD4 count (continuous), assessed individually. The mediator was BMI (continuous) and the outcomes were either diabetes (binary) or hypertension (binary). We adjusted for the confounders, age, sex, and smoking (Figure 1).

Results: The study population was made up of 9,177 (65%) women, 1,694 (12%) were obese (BMI ≥ 30 kg/m^2) and 8,869 (63%) had been exposed to ART. The median(IQR) CD4 count was 373.0 (199.2, 565.0) cells/mm^3 and the median (IQR) viral load was 1.6 (0.0, 1.9) $\log_{10}$ copies/mL. BMI significantly mediated the total effects of ART exposure (estimate: 0.02, 95% CI: 0.015 to 0.025, 43.9% mediated), viral load (estimate: - 0.003, 95% CI: - 0.003 to 0.00, 26.9% mediated) and CD4 count (estimate: 5.23 x 10^{-5}, 95% CI: 4.16 x 10^{-5} to 0.00, 68.7% mediated) on hypertension. However, the mediating effect of BMI on the relationship between ART use, viral load and CD4 count, and diabetes was not observed.

Conclusion: These findings suggest that BMI partially mediates the association between ART use, CD4 count and viral load and hypertension but not diabetes, among people living with HIV when controlled for traditional cardiovascular risk factors. This study underscores the importance of BMI as a useful measure for assessing hypertension and diabetes among people living with HIV.

Mediation model for the association between HIV related factor (ART exposure, CD4 count or viral load) and hypertension or diabetes; with body mass index (BMI) as the mediator and age, sex and smoking as confounders.



657 RACIAL AND HIV DISPARITIES IN HYPERTENSION TREATMENT CASCADE AMONG WOMEN

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Background: Management of hypertension has emerged as a priority among women living with HIV (WLHIV). Our goal was to evaluate cross-sectional associations of race/ethnicity and HIV status with prevalence, awareness, treatment, and control of hypertension among women participating in the Women's Interagency HIV Study (WIHS).

Methods: This study included women who were recruited into WIHS Southern sites between 2013 and 2015. Hypertension was defined as systolic blood pressure ≥140 mmHg, diastolic blood pressure ≥90 mmHg, self-report, or use of anti-hypertensive medication. Awareness was self-reported as ever having hypertension and treatment was reported use of anti-hypertensive medication for hypertension. Blood pressure control was defined as < 140/90

mmHg as aligned with clinical guidelines when baseline data were collected. Prevalence ratios (PRs) for each hypertension outcome were estimated using Poisson regression models with robust variance estimates adjusted for sociodemographic, behavioral, and clinical risk factors.

Results: Among 712 women participating in WIHS Southern sites, 602 (84%) were non-Hispanic (NH) Black, 70 (10%) were NH White, and 40 (6%) were Hispanic, including 493 (69%) WLHIV. The average age was 43 years and 401 (56%) had hypertension. Eighty-three percent of women with hypertension were aware of their diagnosis. Of those aware, 83% were currently taking anti-hypertension medication and 63% of women who were treated for hypertension had documentation of controlled hypertension. We found that NH White and Hispanic women had lower prevalence of hypertension compared to NH Black women [PR 0.70 (95% CI 0.54–0.90) and PR 0.52 (95% CI 0.32–0.85), respectively, p< .0001]. Additionally, Hispanic women had better controlled hypertension compared to NH Black women [PR 2.16 (95% CI 1.54–3.01), p< .0001]. WLHIV who had hypertension were more likely to be on anti-hypertension medication compared to women without HIV [PR 1.19 (95% CI 1.01–1.40), p=.0345] (Figure 1).

Conclusion: In this study population of women living with and without HIV in the U.S. South, prevalence of hypertension was lowest among Hispanic women and highest among NH Black women. Control of hypertension was lowest among NH Black women. Awareness and treatment were similar among race/ethnicity. Women without HIV were less likely to be on anti-hypertensive medication compared to WLHIV although prevalence of hypertension was similar between both groups.

Proportion of hypertension outcomes by race/ethnicity and HIV status

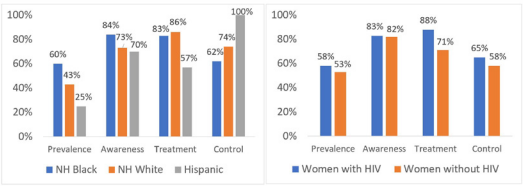

Figure 1. Proportions of hypertension outcomes by race/ethnicity and HIV status

658 DOLUTEGRAVIR EXPOSURE, BUT NOT BICTEGRAVIR, INCREASES *IN VITRO* PLATELET AGGREGATION

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Background: In the modern era of effective antiretroviral therapy (ART), people living with HIV (PLWH) have near-normal life-expectancies, but two times higher occurrence of cardiovascular disease (CVD) that is associated with some antiretrovirals. We have previously reported that certain nucleotide reverse transcriptase inhibitors (NRTIs) enhance platelet and endothelial activation promoting a pro-thrombotic phenotype. Little is known, however, about the off-target cellular effects of integrase inhibitors (INSTIs). Here, we aimed to compare the effects of two commonly prescribed INSTIs, bictegravir (BIC) and dolutegravir (DTG) on platelet activation to better understand their comparative off-target effects on CVD risk.

Methods: Platelets were isolated from whole blood obtained by informed consent from HIV-negative donors (60% male, aged 25 ±3 yrs). Platelets were exposed *in vitro* to clinical plasma C_{max} concentrations of BIC, DTG or vehicle (Veh) control for 30min. Platelet activation was assessed in response to collagen [1-30µg/ml], ADP or thrombin receptor activator peptide (TRAP)-6 [1-30µM] by light transmission aggregometry and flow cytometry. Results were statistically analysed using a 2-way ANOVA with a Tukey's multiple comparison test.

Results: DTG treatment induced a significantly higher degree of ADP-evoked platelet aggregation compared to BIC (+1.79-fold, p=0.0271) and Veh (+1.82-fold, p=0.0040) at low ADP concentrations [3µM]. Similar effects were observed with TRAP-6 [10µM], with DTG-treated platelets showing higher aggregation compared to BIC (+1.45-fold, p=0.0110) and Veh (+1.88-fold, p=0.0131) treatment. Collagen-activated platelets [3µg/ml] exposed to DTG had +1.94-fold higher percentage aggregation compared to Veh group (p=0.0188). No significant changes in platelet degranulation were observed between the different groups.

Conclusion: Our results suggest that DTG may make platelets more sensitive to low level ADP and collagen stimulation, through an as yet undiscovered activation mechanism. This may suggest that DTG, but not BIC, has the potential to increase CVD risk. Further evaluation of platelet activation *in vivo* and in clinical settings is required to determine the contrasting off-target effects of DTG and BIC in patients. Ultimately, this work may lead to the identification of treatment regimens with a lower CVD risk, providing a safer option when treating PLWH.

659 MARIJUANA USE AND THE RISK OF INCIDENT VENOUS THROMBOEMBOLISM IN PEOPLE WITH HIV

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Background: People with HIV (PWH) are at an increased risk of venous thromboembolism (VTE). Among PWH, marijuana use is common. Marijuana has been shown to display both procoagulant and anticoagulant effects on the blood, however its effect on VTE in PWH has not been evaluated. We aimed to assess whether there is an association between marijuana use and incident VTE among PWH.

Methods: We conducted a cohort study using data from the Centers for AIDS Research Network of Integrated Clinical Systems (CNICS), a US-based, multisite cohort of PWH. Marijuana use was obtained from a clinical assessment of patient reported outcomes on substance use collected as part of care using the modified ASSIST instrument. VTEs were assessed using multiple ascertainment criteria and then centrally adjudicated by at least 2 expert physician reviewers. Only first VTEs were included among PWH who have had more than one. Cox models were used to determine the association of incident VTE with marijuana use. Models were adjusted for age, sex, other substance use, CD4 cell count, HIV viral load, diabetes, hypertension, dyslipidemia, chronic kidney disease (CKD [eGFR< 30]), Hepatitis C (HCV), and Hepatitis B (HBV) co-infection.

Results: Among 12,515 PWH in care between 2009 and 2019 at 6 CNICS sites across the US, 213 (1.7%) experienced a VTE. Mean follow up was 4.5 years, mean age was 44 years, 17% were female, 45% were white, and 32% reported current marijuana use (defined as any use in the past 3 months). Around 18% had dyslipidemia, 16% had HCV co-infection, 9% had diabetes, and 1% had CKD. The mean CD4 count was 532 cells/mm^3 and 19% had a viral load >400 copies/mL. In adjusted models, former (adjusted hazard ratio [aHR] 0.83, 95% CI 0.57-1.20) and current (aHR 0.78, 95% CI 0.51-1.13) marijuana use were not associated with a significant increase in VTE incidence compared to never users. Furthermore, no association was observed between frequency of marijuana use and risk of incident VTE, suggesting there is no dose-dependent increase in VTE risk.

Conclusion: Among PWH there seems to be no evidence of increased VTE risk with the use of marijuana, and so VTE risk mitigation does not need to specifically consider marijuana use.

Association between marijuana use and VTE in adjusted Cox models (n=12,515)

Parameter	Adjusted HR (95% CI)	p-value
Model 1		
Marijuana use		
Never (REF)	1.00	
Former	0.83 (0.57-1.20)	0.324
Current	0.76 (0.51-1.13)	0.178
Model 2		
Frequency of marijuana use		
Current Infrequent user (REF)	1.00	
Never	1.35 (0.84-2.16)	0.215
Former	1.12 (0.72-1.74)	0.620
Current Weekly	1.17 (0.61-2.26)	0.630
Current Daily	0.98 (0.55-1.76)	0.952

Note: Model adjusted for age, sex, CD4 cell count, HIV viral load, diabetes, hypertension, dyslipidemia, chronic kidney disease (CKD [eGFR<30]), Hepatitis C (HCV), Hepatitis B (HBV) cigarette smoking, methamphetamine use, and cocaine use.
VTE: Venous Thromboembolism

660 LOW CD4 NADIR AT HIV DIAGNOSIS ASSOCIATES WITH INCREASED RISK OF CLONAL HEMATOPOIESIS

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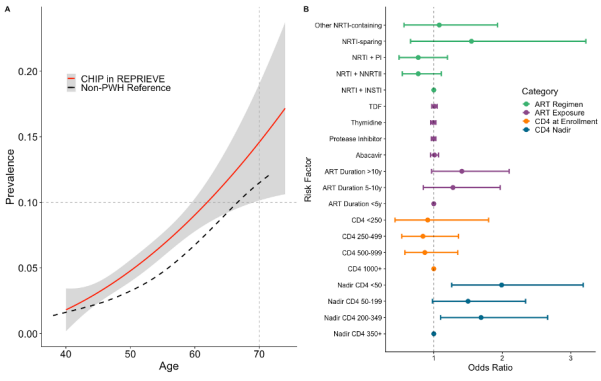
Background: People with HIV (PWH) have excess risk of cardiovascular disease (CVD), which is thought to be related to dysregulated inflammation. Analogously, clonal hematopoiesis of indeterminate potential (CHIP) activates an inflammatory cascade in infiltrating monocytes to promote atherosclerosis. CHIP prevalence is known to be increased in PWH, but whether HIV-specific risk factors are associated with CHIP prevalence or CHIP gene distribution are not known.

Methods: Participants were from a global cohort of ART-treated PWH with low-to-moderate CVD risk enrolled in Randomized Trial to Prevent Vascular Events in HIV (REPRIEVE) with whole exome sequencing (WES) data available. CHIP was identified in blood DNA using the GATK MuTect212 somatic variant calling pipeline. CHIP was defined by the presence of pathogenic somatic variants in genes previously implicated in hematologic cancers with a variant allele fraction (VAF) ≥2% but without hematologic cancer or other non-neoplastic clonal disease. Multiple logistic regression models adjusting for age, sex and race were used to associate CHIP with HIV-specific risk factors.

Results: Among 4486 REPRIEVE participants (mean [SD] age 49.9 [6.4] years, 36.8% female; 46.6% Black, 23.4% Asian, 23.8% White self-reported race), CHIP with a VAF≥2% was identified in 5.0%, and VAF≥10% in 1.9%. CHIP prevalence increased with age and higher than non-PWH reference population (Figure 1A); 2.8% for 40-49, 6.6% for 50-59, 10.2% for 60+ years. The most common driver genes were *DNMT3A* (53.3%), *TET2* (15.6%), *PPM1D* (4.9%), *ASXL1* (4.0%), and *TP53* (4.0%). After adjustment for age, sex and race there were no associations between CHIP and enrollment CD4+ cell count, ART regimen, or specific ART exposures (abacavir, protease inhibitors, thymidine, or TDF (tenofovir disoproxil fumarate)). The odds of CHIP were higher with longer total ART duration, but this trend was not statistically significant (p=0.08). Lower nadir CD4+ was associated with higher odds of CHIP (CD4 nadir < 50 cells/μL vs >350 cells/μL; OR 1.99, p< 0.004, 95% CI 1.26-3.18) (Figure 1B).

Conclusion: Among ART-treated PWH in REPRIEVE, CHIP had a higher prevalence than among a non-PWH reference. A CD4+ cell count nadir < 50 cells/uL was associated with a 2-fold increased odds of CHIP.



661 CIRCULATING BIOMARKERS AND CARDIAC DYSFUNCTION IN WOMEN WITH OR AT RISK FOR HIV

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Background: People with HIV are at greater risk for cardiovascular disease compared with those without HIV, and this risk may be further elevated in women with HIV (WWH). We examined 8 circulating cardiac, metabolic or inflammatory biomarkers in women with or at risk for HIV with echocardiographic data, and assessed whether these markers are associated with cardiac dysfunction.

Methods: Eligible participants from 3 Women's Interagency HIV Study (WIHS) sites underwent transthoracic echocardiography between 2014-2018 and had the following serum biomarkers measured: NT-proBNP, high-sensitivity troponin I (hsTnI), soluble ST2 (sST2), non-esterified free-fatty acids (NEFA), C-reactive protein (hsCRP), interleukin-6 (IL-6), soluble CD14 (sCD14) and growth/differentiation factor-15 (GDF-15). Outcomes included left ventricular (LV) systolic dysfunction (LV ejection fraction < 54%), isolated LV diastolic dysfunction (ASE 2016 definition) and pulmonary hypertension (peak tricuspid regurgitation velocity >2.8 m/s). Biomarkers were $\log_2$-transformed and Z-score standardized, and modified Poisson regression models produced prevalence ratios (PRs) for associations with each outcome, adjusted for demographic, behavioral and cardiometabolic factors.

Results: Data were available for 709 women (68% WWH, median age 52 years, 65% black, 22% Hispanic, 40% smokers). Among WWH, median CD4+ count was 649 cells/uL (IQR 442-869), 93% reported ART use and 69% had HIV viremia < 20 cp/mL. Prevalence was 6% in WWH and 4% without HIV for LV systolic dysfunction, 9% and 8% for isolated LV diastolic dysfunction, and 12% and 9% for pulmonary hypertension. Compared with women without HIV, WWH had higher levels of sCD14 (median 1,792 vs 1,539 ng/mL) and GDF-15 (median 1,069 vs 697 pg/mL, both p< 0.001), with a stepwise gradient by CD4+ count category. In adjusted analyses (**Table**), higher NT-proBNP levels were significantly associated with each outcome, while NEFA, hsCRP and sCD14 levels were associated with LV systolic dysfunction only, and GDF-15 with pulmonary hypertension only. hsTnI was associated with both isolated LV diastolic dysfunction and pulmonary hypertension, and these associations were more pronounced among WWH than women without HIV (e.g., pulmonary hypertension: WWH PR 1.88, 95% CI 1.35-2.62; without HIV PR 1.46, 95% CI 0.95-2.24).

Conclusion: We identified previously unreported associations of several key cardiac biomarkers with cardiac dysfunction, including more pronounced associations of troponin I among WWH.

Associations of circulating biomarkers with cardiac dysfunction*, per Z-score unit.

	LV systolic dysfunction		Isolated LV diastolic dysfunction		Pulmonary hypertension	
Biomarker	Adjusted PR (95% CI)	P-value	Adjusted PR (95% CI)	P-value	Adjusted PR (95% CI)	P-value
NT-proBNP	**1.69 (1.14, 2.49)**	**0.01**	**1.98 (1.51, 2.59)**	**<0.001**	**1.87 (1.45, 2.41)**	**<0.001**
hsTnI	1.27 (0.77, 2.08)	0.35	**2.16 (1.60, 2.92)**	**<0.001**	**1.61 (1.23, 2.12)**	**<0.001**
sST2	1.22 (0.87, 1.71)	0.25	0.96 (0.75, 1.24)	0.77	1.26 (0.99, 1.61)	0.06
NEFA	**1.48 (1.01, 2.17)**	**0.04**	0.74 (0.55, 1.00)	0.05	1.06 (0.84, 1.34)	0.59
hsCRP	**1.41 (1.01, 1.96)**	**0.045**	0.90 (0.69, 1.18)	0.46	1.22 (0.95, 1.58)	0.12
IL-6	1.30 (0.94, 1.79)	0.11	0.97 (0.71, 1.33)	0.87	1.25 (0.96, 1.64)	0.10
sCD14	**1.47 (1.01, 2.14)**	**0.045**	1.19 (0.87, 1.62)	0.28	1.15 (0.86, 1.55)	0.34
GDF-15	1.29 (0.88, 1.90)	0.20	1.18 (0.83, 1.69)	0.35	**1.73 (1.28, 2.34)**	**<0.001**

*LV systolic dysfunction = LV ejection fraction <54%. Isolated LV diastolic function = ASE/EACVI 2016 guidelines definition, only among women with LV ejection fraction ≥54%. Pulmonary hypertension = peak tricuspid regurgitation velocity >2.8 m/s.
CI = confidence interval, LV = left ventricular, PR = prevalence ratio. **Bold** denotes statistical significance at p<0.05. All models adjusted for HIV serostatus, age, race/ethnicity, education, study site, history of injection drug use, crack/cocaine use, current smoking, current alcohol use, history of HCV infection, body mass index, systolic blood pressure, total and HDL cholesterol, use of antihypertension medications, use of lipid-lowering medications, history of diabetes, eGFR and menopause status.

662 CD2/LFA-3 AXIS COSTIMULATION OF CD57+CD28- CD8 T CELLS IN HIV AND ATHEROSCLEROSIS

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Background: Immune activation plays a critical role in people with HIV (PWH) who have an increased risk of cardiovascular disease (CVD), even after controlling for known CVD risk factors. Latent cytomegalovirus (CMV) infection is associated with increased CVD risk for people with and without HIV (PWoH). T cells from CMV+ individuals are enriched with an inflammescent CX3CR1+CD57+CD28- phenotype, suggesting they may require a pathway separate from the canonical CD28 pathway for optimal costimulation. We have shown that CMV coinfection in PWH promotes vascular homing and activation of inflammatory CD4 T cells through the CD2/LFA-3 axis, but a role for CD2/LFA3 costimulation of CD57+CD28- CD8 T cells in CMV+ PWH has not yet been described.

Methods: Cells from PWH (n=46, 17% female), PWoH (n=15, 67% female), and from atherosclerotic plaques of PWoH (n=8, 25% female) were analyzed for expression of CD2, CD28, CD57, CX3CR1 and other markers by flow cytometry and compared by CMV status. Cells were stimulated *in vitro* with anti-CD3 plus either anti-CD28 or plate-bound LFA-3 for up to 7 days and measured for viability, cell cycling/proliferation, cytokine and lytic granule expression, glucose uptake, mitochondrial biogenesis, and Bcl-2 expression. Immunofluorescence imaging for LFA-3 was performed on aortic tissues from SIV/SHIV-infected rhesus

macaques and uninfected animals, and from PWoH ± atherosclerosis. *LFA3* gene expression was assessed by real-time RT-PCR in human aortic endothelial cells stimulated with TNF *in vitro*.

Results: CD2 expression on vascular-homing CX3CR1+CD57+CD28- CD8 T cells was increased on cells from CMV+ PWH. *In vitro*, costimulation with LFA-3 potently enhanced TCR-mediated cytokine (IFNg, TNF, IL-2, MIP-1b) and lytic granule production by these inflammatory CD8 memory T cells compared to CD28 costimulation. Proliferation, glucose uptake, mitochondrial biomass, and Bcl-2 expression were similarly upregulated. Finally, LFA-3 protein was highly expressed in aortas of rhesus macaque HIV model and in atherosclerotic plaques of PWoH. Additionally, human aortic endothelial cells increased *LFA3* gene expression upon TNF exposure.

Conclusion: Our data support a model in which CMV infection enhances CD2 expression on highly proinflammatory inflammescent CD8 T cells, which can then be stimulated by LFA-3 expressed in the inflamed vasculature, even in the absence of CD28 costimulation, highlighting a potential therapeutic target in atherosclerosis development and progression, especially for PWH.

663 ANTIRETROVIRAL THERAPY AMELIORATES SIV-ASSOCIATED MYOCARDITIS IN THE HEART

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Background: With introduction of antiretroviral therapy (ART), human immunodeficiency virus (HIV) progressed to a chronic inflammatory disease with accelerated, subclinical end-organ damage, specifically cardiovascular disease (CVD). People with HIV (PWH) have higher risk and mortality from CVD, such as atherosclerosis, diastolic dysfunction, and heart failure. Several recent clinical reports show maladaptive concentric hypertrophy, increased fibrosis, and left ventricle dysfunction in PWH, and as such, investigation into molecular mechanisms promoting pathological changes in the heart is necessary.

Methods: We utilize the highly translatable simian immunodeficiency virus (SIV)-infected rhesus macaque model to identify changes in the myocardium with and without ART. We performed total RNA-Seq on left ventricle tissue from uninfected animals (n=3), SIV-infected animals (n=4), and SIV-infected animals receiving a clinically relevant ART regimen (n=4).

Results: SIV infection led to high plasma viral load, but little to no SIV RNA was detectable in the left ventricle, shown by minimal of SIV RNA+ cells in the heart and no SIV sequences identified from RNA-Seq. SIV infection produced a highly inflammatory reaction in the heart, predominated by interferon (*IRF9*, *IRF7*, *IFIT2*, *IFIT3*, *ISG15*, *ISG20*) and pathogen response (*TLR3*, *CASP1*, *CD163*, *CCL2*, *MYD88*, *NLRP3*, *VCAM-1*). Reduction of viral load by ART reduced the interferon and cytokine response in the heart; however, SIV-infected animals receiving ART exhibited decreased expression of integral genes directly involved in fatty acid (FA) metabolism, carnitine shuttling, and beta oxidation (*CD36*, *DBI*, *SLC25A20*, *CPT1A*, *CPT1B*, *CPT2*, *UCP2*, *ACAA2*, *ACSL1*, *ACADVL*, *EHHADH*, *z*).

Conclusion: These data provide an important addition to the understanding of inflammatory and metabolic changes in the heart during SIV infection and treatment with ART. Additionally, deficits in FA metabolism and beta oxidation in ART animals could stem from either prolonged low-grade infection, off-target effects of ART, or synergistic effects of infection with ART. Future studies should address the long-term effects of HIV infection with ART on the heart for a clinical understanding of the predisposition of PWH to developing early CVD.

664 EFFECT OF NICOTINE RECEPTOR AGONISTS ON INFLAMMATION AND RISK OF CHD AND DEATH IN HIV

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Background: People with HIV (PWH) have elevated systemic inflammation, even after HIV viral suppression, which is exacerbated by risky drinking and smoking. Nicotine receptor agonists promote smoking cessation, may reduce alcohol consumption, and may directly reduce inflammation via cholinergic stimulation. If varenicline, cytisine, or nicotine replacement therapy (NRT) differentially reduced biomarkers of inflammation and risk for coronary heart disease (CHD) and mortality independent of abstinence from smoking or alcohol this could alter treatment guidelines.

Methods: We conducted a four-arm randomized, double-blinded, placebo-controlled trial among 400 heavy drinking (> 5 heavy-drinking days in the past month) and daily smoking PWH in St. Petersburg, Russia from 2017-2020. All participants received one active medication and one placebo: Arm 1: varenicline + placebo NRT; Arm 2: placebo varenicline + NRT; Arm 3: cytisine + placebo-NRT; and Arm 4: placebo-cytisine + NRT. Treatment regimens ranged from 25 days (cytisine) to 12 weeks (varenicline). Outcomes, assessed at 3 months, were: high sensitivity c-reactive protein (hsCRP; µg/ml) (primary), IL-6 (pg/ml), Reynolds Risk Score (10-year % risk CHD), and VACS Index (5-year all-cause mortality risk). We performed linear regression analyses controlling for randomization stratification factors (alcohol consumption, average daily cigarettes, current antiretroviral therapy).

Results: Randomized groups were similar on baseline characteristics: 66% male, mean age 39 years, mean CD4 count 391 cells/mm^3, and 57% undetectable HIV viral load. There were no significant differences in the three main comparisons for hsCRP at 3 months: arm 1 vs. 2 (adjusted ratio of means [AROM] 1.25; 95%CI 0.61, 2.54, p=0.73), arm 3 vs. 4 (AROM 1.13; 95%CI 0.55, 2.35, p=0.73), or arm 1 vs. 3 (AROM 1.21; 95%CI 0.58, 2.49, p=0.73) (Table). Similarly, 3-month IL-6, Reynolds Risk Score, and VACS Index did not differ by group (Table). In exploratory analyses, participants who quit drinking and smoking appeared to have lower 3-month hsCRP, IL-6, and VACS scores compared to those who continued both behaviors (Table).

Conclusion: Among PWH with heavy drinking and smoking, biomarkers of inflammation and risk of CHD and mortality did not differ by treatment group. These results do not support the hypothesis that nicotine receptor partial and full agonists lower levels of inflammation independent of smoking or alcohol cessation.

Table 1. Effects on Inflammatory Biomarkers, Cardiovascular Risk and Mortality Risk among People with HIV (PWH) with Risky Drinking and Daily Smoking in Russia

Main Outcomes at 3 months	Arm 1 vs. 2	Arm 3 vs. 4	Arm 1 vs. 3
	(Adjusted* Ratio of Means (ARM) + 95% Confidence Interval)		
hsCRP (µg/ml)	1.25 (0.61, 2.54)	1.13 (0.55, 2.35)	1.21 (0.58, 2.49)
IL-6 (pg/ml)	1.00 (0.73, 1.35)	1.03 (0.75, 1.42)	1.01 (0.74, 1.40)
	(Adjusted Mean Differences + 95% Confidence Interval)		
VACS Index Score (Mortality)	-0.24 (-5.67, 5.20)	-0.84 (-6.44, 4.76)	0.73 (-4.80, 6.26)
Reynolds Risk Score (%)	-0.02 (-0.62, 0.58)	-0.54 (-1.13, 0.05)	0.33 (-0.26, 0.93)
Total cholesterol	4.79 (-6.65, 16.24)	-15.71 (-27.29, -4.14)	2.67 (1.04, 24.30)
HDL cholesterol	-3.25 (-7.61, 1.10)	-3.15 (-7.53, 1.24)	4.12 (-0.39, 8.64)
Post hoc Descriptive Analyses at 3 months	Abstinent** from smoking and alcohol (all treatment groups) (N=30)		Not abstinent from smoking and drinking (all treatment groups) (N=260)
hsCRP, Median, IQR (µg/ml)	0.8 (0.4, 2.4)		1.0 (0.3, 3.1)
IL-6, Median, IQR (pg/ml)	0.7 (0.5, 1.1)		1.3 (0.6, 2.5)
VACS Index Score	21.0 (12.0, 35.4)		27.0 (16.0, 40.1)
Reynolds Risk Score (%)	1.2 (0.2, 2.1)		0.7 (0.3, 1.5)

*adjusted for randomization stratification factors (alcohol consumption, average daily cigarettes, current antiretroviral therapy). ** abstinence biochemically-validated by end-expired carbon monoxide (smoking) and blood phosphatidylethanol (PEth)

665 CARDIOVASCULAR RISK AMONG PEOPLE ACCESSING DIFFERENTIATED HIV CARE IN SOUTH AFRICA

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Delivery Optimization of Antiretroviral Therapy (DO ART) Study Team
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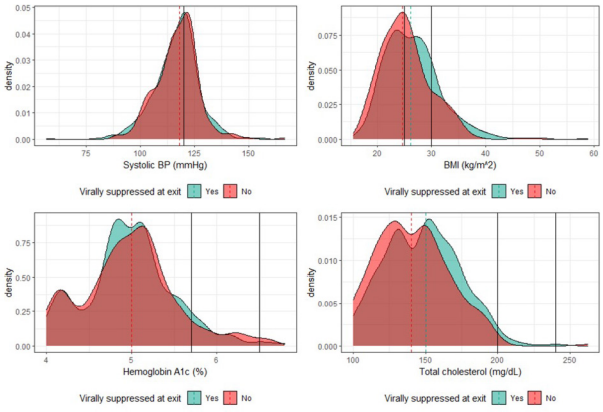
Background: Sub-Saharan Africa has a growing burden of cardiovascular disease (CVD) among people living with HIV. Differentiated antiretroviral therapy (ART) services are being scaled up but do not always integrate management of CVD comorbidities. Our objective was to (1) describe the burden of CVD risk within a randomized trial of community- and facility-based HIV care in South Africa [the DO ART Study], (2) evaluate if effective ART is associated with CVD risk, and (3) determine whether this association differs by mode of HIV service delivery.

Methods: We assessed CVD lifestyle risk factors (tobacco use, exercise, diet) and clinical measures (blood pressure, BMI, hemoglobin A1c, total cholesterol) at 12 months after ART initiation. To compare CVD risk by service delivery mode and viral suppression status, we estimated relative risks of hypertension, obesity/overweight, pre-diabetes/diabetes, hypercholesterolemia (defined using ACC/AHA thresholds), and tobacco use, and differences in underlying continuous measures, using generalized estimating equations for Poisson and linear regression, respectively. We assessed whether the relationship between viral suppression and CVD risk was modified by whether clients received community- or facility-based care.

Results: Among 1010 eligible participants, the median age was 32 years, 505 (50%) were men, 245 (24%) were current smokers, 468 (46%) exercised ≤2 days/week, 280 (28%) rarely ate vegetables, 450 (45%) had elevated blood pressure including 229 (23%) with hypertension, 502 (50%) had BMI ≥25 including 183 (18%) with BMI ≥30, 62 (6%) had prediabetes or diabetes, and 12 (1%) had hypercholesterolemia. CVD risk did not significantly differ by mode of service delivery. Virally suppressed persons had on average 5.75 mg/dL higher cholesterol (p = 0.001), 0.95 kg/m2 higher BMI (p = 0.003), and 16% higher risk of being overweight (p = 0.03) compared with clients who were not virally suppressed. Associations between viral suppression and CVD risk were stronger for community-based care and null for facility-based care.

Conclusion: In a relatively young population in South Africa, clients accessing community- and facility-based HIV care had substantial burden of tobacco use, hypertension and overweight. Among clients accessing community-based care, CVD risk factors were more prevalent among virally suppressed participants at 12 months. As community-based ART is scaled up, programs should evaluate integrated CVD screening and treatment services.

Distribution of clinical measures of cardiovascular risk, by viral suppression status at endline [dashed lines are group medians]



666 EXERCISE CAPACITY IS REDUCED IN HIV INDEPENDENT OF SARS-CoV-2 INFECTION

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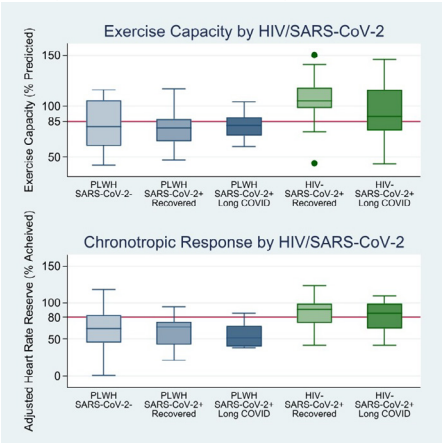
Background: Reduced exercise capacity occurs as a post-acute sequela of COVID-19 ("PASC" or "Long COVID"). Cardiopulmonary exercise testing (CPET) is the gold standard for measuring exercise capacity and identifying reasons for exercise limitations. Only one prior study used CPET to examine exercise limitations among people living with HIV (PLWH). Extending our prior findings in PASC, we hypothesized that PLWH would have a greater reduction in exercise capacity after SARS-CoV-2 co-infection due to chronotropic incompetence (inability to increase heart rate).

Methods: We performed CPET within a COVID recovery cohort that included PLWH (NCT04362150). We evaluated associations of HIV and prior SARS-CoV-2 infection with or without PASC with: (1) exercise capacity (peak oxygen consumption, VO2) and (2) adjusted heart rate reserve (AHRR, marker of chronotropic incompetence) using linear regression with adjustment for age, sex, and body mass index.

Results: We included 83 participants (median age 54, 35% female, 10% hospitalized, 37 (45%) PLWH) who underwent CPET at 16 months (IQR 14-17) after SARS-CoV-2 infection. Among PLWH (median duration living with diagnosed HIV 21 years (IQR 15-28), all virally suppressed on antiretroviral therapy), 14 (39%) had not had SARS-CoV-2 infection, 12 (32%) had prior SARS-CoV-2 infection without PASC, and 11 (30%) had PASC (Long COVID symptoms at CPET). Median CD4 count was 608 (370-736) and CD4/CD8 ratio 0.92 (0.56-1.27). Peak VO2 was reduced among PLWH compared to individuals without HIV with an achieved exercise capacity only 80% vs 99% (p=0.005, Fig.), a difference in peak VO_2 of 5.5 ml/kg/min (95%CI 2.7-8.2, p< 0.001). Exercise capacity did not vary by SARS-CoV-2 infection among PLWH (p=0.48 for uninfected vs infected; p=0.25 for uninfected vs no PASC; p=0.32 no PASC vs PASC). Chronotropic incompetence was present in 38% of PLWH vs 11% without HIV (p=0.002), and AHRR (normal >80%) was significantly reduced among PLWH vs individuals without HIV (60% vs 83%, p< 0.0001, Fig.). Heart rate response varied by SARS-CoV-2 status among those with HIV: namely, 3/14 (21%) without SARS-CoV-2, 4/12 (25%) with SARS-CoV-2 without PASC, and 7/11 (64%) with PASC (p=0.04 PASC vs no PASC). Among PLWH, CD4 count, CD4/CD8 ratio, and hsCRP were not associated with peak VO2 or AHRR.

Conclusion: Exercise capacity is reduced among PLWH, with no differences by SARS-CoV-2 infection or PASC. Chronotropic incompetence may be a mechanism of reduced exercise capacity among PLWH.

Exercise Capacity and Chronotropic Response by HIV/SARS-CoV-2



667 GUT MICROBIOTA ASSOCIATED WITH OBSTRUCTIVE CORONARY ARTERY DISEASE IN HIV INFECTION

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COCOMO study

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Background: We aimed to assess the potential impact of gut microbiota alterations and related pathways, on the presence and severity of stable coronary artery disease (CAD) in people living with HIV (PLWH).

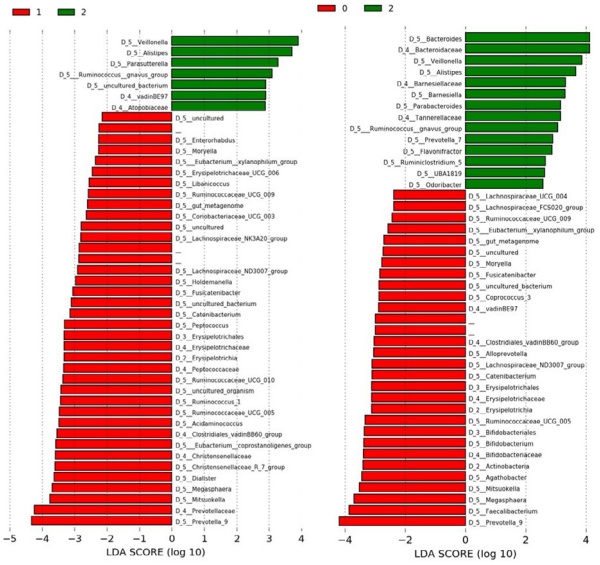
Methods: Gut microbiota profiles from participants of the Copenhagen Comorbidity in HIV infection (COCOMO) study were determined by 16S rRNA sequencing, and CAD severity was assessed by a high-resolution research coronary CT angiography. Obstructive CAD was defined as >50% stenosis and non-obstructive CAD as 1-49% stenosis. Sequencing was performed on the Illumina MiSeq platform. α-diversity, β-diversity and bacterial abundances were analyzed on a rarefied (subsampled) dataset, and differentially abundant bacterial genera were adjusted for False Discovery Rate (FDR) using the Benjamini-Hochberg method. Associations between CAD-related microbiota alterations and obstructive CAD were tested using regression models adjusted for age, sex, and smoking

Results: In a total of 254 participants (mean age 53y, 88% men) with microbiota samples and CT angiography, n=60 had obstructive CAD, n=80 had non-obstructive CAD, and n=114 had no CAD. Participants with obstructive CAD had gut microbiota profiles with significantly lower α-diversity and higher β-diversity compared to both non-obstructive CAD and no CAD. Participants with obstructive CAD also had distinct compositional microbiota profiles, including increased relative abundance of *Ruminococcus Gnavus*, known to produce pro-inflammatory polysaccharides and *Veillonella*, potentially linked to fibrosis, as well as reduced abundance of several bacterial genera, some

with potential for butyrate production, important for gut barrier integrity. These bacterial genera (all $Q_{FDR}< 0.05$) were used to define a CAD-related microbiota index: Log_e (*Veillonella* + *Ruminococcus Gnavus* + *Alistipes*)/ (*Prevotella_9* + *Megashpaera* + *Moryella* + *Catenibacterium* + *Fusicatenibacter* + *Ruminococcacea_UCG_005* + *Ruminococcacea_UCG_009* + *Lachnospiracea_ND3007_group* + *Eubacterium_xylanophilum_group*), which was associated with obstructive CAD independent of age, sex and smoking (adjusted p< 0.001). We observed no differences in gut microbiota composition between PLWH with non-obstructive CAD and no CAD.

Conclusion: PLWH with obstructive CAD have distinct gut microbiota profiles compared to PLWH with non-obstructive CAD and no CAD. Future studies from this longitudinal cohort will determine whether these CAD-related microbiota profiles are predictive of future cardiovascular events in PLWH.

Microbiota alterations associated with obstructive CAD



668 TRYPTOPHAN METABOLISM, THE GUT MICROBIOME, AND CAROTID ARTERY PLAQUE IN WIHS WOMEN

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*Presented at CROI by a nonauthor colleague

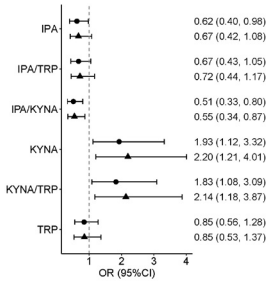
Background: The perturbation of tryptophan (TRP)-kynurenine (KYN) metabolism has been linked with HIV infection and cardiovascular disease (CVD), but the relationship of other TRP metabolites with the gut microbiome and atherosclerosis is not fully understood within the context of HIV infection.

Methods: Ten TRP metabolites, including microbial indole derivatives, were quantified in plasma among women from 3 sites of the Women's Interagency HIV Study between 2018-2019. The gut microbiome was profiled through 16S ribosomal RNA sequencing and shotgun metagenomics in fecal samples that were collected close to the visits of blood collection for TRP metabolites measurements. Carotid artery ultrasound was used to assess the presence of plaque. The Analysis of Compositions of Microbiomes with Bias Correction was performed to select gut microbial features associated with TRP metabolites. We used logistic regression to examine cross-sectional associations of plasma metabolites and selected gut microbial features with carotid artery plaque. Associations analyses were adjusted for sociodemographic factors, study sites and HIV serostatus.

Results: We included 251 women (median age: 52.4 yrs, 71.7% Black; among 138 HIV+ women, 93.5% on ART, 80.4% with undetectable viral load) in the main analysis. After multivariate adjustment, carotid artery plaque was positively associated with kynurenic acid (KYNA) (odds ratio [OR] = 1.93, 95% confidence interval [CI]: 1.12, 3.32, per one Z-score increase) and KYNA/TRP (OR=1.83, 95%CI: 1.08, 3.09), and inversely associated with indole-3-propionate (IPA) (OR = 0.62, 95% CI: 0.4, 0.98) and IPA/KYNA (OR= 0.51, 95%CI: 0.33, 0.8). We identified six gut bacterial genera associated with IPA levels (FDR-q< 0.25), five of which and multiple species within them were positively with IPA, most especially *Roseburia sp.*, *Eubacterium sp. Lachnospira sp.*, and *Coprobacter sp.* No gut bacteria were associated with KYNA levels. Furthermore, a constructed IPA-associated-bacteria score was inversely associated with plaque (OR=0.47, P=0.004), and the association was attenuated after further adjustment for IPA levels (OR=0.54, P=0.02) or IPA/KYNA (OR=0.58, P=0.05). No effect modification by HIV serostatus was observed.

Conclusion: In a subset of WIHS women, plasma IPA levels and related gut bacteria were inversely associated with carotid artery plaque, suggesting a potential beneficial role of IPA and its gut bacterial producers in atherosclerosis and CVD.

Figure1. Associations of selected tryptophan (TRP) metabolites and derived ratios with prevalent carotid artery plaque.Model 1 was adjusted for age, race/ethnicity, study sites, education, smoking and HIV serostatus at visit. Model 2 was additionally adjusted for BMI, total cholesterol, HDL cholesterol, systolic blood pressure,fasting glucose, use of antihypertensive, lipids lowering and antidiabetic medication.



669 MULTI-OMICS ANALYSIS OF GUT MICROBIOME AND ATHEROSCLEROSIS IN WOMEN LIVING WITH HIV

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Background: Alterations in gut microbiota have been implicated in HIV infection and cardiovascular disease. However, how gut microbial alterations relate to host inflammation and metabolite profiles, and their relationships with atherosclerosis, have not been well-studied, especially in the context of HIV infection.

Methods: We examined associations of gut microbial species and functional components measured by shotgun metagenomics with carotid artery plaque assessed by B-mode carotid artery ultrasound in 320 women with or at high risk of HIV (65% HIV+) in the Women's Interagency HIV Study (WIHS). We further integrated plaque-associated microbial features with serum proteomics (74 inflammatory markers measured by the proximity extension assay) and plasma metabolomics (378 metabolites measured by liquid chromatography tandem mass spectrometry) in relation to carotid artery plaque in up to 433 WIHS women.

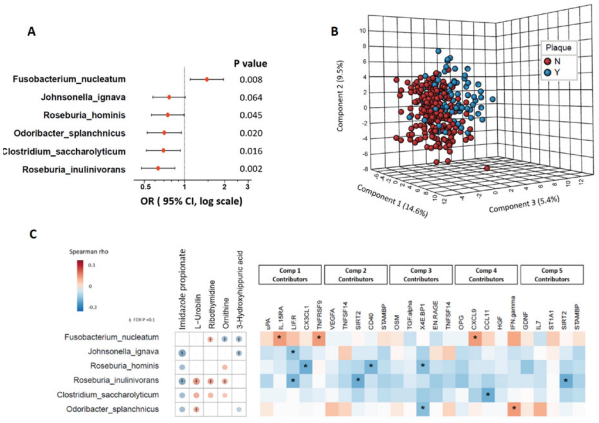
Results: *Fusobacterium nucleatum*, a potentially pathogenic bacteria, was positively associated with carotid artery plaque, while five microbial species (*Roseburia hominis*, *Roseburia inulinivorans*, *Johnsonella ignava*, *Odoribacter splanchnicus*, *Clostridium saccharolyticum*) were inversely associated with plaque (Fig 1A). Results were consistent in both women with and without HIV. *F.nucleatum* was positively associated with and the other plaque-related species were inversely associated with multiple serum proteomic inflammatory markers, such as pro-inflammatory chemokines CXCL9 and CX3CL1, which were also positively associated with plaque (Fig 1B, C). Associations between bacterial species (especially *F.nucleatum*) and plaque were attenuated after further

adjustment for proteomic inflammatory markers. Plaque-associated species were correlated with several plasma metabolites (Fig 1C), including a microbial metabolite, imidazole-propionate (ImP), which was positively associated with plaque (P trend =0.043) and several pro-inflammatory markers (eg. CXCL9 and CX3CL1, all P< 0.001). Further analysis identified additional bacterial species and bacterial *hutH* gene (encoding enzyme histidine ammonia-lyase in ImP production) associated with plasma ImP levels.

Conclusion: Among women living with or at risk of HIV, we identified several gut bacterial species and a microbial metabolite ImP associated with carotid artery atherosclerosis, which might be related to host immune activation and inflammation.

Figure 1. Associations among gut microbiota, circulating proteomic inflammatory markers and metabolites, and carotid artery atherosclerosis.

(A) Associations between gut microbial species and carotid artery plaque status. Data are odds ratios (ORs) and 95% confidence intervals (CIs) for carotid artery plaque per standard deviation increment of centered log-ratio-transformed abundance of bacterial species, adjusted for age, race/ethnicity, study site, antibiotics use, income, education, BMI, current smoking, alcohol, HIV status and ART use.
(B) Serum proteomic inflammatory markers and carotid artery plaque : Partial Least Square-Discriminant Analysis (PLSDA) plot by plaque status.
(C) Associations of plaque-associated bacterial species with circulating metabolites, and proteomic inflammatory markers.



670 IMPROVED GUT MICROBIOTA RECOVERY IN LATE HIV-1 PRESENTERS INITIATING DTG VS DRV/r

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ADVANZ-4 MISTRAL
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Background: Late HIV-1 presenters have severely impaired systemic and intestinal immune function, increased immune activation, inflammation and gut dysbiosis, reflected by loss of microbial richness and diversity alongside disbalances in commensal bacterial species. Whereas immune and inflammation parameters gradually, albeit partially, recover following antiretroviral treatment (ART) initiation, it is unknown if (a) ART initiation is also able to revert gut dysbiosis and (b) if certain ART regimens are more likely to do so than others. Here, we aimed to answer the latter two questions.

Methods: This was a substudy of ADVANZ-4 (NCT02337322), a multicentre, open-label, 2-arm randomized clinical trial, where ART-naïve subjects with HIV-1 and < 100 CD4+ T-cells/mm^3 were allocated 1:1 to initiate dolutegravir (DTG) or darunavir (DRV/r) plus ABC/3TC and were followed for 96 weeks. Their faecal microbiome was characterized at the first day of ART intake (baseline), and weeks 24, 48 and 96, using shotgun metagenomics. Alpha- (gene richness) and Beta-diversity (Bray-Curtis), as well as bacterial abundance were compared between arms using Wilcoxon tests and linear mixed models, as needed. Associations with immune parameters were explored.

Results: 104 patients in the parent trial received their allocated intervention. Of these, 88 subjects (46 DTG and 42 DRV/r) provided fecal samples at 2 or more time points or at least 1 sample at week 0 and were included in this substudy. Their median CD4+ counts at baseline were 33 (13-67) cells/mm^3. Study groups were well-balanced and with no significant differences in the microbiome at baseline. Gene richness increased overall, but increases were greater and only statistically significant in the DTG group (Table) In addition, B. adolescentis, B. longum and O. scatoligenes became significantly more abundant in the DTG that the DRV/r group at weeks 24, 48 and 96. Increases in microbial diversity were nominally larger in subjects increasing their CD4+ counts by more than >150 cells by week 96 (LMM ANOVA, p = 0.082).

Conclusion: ART initiation in very advanced late presenters is associated with improvements in gut microbiome markers of better overall health during the first two years. Such improvements are greater if subjects initiate dolutegravir than darunavir/r, and likely mirror immune recovery kinetics.

Microbiome marker changes per group at baseline and week 96

		DTG	DRV/r	P.val
Gene Richness (median- IQR·10^3)	BL	777 (642-924)	748 (614-948)	0.879
	Wk 96	931 (803-1,040)	800 (664-1,014)	0.047
Gene Richness (LMM BL-w96 slope, p)		1,472 p <0.001	596 p=0.131	N.A
***B. adolescentis* (median, IQR)**	BL	0 (0-0.817)	0 (0-0.582)	0.593
	Wk 96	0.744 (0-5.376)	0 (0-0.270)	0.005
***B. longum* (median, IQR)**	BL	0.375 (0-2.808)	0 (0-1.230)	0.098
	Wk 96	0.221 (0-2.718)	0 (0-0.246)	0.003
***O. scatoligenes* (median, IQR)**	BL	0 (0-0.008)	0 (0-0.011)	0.942
	W96	0.006 (0-0.022)	0 (0-0.003)	0.007

671 WEIGHT LOSS AND METABOLIC CHANGES AFTER SWITCHING FROM TAF/FTC/DTG TO TDF/3TC/DTG

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Background: Use of tenofovir alafenamide (TAF) with emtricitabine (FTC) and integrase inhibitors such as dolutegravir (DTG) has been associated with significant treatment-emergent weight gain and higher risks of metabolic syndrome. Weight gain is particularly high for Black women on first-line antiretrovirals. Efavirenz (EFV) and tenofovir disoproxil fumarate (TDF) could suppress weight gain. It is unclear whether weight gains during first-line treatment are reversible after changes in antiretrovirals.

Methods: In the ADVANCE trial, 1053 treatment naïve participants in South Africa were randomized to TAF/FTC/DTG, TDF/FTC/DTG or TDF/FTC/EFV for 192 weeks. After Week 192, participants were switched to open-label TDF/3TC/DTG for at least 52 weeks in a follow up trial, CHARACTERISE. At follow up, participants were assessed for weight, lipids, fasting glucose, HBA1C and HIV RNA. Changes in weight and laboratory parameters during the first 192 weeks of randomized treatment and then after the switch to TLD were evaluated in each treatment arm using paired non-parametric tests.

Results: Of the 159 participants in the analysis, 102 were female, 100% were Black African with mean age 34 and CD4 count 627 cells/ul. HIV RNA was undetectable for 96%. Table 1 shows changes in weight, lipids, glucose and HBA1C after switch from their original randomized treatment to TDF/3TC/DTG in the CHARACTERISE trial. During the 192 weeks of first-line randomized treatment in ADVANCE, participants taking TAF/FTC/DTG showed significantly higher rises in weight and BMI, compared with the TDF/FTC/DTG arm (p< 0.001 for both comparisons). After switching from TAF/FTC/DTG to TDF/FTC/DTG for 52 weeks, there were statistically significant reductions in weight, lipids, fasting glucose and HBA1C. Reductions in weight were higher for women after this switch. Participants switching from TDF/FTC/EFV to TDF/FTC/DTG showed significant rises in body weight, with reductions in lipids and fasting glucose (Table 1). HIV RNA remained suppressed during follow up for 95% of participants, with intermittent elevations re-suppressed after adherence counselling.

Conclusion: After 4 years of weight gain on first-line TAF/FTC/DTG, switching to TDF/3TC/DTG for 52 weeks led to significant weight loss in this study, particularly for women. There were concurrent reductions in lipids, fasting glucose and HBA1C after switching TAF/FTC/DTG to TDF/3TC/DTG.

Table 1: Outcomes from switch to TDF/3TC/DTG by original treatment received: CHARACTERISE trial

Group	TAF/FTC/DTG	TDF/FTC/DTG	TDF/FTC/EFV
N	n=65	n=69	n=25
Weight (kg)	-1.2 (p=0.01)	-0.05 (n.s.)	+3.2 (p=0.03)
BMI (kg/m2)	-0.40 (p=0.01)	-0.01 (n.s.)	+1.07 (p=0.04)
Total cholesterol (mmol/L)	-0.24 (p=0.005)	+0.17 (p=0.009)	-0.26 (p=0.02)
LDL cholesterol (mmol/L)	-0.32 (p=0.001)	-0.02 (n.s.)	-0.28 (p=0.006)
Fasting glucose (mmol/L)	-0.20 (p=0.001)	+0.0 (n.s.)	-0.10 (n.s.)
HBA1C (mmol/L)	-0.10 (p=0.008)	-0.09 (n.s.)	-0.20 (p=0.01)

p<0.05 paired test

672 FAVORABLE METABOLIC OUTCOMES 48 WEEKS AFTER SWITCH TO DTG/3TC

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Background: Since 1996, triple drug antiretroviral therapy (ART) is standard in HIV care. Nowadays, with the increased viral potency of new antiretroviral drugs, dual ART has become a valid and potentially less toxic alternative considering the (present) lifelong need of ART. Metabolic complications such as weight gain have been reported with newer agents such as integrase inhibitors and the nucleoside reverse transcriptase inhibitor tenofovir alafenamide (TAF). We report week 48 results of Rumba, the first open-label randomized clinical trial evaluating effects on metabolic health of switch from 2nd generation integrase inhibitor based triple ART towards dual ART DTG/3TC.

Methods: Virally suppressed patients were randomized 2:1 to switch to DTG/3TC or to switch or stay on BIC/FTC/TAF. BMI, weight and waist circumference as well as lipids and insulin resistance (HOMA-IR) were compared among both groups. Body composition and fat distribution were measured by dual-energy x-ray absorptiometry (DXA) scans; liver fibrosis by fibroscans. Primary endpoint analysis on the viral reservoir will be discussed separately. Inflammatory cytokines were measured using commercially available ELISA and Luminex kits. Linear mixed models were built to evaluate changes over time between the groups over baseline, week 24 (if available) and week 48.

Results: From 134 randomized patients, 130 (N=87 DTG/3TC, N=43 BIC/FTC/TAF) were included in the intention-to-treat-exposed analysis. The majority is male (118, 90.8%), mean age is 46.5±11.8 years. 102 patients (78.5%) had European and 14 (10.8%) had African ethnicity. Significant changes were observed between the groups from baseline to week 48 (estimated mean difference with 95%CI; BIC/FTC/TAF minus DTG/3TC): ALT (5.37 [0.38, 10.37] U/L; p=0.035), HDL cholesterol (-2.77 [-5.46, -0.08] mg/dL; p=0.044), lean trunk mass (-595.14 [-1121.82,-68.45] g, p=0.027) and fat percentage (1.37 [0.47,2.28] %; p=0.003). The estimated differences in trunk fat mass (617.63 [-43.26, 1278.53] g; p=0.067) and lean body mass (-776.88 [-1684.75, 130.99] g; p=0.093) follow the same trend, yet not significantly different. We did not observe significant divergences in other lipid parameters including triglycerides, LDL and total cholesterol nor in glucose, insulin, HOMA-IR and liver fibrosis.

Conclusion: Our data suggest that treatment with DTG/3TC has a favorable impact on week 48 metabolic outcomes as compared to treatment with BIC/FTC/TAF. More longitudinal data (up to week 144) are being collected.

673 REVERSIBILITY OF TAF- AND/OR InSTI-ASSOCIATED WEIGHT GAIN

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ATHENA National Observational Cohort

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Background: We and others have previously reported that excessive weight gain (WG) is common in virally suppressed people with HIV (PWH) after switching to TAF and/or INSTI. Data on reversibility of TAF and/or INSTI-associated WG are currently limited to case reports.

Methods: From the Dutch ATHENA Cohort, we selected all PWH with ≥7% WG within 24 months after first switch to TAF and/or INSTI whilst being virally suppressed. PWH with comorbidities/co-medication known to be associated with WG were excluded. We subsequently selected those who discontinued only TAF, only INSTI or both TAF+INSTI, with ≥1 weight measurement ≥3 months after discontinuation. Weight change limited to the 24 months both prior and after discontinuation was modelled using mixed-effects linear regression, adjusted for age, last available weight prior to discontinuation, sex and region of origin. We compared change in weight of these individuals to PWH with ≥7% WG who continued TAF and/or INSTI (those initiating or discontinuing TAF or INSTI were not included) with ≥1 weight measurement ≥3 months after first recording of ≥7% WG.

Results: WG ≥7% was observed in 23.1% of the 6,245 PWH switching to TAF and/or INSTI in total, of whom 165 subsequently discontinued TAF and/or INSTI. Sufficient follow-up (median 24 months (IQR 18-54)) was available for 69/165 (**Table 1**). Mean WG on TAF and/or INSTI within 24 months prior to discontinuation was +3.20kg [95%CI, 1.02-5.40] in PWH who subsequently discontinued only TAF (n=21); +5.98kg [3.34-8.37] in the only INSTI (n=37) and +5.84 [2.06-9.30] in the TAF+INSTI group (n=11). At 24 months after discontinuation, weight change was -1.48kg [-4.24 to +1.27]; -2.73kg [-6.22 to +0.66] and -7.95kg [-15.57 to -0.33] in those three groups, respectively. Reductions in proportions overweight/obesity were observed in all three groups, but these were markedly less pronounced than the BMI category shifts having occurred whilst on TAF and/or INSTI (**Table 1**). In the 800 PWH who continued TAF and/or INSTI after ≥7% WG (245 only TAF; 347 only INSTI; 208 TAF+INSTI), the adjusted mean weight change at 24 months after first recording of ≥7% WG was -0.77kg [-1.32 to -0.21].

Conclusion: TAF and/or INSTI-associated WG of ≥7% appears to be only partly reversible after discontinuing TAF and/or INSTI, with relatively modest improvement in BMI category. In contrast, in those continuing TAF and/or INSTI after first recording of ≥7% WG, weight remains relatively unchanged.

Characteristics of 69 PWH with ≥7% WG before starting and after stopping either TAF, INSTI or both; versus 800 PWH with ≥7% WG continuing TAF and/or INSTI

	Stopping only TAF N = 21	Stopping only INSTI N = 37	Stopping both TAF+INSTI N = 11	Continuing TAF and/or INSTI N = 800
Male gender	15 (71.4%)	30 (81.1%)	10 (90.9%)	636 (79.5%)
Regimen prior to stop TAF/INSTI				**Current regimen**
- Only TAF	20 (95.2%)	-	-	245 (30.6%)
- Only RAL	-	11 (29.7%)	-	48 (6.0%)
- Only EVG	-	2 (5.4%)	-	21 (2.6%)
- Only DTG	-	19 (51.4%)	-	276 (34.8%)
- TAF+EVG	0 (0.0%)	2 (5.4%)	6 (5.5%)	153 (19.1%)
- TAF+DTG	1 (4.8%)	3 (8.1%)	0 (0.0%)	16 (2.0%)
- TAF+BIC	0 (0.0%)	0 (0.0%)	5 (45.5%)	39 (4.9%)
BMI at start TAF/INSTI				
- <18.5 kg/m²	0 (0.0%)	3 (8.1%)	1 (9.1%)	35 (4.5%)
- 18.5 to 24.9 kg/m²	16 (76.2%)	25 (67.6%)	7 (63.6%)	467 (59.0%)
- 25.0 to 29.9 kg/m²	3 (14.3%)	5 (13.5%)	2 (18.2%)	218 (27.8%)
- ≥30.0 kg/m²	2 (9.5%)	4 (10.8%)	1 (9.1%)	68 (8.7%)
BMI at stop TAF/INSTI				*Not applicable*
- <18.5 kg/m²	0 (0.0%)	1 (2.7%)	0 (0.0%)	
- 18.5 to 24.9 kg/m²	9 (42.9%)	17 (46.0%)	3 (27.3%)	
- 25.0 to 29.9 kg/m²	9 (42.9%)	12 (32.4%)	6 (54.6%)	
- ≥30.0 kg/m²	3 (14.3%)	7 (10.9%)	2 (10.2%)	
BMI at end of follow-up				
- <18.5 kg/m²	0 (0.0%)	2 (5.4%)	0 (0.0%)	14 (1.8%)
- 18.5 to 24.9 kg/m²	9 (42.9%)	18 (48.7%)	4 (36.4%)	309 (38.6%)
- 25.0 to 29.9 kg/m²	10 (47.6%)	13 (35.1%)	5 (45.4%)	302 (37.8%)
- ≥30.0 kg/m²	2 (9.5%)	4 (10.8%)	2 (18.2%)	175 (21.9%)
Follow-up after stop TAF/INSTI, months, median (IQR)	12 (6 – 18)	24 (12 – 24)	12 (6 – 18)	*Not applicable*
Follow-up after first recording of ≥7% WG, months, median (IQR)	*Not applicable*	*Not applicable*	*Not applicable*	24 (18 – 24)

674 WEIGHT GAIN AMONG PARTICIPANTS SWITCHING TO A DOLUTEGRAVIR-BASED HIV REGIMEN IN KENYA

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Background: Dolutegravir (DTG) use has been associated with increased risk for weight gain. We have previously demonstrated that ART-naïve patients starting DTG in Kenya gain significantly more weight compared to those starting a Non-Nucleoside Reverse Transcriptase Inhibitor (NNRTI). In this study we determined the impact of switching from NNRTI, efavirenz (EFV) or nevirapine (NVP), to DTG-containing ART on weight gain in a low-income east African country with high prevalence of HIV and recent large-scale roll-out of DTG.

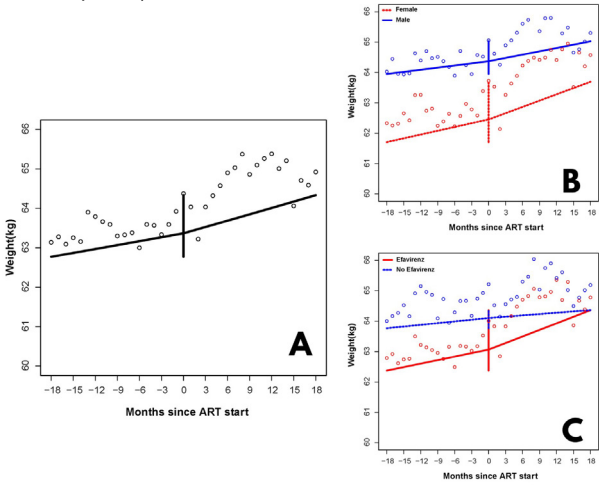
Methods: Participants enrolled in the Kenyan Academic Model Providing Access to Healthcare program who had been on NNRTI for at least 24-months prior to switching to DTG were included in the analysis. We excluded participants who switched due to virologic failure, women who were pregnant within 2 years of switching, and participants with missing BMI data at time of switch. Weights within 18-month of switch were included in the longitudinal models of weights over time and were log transformed to identify linear trends pre- and post- switch. Weights over the follow-up period were modeled using piecewise linear mixed effect models.

Results: 23,131 participants met our inclusion criteria with 52% females, 28% with BMI >25 kg/m², 71% switching from EFV, and 29% switching from NVP. At the time of switch, the mean age was 51 ± 10 years, the mean CD4 count was 201 ± 165 cell/mm³, and the mean BMI was 23 ± 4 kg/m². Compared to males, females were older (52 vs. 49) years and had higher BMI (24 vs. 22) kg/m² at

the time of switch. Participants gained, on average, 1.36 ± 5.7 kgs during the entire study period at an average rate of 0.59 kg/year. The rate weight increase was significantly higher post-switch compared to pre-switch (0.79 vs. 0.44 kg/year, p< 0.0001) (1A). The rate of weight increase post-switch was higher for females compared to males (0.96 kg/year vs 0.62 kg/year, p< 0.0001) (1B), and for participants switching from EFV compared to NVP (1.12 kg/year vs. 0.002 kg/year, p< 0.0001) (1C).

Conclusion: In a large HIV cohort from east Africa, on stable NNRTI treatment, switching to DTG-based regimens was associated with a greater rate of weight gain compared to pre-switch. Despite having greater BMI at time of switch, females had greater weight gain post-switch compared to males. Weight gain was predominantly found in those switching from EFV, thus suggesting EFV is more weight suppressive than NVP.

Figure 1. Changes in weight over time among all HIV patients switching from NNRTI to DTG (A). Weight changes by sex and by baseline NNRTI are shown in (B) and (C) respectively.



675 RANDOMIZED CLINICAL TRIAL OF TRANSGENDER WOMEN SWITCHING TO BIC/F/TAF (MOBETTA TRIAL)

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Background: Cardiometabolic disease in transgender women (TW) is affected by feminizing hormonal therapies (FHT), HIV and ART. We evaluated the tolerability of switching to bictegravir/emtricitabine/tenofovir alafenamide (B/F/TAF) vs continued ART in TW.

Methods: 21 TW on FHT and suppressive ART were randomized 1:1 to switch to B/F/TAF (Arm A) or continue current ART (Arm B) and were followed for 48 weeks. Biomarkers and hormones were measured centrally; fasting glucose and lipids were measured in real time. DXA scan measured bone mineral density (BMD) and lean/fat mass, and FibroScan® hepatic fat (controlled continuation parameter, CAP). Wilcoxon rank-sum/Pearson $\chi 2$ tests compared continuous/categorical variables (two-sided a=0.05).

Results: TW (Arm A n=12, Arm B n=9) had median age 45 years; 95% were non-white, 70% were on elvitegravir- or dolutegravir-based ART with 57% TAF and 24% abacavir, 29% had hypertension, 5% diabetes and 62% dyslipidemia. Arm A/B had 91%/89% undetectable HIV-1 RNA at week 48 (w48). There were no adverse events. Arm B had more frequent moderate/severe hepatic steatosis (42% vs. 89%) and a greater decrease (-25 dB/m) in CAP score vs Arm A (-3 dB/m) at w48 (p=0.03). Baseline (BL) osteopenia (Arm A/B 42%/25%) and osteoporosis (17%/13%) were common. At wk 48, improvement in BMD category was more common in Arm A (36% vs 13%), and only 1 TW (Arm A) worsened BMD category. BL lean/fat mass were similar. At w48, Arm A had stable lean mass but increased limb (3lbs) and trunk (3lbs) fat, with a decrease in android:gynoid fat ratio. Arm B had a slight decrease in limb (-0.4lb) and trunk (-0.1lb) fat. BL and w48 fasting lipid and glucose profiles were similar; however, HOMA-IR decreased in Arm A (2.6 to 1.8) and increased in Arm B (3.5 to 3.9). BL and w48 concentrations of oxidized LDL, adiponectin, sCD14, D-dimer, tissue factor, plasminogen activator inhibitor-1 (PAI-1), endothelin-1, extracellular newly-identified receptor for advanced glycation end-products (EN-RAGE), TNF receptors I/II were similar. Higher estradiol (r=0.45, p=0.04) correlated with higher EN-RAGE, and lower total testosterone (r=-0.51, p=0.002) and sex hormone binding globulin (r=-0.45, p=0.05) correlated with higher PAI-1 at BL.

Conclusion: In this cohort of TW, switch to B/F/TAF was safe and metabolically neutral. Despite greater fat gain on BIC/F/TAF, a trend toward improved insulin sensitivity was observed after switch. Further study is needed to better understand cardiometabolic disease burden in TW with HIV.

676 METABOLOMIC PROFILING SHOWS MORE LIPID ABNORMALITIES IN NNRTI COMPARED TO InSTI USERS

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2000HIV
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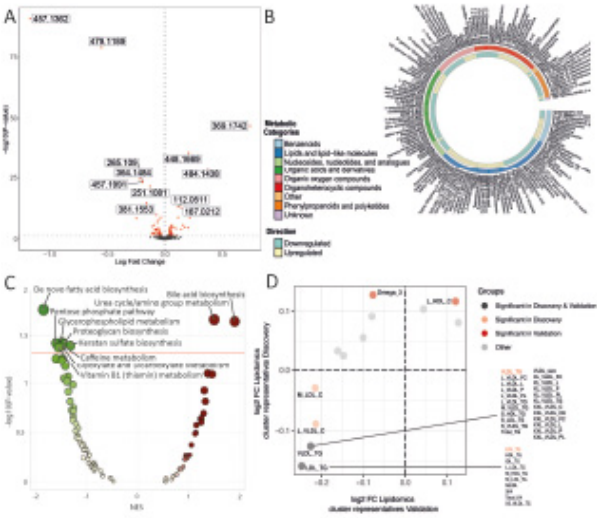
Background: Integrase strand transfer inhibitors (INSTI) are associated with weight gain, in contrast to the also commonly used non-nucleoside reverse transcriptase inhibitors (NNRTI). Plasma metabolomic and lipoprotein profile of INSTI and NNRTI users was therefore compared.

Methods: The present study has a two-phase design and includes a discovery and validation cohort of INSTI and NNRTI users from the 2000HIV study (clinicaltrials NTC03994835) consisting of 1895 virally suppressed participants on long-term antiretroviral therapy (ART). The discovery and validation cohort comprised of 601 INSTI and 469 NNRTI users, and 327 INSTI and 232 NNRTI users, respectively. Untargeted plasma metabolomics profiling was performed using liquid chromatography-mass spectrometry (General Metabolics). Plasma lipoproteins composition was measured using nuclear magnetic resonance spectroscopy (Nightingale). Data on comorbidities and comedication were available for all participants.

Results: INSTI users were a bit younger (51 vs 53 years, P< 0.001), had a slightly higher BMI (25.2 vs 24.8, P=0.016) and shorter duration of ART (8 vs 11 years, P< 0.001). Most recent CD4+ T-cell count, history of cardiovascular disease and frequency of lipid lowering drugs use was not different. Untargeted metabolomics yielded 1,720 metabolites, of which 500 were identified as serum metabolites based on Human Metabolic Database library. Overall, we identified 81/500 (16.2%) significantly different metabolites with modest fold change (-1.2 to 0.7 $\log_{10}$FC) between INSTI and NNRTI users in the two cohorts (**figure 1A**). The majority (30.9%) of these belong to the class of lipids or lipid like molecules (**figure 1B**). Pathway analysis showed two upregulated and eight downregulated pathways in INSTI users (**figure 1C**), with de novo fatty acid biosynthesis being the most downregulated. Furthermore, assessment of 132 lipoprotein related biomarkers showed decreased triglycerides and very low-density lipoproteins in INSTI users (**figure 1D**).

Conclusion: Compared to NNRTI users, INSTI users showed lower fatty acid biosynthesis and lower levels of atherogenic lipids. Despite observed weight gain in INSTI users in previous studies, our results support more favorable lipid profiles in INSTI users than in NNRTI users.

Figure 1A: Differential expression metabolites of INSTI users compared to NNRTI users. Fold change direction indicates change in INSTI users compared to NNRTI users. B: Significant up- and downregulated serum metabolites of INSTI users compared to NNRTI users with compound names and metabolic categories. C: Up- (brown) and downregulated (green) metabolic pathways in INSTI users compared to NNRTI users. D: Differentially expressed group representative lipoproteins in INSTI users compared to NNRTI users. All lipoproteins intercorrelated with representative lipoproteins displayed on the right.



677 INSULIN RESISTANCE, DM 2, AND POTENTIAL IMPACT OF FIRST ART IN NAIVE HIV-SUBJECTS

Maria Luisa Montes[1], Carmen Busca[1], Maria Lagarde[2], Inés Suárez-Garcia[3], Maria Rivero[4], **Arkaitz Imaz**[5], Julián Olalla[6], Cristina Hernández-Gutierrez[7], Félix Gutierrez[8], José Antonio Iribarren[9], Miguel Górgolas[10], Miguel De Zárraga[11], José Ignacio Bernardino[1], Luz Martín-Carbonero[1], Juan González-García[1]
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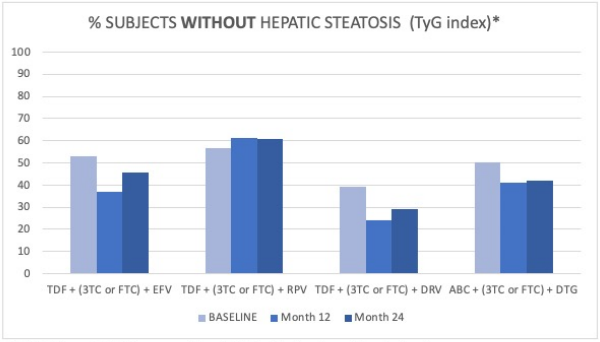
Background: Metabolic alterations related to insulin resistance (IR), development of DM2 and hepatic steatosis (HS) are aspects of great interest in PLWH. There is little knowledge about the metabolic characteristics at the time of diagnosis of HIV infection in individuals who will develop DM2 during follow-up and the impact of initial ART on the evolution of these alterations.
Methods: 6007 patients included in prospective cohort (CoRIS) who initiated ART between Jan-2010 Nov-2019, without HBV/HCV coinfection. All DM2 diagnoses during 5 years follow-up were collected and their characteristics were analyzed. In addition a subanalysis of subjects who initiated and maintained the same ART for at least 24 months, between 01-2010 and 12-2019, was performed. Changes in TyG-insulin resistance and TyG-hepatic steatosis indexes were analyzed according to the four most frequent ART regimens used: TDF + (3TC or FTC)ç + EFV (N=638), TDFç+RPV (N=521), TDFç+DRV (N=211), ABCç+DTG (N=739).
Results: At baseline median age (IQR) was 35 years (29- 43), 12% female, 9.5% stage C3, median CD4+ 375cell/L (224-534). A total of 119 diagnoses of DM2 were recorded. Age, glucose, triglyceride, and BMI values were significantly higher at baseline, prior to ART initiation, in those who developed DM2. 29.5% of the subjects presented IR and 49% HS by TyG indexes, finding significant differences between those who develop DM2 at 5 years and those who do not (TyG-IR TyG-HS 50% vs 25% p< 0.001 and 75% vs 40% p< 0.001). Regarding changes in TyG indexes at 12 and 24 months after initiation of ART, only in patients who received TDFç+RPV the proportion of cases with IR/hepatic steatosis was reduced, this difference being significant (Figure). A multivariate analysis was performed on factors associated with the presence of IR/steatosis by TyG indexes at 12 and 24 months, with TDFç+RPV being associated with less steatosis, OR 0.38 and 0.56 p< 0.05 respectively.
Conclusion: PLWH who develop DM2 have very high prevalence of insulin resistance prior to ART initiation. Patients with recently diagnosed HIV infection in whom metabolic alterations related to insulin resistance are determined should be closely monitored and appropriate measures should be implemented to reduce its impact. First ART regimen could condition a different evolution of metabolic alterations related to IR/hepatic stetatosis. The TDFç+RPV regimen has an excellent metabolic profile and could have a protective effect on IR/liver steatosis, as measured by noninvasive markers.

% Subjects without Hepatic Steatosis (TyG Index)

Figure



TyG: Triglyceride/glucose ratio >8.38 indicates hepatic steatosis
*P<0,001

678 MITOCHONDRIAL HAPLOGROUPS, ANTIRETROVIRAL DRUGS, AND DIABETES RISK AMONG MEN WITH HIV

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MWCCS
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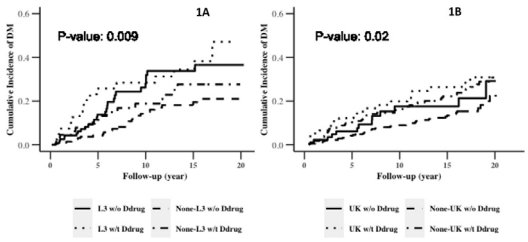
Background: Mitochondrial genetic variability is associated with diabetes mellitus (DM) risk among people with HIV (PWH). However, it is unclear to what extent this association is driven by antiretroviral (ART) exposure.
Methods: We included men without DM who had fasting glucose (FG) data available at baseline from the Multicenter AIDS Cohort Study (MACS). DM was defined by fasting glucose ≥ 126 mg/dL, the use of DM medication, a DM diagnosis, or hemoglobin A1c ≥ 6.5%. Self-reported time-varying exposure to mitochondrial-toxic ART (D-drug; stavudine, zalcitabine, and didanosine) were obtained at 6-monthly visits. Haplogroups were inferred from genotyping data using HaploGrep. We used multivariable Cox regression to examine the race-stratified association between common European (UK, JT) or African haplogroups (L2, L3) and hazard of DM over time. We further examine the association with and without D-drug exposure, as well as with a statistical interaction term. Models were controlled for principal components of genetic ancestry, age, BMI, HCV or HBV infection, and smoking (never, ever, vs. current).
Results: Of 2598 men (1249 PWH and 1349 people without HIV [PWoH]), 667 were Black, 1616 were White, and median age at baseline was 44 years [IQR: 37, 50]. Among PWH of African origin, Haplogroup L3 was associated with increased hazard of incident DM (HR: 1.92, 95% CI 1.2, 3.1), independent of covariates and D-drug exposures. D-drug exposure was independently associated with incident DM (HR: 2.8, 95%CI 1.5, 5.3). Men with haplogroup L3 and exposure to D-drugs took the shortest time to develop DM (median: 3.5 years), while men without L3 and D-drug exposures took the longest time to develop DM (median: 7 years; **Figure 1A**). No association between European haplogroup (UK or JT) and DM risk was observed. However, PWH with European haplogroup UK and exposure to D-drug had a significantly shorter time to incident DM, compared to other groups (**Figure 1B**). Mitochondrial haplogroups were not associated with incident DM among PWoH.
Conclusion: A common mitochondrial haplogroup L3 increases the risk of incident DM in African-ancestry men with HIV. This association was accentuated by exposure to mitochondrial-toxic ART, but was seen in all men having this haplogroup.

Figure 1. Time to incident diabetes mellitus by mitochondrial haplogroups and D-drug antiretroviral therapy exposures in the Multicenter AIDS Cohort Study (MACS)



679 ASSOCIATION OF SEX HORMONES WITH INCIDENT DIABETES IN WOMEN WITH AND WITHOUT HIV

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Background: Higher levels of sex hormone binding globulin (SHBG) are associated with decreased risk for type 2 diabetes mellitus (T2DM) in men and women in the general US population. By contrast, higher total testosterone (TT) has been associated with increased T2DM in women, but not in men. Women with HIV (WWH) are reported to have lower androgen hormone levels but higher SHBG levels than women without HIV (WWOH). Few have examined the association of androgen hormones with incident T2DM in WWH. We evaluated the association of TT, dehydroepiandrosterone sulfate (DHEAS), a marker for adrenal androgen secretion, and SHBG with incident T2DM in WWH and WWOH.

Methods: As part of the sex steroid sub-study of the Women's Interagency HIV Study (WIHS) beginning in April 2003, women had TT, DHEAS, and SHBG measured from morning blood draws. After exclusion of women with prevalent T2DM or who were pregnant, 929 WWH and 364 WWOH were included in the analysis and followed through 2019. Incident T2DM was defined by either report of anti-diabetic medication or by confirmation of a HgbA1c>6.5%, fasting glucose >126mg/dl, or self-reported T2DM. Parametric time-to-event regression models were used with relative times as the measure of association and age as the time scale. All analyses incorporated time-dependent sex steroid and SHBG levels into regression models and were adjusted for current menopausal phase, race/ethnicity, year of WIHS enrollment, current smoking, BMI, HCV status, and HIV-related factors.

Results: Nearly half of the women identified as Black. At the index visit, WWH were older (median 41 vs 36 yrs), less likely to be pre-menopausal (47% vs 65%) and had lower median BMI (27 vs 29 kg/m^2). Among WWH, median CD4 count was 435 cells/mL and 70% reported taking antiretroviral therapy. WWH had 9389 person-yrs of follow-up and 137 (15%) developed T2DM; WWOH had 4009 person-yrs of follow up and 50 (14%) developed T2DM. The table shows that after adjustment, higher DHEAS and SHBG were non-significantly associated with longer time to T2DM whereas higher TT was non-significantly associated with shorter time to T2DM regardless of HIV status. In WWH and WWOH, BMI was significantly associated with shorter time to T2DM.

Conclusion: We found that the association of TT, DHEAS, and SHBG with T2DM were in the expected direction regardless of HIV status, but associations were not significant. Whether the magnitude of these associations is altered in post-menopausal women needs study.

Relative Time to T2DM Among Women With and Without HIV

	Relative Time (95% Confidence Interval)			
	Women with HIV		Women without HIV	
	Unadjusted	Adjusted	Unadjusted	Adjusted
Total Testosterone	0.96 (0.83, 1.11)	0.90 (0.73, 1.10)	0.51 (0.25, 1.04)	0.94 (0.40, 2.17)
DHEAS (per log)	1.11 (0.99, 1.25)	1.08 (0.96, 1.21)	1.27 (0.88, 1.84)	1.18 (0.82, 1.67)
SHBG (per log)	1.09 (0.94, 1.26)	1.01 (0.86, 1.19)	1.53 (1.05, 2.21)	1.39 (0.85, 2.26)

680 IMMUNE CHECKPOINTS AND PANCREATIC BETA CELL DYSFUNCTION IN HIV

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Background: HIV is comorbid with other chronic medical conditions. We have previously shown that HOMA-B as a measure of pancreatic beta cell function is impaired in ART-treated people with HIV (PWH) compared to untreated PWH and to people without HIV (PWOH). Furthermore, proinsulin to C-peptide ratio (PI:C), a marker of beta cell stress, is surprisingly lower in PWH not on ART and with lower CD4 counts, compared to those on ART and to PWOH, thereby suggesting that lack of ART and more impaired T cell function is associated with less beta cell injury. We hypothesized that the immune dysregulation, specifically heightened immune checkpoints (IC), found in untreated HIV is protective against beta cell impairment, similar to Type 1 DM and IC inhibitor-induced DM. Our objectives were to determine the relationships between IC and both HOMA-B and PI:C in HIV.

Methods: We utilized a sample of 105 patients from four groups (39 PWOH, 15 ART naive PWH with CD4 count < 350 cells/µl, 28 ART naive PWH with CD4 count ≥350 cells/µl, 23 PWH receiving suppressive ART). Soluble IC levels were measured using a magnetic bead-based multiplex assay (Human ProcartaPlex™ panel). We used ANOVA to compare mean soluble IC (PD-1, TIM-3, CTLA-4, CD27 and CD40) between each PWH group and the PWOH group. We calculated Pearson correlations to assess the relationships between IC levels, HOMA-B, and PI:C ratio controlling for age, race, sex and BMI.

Results: As shown in the Table, PWH had higher circulating levels of immune checkpoints PD-1, CD27 and CD40 ($p< 0.001$); PWH receiving ART had higher TIM-3 ($p=0.037$). In the entire study population, we found that PD-1, TIM-3, and CD27 were inversely correlated with PI:C ratio (each $p< 0.05$) and that TIM-3 was positively correlated with HOMA-B ($p=0.022$). Stronger correlations were found in the ART-treated PWH group between TIM-3 and PI:C ($p=0.048$) and between CTLA-4 and HOMA-B ($p=0.015$).

Conclusion: In the entire study population, soluble TIM-3 was correlated with better pancreatic beta cell function and inversely correlated with beta cell stress. PD-1, CTLA-4 and CD27 were found to correlate with either HOMA-B or PI:C, but not both markers, making their role in beta cell injury or protection inconsistent. These data suggest that the soluble IC TIM-3 may play a role in the preservation of pancreatic beta cell function in HIV. How these data might reflect effects of cellular bound TIM-3 remains unknown. These results should be confirmed in longitudinal studies of patients initiating ART.

Soluble serum immune checkpoints and markers of pancreatic function

Table 1. Soluble serum immune checkpoints and markers of pancreatic function (and their correlations) among patients with and without HIV separated by CD4 count and treatment status.

Parameter	HIV-negative controls (n=39)	HIV+/ART-; CD4≥350 cells/µl (n=28)	HIV+/ART-; CD4M<350 cells/µl (n=15)	HIV+/ART+ (n=23)
PI:C	0.0221	0.0215	***0.01385****	0.0210
HOMA-B (%)	115.42	110.17	124.20	***77.77****
PD-1	148.06	***588.88****	***478.66****	***267.12****
TIM-3	1802.63	2404.5	2337.77	***2934.26****
CTLA-4	7.54	7.85	5.74	9.06
CD27	962.72	***3785.55****	***3591.87****	***2290.65****
CD40	392.38	***543.50****	***539.83****	***509.49****

Correlation	HIV-negative controls (n=39)	HIV+/ART- (n=43)	HIV+/ART+ (n=23)	Entire study population
PD-1/HOMA-B	-0.20	-0.21	-0.02	-0.11
PD-1/PI:C	0.18	-0.18	-0.29	***-0.26****
TIM-3/HOMA-B	0.17	***0.29****	0.40	***0.24****
TIM-3/PI:C	0.37	***-0.27†***	***-0.43†***	***-0.21****
CTLA-4/HOMA-B	0.14	0.10	***0.51****	***0.19†***
CTLA-4/PI:C	0.14	-0.01	-0.03	0.03
CD27/HOMA-B	0.31	0.01	0.07	0.11
CD27/PI:C	0.17	-0.22	-0.23	***-0.24****
CD40/HOMA-B	-0.06	0.06	0.18	-0.01
CD40/PI:C	0.27	-0.13	-0.32	-0.15

*p<0.05; **<0.01; ***p<0.001; †0.05<p<0.10, p values compared to HIV negative controls
Soluble immune checkpoints: PD-1, Programmed cell death protein 1; TIM-3,T-cell immunoglobulin and mucin-domain containing-3; CTLA-4, Cytotoxic T-lymphocyte-associated protein 4; CD27, Cluster of differentiation 27; CD40, Cluster of differentiation 40.

681 AGREEMENT BETWEEN HBA1C AND INTERSTITIAL GLUCOSE IN PEOPLE LIVING WITH HIV

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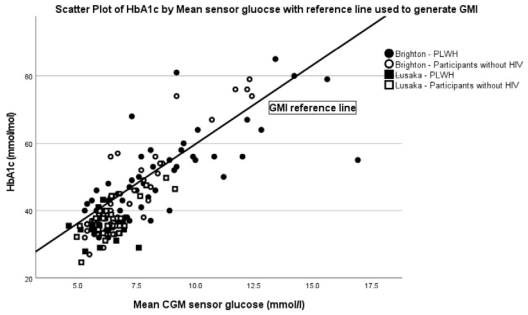
Background: Diabetes is reported to be more common in people living with HIV(PLWH). There is no agreed diagnostic test for diabetes in PLWH. Guidelines advise against HbA1c due to reports that it is falsely low in this group. Continuous glucose monitoring (CGM) is useful to explore the HbA1c-glucose discrepancy but CGM has not been used in PLWH. We aimed to investigate the agreement between HbA1c and interstitial glucose using CGM, according to HIV serostatus in 2 cohorts: Lusaka, Zambia and Brighton, UK.

Methods: PLWH and age-and sex-matched HIV-negative participants wore a Dexcom G6 CGM for up to 10 days and had HbA1c measured. Participants in Lusaka were excluded if they had a diagnosis of type 2 diabetes (T2DM). We used the Bland-Altman plot to assess the agreement between HbA1c and a CGM-derived measure: Glucose Management Indicator(GMI). GMI is calculated from a formula based on a regression analysis of HbA1c against CGM mean sensor glucose, pooled from 4 randomised controlled trials.
Results: In Lusaka, we included 21 PLWH, (33% male, 100% on ART, 81% undetectable viral load (VL), mean age [±SD] 39 [±9] years, mean HbA1c 35.5 [±4.3] mmol/mol, mean sensor glucose 6.1 [±0.7] mmol/l) and 30 people without HIV (30% male, mean age 40 [±10] years, mean HbA1c 37.5 [±5.2] mmol/mol, mean CGM glucose 6.5 [±0.9] mmol/l). The Bland-Altman plot shows a bias between HbA1c and GMI in PLWH of -5.9 mmol/mol (95% limits of agreement: -16.4 to +4.6) and in people without HIV of -5.5mmol/mol (95% limits of agreement: -13.4 to +2.3). In Brighton 60 PLWH (90% male, 50% with T2DM, 98% on ART, 100% undetectable VL, mean age (±SD) 57 [±10.7] years, mean HbA1c 44.5 [±13.6] mmol/mol, mean sensor glucose 7.2 [±1.9] mmol/l) and 48 people without HIV were included (92% male, 30% with T2DM, mean age 57.7 [±8.9] years, mean HbA1c 44.5 [±13.6] mmol/mol, mean CGM glucose 7.2 [±1.9] mmol/l). The Bland-Altman plot shows a bias between HbA1c and GMI in PLWH of -3.0mmol/mol (95% limits of agreement: -20 to +13.9) and in people without HIV of -2.1mmol/mol (95% limits of agreement: -15.1 to +10.9). Fig 1 displays HbA1c against mean CGM glucose for both cohorts, with the regression line used to generate GMI.
Conclusion: In two cohorts, from Zambia and the UK, the bias between HbA1c and GMI was similar in PLWH and HIV-negative controls. Larger controlled studies with additional markers of glycaemia are needed to investigate this issue further, but our data support a role for HbA1c in diagnosing and assessing glycaemia in PLWH.



682 A RANDOMIZED CONTROLLED TRIAL OF BERBERINE EFFICACY ON METABOLIC SYNDROME PLUS HIV

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Background: Antiretroviral therapy has increased the life expectancy of people living with HIV (PLWH). Nevertheless, this increase is not free of comorbidities, and metabolic syndrome is among the most prevalent1. Berberine is an alkaloid that has been shown to ameliorate metabolic syndrome components like glucose tolerance and insulin resistance, but it had not been tested in PLWH2,3. Our aims were to evaluate the efficacy of berberine for improving clinical features, insulin resistance, metabolic profile, and inflammatory markers.
Methods: A randomized, double-blind, placebo-controlled trial was performed in adults living with HIV under virological suppression and with metabolic syndrome diagnosis who were assigned to receive either berberine 500 mg TID or placebo for 20 weeks. The primary outcomes were a composite of weight reduction, insulin resistance decrease, and lipid profile improvement.
Results: Forty-three participants were randomized (22 in the berberine group (BBR) and 21 in the placebo group (CTR)); at the end, 19 in the BBR and 17 in the CTR group completed the intervention period and were analyzed. At 20 weeks, the BBR group showed the following improvements: reduction in weight and body mass index (2.8 kg, $p=0.001$; 0.99, $p=0.003$, respectively), lower insulin resistance revealed by a TyG*BMI decrease of 8 points ($p=0.01$); additionally, a reduction in TNF-alpha of 1 pg/mL was found ($p=0.023$), and a tendency toward benefit was shown in HOMA-IR and HOMA-%beta (decrease 0.59, $p=0.085$; increase 3.5%, p=0.065, respectively). Conversely, the CTR group had higher total cholesterol and c-LDL (increase 22 mg/dL, $p=0.005$; increase 20 mg/dL, $p=0.024$, respectively), and worse IL-6 concentration (increase 0.69 pg/mL, $p=0.018$). Furthermore, an increase in HOMA-IR (increase 0.23, $p=0.041$) was concurrent with a decrease in beta-cell function (HOMA-%beta decreased 1%, $p=0.041$) and higher C-peptide levels (increase 174 pg/mL, $p=0.039$). See table 1. There were no serious adverse effects in both group.
Conclusion: In PLWH under virological suppression, berberine improves metabolic syndrome by reducing weight and body mass index, insulin resistance, and proinflammatory profile, among a tendency to increase beta-cell function, while the control group showed worsening in total cholesterol, c-LDL, IL-6 levels, insulin resistance, and beta-cell function, at the end of the follow-up. Further studies with more people and longer intervention periods need to be explored

A RANDOMIZED CONTROLLED TRIAL OF BERBERINE EFFICACY ON METABOLIC SYNDROME PLUS HIV

Table 1. Cardiometabolic, surrogate indexes for the evaluation of insulin resistance, and glycemia control enzymes

Variables	Group A (BBR) n=19	Intragroup *p*-value	Group B (CTR) n=17	Intragroup *p*-value	Intergroup *p*-value
Age, years, (Media ±SD)	46±9.2	-	47±9.1	-	0.854
Gender: n(%) Male Female	9 (47) 10 (53)	-	13 (76) 4 (23)	-	-
Weight, Kg (Median, IQR) Baseline Week 20	83 (77-97) 82 (73-95)	↓ 2.8 **0.001**	87 (77-91) 86 (76-91)	↓ 0.9 0.463	0.931 0.943
BMI (kg/m²) (Media ±SD) Baseline Week 20	32 ±6.4 31 ±6.2	↓ 0.99 **0.003**	31 ±4.7 31 ±4.4	↓ 0.25 0.338	0.284 0.448
TC, mg/dL (Median, IQR) Baseline Week 20	174 (141-201) 172 (133-206)	↓ 2.3 0.464	163 (146-186) 186 (167-194)	↑ 22 **0.005**	0.278 0.076
LDL-c, mg/dL (Median, IQR) Baseline Week 20	103 (79-123) 90 (68-121)	↓ 5 0.163	94 (70-118) 109 (96-127)	↑ 20 **0.024**	0.419 0.072
TyG index*BMI (Median, IQR) Baseline Week 20	272 (250-309) 264 (231-298)	↓ 8 **0.010**	282 (236-305) 280 (241-304)	↓ 2 0.517	0.817 0.893
HOMA-IR (Media ±SD) Baseline Week 20	2.4 ±1.7 1.8 ±0.92	↓ 0.59 0.065	2.2 ±1.1 2.4 ±1.5	↑ 0.23 **0.041**	0.317 0.083
HOMA-%β (Median, IQR) Baseline Week 20	151 (133-181) 154 (119-164)	↑ 3.5% 0.065	159 (115-186) 158 (128-191)	↓ 1% **0.041**	0.866 0.393
HOMA-%S (Media ±SD) Baseline Week 20	59 ±36 61 ±26	↑ 1.8% 0.859	61 ±36 55 ±29	↓ 5.9% 0.153	0.442 0.267
C-Peptide, pg/mL (Median, IQR) Baseline Week 20	501 (71-801) 554 (63-887)	↑ 37 0.209	431 (199-879) 917 (548-1298)	↑ 174 **0.039**	0.526 **0.035**
TNF-α (Media ±SD) Baseline Week 20	2.3 ±2.1 1.3 ±0.64	↓ 1.0 **0.023**	1.4 ±0.47 1.0 ±0.62	↓ 0.3 0.078	0.092 0.185
IL-6 (Media ±SD) Baseline Week 20	1.4 ±0.42 4.6±2.1	↑ 0.32 0.16	0.89 ±0.3 1.6 ± 0.3	↑ 0.69 **0.018**	0.315 0.187

BBR: Berberine group, CTR: Control group, HOMA-IR: Homeostatic Model Assessment of Insulin Resistance, HOMA-%β: Homeostasis Model Assessment estimates % pancreatic beta cell function (in steady state), HOMA-%S: Homeostasis Model Assessment estimates % insulin sensitivity, IL: Interleukin, TNF-α: Tumor Necrosis Factor alpha, SD: Standard deviation, IQR: Interquartile range. In dependent variable paired t-test or Wilcoxon's test, and independent variable unpaired t-test or Mann–Whitney U test were used.

683 HIV, GENOTYPE, AND CKD: DOES TENOFOVIR EXPOSURE MATTER IN AFRICAN AMERICAN PWH?

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Background: Despite effective antiretroviral therapy (ART), people with HIV (PWH) develop comorbidities such as chronic kidney disease (CKD) at higher rates and earlier ages than their HIV-seronegative counterparts. PWH are at risk of CKD due to HIV-specific risk factors (e.g., Tenofovir Disoproxil Fumarate or TDF) and traditional CKD risk factors (e.g., age, race). Specific genotypes also increase CKD risk: apolipoprotein L1 (APOL1), glutathione-S-transferase-μ1 (GSTM1), and sickle cell trait (SCT) are all associated with CKD and are common among African Americans. Because TDF is still used for HIV prevention and treatment, we sought to understand the relationship between TDF exposure, high risk genotypes, and CKD risk in African American PWH.
Methods: We conducted a retrospective follow-up study in African America (AA) PLWH participating in the Center for AIDS Research (CFAR) Network of Integrated Clinical Systems (CNICS) from 2012 to 2018. We collected both

clinical data and samples for genotype analysis. We defined CKD60 as eGFR < 60 on two consecutive assessments with at least 60 days between values; eGFR was calculated using the 2021 CKD-EPI equation. Uni- and multi-variable Cox proportional hazards analyses were performed to determine associations with CKD60.

Results: Of 1,098 patients, 846 (77%) received a TDF-based regimen. Overall, 60 (12.2%) had a high-risk APOL1 genotype, 130 (26.5%) had a high risk GSTM1 variant, and 36 (7.4%) had SCT. Of the TDF-receiving group, 25 (3.0%) met the criteria for CKD60 compared to 7 (2.8%) of those not receiving TDF. When analyzing CKD60 risk considering APOL1 genotype and TDF exposure, there were no statistically significant relationships. Low rates of CKD60 in those with other high risk genotypes made it difficult to determine relationships with CKD60.

Conclusion: In this multisite cohort of AA PLWH, over 25% had one or more high-risk genotypes. TDF exposure did not significantly increase the risk of CKD60, regardless of genotype. Future studies should evaluate CKD risk with TDF and TAF exposure in larger diverse cohorts, as well as analyze other HIV-associated comorbidities associated with high-risk genotypes.

Table 1. Univariable and multivariable analyses examining association of tenofovir disoproxil fumarate and genotype variants with incident chronic kidney disease (CKD60) overall and by genotype availability

Table 1. Univariable and multivariable analyses[a] examining association of tenofovir disoproxil fumarate and genotype variants with incident chronic kidney disease (CKD60)[b] overall and by genotype availability

Genotype Availability	# of Events # (%)	Univariable Crude HR (95% CI)	Multivariable[a, g] APOL1[c] Adjusted HR (95% CI)	Multivariable[a, g] SCT[d] Adjusted HR (95% CI)	Multivariable[a, g] GSTM1[e] Adjusted HR (95% CI)
Overall (N=1098)					
TDF=No, n=252	7 (2.8)	Ref.			
TDF=Yes, n=846	25 (3.0)	0.68 (0.29 – 1.59)	--	--	--
Genotype available[h] (N=491)					
TDF=No, n=130	4 (3.1)	Ref.	Ref.	Ref.	Ref.
TDF=Yes, n=361	10 (2.8)	0.57 (0.18 – 1.84)	0.57 (0.17 – 6.93)	0.76 (0.20 – 2.86)	0.60 (0.18 – 2.02)
APOL1[c] (N=490)					
Low risk, n =430	11 (2.6)	Ref.	Ref.		
High risk, n=60	2 (3.3)	1.74 (0.41 – 7.30)	1.59 (0.36 – 6.93)	--	--
SCT[d] (N=488)					
Low risk, n =452	12 (2.7)	Ref.		Ref.	
High risk, n=36	1 (2.8)	1.73 (0.30 – 10.03)	--	0.98 (0.13 – 7.60)	--
GSTM1[e] (N=491)					
Low risk, n =361	13 (3.6)	Ref.			Ref.
High risk, n=130	1 (0.8)	0.30 (0.05 – 1.71)	--	--	0.62 (0.10 – 3.90)

APOL1= apolipoprotein L1, CI=confidence interval; GSTM1=glutathione-s-tranferase-u1; HR=hazard ratio, ref=reference category; SCT=sickle cell trait.
[a]Cox proportional hazard regression analyses with Firth's bias correction for small sample size.
[b]Incident event of chronic kidney disease following ART initiation defined as eGFR <60 mL/min using the CKD-EPI Creatinine Equation (2021) on two consecutive assessments with at least 60 days between the two assessments.
[c]*APOL1* high risk variants were defined as those having two high risk alleles.
[d]SCT was defined as the presence of a single sickle mutation.
[e]*GSTM1* high risk group was defined by presence of the active allele [*GSTM1(+/+)*].
[f]Adjusted for: age, sex, and eGFR (all variables at the time of ART initiation).
[g]Adjusted for: age, sex, eGFR, CD4, and VL (all variables at the time of ART initiation).
[h]Data on any genotype variant available.

684 VITAMIN C DYSREGULATION IN HIV: CROSS-SECTIONAL STUDY OF RENAL LEAK IN HIV+ WOMEN

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Background: Reduced plasma vitamin C (vitC) concentrations in chronic diseases may result from abnormal urinary excretion of vitC: a renal leak. While low plasma vitC concentrations may be due to inadequate diet, vitC renal leak indicates underlying pathophysiology. Relationships between HIV+ status, renal leak, and plasma vitC concentrations are unknown. We investigated the prevalence and factors associated with vitC renal leak in a cohort of women with and without HIV

Methods: We conducted an outpatient cross-sectional convenience sampling study of 96 women (40 HIV+, 56 HIV-). Clinical and HIV-related history were obtained using structured questionnaires. To determine primary outcome of vitC renal leak prevalence, subjects fasted overnight, and matched urine and fasting plasma were collected the following morning. VitC was measured by HPLC with coulometric electrochemical detection. VitC renal leak was defined as presence of urinary vitC at fasting plasma concentrations below 43.2µM, the vitC Minimum Elimination Threshold (MET) in women. Exploratory outcomes assessed clinical parameters associated with vitC renal leak.

Results: Compared with HIV- controls, HIV+ cohort had significantly lower mean plasma vitamin C concentration (13.8µM vs 57.3µM, p< 0.001 Wilcoxon), and higher prevalence of vitamin C renal leak (75% vs 4.3%, OR54, p< 0.001 Fisher's Exact). HIV-renal leak and HIV-plasma vitC associations remained significant at 5% level following change-in-effect analyses that adjusted for non-HIV-related covariates with significant between-group differences (age, hypertension, hemoglobin A1c, eGFR, liver enzymes). Among complete-data subsets of the full cohort, renal leak was associated with older age, higher BMI, hypertension, obesity, lower eGFR, and use of HAART therapy (p≤0.01 for all, adjusted for multiplicity). Renal leak was not associated with Race/ethnicity, CD4 count, viral load, or duration of HIV diagnosis (p >0.05 for all).

Conclusion: HIV is associated with measures of vitC dysregulation: low vitC concentrations and high prevalence abnormal vitC urinary loss (renal leak). Older age, HAART therapy and comorbidities associated with metabolic and cardiovascular risk (obesity, hypertension, dyslipidemia) may be more relevant than chronic immune activation from HIV. Further research is needed to explore metabolic and cardiovascular implications of vitC dysregulation in HIV, and potential benefit of early supplementation.

685 RECOVERY OF BONE MASS IN WOMEN ON DEPO-PROVERA AND TDF-BASED ART SWITCHED TO B/F/TAF

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BONE:STAR STUDY TEAM
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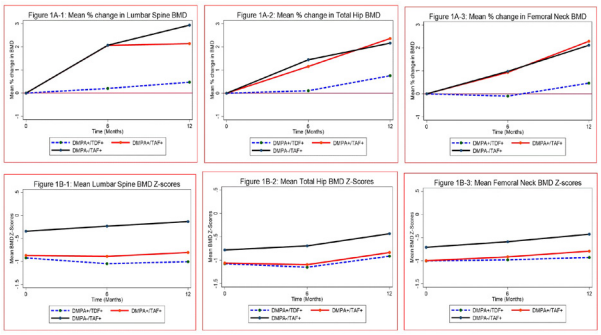
Background: We previously found that concomitant depot medroxyprogesterone acetate (DMPA-IM) contraceptive use resulted in a doubling of BMD loss in women living with HIV (WLWH) initiating tenofovir disoproxil fumarate (TDF) -containing ART in the BONE: CARE study. We sought to determine whether BMD would recover when these women switched to tenofovir alafenamide fumarate (TAF)-containing ART over a two-year period through a Phase IV open-label hybrid randomized and quasi experimental intervention study, the BONE: STAR study.

Methods: At the end of their 2-year follow-up in the BONE: CARE study, WLWH on TDF and DMPA-IM were randomized in a 1:1 ratio to either continue on a TDF based ART regimen or switch to B/F/TAF for 2 years. A third group of WLWH on TDF and using non-hormonal contraception were offered B/F/TAF. Dual energy x-ray absorptiometry was used to measure BMD (lumbar spine (LS), total hip (TH) and femoral neck (FN)) at enrollment and at 6-monthly intervals thereafter. Multivariable linear regression was used to assess differences in mean percent (%) change in BMD. We present 12 months data.

Results: We enrolled 344 virally suppressed women; 125 non-hormonal contraceptive users switching from TDF to B/F/TAF, and 219 DMPA-IM users continuing on TDF (108) or switching to TAF (111). Mean age was 31.3 years (SD 4.2) years. Both non-hormonal and DMPA groups who switched to B/F/TAF had significant improvement in mean % BMD post switch with no significant differences except at the LS; % differences in mean BMD (-0.011% (-0.020, -0.001)) p=0.029 at the LS, (0.254% (1.022, 0.515)), p =0.516 at the TH, and (-0.277(-1.361, 0.806)), P=0.615 at the FN. However, DMPA users had lower mean BMD Z-scores at baseline (Figure) and these remained lower compared to non-hormonal users at the LS -0.805 (-1.017, -0.593) vs -0.131 (-0.321, 0.059), TH -0.835 (-1.050, -0.620) vs -0.432 (-0.639, -0.225), and FN -0.794 (-0.900, -0.590) vs -0.428 (-0.650, -0.206), P ≤ 0.021.

Conclusion: In WLWH receiving TDF-containing ART, switching to B/F/TAF was associated with significant improvement in mean % BMD underscoring the promising role of newer bone-sparing ART in minimizing comorbid risks among WLWH. However, compared to non-hormonal users, DMPA-IM users had lower BMD Z-scores at all time points. Additional research should focus on the impact of interventions that can preserve BMD for DMPA-IM users on ART, including alternative contraceptive methods.

Mean percent change in BMD and mean BMD Z-scores over a 2-year period among women in the BONE: STAR Study



686 QUARTERLY VITAMIN D3 SUPPLEMENTATION TO MITIGATE TENOFOVIR-ASSOCIATED BONE LOSS

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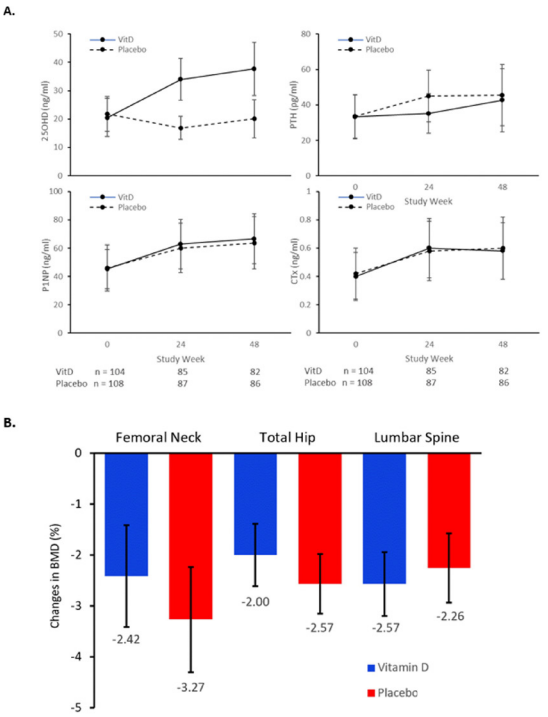
Background: Initiation of antiretroviral therapy (ART) with tenofovir disoproxil fumarate (TDF)-containing regimens is associated with bone loss and fracture in persons with HIV (PWH). Vitamin D3 (VitD) and calcium supplementation attenuates declines in bone mineral density (BMD); however daily oral regimens increase pill burden and complexity.

Methods: We conducted a randomized, double-blind, placebo-controlled trial at three HIV care centers in Beijing, China. ART-naïve adults were randomized to receive 180,000 IU VitD oral solution (equivalent of 2000 IU daily) or placebo with initiation of TDF/lamivudine/efavirenz and at the point-of-care every 12 weeks for 48 weeks. All participants received an educational pamphlet regarding dietary calcium. BMD assessments via dual-energy x-ray absorptiometry were assessed at baseline and 48 weeks; 25-hydroxyvitamin D (25OHD) and bone turnover marker levels were measured at baseline, 24, and 48 weeks.

Results: In total, 198/247 (80.1%) of randomized participants completed 48 weeks of follow up (VitD =96, placebo=102). The study groups were similar at baseline with a mean age of 31 years, 99% men, BMI of 22 kg/m2, HIV viral load of 4.41 mean lg copies/mL, and 50% meeting criteria for vitamin D deficiency (25OHD < 20ng/mL). At 48 weeks 96% of patients in both groups had achieved viral suppression (< 200 copies/mL). Mean 25OHD levels increased in the VitD group from 20.5±6.7 to 37.7±9.4 ng/mL over 48 weeks—with 80.5% of patients achieving vitamin D sufficiency (25OHD >30ng/mL)—but remained unchanged in the placebo group (**Figure 1A**). Within both groups, BMD declined significantly from baseline to 48 weeks at all sites (p< 0.001), however mean percent decrease in BMD did not differ significantly between treatment groups at the lumbar spine (p=0.5), total hip (p=0.19), and femoral neck (p=0.24) (**Figure 1B**). A total of 8 patients in the treatment group and 18 patients in the placebo group reported an adverse event, with no cases of hypercalcemia or nephrolithiasis, and similarly low rates of falls and fractures.

Conclusion: Quarterly administration of an oral vitamin D3 supplement ¬equivalent to 2000 IU daily was well tolerated in our study population but did not attenuate declines in BMD after initiation of TDF/lamivudine/efavirenz or decrease bone turnover markers in comparison to placebo. Potential reasons include insufficient vitamin D dose, lack of calcium co-administration, and limited sample size.

Figure 1. Change in measures from baseline to 48 weeks. A) Mean (95%CI) percent change in BMD from baseline to 48 weeks at the femoral neck, total hip and lumbar spine. B) Changes levels of 25OHD, parathyroid hormone (PTH), and markers of bone formation (Procollagen Type I Intact N-terminal Propeptide, P1NP) and bone resorption (serum cross-linked C-telopeptide of type I collagen, CTx) at baseline, 24 and 48 weeks.



687 IL-1β AND IL-10 ARE ASSOCIATED WITH FASTER LUNG FUNCTION DECLINE IN PEOPLE WITH HIV

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Background: People living with HIV (PLWH) have an increased risk of chronic lung diseases. We aimed to investigate if markers of inflammation and monocyte activation are associated with faster lung function decline in PLWH.

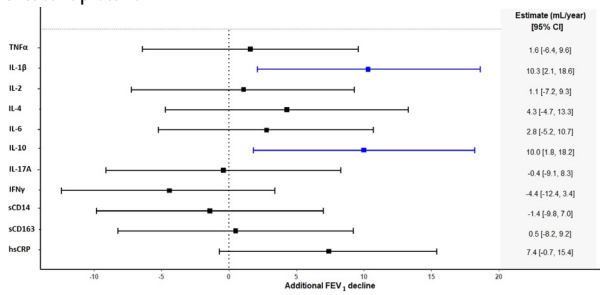
Methods: We included 655 PLWH from the Copenhagen Comorbidity in HIV Infection (COCOMO) Study. Eligible participants were ≥25 years, had two spirometric tests and a baseline plasma sample available, and no evidence of hepatitis B or C co-infection. Inflammatory markers (interleukin (IL)-1β, IL-2, IL-4, IL-6, IL-10, IL-17A, tumor-necrosis-factor-alpha (TNFα) and interferon-gamma (IFNγ)) were measured by Luminex immunoassays and soluble CD14 (sCD14) and sCD163 by the ELISA method. Using linear mixed models with age, sex, ethnicity, smoking status, and BMI as fixed effects, we investigated whether an elevated cytokine level (defined as above the 75th percentile) was associated with faster lung function decline in PLWH.

Results: The majority of PLWH were males (85.2%) with undetectable viral replication (95.3%). The median follow-up time was 2.4 years. We found a faster decline in the forced expiratory volume in one second (FEV_1) in PLWH with elevated IL-1β, with an additional decline of 10.3 mL/year (95% CI:2.1-18.6), p=0.014 (Figure 1). Likewise, elevated IL-10 was associated with an additional FEV1 decline of 10.0 mL/year (95% CI:1.8-18.2), p=0.017. We found no interaction between smoking status and IL-1β on FEV_1 decline (p-interaction=0.688).

Conclusion: IL-1β and IL-10 were independently associated with faster lung function decline in well-treated PLWH, suggesting that persistent systemic inflammation may play a role in the pathogenesis of chronic lung diseases in PLWH.

Figure 1: Additional FEV1 decline (mL/year) in people living with HIV with elevated versus low concentration of the inflammatory markers listed on the Y-axis. Blue color indicates a statistically significant finding. Abbreviations: FEV1, forced expiratory volume in one second; TNFα, Tumor necrosis factor-alpha; IL-1β, interleukin-1 beta; IL-2, interleukin-2; IL-4, interleukin-4; IL-6,

interleukin-6; IL-10, interleukin-10; IL-17A, interleukin-17A; IFNγ, interferon-gamma; sCD14, soluble CD14; sCD163, soluble CD163; hs-CRP, high-sensitivity C-reactive protein.



688 ASSOCIATION OF ANEMIA ON SURVIVAL AMONG PEOPLE WITH HIV AFTER ART INITIATION

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North American AIDS Cohort Collaboration on Research and Design (NA-ACCORD) of IeDEA

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Background: Anemia continues to be an independent predictor of mortality in the ART era, but few analyses have focused on this association. If we are to intervene on anemia, we need to understand it more fully. We estimate the association between anemia and anemia severity with mortality following the initiation of ART among PWH in North America.

Methods: Within the NA-ACCORD, median hemoglobin measurements each year between 01/01/2007-12/31/2016 were categorized into mild (11.0-12.9g/dL men, 11.0-11.9g/dL women), moderate (8.0–10.9g/dL regardless of sex) and severe (< 8.0g/dL regardless of sex) anemia. Discrete time-to-event analyses and complementary log-log link models estimated crude and adjusted mortality hazards ratios (aHR) and 95% confidence intervals for the association between anemia and anemia severity with mortality. Models were adjusted for race/ethnicity, HIV risk, year, age, hepatitis B and C virus, hypertension, diabetes, chronic kidney disease, non-AIDS defining cancer, clinical AIDS diagnosis) median viral load, median CD4 count, and ART use the year of hemoglobin observation. Subgroup analyses were conducted stratified by sex. The change in median hemoglobin was assessed yearly looking back from the year of death or censoring.

Results: Among 67,228 PWH contributing 320,261 annual median hemoglobin observations, 257,293 (80%) were not anemic, 44,041 (14%) had mild, 18,259 (6%) moderate, and 668 (0.2%) severe anemia. Among females 31% of median hemoglobin measures were categorized as anemic with 18% in male PWH. Average follow-up time was similar in those with anemia and without anemia (3.63 years vs. 3.74 years, respectively). The risk of death was 6.4 times higher among PWH with (vs. without) anemia (95% CI 6.0, 6.8); the magnitude of association was greater among males (aHR=6.6 [6.1, 7.1]) than females (aHR=4.5 [3.6, 5.7]). The strength of the association between anemia and mortality increased with greater anemia severity (compared to no anemia) among males and females (Table 1). We noted 3 years prior to death a decline in median hemoglobin levels, with the most dramatic decrease by 0.6 g/dL within the year prior to death.

Conclusion: Anemia among PWH who have initiated ART remains a significant risk factor for death with increasing risk as anemia severity worsens and among males. Anemia is an important predictive marker for mortality among PWH and identification of anemia among PWH should prompt further investigation into the underlying cause.

Table 1: Crude (cHR) and adjusted (aHR) mortality hazards ratios for the association between anemia severity with mortality among people with HIV in the NA-ACCORD and stratified by sex.

	cHR (n=320,261)		aHR (n=320,261)		aHR among Males (n= 282,658)		aHR among Females (n= 37,603)	
Characteristic	**cHR**	**95% CI**	**aHR**	**95% CI**	**aHR**	**95% CI**	**aHR**	**95% CI**
No Anemia	Ref		Ref		Ref		Ref	
Mild Anemia	5.7	5.3, 6.1	3.8	3.5, 4.1	4.0	3.7, 4.3	2.0	1.5, 2.8
Moderate Anemia	25.4	23.8, 27.0	13.7	12.7, 14.8	14.7	13.6, 15.9	7.1	5.5, 9.2
Severe Anemia	59.5	51.0, 69.4	34.5	29.3, 39.7	37.7	31.7, 44.9	14.3	9.0, 22.8

Footnote:
Adjusted models include: Time-fixed covariates sex at birth, race/ethnicity, HIV acquisition risk and cohort. Time varying covariates: year of hemoglobin measurement, age, comorbidities at or prior to hemoglobin measurement (diabetes, hypertension, non-AIDS defining cancer, chronic kidney disease, AIDS diagnoses, HCV, HBV), median CD4 count (≤200cells/mm^3), Median HIV RNA (>200 copies/mL), ART use.

689 ANY LEVEL OF DETECTABLE VIREMIA IS ASSOCIATED WITH SERIOUS NON-AIDS EVENTS

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Background: A proportion of HIV-infected persons on antiretroviral therapy [ART] have detectable viral loads [VL] at low levels without ever meeting criteria for virologic failure [VF]. The clinical consequences of this low-level viremia [LLV] are not well understood. In this study we examined the association between detectable VL and serious non-AIDS events (SNAEs)

Methods: We used data from the US Military HIV Natural History Study (NHS). The NHS is comprised of military beneficiaries who are enrolled early in infection and have access to care and medications. NHS participants who initiated ART after 1996 were included if they had two or more VLs measured using an assay with a lower limit of detection of <50 copies/mL, ≥ 6 months after ART initiation. VLs were categorized as LLV [51-199 copies/mL], high level viremia [HLV- 200-999 copies/mL], VF [≥200 copies/mL on 2 or more successive determinations or a single VL≥1000 copies/mL] and virologic suppression [VS-≤50 copies/mL on all determinations and blips]. SNAEs evaluated are footnoted on table 1. We examined the first occurrence of a SNAE from any category. Factors significant at a $p < 0.05$ in the univariate model were included in the multivariable Cox proportional hazards models. We adjusted for gender, race, time to ART start; Age, VL category, ART regimen and CD4 count were analyzed as time updated variables.

Results: 2814 participants [94% male, 40% Caucasian, 43% African American] were followed for a median of 10.1 years [IQR 4.8 to 18.2]. A total of 490 [17.4%] SNAEs were recorded {107 [3.8%] malignancies, 158 [5.6%] cardiovascular events, 204 [7.25%] cases of chronic kidney disease and 21 [0.8%] cases of cirrhosis}. A third of the participants had one or more episodes of VF, LLV was noted in 16% and HLV in 7.4 %. We observed an association with LLV, HLV, VF and SNAEs with a graded hazard by level of viremia, table 1. Other factors associated with SNAEs were older age, female gender, Caucasian race, delays in ART initiation and regimen type. In comparison with boosted PI, InSTIs and NNRTIs were protective, whereas unboosted PI use had a greater risk. Higher CD4 counts were protective.

Conclusion: The results of this study add to a growing body of literature that suggest detectable viremia including LLV could have adverse clinical consequences. We confirm previously observed negative clinical consequences of delays in ART initiation and lower CD4 counts. The association with race gender and ART categories, need further evaluation.

Table 1- Factors associated with Serious Non-AIDS Events in the NHS

Table 1 - Factors associated with Serious Non-AIDS events

	Unadjusted				Adjusted			
	HR	**95%CI**		**P-value**	**HR**	**95% CI**		**P-value**
Time updated viral load categories (Referent: VS)								
LLV	1.590	1.498	1.688	<.0001	1.240	1.163	1.323	<.0001
HLV	2.095	1.960	2.238	<.0001	1.587	1.478	1.705	<.0001
VF	2.707	2.615	2.802	<.0001	1.731	1.657	1.808	<.0001
Gender								
Female vs. Male	1.456	1.385	1.531	<.0001	1.458	1.378	1.543	<.0001
Race (Referent: Caucasian)								
African-American	0.647	0.626	0.669	<.0001	0.687	0.662	0.712	<.0001
Hispanic/Other	0.641	0.610	0.673	<.0001	0.818	0.775	0.863	<.0001
Time updated age (per 10-year increase)	1.700	1.673	1.726	<.0001	1.633	1.603	1.664	<.0001
log(VL) at ART initiation (copies/ml)	0.962	0.947	0.978	<.0001	1.017	0.999	1.034	0.0587
Time from HIV dx to ART initiation (per year increase)	1.070	1.067	1.073	<.0001	1.018	1.014	1.022	<.0001
Time updated CD4 counts (per 100 cells increase/ul)	0.862	0.857	0.867	<.0001	0.940	0.934	0.946	<.0001
Time updated ART regimen (Referent: Boosted PI)								
INSTI	0.195	0.179	0.213	<.0001	0.278	0.252	0.306	<.0001
NNRTI	0.618	0.591	0.645	<.0001	0.733	0.698	0.769	<.0001
Other Combinations	1.514	1.439	1.593	<.0001	1.189	1.125	1.257	<.0001
Unboosted PI	1.322	1.263	1.383	<.0001	1.326	1.261	1.394	<.0001

N = 2,776 due to missing values for exploratory variables. SNAE cases, n = 484.
SNAE categories: Cardiovascular events include Coronary artery disease without Myocardial Infarction (n=59), Cerebrovascular Disease (n=20), Cardiomyopathy (n=9), Congestive Heart Failure (n=5), Deep Vein Thrombosis (n=37), Myocardial Infarction (n=22), Peripheral artery disease (n=6), Pericarditis (n=9), Pericardial Effusion (n=1), Cancers including Anal Cancer (n=25), Breast Cancer (n=6), Colon Cancer (n=1), Leukemia (n=1), Lung Cancer (n=3), Hodgkin's Lymphoma (n=7), Melanoma (n=12), Multiple Myeloma (n=1), Prostate Cancer (n=23), Other Cancers (n=26); Chronic Kidney disease defined as sustained decline in eGFR to <60 mL/min for 90 or more days (n=200); Cirrhosis (n=21)

690 CD4/CD8 AT 2 YEARS OF ANTIRETROVIRAL THERAPY AND INCIDENCE OF SERIOUS NON-AIDS EVENTS

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CoRIS group
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Background: While a low CD4/CD8 ratio during HIV treatment correlates with immune activation, its predictive value for identifying people living with HIV (PWH) at increased risk of serious non-AIDS events (SNAEs) remains debated. We used data from the Spanish CoRIS cohort to assess whether the CD4/CD8 ratio at year 2 of antiretroviral therapy (ART) predicts the incidence of SNAEs in the following 5 years.

Methods: Eligible individuals were PWH with ART initiation up to 2014 (to allow for a 7-year follow-up) and HIV-RNA < 50 copies/mL at 2 years. Participants with a history of AIDS events or SNAEs were excluded. The predictor variable was achieving a CD4/CD8 ratio above the cutoff (0.25, 0.5, and 1.0) at year 2 of ART initiation. The primary outcome was the cumulative incidence of SNAEs (major adverse cardiovascular event, neoplasia, or death) during the subsequent 5 years. Follow-up started at year 2 after ART initiation and ended at the earliest of loss to follow-up, ART discontinuation, or administrative end of follow-up. We estimated the 5-year risk via a double-weighted pooled logistic regression to account for selection bias due to censoring. Covariates included age, sex, date of enrolment, risk group, education level, geographical origin, AIDS diagnosis, HIV-1 RNA, and CD4/CD8 at ART initiation. We computed survival curves introducing a time-varying intercept to allow the hazard to vary over time.

Results: We included 4625 participants. Median age was 37 years, 87% were male, median CD4/CD8 ratio at ART initiation was 0.29 (IQR 0.17, 0.46). At 2 years after ART initiation, 75%, 53%, and 16% of participants achieved a CD4/CD8 ratio >0.25, >0.5, and >1.0, respectively. 11% were censored due to loss to follow-up or ART discontinuation, and 4% had a SNAE during follow-up. **Figure 1** shows the survival curves and the odds ratio for the event during follow-up. Participants who did not reach a CD4/CD8 ratio of 0.5 had a significantly increased risk of SNAEs, which was higher if CD4/CD8 < 0.25. Sensitivity analyses with additional adjustment for CD4+ at year 2 yielded similar results. Exploratory analyses for each 0.10 increase in CD4/CD8 showed that 0.50 was the highest ratio that maintained a statistically significant association with the incidence of SNAEs.

Conclusion: This study provides new evidence that a low CD4/CD8 ratio (< 0.5) after 2 years of ART is associated with an increased risk of SNAEs during the following 5 years. Future studies should address possible differences over the longer term.

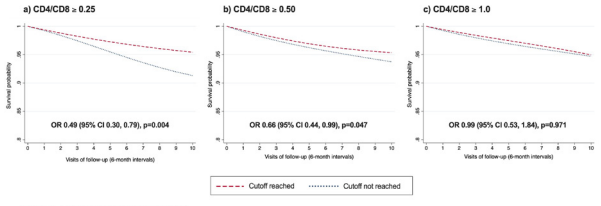

Figure 1. Survival curves for each cutoff

The figure shows the adjusted survival curves for participants who reached or did not reach the CD4/CD8 ratio cut-off points a) 0.25, b) 0.50 and c) 1.0 at 2 years of ART initiation. Results derived from the weighted pooled logistic regression model. For survival curves, a time-varying intercept was introduced to allow the hazard to vary over time.

691 SOLUBLE IMMUNOREGULATORY PROTEINS PREDICTIVE FOR COMORBID EVENTS IN PEOPLE WITH HIV

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Background: People with HIV (PWH) experience an increased risk of morbidity, partly driven by chronic immune dysfunction despite effective antiretroviral drug therapy (ART). HIV infection is characterized by persistent inflammation that promotes the accumulation of activated/exhausted lymphocytes with reduced effector function. We previously identified that several soluble immunoregulatory proteins associated with diminished lymphocyte effector function are predictive of comorbid outcomes in PWH. Using a unique panel of soluble immunoregulatory proteins and a nested case-control study from the AIDS Clinical Trials Group ALLRT cohort, we aimed to identify additional predictors of comorbid events to improve biomarker delineation that may, in conjunction, contribute to driving disease progression.

Methods: Study participants were evaluated at one-year post-ART at viral suppression and immediately preceding a comorbid event. Cases experienced a myocardial infarction (MI)/stroke event or cancer development. Controls were matched for age (median 45 years), sex (84% male), pre-ART CD4+ T cell count (median 213 cells/mm^3), ART regimen at 1 year, and parent study. A novel soluble immunoregulatory multiplex panel was developed and measured by Luminex. Conditional logistic regression analysis assessed biomarkers as predictors for comorbid events at each timepoint. Regression models were adjusted for CD4 counts at year 1 and pre-event; noteworthy associations used a threshold of an effect size (adjusted odds ratio (OR) per 1 IQR) ≥1.5. Support vector machine modeling with recursive feature elimination selection designed to preserve case-control dynamic was used to assess models and area under the curve of the receiver characteristic (AUC-ROC) were used to measure model accuracy.

Results: Higher levels of APRIL, CD226, and Gal-1 were significantly associated with MI/stroke at year 1 and pre-event timepoints (Figure 1A). Higher levels of CD137, Gal-3, and Siglec-7 were significantly associated with cancer at both timepoints. Machine learning-based modeling showed an improvement in case classification accuracy with the inclusion of newly measured biomarkers in identifying PWH who at year 1 and pre-event would develop MI/stroke or malignancy (Figure 1B).

Conclusion: We provide expanded insight on immunoregulatory proteins that appear predictive of cardiovascular and cancer events in PWH initiating ART and these multiple pathways may synergize in driving disease.

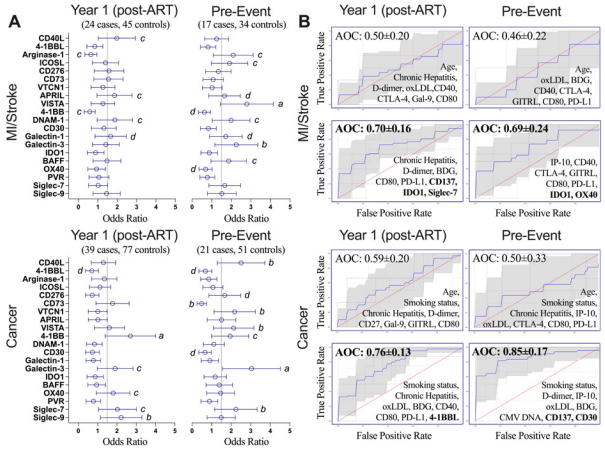

Figure 1. Soluble immunoregulatory proteins in predicting myocardial infarction (MI)/stroke or malignancy at one-year post-ART initiation and pre-event. Conditional logistic regression models adjusted for CD4 counts (A). [a]P<0.001, [b]P<0.01, [c]P<0.05, [d]P<0.1. Support vector machine modeling with recursive feature elimination selection assessed area under the curve (AOC) of receiver operating characteristic (ROC) to measure model accuracy (B). Model parameters are listed (lower right corner) for each ROC; inclusion of newly measured biomarkers in bold. Blue line=mean ROC; Light grey area = ±1 standard deviation; red dotted line=chance.

692 TELOMERE LENGTH IN AVIREMIC PWH: HOW DIFFERENT IS IT FROM PERSONS WITHOUT HIV?

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Background: Blood telomere length (BTL) attrition is a surrogate biomarker of immunosenescence and aging associated with HIV infection. BTL recovers in long-term virologically suppressed PWH, but it is unknown if recovery is complete compared with persons without HIV

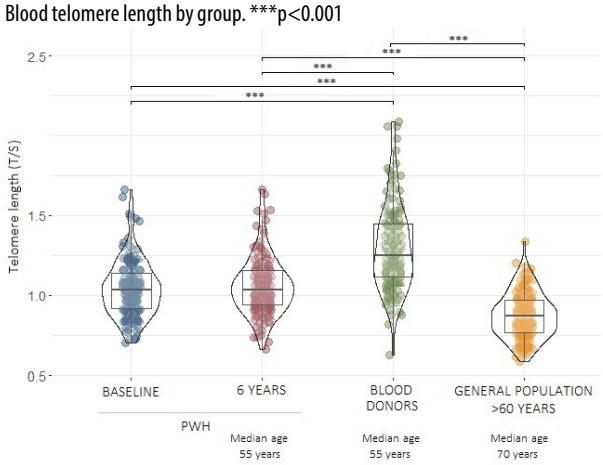
Methods: Prospective 6-year observational study assessing the evolution of BTL in virologically suppressed PWH and a cross-sectional analysis comparing BTL with age and sex-matched blood donors, and sex matched persons older than 60 from a general population cohort. Relative BTL was determined by

monochrome quantitative multiplex PCR assay and expressed as the ratio of telomere to single-copy gene (T/S)

Results: We included 135 PWH, 135 blood donors, and 135 persons over 60. Median age was 55 (IQR: 51-60), 55 (IQR: 51-60), and 70 (IQR: 68-73) years, respectively. 29.6 % were women in each group. In the PWH group 43.7% and 34.8% were active/former smokers, 5.9% had hazardous alcohol consumption, 28.9% had ever been injected drugs users, 92.6% were Caucasian, 33.3% resolved hepatitis C virus infection, 91.1% positive CMV IgG and 70.4% with ≥ 1 comorbidity. At 6 years of follow-up, the median time with known HIV-1 infection and virological suppression was 23.1 (IQR: 18.4-27.6) and 13.4 (IQR: 12.5-14.0) years, respectively. Nadir/current median CD4 count were 180 (IQR: 71.5-258) and 780 (IQR: 535-1000) cells/μL, and the median CD4/CD8 ratio was 1.12 (IQR: 0.79-1.40). In the ederly population 9.6%, 45.2% and 45.2% were active, former and never smokers, respectively. BTL of PWH remained stable after 6 years of virological suppression (median BTL at baseline 1.03 [IQR: 0.92-1.14] vs. 1.03 [IQR:0.94-1.15] after 6 years [p=NS]), without reaching the median BTL of blood donors of the same age and sex (1.25 [IQR: 1.11-1.45]; p< 0.001), but significantly above the median BTL of the older than 60 general population group (0.87 [IQR: 0.77-0.97]; p< 0.001) (Figure 1). 33 (24.4%) of PWH had BTL that was within ± 10% of the BTL of his/her age/sex matched blood donor. 27 (26.5%) of PWH < 60 had BTL that was within the ± 10% of the median BTL of the gender matched ≥ 60 participants from the general population

Conclusion: During the 6 years of follow-up the median BTL of aviremic PWH remained stable but still was shorter than the BTL of age/sex matched blood donors. However, compared to the elderly population our data do not support that aviremic PWH have a very pronounced BTL shortening

Blood telomere length by group. ***p<0.001



693 BLOOD TELOMERE LENGTH GAIN IN PLWH SWITCHING TO DTG+3TC VS CONTINUING TRIPLE REGIMEN

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Background: People living with HIV (PLWH) on long-term ART who maintain virological suppression continue experiencing blood telomere length (BTL) gain. However, ART containing NRTIs, such as tenofovir (TFV) or abacavir (ABC), which are potent inhibitors of human telomerase activity, has been shown to negatively affect the BTL increase. We investigated the effect on BTL at 1 year after switching to a dual therapy (DT) with dolutegravir (DTG) plus lamivudine (3TC) as the only NRTI vs maintaining a standard triple therapy (TT) with an anchor drug plus two NRTIs, one of which was TDF/TAF or ABC.

Methods: This was a prospective, longitudinal, matched, controlled study. We enrolled adults on stable (≥1 year) 3-drug ART and HIV-RNA< 50cps/mL who switched at baseline (BL) to DT or maintained TT; DT and TT groups were 1:1 matched for age, sex, years since HIV diagnosis, years on ART and anchor drug in the BL 3-drug regimen. BTL was assessed by a monochrome multiplex qPCR at BL and after 48 weeks (W48) and it was calculated as the telomere to albumin single copy gene (T/S) ratio. Comparison of BTL between and within groups was evaluated with parametric tests. Linear regressions were carried out to identify the variables associated with BL BTL and BTL changes over time.

Results: Between 2018-2021 we enrolled 120 PLWH, 60 in each group. The two groups were homogeneous for all main characteristics, except for slightly higher CD4 count in DT (Table 1). At BL, the BTL means (95%CI) were comparable between the two groups: 1.03 (0.98-1.08) for DT and 1.02 (0.96-1.07) for TT (p=0.704). At W48, viro-immunological status was stable and an overall increase in the mean (95%CI) BTL was observed, +0.05 (0.02-0.08) (p=0.001). However, a within-group analysis showed a significant mean BTL gain in the DT group [+0.08 (0.04-0.12), p< 0.001], but not in the TT group [+0.03 (-0.02-0.072), p=0.285]. In a multivariable regression, younger age (-0.009 per +1 year increase; -0.011/-0.006; p< 0.001), being female (vs male +0.098; 0.014/0.181; p=0.022) and higher CD4/CD8 ratio (+0.060; 0.0002/0.119; p=0.050) were independently associated with higher BL BTL. Higher BTL change was associated with DT group (+0.060; 0.003/0.117; p=0.041) and with shorter BL BTL (-0.297; -0.440/-0.153; p< 0.001).

Conclusion: In this setting, switching to a dual regimen with 3TC plus DTG was associated with higher gains in BTL than maintaining triple therapy after the 1-year follow-up. These data suggest that dual therapy could have a positive effect on BTL.

Table 1. Characteristics of participants at baseline

	Dual therapy (DT) n=60	Triple therapy (TT) n=60	p
Male sex, n (%)	48 (80)	48 (80)	1.000
Age, median (IQR)	54 (41 - 59)	53 (42 - 60)	0.851
BMI, median (IQR)	24 (22 - 27)	23 (20 - 26)	0.066
Smokers, n (%)[a]	28 (46.7)	26 (43.3)	0.714
Alcohol use, n (%)[b]	25 (41.7)	25 (41.7)	1.000
Time since HIV diagnosis, years, median (IQR)	13 (6 - 21)	13 (5 - 24)	0.514
Time on ART, years, median (IQR)	11 (3 - 20)	12 (4 - 21)	0.828
Time of virological suppression (<50cps/mL), years, median (IQR)	8 (2 - 12)	7 (3 - 11)	0.479
CD4 cell count, cells/mm³, median (IQR)	728 (579 - 875)	671 (479 - 780)	**0.046**
CD4/CD8 ratio, median (IQR)	0.93 (0.55 - 1.22)	0.82 (0.58 - 1.17)	0.657
CMV, n (%)	1 (1.7)	4 (6.7)	0.171

[a] >10 cigarettes per day; [b] ≥10 alcoholic units/week

694 COMPARISON OF TELOMERE LENGTH CHANGES OVER 48 WEEKS IN SALSA STUDY: DTG/3TC VS CAR

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Background: Telomere length (TL) shortens with biological age, and decreased TL is associated with disorders such as cardiovascular disease, stroke, and diabetes. For people living with HIV-1 (PWH) without treatment, TL shortening is seen, and has been associated with immune activation and lower immunological response. ARVs and regimen received can impact TL; tenofovir has been shown to inhibit telomerase activity *in vitro*, and in clinical studies may be associated with shorter TL. The SALSA study showed switching to DTG/3TC fixed-dose combination (FDC) was non-inferior to continuing current antiretroviral regimen (CAR) at Week 48 (respectively, 94% vs 93% with viral load (VL) < 50c/mL) by Snapshot analysis. This post-hoc analysis assesses TL from baseline (BL) through 48 weeks.

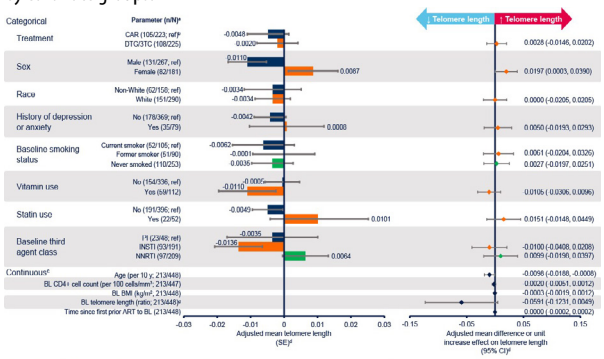
Methods: Adults with VL < 50c/mL for ≥6 months were randomized to DTG/3TC FDC or continued CAR with 81% (200/247) receiving TAF or TDF. qPCR using genomic DNA extracted from whole blood samples was performed to generate ratios of telomere TTAGGG repeats to a single-copy gene (T/S ratios) reflecting average TL of the total cell population. The adjusted mean difference in TL at Week 48 between treatment groups (DTG/3TC vs CAR) was calculated using an ANCOVA model including the following pre-specified covariates (Figure 1): CD4+ cell count, age, sex, race group, depression or anxiety, BMI, smoking status, vitamin use, statin use, BL TL, time since first prior ART, and BL third agent class (PI, INSTI, or NNRTI).

Results: Adjusted mean changes from baseline in T/S ratio in the DTG/3TC and CAR groups were similar, −0.0020 vs −0.0048, respectively (treatment difference, 0.0028; 95% CI, −0.0146, 0.0202; *P*=0.751). Baseline factors associated with TL included age and sex (women had longer TL) as summarized in Figure 1.

Conclusion: In the SALSA study, we show that age and sex significantly influenced TL as expected, however continuing TDF or TAF in the CAR arm did not appear to have an impact, though limitations include that 19% of participants in CAR arm did not receive a tenofovir prodrug. Of note, there was no impact on TL when switching to DTG/3TC over 48 weeks. This data, alongside non-inferior efficacy and minimal impact across inflammatory markers seen

with DTG/3TC, challenges the value of the 2nd NRTI in a virologically suppressed switch population.

Figure 1. Forest plot view of telomere length change from baseline at Week 48 by covariate groups.



BL, baseline; Ref, reference. *N represents the number of participants with non-missing baseline covariate data and n represents the number of participants with at least one telomere length data at either baseline or Week 48. †Reference for adjusted mean difference. ‡Reported as increase (>0) or decrease (<0) in adjusted mean change in telomere length. #Telomere length is measured as a ratio of telomere to single-copy gene

695 SEVERAL InSTI AFFECT IMMUNE CELL MITOCHONDRIA, PROLIFERATION, AND APOPTOSIS Ex vivo

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Background: HIV integrase strand transfer inhibitors (InSTI) are popular among people living with HIV for their tolerability and low pill burden. However, compared to older antiretrovirals (ARVs), little is known about their mitochondrial toxicities. Dolutegravir has been associated with weight gain in adults, which may reflect changes in cellular metabolism regulated by mitochondria. Mitochondrial toxicity of more recently approved InSTIs bictegravir, elvitegravir+cobicistat, and cabotegravir remains unclear. We herein characterized the effects of InSTI exposure on cultured immune cell mitochondrial health, and proliferation.

Methods: PBMCs from healthy volunteers were treated with T cell activator anti-CD3/CD28 for 6 days while also exposed to 1xC_{max} InSTIs in medium + 0.1% DMSO (ARV diluent). Mitochondrial intermembrane potential (MMP), reactive oxygen species (mtROS), and mass (mtmass), along with cellular proliferation and apoptosis, were determined by flow cytometry. Comparisons with the DMSO-exposed control cells were done by paired t-test. Additional experiments were performed to further explore changes in T-cell activation markers and T-cell memory compartments when exposed to InSTIs. These were carried out as above, with new antibodies for activation and differentiation.

Results: Compared to DMSO controls (n=9 biological replicates), bictegravir exposure exerted the most pronounced effects, with two-fold decreased mtmass, mtROS, MMP, a five-fold decrease in proliferation, and one-fold increase in apoptosis, while elvitegravir+cobicistat decreased MMP and proliferation two-fold (all $p < 0.001$). In contrast, dolutegravir and cabotegravir both increased MMP by half-fold ($p \leq 0.045$), while first generation InSTI raltegravir had no effect on these parameters. In preliminary experiments (n=3), exposure to some InSTIs appeared to decrease the relative proportion of CD4 central memory cells and/or increase expression of early activation marker when compared to DMSO controls.

Conclusion: These data clearly show that some second generation InSTIs can affect mitochondria in cultured PBMCs. Furthermore, the effects of bictegravir *ex vivo* suggest a potential underlying metabolic mechanism which could hinder immune responses. Further exploration of the effect of InSTIs on T-cell activation is required as these types of toxicities may not be revealed by clinical trials yet could exert long-term immunological and health consequences.

696 SARCOPENIA, FRAILTY, NUTRITION, AND HCV INFECTION AMONG OLDER PEOPLE WITH HIV

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Background: Sarcopenia is a geriatric syndrome associated with a loss of muscle mass and functionality. It may increase morbidity and mortality. As Asian data are limited, we investigated the prevalence and risk factors for sarcopenia in older people living with HIV (PLWH).

Methods: We conducted a cross-sectional study in a cohort of virologically well-suppressed PLWH and age- and sex-matched HIV-negative controls, aged ≥50 years, from 2017 to 2018 in Bangkok, Thailand. Diagnosis of sarcopenia was based on Asian Working Group for Sarcopenia 2019 criteria: handgrip strength by a handheld dynamometer (male < 28kg, female < 18kg), walking speed 4-meter-walk < 0.8m/s and skeletal muscle mass (male < 7.0kg/m^2, female < 5.7kg/m^2) by bioelectrical impedance analysis. Osteoporosis was defined as T-score cutoff-points ≤-2.5 at any site of DEXA scan (lumbar spine, total hip and femoral neck). Frailty and nutritional status were evaluated using Fried's criteria and Mini Nutritional Assessment, respectively. Multivariable regression analysis was used to assess the relationship between sarcopenia and participant demographic and clinical variables. We also compared bone turnover markers between those with or without sarcopenia.

Results: A total of 407 participants (277 PLWH and 130 controls) were included; 36% were female. Median age was 55 (interquartile range (IQR): 52-60) years and median duration of ART was 16 (IQR :13-19) years. PLWH had a higher prevalence of sarcopenia (8.3% vs 3.1%, p=0.05), HCV infection (9.0% vs 2.3%, p=0.011), frailty (9% vs 3.1%, p=0.001) and at higher risk of malnutrition or malnourishment (18% vs 7%, p=0.002). Osteoporosis at any site was almost double in PLWH than controls (15% and 8.5% (p=0.06). Serum 25(OH)D, phosphorous, calcium, C-terminal telopeptide (CTX), amino-terminal pro-peptide of type-1 procollagen (P1NP) and intact Parathyroid Hormone (iPTH) were not significantly different between the sarcopenia groups. In a multivariate model among PLWH, BMI < 18.5kg/m^2, male sex, HCV coinfection, frailty and malnutrition were significantly associated with sarcopenia (Table).

Conclusion: In this aging cohort, PLWH had a higher burden of sarcopenia than HIV-negative individuals. Besides low BMI and male gender, hepatitis C co-infection, poorer nutritional status and frailty were identified as predictive risk factors. Therefore, interventions to improve nutritional status and early HCV treatment may reduce the risk of sarcopenia in older PLWH.

Association between sarcopenia with sociodemographic and clinical-related factors among people living with HIV identified by multivariate logistic regression.

Table: Association between sarcopenia with sociodemographic and clinical-related factors among people living with HIV identified by multivariate logistic regression.

Variables		Outcome		Univariate		Multivariate	
		No sarcopenia (n=254)	Sarcopenia (n=23)	OR (95%CI)	p-value	OR (95%CI)	p-value
Sex	Male	153 (88.44)	20 (11.56)	4.40 (1.27-15.20)	**0.019**	7.9 (1.48-42.23)	**0.016**
	Female	101 (97.12)	3 (2.88)	1 (ref)			
BMI (kg/m^2)	<18.5	12 (70.59)	5 (29.41)	5.60 (1.78-17.65)	**0.003**	12.22 (2.22-67.22)	**0.004**
	≥18.5	242 (93.08)	18 (6.92)	1 (ref)		1 (ref)	
HCV coinfection	No	234 (92.86)	18 (7.14)	1 (ref)		1 (ref)	
	Yes	20 (80.00)	5 (20.00)	3.25 (1.09-9.68)	**0.034**	4.05 (1.1-14.93)	**0.036**
Frailty	Robust	92 (95.83)	4 (4.17)	1 (ref)			
	Pre-frail or frail	162 (89.5)	19 (10.5)	2.70 (0.89-8.17)	0.079	4.67 (1.2-18.16)	**0.026**
Nutritional status	Normal	215 (95.13)	11 (4.87)	1 (ref)		1 (ref)	
	At risk of malnutrition or being malnourished	39 (76.47)	12 (23.53)	6.01 (2.48-14.59)	**<0.001**	5.69 (1.86-17.44)	**0.002**

697 CMV IgG IS ASSOCIATED WITH MUSCLE FUNCTION BUT NOT QUALITY OR MASS IN PEOPLE WITH HIV

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REPRIEVE Study Team
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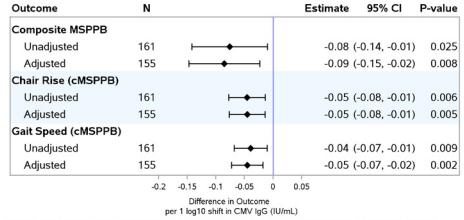
Background: Cytomegalovirus (CMV) infection is associated with poor outcomes, including physical function impairment, in people without HIV. We examined associations of CMV IgG antibody titers with physical function and muscle quality/quantity in virologically suppressed middle-aged people with HIV (PWH), leveraging REPRIEVE baseline data.
Methods: REPRIEVE is a double-blind randomized trial evaluating pitavastatin for primary prevention of cardiovascular disease in PWH. This cross-sectional analysis focuses on participants enrolled in a substudy with additional biomarker testing and imaging at study entry. CMV IgG was measured in duplicate using the human CMV IgG enzyme immunoassay by Genway Biotech. Paraspinal muscle area (MA) and density (MD) were assessed on non-contrast CT. Physical function and frailty were obtained by Short Physical Performance Battery (SPPB), a modified version (mSPPB) and the Fried Frailty Phenotype, respectively. Associations between CMV IgG (risk factor) and outcomes were evaluated using partial Spearman correlation, and linear and log-binomial regression.
Results: Of 717 participants with CMV IgG measurements, the median age was 51 (Q1, Q3: 46, 55) years; 18% were natal female, 51% White, 37% Black, and 25% Hispanic; median BMI was 27 (24, 30) kg/m^2, 93% had HIV-1 RNA < 50 copies/mL, and 50% nadir CD4< 200 cells/mm^3. Median CMV IgG was 2716 (807, 6672) IU/mL, none below the limit of quantification. There was no evidence of association between CMV IgG and MD or MA among n=631 with CT-based measures, controlling for age, sex and BMI (r=-0.03, p >0.5). Among 161 participants with physical function data, higher CMV IgG was associated with poorer physical function (mSPPB), largely driven by chair rise and gait speed components (Figure). Similarly, higher CMV IgG was associated with impairment on SPPB (score≤10) (relative risk=1.74 per 1 $\log_{10}$ shift, 95% CI: 1.13, 2.69). The effect sizes were similar after adjusting for CD4 nadir and hsCRP. While the number of frail participants was limited (n=7), trends were consistent for associations with pre-frailty and frailty.
Conclusion: The known association between CMV IgG and physical function or frailty is replicated in PWH and does not appear to be explained by changes in muscle quantity or quality, nadir CD4 or inflammation. Further mechanistic studies are needed to understand this association and whether CMV eradication or CMV-specific therapy can impact physical function in PWH.

Figure: Associations of CMV IgG with Physical Function



Estimates are from linear regression models with CMV IgG as risk factor and physical function measures as outcomes, unadjusted and adjusted for age, sex, BMI, nadir CD4 and hsCRP.

698 VALIDITY OF A SELF-REPORTED MODIFIED FRAILTY PHENTOYPE AMONG PEOPLE WITH HIV

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Background: Modifications to Fried's frailty phenotype (FFP) are common, particularly to address data collection limitations in clinical care settings. We evaluated a self-reported modified frailty phenotype (Mod-FP) used among people with HIV (PWH) within a US-based cohort and compared it to the original FFP.
Methods: Among 522 PWH who completed visits in the Impact of Physical Activity Routines and Dietary Intake on the Longitudinal Symptom Experience of people living with HIV (PROSPER-HIV) study within the Centers for AIDS Research Network of Integrated Clinical Systems (CNICS) cohort, we assessed validity of the Mod-FP using FFP as the gold standard. FFP includes unintentional weight loss, fatigue, and inactivity by self-report, and observed slow gait speed and weak grip strength. The Mod-FP includes unintentional weight loss, fatigue, inactivity, and poor mobility all collected via self-report. Each component is assigned a point if present. FFP is scored 0-5 while Mod-FP is scored 0-4. FFP categorizes frail as a score ≥3, prefrail as 1-2, and not frail as 0, and we identified cut points for Mod-FP in this analysis. We compared the Mod-FP with FFP via correlation, receiver operator characteristic (ROC) curves, agreement in classifying frailty status, and criterion validity via cross-sectional association with risk of having experienced falls.
Results: The median age of the cohort was 54 (IQR: 44-61), 21% were female, and 58% non-White. The Mod-FP and FFP were highly correlated (Pearson *r*: 0.83), and the Mod-FP classified 8% of PWH as frail, while FFP classified 9%. The area under the ROC curve for Mod-FP classifying frailty was 0.93 (95%CI:0.91-0.96) with 62% sensitivity and 97% specificity at a cutoff of 3 components (Table 1). For prefrailty, at a cutoff of 1 component, the AUC was 0.86 (95%CI:0.83-0.89). ROC values were consistent in age (over/under 55), sex (male/female assigned at birth), and race (Black/White) stratification. We observed 80% agreement (unweighted kappa=0.64, quadratic weighted kappa=0.75) between the phenotypes for categorizing PWH as not frail, prefrail, or frail. Both phenotypes found frailty associated with falls; FFP (OR:1.63, 95%CI:1.22-2.18) estimated a greater magnitude for the association than Mod-FP (OR:1.36, 95%CI:1.02-1.81), though the confidence intervals overlapped.
Conclusion: The Mod-FP has good performance in measuring frailty among PWH and is reasonable to use when the gold standards of observed assessments (i.e., weakness and slowness) are not feasible.

Receiver operator characteristic (ROC) results for the classification of frailty and prefrailty by the Mod-FP compared to FFP.

Table 1. Receiver operator characteristic (ROC) results for the classification of frailty and prefrailty by the Mod-FP compared to FFP.

FFP Stage	ROC AUC (95% CI)	Cut point (Mod-FP score)	Sensitivity	Specificity	Correctly classified
Frail	0.93 (0.91-0.96)	≥1	100%	57%	60%
		≥2	89%	83%	84%
		≥3	**62%**	**97%**	**94%**
		≥4	27%	100%	94%
Prefrail	0.86 (0.83-0.89)	**≥1**	**77%**	**92%**	**84%**
		≥2	33%	100%	65%
		≥3	6%	100%	52%

Abbreviations: AUC: area under curve; FFP: Fried's Frailty Phenotype; Mod-FP: Modified Fried Phenotype; PWH, people with HIV

699 COMORBIDITIES AND SYMPTOMS ASSOCIATED WITH FALLS: 2020-2021

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Background: Falls are associated with aging-related decline in health, occurring more frequently among people 65 years-old and older. People with HIV (PWH) experience aging-related complications earlier than the general population. While falls have previously been associated with aging-related complications among PWH, this work is limited by small sample sizes, focused on only healthcare-reported falls, and often includes falls prior to the current antiretroviral treatment (ART) era.
Methods: We examined falls reported within the previous 12 months between 2020-2021 among PWH in the Center for AIDS Research Network of Integrated Clinical Systems (CNICS) cohort at 7 US sites. Data were collected via patient reported and clinical measures. Associations of clinical, demographic and behavioral factors with any and number of falls were examined using relative risk regression models.
Results: Among 2386 PWH with complete data (mean age was 51 years and ranged 18-89 years; 14% were female and 53% non-white), 18% (*n*=435) reported falling at least once in the past year, among whom 50% fell once, 28% twice, and 22% ≥ 3 or more, with 27% (*n*=118) seeking medical care due to a fall. Falls were reported significantly more among PWH ≥ 50 years-old, however 9% of those under 40 years-old reported falling with half reporting more than one fall. Falls were also more likely to be reported by PWH who were white and lived near the West coast of the US. When adjusted for age, sex, location and race/ethnicity, falls were associated with reporting symptoms of

neuropathy, forgetfulness, fatigue, feeling dizzy, and depression. A prefrail or frail phenotype, diabetes, lower quality of life (QoL) scores and more emergency visits were also associated with falls. Risk ratios generally increased with more falls (Table). However, HIV viral load and current and nadir CD4 count were not consistently associated with falls.

Conclusion: Almost 20% PWH in routine clinical care reported falling in the past year, including 100 PWH < 40 years-old. Neurological and mental health symptoms, frailty, diabetes, and lower QoL were strongly associated with both falls and number of falls. Our finding suggest that a high proportion of PWH, even younger people, experience falls, which may be indicative of aging-related issues. Monitoring of neurological, cognitive, and mental health symptoms across the age spectrum in routine clinic visits may be important among PWH to minimize complications with early onset aging.

Table: Factors associated with any and number of falls in the past 12 months adjusted for age, race/ethnicity (white vs all others), geographic location (west vs all others), and birth sex (N=2386)

		Any Falls (N=435)	1 vs 0 Falls (N=218)	2 vs 0 Falls (N=120)	3 vs 0 Falls (N=97)
		RR (95% CI)	RR (95% CI)	RR (95% CI)	RR (95% CI)
Neuropathy symptoms: (None = REF)	Not/ a little bothersome	1.74 (1.41, 2.15)	1.50 (1.12, 2.01)	1.69 (1.06, 2.69)	2.35 (1.47, 3.77)
	Bothersome/ highly bothersome	2.85 (2.34, 3.46)	1.76 (1.30, 2.40)	2.41 (1.62, 3.59)	6.77 (4.39, 10.4)
Difficulty remembering: (None = REF)	Not/ a little bothersome	2.18 (1.79, 2.65)	1.62 (1.24, 2.13)	3.35 (2.29, 4.90)	1.65 (1.06, 2.60)
	Bothersome/ highly bothersome	3.18 (2.67, 3.95)	1.71 (1.21, 2.42)	3.98 (2.63, 6.01)	4.37 (2.81, 6.80)
Fatigue or Loss of Energy: (None = REF)	Not/ a little bothersome	2.39 (1.89, 3.02)	1.59 (1.18, 2.15)	3.24 (2.08, 5.03)	2.09 (1.25, 3.51)
	Bothersome/ highly bothersome	3.57 (2.83, 4.51)	2.04 (1.49, 2.79)	4.09 (2.62, 6.40)	4.81 (2.93,7.92)
Feeling dizzy: (None = REF)	Not/ a little bothersome	2.49 (2.07, 3.00)	1.70 (1.28, 2.24)	2.78 (1.93, 3.99)	3.29 (2.22, 4.89)
	Bothersome/ highly bothersome	3.91 (3.20, 4.77)	1.49 (0.98, 2.30)	4.95 (3.34, 7.34)	6.90 (4.60, 10.3)
Frailty Phenotype: (None = REF)	Prefrail	2.42 (1.94, 3.01)	1.71 (1.30, 2.25)	1.64 (1.10, 2.44)	4.45 (2.82, 7.02)
	Frail	4.67 (3.69, 5.92)	1.69 (1.14, 2.52)	4.22 (2.70, 6.60)	10.13 (6.42, 16.0)
Depression Symptoms: (None = REF)	Mild/ moderate	2.33 (1.95, 2.78)	1.97 (1.52, 2.56)	2.15 (1.50, 3.08)	3.07 (2.06, 4.59)
	Moderately sever/ Severe	3.50 (2.72, 4.50)	1.72 (1.08, 2.75)	2.61 (1.49, 4.56)	6.39 (4.07, 10.04)
Diabetes		1.43 (1.20, 1.72)	1.44 (1.09, 1.90)	1.34 (0.91, 1.97)	1.58 (1.04, 2.42)
EQ-5D index	per SD	0.41 (0.35, 0.47)	0.54 (0.46, 0.62)	0.45 (0.38, 0.53)	0.30 (0.25, 0.36)
# Emergency visits (2 years)	per visit	1.07 (1.05, 1.09)	1.09 (1.03, 1.15)	1.10 (1.03, 1.17)	1.18 (1.12, 1.25)

700 PREVALENCE, INCIDENCE, AND RISK FACTORS FOR FALLS IN OLDER PEOPLE WITH AND WITHOUT HIV

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Background: Falls are a clinically relevant outcome in geriatric patients. The objective was to compare prevalence of falls in people with and without HIV (OPWH vs OPW/oH) aged >65 years and to assess incidence and risk factors for falls in OPWH.

Methods: This was a prospective study of participants of the GEPPO cohort including OPWH and community-dwelling controls aged ≥65 yrs (OPW/oH). Inclusion criteria was availability of at least one evaluation of self-administered standardized falls questionnaire. Multimorbidity (MM) was defined as ≥3 comorbidities.

Step 1: to compare risk of falls in OPWH vs OPW/oH, we analyzed available falls records and variables collected at the previous visit with a Cox regression model.

Step 2: to identify falls incidence and its specific risk factors in OPWH, we analyzed the entire population of the GEPPO cohort enrolled between 2017 and 2021, with a survival model for time varying covariates for multiple events.

Results: Step 1: out of 311 OPWH (median age 79.8, 51% males, 28% with MM) and 109 OPW/oH (median age 70.4, 78% males, 68% with MM) we observed 180 falls, 158 (51%) in OPWH and 22 (20%) in OPW/oH.

After adjustment for age, gender and MM, OPWH had higher risk of fall compared to OPW/oH (HR 1.62 95%CI 1.07-2.46; p=0.024).

Step 2: among a total of 1331 OPWH in the GEPPO Cohort (median age 68.4 yrs, 82% males, median BMI 25.1) we observed a total of 437 falls during a median 3.4 years of follow up. Falls incidence was 437 per 650/PY FUP.

Median CD4 of the cohort was 616 cells, 97% with undetectable HIV RNA, 46% with an HIV duration >20 years, MM was present in 717 (55%) patients, 330 patients (25%) received InSTI and 273 patients (21%) received InSTI + NNRTI and/or PI.

After adjusted for current age, HIV duration, CD4, HIV RNA undetectability and BMI, higher age was protective from falls (HR 0.92 95%CI 0.889-0.96; p=< 0.001), while presence of MM was a risk factor for falls (HR 2,23 95%CI 1.19-4.21; p=0.013).

Conclusion: This is the first study which compared falls prevalence in OPWH vs OPW/oH being also able to identify falls incidence and variables associated with this geriatric syndrome.

701 A 12-WEEK MULTICOMPONENT EXERCISE PROGRAM REVERSES FRAILTY IN OLDER ADULTS WITH HIV

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Background: Frailty is associated with adverse health events including mortality among older adults with HIV (OAWH). A multicomponent exercise program (MEP) reverses frailty to pre-frailty and improves physical performance in the older population overall but there is no data in OAWH. Our aim is to analyze the effects of a personalized MEP (PEMP) on frailty, physical function, and quality of life in OAWH.

Methods: A prospective longitudinal study was performed. Sedentary adults 50 or over with and without HIV were included. The intervention was a 12-week PEMP (resistance, endurance, balance, and flexibility training) at home. Sociodemographic characteristics, comorbidity, medications, HIV-related data, and physical activity (IPAQ) were recorded. The dependent variables were frailty (Frailty Phenotype), physical function (Senior Fitness Test (SFT), hand grip strength, SPPB), mood (HADS, GDS-SF), and quality of life (WHOQOL-HIV-BREF).

Results: 51 participants were included (31 HIV+, 20 HIV-). Median age was 57 (53-63) years. 25% were women. 100% of the HIV+ participants were virologically controlled. The significant effects of the PEMP on frailty, physical function and physical activity are shown in Table 1. Significant improvement in quality of life was also found in physical health and level of independence (WHOQOL-HIV-BREF). No differences were found between HIV+ and HIV- participants.

Conclusion: Our results demonstrate that a 12-week PEMP reverses frailty and improves the physical function (lower body strength, upper body strength, aerobic endurance and balance), and the quality of life of older adults with or without HIV.

Table 1. The significant effects of the PEMP on frailty, physical function and physical activity.

Median (p25-p75)	Baseline visit	3-month visit	p
Physical activity (IPAQ)	743.25 (264-2079)	1776 (1039.5-2973)	0.0006
Lower body strength The Chair Stand Test (SFT)	13 (11-14.5)	14 (12-16)	0.006
Upper body strength The Biceps Curl Test (SFT)	13 (12-15)	15 (14-18)	0.0001
Aerobic endurance The 2-minute Step test (SFT)	59 (50-68.5)	61.5 (56-79)	0.0008
Agility and dynamic balance Up & go test (SFT) (m/s)	7.09 (6.25-8.1)	6.4 (5.63-7.45)	0.001
Frailty. N (%) Robust Prefrail Frail	 15 (29.4) 30 (58.8) 6 (11.7)	 22 (43.1) 27 (52.9) 2 (3.9)	0.019

702 SMOKING CESSATION AND ASSOCIATED FACTORS IN THE HIV OUTPATIENT STUDY: 2007-2021

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Background: The U.S. Preventive Service Task Force (USPSTF) recommends smoking screening and cessation strategies as a part of routine care. However, people with HIV (PWH) are more likely to smoke and less likely to quit than the general population. This study aimed to assess factors associated with prescription of smoking cessation medications among smokers seen in care at outpatient clinics of the HIV Outpatient Study (HOPS).

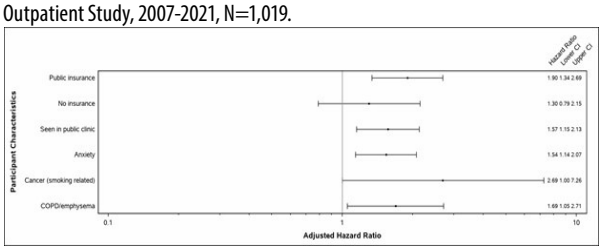
Methods: We analyzed medical records and risk behavior survey data from HOPS participants enrolled from January 1, 2007 to December 31, 2021. We included persons with evidence of current cigarette use and not receiving smoking cessation medications at HOPS enrollment (baseline). Smoking cessation medications included varenicline (Chantix), bupropion (Zyban), and

nicotine products. We identified smoking-related comorbidities based on laboratory results, clinical diagnoses, and treatments at baseline. We assessed associations between sociodemographic and clinical factors and prescription of smoking cessation medications using multivariable Cox proportional hazards analyses.

Results: Among 1,019 eligible PWH, 77% were men, 31% White, 48% Black/African American, 18% Hispanic/Latino, 46% aged 40 years and older. At baseline, 36% had smoking-related comorbidities including hypertension, chronic obstructive pulmonary disease (COPD)/emphysema, cardiovascular diseases (CVD), and cancers. During a median follow-up time of 2.6 years (interquartile range: 1.0-6.0), 342 (34%) were prescribed smoking cessation medications (Varenicline 106, Bupropion 53, nicotine products 273), and 241 (24%) quit smoking. In the multivariable analysis, having public insurance (hazard ratio [HR]:1.90, 95% confidence interval [CI]:1.34-2.69), care at a public clinic (HR: 1.57, CI:1.15-2.13), anxiety (HR: 1.54, CI:1.14-2.07)), smoking-related cancer (HR:2.69, CI:1.00-7.26), and COPD/emphysema (HR:1.69, CI:1.05-2.71) were positively associated with prescription of smoking cessation medications (Figure).

Conclusion: Low percentages of smoking cessation medications prescription and smoking cessation among HOPS patients demonstrate gaps in primary prevention of smoking-related chronic diseases in PWH. Given the high burden of baseline comorbidities, enhanced smoking cessation efforts are warranted for protecting the health of this aging cohort of PWH.

Figure: Final Multivariable Cox Proportional Hazards Analysis Results of Factors Associated with Prescription of Smoking Cessation Medications, the HIV Outpatient Study, 2007-2021, N=1,019.



703 MITOCHONDRIAL HAPLOGROUPS AND WEIGHT GAIN AFTER INITIATING ART IN PATIENTS WITH HIV

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*Presented at CROI by a nonauthor colleague

Background: Mitochondrial DNA (mtDNA) haplogroups have been associated with obesity among various populations and with weight gain following the switch to integrase strand transfer inhibitor (INSTI)-based antiretroviral therapy (ART) among people with HIV (PWH). We studied the association of mtDNA haplogroups with weight gain after ART in PWH.

Methods: Participants were ART-naïve PWH, recruited in the Spanish HIV Research Cohort, who started ART from 2014 onwards and had blood/DNA deposited in the cohort Biobank. The primary outcome was a change in weight at 96 weeks after starting ART. mtDNA genotyping was performed using the iPLEX Gold technology and Agena Bioscience's MassARRAY platform (San Diego, CA, USA). Changes over time in weight and BMI were studied using adjusted linear mixed models (LMM).

Results: A total of 1,019 PWH were included. The mean weight gain over 96 weeks was 2.90 (95% CI: 2.54 – 3.26) Kg. Factors associated with weight gain were female sex, birth in Sub-Saharan Africa, prior AIDS, CD4+ < 200 cells/uL, HIV-RNA > 100,000 copies/mL, negative HCV serology, and tenofovir alafenamide. The distribution of major mtDNA haplogroups was 376 (36.9%) HV, 158 (15.5%) UK, 138 (13.5%) JT, 45 (4.4%) IWX, 187 (18.3%) non-N, and 115 (11.3%) N-undefined. The results of LMM adjusted by age, sex, BMI at baseline, country of birth, prior AIDS-defining conditions, CD4+ cell count, HIV-RNA viral load, type of ART regimen according to anchor drug, and NRTI backbone showed an association between mtDNA haplogroup UK and a lower increase in weight and BMI at 96 weeks (**Table**).

Conclusion: The presence of the UK mtDNA haplogroup was associated with a lower increase in weight and BMI after ART in PWH. Our findings suggest that mitochondrial genomics plays a role in weight gain in this clinical context.

Estimated means (95% CI) of weight (Kg) and BMI at baseline and 96 weeks and increase according to major mtDNA haplogroups

	Haplogroup		N	Baseline	96wks	Increase	P
Weight	HV	No	643	72.4 (71.8; 73.1)	75.4 (74.6; 76.2)	2.94 (2.46; 3.43)	0.592
		Yes	376	73.7 (72.8; 74.6)	76.5 (75.5; 77.5)	2.79 (2.25; 3.33)	
	UK	No	861	72.9 (72.3; 73.4)	75.9 (75.2; 76.6)	3.03 (2.63; 3.44)	0.037
		Yes	158	73.1 (71.7; 74.5)	75.2 (73.6; 76.7)	2.10 (1.32; 2.88)	
	JT	No	881	72.9 (72.4; 73.5)	75.9 (75.2; 76.5)	2.93 (2.54; 3.33)	0.552
		Yes	138	72.7 (71.3; 74.2)	75.3 (73.6; 77.1)	2.61 (1.63; 3.58)	
	IWX	No	974	72.9 (72.4; 73.4)	75.8 (75.2; 76.4)	2.89 (2.52; 3.26)	0.984
		Yes	45	73.0 (70.4; 75.6)	75.9 (72.7; 79.1)	2.91 (0.93; 4.89)	
	Non-N	No	832	73.3 (72.7; 73.9)	76.0 (75.3; 76.7)	2.73 (2.34; 3.12)	0.074
		Yes	187	71.3 (69.7; 72.9)	74.9 (73.1; 76.8)	3.60 (2.63; 4.56)	
	N undefined	No	904	73.0 (72.4; 73.5)	75.8 (75.1; 76.4)	2.82 (2.44; 3.20)	0.361
		Yes	115	72.4 (70.7; 74.2)	75.9 (73.7; 78.0)	3.42 (2.14; 4.70)	
BMI	HV	No	643	24.1 (23.9; 24.3)	25.1 (24.9; 25.3)	0.98 (0.82; 1.15)	0.579
		Yes	376	24.5 (24.3; 24.7)	25.5 (25.2; 25.7)	0.93 (0.75; 1.11)	
	UK	No	861	24.3 (24.1; 24.4)	25.3 (25.1; 25.5)	1.01 (0.88; 1.15)	0.043
		Yes	158	24.1 (23.8; 24.5)	24.8 (24.4; 25.2)	0.70 (0.45; 0.96)	
	JT	No	881	24.3 (24.1; 24.4)	25.2 (25.1; 25.4)	0.98 (0.85; 1.11)	0.577
		Yes	138	24.2 (23.9; 24.6)	25.1 (24.6; 25.6)	0.88 (0.55; 1.20)	
	IWX	No	974	24.3 (24.1; 24.4)	25.2 (25.1; 25.4)	0.96 (0.84; 1.09)	0.988
		Yes	45	24.1 (23.5; 24.6)	25.0 (24.2; 25.8)	0.96 (0.31; 1.62)	
	Non-N	No	832	24.4 (24.2; 24.5)	25.3 (25.1; 25.5)	0.91 (0.78; 1.04)	0.079
		Yes	187	23.7 (23.3; 24.1)	24.9 (24.4; 25.3)	1.19 (0.88; 1.51)	
	N undefined	No	904	24.2 (24.1; 24.4)	25.2 (25.0; 25.3)	0.94 (0.81; 1.07)	0.388
		Yes	115	24.5 (24.1; 24.9)	25.7 (25.2; 26.2)	1.16 (0.71; 1.60)	

Variables for adjustment were age, sex, BMI at baseline, country of birth, prior AIDS-defining conditions, CD4+ cell count, HIV-RNA viral load, type of ART regimen according to anchor drug, and NRTI backbone.

704 WEIGHT CHANGE AFTER 48 WEEKS ON DOLUTEGRAVIR: A PROSPECTIVE STUDY OF PWH IN UGANDA

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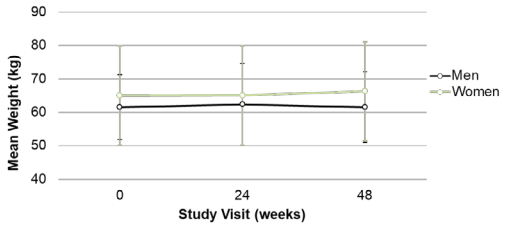
Background: Significant weight gain has been reported among people with HIV (PWH) initiating integrase inhibitor-based antiretroviral therapy (ART). We aimed to describe weight change over 48 weeks among PWH in Uganda who were transitioned from non-nucleoside reverse transcriptase inhibitor (NNRTI)-based ART to a regimen containing tenofovir, lamivudine, and dolutegravir (TLD).

Methods: The DISCO cohort study followed PWH from a public-sector clinic in Mbarara, Uganda. Eligible participants were >18 years of age, on NNRTI-based, first-line ART for >6 months, and switched to TLD by clinic staff. Weight (in kilograms [kg]) and height (in meters) were measured at the enrollment, 24-week, and 48-week study visits. We describe weight change from baseline (week 0) to 48 weeks overall and stratified by sex, age, and regimen prior to switch. We then fit a multivariable linear regression model to examine correlates of weight increase, including regimen prior to switch, age, sex, education, and baseline body mass index.

Results: We analyzed data from 428 participants, with a mean age of 46.4 years and 43% women. Regimens prior to switch were 3TC/AZT/NVP (40%), 3TC/TDF/EFV (42%) or Other (18%). 95% of participants were virally suppressed at < 50 copies per mL at the time of switch to TLD. The mean body mass index prior to switch to TLD for men was 21.3 kg/m^2 (SD=2.9) and 25.2 kg/m^2 (SD=5.4) for women. We found no change in weight among men (0.08 kg, 95% CI: -0.45 – 0.62) and a modest change in weight among women (1.23 kg, 95% CI: 0.50-1.96). Mean weight at 0, 24 and 48 weeks by sex is shown in Figure 1. After adjustment for regimen, education, and age, being female remained significantly associated with an increase in body weight over 48 weeks.

Conclusion: Women experienced modest weight gain over 48 weeks after switching to TLD in Uganda. We found no weight change in men and no relationship between prior regimen and weight change. These findings suggest a heterogeneous impact of TLD on body weight across contexts.

Figure 1. Mean body weight for women and men with HIV at 0, 24 and 48 weeks after switching to TLD in Uganda



705 WEIGHT GAIN FOLLOWING SWITCH TO DOLUTEGRAVIR AMONG ADULT HIV COHORTS IN WEST AFRICA

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IeDEA West Africa Collaboration

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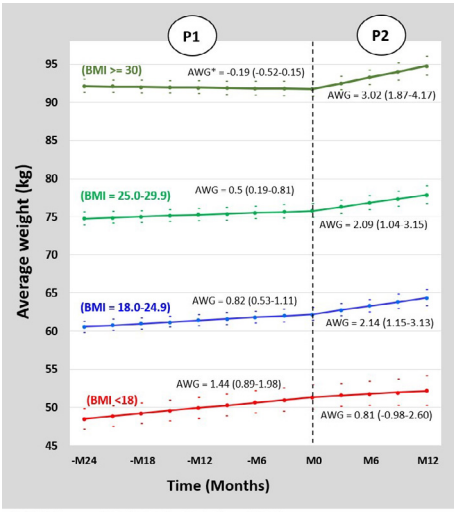
Background: Following WHO recommendations, most countries have transitioned to Dolutegravir (DTG)-based regimens as first-line antiretroviral therapy (ART). Despite documented adverse metabolic effects from developed countries, limited information is available from resource-limited settings. We explored changes in body weight before and after switch to a DTG-based regimen and assessed the association between switch to DTG and significant weight gain (≥10% increase) over a 12-month period in adults living with HIV (ALHIV) on ART in West Africa.

Methods: We first included all ALHIV followed in the IeDEA West Africa cohorts with a documented switch to DTG-based ART during 2019-2021. Participants had to be in care ≥36 months at the day of switch, with ≥1 weight measure during the 24-months pre-switch period (P1) and the 12-months post switch period (P2). Weight change was estimated with a linear mixed model within P1 & P2, stratified by body mass index (BMI) class. A secondary analysis compared significant weight gain (≥10%) in ALHIV on ART, prior and after the date of DTG introduction (site level dependent) between ALHIV who switched to DTG and those who did not at the date of database closure (control group), through a multivariate logistic regression with random effect analysis.

Results: In the first analyses, 5,294 ALHIV were included from three countries (Burkina, Côte d'Ivoire, Nigeria); 63% were women. Median age at day of switch was 48 years (IQR: 42-54) and median follow-up was 9 years (IQR: 6-12). Patients switched mainly from NNRTIs (83%) and PI-based (15%) ART regimens. Weight gain increased significantly during P2 compared to P1 period with significant interaction with BMI during both P1 & P2 periods. While AWG was not significant in underweight patients (0.81 [95%CI: -0.98-2.60]), it increased significantly in normal weight (2.14[CI: 1.15-3.13]), overweight (2.09 [CI: 1.04-3.15]) and obese (3.02 [CI: 1.87-4.17]) ALHIV during P2 period. In logistic regressions analyses, adjusted for sex, age and baseline ART regimen, switching to DTG was associated with weight gain≥10% (aOR=1.77 [95%CI: 1.38-2.26]).

Conclusion: In West African ALHIV, a 12-month DTG exposure was associated with a significant weight gain, particularly among those with a high BMI. As transition to DTG proceeds, close monitoring of weight and metabolic profile should be supported to characterize long-term health impact of DTG. Alternative ART regimen may be considered in individual with or at-risk for cardiometabolic disorders.

Figure 1. Linear mixed model predictions of weight evolution from month-24 pre-switch to month-12 post switch to a DTG-based ART regimen in ALHIV by body mass index (BMI) class. The IeDEA West Africa collaboration.



* AWG (Average Weight Gain) unit = kg/year (95%CI)
Final model was adjusted on sex, age, BMI at month 24 pre-switch and treatment line (1st, >=2nd line)

706 CHANGES IN BODY MASS INDEX WITH INTEGRASE INHIBITOR USE IN REPRIEVE

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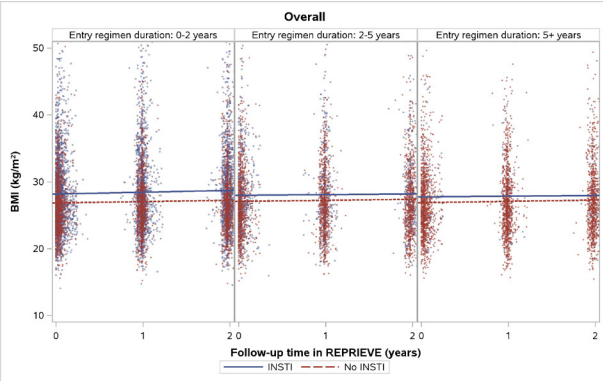
Background: Multiple studies have reported higher weight gain among people with HIV (PWH) with integrase strand transfer inhibitors (INSTIs), most notably in ART-naïve PWH and among women and Blacks/African Americans. However, knowledge gaps remain regarding long-term patterns of weight gain beyond the first two years after starting INSTI-based regimens in ART-experienced PWH.

Methods: An analysis of the effect of INSTIs on body mass index (BMI) was conducted in a large international cohort of PWH enrolled in REPRIEVE using mixed effect models with time-on-study as a continuous covariate. A stratified analysis was done evaluating 2-year change in BMI among participants on their entry ART regimen for 0-2 years, 2-5 years, and 5 or more years.

Results: On average, BMI increased by +0.23 kg/m^2 per year (95% CI: 0.19-0.28) with an INSTI and +0.17 kg/m^2 per year with a non-INSTI regimen (95% CI: 0.13-0.21). For participants on their ART regimen for 2 years or less prior to study entry, INSTI use over the next 2 years in the trial was associated with greater increase in BMI per year compared to non-INSTI users: (0.29 (95% CI: 0.23-0.35) vs 0.17 (95% CI: 0.11-0.22)) [Figure 1], particularly among women (0.51 (95% CI: 0.33-0.69) vs men 0.23 (95% CI: 0.06-0.40)) and Blacks/African Americans (0.38 (95% CI: 0.27-0.49) vs non-Black 0.11 (95% CI: 0.001-0.21)). There were no significant differences in rate of BMI change between those on INSTIs and those not on INSTIs among participants on their entry regimen for more than 2 years: (0.14 (95% CI: 0.07-0.22) vs (0.14 (95% CI: 0.05-0.23) 2-5 years; 0.24 (95% CI: 0.11-0.38) vs 0.20 (95% CI: 0.12-0.28) > 5 years). Participants with lower BMI at entry gained more weight over time. Among INSTI users, the highest BMI increase was associated with elvitegravir, regardless of TDF or TAF use. In sensitivity analyses, results were generally similar after accounting for differences in TDF and TAF use between groups.

Conclusion: Among a global cohort of PWH in REPRIEVE, the average rate of change in BMI associated with INSTI use was modest over 2 years of observation, but most significant among those on their entry ART 0-2 years prior to the observation period. Women and Black /African American participants were more likely to gain excess weight with INSTI use during this period. Lower BMI at study entry was predictive of higher weight gain on INSTIs. These data provide reassurance that long-term INSTI use may not be associated with substantial ongoing weight gain among PWH.

2-year change in BMI by INSTI use stratified by duration of entry regimen



707 DISCOVERING SUBGROUPS WITH LARGER WEIGHT GAIN WHEN TAKING DOLUTEGRAVIR

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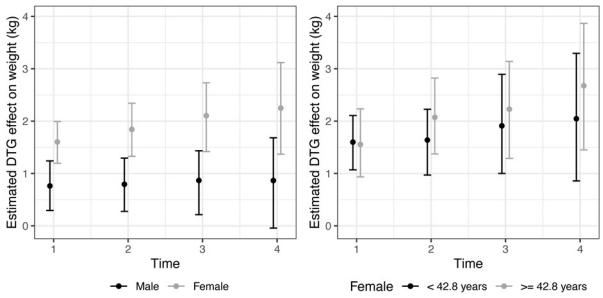
Background: Clinical trials have shown that dolutegravir (DTG)-containing antiretroviral therapy results in larger weight gains than other antiretroviral therapies (ARTs). Not all people are expected to have the same risk for increased weight gain with DTG-containing ARTs. Discovering subgroups for whom DTG is more likely to cause substantial weight gain allows treatment recommendations to be tailored to a person's risk profile.

Methods: We developed the Subgroup Discovery for Longitudinal Data (SDLD) algorithm, a data-driven tree-based algorithm that combines modern machine learning and causal inference methods for discovering subgroups with heterogeneous treatment effects using longitudinal data. We applied the algorithm to electronic health records (EHRs) from the Academic Model Providing Access to Healthcare (AMPATH) partnership in Eldoret, Kenya to discover subgroups who are at higher risk of weight gain when on DTG-containing ARTs.

Results: A total of 84,445 individuals who were at least 18 years old, were initiating or on ART, and had data on or after July 1, 2016 with 1,178,016 unique clinic visits were included. The average causal effect on 1,000-day weight gain was 1.41 kilograms (kg) higher comparing always to never on DTG-containing ARTs (95% confidence interval (CI) [0.99, 1.82]). After searching over a large space of subgroups, the SDLD algorithm identified gender as the primary source of heterogeneity in DTG effects and the average weight gain in 1,000 days when always on a DTG-containing ART was larger for females (2.25 kg, 95% CI [1.37, 3.12]) than males (0.87 kg, 95% CI [-0.04, 1.68]). The algorithm further split the female subgroup into whether they were older than or equal to 42.8 years old or not with older females having higher estimated weight gain. The figure shows the estimated weight trajectories among the subgroups.

Conclusion: We developed a novel algorithm that combines modern machine learning and causal inference methods to discover subgroups with heterogeneous treatment effects. We applied the algorithm to a large EHR database on people living with HIV in western Kenya. Our findings are consistent with prior research showing larger weight gains associated with DTG-containing ARTs. Gender was found to be the primary source of heterogeneity when we applied the first data-driven discovery of subgroups with larger weight gain when on DTG-containing ARTs.

Estimated weight trajectories among subgroups with differential weight gain when taking dolutegravir



708 SUBCUTANEOUS ADIPOSE TISSUE CELL COMPOSITION IS ASSOCIATED WITH VISCERAL FAT VOLUME

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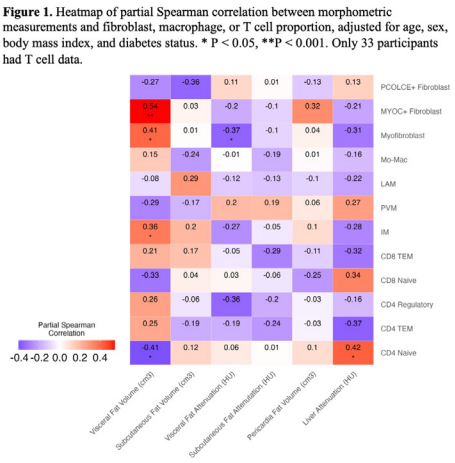
Background: Persons with HIV (PWH) are at increased risk for metabolic diseases compared with the general population, due, in part, to alterations in body fat distribution and the preferential expansion of visceral adipose tissue (VAT). While dysregulation of the subcutaneous adipose tissue (SAT) is thought to promote VAT expansion, the cellular mechanisms that link SAT health with VAT expansion in PWH remain unknown.

Methods: We performed single-cell RNA sequencing (scRNA-seq) on SAT biopsies from individuals with long-term virologic suppression and a spectrum of metabolic fitness. Computed tomography was used to measure VAT volume, VAT attenuation, liver attenuation, pericardial adipose tissue volume, SAT volume, and SAT attenuation. We assessed the relationships between morphometric measurements and the proportions of select cell types in SAT from single-cell data, including fibroblasts, macrophages, and T cells. Statistical analysis was performed using partial Spearman's adjusted for age, sex, body mass index (BMI), and diabetes status.

Results: A total of 44 participants were included in this study (non-diabetic = 13, prediabetic = 13, diabetic = 18). The median age was 51.5 years, BMI 32.0 kg/m^2, 70% male, 53% White, 77% treated with an integrase strand transfer inhibitor-based regimen, and 18% with thymidine analogue exposure. VAT volume was significantly associated with proportion of intermediate macrophages (IMs) ($r_{adj} = 0.36$, $p = 0.03$), myofibroblasts (radj = 0.41, $p = 0.02$) and MYOC+ fibroblasts ($r_{adj} = 0.54$, $p < 0.001$). CD4+ naïve cells were associated with liver attenuation ($r_{adj} = 0.42$, $p = 0.02$) and inversely associated with VAT volume ($r_{adj} = -0.41$, $p = 0.02$). Myofibroblasts were also inversely associated with VAT attenuation ($r_{adj} = -0.37$, $p = 0.02$). Other fibroblast, macrophage, and T cell populations were not significantly associated with morphometric measurements (Figure 1). Adjusting for thymidine analogue exposure did not alter these findings.

Conclusion: In PWH, increased proportion of myofibroblasts (a marker of fibrosis), anti-adipogenic MYOC+ fibroblasts, and IMs are independently associated with VAT volume even after adjustment for BMI. CD4+ naïve T cells were inversely associated with VAT volume. These results support the hypothesis that increased fibrosis and inflammation in SAT impair lipid storage and promote VAT expansion. Longitudinal studies are necessary to investigate causal relationships and underlying mechanisms that contribute to VAT expansion.

Figure 1. Heatmap of Partial Spearman's Correlation Between Morphometric Measurements and Cell Proportions



709 VISCERAL FAT REDUCTION WITH TESAMORELIN ASSOCIATED WITH METABOLIC SYNDROME REVERSAL

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Background: Among recent concerns surrounding weight gain in people with HIV (PWH) is the increasing incidence of Metabolic Syndrome (MetS). MetS, a component of which is central adiposity, is associated with increased risk of cardiovascular disease, stroke, and type 2 diabetes in PWH. Tesamorelin, a growth hormone releasing hormone analogue, was previously shown to reduce visceral adipose tissue (VAT) by over 15% in 26 weeks in PWH with lipohypertrophy. Due to the association between excess VAT and MetS, we investigated whether treatment with tesamorelin was also associated with changes in MetS classification

Methods: We leveraged data from 2 Phase III trials of tesamorelin among PWH with excess VAT. Participants were randomized to receive tesamorelin (2 mg) or placebo subcutaneously daily for 26 weeks. In a per-protocol analysis of 400 participants assigned to receive tesamorelin, responders (R) were defined a priori by ≥8% reduction in VAT. Participants were evaluated and classified for MetS longitudinally by its 5 components - elevated waist circumference, high triglycerides, low HDL cholesterol, increased blood pressure, and elevated fasting blood glucose – according to both NCEP and IDF guidelines. Post hoc analyses were then performed to assess changes in MetS classification between responders and non-responders

Results: The prevalence of MetS was high at baseline among study participants (37%) and did not significantly differ between responders (R) and non-responders (NR) (R: 34.2%; NR: 43.8% by NCEP; p=0.077). However, following 26 weeks of tesamorelin treatment, the prevalence of MetS decreased in responders resulting in a significantly lower prevalence of MetS compared to non-responders (R: 30.8%; NR: 48.5%; p< 0.001). While the overall prevalence of MetS by IDF was lower than under NCEP guidelines, the treatment effect of tesamorelin remained consistent (data not shown; p< .0001). Differences in MetS status were driven predominantly by resolution of triglycerides (R: 26.3%; NR: 5.0% p=0.005) and waist circumference (R: 25.6%; NR: 10.0%; p=0.031)

Conclusion: These data suggest that VAT reduction with tesamorelin is associated with a reversal of MetS classification among PWH. This is consistent with previous data indicating that visceral fat reduction is associated with improvements in metabolic parameters of PWH, and thus supports the use of tesamorelin in PWH with central adiposity to improve metabolic profiles

710 INFLAMMATORY PROFILES ARE ASSOCIATED WITH LONG COVID 6 MONTHS AFTER ILLNESS ONSET

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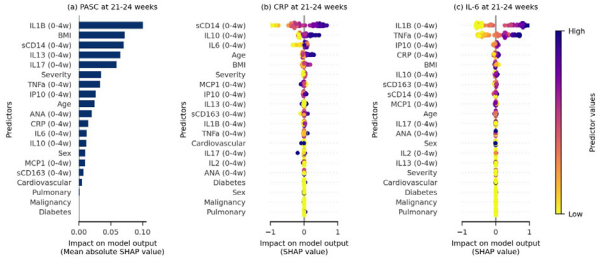
Background: Systemic hyperinflammation is key to the pathogenesis of severe, acute COVID-19. However, few studies have analysed inflammatory profiles in adults with mild/moderate COVID-19, or in those with post-acute sequelae of COVID-19 (PASC). We aimed to i) describe trajectories of cytokines in a prospective cohort of adults with mild to severe COVID-19, compared to uninfected, healthy controls and ii) identify early (< 4 weeks after illness onset onset) predictors of ongoing PASC and inflammation at 6 months after illness onset.

Methods: RECoVERED is a prospective cohort of adults with laboratory-confirmed SARS-CoV-2 infection between May 2020 and June 2021 in Amsterdam, the Netherlands. Serum was collected at weeks 4, 12 and 24. Participants completed monthly symptom questionnaires. PASC was defined as having at least one ongoing symptom that originated < 1 month of illness onset. Cytokine concentrations were analysed by human magnetic Luminex screening assay. We performed random forest regression to identify early predictors of PASC and raised CRP/IL-6 at 24 weeks, using Shapley additive explanation values as measures of importance for the different predictors.

Results: Of 349 RECoVERED participants, 186 (53%) had ≥2 serum samples and were included in current analyses. Of these, 101 (54%: 45/101 [45%] female, median age 55 years [IQR=45-64]) reported PASC at 12 weeks after illness onset, of whom none recovered by 24 weeks. We included 37 uninfected controls (17/37 [46%] female, median age 49 years [IQR=40-56]). At 4 weeks after illness onset, levels of IP10, IL10, IL17, IL1β, IL6 and TNFα were significantly elevated among participants infected with SARS-CoV-2 compared to controls. Ongoing PASC was independently associated with raised CRP at 24 weeks. Early raised IL1β and sCD14 levels and greater BMI at illness onset were the strongest predictors of PASC at 24 weeks. Those with higher early sCD14 or IL1β and TNFα levels were also more likely to have persistently raised CRP and IL6, respectively, at 24 weeks (Fig.1).

Conclusion: Differences in cytokine concentrations between individuals with COVID-19 and uninfected controls largely were greatest < 4 weeks after illness onset. In our study, ongoing PASC was associated with persistently elevated CRP at 24 weeks. Early immune dysregulation was, alongside BMI, an important determinant for persistent PASC. Further investigation of individuals with PASC and long-term aberrant cytokine levels may help improve our understanding of the condition.

Early (0-4 week) predictors of PASC and CRP/IL-6 levels at 21-24 weeks after illness onset



711 CYTOKINE PROFILE IN DIFFERENT POST-COVID-19 CONDITION PHENOTYPES

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Background: At least 10% of SARS-CoV-2 infected patients suffer from persistent symptoms for >12 weeks, known as post-COVID-19 condition (PCC) or Long Covid. Reported symptomatology is diverse with >200 physical and neurological debilitating symptoms. Here, we analyzed pro-inflammatory cytokine levels as a potential mechanism underlying persistent symptomatology.

Methods: Clinical data and samples used belong to the KING cohort extension, which includes clinically well characterized PCC (N=358, 59 persistent symptoms evaluated), COVID-19 recovered and uninfected subjects. We used Gower distances to calculate symptom's similarity between PCC and Ward's hierarchical clustering method to identify different symptom patterns among PCC patients. Cytokine levels of randomly selected PCC, recovered and

uninfected subjects (N=193) were measured on plasma samples collected >6 months after acute infection using the *30-Plex Panel* for Luminex. Mann-Whitney t-test was used to compare PCC vs recovered groups and Kruskal-Wallis t-test for >2 groups comparisons (PCC vs recovered vs Uninfected and within PCC clusters). FDR correction was applied for statistical significance (p-adj).

Results: Hierarchical clustering identified 5 different PCC clusters according to their symptomatology, where PCC3 and PCC5 clusters showed higher prevalence of women (>80%) and more persistent symptoms, while acute COVID-19 was mild in >80% of the patients. We selected 91 PCC (belonging to each cluster), 57 recovered and 45 uninfected subjects for cytokine profiling (Table 1). 13 soluble markers were significantly elevated (IL-1β, Eotaxin, MIP-1β, MCP-1, IL-15, IL-5, HGF, IFN-α, IL-1RA, IL-7, MIG, IL-4 and IL-8) in PCC and recovered groups compared to uninfected subjects (all p-adj< 0.04). In addition, PCC subjects tended towards higher levels of IL-1RA compared to recovered group (p-adj=0.071). Within PCC clusters, FGF-basic and RANTES were elevated while IL-2 and MIG were decreased in PCC3 and PCC5 compared to the other PCC clusters (all p-adj< 0.04). TNF-α, IP-10, G-CSF and MIP-1α were decreased in PCC3 and PCC5 not reaching statistical significance (all p-adj=0.07).

Conclusion: Some cytokines remained altered in all SARS-CoV-2 infected subjects independently of persistent symptoms after 6 months from acute infection. Differences between PCC and recovered individuals are limited after correction. Importantly, PCC cytokine profiles showed differences between clusters, which suggests different PCC subsyndromes with distinct etiology.

Subjects Characteristics

N=193 subjects	PCC	Post-COVID-19 condition (PCC)					Recovered	Uninfected
		PCC1	PCC2	PCC3	PCC4	PCC5		
N (%)	91 (47)	16 (18)	23 (25)	12 (13)	21 (23)	19 (21)	57 (30)	45 (23)
Female, n (%)	69 (76)	10 (63)	15 (65)	10 (83)	16 (76)	18 (95)	32 (56)	30 (67)
Age, years, median [IQR]	50 [40-56]	50 [41-61]	51 [43-62]	50 [41-62]	52 [43-62]	49 [40-62]	49 [40-59]	50 [43-59]
Hospitalization, n (%)	21 (23)	3 (19)	4 (17)	1 (8)	8 (38)	5 (26)	31 (54)	-
Severe COVID-19, n (%)	14 (15)	3 (19)	4 (17)	0 (0)	6 (29)	1 (5)	16 (28)	-
Months after symptoms initiation, median [IQR]	8.1 [7-9]	7.8 [6-8]	7.4 [7-8]	11.1 [7-12]	8.2 [8-9]	8.8 [8-12]	7.5 [7-8]	-
Number of persistence symptoms, median [IQR]	7 [4-9]	3.5 [3-6]	3 [2-4]	12 [10-14]	8 [6-9]	8 [7-10]	-	-
Selected Persistents symptoms , n (%)								
Fatigue	76 (83.5)	11 (69)	14 (61)	12 (100)	21 (100)	18 (95)	-	-
Neurocognitive complaints	64 (70)	3 (19)	12 (52)	12 (100)	20 (95)	17 (89)	-	-
Headache	48 (53)	3 (19)	6 (26)	10 (83)	16 (76)	13 (68)	-	-
Dyspnea	58 (64)	12 (75)	6 (26)	11 (92)	17 (81)	12 (63)	-	-
Cough	33 (36)	1(6)	5 (22)	10 (83)	11 (52)	6 (32)	-	-
Dysphonia	20 (22)	0 (0)	3 (13)	6 (50)	5 (24)	6 (32)	-	-
Dysphagia	26 (29)	2 (13)	1 (4)	2 (17)	4 (19)	8 (42)	-	-
Smell alteration	30 (33)	1 (13)	6 (26)	7 (58)	3 (14)	12 (63)	-	-
Arthralgia	59 (65)	7 (44)	9 (39)	12 (100)	17 (81)	14 (74)	-	-
Myalgia	40 (44)	2 (13)	4 (17)%	19 (83)	13 (62)	11 (58)	-	-
Chest pain	49 (54)	9 (56)	2 (9)%	6 (50)	1 (5)	3 (16)	-	-
Tachychardia	38 (42)	4 (25)	1 (4.3)	11 (92)	10 (48)	12 (63)	-	-
Fever	3 (3.3)	0 (0)	0 (0)	1 (8.3)	1 (4.8)	1 (5.2)	-	-
Low grade Fever	23 (25)	1 (6)	4 (17.4)	5 (42)	3 (14)	10 (53)	-	-
Diarrhea	39 (33)	1 (6)	4 (17)	5 (42)	11 (52)	9 (47)	-	-

712 NEW ONSET AUTOIMMUNE DISEASE MORE COMMON AFTER COVID-19

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Background: Viral infections including SARS-CoV-2 may trigger autoimmune disease through T-cell-mediated autoimmune response through molecular mimicry-cross-reactive T-cell recognition or bystander T-cell activation. Autoantibodies have been detected in patients with COVID-19 and some human proteins have homologous regions with SARS-CoV-2 peptides that could function as autoantigens. While there are scattered reports of various autoimmune diseases diagnosed after COVID-19, the risk is not known.

Methods: TriNetX (a global federated health research network providing access to electronic medical records across 72 large healthcare organizations) was utilized to define a cohort of adults 18 years or older seen on or after January 1, 2020 with at least one follow-up visit after an index date. Exposure was defined as COVID-19 diagnosis by ICD10 code or positive laboratory test. Controls did not have COVID-19 (by the same criteria) and were propensity score-matched to patients who had COVID-19 by age and female sex. Index date was the date of COVID-19 diagnosis or first provider visit for any reason during the study period for controls. Outcomes (see table) were assessed starting one month after index date (to exclude prior undiagnosed autoimmune disease) until one year after. Patients with a specific outcome prior to the index date or within one month after the index date were excluded from the analysis for that outcome. Incidence by COVID-19 exposure status and risk ratios for each outcome were assessed.

Results: 4,016,472 patients were included (2,008,236 in both groups). Overall, mean (SD) age was 49.2 (17.9) and 57.7% were female. Patients who had COVID-19 were more likely to be white (63 vs 56.9%; p< 0.001). Rheumatoid arthritis, psoriasis and type 1 diabetes mellitus had the highest incidence after COVID-19 (0.24, 0.22 and 0.19%, respectively). While the incidence of most of the autoimmune diseases assessed were low in both groups, the risk ratios for all but one condition (Grave's) showed statistically significant higher risk in patients after COVID-19 than in those without COVID-19 (see table). Risk ratios were highest for polyarteritis nodosa (4.43, 3.27-6.01), reactive arthritis (3.56, 2.05-6.2) and ANCA-associated vasculitis (3.36, 2.6-4.34).

Conclusion: Autoimmune diseases were more likely to be diagnosed within the first year after COVID-19 than in age-, sex-matched controls. Future work will assess the validity of autoantibodies in predicting autoimmune disease after COVID-19.

Risk of Autoimmune Disease Within One Year of COVID-19 Diagnosis

	Risk Ratio (95% Confidence Interval)
Rheumatoid Arthritis	1.32 (1.26 – 1.38)
Axial or Peripheral Spondyloarthritis	1.36 (1.20 – 1.55)
Reactive Arthritis	3.56 (2.05 – 6.20)
Adult Onset Still Disease	2.80 (1.55 – 5.05)
Giant Cell Arteritis	1.36 (1.24 – 1.50)
Polyarteritis Nodosa	4.43 (3.27 – 6.01)
CNS Vasculitis	2.20 (1.20 – 4.05)
ANCA Associated Vasculitis	3.36 (2.60 – 4.34)
Cutaneous Vasculitis	2.12 (1.87 – 2.39)
Anti-GBM Disease	2.25 (1.70 – 2.98)
Systemic Lupus Erythematosus	1.15 (1.06 – 1.24)
Sarcoidosis	1.24 (112 – 1.37)
Systemic Sclerosis	1.54 (1.32 – 1.81)
Psoriasis	1.41 (1.34 – 1.47)
Sjögren Syndrome	1.27 (1.18 – 1.37)
Crohn's Disease	1.53 (1.42 – 1.65)
Ulcerative Colitis	1.57 (1.47 – 1.68)
Dermatopolymyositis	1.34 (1.09 – 1.63)
Mixed Connective Tissue Disease	2.49 (2.31 – 2.68)
Diabetes Mellitus Type 1	1.69 (1.61 – 1.78)
Celiac Disease	1.68 (1.54 – 1.83)
Autoimmune Hepatitis	1.99 (1.70 – 2.34)
Autoimmune Thyroiditis	1.18 (1.12 – 1.25)
Graves' Disease	0.972 (0.89 – 1.06)

Analysis was performed on the cohort after propensity score matching by age and sex. Patients with an outcome prior to the study window were excluded from the analysis of that outcome.

713 INCIDENT NEW ONSET DIABETES AFTER COVID-19 INFECTION: A NATIONAL MULTICENTER COHORT

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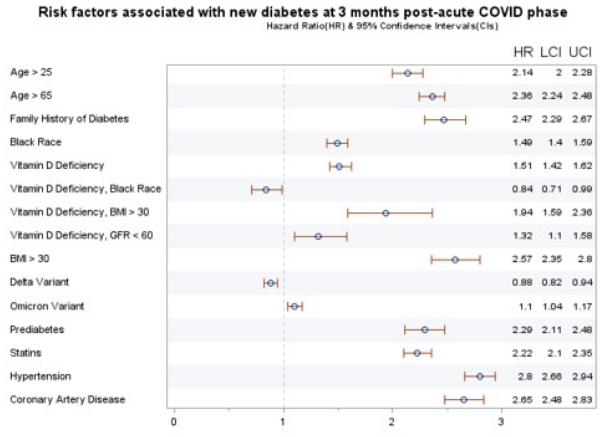
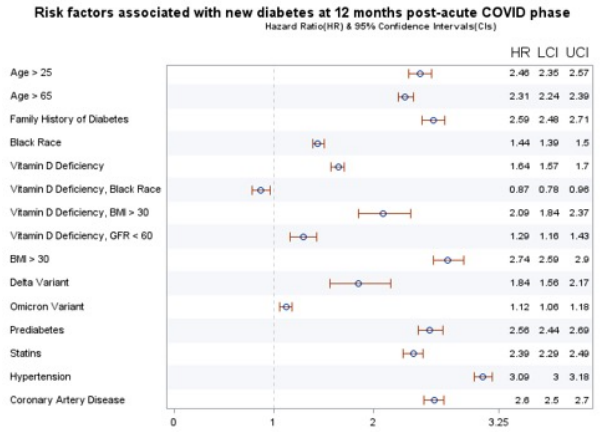
Background: It is known that survivors of acute SARS-CoV-2 infection can experience a complex disease known as post-acute sequelae of COVID-19 (PASC). The clinical manifestations of acute COVID-19 have been well characterized however less is known about the risk of new onset diabetes mellitus (DM) in the post-acute phase of COVID-19.

Methods: An adult cohort with confirmed COVID-19 (by diagnosis or positive test) and without COVID-19 was sampled from a large national health research network between January 1st, 2020 and July 8th, 2022. We investigated the outcomes of a new diagnosis of DM (type I or II) occurring after COVID-19 through 12 months after infection. Risk estimates [incidence, relative risk (RR), attributable risk] were used to describe the probability of incident post-COVID diabetes. Hazard ratios and 95% confidence intervals were used to describe risk factors associated with new diabetes.

Results: The 3-month probability of new diabetes was 2.48/1,000 among COVID+ and the relative risk (RR) of new diabetes was highest at 12 months [8.94 (8.54, 9.36)]. Vitamin D deficiency [HR: 1.52 (95% CI: 1.42, 1.63)] was associated with increased risk of T2DM and having vitamin D deficiency with either obesity (BMI > 30 kg/m_2) or kidney dysfunction (GFR < 60) was associated with more than five times increased risk of T1DM.

Conclusion: We observed a large proportion of excess diabetes starting at 3 months post COVID infection. Traditional risk factors for diabetes, omicron variant, and vitamin D deficiency are associated with increased risk of new diabetes outcome. PASC care should involve identification and management of diabetes.





714 WORSE ARTERIAL STIFFNESS, AND NOT ENDOTHELIAL DYSFUNCTION, IS ASSOCIATED WITH PASC

Sokratis N. Zisis[1], Jared C. Durieux[2], Christian Mouchati[1], Mary Chong[1], Danielle Labbato[2], Grace A. McComsey[3]

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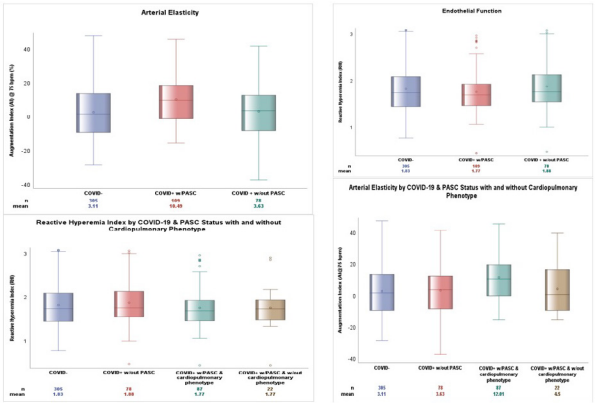
Background: COVID-19 survivors can experience lingering symptoms known as PASC that appear in different phenotypes. The etiology remains elusive and endothelial dysfunction has been postulated as a main driver of PASC.

Methods: Prospective cohort including COVID- and COVID+ with (COVID+PASC+) or without (COVID+PASC-) PASC. We measured endothelial function using Endopat, an FDA approved test, with derived reactive hyperemic index RHI (endothelial dysfunction≤1.67) and arterial elasticity (augmentation index standardized at 75 bpm or AI@75; (lower =better). PASC symptoms were categorized into three non-exclusive phenotypes: Cardiopulmonary CP (post-exertional malaise, shortness of breath, cough, palpitations), Neurocognitive N (change in smell/taste, neuropathy, 'brain fog', headache), and General G (fatigue, gastrointestinal or bladder problems).

Results: We included 491 participants with 109 of the 186 with confirmed COVID+ experiencing PASC. Median number of days between COVID diagnosis and study visit was 249 days (IQR: 144, 510). Among COVID+PASC+, the median number of symptoms was 7.0 (IQR: 3.0,13.0); 97 experienced symptoms categorized as G, 90 as N, and 87 as CP. COVID+ PASC+ had the lowest RHI (1.77±0.47) and the largest proportion [46.79% (n=51)] with RHI≤1.67 (Figure). AI@75 was the lowest in COVID- (3.11±15.97) followed by COVID+PASC- (3.57 ± 16.34). Within COVID+PASC+, the mean AI@75 among G was 10.11±14.85, 11.36±14.67 with N, and highest (12.01 ± 14.48) with CP. Symptoms' number was positively associated with AI@75 (p=0.01). The estimated mean difference in AI@75 between COVID+ PASC+ with CP and COVID+ PASC- was 8.44±2.46 (p=0.001), between COVID+ PASC+ with CP phenotype and COVID- was 8.9±1.91 (p< .0001), and between COVID+ PASC+ with CP phenotype and COVID+ PASC without CP phenotype was 7.51±3.75 (p=0.04)

Conclusion: PASC was associated with worse arterial elasticity and within PASC, the cardiopulmonary phenotype had the highest arterial stiffness.



715 OLFACTORY PERFORMANCE IN POST MILD-TO-MODERATE ACUTE COVID-19 ACROSS 2 YEARS

Lucette Cysique[1], Faye Yang[1], Amy Regan[1], Valerie Bramah[2], Benjamin Heng[3], Sharron Chow[4], David Darley[3], Anthony Byrne[3], Anthony D. Kelleher[5], Gregory Dore[1], Gail Matthews[1], Gilles Guillemin[4], **Bruce Brew**[3]

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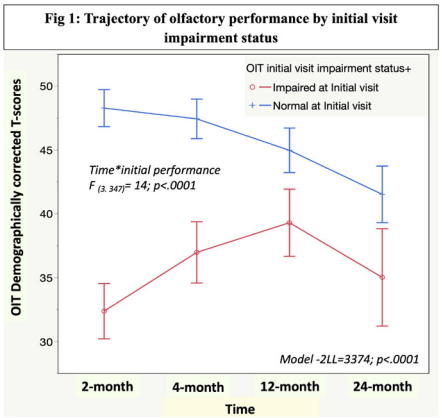
Background: Previous longitudinal studies (n=6) of objective olfaction performance post-acute COVID-19 have a maximum follow-up of 6-month and do not often test biomarkers. Although olfactory dysfunction appears to improve within two months of symptom onset, 4/6 longitudinal studies show persistent olfactory impairment.

Methods: PCR-confirmed COVID-19 patients in the prospective ADAPT cohort (Sydney, Australia) were assessed across 18 acute symptoms and hospitalization status: 40% mild, 50% moderate, 10% severe/hospitalised – none deceased). Blood samples were taken 2 (N=179), 4 (N=148) and 12-month (N=118) post-diagnosis. The NIH Odor Identification Test (OIT) and the Cogstate brief cognitive battery were performed. 58 also had an olfaction test at 24-month. The OIT raw data were transformed into demographically-corrected T-scores. OIT's attrition was completely random and only initial age (40±15 versus 47±15) differed between patients lost to follow-up and those in the study at 24-month. We tested peripheral neurobiomarkers (NFL, GFAP, S100B, GM-CSF) and immune markers (Interleukin-IL panel: 1-β, 1Rα, 4, 5, 6, 8, 10, 12p40, 12p70, 13, and MCP-1, TNF-α and INF-γ), analyzed as Log transformed and elevated/normal range using published references. Our previous analyses had shown no relationship with the kynurenine pathway, but an association of impaired olfaction and impaired cognition at 2-month only. Linear mixed effect regressions with time effect (months) tested olfaction trajectories (random subject effect) and their association with the biomarkers (main and time interaction).

Results: At 2 months post-diagnosis 30% had impaired olfaction and those who had acute severe disease were more likely to be impaired (54% versus 26%, p=.009). 21%, 31% and 37% had impaired olfaction at 4, 12 and 24-months. Olfactory performance declined over time (p< .0001), which was dependent on the initial performance (Fig 1). Neurobiomarkers were within the normal range. IFN-γ, IL-1Rα, IL-13 and TNF-α increased across time, p< .03-p< .0005. TNF-α and IFN-γ showed a time covariance with poorer olfaction performance.

Conclusion: Post-acute mild to moderate COVID-19 is associated with a declining olfactory performance up to 2-yr post-diagnosis, especially when initially impaired with the provisio of attrition although random. Olfactory performance decline may be mediated by upregulated immune parameters which are distinct from those driving cognitive changes.

Trajectory of olfactory performance by initial visit impairment status on the NIH Odor Identification Test (OIT)



716 OLFACTORY FUNCTION AND BRAIN STRUCTURAL EFFECTS FOLLOWING SARS-CoV-2 INFECTION

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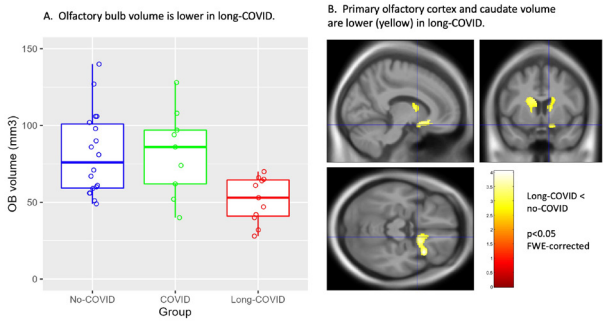
*Presented at CROI by a nonauthor colleague

Background: SARS-CoV-2 infection is accompanied by acute olfactory disturbance in as high as 70% of cases. This loss is associated with decreased olfactory bulb volume. As time passes, the anosmia tends to subside, but the OB volume decrease does not. Volume reductions in primary and secondary olfactory cortex are also seen following SARS-CoV-2 infection. Nevertheless, concurrent SARS-CoV-2 infection effects on olfactory discrimination, olfactory bulb volume, primary olfactory cortex and its targets have not been investigated. To explore this possibility, we measured olfactory discrimination, olfactory bulb volume, primary olfactory cortex and basal ganglia volume in patients who had SARS-CoV-2 infection more than 12 weeks previously, who were then divided into COVID and long-COVID groups on the basis of self-reported fatigue and concentration complaints.
Methods: This cross-sectional study included 25 post-infection and 19 demographically-matched, no-COVID control participants, we investigated effects on olfaction using NIH Toolbox Odor Identification Test and the Monell Smell Questionnaire. GM structure was assessed with voxel-based morphometry and manual delineation of high resolution (1mm^3), T1- and T2-weighted MRI data. Linear regression was used to model group effects on GM structure, adjusting for age, sex, education and total intracranial volume. CAT12/SPM12 and R were used for image processing and statistical modeling.
Results: Results. The NIH Toolbox Odor Identification Test failed to show differences among the groups. In contrast, the Monell Smell Questionnaire revealed persistently diminished and distorted smell in 50% of the long-COVID sample. Olfactory bulb volume was lower in the long-COVID group (p=0.02). Primary olfactory cortex volume was reduced in the long-COVID group (p=0.004). Caudate volume was also lower in the long-COVID group (p=0.04).
Conclusion: Conclusions. In the absence of olfactory discrimination problems, long-COVID, but not COVID, patients experience persistent olfactory loss and distortion. These perceptual problems are associated with lower olfactory bulb, primary olfactory cortex, and caudate volume, suggesting that the effects of SARS-CoV-2 infection can extend beyond the olfactory periphery in some cases to affect central targets.

Lower olfactory bulb, primary olfactory cortex, and caudate volume in Long-COVID.



717 SEX MODIFIES THE EFFECT OF COVID-19 AND PASC STATUS ON ARTERIAL STIFFNESS

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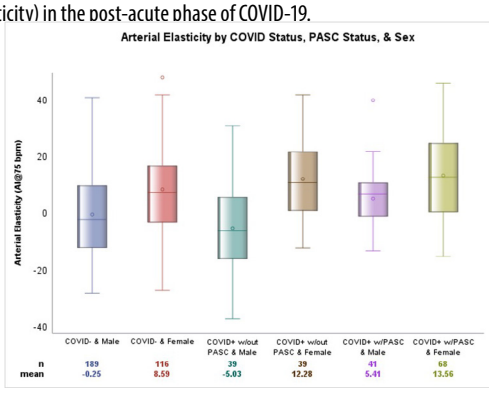
Background: Sex differences in immunological responses to COVID-19 infection and mechanisms that may contribute towards post-acute sequelae of SARS-Co-V2 (PASC) have been reported. However, evidence on the effects of COVID infection on vascular dysfunction and PASC are limited.
Methods: FDA approved EndoPAT device was used to measure endothelial function [Reactive Hyperemia Index (RHI)] and arterial stiffness [Augmentation Index standardized at 75 beats/min (AI@75; higher AI = worse arterial elasticity)] in an adult cohort (age ≥18 years) with a history of COVID-19 infection (COVID+) or confirmed SARS-CoV2 antibody negative (COVID-). Generalized linear regression was used to compute estimates of RHI and AI@75. Adjusted models included age, sex, race, blood pressure, lipids, body mass index (BMI), smoking status, and pre-existing comorbidities. Two-way interactions were used to determine if the effects of COVID or PASC status on endothelial function depends on age, sex, race, smoking status, or prevalent comorbidities.
Results: 61.99% (n=305) of study participants were COVID- and 187 (38.01%) were COVID+. Among COVID+, 57.22% (n=107) were female, 31.72% (n=59) were non-white race, and the average age was 46.64±13.79 years. COVID- participants had a smaller proportion (38.03%) of female sex (p< .0001), lower BMI [COVID+ (30.79±8.95 kg/m^2) vs. COVID- (27.76±5.89 kg/m^2); p< .0001], and higher proportion of smokers [COVID+ (17.78%) vs. COVID- (58.22%); p< .0001]. The average follow-up was 349.68±276.76 days and 109 (22.15%) COVID+ experienced PASC. 42.48% (n=80) of COVID+ and 41.64% (n=127) of COVID- had RHI≤ 1.67 (p=0.8). The average AI@75 among COVID+ without PASC was 3.63±16.24, with PASC was 10.5±14.72, and 3.11±15.97 among COVID- (p=0.0001). Male sex had the lowest AI@75 (-0.08±14.9) compared to female sex (10.75±15.3; < .0001). In adjusted models, PASC, female sex had 8.14±2.95 higher AI@75 compared to PASC, male sex (p=0.006), 18.58±2.99 higher AI@75 compared to COVID+ without PASC, male sex (p< .0001), 13.81±2.11 higher AI@75 compared to COVID-, male sex (p< .0001), and 4.97±2.28 higher AI@75 compared to COVID-, female sex (p=0.03). Sex was not associated with RHI or modified the effect of COVID or PASC status on endothelial function
Conclusion: The effect of COVID and PASC status on arterial stiffness depends on sex. Female sex is associated with increased arterial stiffness (worse arterial elasticity) in the post-acute phase of COVID-19.



718 INCIDENCE OF LONG COVID SYMPTOMS IN PATIENTS PREVIOUSLY HOSPITALIZED FOR COVID-19

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Background: Long COVID, also known as post-acute sequelae of COVID (PASC), affects more than 144 million people globally. While there is no broadly accepted consensus on a definition for the term "long COVID," studies have found symptoms persist or begin weeks or months after the end of SARS-CoV-2 infection. This study assessed the incidence of codes found in medical claims and hospital chargemasters that were consistent with long COVID symptoms commonly found in the literature.

Methods: Using the HealthVerity database, which provides closed claims and linked hospital chargemaster data on more than 25 million US patients, we examined patients aged 12 and above hospitalized between May 1, 2020 and September 30, 2021 with a diagnosis of COVID-19 who had at least 365 days of closed medical claims enrollment prior to index hospitalization admission and 90 days after admission, and did not have a long COVID diagnosis (ICD-10-CM U09.9) prior to the index hospitalization. Patients were allowed to have symptoms prior to hospitalization. The assessment period for the outcomes, which included 10 symptoms, was 90 days to 270 days after the date of hospitalization. Incidence rate per 100 person-years was calculated as the number of patients with the outcome divided by total person-time contributed (90 days after admission to the minimum of the following: outcome, inpatient death, disenrollment, end of data (April 30, 2022), or 270 days after admission).

Results: The dataset included 3,661,303 patients with an inpatient hospitalization during the study period. The final study cohort included 44,922 patients hospitalized with COVID-19, 20,627 of whom experienced at least one of the long COVID symptoms. Anosmia and dysgeusia were the rarest events captured in medical claims. More commonly found symptoms were joint pain, fatigue and breathlessness (see table).

Conclusion: This study examined diagnosed symptoms commonly found post-hospitalization among COVID-19 patients and reported the incidence of these symptoms in a representative population. The start period of long COVID used in this study (90 days post hospitalization) is consistent with the WHO definition of long COVID. In the absence of an understanding of the pathophysiology of long COVID, the use of diagnosed symptoms to define long COVID has the advantage of ease of use and availability of data. Further studies of additional symptoms and predictors of long COVID are needed.

Number of diagnosed long COVID symptoms and rate per 100 person-years among patients who had been hospitalized for COVID-19

Symptom	N	Rate per 100 person-years*
Taste disturbance/dysgeusia/ageusia	40	0.20
Smell disturbance/anosmia	45	0.22
Muscle pain/myalgia	1,215	6.10
Headache	1,373	6.89
Diarrhea	1,983	10.04
Cough	3,492	18.11
Chest pain	6,605	35.86
Joint pain/arthralgia	7,679	42.56
Fatigue	8,067	45.04
Dyspnea/breathlessness	8,356	46.93
Any of the above symptoms	20,627	150.92

*Person-time is calculated as the number of days between day 90 post-admission and the minimum of the following events: outcome, inpatient death, disenrollment, day 270 post-admission, or end of data (April 30, 2022).

719 FACTORS ASSOCIATED WITH LONG COVID-19 IN ZAMBIA, 2020 TO 2022

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Background: Following acute COVID-19, some (~10-20%) individuals continue to experience a persistent variety of symptoms often referred to as long COVID-19. However, evidence on long COVID-19 is limited from countries in Africa. We sought to describe the clinical presentation and factors associated with long COVID-19 in Zambia.

Methods: We conducted a cross-sectional analysis of routinely collected clinical information from patients receiving care in Zambia following SARS-CoV-2 infection. Data were collected from 13 'post-acute COVID-19' (PAC-19) clinics established across Zambia to care for people following their acute infection. Long COVID-19 was defined as experiencing persistent symptoms ≥4 weeks after initial diagnosis. Comorbidities detected at the time of SARS-CoV-2 infection were considered newly diagnosed. Severe illness was defined as acute COVID-19 that required supplemental oxygen therapy. We analyzed data from the first visit to the PAC-19 clinics and developed logistic regression models to assess factors associated with long COVID-19 at first visit to a PAC-19 clinic.

Results: In total, 1,238 persons (< 1%) had ≥1 visit to a PAC-19 clinic from August 2020 to April 2022 (out of ~319,500 confirmed cases in Zambia). Eight hundred twenty-three (66%) persons had been hospitalized for acute COVID-19 and the median length of stay was 8 days (interquartile range [IQR]: 4-16 days). Of these 1,238 persons, 641 (52%) were female while 403 (33%) had long COVID-19. The median age in persons with long COVID-19 was 54 years (IQR: 44-63) compared to 50 years (IQR: 37-61) in those without (p< 0.001). Cough (22%), fatigue (21%), and shortness of breath (15%) were frequently reported symptoms among persons with long COVID-19, while 4% had forgetfulness. Having severe illness (adjusted odds ratio [aOR] 2.8) and hospitalization for acute COVID-19 with length of stay ≥15 days (aOR 13) were associated with having long COVID-19 (Table 1).

Conclusion: Long COVID-19 was common among people attending PAC-19 clinics in Zambia, yet few persons with COVID-19 had attended a PAC-19 clinic. Those with severe illness were more likely to experience long COVID-19, which is consistent with other studies of long COVID-19. Given the burden of COVID-19 in Zambia, systems to care for patients with long COVID-19 might be needed in the future. Scaling up PAC-19 services and integrating into routine clinical care could improve access and further aid in understanding long COVID-19 in Zambia.

Table 1: Odds Ratios for Factors Associated with Long COVID-19 in Zambia, August 2020 to April 2022

Variables	Unadjusted ORs (CI†)	p-value	Adjusted ORs (CI†) *	p-value
Sex		0.389		
Female	*Referent*		-	-
Male	1.2 (0.8, 1.6)		-	-
Age Group		**<0.001**		
<29	*Referent*		*Referent*	-
30-39	3.0 (1.3, 7.0)		2.0 (0.7, 6.0)	0.216
40-49	4.9 (2.4, 10.7)		2.5 (0.9, 6.9)	0.070
50-59	3.6 (1.7, 7.8)		2.2 (0.9, 6.0)	0.108
60+	4.2 (2.1, 9.0)		1.8 (0.7, 4.6)	0.240
COVID-19 Wave		**<0.001**		
1	*Referent*		*Referent*	-
2	0.7 (0.3, 1.7)		1.7 (0.1, 53)	0.737
3	2.1 (1.0, 4.6)		4.7 (0.3, 140)	0.305
4	0.65 (0.3, 1.5)		3.9 (0.2, 124)	0.365
Newly Diagnosed‡		**0.008**		
No	*Referent*		*Referent*	-
Yes	1.9 (1.2, 3.1)		1.7 (0.9, 3.3)	0.084
Presence of Comorbidities		0.058		
No	*Referent*		-	-
Yes	1.4 (1.0, 1.9)		-	-
Oxygen Therapy		**<0.001**		
No	*Referent*		*Referent*	-
Yes	5.6 (3.6, 8.9)		2.8 (1.6, 5.0)	**<0.001**
Intensive Care Unit Admission		**0.039**		
No	*Referent*		*Referent*	-
Yes	2.0 (1.0, 4.1)		1.3 (0.6, 3.5)	0.531
Hospitalization Duration (days)		***<0.001***		
0-3	*Referent*		*Referent*	-
4-7	3.2 (1.9, 5.6)		2.0 (1.1, 3.7)	**0.038**
8-14	5.1 (2.9, 9.2)		2.9 (1.5, 5.7)	**0.002**
15+	27 (13, 56)		13 (6.2, 31)	**<0.001**
Vaccination Status		0.218		
Unvaccinated	*Referent*		-	-
Full	0.5 (0.2, 1.4)		-	-
partial	1.5 (0.7, 3.4)		-	-
Indeterminate	0.8 (0.1, 6.3)		-	-
Unknown	1.9 (0.9, 4.4)		-	-

* Best fit model

† 95% confidence interval (CI)

‡ Diabetes mellitus, hypertension, deep vein thrombosis/pulmonary embolism, kidney injury/disease or any other

720 15-MONTH ATTRIBUTES OF POST-COVID SYNDROME IN THERAPEUTICALLY VACCINATED OUTPATIENTS

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Background: In the third year of the coronavirus disease 2019 (COVID-19) pandemic, long-term post-COVID syndrome (PCS) following *severe acute respiratory syndrome coronavirus type 2* (SARS-CoV-2) infections poses the significant challenge for patients and health systems globally. Whilst COVID-19 vaccinations prior to *SARS-CoV-2* infection reduce the risk of PCS, the role of therapeutic vaccination in PCS recovery remains controversial. We present a 15 months longitudinal, prospective observational cohort study to examine long-term clinical courses, PCS recovery with and without vaccination as well as humoral immune responses in initially unvaccinated PCS patients.

Methods: A total of 227 COVID-19 convalescents of our initial mild COVID-19 outpatient cohort (N=958) from which longitudinal data was available were included in this study. PCS was defined according to the WHO definition. 76.7% (174/227) of individuals received at least one vaccination between 10 and 15 months after first SARS-CoV-2 infection. Receptor binding domain (RBD)-specific SARS-CoV-2 immunoglobulin G (IgG) and distinct symptom phenotypes (P) were longitudinally assessed for 15 months. Using binomial regression models, odds ratios (OR) with 95% confidence interval (95%CI) of descriptive, longitudinal variables associated with long-term PCS were calculated.
Results: 35.8% (82/227) and 31.3% (71/227) of patients had PCS at months 10 and 15 (figure 1A). SARS-CoV-2 IgG titers were equally distributed over time among age groups, sex, and PCS. PCS occurred in 30.5% (53/174) of vaccinated and 34.0% (18/53) of unvaccinated patients. Between 6 and 10 months (ΔT2/T3: not yet vaccinated) and 10 and 15 months (ΔT3/T4: vaccinated) after symptom onset (figure 1B), a comparable fraction of PCS patients recovered (ΔT2/T3: 22.5% and ΔT3/T4: 20.0%). Fatigue/dyspnea (P2) and not anosmia/ageusia (P1) constituted PCS at month 15 (P2 23.9% versus P1 1.4%). Headache (P4) and diarrhea (P5) at baseline were risk factors for PCS at months 15, respectively (P4: OR 2.01 (95%CI 1.11-3.52), p= .018; P5: OR 3.01(95%CI 1.44-5.94), p= .002).
Conclusion: Our results indicate, that distinct symptom phenotypes can constitute and predict long-term PCS 15 months after mild COVID. Recovery of PCS was observed similarly in both therapeutically vaccinated and unvaccinated patients. Thus, development of targeted PCS therapeutics is needed to improve patient care and future epidemiological investigations.

Figure 1

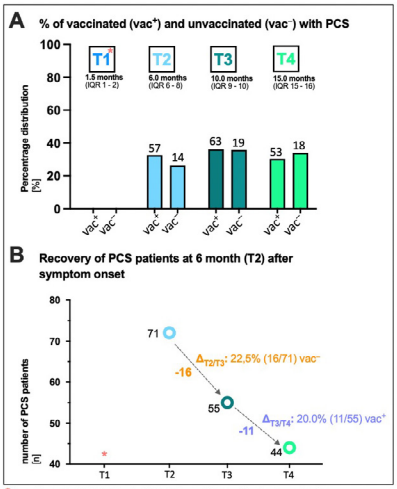

Figure 1 Post-COVID syndrome (PCS) in vaccinated and unvaccinated COVID-19 convalescents
A Absolute (n) and percentage (%) distribution of patients with post-COVID syndrome (PCS) at the respective visit (T1, T2, T3, T4). **B** Recovery of PCS patients between T2 and T3 (ΔT2/T3) without vaccination and between T3 and T4 (ΔT2/T3) following vaccination, respectively. WHO, world health organisation.

721 POST-ACUTE COVID OUTCOMES: AMUBARVIMAB/ROMLUSEVIMAB VS PLACEBO IN THE ACTIV-2 TRIAL

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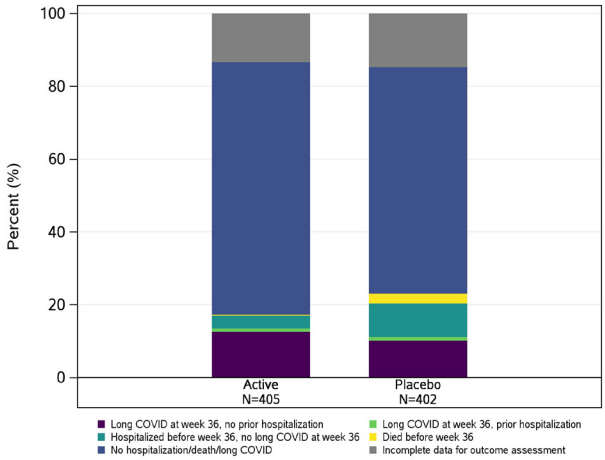
Background: Whether early antiviral therapy reduces the risk of Long COVID is not known. The combination SARS-CoV-2 monoclonal antibodies amubarvimab+romlusevimab (A+R) were highly effective in reducing 28-day all-cause hospitalization/death among high-risk adults with mild-to-moderate COVID-19 in the randomized, placebo-controlled ACTIV-2/A5401 trial. We assessed the impact of A+R on late outcomes including Long COVID in ACTIV-2.
Methods: A long-term (LT) symptom diary and 2 health-related quality of life questionnaires (EQ-5D-5L and SF-36v2) were completed at week 36. The primary analysis compared the proportion of participants with the composite outcome of self-reported Long COVID (having any COVID-19 symptoms present on a global assessment question in LT diary) at week 36, or hospitalization or death by week 36 between A+R and placebo using regression models with inverse probability weighting to account for incomplete outcome data; supplemental analysis compared the proportion with Long COVID among those alive. Other analyses were restricted to observed data only.
Results: 807 were randomized and received A+R (n=405) or placebo (n=402) from Jan-July 2021. At entry, median age was 49 years, 51% were female, >99% cis-gender, 17% Black/African American, 50% Hispanic/Latino, and 9% previously received COVID vaccination. 70 (17%) on A+R and 93 (23%) on placebo met the primary outcome; 113 (14%) had incomplete data for determining the outcome (Figure 1). Accounting for incomplete data, weighted Risk Ratio [wRR]=0.74; 95% CI: 0.56, 0.97; p=0.03. The difference was driven by fewer hospitalizations/deaths in the A+R arm (5%) than placebo arm (15%), particularly by day 28. Excluding 12 participants who died by week 36, frequency of Long COVID was similar in the arms, 16% for A+R and 14% for placebo (wRR=1.09; 95%CI: 0.75, 1.58; p=0.64). There were no differences in the proportions reporting return to pre-COVID health (global assessment) or individual symptoms, or in number of symptoms reported or distribution of worst symptom severity. RRs favored the A+R arm on several EQ-5D-5L domains, but none met statistical significance. No differences were observed on SF-36v2 assessments.
Conclusion: While A+R was highly effective in preventing all-cause hospitalizations and deaths in high-risk outpatients with mild-to-moderate COVID-19, there was no meaningful effect of treatment on measures of Long COVID at 36 weeks. Additional interventions are needed for Long COVID prevention.

Week 36 Long COVID, Hospitalizations, and Death by Amubarvimab+Romlusevimab (Active) vs Placebo Treatment



722 SYMPTOMS AND BIOMARKERS OF LONG COVID IN PEOPLE LIVING WITH AND WITHOUT HIV

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Background: HIV is a risk factor for severe acute COVID-19, but it is unknown whether HIV is a risk factor for long COVID.
Methods: We conducted a prospective observational cohort study of US adults with HIV (PWH) and HIV-seronegative adults with first SARS-CoV-2 infection within 4 weeks together with people who never had COVID-19. At enrollment, participants recalled the presence and severity of 49 long COVID-associated symptoms in the month prior to COVID-19. The same symptom survey was administered at 1, 2, 4, and 6 months post-COVID or post-enrollment for never-COVID participants. Post-COVID participants donated blood 1 and 4 months post-COVID, and never-COVID participants donated blood 0-1 times. Antibody

titers to 18 coronavirus antigens and levels of 30 cytokines and hormones were quantified (Meso Scale Discovery). The Mann Whitney U test was used to compare continuous variables between groups, and Pearson's chi-squared test for categorical variables. Spearman correlation analyses were used to build networks of associations between cytokines and symptoms.

Results: 341 participants enrolled between June 2021 and September 2022. Of these, 73 were PWH post-COVID, 121 were HIV-seronegative post-COVID, 78 were PWH never-COVID, and 69 were HIV-seronegative never-COVID. Over 85% of participants were vaccinated prior to COVID-19. Most participants with HIV were male sex at birth (83% post-COVID, 59% never-COVID), on ART (>95%), with median CD4 counts >500.

Over 60% of participants reported 1+ new or worsened symptoms 2-6 months post-COVID, with higher percentages in PWH at 2 months post-COVID ($p < 0.05$). PWH were more likely to report body ache, pain, confusion, memory problems, and thirst and had higher levels of creatine phosphokinase post-COVID than HIV-seronegative people. SARS-CoV-2 and non-SARS human coronavirus antibody titers did not differ between PWH and HIV-seronegative post-COVID participants. Cytokine associations with each other (network density) were significantly enriched at 1 month post-COVID in both PWH and HIV-seronegative people, with significantly less enrichment at 4 months post-COVID and in never-COVID participants. Levels of four analytes (cortisol, C5a, TGF-β1, and TIM-3) associated with specific symptoms of long COVID.

Conclusion: PWH may experience more symptoms post-COVID with a slightly different symptom profile than people without HIV. Inflammatory networks were active in PWH and people without HIV at 1 month post-COVID.

723 SEVERITY CLUSTERS AND LIKELIHOOD OF RECOVERY FROM POST-COVID-19 CONDITION

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Background: The Post-COVID-19 Condition (PCC) is a novel, long-lasting, poorly understood and highly disabling post-viral syndrome, which poses enormous healthcare, economic and socio-political challenges. Lack of validated biomarkers forces clinical management to be based on clinical definitions, which are imprecise. In the clinic, symptoms tend to present in clusters, which have yet to be properly defined. Also, it is unclear how often PCC resolves, and which factors influence PCC resolution.

Methods: To delineate PCC presentation clusters and explore factors related with PCC resolution, we performed a 2-year prospective cohort study in individuals who recovered from acute COVID-19 regardless of its acute and post-acute severity. All subjects were systematically followed in the outpatient post-COVID-19 clinic of a tertiary care hospital in Spain. PCC was defined as per the WHO 2021 definition. Persistent symptoms were those present >3 months after acute COVID-19, and lasting for >2 consecutive months. PCC recovery was the absence of PCC symptoms during >3 consecutive months. Symptom clusters were identified using Gower's distance matrices, dendograms, PCA and Silhouette techniques. Factors associated with PCC recovery were identified using a directed acyclic graph approach.

Results: 548 subjects were included; 341 (62%) had PCC. The latter were mostly females (69.8%) with mean age of 47.9 (SD 12.2) years. Only 38.1% required hospitalization and 9% required high-flow oxygen during acute COVID-19. Their most frequent comorbidities were allergy (31.4%), obesity (24.8%), dyslipidemia (24.0%) and hypertension (19.6%). At least 3 symptom clusters with additive symptoms were identified: considering only symptoms present in >35% of subjects, Cluster A was enriched in fatigue and dyspnea; Cluster B had Cluster A symptoms plus headache, arthralgia and neurocognitive complains; Cluster C had Cluster B symptoms plus chest pain and tachycardia. PCC recovery was achieved by 26 (7.6%) individuals over 2 years. Male sex (RR 3.01; CI 1.4-6.3), ICU admission (RR 7.85; CI 2.6-23.2), metabolic comorbidity (RR 2.07; CI 1.1-4.1), and mild acute COVID-19 (RR 2.70; CI 1.1-4.6) increased the likelihood of PCC recovery. Conversely, subjects with muscle pain, impaired attention, dyspnea, and tachycardia were less likely to recover from PCC (RR 0.26; CI 0.13-0.52).

Conclusion: At least 3 severity clusters can be identified in the PCC. Over the first 2 years, only a minority of subjects fully recover from PCC.

724 HIV INFECTION INCREASES RISK OF PASC WHILE COVID-19 VACCINATION IS PROTECTIVE

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Background: People with HIV (PWH) are at a higher risk of severe acute COVID-19; however, their risk of subsequently developing post-acute sequelae of SARS-CoV2 (PASC) remains unclear. Furthermore, although vaccination has been shown to be protective against PASC in the general population, few studies have evaluated its effectiveness in PWH.

Methods: We used the TriNetX health research database to source data from 69 healthcare organizations within the US. We included any adults aged ≥ 18 years with positive SARS-CoV-2 between January 1, 2020 and September 16, 2022 and categorized them based on their HIV status, baseline sociodemographic characteristics, comorbidities and COVID-19 vaccination status. The primary outcome was risk of PASC, compared by HIV and vaccination status after 1:1 propensity score matching. PASC was defined as either the persistence of COVID-attributable symptoms or the occurrence of new-onset health conditions at least 28 days following COVID-19 diagnosis. For all analysis, statistical significance was set at $p < 0.05$.

Results: Of 3,048,792 people with confirmed SARS-CoV-2 infection, 1% (n=28,904) were PWH, with 9% of PWH (n=2592) vaccinated. At 28 days post-COVID-19 diagnosis, PWH had lower mortality compared with their non-HIV counterparts (OR 0.78, 95% CI 0.70-0.87), but higher risk of developing new-onset diabetes (DM) (OR 1·26, 95% CI 1·11-1·42), heart disease (OR 1·27, 95% 1·14-1·41), malignancy (OR 1·66, 95% CI 1·45-1·89), thrombosis (OR 1·25, 95% CI 1·12-1·39) and mental health disorders (OR 1·70 (95% CI 1·53-1·90). Furthermore, vaccinated PWH had significantly lower odds of death (OR 0·63, 95% CI 0·42-0·93) and each new-onset PASC outcome, as follows: DM (OR 0·51, 95% CI 0·32-0·82), heart disease (OR 0·44, 95% CI 0·29-0·67), malignancy (OR 0·43 (95% CI 0·25-0·74), thrombosis (OR 0·51, 95% CI 0·33-0·78) and mental health disorders (OR 0·49, 95% CI 0·30-0·79). The risk of PASC was higher during the pre-Delta variant period but did not vary based on CD4 count or HIV viremia.

Conclusion: HIV infection confers a higher risk of PASC. Importantly, COVID-19 vaccination significantly lowered mortality and was protective against PASC among PWH. With the increase in the number of COVID-19 survivors, vaccination offers an effective preventive strategy to address a burgeoning public health problem.

PASC outcomes and effect of vaccination on PASC among HIV+ after propensity score matching

Table 1. PASC outcomes and effect of vaccination on PASC among HIV+ after propensity score matching

	PASC risk		Effect of COVID-19 vaccination			
Outcomes	HIV +	HIV -	OR (CI)	HIV + Vaccinated	HIV + Unvaccinated	OR (CI)
Mortality	597 (2%)	31411 (1%)	2·01 (1·85, 2·18)	39 (2%)	62 (3%)	0·62 (0·42,0·93)
Diabetes	598 (3%)	33668 (1%)	2·61 (2·4, 2·83)	27 (2%)	48 (4%)	0·51 (0·32, 0·82)
Heart Disease	763 (5%)	55872 (2%)	2·44 (2·27, 2·62)	33 (3%)	76 (7%)	0·44 (0·29, 0·67)
Malignancy	517 (3%)	29644 (1%)	3·15 (2·89, 3·45)	19 (2%)	43 (4%)	0·43 (0·25, 0·74)
Thrombosis	699 (3%)	32612 (1%)	3·04 (2·82, 3·28)	33 (2%)	62 (6%)	0·51(0·33, 0·78)
Mental Disorders	681 (9%)	72369 (3%)	2·79 (2·58, 3·02)	24 (5%)	61 (9%)	0·49 (0·30, 0·79)

OR, adjust odds ratio; CI, 95% confidence interval

725 IMMUNE STATUS AND SARS-CoV-2 VIRAL DYNAMICS

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ACTIV-2/A5401

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Background: Immunocompromised persons are disproportionately affected by severe SARS-CoV-2 infection, but immune compromise is heterogenous, which may impact viral dynamics. We hypothesized that higher degrees of compromised immunity are associated with higher viral shedding and slower viral clearance in the absence of COVID-19 therapeutics.

Methods: Participants enrolled in ACTIV-2/A5401, a platform trial for COVID-19 therapeutics in non-hospitalized adults within 10 days of symptom onset, received either an active treatment or placebo between 8/2020 and 7/2021. Participants were categorized based on the extent of immunosuppression into

none, mild, moderate and severe categories at enrollment (day 0). Longitudinal anterior nasal (AN) and plasma SARS-CoV-2 levels were measured with a quantitative PCR assay. Regression models assessed associations between immunocompromise severity and viral levels (VL) at day 0, and longitudinally among those on placebo with quantifiable RNA at day 0. Multivariate analyses adjusted for demographics and symptom duration and vaccination status at day 0.

Results: Immunocompromised (mild 383, moderate 159, severe 35) and immunocompetent (1956) participants had comparable symptom durations at day 0 (median 6 days) and most were unvaccinated (~95%). AN VL at day 0 was higher in the moderate/severe group compared to the immunocompetent group (adjusted difference in means: 0.47 $\log_{10}$ copies/mL, 95% CI 0.12, 0.83). While AN VL decayed at similar rates among all groups from day 0 to 3, there was a trend towards higher cumulative AN VLs across the 28-day follow-up in the moderate/severe group compared to immunocompetent group (adjusted fold difference in VL AUC 1.63, 95%CI 0.95, 2.77). The mild group showed no differences in day 0 VL or AUC compared to the immunocompetent group. The frequency of detectable plasma SARS-CoV-2 RNA was similar at day 0 across all groups (overall 21%), but there appeared to be a higher proportion of immunocompromised participants with detectable plasma viral RNA at day 7 (moderate/severe 2/23 [9%], mild 5/44 [11%]) compared to the immunocompetent group (8/282, 3%).

Conclusion: Before emergence of Omicron and widespread vaccination, moderate/severe immunocompromised status was associated with higher nasal viral levels at study enrollment and showed a trend towards higher cumulative AN viral load, and all immunocompromised groups appeared to have more persistent plasma viremia during follow-up.

726 PROLONGED VIABLE VIRAL SHEDDING IN IMMUNOCOMPROMISED PATIENTS WITH COVID-19

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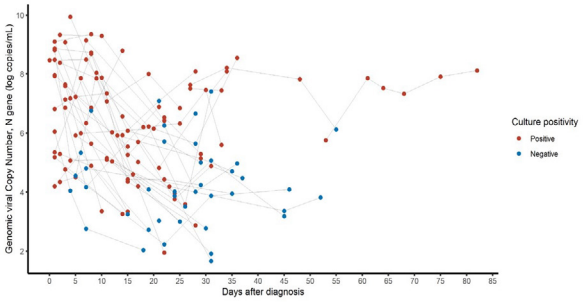
Background: Immunocompromised patients with COVID-19 tend to shed viable virus for a prolonged period. Therefore, for moderately or severely immunocompromised patients with COVID-19, CDC recommends an isolation period of at least 20 days and ending isolation in conjunction with serial testing and consultation with an infectious disease specialist. However, data on viral kinetics and risk factors for prolonged viral shedding in these patients are limited.

Methods: From February 1, 2022 to April 1, 2022, we collected weekly saliva samples from immunocompromised patients with COVID-19 admitted to a tertiary hospital in Seoul, South Korea. Genomic and subgenomic RNAs were measured, and virus culture was performed.

Results: A total of 41 patients were enrolled; 29 (70%) were receiving chemotherapy against hematologic malignancies and the remaining 12 (30%) had undergone solid organ transplantation. Of the 41 patients, 14 (34%) had received 3 doses or more of COVID-19 vaccines. Real-time RT-PCR revealed that 7 (17%) were infected with Omicron BA.1, and 33 (80%) with Omicron BA.2. The median duration of viable virus shedding was 4 weeks (IQR 3–6). Patients undergoing B-cell depleting therapy shed viable virus for longer than the comparator (p=0.01). Multivariable analysis showed that 3-dose or more vaccination (HR 0.33, 95% CI 0.12 – 0.93, p = 0.04) and B-cell depleting therapy (HR 12.50, 95% CI 2.44 – 100.00, p = 0.003) independently affected viable virus shedding of SARS-CoV-2.

Conclusion: Immunocompromised patients with COVID-19 shed viable virus for median 4 weeks. B-cell depleting therapy increases the risk of prolonged viable viral shedding, while completion of a primary vaccine series reduces this risk.



Overall distribution of samples according to genomic viral copy number and culture positivity. Red dot indicates positive culture results, whereas blue dot indicated negative culture results.

727 SUICIDAL RISK AMONG PEOPLE WITH HIV AFTER LOCKDOWN DUE TO COVID-19 PANDEMIC

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Background: People with HIV (PWH), are known to be at increased risk for mental disorders and suicidal risk (SR) when compared to general population. Despite the fact that suicide represents the 7th cause of death, routine assessment of SR among PWH is uncommon. The COVID19 pandemic caused a significant increase in mental disorders in the general population. Few studies have described the impact of the pandemic on SR in PWH. We aim to describe the trend in SR prevalence in PWH who attended our HIV clinic before (2018 and 2019), during (2020) and after (2021) the lock-down due to COVID19, as well as the factors associated.

Methods: PWH (adults) receiving care in a third level facility in Mexico City during 2018-2021 were included. Since 2018, a questionnaire based on the Columbia Severity Rating Scale, has been routinely applied to screen for SR in all HIV clinic visits. We described and compared the sociodemographic characteristics of those classified with SR vs those without SR. We estimated SR using the responses of patients assessed through the questionnaire, by calendar year. We evaluated the potential association of calendar year on the SR probability using a mixed effects logistic regression model, including sex, being undetectable, CD4count and efavirenz(EFV)-based ART use, at evaluation date; cumulative time in ART, year and route of HIV transmission as fixed effects.

Results: During the study period, 2275 patients were included; 93%(n=2130) were routinely evaluated for SR at least once. Fifty-nine (3%) had SR. Those with SR, compared with those without SR, were more frequently women (19%vs10%), 27% vs 28% used EFV, and had 2.17(SD:1.39) assessments/year vs 1.62 (SD:0.84). SR rates per 1000 patients among those who were evaluated, increased significantly from 0.03 in 2018, 0.26 in 2019, 3.14 in 2020 and 10.58 in 2021. Throughout the model, independently of other covariables, no significant changes in SR were observed during 2019 and 2020, compared to 2018: OR 1.21 (0.57–2.52), p=0.61 and OR 0.21 (0.05–1.00), p=0.06; but we found a significant increase in the SR in 2021; OR 3.71 (1.55–8.88), p=0.003. In this model, EFV use vs non-EFV use was not associated with SR: OR:0.78 (0.39–1.56), p=0.48.

Conclusion: After an adjusted analysis, suicidal risk in PWH was significantly higher after the lock-down due to COVID19, independently of EFV use. These results should encourage HIV health providers to actively look for suicidal risk and incorporate specialized mental care.

728 SIGNIFICANCE OF ELEVATED SARS-CoV-2 ANTIGEN LEVELS DURING EARLY HOSPITALIZATION

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Background: Patients hospitalized with COVID-19 randomized to standard of care (SoC) plus placebo or SoC plus monoclonal antibody (mAb)[bamlanivimab, sotrovimab, amburvimab-romlusevimab, or tixagevimab-cilgagavimab] as separate arms of TICO/ACTIV-3 did not show differences in the time to sustained recovery through day 90. Combining these cohorts, we assessed if early changes in plasma nucleocapsid antigen(pNA) were associated with clinical outcomes.

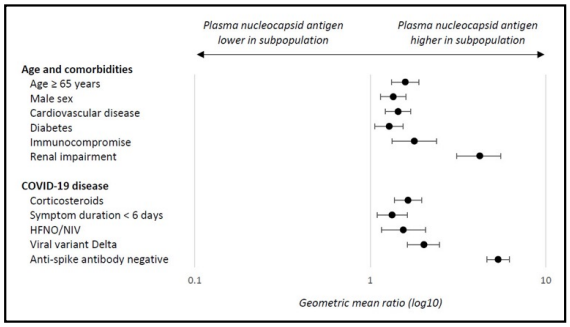
Methods: TICO/ACTIV-3 enrolled 2,254 patients between 8/5/2020 to 9/30/2021. We used the Quanterix assay to measure pNA of stored samples. We selected those with pNA in the top quartile at baseline through day 5 and examined the association with baseline factors and clinical outcomes through

day 90 using regression methods (proportional odds logistic, Cox proportional hazard, and Fine-Gray competing risk models as appropriate).

Results: Of the 2,149 patients with a baseline value and at least one measurement of pNA on Days 1-5, we found a median age 57 (IQR 46-68), 58% male, 64.9% with one or more co-morbidities, 82.1% unvaccinated, 37.6% with delta variant, median symptom duration 8 days (IQR 6-10), and 9.2% on high flow nasal oxygen (HFNO) or non-invasive ventilation (NIV). Participants with pNA in the top quartile (>4693.5 ng/L at baseline and >29.9 ng/L at day 5) occurred more commonly among those with baseline renal impairment [OR 4.1 (95% CI 2.8 to 5.9)], and pulmonary severity of illness requiring oxygen of < 4 L/min [OR 2.2 (95 %CI: 1.5 to 3.4)], >4 L/min [OR 4.9(95% CI: 3.3, to 7.4)], and HFNO/NIV [OR 5.3 (95% CI: 3.1 to 9.0)] compared to those not using supplemental oxygen at study entry. Patients with positive anti-spike antibody at baseline had lower odds of persistently high pNA [OR 0.15 (95%CI: 0.10 to 0.20)]. Participants with pNA levels in the top quartile through day 5 were associated with increased risk of all-cause day 90 mortality [HR 4.4 (95% CI: 3.2, 5.9)], and reduced incidence of sustained recovery through day 90 [RRR 0.40 (95% CI: 0.35 to 0.45)].

Conclusion: PNA levels in the top quartile over the first 5 days were associated with elevated risk for death and reduced recovery. This group includes those with renal impairment, use of oxygen for COVID-19, and negative for anti-spike antibody. Top quartile pNA in early infection identified subjects on lower level of oxygen that were high risk for poor outcomes potentially identifying those that would benefit from additional treatment.

Figure 1: Longitudinal difference 5-day trajectories of pNA levels in selected subpopulations compared to complemental subpopulation, expressed as geometric mean ratios.



729 IMMEDIATE AND CONTRIBUTORY CAUSES OF DEATH IN PATIENTS HOSPITALIZED WITH COVID-19

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Background: Accurate determination of the immediate and contributory causes of death in patients with COVID-19 is important for optimal care and instituting mitigation strategies.

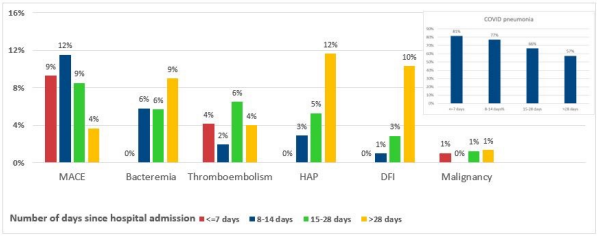
Methods: All deaths in Qatar between March 1, 2020 and August 31, 2022 flagged for likely relationship to COVID-19 by were evaluated by two independent reviewers trained to determine and assign the most likely immediate underlying cause of death. Each decedent's electronic medical records was comprehensively reviewed, and the cause of death was assigned based on the most plausible underlying event that triggered the event(s) that led to death based on clinical documentation and a review of laboratory, microbiology, pathology, and radiology data. After cause assignment, each case was categorized into major diagnostic groups by organ system, syndrome, or disease classification.

Results: Among 749 deaths flagged for likely association with COVID-19, the most common admitting diagnoses were respiratory tract infection (91%) and major adverse cardiac event (MACE, 2.3%). The most common immediate cause of death was COVID pneumonia (66.2%), followed by MACE (7.1%), hospital associated pneumonia (HAP, 6.8%), bacteremia (6.3%), disseminated fungal infection (DFI, 5.2%), and thromboembolism (4.5%). The median length of hospital stay was 23 days (IQR 14,38). COVID pneumonia remained the predominant cause irrespective of the time from admission, though the proportion dropped with increasing length of stay in the hospital. Other than COVID pneumonia, MACE was the predominant cause of death in first two weeks but declined thereafter. No death occurred due to bacteremia, HAP, or DFI in the first week after hospitalization, but became increasing common with increased length of stay in the hospital accounting for 9%, 12%, and 10% of all deaths after 4 weeks in the hospital respectively. The majority of deaths (86%) occurred in the intensive care unit setting. COVID pneumonia accounted for approximately two-thirds of deaths in each setting. MACE and HAP were approximately equally represented in both settings while bacteremia and disseminated fungal infection were more common in the intensive care unit setting.

Conclusion: Nearly one-third of patients with COVID infection die of non-COVID causes, some of which are preventable. Mitigation strategies should be instituted to reduce the risk of such deaths.

Figure 1. Immediate cause of death by time of death after hospital admission.

Figure 1. Immediate cause of death by time of death after hospital admission. Main graph shows major causes of death other than COVID pneumonia, which is shown in the inset.



MACE, major adverse cardiovascular event; HAP, hospital associated pneumonia; DFI, disseminated fungal infection.

730 ANTI-S-RBD TITER AND RISK OF CLINICAL PROGRESSION IN PATIENTS WITH COVID-19 PNEUMONIA

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Background: Antibodies (Ab) against the receptor-binding-domain of the spike protein (anti-S-RBD) elicited by SARS-CoV-2 infection or vaccination are deemed to be a correlate of protection. We aimed at assessing whether anti-S-RBD titer is associated with the outcome of subjects hospitalized with COVID-related pneumonia.

Methods: Adults hospitalized between Jul 2021 and Jul 2022 for COVID-19 with respiratory failure (SpO2 < 93% on room air) or radiological evidence of pneumonia were included if anti-S-RBD titer was measured within 72h of admission.

Time between admission and death/need for intubation was described using Kaplan-Meier curves. Cox Regression analysis, stratified by vaccination status, was used to explore the association between anti-S-RBD titer and survival. Age, gender, days since symptom onset, immunosuppressive conditions and use of monoclonal Ab (mAb) were explored as possible confounders.

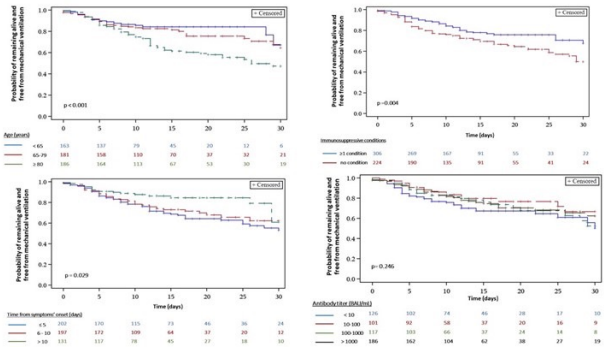
Results: 534 patients were enrolled. Their mean age was 71 years, 63% were male and 61% vaccinated; 42% had ≥1 immunosuppressive condition among hematological or solid malignancy, HIV, diabetes, end-stage renal failure, liver cirrhosis, organ transplant or immunosuppressive treatment. Antibody titer was significantly higher among vaccinated than among unvaccinated patients (1166 *vs* 158 BAU/ml; p< 0.001). Among vaccinated subjects, lower titer of anti-S-RBD were measured among those with hematological malignancies (1282 vs 471 BAU/mL; p< 0.001) or who were receiving immunosuppressive therapy (1287 vs 537 BAU/ml; p< 0.001).

Older age, shorter time between onset of symptoms and hospitalization and immunosuppressive conditions were associated with higher rates of death or intubation (Fig 1).

Using Cox regression stratified for vaccination, a significant association between anti-S-RBD titer and risk of death/intubation was observed (per $\log_2$ BAU/ml increase, HR 0.93; 95%CI 0.88-0.99; p=0.020), independently of age (per year increase, HR 1.03; 95%CI 1.01-1.04), male gender (HR 1.00; 95%CI 0.70-1.42) and presence of immunosuppressive conditions (HR 1.46; 95%CI 1.01-2.10). Adjustment for mAb treatment did not change the results to a significant extent.

Conclusion: Low anti-S-RBD titer was associated with poor outcome among patients hospitalized for COVID19-related pneumonia, regardless of vaccination. In addition, older age and presence of immunosuppressive conditions remain important predictors of mortality.

Kaplan-Meier Curves for intubation-free survival according to age, days from symptoms' onset, presence of immunosuppressive conditions and anti-S-RBD titer.



731 AI-BASED PREDICTION OF LUNG TISSUE INVOLVEMENT IS PREDICITIVE OF COVID-19 SEVERITY

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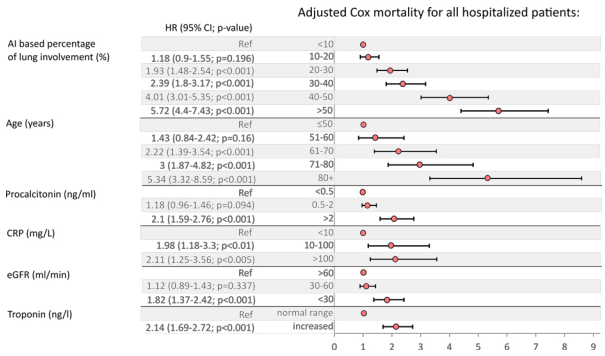
Background: During COVID-19 epidemics several artificial-intelligence neural networks (ANN) systems were developed classify the risk of disease progression to respiratory failure and death, providing aid for clinical decision. However, for optimal results these models should link multiple medical data in a simple model. In this study we analyse the in-hospital mortality and mechanical ventilation risk using combination ANN based rapid computed tomography assessment tool and selected clinical variables.

Methods: Data of 4317 COVID-19 hospitalized patients including 266 cases required mechanical ventilation were analysed using newly constructed and locally trained ANN algorithm. Demographic, clinical, laboratory, and ANN-based lung inflammation data were analysed using proportional Cox Hazards model and estimate in-hospital mortality and intensive care admission risk.

Results: Overall in-hospital mortality associated with ANN-assigned percentage of the lung involvement (HR 5.72 (95%CI: 4.4-7.43), p< 0.001 for the patients with >50% of lung tissue affected by COVID-19 pneumonia), age category (HR 5.34 (95%CI: 3.32-8.59) for cases >80 years, p< 0.001), procalcitonin > 2 (HR: 2.1 (95%CI: 1.59-2.76) ng/ml p< 0.001, C-reactive protein level category (max. HR 2.11 (95%CI: 1.25-3.56) for CRP >100 mg/dL, p=0.004), estimated glomerular filtration rate (max HR 1.82 (95%CI: 1,37-2,42), p< 0.001 for eGFR < 30 ml/min) and troponin increase above upper limit normal level (HR: 2.14 (95%: 1.69-2.72, p< 0.001) (Figure 1). Furthermore, risk of mechanical ventilation also associated with ANN-based percentage of lung inflammation (HR 13.2 (8.65-20.4), p< 0.001 for patients with >50% involvement), age, procalcitonin > 2 ng/ml (HR: 1.91 (95%CI: 1.14-3.2), p=0.14 estimated glomerular filtration rate (HR 1.82 (1.2-2.74), p=0.004 for eGFR < 30 ml/min) but also clinical variables, including (HR: 2.5 (95%CI: 1.91-3.27), p< 0.001), cardiovascular and cerebrovascular disease (HR: 3.16 (95%CI: 2.38-4.2), p< 0.001), and chronic pulmonary disease (HR: 2.31 (95%CI: 1.44-3.7), p< 0.001).

Conclusion: ANN-based lung tissue involvement was the strongest predictor of unfavorable outcomes in COVID-19, and represent valuable support tools for clinical decisions.

Adjusted multivariate model for the risk of COVID-19 in-hospital mortality



732 A JOINT ANALYSIS OF TWO RANDOMIZED CONTROLLED TRIALS ON ENOXAPARIN FOR COVID-19

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Background: COVID-19 carries a high risk of vascular thrombosis. This joint analysis of two randomized-controlled trials (RCTs) aims to assess the safety and efficacy of enoxaparin at therapeutic dose compared to prophylactic dose in people hospitalized with COVID-19.

Methods: A joint analysis of two RCTs, COVID-19 HD (NCT044082359) and EMOS-COVID (NCT04646655), was performed.

Both studies enrolled inpatients with COVID-19- associated respiratory compromise (as identified by respiratory rate ≥25 breaths/min or arterial oxygen saturation ≤93% at rest or PaO2/FiO2 ≤300 mmHg for COVID-19 HD and by PaO2/FiO2 ≤250 mmHg for EMOS-COVID) and/or coagulopathy (D-dimer > 2000 ng/ml for both RCTs or sepsis-Induced coagulopathy score >4 for COVID-HD).

In both RCTs patients were randomly assigned to two arms: enoxaparin at prophylactic dose (standard 4.000 IU; in the EMOS-COVID 6000 IU if body weight >100 kg) and at therapeutic dose (70 U/Kg every 12 h).

The primary efficacy endpoint of the joint analysis was clinical worsening, defined as the occurrence of at least one among: in-hospital death; acute myocardial infarction; symptomatic arterial or venous thromboembolism; need of either Continuous Positive Airway Pressure (Cpap) or Non-Invasive Ventilation (NIV) in patients who were in standard oxygen therapy at randomization; need for IMV in any patient. The primary outcome was assessed as time-to-event, described with hazard ratio (HR) and with Kaplan-Meier survival estimate.

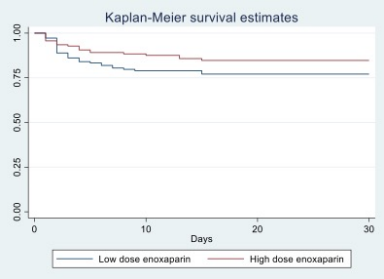
The primary safety endpoint was major bleeding for both trials and for the joint analysis.

Results: COVID-19 HD enrolled 142 people between July 2, 2020 and February 15, 2022, while EMOS-COVID enrolled 141 people from July 27, 2020 to June 5, 2021, resulting in 283 patients included in this joint analysis. Two-hundred-seven (73.1%) were males, with a mean age of 61.1 years (SD ±10.7), a mean BMI of 29.7 kg/m^2 (SD ±5.0), and 115 (40.6%) were on NIV or Cpap at randomization, with no significant difference between the study groups. 21/139 people in the high dose group reached the primary endpoint compared to 32/144 in the prophylactic group (HR 0.63, 95%CI 0.36 to 1.10). Figure 1 shows the Kaplan-Meier survival estimates of clinical worsening.

No major bleeding was observed during the study time.

Conclusion: The results of this joint analysis did not highlight significant differences in clinical worsening between COVID-19 patients that received enoxaparin at therapeutic compared to prophylactic dose.

Figure 1. Kaplan-Meier survival estimates of clinical worsening.



733 THE IMPACT OF EARLY OUTPATIENT TREATMENTS FOR COVID-19: A RETROSPECTIVE STUDY

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Background: Oral antivirals (nirmatrelvir/ritonavir and molnupiravir), intravenous short treatment of remdesivir and anti-SARS-CoV-2 monoclonal antibodies (mAbs) have been used for early COVID-19 treatments in high risk of disease progression patients. Little is known about the impact of therapies on post-acute COVID-19 (PACS). We aimed to compare the efficacy of these therapies in terms of death, hospitalization rate and PACS at 3 months.

Methods: We conducted a retrospective observational study including all eligible outpatients aged ≥18 evaluated from April 2021 to March 2022 at our COVID-19 Clinic. Patients were stratified into 3 groups: mAbs, antivirals (oral and short-course remdesivir) and controls (eligible patients who refused treatment). Persistence of symptoms (fever, dysgeusia/anosmia, cough, pharyngodynia, dyspnea, chills, nasal congestion, myalgia, headache, gastrointestinal disease, and neuro-behavioural symptoms, such as asthenia, anxiety/mood disorder, memory and concentration deficit) were evaluated after 3 months. We estimated the associations between each considered outcome and treatment through univariate and multivariable logistic models adjusted by sex, age, vaccination, early COVID treatment, treatment group and number of comorbidities (when appropriate).

Results: We included 649 patients (51.6% males, median age 67 years, 14% unvaccinated): 242 patients were treated with mAbs, 197 with antivirals and 210 received no treatment. Overall, 36.7% of subjects had cerebro-cardiovascular disease, 22% were obese and 50% had more than one comorbidity. Overall, 29 patients (4.5%) died or were hospitalized. Death or hospitalization was positively associated only with older ages with a significant linear trend (p for trend: 0.033). Data on PACS at 3 months were available for 323 (49.8%) patients. Females showed a positive association with long COVID, with an OR of 2.14 (95% CI: 1.30-3.53) as compared to men. Patients treated with antiviral drugs showed an inverse association with long COVID (OR: 0.43, 95% CI: 0.21-0.87 as compared to not treated patients). Patients who were treated with monoclonal antibodies showed an OR of 0.48 (95% CI: 0.25-0.92) as compared to those in the control group (**Table 1**).

Conclusion: The impact of early COVID-19 therapies on PACS is unknown. Our results showed that these treatments, in particular mAbs, can reduce persistence of neuro-behavioural symptoms at 3 months.

Table 1. Numbers and percentages of "long COVID" according to selected covariates and results from the logistic regression models.

Table 1. Numbers and percentages of "long COVID" according to selected covariates and results from the logistic regression models.

	At least one symptom					At least one neuro-behavioural symptom				
	No		Yes		Adjusted OR[1] (95% CI)	No		Yes		Adjusted OR[1] (95% CI)
	n	%	n	%		n	%	n	%	
Total	229	70.9	94	29.1		260	80.5	63	19.5	
Sex										
Male	135	77.6	39	22.4	1[2]	151	86.8	23	13.2	1[2]
Female	94	63.1	55	36.9	**2.14 (1.30-3.53)**	109	73.2	40	26.8	**2.69 (1.50-4.83)**
Age group										
≤65	98	67.1	48	32.9	1[2]	116	79.5	30	20.5	1[2]
>65	131	74.0	46	26.0	0.68 (0.42-1.12)	144	81.4	33	18.6	0.83 (0.47-1.47)
Vaccination										
No	34	68.0	16	32.0	1[2]	40	80.0	10	20.0	1[2]
Yes	194	71.3	78	28.7	1.06 (0.53-2.10)	219	80.5	53	19.5	1.09 (0.50-2.40)
Treatment										
No	69	65.7	36	34.3	1[2]	78	74.3	27	25.7	1[2]
Yes	160	73.4	58	26.6	0.64 (0.38-1.09)	182	83.5	36	16.5	**0.49 (0.27-0.89)**
Treatment group										
Control	69	65.7	36	34.3	1[2]	78	74.3	27	25.7	1[2]
Monoclonal antibodies	99	70.2	42	29.8	0.78 (0.44-1.36)	119	84.4	22	15.6	**0.48 (0.25-0.92)**
Antiviral drugs	61	79.2	16	20.8	**0.43 (0.21-0.87)**	63	81.8	14	18.2	0.51 (0.24-1.10)

[1]Estimates obtained through logistic regression models mutually adjusted by sex, age (continuous), vaccination (yes, no), treatment (yes, no), and number of diseases (continuous), when appropriate.
[2]Reference category.
The estimates resulted statistically significant were highlighted in bold.

734 CLINICAL PREDICTORS OF MPOX SEVERITY IN AN ITALIAN MULTICENTER COHORT (MPOX-ICONA)

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MPOX-ICONA Study Group

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Background: Mpox is a pivotal example of how old viral pathogens can emerge as the cause of new outbreaks with novel clinical presentation and topical route of transmission. Here we present an analysis to explore potential predictors of Mpox severity and viral persistence in relevant biological fluids.

Methods: Italian multicenter cohort study. Severe cases were those who needed hospitalization or had proctitis, pharyngotonsillitis, ocular lesions, or >20 skin lesions. Recovery was defined as the resolution of all mucocutaneous lesions. Bivariable analysis of severity predictors was carried out with X^2 test. Logistic regression model was used for multivariate analysis. The analysis to assess early viral load (VL) as predictor of severity was done by Student T-Test and logistic regression model.

Results: Between 16 May and 31 Oct 2022, 202 pts were enrolled; they were all male with a mean age of 38 years (range 21-75). Mean duration of disease was 22.14 days (95%CI 20.93-23.34). Multivariable analysis to explore severity predictors (Fig1A) showed that fever (p=0.001), facial lesions (p= 0.045), anal lesions (P=0.013), and concurrent STIs (P=0.032) were associated with severe Mpox. Quantitative determination of VL load in the upper respiratory tract (oropharyngeal swab or saliva, URT) was available for 79 pts (39 mild and 40 severe). Mean Ct-value was 31.91 (95%CI 29.29-34.54) and 26.68 (95%CI 24.68-28.68) in mild and severe cases, respectively (P< 0.002; Fig1B). Logistic model showed that probability to develop severe disease had a strong inverse association with Ct-value dropping by 9.38% (95%CI 3.21-15.16%) per Ct-value unit (P=0.002; Fig1C B). We found no association between severity and VL in specimen from skin lesions, urine, blood, and anorectal region. Finally, we found that MPXV persists in body fluids despite clinical recovery: detectable amount of MPXV was found in sperm (12/28 pts), urine (3/50), anorectal (6/31), and URT (17/51) specimens.

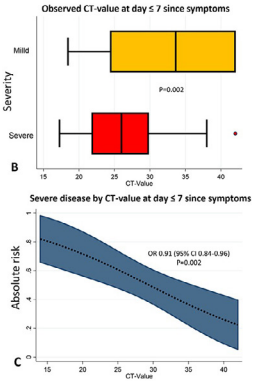
Conclusion: We found that pts presenting with fever, facial/anal lesions, and concurrent STIs may develop more severe Mpox. Moreover, higher VL in URT during the first week after symptoms onset was associated with severe disease. Our findings may serve to guide management of pts with Mpox in terms of need for hospitalization and drug therapy. Finally, our study claims an urgent need to assess whether the persistence of MPXV in biological samples after clinical recovery may lead to a status of persistent infectivity.

Figure legend. A) Analysis of risk for severe disease (N=202 patients). Left columns descriptive analysis. Middle columns bivariable analysis of risk (p-values are reported according to X2 test). Right columns adjusted analysis according to multivariable logistic model (P-values are reported according to Wald's test). B) Observed CT-value in upper respiratory tract during the first week of disease (N=79 patients; P-values are reported according to Student T-test). C) Association between severe disease and CT-values in the upper respiratory tract during the first week of disease (N=79 patients; P-values are

reported according to Student Walds's test). OR= odd-ratio, STI= sexually transmitted infection, 95%CI= 95% confidence interval.

A

Descriptive analysis				Bivariable analysis				Adjusted analysis			
Patients feature		Severity*		OR			P-value	OR			P-value
		yes	no	est	95% CI			est	95% CI		
Overall		84	118	-	-	-	-	-	-	-	-
Fever	yes	69 (82.1%)	63 (53.4%)	4.02	2.08	7.76	<0.001	3.69	1.72	7.93	0.001
	no	15 (17.9%)	55 (46.6%)								
Fatigue	yes	9 (10.7%)	19 (16.1%)	0.63	0.27	1.44	0.275	-	-	-	-
	no	75 (89.3%)	99 (83.9%)								
Headache	yes	17 (20.2%)	18 (15.3%)	1.41	0.68	2.90	0.356	-	-	-	-
	no	67 (79.8%)	100 (84.7%)								
Sore Throat	yes	14 (16.7%)	12 (10.2%)	1.77	0.78	3.98	0.174	-	-	-	-
	no	70 (83.3%)	106 (89.8%)								
Lymphoad.	yes	34 (64.3%)	61 (51.7%)	1.68	0.95	2.98	0.075	1.37	0.72	2.62	0.341
	no	30 (35.7%)	57 (48.3%)								
Low mood	yes	1 (1.2%)	3 (2.5%)	0.46	0.00	3.80	0.497	-	-	-	-
	no	83 (98.8%)	115 (97.5%)								
Myalgia	yes	17 (20.2%)	14 (11.9%)	1.88	0.88	4.03	0.104	-	-	-	-
	no	67 (79.8%)	104 (88.1%)								
diarrohea	yes	8 (9.5%)	5 (4.2%)	2.38	0.79	7.18	0.131	-	-	-	-
	no	76 (90.5%)	113 (95.8%)								
Face rash	yes	56 (66.7%)	54 (45.8%)	2.37	1.33	4.22	0.003	1.91	1.01	3.61	0.045
	no	28 (33.3%)	64 (54.2%)								
Sole/palm rash	yes	14 (16.7%)	16 (13.6%)	1.28	0.59	2.75	0.541	-	-	-	-
	no	70 (83.3%)	102 (86.4%)								
Genital rash	yes	37 (44.0%)	59 (50.0%)	0.79	0.45	1.38	0.404	-	-	-	-
	no	47 (56.0%)	59 (50.0%)								
Anal lesions	yes	44 (52.4%)	30 (25.4%)	3.23	1.78	5.84	0.000	2.28	1.19	4.34	0.013
	no	40 (47.6%)	88 (74.6%)								
Age >=46	yes	15 (17.9%)	34 (28.8%)	0.54	0.27	1.06	0.073	0.90	0.40	2.00	0.795
	no	69 (82.1%)	84 (71.2%)								
Caucasian	yes	68 (81.0%)	98 (83.1%)	0.87	0.42	1.78	0.701	-	-	-	-
	no	16 (19.0%)	20 (16.9%)								
MSM/Bisex	yes	79 (94.0%)	105 (89.0%)	1.96	0.69	5.48	0.213	-	-	-	-
	no	5 (6.0%)	13 (11.0%)								
Variola vaccine	yes	7 (8.3%)	12 (10.2%)	0.80	0.31	2.08	0.660	-	-	-	-
	no	77 (91.7%)	106 (89.8%)								
Sexual transmission	yes	76 (90.5%)	105 (87.5%)	1.38	0.57	3.35	0.482	-	-	-	-
	no	8 (9.5%)	15 (12.7%)								
HIV pos.	yes	36 (42.9%)	55 (46.6%)	0.86	0.49	1.51	0.597	-	-	-	-
	no	48 (57.1%)	63 (53.4%)								
Concurrent STI	yes	42 (50.0%)	42 (35.6%)	1.81	1.03	3.19	0.041	2.03	1.06	3.89	0.032
	no	42 (50.0%)	76 (64.4%)								



735 SEVERE MPOX AMONG PEOPLE LIVING WITH HIV RECEIVING TECOVIRIMAT IN NEW YORK CITY

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Background: The mpox clinical course among people with HIV (PWH) during the 2022 outbreak is poorly understood. We describe mpox among PWH in New York City (NYC) who received >14 days of tecovirimat and/or coadministration of additional mpox treatments.

Methods: We identified PWH with persistent or worsening mpox during tecovirimat treatment through healthcare providers who called NYC Department of Health and Mental Hygiene (DOHMH) or Centers for Disease Control and Prevention's clinical team for consultation between 8/2/2022 and 12/16/2022. We collected demographics and HIV/mpox clinical information. We crossmatched cases with DOHMH HIV surveillance for CD4 and viral load (VL), Citywide Immunization Registry for Jynneos vaccination, and NYC Department of Social Services (DSS) for DSS housing status.

Results: We identified 11 cases. Median age was 38 years (range: 29–45); 9 (73%) were Black non-Hispanic and 2 (18%) were Hispanic. Six (50%) had a recent history of being unstably housed, with 4 (36%) unstably housed at mpox diagnosis. Nine (82%) were not on HIV treatment at mpox diagnosis. Median HIV VL was 237,000 copies/mL (range: 73,000–2 million). All had CD4 < 200 cells/mm^3; 8 (73%) had CD4 < 50 cells/mm^3. Three (27%) received one dose of Jynneos vaccine, all of whom were diagnosed with mpox within 5 days of vaccination. Median time from initial specimen collection to tecovirimat initiation was 5.5 days (range: 0-16, data available for 10 cases). Tecovirimat duration ranged from 21 to 120 days. Other medications coadministered with tecovirimat included vaccinia immune globulin (VIG) (n=9, 82%), cidofovir, brincidofovir, and trifluridine eye drops (each with n=2, 18%). Of cases receiving VIG, 5 (56%) received multiple doses. All 11 PWH were hospitalized with severe mpox manifestations. Examples included necrotic facial lesions, severe eye involvement and airway edema, and uncontrollable rectal bleeding. As of 12/16/2022, 1 case (9%) had lesion resolution, 5 (45%) were still hospitalized on treatment, 4 (36%) died, and 1 (9%) had unknown clinical disposition.

Conclusion: This group of PWH with advanced HIV had severe mpox manifestations and poor response to tecovirimat. Early and extended tecovirimat with coadministration of other mpox treatments in the setting of limited options is important to try to improve outcomes. Findings of severe disease and high mortality highlight the urgency of mitigating deep social inequities and high-quality research to optimize care in this group of PWH.

736 MANAGEMENT OF MPOX IN PWH ATTENDING A SEXUAL HEALTH DEPARTMENT IN LONDON, UK

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Background: MPOX has disproportionately affected people with HIV (PWH) since its global spread and preliminary data suggest a higher burden of complications and worse outcomes in this group.

Methods: Aggregated and anonymised data on clinical characteristics, medical management and concurrent STIs rates in PWH with PCR-confirmed MPOX infection between May 15th- Dec 15th 2022 attending a large, UK sexual health service were retrospectively collected from electronic patient records. Risk factors for clinical complications and hospital admission were extrapolated using Fisher's exact test.

Results: 249 PWH were included (28.5% of the 873 total MPOX diagnoses) (Table 1), median age 39 years (IQR 33-47), 98% MSM, 74% white ethnicity. Four individuals were newly diagnosed with HIV at time of MPOX presentation, with 5% having a HIV viral load >200 copies/mL and 95% being on cART. Ten individuals had a CD4 count < 350/mm^3 with an overall median CD4 count of 697/mm^3 (IQR 544-897). Prodromal symptoms were common (fever 59%, fatigue 41%, myalgia 30%, sore throat 16%) and whilst 3% did not report any skin lesions, 10% presented with at least one skin lesion, 62% with 2-10 lesions and 24% over 10 lesions. Skin involvement had a predominantly perianal (52%), limb (45%) and genital (38%) distribution, with only a fifth of cases without perianal or the genital involvement. Complications occurred in 43% of cases, with perianal pain (26%), proctitis (14%), bacterial superinfection/cellulitis (12%), constipation (8%), penile oedema (4%) and tonsillitis (2%) being the most common. Additional medical management was often required (43%), with analgesia (32%), antibiotic therapy (26%) or laxatives (8%) prescribed most frequently. Eight individuals (3%) required hospital admission, with no fatal outcomes. The presence of anal lesions and/or a CD4 count < 350/mmc were associated with a higher burden of medical complications (p< 0.02), with the latter also associating with hospitalization (p=0.05). A total of 31% individuals had a concurrent STI at time of MPOX presentation: 18% had gonorrhoea (67% were rectal infections), 15% chlamydia (81% were rectal infections) and 8% syphilis.

Conclusion: Despite low hospitalization rates in PWH with MPOX, medical complications and STI rates requiring further management are significantly high. Further comparative analysis with people without HIV and PWH with severe immunodepression are needed to define risk factors for hospitalization and clinical complications.

Table 1. Demographics and clinical characteristics of Mpox in PWH attending the sexual health clinics at Chelsea and Westminster Hospital NHS Foundation Trust (London, UK).

PLWH diagnosed with Mpox (*n*=249)	*n*	(%)
Demographics		
Median age, years (IQR)	39 (33-47)	
United Kingdom-born	75/245	(31)
Gay, bisexual or other men having sex with men	244/249	(98)
Trans women	5/249	(2)
White ethnicity	171/231	(74)
Mixed ethnicity	22/231	(10)
Black British / Afro-Caribbean / Black African ethnicity	17/231	(7)
Median number of sex partners within 90-days prior Mpox, (IQR)	3 (2-6)	
cART history		
On cART at time of Mpox diagnosis	227/239	(95)
Latest HIV viral load >200 copies/mL	12/242	(5)
Median CD4 cell count /mmc (IQR)	697 (544-897)	
Latest CD4 cell count <350/mmc	10/200	(5)
Clinical presentation		
- Fever, febrile chills	147/248	(59)
- Fatigue / asthenia / lethargy	101/248	(41)
- Myalgia	74/248	(30)
- Sore throat	39/248	(16)
- Headache	8/248	(3)
No prodromal symptoms	66/248	(27)
Prodromal symptoms presenting after the onset of skin lesions	11/141	(8)
Skin lesions localization		
- Perianal	130/249	(52)
- Limbs	113/249	(45)
- Genital (penile, scrotal, pubic)	94/249	(38)
- Body (chest, torso, abdomen, back)	80/249	(32)
- Facial (forehead, scalp, neck, nose, lip)	71/249	(29)
Number of skin lesions		
- No skin lesions	7/241	(3)
- Single lesion	25/241	(10)
- 2-10	150/241	(62)
- 11-25	51/241	(21)
- 26-100	8/241	(3)
Inguinal lymphadenopathy	112/249	(45)
Oral mucosa involvement	11/249	(4)
Clinical complications	108/249	(43)
- Anal pain	64/249	(26)
- Proctitis	35/249	(14)
- Cellulitis / bacterial skin superinfection	31/249	(12)
- Constipation	21/249	(8)
- Penile oedema	9/249	(4)
- Tonsillitis	6/249	(2)

737 MOSAIC CLADE 2B MPOX COHORT STUDY: CLINICAL CHARACTERISATION AND OUTCOMES

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Background: Over 80,000 cases of clade 2b Mpox were reported in 2022 outside traditionally endemic African countries. The transmission and features of clade 2b Mpox differ from clade 1, requiring systematic clinical characterization.

Methods: MOSAIC is a cohort study of clinical and virological outcomes of patients with laboratory-confirmed Mpox in 10 European countries started in May 2022. Administration of tecovirimat is at the discretion of the patient's treating clinician under routine care and subject to drug availability.

The primary outcome is time to lesion resolution from the date of a positive test result (or the date of treatment start, if treatment was delayed) through D14 without any serious complications. Results presented here were obtained from Kaplan-Meier estimates.

Secondary outcomes presented are virologic status at D14, and clinical status at D28 using a four-point scale: all lesions resolved and no serious complications; active lesions and no serious complications; hospitalized due to a serious mpox complication; death.

We selected 10 non-tecovirimat-treated patients with oropharyngeal and anal swabs, and plasma samples (except one) available at inclusion and D14. qPCR was performed using a G2R target of MXPV (Ct value >40 was considered as negative).

Results: We report on the first 122 cases enrolled by November 15th 2022 (94 recruited in France, 24 in Switzerland, 4 in the UK), 98% male, median [IQR] age 35 [29, 44], of whom 21 received tecovirimat. Patients presented ~1 week after symptoms onset. A third of patients treated with tecovirimat had lesions or complications remaining at D28 (see table).

The 10 patients with virologic data had a median [range] qPCR baseline Ct values of 39 [28, 40], 37 [32, 40], and 24 [17, 40] for oropharyngeal, plasma and anal samples, respectively. All plasma and oropharyngeal samples were negative at D14; 3 patients had positive anal samples at D14 with all lesions resolved without serious complications.

Conclusion: MOSAIC is an international study describing characteristics and outcomes of Clade 2b Mpox; it does not support direct comparison between tecovirimat-treated and non-treated patients. Lesions and symptoms resolved within 28 days in most uncomplicated cases with supportive treatment without hospitalization. A higher proportion of patients presented with complications at baseline in the tecovirimat-treated group. There was also a lower proportion of patients in this group whose lesions had resolved with no serious complications at D28.

Baseline characteristics and outcomes

Variable, n/total (%)	tecovirimat N = 21	other N = 101
Time from onset to enrolment, median [IQR] (days)	7 [3 - 10]	6 [4 – 9]
HIV/AIDS [on ARV]	5/21 (24%) [4/5 (80%)]	33/101 (33%) [30/33 (91%)]
Smallpox vaccine PEP/PREP	1 / 21 (4.8%)	16 / 95 (16.8%)
Outpatient	11 / 21 (52%)	81 / 89 (91%)
Baseline infectious complications	10 / 19 (53%)	11 / 86 (13%)
Lymphadenopathy	17 / 20 (85%)	44 / 84 (52%)
>25 active skin and mucosal lesions	10 / 20 (50%)	8 / 77 (10%)
Genital/peri-genital lesions	14 / 19 (74%)	36 / 78 (46%)
Anal/peri-anal/rectal lesions	9 / 20 (45%)	29 / 82 (35%)
Kaplan-Meier estimate of lesion resolution by D14	39% [95%CI: 11-58]	58% [95%CI: 45-68]
All lesions resolved and no serious complications at D28	13 / 19 (68%)	84 / 89 (94%)

738 DEVELOPMENT AND PILOT OF AN MPOX SEVERITY SCORING SYSTEM (MPOX-SSS)

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Background: Clinical severity scores facilitate standardized quantitative comparison of disease severity between groups of patients to understand risk factors for severe illness and evaluate treatment efficacy. Relevant severity scoring tools provide reliable discrimination across the spectrum of illness severity and are parsimonious, easy to use, and universally applicable. Prior mpox severity scores, based on numbers of skin lesions and individual functional capacity, have been less applicable to the 2022 outbreak.

Methods: Using expert opinion and literature review, we developed an MPOX-SSS with an initial set of possible variables that we refined based on data availability, prior association with severity, and parameter correlation to include 7 final elements: number of active lesions, anatomic extent of lesion involvement, presence of confluent lesions, presence of bacterial superinfection, extent of mucosal areas affected, level of care, and analgesia requirement (tool available at mpoxseverityscore.com). We piloted this MPOX-SSS via a retrospective chart review at a single academic urban medical center and compared scores using the Wilcoxon rank sum test.

Results: Among the first 200 patients presenting with mpox (median age 34, 99% born male, 38% Hispanic, 28% Black, 49% with HIV [10% CD4 count < 200 cells/mm^3 or VL >1000 copies/mL], 57% treated with tecovirimat), an MPOX-SSS score could be calculated for 86%; missing data that precluded scoring included lesion number (13%) and presence of confluent lesions (7%). Median scores were similar in patients with and without HIV (8 vs 9, p=0.12)(Figure 1A). Scores were higher in patients treated with tecovirimat (10 vs 4, p< 0.001), patients with CD4 counts < 200 cells/mm^3 (10 vs 8, p=0.073), and patients presenting >3 days after symptom onset (9 vs 6, p=0.007). For a subset of individuals with multiple visits for mpox, changes in MPOX-SSS scores were detected and concordant with clinical experience (Figure 1B).

Conclusion: Our pilot MPOX-SSS was able to produce a severity score retrospectively from 86% of charts, demonstrated good discrimination with statistically higher scores in groups expected to have more severe disease, and was able to distinguish change over time for individual patients that correlated with clinical illness. We propose this tool be assessed for utility in clinical trials of mpox treatment, in prospective observational cohort studies, and in comparisons of illness caused by different mpox clades.

Figure 1: MPOX Severity Score by HIV Status and Time

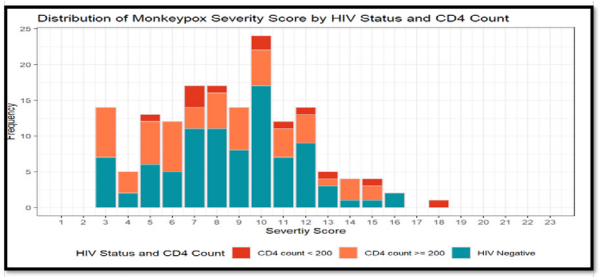
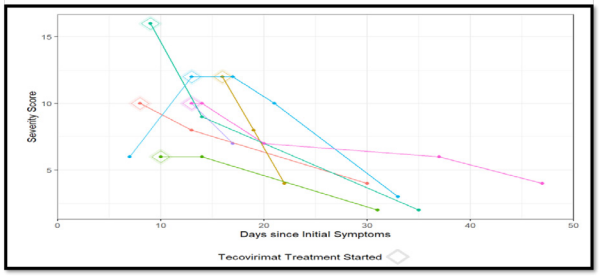


Figure 1B: MPOX Severity Score Over Time



739 CLINICAL PRESENTATION OF MPOX IN PEOPLE WITH AND WITHOUT HIV

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Background: Early UK surveillance data revealed that people living with HIV (PLWH) were overrepresented within monkeypox (mpox), with one third of mpox cases reported in PLWH. However, it is unknown whether mpox infection is more severe in people living with HIV.

Methods: All laboratory confirmed mpox cases seen between May-December 2022 in one London hospital trust were identified via a search of pathology reporting systems. Under existing clinical pathways, patients received regular telephone reviews (virtual ward) until deemed safe to discharge. We

extracted demographic and clinical data, including length of follow up and hospitalisations to allow comparison of HIV positive and negative cases. Data were analysed using STATA 17.

Results: 150 cases of mpox were identified (mean age 37.4, 99.3% male, 92.7% MSM), 58 (38.7%) of whom were in PLWH (mean CD4 cell count 513 cells/mm^3 and 47 (81.0%) with HIV RNA < 200 copies/mL). HIV positive mpox cases were older (40.4 vs 35.4yrs, p=0.0013) but otherwise similar to those without HIV. Compared with HIV negative mpox cases, HIV positive cases had similar clinical presentations with similar risk of more widespread manifestations of disease, such as non-dermatological symptoms (87.9% vs 82.6%, p=0.38) and extra-genital lesions (74.1% vs 64.0%, p=0.199). PLWH experienced a similar time to from onset of symptoms to discharge (mean days 17.1 vs 15.4, p=0.39) and total time under virtual ward review (mean days 11.7 vs 9.01, p=0.13). A similar proportion of people with HIV required review in the emergency department (36.2% vs 25.6%, RR=1.41, 95%CI=0.86 to 2.33). A higher proportion of PLWH were admitted to hospital, but this did not reach statistical significance (19.0% vs. 9.30%, RR=2.04, 95%CI=0.86 to 4.76). Of the small sample of PLWH with uncontrolled viral loads (RNA >=200), 2/5 patients (40%) were hospitalised. There were no recorded deaths.

Conclusion: In this cohort of mpox cases there was a high prevalence of well-controlled HIV co-infection, but we find no evidence that PLWH experience more severe mpox.. Whilst there are a higher proportion of hospitalisations, this is not statistically significant and is likely to be impacted by additional caution shown by clinicians in making decisions around mpox care in these patients. All other outcomes analysed indicate that mpox infections are of similar severity in people with and without HIV, providing reassurance for patients and clinicians providing future care for patients with mpox and HIV co-infection.

740 TB OUTCOMES IN PEOPLE LIVING WITH HIV: AN INTEGRATIVE DATA ANALYSIS OF PHASE 3 TRIALS

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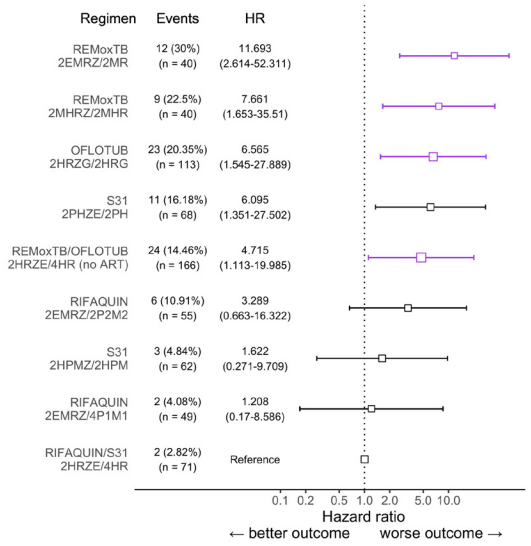
Background: People with HIV (PWH) and tuberculosis (TB) have been historically at higher risk of TB-related unfavorable outcomes than those without HIV. Our goal is to understand risk factors for TB-related outcomes in PWH, by performing an integrative data analysis of PWH in 4 recent Phase 3 TB trials.

Methods: Integrative analysis included data from PWH in 4 recent Phase 3 TB treatment trials (OFLOTUB NCT00216385, REMoxTB NCT00864383, RIFAQUIN ISRCTN44153044, S31/A5349 NCT02410772). Overall, PWH received 9 unique TB regimens of 4- and 6-month duration. Primary endpoint was TB-related unfavorable outcomes, including TB treatment failure, relapse, or death. Risk factors included demographics, baseline smear grade, CD4 counts, baseline cavitation on chest radiograph, TB treatment including adherence (percentage pills taken), and antiretroviral therapy (ART) initiated before or during the trial. The relationship between risk factors and outcome was tested through Cox proportional hazard controlled for treatment arm.

Results: The dataset included 711 (11.2% of dataset) PWH (of which 45.4% female). Median (range) baseline CD4 count was 339 (19-1155) cells/mm^3 and 359 (50.5%) were not on ART. Ninety-three unfavorable events occurred. RIFAQUIN's 6-month moxifloxacin-, and S31's 4-month rifapentine-moxifloxacin regimens performed similarly to standard-of-care (**Figure 1**). ART use (89% efavirenz-based) correlated with trial (only S31 and RIFAQUIN allowed ART); however PWH receiving ART (7.1%) had fewer TB-related unfavorable outcomes compared to PWH not receiving ART (18.9%). Multivariate analysis showed that male PWH (adjusted hazard ratio [HR] with 95% confidence interval 2.08 (1.34-3.24) compared to female) with high baseline smear grade (HR 1.25 (0.62-2.53) and 2.27 (1.26-4.09) for 2+ and 3+, respectively, compared to negative or 1+), and with decreased adherence (HR 1.04 (1.01-1.07) per percent point decrease) were predictive of unfavorable outcomes. Male PWH with smear grade 2+ or 3+ had high rates of TB-related unfavorable outcomes (12.9% with ART and 25.8% without ART) compared to patients at lower risk (defined as female PWH or male PWH with negative smear grade or 1+) (7.1% with ART and 13.5% without ART).

Conclusion: PWH are efficaciously treated with anti-TB regimens containing rifapentine and moxifloxacin. Male PWH with baseline smear grade 2+ or 3+ and lower treatment adherence are at highest risk of unfavorable TB outcome. Positive effects of ART while undergoing TB treatment are confirmed.

Cox proportional hazard of the integrated data analysis of four Phase 3 clinical trials showing hazard ratios (HR) with 95% confidence intervals. ART = antiretroviral therapy, 2EMRZ/2MR: 2 months of daily ethambutol, moxifloxacin, rifampin, and pyrazinamide followed by 2 months of daily moxifloxacin and rifapentine (REMoxTB), 2MHRZ/2MHR: 2 months of daily moxifloxacin, isoniazid, rifampin, and pyrazinamide followed by 2 months of daily moxifloxacin, isoniazid, and rifapentine (REMoxTB), 2HRZG/2HRG: 2 months of daily isoniazid, rifampin, pyrazinamide, and gatifloxacin followed by 2 months of daily isoniazid, rifampin and gatifloxacin (OFLOTUB), 2PHZE/2PH: 2 months of daily rifapentine, isoniazid, pyrazinamide, and ethambutol followed by 2 months of daily rifapentine and moxifloxacin (S31), 2HRZE/4HR: 2 months of daily isoniazid, rifampin, pyrazinamide, and ethambutol, followed by 2 months of daily moxifloxacin and rifapentine (REMoxTB, RIFAQUIN, OFLOTUB, S31), 2EMRZ/2P2M2: 2 months of daily ethambutol, moxifloxacin, rifampin, and pyrazinamide followed by 2 months of twice weekly rifapentine and moxifloxacin (RIFAQUIN), 2HPMZ/2HPM: 2 months of daily isoniazid, rifapentine, moxifloxacin, and pyrazinamide followed by 2 months of daily isoniazid, rifapentine, and moxifloxacin (S31), 2EMRZ/4P1M1: 2 months of daily ethambutol, moxifloxacin, rifampin, and pyrazinamide followed by 4 months of once weekly rifapentine and moxifloxacin (RIFAQUIN). Purple indicates trials where no ART was used.



741 ADVERSE DRUG REACTIONS ON TB TREATMENT: A PREDICTION MODEL INCLUDING HIV AND HBA1C

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Regional Prospective Observational Research in Tuberculosis (RePORT)-Brazil consortium
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Background: Adverse drug reactions (ADR) can influence treatment completion rates and the effectiveness of tuberculosis (TB) treatment. The rate of ADR related to anti-TB treatment (ATT) can be affected by HIV and diabetes mellitus. Given the paucity of prediction models for ATT-associated ADR, we developed a prediction model of ADR on TB treatment, incorporating important clinical variables.

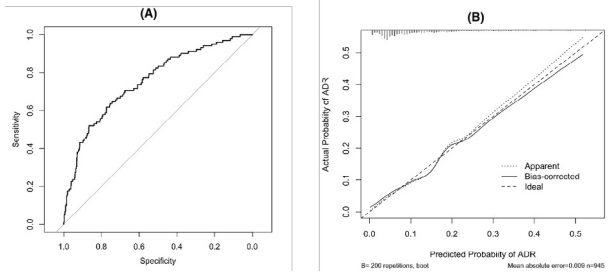
Methods: We included culture-confirmed, drug-susceptible, pulmonary TB participants from the RePORT-Brazil cohort, who received standard ATT between 2015-2019. ADR was defined based on physician-assigned attribution of relation to ATT and described according to the affected organ system, HIV

status, severity, timing, and duration. Diabetes was categorized as HbA1c < 5.7% (no diabetes); ≥5.7% to < 6.5% (pre-diabetes); and ≥6.5% (diabetes). The predictive model of ADR risk used a bootstrapped backward selection approach. Of 13 candidate predictors (e.g., HIV status, HbA1c, ancestry markers), the variables retained in at least 70% of prediction models across 500 bootstrap replications were included in the final model. Model discrimination was evaluated by c-statistic and calibration with a calibration plot.

Results: Of 945 participants, 102 (11%) experienced ADR. Among 156 ADR occurrences, most (78%) were of moderate severity and occurred during the first two months of ATT (77%). Hepatic ADR were the most frequent (n=82, 53%). ADR occurred in 38 (21%) people living with HIV/AIDS (PLWHA) and in 64 (8%) HIV-seronegative. Overall, 35 (10%) normoglycemic participants had ADR, while 47 (13%) and 19 (9%) participants with pre-diabetes and diabetes, respectively, experienced ADR. Variables included in the final prediction model for ADR were HIV status, HbA1c, age, ancestry markers, and concomitant medication use. Use of concomitant medication (mainly other antibiotics) and HIV status were highly predictive of ADR; they were included in 100% and 82% of all prediction models, respectively. The final prediction model demonstrated reasonable accuracy (c-statistic=0.75 [95%CI=0.70-0.80]) (**Figure 1A**) and suitable calibration (**Figure 1B**). Bootstrap internal validation indicated that the model was robust (optimism-corrected c-statistic of 0.73 [95% CI: 0.68-0.78]).

Conclusion: We developed a robust, accurate, and reliable prediction model of ATT-related ADR. Knowledge and intervention based on important factors such as use of concomitant medication at the time of ATT initiation and HIV status could improve treatment tolerability.

Figure 1. Performance of prognostic model for predicting ADR in TB treatment. (A) the receiver operating characteristic curve indicates good fit, with c-statistic of 0.75 (95% CI: 0.70-0.80) indicating good discriminatory ability. (B) The calibration curve also indicated good fit with an optimism-corrected intercept and slope of -0.22 and 0.87, respectively.



742 PREDICTORS OF POOR OUTCOMES IN PATIENTS WITH TUBERCULOSIS SYMPTOMS AT HIV DIAGNOSIS

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Background: Standard of care has shifted to minimize delays in ART initiation. Data are limited on predictors of poor outcomes for patients who present with TB symptoms at HIV diagnosis, and initiate treatment with current, faster models of treatment initiation.

Methods: We recently completed a randomized trial to compare same-day treatment vs. standard care for participants with TB symptoms (cough, fever, night sweats, and/or weight loss) at HIV diagnosis. Both groups received a digital chest radiograph, 2 Xpert Ultra tests, and 2 mycobacterial cultures within 2 days after enrollment. The current analysis includes predictors of retention, and retention with viral suppression, using univariable and multivariable logistic regression.

Results: From November 6, 2017 to January 16, 2020, 500 participants were enrolled in the trial (250/group). In the total cohort, the median age was 37 years (IQR: 30, 45) and 234 (46.8%) were female. Median BMI was 20.6 (IQR: 18.7, 22.9) and median CD4 count was 274 (IQR: 128, 426). Baseline TB was diagnosed in 88 participants (17.6%), and all initiated TB treatment; among patients without TB, median time to ART was 0 days (IQR: 0,0) in the same-day and 7 days (IQR: 7, 10) in the standard group. In the standard and same-day groups, 6 (2.4%) and 9 (3.6%) died (RD: 0·01; 95% CI: -0·02, 0·04), 229 (91.6%) and 218 (87.2%) were retained in care (RD -0.04; 95% CI: -0.10, 0.01), and 168 (67.2%) and 152 (60.8%) were retained in care with 48-week HIV-1 RNA < 200 copies/mL (RD -0.06; 95% CI: -0.015, 0.02), respectively. In the multivariable analysis, older age (OR 0.60; 95% CI: 0.50, 0.98), higher education (0.20; 95% CI: 0.09, 0.46)), and baseline TB (OR: 0.34; 95% CI: 0.13, 0.94) were associated with retention in care, and older age (OR: 0.75; 95% CI: 0.61, 0.93) and higher education (OR: 0.60; 95% CI: 0.40, 0.91) were associated with retention and viral suppression (see Table 1). Sex, income, BMI, CD4 count, and randomization group (same-day vs. standard) were not associated with either outcome.

Conclusion: With rapid treatment initiation, traditional risk factors such as male sex, low BMI and low CD4 count are not associated with poor ART outcomes among patients with TB symptoms at HIV diagnosis. Baseline TB diagnosis is associated with improved retention in care. Additional services are needed to support retention and adherence for younger patients,and those with lower education levels.

Table 1. Predictors of Retention in Care and Viral Suppression

Variable	Univariable Analysis		Multivariable Analysis*	
	OR (95% CI)	p-value	OR (95% CI)	p-value
Not Retained in Care at 48 Weeks after Enrollment (n=53/500)				
Age, per decade	0.84 (0.62, 1.13)	0.25	0.60 (0.50, 0.98)	**0.04**
Female sex	1.02 (0.58, 1.80)	0.95	0.83 (0.44, 1.57)	0.57
Income <$US 1.00/day	1.20 (0.61, 2.36)	0.60	1.28 (0.61, 2.69)	0.52
Education – at least some secondary (vs. less than secondary)	0.30 (0.14, 0.62)	0.001	0.20 (0.09, 0.46)	**0.0001**
Marital status – single/formerly married (vs. married)	1.22 (0.69, 2.17)	0.50	1.42 (0.77, 2.65)	0.26
CD4 count at enrollment, per 50 cells*	0.99 (0.93, 1.05)	0.67	0.97 (0.91, 1.04)	0.49
Body mass index, per 1 unit	0.99 (0.92, 1.07)	0.85	1.01 (0.91, 1.11)	0.92
Tuberculosis (vs. no TB)	0.46 (0.18, 1.18)	0.11	0.34 (0.13, 0.94)	**0.04**
Same day treatment (vs. Standard)	1.60 (0.90, 2.86)	0.11	1.76 (0.95, 3.29)	0.07
No 48-Week Viral Load, or ≥200 copies/mL (n=180/500)				
Age, per decade	0.78 (0.65, 0.95)	0.01	0.75 (0.61, 0.93)	**0.007**
Male sex	0.96 (0.66, 1.38)	0.82	0.98 (0.66, 1.46)	0.92
Income <$US.100/day	1.10 (0.72, 1.68)	0.66	0.94 (0.60, 1.47)	0.78
Education – at least some secondary (vs. less than secondary)	0.69 (0.47, 1.01)	0.05	0.60 (0.40, 0.91)	**0.02**
Marital status – single/formerly married (vs. married)	0.81 (0.56, 1.17)	0.27	0.88 (0.6, 1.30)	0.53
CD4 count at enrollment, per 50 cells	0.98 (0.94, 1.02)	0.34	0.99 (0.95, 1.03)	0.61
Body mass index	0.95 (0.90, 1.00)	0.06	0.97 (0.92, 1.03)	0.33
Tuberculosis (vs. no TB)	1.62 (1.02, 2.58)	0.04	1.32 (0.80, 2.18)	0.28
Same day treatment (vs. Standard)	1.32 (0.92, 1.91)	0.14	1.26 (0.86, 1.84)	0.24

*5 persons excluded due to missing data.

743 ISONIAZID TOXICITY AMONG PWH WITH LATENT TB WHO CONSUME ALCOHOL: A SINGLE ARM TRIAL

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Background: Isoniazid (INH) preventive therapy (IPT) reduces the incidence of TB disease among persons living with HIV (PWH). However, IPT deferral is suggested for persons with harmful alcohol use due to dual liver toxicity concerns.

Methods: We conducted a single arm study evaluating liver toxicity rates of 6 months of IPT in PWH on antiretroviral therapy (ART) with latent TB (≥5 mm on tuberculin skin test) who reported either recent (prior 3 months) alcohol consumption (n=200) or no prior year alcohol consumption (n=101) at screening. Enrollment was limited to those with alanine aminotransferase (ALT) and aspartate aminotransferase (AST) ≤2 times the upper limit of normal (ULN). Toxicity was detected by ALT, AST, and symptom monitoring. We defined Grade 3 or higher toxicity as ALT or AST ≥5 times the ULN or severe INH-related symptoms and stopped IPT upon detection. Grade 2 toxicities were defined as ALT or AST 2-5 times the ULN or moderate symptoms. We also examined the independent association of biomarker-confirmed alcohol use (none, low, medium, and high/very high, defined in Table), determined by the Alcohol Use Disorders Test – Consumption (AUDIT-C), modified to include the prior 3 months, and phosphatidylethanol (PEth), with Grade 3 or higher and Grade 2 toxicity.

Results: Half (51.2%) of the participants were female, median age was 40 years (IQR 33-47), and 92.1% were virally suppressed. Twelve of 200 PWH reporting recent alcohol use (6.0%, 95% CI: 3.1-10.2) and 13/101 reporting no prior year alcohol use (12.9%, 95% CI: 7.0-21.0) experienced a Grade 3 or higher toxicity. Among those with no Grade 3 toxicity, 47/188 reporting recent alcohol use (25.0%, 95% CI: 19.0-31.8) and 13/87 reporting no prior year alcohol use (14.8%, 95% CI: 8.1-23.9) experienced at least one Grade 2 toxicity. We found no association between biomarker-confirmed alcohol use and Grade 3 or higher toxicity but did find an association of biomarker-confirmed alcohol use with Grade 2 toxicity (Table).

Conclusion: Grade 3 or higher IPT toxicities among PWH with latent TB reporting recent alcohol use were infrequent. Biomarker confirmed alcohol use was not associated with having a Grade 3 or higher toxicity. Grade 2 toxicities were more common and high/very high-risk alcohol use was associated with their occurrence. Alcohol use does not appear to pose an increased risk for serious IPT toxicity among those without significant liver enzyme elevations at baseline (< 2x ULN) in PWH on ART and should therefore not be deferred.

Adjusted odds ratios for the associations of biomarker-confirmed alcohol use with Grade 3 and higher toxicity and Grade 2 toxicity.

		Grade 3 or higher toxicity		Grade 2 toxicity	
	N (%)	Adjusted Odds Ratio (95% CI) Adjusted for age, sex, health status, and study visit	p-value	Adjusted Odds Ratio (95% CI) Adjusted for age, sex, health status, study visit, and antiretroviral adherence	p-value
Biomarker-confirmed alcohol use			0.32		<0.01
None (AUDIT-C=0 and PEth<8 ng/mL)	86 (28.6)	1.00		1.00	
Low (AUDIT-C 1-2 for women, 1-3 for men, and PEth<50 ng/mL)	66 (21.9)	0.43 (0.13, 1.44)		1.11 (0.44, 2.76)	
Medium (AUDIT-C 3-5 for women, 4-5 for men, and PEth≤200 ng/mL)	56 (18.6)	0.36 (0.10, 1.29)		0.69 (0.25, 1.91)	
High/very high (AUDIT-C ≥6 or PEth>200 ng/mL)	93 (30.9)	0.56 (0.16, 1.93)		3.63 (1.48, 8.93)	

744 RISK FACTORS FOR ADRS RELATED TO IPT AMONG PLHIV ON DOLUTEGRAVIR-BASED ART IN UGANDA

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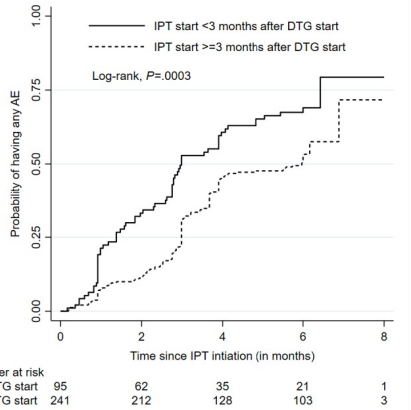
Background: Isoniazid preventive therapy (IPT) is recommended for the treatment of latent tuberculosis (TB) infection and is beneficial for persons living with HIV (PLHIV) even after initiation of antiretroviral therapy (ART). After the roll out of dolutegravir (DTG)-based ART in 2018, the Uganda Ministry of Health rapidly expanded IPT coverage among PLHIV. We assessed if concomitant IPT and DTG administration (C-IPT) increased the risk of IPT-related adverse drug reactions (ADRs) compared to sequential administration (S-IPT).

Methods: We carried out a retrospective cohort review of PLHIV ≥18 years initiated on IPT from July 2019–March 2020. We excluded records of patients without any recorded IPT follow-up visits and those who started DTG after IPT initiation. We defined C-IPT as IPT initiation < 3 months after DTG initiation, and S-IPT as IPT initiation ≥3 months after DTG initiation. We defined IPT-related ADRs as new symptoms reported after IPT initiation. We compared ADRs among patients who had C-IPT with those who had S-IPT using a Pearson Chi-square test and a Poisson regression model with robust standard errors adjusting for potential baseline confounders. We plotted Kaplan Meier curves for the probability of any ADR and compared the two groups using the log rank test.

Results: We analysed data from 336/376 patients. Overall, 193(57.4%) patients reported any IPT-related ADR. A total of 410 ADRs were reported. The commonest ADRs were flu-like syndrome 108(26.3%), joint aches 44(10.7%) and skin rashes 45(10.9%) and peripheral neuropathy 37 (9.0%). A high proportion 64 (67.4%) patients with C-IPT reported ADRs compared to those with S-IPT 129(53.5%) (Chi-square P-value=0.02). After adjusting for HIV-1 RNA viral load, calendar year, history of hypertension and diabetes, only C-IPT was associated with an increased risk of IPT-related ADRs (risk ratio: 1.30; 95%CI: 1.07–1.58)

Conclusion: PLHIV initiating both DTG-based ART regimens and IPT had higher occurrence of ADRs and may benefit from close monitoring.

Figure 1: Kaplan-Meier Curves for the probability of any adverse event after IPT administration



Legend: solid line denotes group of patients administered IPT within 3 months after DTG administration (*probability of failure at 6 months [0.69, 95%CI 0.60-0.78]*). Dashed line denotes patients administered IPT more than 3 months after DTG administration (*probability of failure at 6 months [0.53, 95%CI 0.46-0.59]*).

745 TREATMENT OUTCOMES OF PERSONS WITH DSTB ON A MEDICATION MONITOR AND ADHERENCE SUPPORT

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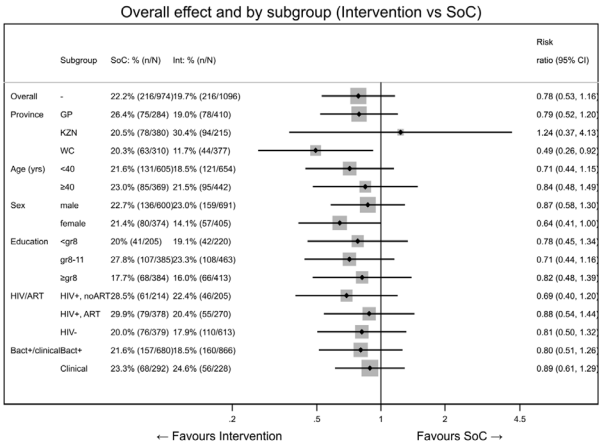
Background: Digital adherence technologies have gained traction recently with medication monitors showing improved adherence. Data on the impact on long-term clinical outcomes is lacking. We conducted a cluster-randomized trial to measure outcomes amongst persons with drug-susceptible TB (DS-TB) supported by medication monitors and differentiated care (intervention) versus standard care (SoC). Participants had improved adherence in the intervention versus SoC arms. Here we compare 18-month clinical outcomes by study arm.

Methods: DS-TB (≥2 years) persons were enrolled from 18 primary health clinics in three provinces (Gauteng, KwaZulu Natal, Western Cape) in South Africa. Intervention arm participants had visual/audio reminders for medication intake with monitoring and support depending on the number of missed doses/ week. SoC arm received monitors in silent mode to document adherence. Participants were followed-up with sputum (culture) at treatment end and 18 months. Unfavorable outcome was defined as: on treatment - treatment failure, lost to follow-up, death, culture-positive at 6 months or MDR diagnosis; or recurrence to 18 months.

Results: We enrolled 2727 participants, reporting on 2657 participants: 38% female, median age 36 years, and 53% HIV-positive. Of 2070 participants (587 had outcome undefined), 20.9% (432/2070) had an unfavorable outcome. By arm, unfavorable outcomes were similar (geometric means: 22.3% in SoC versus 17.1% in intervention clusters). The risk ratio was 0.78 (0.53- 1.16), adjusting for age, sex, TB diagnosis, ethnic group, education, marital status, HIV/ART status, and province. The effect of the intervention appeared to be greater among females and those in Gauteng and Western Cape as shown in the figure attached.

Conclusion: Although adherence was improved, there does not seem to be a difference in unfavorable outcomes in persons with DS-TB in the intervention versus SoC arms. Although these interventions are less likely to show an impact on clinical outcomes in routine settings, the effect on adherence is important and warrants continued use and evaluation of these technologies. Adaptation of these technologies to cater for those on both TB and HIV treatment is required.

Overall effect of unfavorable outcome by subgroup



746 HIGH MORTALITY IN HOSPITALISED VIRALLY SUPPRESSED ADULTS WITH HIV IN SOUTH AFRICA

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Background: Mortality in PWH has been markedly improved by antiretroviral therapy (ART) but there are few reports describing this in the ~5 million virally suppressed (VS) PWH in South Africa(SA). We describe cause of death(CoD) in adults admitted to hospital with suspected pneumonia in SA.

Methods: We enrolled patients from June 2019-October 2021 at four hospitals and then followed them up for ≥1 year. Eligibility included: Age >18 years, ≥2 signs/symptoms of pneumonia, < 48 hrs since admission. Medical records were reviewed. All had HIV status ascertained and sputum sent for Xpert Ultra and mycobacterial culture. In PWH CD4 count, viral load (VL) and urine lipoarabinomannan were assessed. For those who died, CoD were abstracted from medical charts and interview of family. We categorised deaths as early: while admitted or to < 30 days after discharge; or late: ≥30 days after discharge. We report mortality and CoD in VSPWH (VL≤50 copies/ml), unsuppressed and HIV uninfected(HUI) adults.

Results: Of 1999 adults, 54% were PWH; 61.2% reported receiving ART of whom 43.1% were VS; 55.5% were women. Overall median age of VS was 48 years (IQR: 40-55) at entry; 34.3% had comorbidities: hypertension (70.1%, obesity 41.3%, diabetes 28.9%) . Only 11.3% were diagnosed with HIV in the past year, 35.0%, had prior TB. Median CD4 count of VS patients was 289 cells/mm^3 (IQR:133-490) and Hb, 12.5g/dL (IQR:10.5-14.0); 53.0% had CRP >100mg/dL and 69.6% had oxygen saturation < 93% on room air; 14.8% had ≥1 assay positive for TB; and 42.9% were SARS-CoV-2 positive. Overall 25.4% VSPWH died compared to 31.2% and 22.9% of unsuppressed and HUI, respectively; median ages at death were 49 (IQR:43-59), 38 (IQR: 32-47) and 62 (IQR: 53-69) years respectively. Overall median times to early and late death was 8 (IQR: 4-16) and 104 (IQR: 75-254) days, respectively. The leading CoD in VSPWH were: COVID-19 (22.9%), chronic lung disease(CLD) (17.1%),malignancy (12.9%),sepsis, (12.9%) and TB (8.7%); in HIV unsuppressed, CoD were: advanced HIV and opportunistic infections-(TB,PJP)(55.5%), sepsis(9.6%), COVID-19(8.6%); and in HUI: COVID-19(43.0%), cardiovascular disease (9.0%), TB(9.0%), malignancy (8.5%).

Conclusion: Mortality in VSPWH admitted with suspected pneumonia was higher than in HUI and occurred 12 years earlier. The challenge for clinicians is to screen for diseases that disproportionately affect VSPWH and to try to prevent recurrent lung infections thereby increasing their comorbidity-free years and reduce mortality gaps.

747 LONG-TERM OUTCOMES OF PNEUMOCYSTIS JIROVECII PNEUMONIA IN THE ANTIRETROVIRAL ERA

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Background: Late HIV diagnosis remains a reality, especially in people with poor access to care and in resource-limited settings. Pneumocystis *jirovecii* pneumonia (PCP) is one of the most frequent opportunistic infections in people with HIV (PWH) with low CD4+ T-cell counts. While earlier studies have focused on in-hospital and short-term mortality from PCP, there are limited data on long-term outcomes in the antiretroviral therapy (ART) era, especially with respect to long-term morbidity.

Methods: A retrospective review of 307 PWH with a median follow-up of 96 weeks was conducted (602 patient-years). Eighty had a history of PCP and 227 did not. Twelve pulmonary function tests of patients with PCP and 19 without PCP were also reviewed, at a median of 74 days after ART initiation. Seventy-three patients with PCP had at least one chest computerized tomography (CT) scan completed. Statistical analyses were conducted in R (version 4.1.0).

Results: A diagnosis of PCP within 3 months of ART initiation was not associated with decreased 96-week survival (hazard ratio (HR) of 2.32), unless the illness was severe (defined as requirement of an advanced oxygen delivery device), which increased the HR to 7.13 (p = 0.03). No deaths were directly related to PCP. There were no differences in 96-week plasma HIV viral load, CD4+ and CD8+T-cell counts, total white blood cell count, hemoglobin, platelets, creatinine, D-dimer, or C-reactive protein. 22.4% of patients treated with corticosteroids for PCP were found to have concurrent cytomegalovirus (CMV) end-organ disease, compared to 7.9% of PWH without prior PCP or steroid use (p = 0.03). Notably, the only cases of CMV pneumonitis occurred concurrently with severe PCP. Patients with PCP had a significant decrease in forced expiratory volume at 1 second (FEV1), forced vital capacity (FVC), total lung capacity, vital capacity, and diffusion capacity for carbon monoxide compared to those without (Table 1), at a median follow-up of 153 days after PCP. There was no effect on FEV1/FVC ratio. Upon review of the CT scans of patients with a history of PCP, 10% had traction bronchiectasis and 10% had subpleural cysts.

Conclusion: PCP continues to be an important opportunistic infection in the ARV era without negatively affecting CD4 reconstitution but with possible residual pulmonary sequelae as suggested by PFT and CT findings. Our findings imply that PCP and its management may contribute to long-term morbidity in PWH even in the ART era.

Table 1: Pulmonary Function Test Findings

	History of PCP (N=12)	No history of PCP (N=19)	
FEV1 (liters), mean (SD)	2.32 (0.499)	2.56 (0.722)	p = 0.002
FVC (liters), mean (SD)	3.06 (0.731)	3.47 (0.843)	p < 0.001
FEV1/FVC, mean (SD)	76.6 (7.28)	74.3 (12.1)	NS
TLC (liters), mean (SD)	4.24 (1.21)	5.32 (1.23)	p = 0.001
Vital capacity (liters), mean (SD)	3.02 (0.716)	3.54 (0.919)	p < 0.001
DLCO (ml/(min*mmHg)), mean (SD)	14.7 (4.69)	15.1 (5.34)	p = 0.04
Restriction severity			
Mild	4 (33.3%)	1 (5.3%)	
Moderate	4 (33.3%)	1 (5.3%)	
Severe	0 (0%)	0 (0%)	
Diffusion impairment severity			
Mild	1 (8.3%)	7 (36.8%)	
Moderate	7 (58.3%)	7 (36.8%)	
Severe	4 (33.3%)	2 (10.5%)	

Abbreviations: FEV1: forced expiratory volume in 1 second, FVC: forced vital capacity, TLC: total lung capacity, DLCO: diffusing capacity for carbon monoxide, SD: standard deviation, NS: not significant.

748 RISK FACTORS ASSOCIATED WITH NEURO-COGNITIVE IMPAIRMENT IN CRYPTOCOCCAL MENINGITIS

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Background: The magnitude and causes of sustained neurocognitive impairment in cryptococcal meningitis are not well described. We sought to understand the clinical risk factors associated with sustained neurocognitive impairment among cryptococcal meningitis survivors.

Methods: At week 12 (+3) from diagnosis, HIV+ participants with first episode cryptococcal meningitis underwent neuropsychological testing consisting of a battery of tests evaluating eight neurophysiological domains. A composite quantitative neurocognitive performance z-score (QNPZ) was calculated as the mean of eight individual z-scores. Impaired neurocognitive function is defined as a QNPZ-8 z-score< -1. We compared demographic variables and clinical characteristics by QNPZ-8 group (QNPZ-8< -1 vs. ^{3}-1).

Results: QNPZ scores of 210 participants with cryptococcal meningitis were analyzed. Overall, 72% (152/210) demonstrated sustained neurocognitive impairment at 12 weeks. There were no differences in antiretroviral therapy (ART) use (p=.80) or CD4 count (p=.36) at baseline, between the impaired and non-impaired. Impaired subjects with a QNPZ-8< -1 were more likely to present with a baseline Glasgow Coma Score (GCS)< 15 (p< .01), seizures (p=.04), and lower serum sodium (p=.03) than those non-impaired. We observed no significant difference between CSF opening pressures (p=.84) or quantitative CSF culture burden (p=.13) between impaired and non-impaired groups. We however, found that persons presenting with baseline sterile CSF cultures were more likely to be non-impaired at week 12 (p=.04). While we observed no differences between baseline CSF WBCs (p=0.09) between groups, non-impaired subjects had higher median CSF WBC on day 7 (median 25, IQR < 5 to 100 cells/mcL) as compared to the impaired group (median < 5, IQR < 5 – 8 cells/mcL; p=0.03).

Conclusion: Neurocognitive impairment at week 12 is common among cryptococcal meningitis survivors. Baseline GCS< 15, seizures, and low serum sodium are risk factors for sustained neurocognitive impairment. Baseline sterile CSF cryptococcal cultures and early rise in CSF WBC is associated with better neurocognitive performance at week 12. Studies looking into the impact and degree of immune recovery during cryptococcal meningitis induction therapy to improve neurocognitive outcomes are warranted.

Table 1: Demographic and clinical characteristics by QNPZ-8 score

	N	QNPZ-8 < -1 (Impaired)	N	QNPZ8 >= -1 (Non-Impaired)	p-value[1]
Currently on ART	152	73 (48.0%)	58	29 (50.0%)	0.80
CD4+ cell count/μL	152	21 [8, 57]	58	13 [6, 53]	0.36
Glasgow Coma Score <15	152	66 (56.6%)	58	12 (79.3%)	**<0.01**
Seizures	152	24 (15.8%)	58	3 (5.2%)	**0.04**
Serum Sodium, mmol/L	152	129 [126, 133]	58	132 [128, 134]	**0.03**
CSF Opening pressure, cmH_2O	152	26 [20, 38]	58	27 [20, 35]	0.84
CSF *Cryptococcus* log_{10}CFU/mL	152	4.51 [2.78, 5.32]	58	4.11 [2.59, 4.85]	0.13
Day 0 – Sterile CSF Culture	151	8 (5.3%)	58	8 (13.8%)	**0.04**
Day 0 – CSF WBC cells/μL	149	<5 [<5, 100]	57	<5 [<5, 45]	0.09
Day 7 – Sterile CSF Culture	152	41 (27.0%)	58	20 (34.5%)	0.28
Day 7 – CSF WBC cells/μL	34	<5 [<5, 8]	14	25 [<5, 100]	**0.03**
Day 14 – Sterile CSF Culture	152	87 (57.2%)	58	36 (62.1%)	0.53
Day 14 – CSF WBC cells/μL	47	<5 [<5, 45]	16	5 [<5, 19]	0.86

[1]Kruskall-Wallis test for medians; Chi-square test for proportions
Data presented as either N (%) or Median [IQR]

749 CEREBROSPINAL FLUID PROTEIN CLINICAL IMPACT IN HIV-ASSOCIATED CRYPTOCOCCAL MENINGITIS

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ASTRO-cm group

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Background: Cryptococcal meningitis is a leading cause of mortality among HIV-infected patients in sub-Saharan Africa. Patients with HIV-Associated cryptococcal meningitis have varying levels of cerebral spinal fluid (CSF) protein. However, CSF protein clinical utility and associated cytokine profile remain poorly defined.

Methods: We performed post-hoc analyses of 874 prospectively enrolled patients with cryptococcal meningitis consented in Uganda between 2015 and 2021. We stratified baseline CSF protein using a cutoff level of 100mg/dL to group patients into a high (n=247) or low (n=627) CSF protein group. We performed univariate and logistic regression analyses to evaluate clinical and cytokine profile differences between the two groups.

Results: The two groups did not differ by gender and age (P >0.05). Participants with high baseline CSF protein had lower cryptococcal fungal burden (p< 0.001), lower CSF opening pressure on day 14 (p< 0.01), higher baseline CD4 cell counts (p< 0.001), and higher CSF white cell counts (p< 0.001). The low CSF protein group had fewer seizures (p=0.03), fewer episodes of altered consciousness (p< 0.01), and fewer day 14 sterile fungal cultures (p=0.02). Patients with higher CSF protein had lower 18-week mortality: 24.4% (85/247) versus 43% (272/627) (p=0.018). Of the forty-five baseline CSF cytokine and chemokines assayed, IL-1b, IL-1ra, IL-6, IL-8, IL-17a, granzymeB, GROa, and PDL-1 significantly differed between the groups (P >0.05) and were higher in the high CSF protein group. Quantitative Neurocognitive Performance Z-score 8 at 3 months was comparable between the groups (P=0.18)

Conclusion: Patients with CSF protein >100mg/dL have a better antifungal response and 18 weeks mortality outcomes, despite increased seizures and altered mental status. These patients also have a robust pro-inflammatory and type-3 cytokine profile. While high CSF protein is associated with lower day 14 CSF opening pressures, it does not influence long-term neurocognitive performance

Cytokine expression by CSF protein level in HIV associated cryptococcal meningitis

Baseline CSF Biomarker	Function	CSF Protein <100 mg/dL	CSF Protein ≥100 mg/dL	Adjusted P-value[1]
		Mean (pg/mL)	Mean (pg/mL)	
IL-6	Mediate inflammatory responses	116.4	380.2	0.017
IL-1b		2.4	3.3	0.042
GranzymeB	Type 1 immune response, ideal for effectively killing crypto but destructive to the brain	12.3	21.1	<0.001
IL-5	Type 2 immune response, not protective against crypto but is less destructive to the precious brain	0.9	2.8	0.004
IL17a	Type 3 immune response involves neutrophils-mediated inflammation	2.0	3.9	0.024
GROa/CXCL1		114.5	361.7	0.021
IL8/CXCL8		288.9	583.6	0.035
IL1ra	Modulate/dampen all three types of immune responses	4198.7	7237.0	0.044
PDL-1	Immune exhaustion (with HIV and crypto chronic infections)	97.9	161.5	0.017

[1]Adjusted P value by Benjamin Hoxberg to control false discovery rate.

750 HIGH-DOSE ISONIAZID EARLY BACTERICIDAL ACTIVITY AGAINST DRUG-RESISTANT TUBERCULOSIS

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Background: High-dose isoniazid (INH) has been reported to be beneficial in treating multidrug-resistant tuberculosis (MDR-TB) and is part of the World Health Organization recommended shorter MDR-TB regimen. However, the optimal dose and its efficacy against *katG*-mutated *Mycobacterium tuberculosis* (*M.tb*) are not established.

Methods: AIDS Clinical Trials Group (ACTG) A5312 is a Phase 2A randomized, open-label trial. Group 3 participants had MDR-TB with INH resistance mediated by katG mutation and were randomized to receive INH monotherapy doses of 15 or 20mg/kg daily for 7 days. Sputum was collected daily and processed in Mycobacteria Growth Indicator Tube to determine time to positivity (TTP). Intensive PK sampling was performed on day 6. We report here preliminary

results. INH early bactericidal activity (EBA) was estimated using daily average change in TTP between day 0 and 7 ($EBATTP_{0-7}$). Linear mixed-effects modelling was used to evaluate the entire TTP profile, exploring the effect of INH area under concentration curve (AUC0-24) covariation with longitudinal changes in TTP.

Results: 21 participants were enrolled (11 in Haiti, 10 in South Africa). The majority (71%) were men, median age was 38 years, 19% were HIV-positive, and 62% had cavitary lung disease. INH AUC0-24 median (IQR) was 67 (49, 90) mg.h/L and heavily overlapped between the two dose levels. Median (IQR) $EBATTP_{0-7}$ in 15 and 20mg/kg dose groups was 1.79 (−1.66, 7.31) and 2.38 (−1.29, 5.52) hours/day, respectively. Linear mixed-effects model estimated a baseline TTP of 143 hours, slope of 3.75 hours/day (corresponding to an individual with AUC_{0-24} of 100mg.h/L), and a positive relationship between higher log AUC0-24 values and increase in TTP (P-value=0.008). The observed INH EBA was significantly lower than our previously reported EBA of 10 hours/day in drug-sensitive TB on 5mg/kg INH. No study drug-related adverse events were observed.

Conclusion: Our results suggest limited to no INH EBA over 7 days against *M.tb* strains with *katG* mutations among patients with MDR-TB. The drug effect was apparent in participants with high INH AUC, which did not correlate well with dose and was highly variable, likely due to *NAT2* genotype. INH is primarily activated by katG; the EBA of INH supports the hypothesis that small quantities of INH are activated either by incomplete inactivation of katG or alternative pathways. Therefore, INH may not be useful for *katG*-mutated *M.tb* as even 20mg/kg did not reach measurable EBA except in select patients.

751 TWICE DAILY DOSING OF ATAZANAVIR SAFELY OVERCOMES THE INTERACTION WITH RIFAMPICIN

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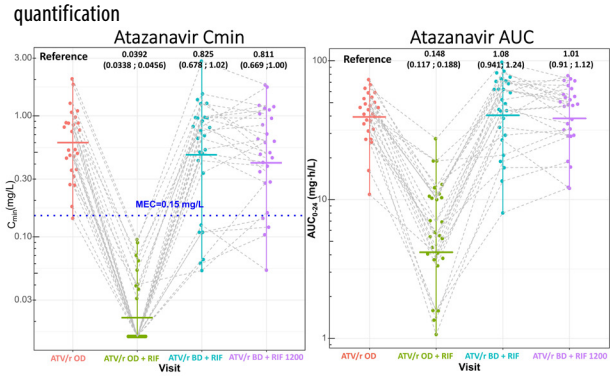
Background: Critical drug-drug interactions (DDI) exist between rifampicin and boosted protease inhibitors. Hepatotoxicity has occurred frequently in DDI studies of adjusted doses of protease inhibitors with rifampicin. We aimed to determine if dose escalation of atazanavir/ritonavir could safely overcome the DDI with rifampicin used at standard and double doses.

Methods: DERIVE (NCT04121195, EDCTP) was a dose-escalation trial in people living with HIV without tuberculosis on atazanavir/ritonavir-based ART in Uganda. Four intensive pharmacokinetic (PK) visits were performed at steady-state: PK1 300/100 mg OD (baseline); PK2 300/100 mg OD with rifampicin 600 mg; PK3 300/100 mg BID with rifampicin 600 mg OD; PK4 300/100 mg BID with rifampicin 1200 mg OD. Due to the potential risk of sub-therapeutic atazanavir concentrations with rifampicin, dolutegravir 50 mg BID was co-administered. Target atazanavir level against HIV is a minimum effective concentration (MEC) of 0.15 mg/L. Noncompartmental analysis was used to describe the pharmacokinetic data. Concentrations below the lower limit of quantification (LLOQ) of 0.03 mg/L were replaced by LLOQ/2.

Results: 26 participants were enrolled with a median (range) weight and age of 44 (28 - 61) years and 67 (50 - 75) kg, respectively, and 23 (88%) were female. Compared with PK1, atazanavir concentrations were significantly reduced at PK2: geometric mean ratio (GMR, 90%CI) of C_{min} and AUC_{24} were 0.04 (0.03 - 0.05 and 0.15 (0.12 - 0.18), respectively. The escalation to BID dosing (PK3) when compared to PK1, had a GMR of 0.83 (0.68 - 1.02) and 1.08 (0.97 - 1.21), respectively. The comparable exposures were maintained with double doses of rifampicin, GMR of C_{min}, and AUC_{24} 0.81 (0.67 - 1.00) and 1.01 (0.93 - 1.09) compared to PK1, respectively. The percentage of participants with concentrations below the MEC target was 4%, 100%, 23%, and 19% during PK1, PK2, PK3, and PK4 visits, respectively. No participant developed significant elevation of liver enzymes, reported an SAE, or experienced rebound viraemia.

Conclusion: These results indicate that increasing the dose of atazanavir/ritonavir to twice daily was well-tolerated and achieved acceptable atazanavir plasma concentrations

Figure 1: Beeswarm plot of atazanavir Cmin and AUC0-24 across the 4 PK visits with geometric mean ratios of the three visits vs first visit at the top of the figure. The horizontal and vertical line represent geometric mean and range respectively. The Cmin of 0.015 belong to values below the lower limit of quantification



752 LINEZOLID REACHES TARGET SITE IN PATIENTS WITH TB MENINGITIS AND HIV COINFECTION

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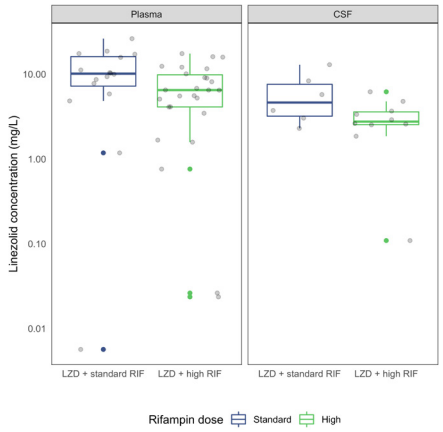
Background: Tuberculous meningitis (TBM) is a devastating form of TB. Several anti-TBM medications poorly penetrate the cerebrospinal fluid (CSF). Linezolid has good CSF penetration, but data for treating TBM with linezolid are limited. We assessed the pharmacokinetics (PK) and pharmacodynamics (PD) of linezolid in CSF and plasma from the ALTER trial, an ongoing Phase II, open-label, randomized clinical trial (NCT04021121) of adjunctive linezolid with high (35 mg/kg) or standard (10 mg/kg) dose rifampin in patients with definite or suspected TBM.

Methods: Participants (≥18 years) were recruited from Masaka, Uganda, and were randomized 1:1 to high versus standard dose rifampin, and then 1:1 to linezolid 1200 mg versus no linezolid for the first 4 weeks of treatment, all on a background regimen of isoniazid, pyrazinamide, and ethambutol. CSF and plasma were sampled on days 2, 14, and/or 28. We quantified the linezolid population PK in CSF and plasma, testing demographics and rifampin dose as covariates. Clinical trial simulations (n=50, 80 patients per trial) were performed to assess the proportion of participants reaching the trial targets of $AUC_{0-24,ss}$ (160 µg*h/mL), time above MIC (85% of 24h interval), and $AUC_{0-24,ss}$/MIC (100).

Results: Of the first 15 enrolled participants (53% women, median age 37, median weight 50 kg, 100% with HIV), median linezolid CSF and plasma peak concentrations were 3.20 and 11.0 mg/L, respectively. The PK was best described by a one compartment (distribution volume 46.1 L) model with first-order absorption (6.86 h-1), and allometrically scaled clearance (7.95 L/h) with inter-individual variability. Women had 36% lower clearance than men. Plasma-to-CSF rate was fast, with a partition coefficient of 55%. A trend towards an effect of high dose rifampin on linezolid PK in both CSF and plasma was observed (Figure). Based on clinical trial simulations, efficacy targets for linezolid (1200 mg QD/600 mg BID) were achieved in 30%/28% for AUC0-24,ss, 63%/87% for time above MIC, and 65%/55% for AUC0-24,ss/MIC.

Conclusion: Linezolid reached the target site in patients with TBM and HIV co-infection as quantified by our model-based approach of the preliminary trial data, and clinical trial simulations indicated that trial targets were achieved in a moderate to major proportion of simulated patients. Upon trial completion, this workflow will be used to confirm these results, including the effect of rifampin dosing on linezolid PK, and support therapeutic recommendations.

Linezolid (LZD) concentrations in plasma and cerebrospinal fluid (CSF) in patients with tuberculous meningitis and HIV when given with standard (10 mg/kg) or high (35 mg/kg) dose rifampin (RIF).



753 PREDICTIVE VALIDITY OF POPULATION MODELS FOR LINEZOLID EXPOSURE AND TOXICITY IN ZeNix

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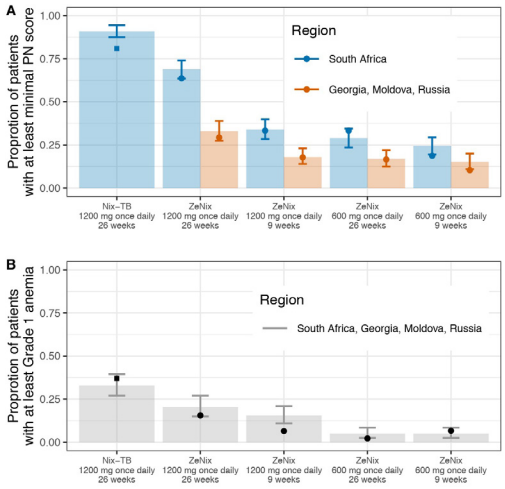
Background: Previously, using data from Nix-TB (NCT02333799, N=104), we published models relating linezolid exposure to peripheral neuropathy (PN) and hemoglobin (Hb), and we suggested how those models might guide patient management to reduce linezolid-related toxicity. Effective application of model-based insights to patient care requires model validation on independent data. Here we assess the predictive validity of the models and update them using the new and more diverse data from ZeNix (NCT03086486, N=179).
Methods: Quantifications of individual prediction errors and comparisons of observed versus simulated distributions of outcomes were used to assess the models from Nix-TB on the data from ZeNix. Models were then refitted to the combined data from ZeNix and Nix-TB and reassessed for consistency with the totality of the data. Model simulations were then compared to rates of investigator-reported adverse events in each trial.
Results: Linezolid PK in ZeNix was well predicted by the two-compartment model with nonlinear elimination developed with data from Nix-TB.
The Nix-TB PK/PD model for PN predicted incidence and severity in ZeNix well for patients from South Africa on 1200 mg linezolid for 6 months, but over-predicted PN in Eastern Europe (EE) and at less intensive linezolid dosing. Refitting found both a lower overall potency of the linezolid effect on PN and a lower base probability and maximum effect for EE, and these changes improved the model fit for the combined data. The original Nix-TB model did predict the duration of PN episodes well in ZeNix.
The Nix-TB PK/PD model for Hb predicted temporal distributions of Hb well in all four linezolid groups of ZeNix. The Nix-TB model's finding that Hb change after 4 weeks of treatment was superior to linezolid trough concentrations for predicting anemia was not recapitulated in terms of the ROC AUC but did manifest in the precision-recall (PR) AUC, which emphasizes prediction of positive cases: PR AUC 0.37 (95% CI: 0.13-0.63) for percent Hb change at week 4 vs 0.15 (0.05-0.25) for observed linezolid troughs.
Simulations using the refitted models for PN and Hb showed that rates of investigator-reported PN and anemia observed in the Nix-TB and ZeNix trials were well predicted (Figure).
Conclusion: Linezolid toxicity in TB is generally related to extent and duration of linezolid exposure. This work validates and refines existing models to build confidence in their application for regimen selection and patient management.
Peripheral neuropathy and hemoglobin models predict rates of investigator-reported adverse events. A. Model predicted peripheral neuropathy adverse events. Bar plots show the median simulated proportion of patients with at least a minimal score for each regimen tested in Nix-TB and ZeNix and stratified by region. B. Model predicted anemia adverse events. Bar plots show the median simulated proportion of patients with at least Grade 1 anemia for each regimen tested in Nix-TB and ZeNix. Error bar shows the 95% confidence interval of the predicted median. Points are the rates of investigator-reported adverse events in the trials. Model predicted median and 95% confidence intervals were summarized based on 500 model simulations with 100 bootstrapped participants in each trial.



754 HARD-TO-TREAT PHENOTYPES INCREASE TIME TO CULTURE CONVERSION IN DRUG-RESISTANT TB

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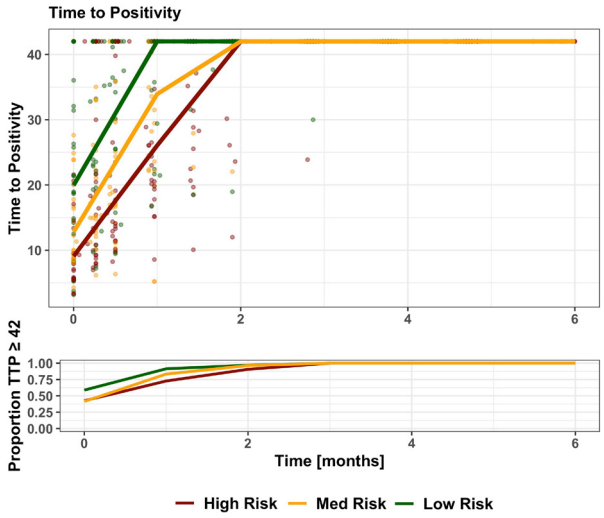
Background: Safer, better, and shorter treatment for highly resistant tuberculosis (TB) is an urgent global health need. The phase 3 Nix-TB (NCT02333799) clinical trial developed a six-month treatment consisting of high-dose linezolid, bedaquiline and pretomanid (BPaL) for MDR and XDR-TB. Here, we investigate the relationship between patient characteristics and efficacy endpoints collected in the Nix-TB trial.
Methods: Efficacy endpoints collected in Nix-TB included the primary efficacy endpoint (treatment failure or disease relapse), time to stable culture conversion, and longitudinal time to positivity (TTP) in the MGIT assay.
Each endpoint was characterized using nonlinear mixed effects modeling. Relationship of patient, drug exposure, and disease characteristics with efficacy endpoints were evaluated. A previously developed risk score algorithm that includes HIV status, smear, sex, BMI, and the presence of cavities was used to calculate individual risk scores. Hard-to-treat participants were defined as those with risk scores greater than the third quartile of the risk-score distribution.
Results: Analysis included the 93 of 109 participants with positive baseline cultures, with 8 (9%) having unfavourable outcomes (6 were deaths during treatment and 2 were relapses during follow-up). Higher baseline BMI was associated with a lower incidence of unfavourable outcomes ($p< 0.05$). Median time to stable culture conversion was 3 months in patients with lower baseline disease burden (baseline TTP greater than the median of 16 days) compared to 4.5 months in patients with high baseline burden ($p< 0.01$). A linear model described longitudinal TTP. Baseline TTP and the slope of TTP varied among risk groups with higher baseline and steeper slopes in the low-risk group (median baseline: 26 days, slope: 1.75 days^{-1}) compared to the moderate- (16 days, 1.13 days^{-1}) and high-risk (11 days, 1.00 days^{-1}) group ($p< 0.005$).
Conclusion: Participants quiet hard-to-treat characteristics were associated with increased rate of unfavourable outcomes, delayed time to culture conversion and delayed bacterial clearance.

Figure 1. Risk groups predict individual trajectory of time to positivity. Raw TTP longitudinal profiles over six months of treatment stratified by risk group. Upper panels show the actual values of the MGIT assay over time, with lines representing the first quantile of the data, and lower panels show the percentage of patients with a censored measurement (TTP value ≥ 42).



755 EFFECTIVENESS OF DOLUTEGRAVIR IN PEOPLE ON RIFAMPIN-BASED TUBERCULOSIS TREATMENT

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Background: Tenofovir-lamivudine-dolutegravir (TLD) is the WHO-preferred first-line regimen for people with HIV, but drug-drug interactions between dolutegravir (DTG) and rifampin (RIF) require an additional 50mg DTG (TLD+50) in people receiving tuberculosis (TB)/HIV co-treatment. RIF is a key drug in TB treatment, but is a potent inducer of metabolizing enzymes and efflux transporters, which can markedly lower drug concentrations. There are limited data on the effectiveness of TLD+50 in people with TB/HIV from program settings.
Methods: We conducted a prospective, observational study at 12 sites in 6 countries (Haiti, Kenya, Malawi, South Africa, Uganda, Zimbabwe). Participants received concomitant TLD+50 and RIF-based TB treatment provided as standard of care by HIV and TB treatment programs. Primary outcome was HIV-1 RNA <1000 copies/mL (cpm) at end of TB treatment. New DTG resistance mutations were defined as those present at end of TB treatment but not present at start.
Results: From 11/2019–6/2021, we enrolled 91 participants with TB/HIV, including 75 ART-naïve participants (82%) starting TLD+50 after a median of 15 days on TB treatment, 10 ART-naïve participants (11%) starting TLD+50 and RIF together, 5 (5%) starting TB treatment and changing to TLD+50 after a median of 3.3y on TLD, and 1 (1%) starting RIF and TLD+50 after changing from EFV/3TC/TDF. Median age was 37y (IQR 32–43), 35% were female, 100% cis-gender, median CD4 count was 120 cells/mm^3 (IQR 50–295), 87% had HIV-1 RNA >1000 copies/mL. Two participants died during TB treatment (week 4 disseminated TB, week 12 suspected COVID-19), 1 interrupted TLD+50 due to jaundice; and 1 discontinued TB treatment due to drug-induced liver injury. Among 89 surviving participants, 6 were lost to follow-up and a further 10 had no HIV-1 RNA result due to missed or remote visits. Primary virologic outcome was therefore assessed in 73 (80%), of whom 69 (95%, Wald 95% CI 89–100%) had HIV-1 RNA ≤1000 cpm; 68 (93%) had HIV-1 RNA <200 cpm. No sex specific differences in viral suppression were observed. No DTG resistance mutations were detected among 4 participants with HIV-1 RNA >1000 cpm.
Conclusion: Concomitant RIF-containing TB treatment and TLD+50 was well-tolerated and achieved excellent viral suppression in a cohort of predominantly ART-naïve people with TB/HIV. These multi-country data from program settings support feasibility and effectiveness of current treatment approaches for TB/HIV co-infection.

756 DIFFERENTIATED SERVICE DELIVERY FOR PEOPLE COINFECTED WITH DRUG RESISTANT TB AND HIV

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Prospective study of Adherence in M/XDR-TB Implementation Science (PRAXIS) Research Group
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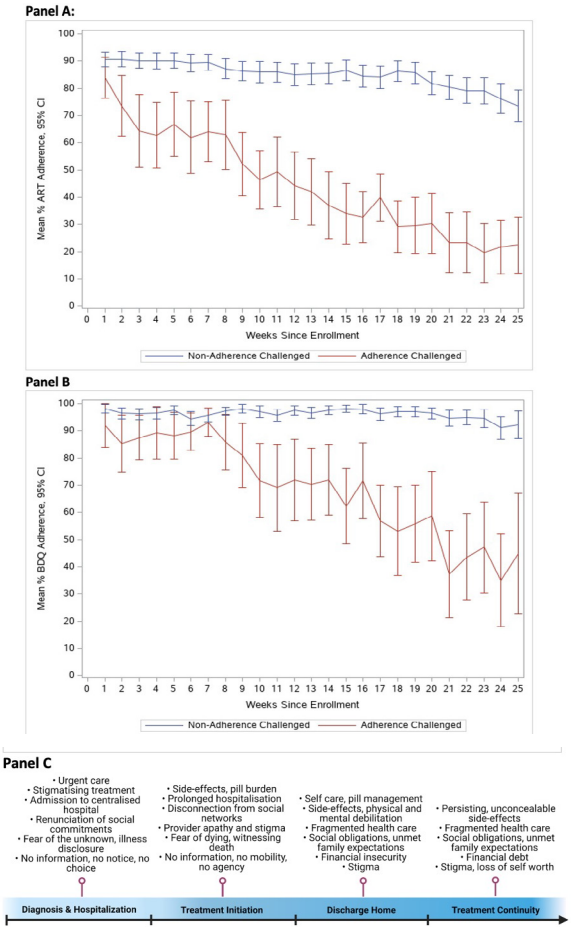
Background: For people living with HIV/AIDS, Differentiated Service Delivery (DSD) has focused on enhancing resilience, self-efficacy, and engagement. For people co-infected with HIV/AIDS and multidrug resistant tuberculosis (MDR-TB), particularly in subSaharan Africa, there are severe challenges associated with treatment, including stigma, social and structural barriers. We used empirical adherence data and qualitative research to identify longitudinal barriers to medication adherence to inform MDR-TB HIV DSD models.
Methods: Adults with MDR-TB and HIV initiating bedaquiline (BDQ) and receiving antiretroviral therapy (ART) in KwaZulu-Natal, South Africa were prospectively enrolled and followed through the end of MDR-TB treatment. Separate electronic dose monitoring devices (EDM) (Wisepill RT2000) measured BDQ and ART adherence through six months, calculated as observed versus expected doses aggregated at a weekly level. We defined severely adherence challenged as < 85% cumulative EDM measured doses of ART and BDQ. Longitudinal focus groups were conducted by trained staff and transcripts were analyzed thematically to describe early, middle, and late-stage treatment challenges.
Results: From November 2016 through February 2018, 199 participants with MDR-TB and HIV were enrolled and followed through treatment completion (median 17.2 months IQR 12.2–19.6). 12 focus groups were conducted. While the majority (83.2%, 166/199) maintained high adherence, a severely adherence challenged subpopulation (16.8%, 33/199) had a precipitous decline in mean BDQ adherence from 91.9% to 44.7% and mean ART adherence from 84.5% to 21.6% over six months (F1, Panel A, B). Qualitative analysis identified discrete treatment stages associated with specific barriers (F1, Panel C) which, when aligned with quantitative data, suggests that declining medication adherence may relate to psychosocial, behavioral, and structural barriers.
Conclusion: Based on these data, MDR-TB HIV DSD frameworks should 1) intensify support for severely adherence challenged subpopulations while adherent patients may require less intensive support, 2) address decreased adherence over time and 3) account for psychosocial, behavioral, and structural challenges linked to discrete treatment stages. DSD models that offer evaluation and intervention at key stages, tailored to needs of both vulnerable and adherent populations, have the potential to improve adherence and outcomes in MDR-TB HIV treatment.

Panel A: Weekly mean antiretroviral (ART) adherence with 95% confidence intervals calculated weekly based on observed versus expected electronic pill box opening through six month stratified by severe adherence challenged (<85% adherence). (N=199) Panel B: Weekly mean bedaquiline (BDQ) adherence with 95% confidence intervals calculated weekly based on observed versus expected electronic pill box opening through six month stratified by severe adherence challenged (<85% adherence). (N=199) Panel C: Qualitative stages of MDR-TB HIV treatment with thematically derived stage specific care & treatment challenges.



757 ACCELERATING TUBERCULOSIS PREVENTIVE TREATMENT AMONG TANZANIANS LIVING WITH HIV

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Background: People living with HIV (PLHIV) bear 20 times higher risk of acquiring tuberculosis (TB) compared to people without HIV. The World Health Organization recommends TB preventive treatment (TPT) for PLHIV to reduce this risk. However, according to the 2020 Global TB Report, only half of PLHIV were started on TPT globally in 2019, with the lowest coverage observed in low-income countries including Tanzania, where TPT provision is part of the standard of care for eligible PLHIV in Tanzania. We describe programmatic efforts to scale up TPT in 11 regions accounting for half of the 1.5 million PLHIV on ART in Tanzania.

Methods: Starting in 2018, PEPFAR, through the U.S. Centers for Disease Control and Prevention (CDC), supported the Government of Tanzania to accelerate TPT provision by: (1) training and mentoring healthcare workers, (2) integrating isoniazid into supply chain plans at the regional level, and (3) convening quarterly meetings at national and regional levels for program and supply chain monitoring and coordination. Additionally, CDC launched focused regional support interventions, with TPT among its priorities, aiming to facilitate real-time data-driven site monitoring, increased accountability, and on-the-ground coordination with local health authorities and implementing partners. We analyzed routine programmatic data reported in PEPFAR's data reporting system for fiscal years (FY) FY2018 through FY2021.

Results: The number of PLHIV of all ages who initiated TPT increased from 67,510 in FY2018 to 268,909 in FY2019. Despite coinciding with the COVID-19 pandemic, the initiation numbers in FY2020 were sustained at 264,465 and dropped by about one-third in FY2021 (182,823) compared to the previous year. TPT completion rates among those initiated also showed a positive trend; 38% in FY2018, 85% in FY2019, 90% in FY2020, and 91% in FY2021.

Conclusion: Our findings demonstrate substantial acceleration of TPT initiation and a significant increase in TPT completion rates over the four-year period in 11 regions in Tanzania. The policy of once-in-a-lifetime TPT for PLHIV means fewer people are eligible for TPT over time, which might account for lower numbers of PLHIV initiated on TPT in FY2021. Completion remained high among those who initiated TPT. The strategic shift focusing on capacity building, supply chain strengthening, and site-level monitoring may have contributed to the improvements in TPT initiation and completion.

758 LOWER TB INCIDENCE AMONG PWH AFTER PREVENTIVE TREATMENT IN HIGH-BURDEN MDR TB SETTING

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Background: Tuberculosis (TB) is the leading cause of morbidity and mortality among people with HIV (PWH) worldwide. The World Health Organization recommends six months of isoniazid to prevent TB disease among PWH. However, it is unclear how effective isoniazid TB preventive treatment (TPT) is in settings with high incidence of multidrug-resistant (MDR) TB — defined as TB that is resistant to at least isoniazid and rifampin. We assessed the relationship between isoniazid TPT and TB incidence among PWH in Ukraine, a high burden (31.0%) MDR TB setting, during 2018–2022.

Methods: We conducted a retrospective (January 2018 – February 2022) cohort analysis of the Ukraine national HIV and TB electronic case-based surveillance database, where all PWH are enrolled. TPT was categorized as complete if documentation confirmed adherence to >= 146 days of isoniazid, partial if 28–146 days, and none if < 28 days. TB incidence rates (cases per 100 person-years) and incidence rate ratios (IRRs) were calculated for each of the TPT completion categories using a Poisson model, adjusting for demographic and clinical variables.

Results: Of the 166,365 PWH, 123,884 (74.5%) included complete data on TPT duration and TB diagnosis. Overall, 24.7% completed TPT, 9.6% had partial completion, and 65.7% did not receive TPT. Adjusted TB incidence rate was 1.9, 2.8, and 5.0 among those that completed, partially completed (IRR 1.45), and did not receive TPT (IRR 2.58), respectively. Among PWH with newly diagnosed TB, drug resistance occurred in 21.9%, 20.4%, and 21.6% among those that completed, partially completed, and did not receive TPT, respectively.

Conclusion: In Ukraine, TB incidence showed a dose response relationship to TPT duration and was lowest in PWH who completed TPT. Multidrug resistance was commonly observed in this setting and comparable across TPT groups. These findings suggest TPT may benefit PWH in high-burden MDR-TB settings.

759 MONOCYTE-TO-LYMPHOCYTE RATIO AND HEMOGLOBIN LEVEL TO PREDICT TB AFTER ART INITIATION

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Background: Tuberculosis (TB) is an important cause of morbidity and mortality in people with HIV (PWH). A prediction test that accurately identified those at risk of active TB would allow targeted chemoprophylaxis. The monocyte to lymphocyte ratio (MLR) and hemoglobin level collected routinely in HIV care both display an ability to predict active TB development.

Methods: We previously identified an MLR threshold ≥ 0.23 optimally predicted incident TB after ART initiation. In this study, we used ACTG A5175 trial data as a validation cohort. We assessed the utility of baseline MLR and anemia severity, alone and in combination, for predicting incident TB in PWH in the first year after ART initiation. Participants starting ART were included in this analysis if they had no active TB at study entry or the 12 months before enrollment. Cox regression was used to assess associations of MLR and anemia severity with incident TB. Harrell's C index was used to describe single model discrimination and model prediction was compared using log-likelihood based methods.

Results: Total of 1,455 participants were included. Median (IQR) age was 34(29,41) years; baseline CD4 was 174(92,234) cells/mm^3; 1,246(86%) participants were from high TB burden countries and 48% were women. Fifty-four participants were diagnosed with TB within 1 year of ART initiation. Median time from ART start to TB diagnosis was 4.1 (IQR 1.3,8.4) months. The hazard ratio (HR) for incident TB was 1.77[95% confidence interval (CI); 1.01-3.07]; p = 0.04 for those with MLR ≥0.23 versus MLR < 0.23. Compared to non anemic participants, the HR for mild/moderate anemia was 3.35[95%CI; 1.78-6.29; p < 0.001] and 18.16[95%CI; 5.17-63.77; p < 0.001] for severe anemia. After combining parameters, there were small increases in adjusted HR (aHR) for MLR ≥0.23 to 1.83[95%CI; 1.05-3.18], and increasing degrees of anemia severity (aHR 3.38[95%CI; 1.80-6.35] for mild/moderate anemia and 19.09[95%CI; 5.43-67.12] for severe anemia, respectively). C indices (95%CI) were 0.57(0.51–0.63), 0.66(0.60–0.72) and 0.69(0.62-0.76) for MLR, anemia severity and both factors combined, respectively. The model AIC decreased from 762.34 for anemia severity alone to 759.56 after addition of MLR (P=0.03).

Conclusion: Addition of MLR to anemia severity improved prediction of incident TB. Routinely measured MLR and hemoglobin levels should be accessed at ART initiation to help identify those who would benefit from TB preventive interventions.

The Cox proportional hazard model and C index of MLR and anemia severity for incident tuberculosis among participants

Table. Cox proportional hazard model and C index of MLR and anemia severity for incident tuberculosis among participants

Model	Hazard Ratio (95% CI)	P-value	Harrell's C index	95% CI
1. MLR (≥ 0.23 vs < 0.23)	1.77 (1.02-3.07)	0.043	0.57	0.51 - 0.63
2. Anemia severity*			0.66	0.60 - 0.72
• Mild-Moderate anemia	3.35 (1.78-6.29)	<0.001		
• Severe anemia	18.16 (5.17-63.77)	<0.001		
3. MLR + Anemia severity*			0.69	0.62 - 0.76
• MLR	1.83 (1.05-3.18)	0.032		
• Mild-Moderate anemia	3.38 (1.80-6.35)	<0.001		
• Severe anemia	19.09 (5.43-67.12)	<0.001		

MLR: monocyte to lymphocyte ratio
Anemia severity*: mild (11.0-12.9g/dL men, 11.0-11.9g/dL women), moderate (8.0–10.9g/dL) and severe (<8.0g/dL).

760 IMMUNE OMIC PROFILES TO DISTINGUISH TUBERCULOSIS AMONG ADVANCED HIV ADULTS IN INDIA

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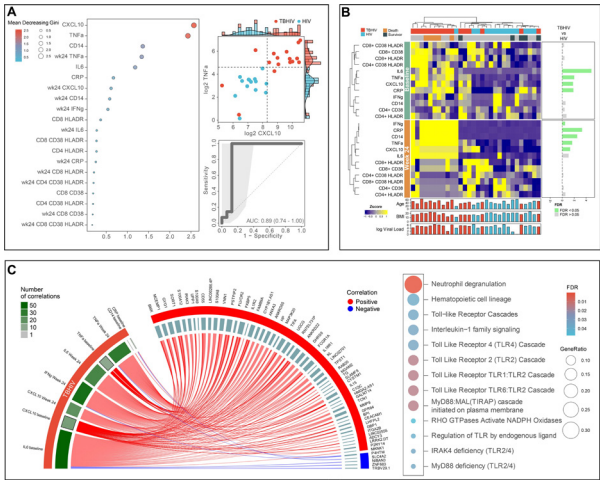
Background: Diagnosis of tuberculosis (TB) in people with HIV (PWH) with significant immunosuppression remains a challenge. Integration of flow cytometry, cytokine, and gene expression data is a promising approach for developing diagnostic TB biomarkers but such "multi-omic" analysis remains poorly explored.

Methods: We enrolled 30 adults with advanced HIV(CD4< 100cells/mm^3) in India; 16 with microbiologically confirmed active pulmonary TB and 14 without. Transcriptomics (RNA-seq), flow cytometry to track T-cell (CD4+/CD8+) activation markers (CD38/HLA-DR), and Luminex-based measurement of plasma cytokines/chemokines performed at baseline and week 24 of anti-TB therapy. Comparisons between HIV and TBHIV groups performed using the Mann-Whitney U test. Feature selection analysis with a random forest algorithm was employed to determine the most predictive variables for classification of HIV and TBHIV. Accuracy was depicted using c-statistics. Associations between measurements of biomarkers in different assays were assessed using Spearman correlation networks defined with False Discovery Rate < 0.05.

Results: Comparison between HIV and TBHIV did not show significant differences in the expression of CD38+HLADR+ on CD4+/CD8+ T-cells. Levels of CRP, CXCL10, IL6, CD14, and TNF were higher in TBHIV at baseline and week 24. Baseline levels of CXCL10 and TNF accurately identified TB cases with an AUC of 0.89. Age, BMI, and Viral load values did not directly influence cytokine levels. While examining relationships between protein, cellular markers, and overall profile of gene expression, we noted only TBHIV group exhibited statistically significant correlations. Pathway enrichment analysis uncovered a variety of processes associated with innate immunity, such as neutrophil degranulation and toll-like receptor cascades, hallmarked the transcriptional profile of TBHIV but not in HIV without TB(Fig1).

Conclusion: Circulating levels of TNF and CXCL10 are uniquely distinct among PWH with advanced disease with or without TB coinfection both at baseline and week 24 of anti-TB therapy. Integrative multi-omic analysis suggests a distinctive inflammatory profile is linked to the activation of key processes related to innate immunity. Major contributions of the findings presented are twofold as they (i) reveal parsimonious biomarker signatures highly accurate in identifying TB cases among PWH with advanced disease (ii) underscore biologic pathways that may further explore as therapeutic targets to reduce disease severity.

IMMUNE OMIC PROFILES TO DISTINGUISH TUBERCULOSIS AMONG ADVANCED HIV ADULTS IN INDIA



761 PERFORMANCE OF URINE XPERT ULTRA VS ALERE LAM FOR DIAGNOSING TB IN HIV IN-PATIENTS

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Background: Rapid urine-based TB diagnostics, including lateral flow urinary lipoarabinomannan (LF-LAM), reduce mortality in HIV-positive in-patients. *Xpert MTB/RIF Ultra* (Ultra) has improved sensitivity on sputum, and may be a useful urine-based diagnostic test for disseminated TB.

Methods: We conducted a cross-sectional diagnostic accuracy study at two hospitals in East London, South Africa. From August 2018 - February 2019, consecutive HIV-positive adults admitted with ≥1 WHO TB symptom or clinical concern for TB were enrolled and underwent TB cultures of blood, sputum, and urine. Urine was obtained for bedside urine Alere LF-LAM testing and Ultra was performed on the pellet of 15ml centrifuged urine. Vital status was assessed by phone call at 12 weeks. Diagnostic classifications were: 'definite TB' (positive TB culture or molecular test), 'probable TB' (clinico-radiological features of TB and response to TB therapy), and 'not TB' (remained well without TB therapy). The primary outcome was sensitivity of urine Ultra for definite TB. We also calculated diagnostic yield (proportion positive tests among TB cases) and compared the diagnostic performance of urine-based tests and sputum Ultra.

Results: 238 participants were enrolled. Median age was 39 years (IQR 32- 48), 124 (52%) female, median CD4 count 76 cells/mm^3 (IQR 22- 203). Definite TB was diagnosed in 62 (26%) and either definite or probable TB in 92 (39%). Diagnostic yields for definite TB were 34% (n=21) for sputum Ultra, 45% (n=28) for urine LF-LAM, 68% (n=42) for urine Ultra, and 73% (n=45) for urine LF-LAM and urine Ultra combined. Respective yields for definite plus probable TB were 23% (n=21), 39% (n=36), 57% (n=52), and 64% (n=59). The sensitivity and

specificity using definite TB as a reference were 55% and 90% for urine LF-LAM, and 70% and 100% for urine Ultra, respectively. Positive urine Ultra results were 68.5% (n=37) rifampicin susceptible, 9.3% (n=5) resistant, and 22.2% (n=12) indeterminant, with no discordancies with culture or sputum Ultra rifampicin susceptibility results.

Conclusion: Combined urine testing (Ultra + LF-LAM) identified three-quarters of HIV-positive medical in-patients with definite TB. Urine Ultra had improved sensitivity and specificity compared to LF-LAM and has added benefit of providing rapid rifampicin susceptibility results.

762 CSF IMMUNE RESPONSE ASSOCIATED WITH FUNGAL BURDEN IN CRYPTOCOCCAL MENINGITIS

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Background: Cryptococcal meningitis causes substantial mortality in persons with advanced HIV. The cerebrospinal fluid (CSF) cellular immune response in cryptococcal meningitis remains poorly defined. We used flow cytometry to characterize the immune response in CSF and assessed correlations with baseline cryptococcal CSF fungal burden.

Methods: CSF was obtained from 20 patients with HIV-associated cryptococcal meningitis diagnosed by CSF cryptococcal antigen and quantitative CSF fungal culture. We centrifuged CSF and fixed cells within <1 hour of collection. We stained fixed CSF cell pellets with a repertoire of antibodies to identify innate and adaptive immune cells and analyzed cells on a 13-color flow cytometer. We calculated absolute cells/mL of CSF by dividing sample cell counts by the pre-centrifuged CSF volume. We determined the correlation between the CSF cellular subsets and cryptococcal CSF fungal burden by Spearman's rank testing. We performed analyses using FlowJo v10.8.1 and GraphPad Prism.

Results: In blood, the median CD4 count was 25 cells/μL (range: 3-380 cells/uL, IQR 41.5). In CSF, the median Cryptococcus quantitative culture was 17,875 CFU/mL (range: 0-985,000 CFU/mL), and the median absolute white cells (CD45+) was 17,303 cells/mL, with 111 CD4+ cells/mL and 2,531 CD8+ cells/mL. We found a moderate negative correlation between baseline CSF quantitative culture and absolute CSF white cells/mL (Spearman rho= -0.58, P=0.007). Other immune cell subsets also showed a negative correlation including: CD8+ T cells (rho= -0.40), monocytes (rho= -0.35), natural killer cells (rho = -0.35), granulocytes (rho = -0.31), and CD4+ T cells (rho= -0.20) with CSF quantitative culture. B cells were not correlated with CSF culture burden in our population (rho = 0.03). Additionally, when assessing CD45-neg CSF cells (probable yeasts) by flow cytometry, we found a positive correlation between $\log_{10}$CD45-neg cells/mL and $\log_{10}$ CSF CFU/mL (Pearson's r = 0.45; P= 0.047).

Conclusion: Our findings suggest a higher CSF fungal burden correlates with a weakened immune response at the site of infection. A subset of CSF CD45-neg cells are probable Cryptococcus yeasts; however, further investigation is required for the future validation of CD45 via flow cytometry as a real-time marker of fungal burden instead of quantitative CSF culture that can take up to 10 days.

763 COST-EFFECTIVENESS OF CRAG SCREENING FOR PLHIV WITH ADVANCED HIV DISEASE IN MALAWI

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Background: Cryptococcal meningitis (CM) remains a leading cause of death among PLHIV; diagnosis and treatment of asymptomatic cryptococcal disease can prevent progression to symptomatic CM. We projected the clinical impact and cost-effectiveness of cryptococcal antigen (CrAg) screening with pre-emptive fluconazole therapy in PLHIV with CD4< 200/μL and no meningitis symptoms initiating ART in Malawi.

Methods: We used the validated CEPAC model to examine 2 strategies at ART initiation: 1) no CrAg screening and 2) a serum CrAg screening test. The simulated population was 51% female, age >15y (mean age 37y), mean CD4 97/μL, including 4% with cryptococcal infection (31%, asymptomatic CM; 69% cryptococcemia alone). Progression to symptomatic CM occurs more frequently in asymptomatic CM (80% without pre-emptive fluconazole (FLU; $50), 25% with FLU) vs cryptococcemia (7% without FLU, 0% with FLU). Serum CrAg (Se, 97.6; Sp 98.1; $4.70/test) has 95% testing uptake and 80% pre-emptive fluconazole initiation. PLHIV who progress to symptomatic CM receive amphotericin B/fluconazole (AmB/FLU, 35% mortality; $590). Model outcomes included 1y survival, CM deaths, life expectancy, costs, and incremental cost-effectiveness ratios (ICER, $/year of life saved (YLS)); we considered ICERs < $640 (Malawi 2021 *per capita* GDP) to be cost-effective. We evaluated single-dose liposomal AmB (LAmB) with flucytosine/FLU (17% mortality; $1100) as preferred CM treatment. We evaluated key input parameters in sensitivity analyses.

Results: Compared with no CrAg screening, CrAg screening would result in 23.6% reduction in CM deaths, 0.10 years of life saved (YLS), and would be cost-effective (ICER, $270/YLS). In people with asymptomatic cryptococcal disease, CrAg screening would reduce CM deaths by 39.7%, resulting in 1.80 YLS. Screening remained cost-effective with LAmB-based CM treatment. In sensitivity analysis, screening was cost-effective at 1x per capita GDP even at asymptomatic cryptococcal prevalence < 1% or when linkage to FLU pre-emptive therapy was >50%. Sex at birth; LAmB cost; and CrAg cost, sensitivity, and specificity did not substantially impact cost-effectiveness.

Conclusion: Serum CrAg screening at ART initiation would offer substantial clinical benefits and would be cost-effective in Malawi. Screening would likely remain cost-effective at lower prevalence and linkage, and as LAmB-based CM treatment becomes more widely available.

Table 1. Clinical benefits, costs, and cost-effectiveness of CrAg screening among people with Advanced HIV Disease (AHD) in Malawi.

	Strategy	Survival at 1y (%)	Reduction in CM deaths (%)	Total LYs [undisc.] [a]	Total LYs [disc.] [b]	Cost, $ [disc.]	ICER, $/YLS*
Base case							
AmB/FLU to treat CM	No CrAg screening	89.0	--	17.99	11.64	2070	--
	CrAg screening	89.5	23.6	18.09	11.70	2090	270
Cryptococcal disease cohort							
AmB/FLU to treat CM	No CrAg screening	62.7	--	11.34	7.40	1470	--
	CrAg screening	72.9	39.7	13.14	8.56	1690	190
Scenario analysis							
LAmB/5FC/FLU to treat CM	No CrAg screening	89.0	--	18.00	11.64	2070	--
	CrAg screening	89.5	23.3	18.09	11.70	2090	270
Sensitivity analyses							
Prevalence of asymptomatic cryptococcal disease (base case = 4%)							
1%	No CrAg screening	89.8	--	18.20	11.77	2090	--
	CrAg screening	90.0	12.6	18.24	11.79	2100	380
8%	No CrAg screening	87.9	--	17.71	11.46	2040	--
	CrAg screening	88.8	29.5	17.88	11.57	2070	240
Linkage to pre-emptive fluconazole after CrAg screening (base case = 80%)							
50%	No CrAg screening	89.0	--	17.98	11.64	2070	--
	CrAg screening	89.3	12.7	18.05	11.67	2080	310
95%	No CrAg screening	89.0	--	17.98	11.64	2070	--
	CrAg screening	89.5	28.8	18.11	11.71	2090	270

* We considered ICERs <$640 (Malawi 2021 *per capita* GDP) to be cost-effective.
[a] Lifetime horizon. [b] Annual discount rate of 3%.
Abbreviations: CrAg: cryptococcal antigen; CM: cryptococcal meningitis; LY: life year; undisc: undiscounted; disc: 3% discounted; ICER: incremental cost-effectiveness; YLS: years of life saved; AmB: amphotericin B; FLU: fluconazole; LAmB: liposomal ambisome; 5FC: flucytosine.

764 MYCO/F LYTIC VS STANDARD BLOOD CULTURES IN FUNGAL DETECTION IN AIDS PATIENTS

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Background: Invasive mycoses are prevalent in hospitalized patients with advanced HIV disease, but fungal blood culture is rarely performed in Southeast Asia. The standard 5-day incubation of the BD BACTEC or BACT/ALERT blood cultures misses slow-growing fungi endemic in Southeast Asia like *Talaromyces marneffei* (Tm) and *Histoplasma capsulatum* (Hc). We report preliminary results of an on-going multi-center study comparing the use of Myco/F Lytic blood culture with the standard BACTEC and BACT/ALERT systems in detecting invasive mycoses in patients with advanced HIV disease.

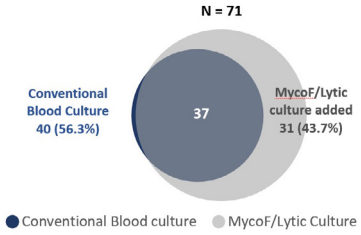
Methods: We prospectively enrolled adult patients with CD4 ≤ 100 cells/μL or WHO stage III or IV disease, were not on ART or were on ART for ≤ 3 months or >12 months, who were hospitalized at the National Hospital for Tropical Diseases (NHTD) in Hanoi and the Hospital for Tropical Diseases in Ho Chi Minh City. Myco/F Lytic and standard blood culture were performed for all study participants. Incubation was up to 5 days and 42 days for standard bottles and Myco/F Lytic bottle, respectively. For all positive bottles, microscopy with Gram and Giemsa stains, followed by standard MALDITOF identification and fungal

sub-culturing on SDA were performed to demonstrate dimorphism. The two culture procedures were compared for the number of positive fungal blood cultures using Student's t-tests, and culture turnaround time was described.

Results: We recruited 319 eligible patients between 22 Feb 2021 and 31 May 2022. A total of 71 patients (22.3%) had a fungal pathogen detected in blood culture: 59/71 cases (83.1%) had Tm; 06/71 cases (8.5%) had Hc, and 06/71 cases (8.5%) had *C. neoformans*. Of the 71 fungal infections, the standard blood cultures only detected 40 (56.3%) cases while Myco/F Lytic blood culture detected 68 (95.8%) cases. The median time to detection of Tm cases and Hc cases by Myco/F Lytic blood culture were 13 days (IQR 8 – 17.5) and 31 days (IQR 23.5 – 45.5), respectively.

Conclusion: Invasive mycoses were prevalent in 22.3% of hospitalized patients with advanced HIV disease. Tm was most prevalent (83/1), followed by Hc and Cryptococcus (each 8.5%). Myco/F Lytic blood culture detected 25 additional Tm cases and all 6 Hc cases. A total of 43.7% of infections would have been missed by standard blood cultures. Our data demonstrate the need to urgently implement MycoF Lytic blood culture system into routine diagnostic for hospitalized patients with advanced HIV disease in Southeast Asia.

Venn diagram demonstrating the detection of invasive mycoses by the standard versus MycoF Lytic blood culture systems



765 MULTI-CENTER PROSPECTIVE VALIDATION STUDY OF A NOVEL ANTIGEN ASSAY FOR TALAROMYCOSIS

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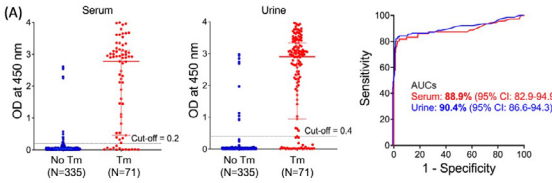
Background: Talaromycosis – caused by the dimorphic fungus *Talaromyces marneffei* (Tm) endemic in Southeast Asia - is a leading cause of death in patients with advanced HIV disease (AHD). Blood culture is the mainstay of diagnosis but is only positive during late-staged infection and can take up to 28 days, leading to delayed treatment and high mortality. We report interim results of an ongoing multi-center diagnostic validation study of a novel Tm-specific Mp1p antigen enzyme immunoassay (EIA) for diagnosis of talaromycosis.

Methods: We prospective recruited hospitalized adult patients with AHD (CD4 < 100 cells/µL or WHO stage III/IV disease) who were ART-naïve or on ART for ≤3 months or >12 months at the National Hospital for Tropical Diseases in Hanoi and the Hospital for Tropical Diseases in Ho Chi Minh City. Mp1p EIA was performed on serum and urine samples at enrollment for all patients. Talaromycosis is diagnosed by conventional blood culture for all patients, alongside microscopic examination and cultures of skin lesions, lymph node, bone marrow or other body fluids as clinically indicated. We followed patients monthly over 6 months for development of culture-confirmed talaromycosis.

Results: 426 patients were recruited between Feb 2021 and July 2022 (follow up ongoing). Talaromycosis was diagnosed in 16.7% (71/426). Compared to the reference standard of culture-confirmed talaromycosis from any specimen over the 6-month follow-up period, the Mp1p EIA has a preliminary sensitivity of 84.5% (60/71, 95% CI: 73.5-91.4), specificity of 94.9% (337/355, 95% CI: 92.0-96.9), positive predictive value of 76.9% (95% CI: 65.7-85.4), and negative predictive value of 96.8% (95% CI: 94.2-98.3). The Mp1p EIA was significantly more sensitive than conventional blood culture: 84.5% (60/71) vs. 66.2% (47/71) patients (P=0.021, McNemar's Chi-Square). Sensitivities were similar when tested in serum vs. urine samples (81.7%), but urine had a higher specificity (97.5% vs. 95.8%).

Conclusion: We report a high prevalence of talaromycosis (16.7%) in hospitalized patients with AHD. The Mp1p EIA is superior to blood culture in sensitivity and his highly specific, making it an excellent rapid rule-in test for talaromycosis, allowing early antifungal treatment to reduce mortality. The assay performs very well in urine sample, potentially unlocking the ability to diagnose and screen for disease using a non-invasive sample.



(B)

	Serum or Urine (N=426)		Serum (N=426)		Urine (N=426)	
	No Tm (N=355)	Tm (N=71)	No Tm (N=355)	Tm (N=71)	No Tm (N=355)	Tm (N=71)
TmAg Pos	18	60	15	58	9	58
TmAg Neg	337	11	340	13	346	13
Sensitivity	84.5% [73.5-91.6]		81.7% [70.4-89.5]		81.7% [70.4-89.5]	
Specificity	94.9% [92.0-96.9]		95.8% [93.0-97.5]		97.5% [95.1-98.8]	
PPV	76.9% [65.7-85.4]		79.5% [68.1-87.7]		86.6% [75.5-93.3]	
NPV	96.8% [94.2-98.3]		96.3% [93.6-97.9]		96.4% [93.7-98.0]	

Figure 1 A) OD distribution of Mp1p in patients with and without Tm in serum and urine samples and the corresponding diagnostic ROC curves. **B)** Clinical performance in paired serum and urine samples of 426 patients with advanced HIV diseases

766 QUANTIFIED PRENATAL PrEP EXPOSURE AND PERINATAL OUTCOMES AMONG KENYAN WOMEN

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Background: Safety studies of prenatal PrEP use to date have relied on maternal self-report of PrEP adherence which may not accurately measure infant PrEP exposure. We evaluated perinatal outcomes following maternal PrEP use confirmed with tenofovir-diphosphate (TFV-DP) concentrations in dried blood spots (DBS).

Methods: Data were analyzed from a subset of women enrolled in a cluster RCT (NCT03070600) evaluating PrEP delivery strategies at 20 clinics in Western Kenya. HIV-negative women were enrolled and offered PrEP during pregnancy and followed through 9 months postpartum regardless of PrEP status. DBS samples were collected at every visit from women who initiated PrEP. A subset of women who self-reported PrEP use in the prior 30 days at antenatal visits were randomly selected and TFV-DP levels were measured in DBS using liquid chromatography/tandem mass spectrometry. Women who were randomly selected but did not have detectable TFV-DP were excluded. PrEP-exposure during pregnancy was defined as having detectable TFV-DP in DBS. Outcomes among women with and without prenatal PrEP exposure were compared, adjusting for partner HIV status, maternal age, gestational age, and syphilis status.

Results: Overall, 3608 women were included in the analysis; 3505 women were PrEP-unexposed and 103 PrEP initiators were randomly selected and had detectable TFV-DP during pregnancy (18% of all PrEP initiators). Median maternal age at enrollment was 24 years (IQR: 21-28), median gestational age was 24 weeks (IQR: 21-28) and 27% were primigravida. Compared to PrEP-unexposed women, women with confirmed PrEP exposure during pregnancy experienced similar frequencies of stillbirth (4% v 3%, aPR=1.03, 95% CI:0.12-8.93, p: 0.98), preterm birth (16% v 19%, aPR=0.92, 95% CI:0.58-1.47, p: 0.73), low birthweight (0% vs. 2%, p: 0.18), small-for-gestational-age (13% v 10%, aPR=1.41, 95% CI:0.78-2.54, p=0.26), and neonatal death (1% v 2% aPR=0.69, 95% CI:0.09-5.26, p: 0.72). At 9 months, there was no association between prenatal PrEP exposure and frequency of underweight (p=0.68), stunting (p=0.39), or of wasting (p=0.79); results were similar at 6 weeks and 6 months. Among women with any detectable TFV-DP, frequency of adverse perinatal outcomes were similar by TFV-DP levels based on PrEP dosing benchmarks (Table 1).

Conclusion: Similar to prior safety data that relied on self-reported PrEP use, we found no differences in adverse perinatal outcomes among Kenyan women with prenatal PrEP exposure confirmed with a biologic measure.

Table 1. Birth and infant growth outcomes by confirmed prenatal PrEP exposure status

Table 1. Birth and infant growth outcomes by confirmed prenatal PrEP exposure status

		PrEP Unexposed n=3505	Any PrEP Exposure n=103	P*	<2 pills/week^ n=31	2-6 pills/week^ n=61	7 pills/week^ n=11	P§
Birth Outcomes, n (%)								
Miscarriage		10(1)	0(0)	0.58	0(0)	0(0)	0(0)	-
Stillbirth		26 (3)	1(4)	0.83	0(0)	1(8)	0(0)	0.55
Preterm Birth		661 (19)	16 (16)	0.35	4 (13)	10 (16)	2 (18)	0.88
Congenital Malformation		16 (1)	0(0)	0.49	0(0)	0(0)	0(0)	-
Low Birth Weight (<2.5 kg)		50 (2)	0(0)	0.18	0(0)	0(0)	0(0)	-
Small for Gestational Age		212(10)	10(13)	0.32	2(9)	7(16)	1(11)	0.73
Neonatal death		55 (2)	1(1)	0.63	0(0)	1(2)	0(0)	0.70
Infant growth outcomes#, n (%)								
6-weeks	Underweight	65 (3)	0(0)	0.17	2(3)	0(0)	0(0)	0.56
	Stunting	201(10)	5(9)	0.81	10(14)	2(6)	1(17)	0.44
	Wasting	121(6)	4(7)	0.71	2(3)	2(6)	2(0)	0.65
6-months	Underweight	59 (3)	1(2)	0.51	1(2)	1(3)	0(0)	0.88
	Stunting	150 (9)	7(13)	0.32	4(7)	5(13)	1(17)	0.47
	Wasting	67 (4)	0(0)	0.14	1(2)	0(0)	0(0)	0.69
9-months	Underweight	67 (4)	2 (3)	0.78	2 (3)	1(3)	0(0)	0.89
	Stunting	157 (9)	2(3)	0.11	5 (8)	2 (5)	0(0)	0.67
	Wasting	60 (4)	3(5)	0.57	1(2)	2(5)	0(0)	0.46

*Fisher's exact comparing any PrEP exposure to PrEP unexposed
^TFV concentrations were classified into categories according to dosing benchmarks from directly observed pharmacokinetic studies among pregnant in the IMPAACT 2009 study (Stranix-Chibanda et al. 2021)
§Fisher's exact comparing dosing benchmark categories
#Underweight, stunting, and wasting were defined as z-score<-2 calculated using WHO standards of weight-for-age, height-for-age, and weight-for-height z-scores

767 HIGH ACCEPTABILITY OF STI TESTING AND EPT AMONG PREGNANT KENYAN WOMEN INITIATING PrEP

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Background: Sexually transmitted infections (STIs) are common among women who use PrEP in Kenya. Consequences of STIs are exacerbated in pregnancy; when infections are detrimental to both women and their infants. Few data are available on the burden of STIs among pregnant PrEP users.
Methods: We analyzed data from an ongoing RCT enrolling pregnant women at high risk of HIV newly initiating PrEP at 5 antenatal clinics in Western Kenya (NCT04472884). All participants were HIV-negative, ≥18 years, initiating PrEP that day within routine antenatal care, screened for syphilis per national guidelines, and had high HIV risk scores (corresponding to 8.9 HIV infections per 100 person-years). From February to September 2022, women at a subset of facilities were offered chlamydia and gonorrhea (CT/NG) testing using Xpert CT/NG® with same-day results. Women diagnosed with CT or NG were offered immediate directly observed treatment (DOT) and expedited partner therapy (EPT) as per the national guidelines.
Results: As of September 2022, 237 HIV-negative pregnant women newly initiating PrEP were enrolled at a median gestational age of 27 weeks (IQR 25-29). The median age of women was 26 years (IQR 22-30), most women were married (73%), and 15% reported a previous pregnancy loss. Overall, 3% of women had syphilis, and 2% reported having a partner known to be living with HIV; 92% reported unknown partner(s) HIV status. Among women offered CT/NG testing, all accepted testing, and the CT prevalence was 8% while NG prevalence was 5%; one participant had syphilis and NG, but no other co-infections were detected. Among women with any STI, only 14% reported STI symptoms (e.g., abnormal vaginal discharge and/or vulvar burning/itching). Frequency of having any STI was higher among women < 20 years compared to women ≥20 years (20% vs. 4%, p=0.002). All participants with STIs accepted DOT while 88% of women with STIs accepted EPT for their partners. One month after accepting EPT, all women had dispensed EPT to male partners and all partners accepted—no social harms were reported.
Conclusion: In our study among pregnant women at high risk for HIV and taking PrEP, STIs are relatively common, especially among younger women, and frequently asymptomatic. CT/NG testing and EPT is highly acceptable and integrating CT/NG screening for pregnant women on PrEP may be a high-yield intervention with benefits for women and their infants, and partners of women testing positive for STIs.

768 INTEGRATING PrEP INTO ANTENATAL CARE FOR HIV-NEGATIVE PREGNANT WOMEN IN SOUTH AFRICA

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Background: HIV incidence is high during pregnancy and postpartum. Oral PrEP was introduced in South Africa in 2016 and guidelines were updated in 2021 to include PrEP for pregnant and postpartum women.
Methods: The PrEP in pregnancy and postpartum (PrEP-PP) study is an observational cohort in one public health clinic in Cape Town, South Africa. We recruited pregnant women not living with HIV attending their first antenatal care (ANC) visit between August 2019 and October 2021. Study criteria included pregnant women: = >16 years old; confirmed HIV-negative; intending on giving birth in Cape Town; without contraindications to PrEP. We enrolled consecutive eligible, consenting women (N=1200) and followed up through 12-months postpartum. HIV counselling and testing was offered, followed by HIV prevention counseling, including on safety/effectiveness of PrEP and offered PrEP. We evaluate PrEP initiation, continuation and risk factors of discontinuation with multivariate logistic regression.
Results: We screened 2448 pregnant women without HIV at their first ANC visit, 2039 (61%) were interested in study participation, 409 (12%) declined participation. Of those interested and screened (n=2039), 839 (41%) were ineligible and 1200 (59%) were eligible and enrolled. Of those enrolled, 1013 (84%) accepted a PrEP prescription at first ANC visit and 187 (16%) did not. Among women who accepted a PrEP prescription at enrolment, 829 (82%) returned at 1 month and confirmed they had initiated PrEP. Of 829 women who initiated PrEP, 76% returned and received a repeat prescription at 1 month, 58% at 3 months, 44% at 6 months, and 35% at 9 months (Table 1). Of the 187 women who did not accept a PrEP prescription at enrolment, 104 (56%) returned and initiated PrEP sometime during their follow-up visits and 83 (7%) never started PrEP by the 9-month visit. Risk factors associated with PrEP discontinuation compared to PrEP persistence at 9 months included perceived low risk of HIV at baseline (aOR=1.56; 95% CI=1.03, 2.36) and earlier gestational age at baseline (aOR=0.55; 95% CI=0.41, 0.72) adjusted for age.
Conclusion: Despite high PrEP initiation at first ANC visit, almost one-fifth did not return for the 1-month refill visit, and < 50% continued after 6 months when all were in postpartum period. A subset of women started PrEP in postpartum period, or restarted PrEP in postpartum. There is an urgent need for PrEP integration into antenatal and postpartum care including interventions to improve PrEP continuation.

Table 1. PrEP continuation in pregnant and postpartum women in antenatal and postpartum care in Cape Town, South Africa (n=829)

	1 month visit N (%)	3 months visit N (%)	6 months visit N (%)	9 months visit N (%)
Continued with PrEP	631 (76)	481 (59)	345 (43)	273 (35)
Censored for reasons given**	8 (1)	12 (1)	28 (3)	6 (1)
Discontinued taking PrEP	52 (6)	59 (7)	27 (3)	129 (16)
Missed visits	138 (17)	190 (23)	349 (43)	302 (39)
Restarted PrEP	-	79 (10)	60 (7)	73 (9)

769 PrEP CONTINUATION AMONG PERI-CONCEPTION, PREGNANT, AND LACTATING WOMEN IN KENYA

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Background: Pregnant and breastfeeding persons living in high HIV prevalence settings are a priority population for oral pre-exposure prophylaxis (PrEP) for HIV prevention, due to disproportionally high risk of HIV acquisition during pregnancy and postpartum periods. Data are limited on PrEP use during peri-conception, pregnancy, and breastfeeding periods.
Methods: Data are from the Partners Scale-Up Project (NCT03052010), a stepped-wedge cluster randomized pragmatic trial to catalyze scale-up of PrEP delivery integrated in 25 public HIV clinics in Kenya. We examined the pattern and relation between PrEP continuation and fertility intentions, pregnancy and breastfeeding status during the first year of PrEP.
Results: A total of 2640 women initiated PrEP: median age was 31 years [IQR 24-36], most (80%) were in serodifferent relationships, 44% reported inconsistent condom use, and 12% reported multiple sex partners. Overall, 11% were pregnant, and 16% were breastfeeding; among non-pregnant women at baseline (n=1319), 15% were actively trying to conceive, 25% had

future pregnancy intention, and 33% had no pregnancy intention. Among all women, PrEP continuation at 1, 3, and 6 months was 59%, 45%, and 36%, respectively, and did not differ by breastfeeding or pregnant status. At 1, 3 and 6 months, PrEP continuation rates for women who were neither pregnant nor breastfeeding were 59%, 43%, and 35%; pregnant: 65%, 49%, and 35%; breastfeeding: 59%, 42%, and 34%, respectively ($p > 0.05$ for all comparisons). Among non-pregnant women at baseline, continuation was higher for those actively trying to conceive versus those with future conception plans and those with no plans for conceive: 70%, 61%, and 58% at month 1; 55%, 44%, and 44% at month 3; and 46%, 34% and 37% at month 6, respectively ($p <= 0.01$ for all comparisons).

Conclusion: In this large real-world PrEP implementation program in Kenya, intention to conceive was associated with better continuation on PrEP and pregnancy and breastfeeding periods had similar continuation patterns on PrEP as non-pregnant periods.

770 PrEP LEVELS STRONGLY CORRELATED IN HAIR AND DBS DURING PREGNANCY AND POSTPARTUM

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Background: Lower tenofovir (TFV) & metabolite concentrations have been observed in plasma and dried blood spots (DBS) among women during pregnancy compared to non-pregnant periods. Hair TFV levels, which measure long-term adherence, may be less affected by physiologic changes during pregnancy that can influence blood-based measures. To date, PrEP levels have not been compared in hair and DBS during pregnancy and postpartum.

Methods: The PrEP Implementation for Mothers in Antenatal Care Study evaluated PrEP delivery strategies for pregnant women who were followed 9-months postpartum. Hair and DBS samples were collected at visits from a subset of women who reported using PrEP in the last 30 days. PrEP drug levels were measured using liquid chromatography/tandem mass spectrometry. The correlations between TFV levels in hair and tenofovir-diphosphate (TFV-DP) levels in DBS were calculated using the Spearman coefficient. Median hair TFV levels were calculated based on benchmarks for PrEP dosing in DBS among pregnant/postpartum women in the IMPAACT 2009 study and hair benchmarks in non-pregnant women.

Results: Overall, 34 hair-DBS paired samples were evaluated; 12 (35%) from pregnancy visits at a median of 32 weeks gestation and 22 (65%) from postpartum visits at a median of 3.5 months since birth. Median time since PrEP initiation was 18 weeks (IQR 7-33) at sample collection. TFV levels in hair were strongly correlated with TFV-DP levels in DBS ($r=0.77$, $p<0.001$), with stronger correlation postpartum ($r=0.82$, $p<0.001$) compared to pregnancy ($r=0.57$, $p=0.05$). Based on DBS benchmarks, 44% of DBS samples had TFV-DP levels indicative of ≥2 doses/week; 41% of hair samples had TFV levels indicative of ≥2 doses/week based on benchmarks from non-pregnant women. Median hair TFV levels for women who took < 2 and ≥2 doses/week were 0 ng/mg (IQR 0-0.006, n=19) and 0.035 ng/mg (0.021-0.039, n=15), respectively, based on DBS benchmarks; results were similar by pregnancy status (0.029 ng/mg pregnancy vs. 0.035 ng/mg postpartum, $p=0.37$, Table 1).

Conclusion: Our findings suggest that hair PrEP measures are strongly correlated with DBS and may not need adjustment for PK differences over the perinatal period when used as adherence metrics. These data suggest an advantage of using hair measures for PrEP adherence during pregnancy and postpartum over blood-based measures which are more influenced by physiologic changes during the perinatal period.

Table 1. Tenofovir hair levels among women enrolled in the PrEP Implementation for Mothers in Antenatal Care Study (NCT03070600) during pregnancy and postpartum, by dosing benchmarks established in dried blood spots (DBS) and hair.

		Median (IQR)			
		Based on DBS benchmarks [1]		Based on hair TFV benchmarks [2]	
Pregnancy status	PrEP benchmarks (doses/week)	No. of hair samples	TFV hair levels (ng/mg)	No. of hair samples	TFV hair levels (ng/mg)
Overall	<2	19	0.000 (0-0.006)	20	0.000 (0-0.006)
	2-7	15	0.035 (0.021-0.039)	14	0.035 (0.03-0.04)
Pregnant	<2	7	0.000 (0-0.005)	9	0.000 (0-0.006)
	2-7	5	0.029 (0.01-0.038)	3	0.038 (0.033-0.039)
Postpartum	<2	12	0.003 (0-0.007)	11	0.000 (0-0.006)
	2-7	10	0.035 (0.029-0.041)	11	0.035 (0.03-0.039)

[1] TFV hair concentrations were classified into categories according to dosing benchmarks established in DBS from directly observed pharmacokinetic studies among pregnant and postpartum women in the IMPAACT 2009 (*Stranix-Chibanda* et al. 2021)

[2] TFV hair concentrations were classified into categories according to dosing benchmarks established in hair from directly observed pharmacokinetic studies among non-pregnant women (*Liu* et al. 2014 and *Koss* et al. 2018) as benchmarks for pregnant women are unavailable

771 LONGITUDINAL PrEP ADHERENCE AMONG KENYAN WOMEN WHO INITIATED PrEP DURING PREGNANCY

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Background: PrEP is scaling up among pregnant and postpartum women in Kenya, yet few longitudinal data exist on PrEP adherence in this population. We evaluated PrEP adherence measured via tenofovir-diphosphate (TFV-DP) concentrations in dried blood spots (DBS) collected from Kenyan women who initiated PrEP during pregnancy and were followed postpartum.

Methods: We prospectively analyzed data from a subset of participants in the PrIMA Study (NCT03070600) who enrolled during the 2nd trimester, initiated PrEP during pregnancy, and were followed through 9-months postpartum. At follow-up visits (monthly in pregnancy; 6 weeks, 6 months, 9 months postpartum), self-reported PrEP use was assessed and DBS were collected. Among a random subset of participants, DBS quantifying TFV-DP concentrations were tested from all visits with any self-reported PrEP use in the last 30 days. TFV-DP benchmarks were defined by thresholds from directly observed studies (IMPAACT 2009) among women in the 2nd trimester of pregnancy and postpartum.

Results: Overall, 198 participants met inclusion criteria for this analysis and were randomly selected (28% of all PrEP initiators in PrIMA); each participant contributed a median of 3 visits to the analysis (IQR 2-4). The median gestational age at PrEP initiation was 27 weeks (IQR 22-30), 91% of participants were married, and 19% had a partner known to be living with HIV. Among visits where participants continued with PrEP (n=454), 94% (427/454) reported any PrEP use in the last 30 days. Among DBS from these visits (n=427), 48% had detectable TFV-DP of which 28% had TFV-DP concentrations indicating < 2 doses/week, 64% 2-6 doses/week, and 8% 7 doses/week. Having a partner known to be living with HIV was associated with a 2-fold higher likelihood of any detectable TFV-DP compared to having partners who were HIV-negative or of unknown HIV status (risk ratio [RR]=2.0, 95%CI:1.6-2.7, p< 0.001). Detectable TFV-DP was also more likely during pregnancy compared to postpartum (RR=1.4, 95%CI:1.1-1.7, p=0.002) and among women aged ≥24 years compared to younger women (RR=1.8, 95%CI:1.3-2.6, p< 0.001).

Conclusion: Similar to studies of antiretroviral therapy among women living with HIV, we found that PrEP adherence was higher during pregnancy than postpartum, though adherence to 7 doses/week was low overall. Interventions should prioritize sustaining adherence in the postpartum period and increasing knowledge of partner HIV status, especially among younger women.

772 INCIDENT HIV INFECTIONS IN PREGNANT/BREASTFEEDING WOMEN AND INFANTS IN MOZAMBIQUE

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Background: According to UNAIDS, 40% of new pediatric infections in Mozambique are linked to incident maternal infection during pregnancy or breastfeeding. Since 2021, Mozambique has been implementing a policy of retesting all pregnant and breastfeeding women (PBFW) with unknown HIV status every three months until nine months postpartum. We aim to describe the provincial-level coverage of maternal retesting as after the new policy was introduced and the association of incident maternal infections and positivity rates among HIV exposed infants

Methods: We analyzed the President's Emergency Plan for AIDS Relief (PEPFAR) Monitoring, Evaluation, and Reporting data from April 1,2021 to March 31, 2022. We report HIV prevalence at ANC1, the number of pregnant women who had HIV testing performed after first antenatal care visit (ANC1), maternal HIV retesting positivity and coverage (percent tested after ANC1/ HIV negative at ANC1) and early infant diagnosis (EID) positivity at 12 months by province. We assessed the association of maternal incident HIV infection and new pediatric infections, using a Pearson's correlation coefficient

Results: Between April 2021 and March 2022,99.3% (1,883,920/ 1,896,554) of pregnant women attending antenatal care had their HIV status assessed at ANC1. Of these, 116,354 (6.2%) were positive, which included newly positive and known HIV positive. During this time period, 568,601 PBFW were tested after ANC1, achieving a retesting coverage of 32%. Retesting coverage was highest in Maputo City (112.6%), Maputo Province (92.8%) and below 60% in all other provinces. Positivity for HIV exposed infants ranged between 1.3% in Maputo City to 5.1% in Cabo Delgado. There was a significant positive correlation between retesting positivity at provincial level and EID positivity at 12 months (correlation coefficient 0.7, p-value 0.01) and a significant negative correlation between Post ANC1 coverage and 12 months' EID positivity (correlation: -0.6, p-value 0.04) at provincial level

Conclusion: Higher provincial HIV positivity among retested PBFW, a measure of incident HIV infections during pregnancy or breastfeeding, was associated with higher HIV positivity among infants in Mozambique. Lower provincial HIV retesting coverage of PBFW was negatively correlated with higher infant HIV positivity suggesting that uptake of maternal retesting may be a proxy for uptake of critical PMTCT services. It is important to invest in preventing incident infections in PBFW through targeted interventions

Table 1 MER indicators by province

Province	ANC1 HIV prevalence (%)	Retesting coverage (%)	Retesting positivity (%)	EID pos less than 12 months (%)
Cabo Delgado	5%	24.20%	0.50%	5.10%
Sofala	9%	30.80%	0.70%	4.50%
Niassa	4%	5.20%	0.30%	3.70%
Nampula	4%	27.20%	0.50%	3.40%
Zambezia	7%	37.40%	0.40%	3.10%
Inhambane	7%	19.20%	0.20%	2.80%
Manica	7%	26.20%	0.30%	2.50%
Gaza	12%	58.90%	0.10%	1.90%
Maputo province	12%	92.80%	0.20%	1.70%
Tete	4%	19.70%	0.30%	1.70%
Maputo city	12%	112.60%	0.30%	1.30%
National	7.5%	41.29%	0.35%	2.88%

773 HIV RISK PERCEPTION AND PrEP USE AMONG KENYAN WOMEN DURING AND AFTER PREGNANCY

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PrIMA Study
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Background: Self-perceived HIV risk influences PrEP use and may be altered during pregnancy and after delivery when women are motivated to protect their infants from HIV.

Methods: We analysed data from the PrIMA Study (NCT03070600), a cluster RCT that evaluated PrEP delivery models at 20 antenatal clinics in Western Kenya. Participants were enrolled and offered PrEP in pregnancy and followed through 9 months postpartum with HIV testing at each visit. A validated risk score developed to predict HIV acquisition among perinatal women defined high HIV risk (corresponding to 8.9 HIV infections per 100 person-years). HIV risk perception was assessed by asking "what is your gut feeling about how likely you are to get infected with HIV?" dichotomized as low ("extremely/very unlikely") versus high ("extremely/very likely").

Results: Among 2249 women included in the analysis, median age was 24 years (IQR:21–28), 82% were married, 22% did not know their partner's HIV status, and 4% had a partner living with HIV. A quarter of women (27%) had high HIV risk during pregnancy, yet 57% of these women self-perceived low risk. Among women with high-risk (n=617), 194 (31%) women accepted PrEP. Women who perceived high-risk were more likely to have a partner known to be living with HIV (21% vs.5%, prevalence ratio [PR]=1.5, 95% CI:1.2-2.1) and more likely to initiate PrEP (40% vs. 18%, PR=2.2, 95% CI:1.5-3.4). Among high-risk women, perceiving high HIV risk was associated with age >24 years (PR=:1.4, 95%CI:1.0-1.9), prior pregnancy (PR=1.8, 95% CI:1.0-3.1), polygamous marriage (PR=1.6, 95% CI:1.2-2.2), and syphilis diagnoses in pregnancy (PR=2.6, 95% CI:1.5-4.4). Overall, 9 women acquired HIV during follow-up, of these 5 perceived their risk as low at HIV seroconversion; 2 had initiated PrEP but discontinued prior to seroconversion and all others declined PrEP. Forty-five percent of women who were high-risk in pregnancy were no longer high-risk at 9-months postpartum, mostly due to diagnosis of partner HIV-negative status via HIV self-test distribution. Among high-risk women, low-risk perception was more common postpartum than during pregnancy (64% vs. 36% p< 0.001).

Conclusion: In this cohort, most high-risk women did not self-perceive high risk and most declined PrEP. Ensuring syphilis testing and improving knowledge of partner HIV status in PrEP delivery programs, may refine risk perception and encourage PrEP uptake, particularly among younger women.

774 ANTEPARTUM WEIGHT GAIN AND ADVERSE PREGNANCY OUTCOMES: A MEDIATION ANALYSIS

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IMPAACT 2010
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Background: IMPAACT 2010 previously reported that low antepartum weight gain (< 0.18 kg/week) was associated with higher hazard of adverse pregnancy outcomes compared to normal weight gain (HR: 1.4, 95% CI: 1.04, 2.00), and that rates of adverse pregnancy outcomes differed by randomized ART arm. In this exploratory analysis, we evaluated whether change in antepartum weight was a mediator of by-arm differences in adverse pregnancy outcomes.

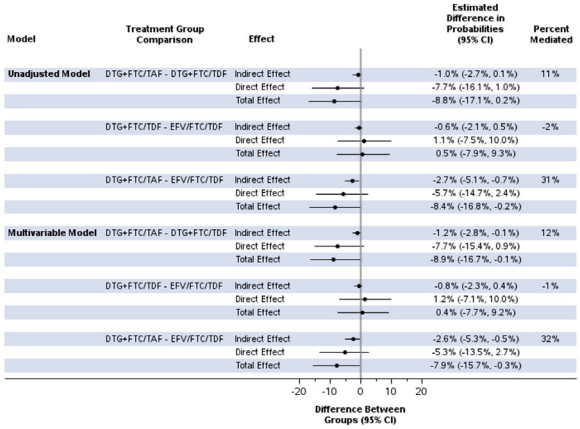
Methods: Women with HIV-1 in 9 countries were randomized at 14-28 weeks gestational age (GA) to start dolutegravir(DTG)+emtricitabine(FTC)/tenofovir alafenamide fumarate(TAF) vs. DTG+FTC/tenofovir disoproxil fumarate(TDF) vs. efavirenz(EFV)/FTC/TDF. We defined a composite adverse pregnancy outcome as occurrence of stillbirth (GA ≥20 weeks), preterm delivery (GA < 37 weeks), or small for gestational age (SGA) < 10th percentile. Causal mediation analysis was used to separate the estimated effect of study arm on the risk of the composite pregnancy outcome into two effects: 1) effect mediated through the change in weight (indirect effect, modeled continuously), and 2) effect not mediated through the change in weight (direct effect, modeled as a binary outcome). We also performed a multivariable analysis adjusting for baseline GA, body mass index (BMI), CD4 count, country, and age.

Results: 643 participants were randomized: 217 in DTG+FTC/TAF, 215 in DTG+FTC/TDF, and 211 in EFV/FTC/TDF arms. Baseline medians were: GA 21.9 weeks, HIV RNA 903 cp/mL, CD4 count 466 cells/uL, and BMI 26 kg/m^2. The proportion with an adverse pregnancy outcome was lower in the DTG+FTC/TAF arm (24%) compared to the EFV/FTC/TDF (32%) and DTG+FTC/TDF (33%) arms. Low weight gain was least common in the DTG+FTC/TAF arm (15%) compared to EFV/FTC/TDF (30%) and DTG+FTC/TDF (24%). For comparisons with the DTG+FTC/TAF arm, the percent of risk of adverse pregnancy outcome

mediated by weight change was 31% for DTG+FTC/TAF vs EFV/FTC/TDF and 11% for DTG+FTC/TAF vs DTG+FTC/TDF. These results did not differ after adjustment (Figure).

Conclusion: In this population in which low antepartum weight gain was associated with a higher risk of adverse pregnancy outcomes, up to one-third of observed differences in adverse pregnancy outcomes between the randomized arms appear to be mediated by ART-related weight change. Further study is needed on the role of weight as well as additional ART-related mechanisms associated with these adverse outcomes in women living with HIV.

Mediation analysis of study arm, weight change, and the composite adverse pregnancy outcome*



*The estimates and confidence intervals were computed using a mediator model with the change in weight as a continuous variable and the adverse composite pregnancy outcome as a binary variable.

775 UNIQUE EICOSANOID/LIPID PROFILES IN PREGNANT WOMEN LIVING WITH HIV IN BOTSWANA

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Background: Few data exist on maternal eicosanoid/lipid profiles in pregnant women living with HIV (WLHIV) and their relationship to infant insulin sensitivity.

Methods: We measured ~800 eicosanoids/lipid subspecies via liquid chromatography mass spectrometry in fasting plasma samples collected at 24-28 weeks gestational age (GA) from pregnant WLHIV and HIV-seronegative (HIV-) pregnant women enrolled in the Tshilo Dikotla study in Botswana. To evaluate insulin sensitivity in their infants at 1 month (mo) of age, the Homeostasis Model Assessment for Insulin Resistance (HOMA) was assessed and log-transformed; Z scores for birth weight (BWZ) and length (BLZ) were calculated. Volcano plots were used to visualize differences in eicosanoids/lipid subspecies between groups. Lasso regression models were fit to assess maternal factors (age, gestational diabetes) and eicosanoid/lipid subspecies predictive of infant log HOMA at 1 mo of age, stratified by maternal HIV status.

Results: Of 223 pregnant individuals, 146 were WLHIV. Maternal age (30 vs. 26 years, $p < 0.01$) and gravidity (3 vs. 1, $p < 0.01$) were higher in WLHIV compared to HIV- women; family history of diabetes, maternal BMI, gestational diabetes, as well as infant GA, BWZ, BLZ, and exclusive breastfeeding were similar between groups. Among WLHIV 47% had a CD4 >500 cells/mm^3 and 92% a viral load < 40 copies/mL at enrollment. All WLHIV received tenofovir/emtricitabine plus dolutegravir (DTG) (55%) or efavirenz (EFV) (45%); their infants were randomized to 4 weeks of zidovudine (50%) or nevirapine (50%). Pregnant WLHIV exhibited an eicosanoid profile indicating a presence of pro- and anti-inflammatory mediator production compared to HIV- women. Findings were similar comparing EFV- and DTG-treated women separately to HIV- women. However, EFV-treated women had higher levels of complex lipids, unlike DTG-treated women. (Fig) This maternal dyslipidemic profile included lipid subspecies (lysophosphatidylcholine 20:4 and 22:4) predictive of infant HOMA at 1 mo among WLHIV in lasso regression. No maternal lipid subspecies were associated with infant HOMA in HIV- women.

Conclusion: In our cohort WLHIV showed partial compensation of pro-inflammatory eicosanoid mediator production. Compared to DTG, EFV was associated with maternal dyslipidemia in pregnancy which was predictive of lower infant insulin sensitivity. Further studies are warranted to delineate whether enhancement of anti-inflammatory mediator production may benefit maternal/infant metabolic outcomes.

Volcano plots comparing eicosanoid/lipid profiles in pregnancy between (A) WLHIV and HIV-seronegative women and (B) WLHIV on EFV vs. DTG

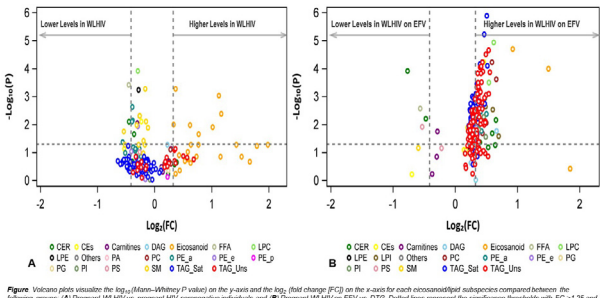

Figure Volcano plots visualize the $\log_{10}$(Mann–Whitney P value) on the y-axis and the $\log_2$ (fold change [FC]) on the x-axis for each eicosanoid/lipid subspecies compared between the following groups: (**A**) Pregnant WLHIV vs. pregnant HIV-seronegative individuals and (**B**) Pregnant WLHIV on EFV vs. DTG. Dotted lines represent the significance thresholds with FC >1.25 and <0.75 on x-axis and p value >0.05 on y-axis. Cer=ceramides; CE=cholesterol ester; DAG=diacylglyceroldiglyceride; DTG=dolutegravir; EFV=efavirenz; FFA=free fatty acid; LPC= lysophosphatidylcholine; LPE=lysophosphatidylethanolamine; LPI=lysophosphatidylinositol; LPG=lysophosphatidylglycerol; PA=phosphatidic acid; PC=phosphatidylcholine; PE_a=phosphatidylethanolamine acyl; PE_e=phosphatidylethanolamine ether; PE_p=phosphatidylethanolamine plasmalogen; PI=phosphatidylinositol; PS=phosphatidylserine; Sat=saturated; SM=sphingomyelin; TAG=triacylglycerol/triglyceride; Uns=unsaturated; WLHIV=women living with HIV

776 CARDIOMETABOLIC RISK IN SOUTH AFRICAN POSTPARTUM WOMEN LIVING WITH HIV

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Background: Conflicting evidence suggests HIV and ART, including dolutegravir (DTG), increase the risk of cardiometabolic disease, but there is limited data in postpartum women living with HIV (WLH) or initiating DTG in pregnancy.

Methods: Among women living with HIV (WLH) and HIV- women enrolled in pregnancy and followed up to 26 months postpartum, cardiometabolic health was examined by HIV and by ART regimen (DTG vs efavirenz (EFV)) among post-conception initiators. Anthropometry (weight, height) and blood pressure (BP) were assessed by a trained study nurse using calibrated instruments. Body mass index (BMI) was calculated as weight divided by squared height and categorized per WHO guidelines. Postpartum weight change was calculated as weight measured postpartum minus self-reported pre-pregnancy. Participants underwent a 2-hour oral glucose tolerance test (OGTT) after an overnight fast. Lipids and insulin levels were also assessed in fasted samples.

Results: In 240 women (111 HIV-, 129 WLH), the median age was 30y (IQR, 26-35) and 15% were primigravid. Among WLH, 57% (n=73) initiated ART post-conception (73% [n=53] DTG; 27% [n=20] EFV); there were no differences in baseline characteristics by ART regimen. The median period for postpartum visit was 10 months (IQR, 7-12) and WLH came earlier than HIV- women (9 vs 10 months, p< 0.01). Overall, high levels of postpartum obesity were observed in both WLH and HIV- women (52% vs 65%, p=0.01). Women on post-conception DTG had similar obesity levels as those on EFV (43% vs 55%, p=0.24). Most women gained rather than lose weight postpartum (3.4 kg IQR -2.6;9.0) overall. However, WLH experienced both high levels of postpartum weight gain (44%) and loss (45%). A similar trend of postpartum weight gain (36% vs 35%, p=0.62) and loss (57% vs 50%, p=0.62) was observed in both DTG and EFV groups. Overall, 18% of women had elevated BP, 23% stage 1 and 11% stage 2 hypertension, with no differences by HIV status and post-conception ART regimen. There were low levels of pre-diabetes overall and no differences by HIV status and post-conception ART regimen. However, WLH had lower LDL (2.07 mmol/L IQR, 1.95-2.19 vs 3.00 mmol/L IQR, 2.17-2.43, p< 0.01) compared to HIV- women. DTG did not lead to changes in lipid levels compared to EFV.

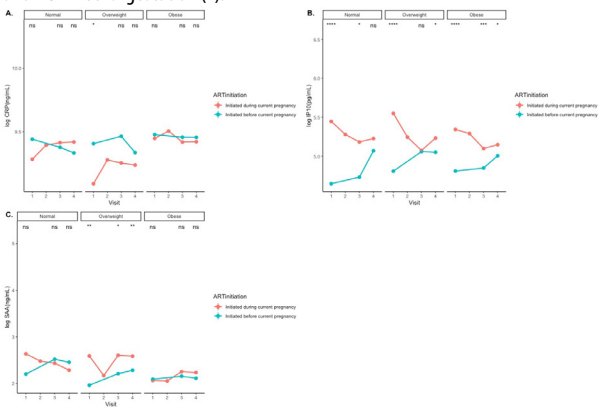
Conclusion: Postpartum weight gain, obesity and abnormal BP were common in WLH but were not related to DTG. Larger sample size studies are needed to confirm the impact of HIV and DTG on cardiometabolic health.

Table 1. Postpartum cardiometabolic risk factors, overall and stratified by maternal HIV status and post-conception ART regimen

		HIV status			Post-conception ART		
	Overall N = 240	Without HIV N = 111 (46%)	With HIV N= 129 (54%)	p value	EFV N= 20 (27%)	DTG N= 53 (73%)	p value
	Median (IQR)				Median (IQR)		
HOMA-IR (mmol/L)	2.19 (1.45-3.34)	3.06 (2.62-3.51)	2.69 (2.29-3.51)	0.23	2.68 (1.92-3.44)	2.32 (1.84-2.79)	0.42
HDL (mmol/L)	1.19 (1.02-1.46)	1.27 (1.20-1.34)	1.28 (1.21-1.34)	0.89	1.34 (1.19-1.49)	1.27 (1.18-1.36)	0.42
LDL (mmol/L)	2.14 (1.67-2.62)	**3.00 (2.17-2.43)**	**2.07 (1.95-2.19)**	**0.01**	2.15 (1.90-2.40)	1.98 (1.83-2.13)	0.25
Triglycerides (mmol/L)	0.73 (0.58-0.97)	0.80 (0.72-0.87)	0.88 (0.81-0.96)	0.11	0.85 (0.63-1.07)	0.81 (0.68-0.95)	0.79
Total Cholesterol (mmol/L)	3.76 (3.24-4.35)	3.93 (3.78-4.08)	3.76 (3.62-3.90)	0.11	3.88 (3.57-4.19)	3.60 (3.41-3.97)	0.13
	N (%)				N (%)		
BMI (kg/m²)				**0.01**			0.24
Underweight (<18.5)	2 (1)	1 (1)	1 (1)		1 (5)	0	
Normal (18.5-24.9)	38 (16)	8 (7)	30 (23)		5 (25)	15 (28)	
Overweight (25-29.9)	61 (25)	30 (27)	31 (24)		3 (15)	15 (28)	
Obese (≥30)	139 (58)	**72 (65)**	**67 (52)**		11 (55)	23 (43)	
Median (IQR)	32 (27-38)	**35 (28-39)**	**31 (25-36)**	**0.01**	31 (24-36)	29 (25-34)	0.87
Postpartum weight change (kg)				**<0.01**			0.62
Lost weight (<0kg)	84 (35)	**26 (23)**	**58 (45)**		10 (50)	30 (57)	
Stayed the same (0-2kg)	23 (10)	9 (8)	14 (11)		3 (15)	4 (8)	
Gained weight (>2kg)	133 (55)	**76 (68)**	**57 (44)**		7 (35)	19 (36)	
Median (IQR)	3.4 (-2.6,9.0)	**5.1 (0.3-11.2)**	**0.8 (-5.0,7.6)**	**<0.01**	-0.15 (-4.0,6.7)	-1.7 (-5.6,5.6)	0.51
Blood pressure (mmHg)				0.96			0.41
Normal	110 (46)	50 (45)	60 (47)		9 (45)	16 (30)	
Elevated	44 (18)	20 (18)	24 (19)		5 (25)	12 (23)	
Stage 1 hypertension	56 (23)	28 (25)	28 (22)		2 (10)	16 (30)	
Stage 2 hypertension	27 (11)	12 (11)	15 (12)		4 (20)	8 (15)	
Missing	3 (1)	1 (1)	2 (1)		0	1 (2)	
Systolic BP median (IQR)	122 (113-132)	123 (121-126)	123 (120-125)	0.68	126 (122-129)	126 (122-129)	0.61
Diastolic BP median (IQR)	75 (70-81)	75 (74-77)	76 (74-78)	0.56	75 (72-80)	77 (75-80)	0.60
Fasting glucose (mmol/L)				0.15			0.08
Normal	219 (91)	103 (93)	116 (90)		17 (85)	51 (96)	
Pre-diabetes	14 (6)	3 (3)	11 (9)		3 (15)	1 (2)	
Diabetes	4 (2)	3 (3)	1 (1)		0	0	
Missing	3 (1)	2 (2)	1 (1)		0	1 (2)	
Median (IQR)	4.6 (4.3-4.9)	4.8 (4.6-5.1)	4.7 (4.5-5.0)	0.53	4.7 (4.5-4.9)	4.5 (4.4-4.7)	0.30
2hr glucose (mmol/L)				0.54			0.68
Normal	226 (94)	102 (92)	124 (96)		20 (100)	51 (96)	
Pre-diabetes	6 (3)	4 (4)	2 (2)		0	1 (2)	
Diabetes	2 (1)	1 (1)	1 (1)		0	0	
Missing	6 (3)	4 (4)	2 (1)		0	1 (2)	
Median (IQR)	5.3 (4.6-6.0)	5.8 (5.2-6.4)	5.3 (4.8-5.9)	0.23	5.3 (4.8-5.8)	5.4 (5.1-5.7)	0.61

*Blood pressure, fasting & 2h glucose, HOMA-IR and lipid profile were adjusted for postpartum BMI

Figure. Median serum concentration of biomarkers at each visit (logarithmic scale): Baseline (1), 2 weeks post-ART initiation (2), ~ 28 weeks' gestation (3) and ~34 weeks' gestation (4).



777 IMMUNE MARKERS IN PREGNANT WOMEN LIVING WITH HIV ON ART THERAPY BY MATERNAL BMI

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Background: Obesity impairs immune functioning so concerns exist that elevated body mass index (BMI) in HIV+ pregnant women could lead to immune dysregulation. This disruption of pregnancy associated immune processes could increase risk of pregnancy complications. We investigated temporal trends of inflammatory biomarkers and impact of maternal BMI.

Methods: We recruited a cohort of ART-eligible HIV+ pregnant women (n=521) making their first antenatal visit at a primary care facility in Cape Town, South Africa (April 2015-October 2016). Women were followed from their first antenatal visit through delivery with levels of inflammatory biomarkers (C-reactive protein, CRP; interferon gamma-induced protein 10, IP10; serum amyloid A, SAA) and maternal BMI measured at three visits (< 22 weeks, ~ 28 weeks and ~34 weeks) in pregnancy with an additional visit (2 weeks post-ART initiation) for women initiating antiretroviral therapy (ART) in pregnancy. Analyses compared levels of biomarkers by timing of ART initiation (before vs during pregnancy) and by BMI status (normal < 24.9 kg/m2, overweight 25-29.9 kg/m^2, obese ≥ 30 kg/m^2).

Results: In the cohort (median age, 30y; 24% nulliparous); 47% (n=247) were on preconception ART (pre-ART) (84% TDF+XTC+EFV, 9% PI-based regimen) and the remaining 53% (n=274) initiated (97% TDF+XTC+EFV, 1% PI-based regimens). The majority of women in the cohort had an elevated BMI classified as obese (51%) or overweight (28%). Throughout pregnancy, CRP levels were relatively constant and no statistically significant differences were observed by ART status in normal, overweight or obese women (Figure). Overall SAA levels appeared to increase slightly throughout pregnancy however no differences were observed by ART status in normal and obese women, although obese women had lower SAA levels (p< 0.05). Among overweight women those initiating during pregnancy had higher levels throughout pregnancy. Women initiating during pregnancy had higher IP10 levels than their preconception ART counterparts, particularly among normal weight women. In the initiating women, IP10 levels declined following ART initiation (visit 1) across all BMI groups, while the levels appeared to increase in pregnancy in the women on preconception ART.

Conclusion: Differences observed in IP10 by ART status and BMI status are important findings IP10 has previously been implicated in the development of preeclampsia and which could impact pregnancy and birth outcomes.

777.5 MATERNAL HIV VIRAL LOAD THRESHOLD FOR GUIDING EXTENDED INFANT PROPHYLAXIS INITIATION

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Background: The WHO recommends considering infant postnatal prophylaxis (PNP) for breastfed HIV-exposed uninfected (HEU) children when their mother viral load (VL) is >1000 cp/mL. We aimed to assess the relevance of this threshold (derived from sexual transmission) by assessing whether mothers with a detectable VL below 1000 cp/mL were more likely to reach the 1000cp/mL threshold during the breastfeeding period.

Methods: We pooled data from a phase 2 and a phase 3 clinical trials conducted in Burkina Faso and Zambia and evaluating similar preventive strategies. We recruited breastfed HEU infants and their mothers at 6-8 weeks (EPI visit 2) between 2019 and 2021. In the phase 2 trial and the intervention arm of the phase 3 trial, maternal VL was monitored by point of care (Xpert® HIV RNA) at 6-8W, M6 and M12 and the results were promptly given to mothers. Only HIV positive mothers with a VL < 1000 cp/mL at 6-8W postpartum and with available VL at M6 and/or M12 were selected for these analyses. The relative risk of having a VL >1000cp/ml at M6 or M12 was calculated in light of maternal VL at 6-8W.

Results: Among the 679 selected mothers (140 from Burkina Faso and 539 from Zambia), 96 mothers had VL >40 copies/mL at 6-8W. Their median age was 30.9 years (IQR: 26.6-35.0), 73.6% of them were on antiretroviral treatment (ART) before this last pregnancy. During follow-up, 22(3.8%) and 19(19.8%) of women with VL< 40 and VL > 40 copies/mL at EPI-2 had one episode of VL >1000 cp/mL. Dolutegravir coverage increased from 29% at baseline to 87.3% at M12. Mothers with VL between 40 and 1000cp/mL at baseline were 5.2 [IC_{95}%: 3.0-9.3] times more likely to have VL >1000cp/mL during follow-up than mothers with baseline VL < 40 cp/mL. Adjusting for maternal age, time to ART initiation, dolutegravir containing regimen at 6-8W, educational level, infant sex, country or parity did not modify the association between initial viral load measure and the subsequent risk of HIV VL > 1000 cp/mL.

Conclusion: Mothers with viral load between 40 to 1000 cp/mL are at high risk of turning the 1000 threshold during breastfeeding, exposing their child to high risk of transmission while they are not considered for PNP. These findings challenge the '1000 cp/mL' threshold for PNP initiation. Using the same threshold for PNP indication as the one for clinical HIV management could be programmatically simpler and could reduce the period at risk for HEU and therefore

778 VERTICAL TRANSMISSION IN INFANTS BORN TO WOMEN WITH HIV ON ANTIRETROVIRAL TREATMENT

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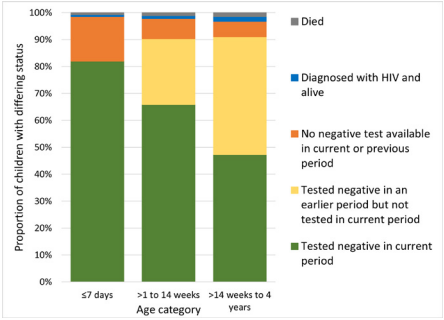
Background: Monitoring mother-infant pairs with HIV exposure is needed to assess effectiveness of vertical transmission prevention programmes and progress towards vertical transmission elimination.

Methods: We used routinely-collected data on infants with HIV exposure, born May 2018 – April 2021 to mothers diagnosed with HIV prior to delivery, in the Western Cape, South Africa, with follow-up through mid-August 2022. We assessed proportion of infants with HIV exposure who were diagnosed with HIV at birth (≤7 days), 10 weeks (>1to 14 weeks) and >14 weeks as proxies for intrauterine, intrapartum/early breastfeeding and late breastfeeding transmission, respectively.

Results: Among 49 824 HIV-exposed infants, 925 (2%) were diagnosed with HIV. Among the mothers, 68% started antiretroviral treatment (ART) before and 27% during pregnancy; 90% received any ART during pregnancy and 86% received any ART in the year after delivery. Most pregnancy regimens included non-nucleoside reverse transcriptase inhibitors (84%); 11% integrase strand transfer inhibitors and 5% protease inhibitors. Of mothers with available results, 74% had viral load < 100 copies/ml and 62% CD4 count ≥350 cells/μl at delivery. HIV-PCR test results were available for 83%, 67% and 48% of eligible infants at birth, 10 weeks and >14 weeks. Among eligible infants who were tested, 0.8%, 0.4% and 1.1% were positive at birth, 10 weeks and >14 weeks, respectively, and among infants with positive HIV-PCR tests, 47%, 18% and 35% were diagnosed at these respective time periods. Of infants who first tested positive at 10 weeks, 68% had previous negative birth tests (suggesting intrapartum/early breastfeeding transmission) and 52% who first tested positive at >14 weeks had previous negative tests at 1-14 weeks (suggesting late breastfeeding transmission). Of infants with HIV, 94% had mothers who started ART before or during pregnancy. Overall infant mortality was 1% (n=720/49824) but was 4% (n=41/925) among infants with HIV. An additional 742 infants were diagnosed with HIV in the study period but were excluded as maternal evidence of HIV was after delivery (n=341) or no linked maternal data was available (n=401).

Conclusion: Despite high maternal ART coverage, ongoing vertical transmission is a concern. Interventions to improve maternal viral suppression and reduce vertical transmission in pregnancy and breastfeeding are needed to achieve an HIV-free generation.

Vital status and HIV status at different time points for infants with HIV exposure



779 HIV DRUG RESISTANCE IN CASES OF PERINATAL TRANSMISSION IN IMPAACT 2010 (VESTED)

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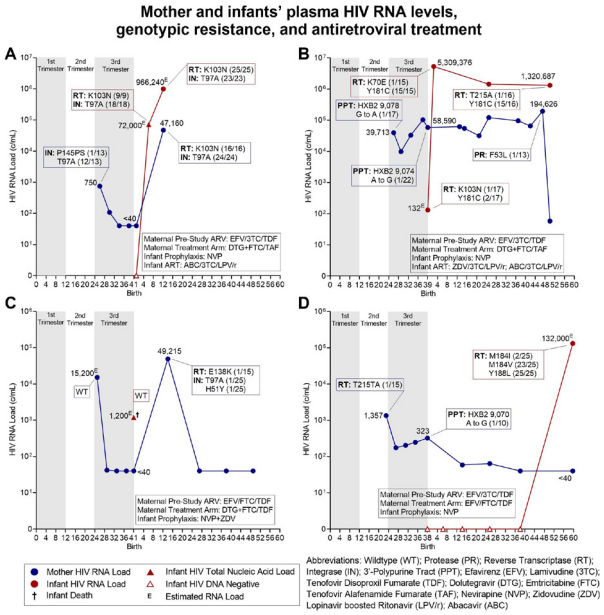
Background: VESTED was a multicenter open-label, randomized phase III trial comparing the safety and efficacy of dolutegravir (**DTG**)- and efavirenz (**EFV**)-based regimens in pregnant and breastfeeding women. Perinatal transmission to the infant occurred in 4/617 (0.6%) mother-infant pairs. This sub-study evaluated HIV drug resistance (**HIVDR**) in these 4 mother-infant pairs.

Methods: Pregnant women with HIV between 14-28 weeks of gestation were randomized to initiate DTG+FTC/TAF, DTG+FTC/TDF, or EFV/FTC/TDF and followed through 50 weeks postpartum. HIVDR genotyping was performed on plasma (HIV RNA ≥200 cp/mL) or whole blood from study entry, infant HIV diagnosis, and study exit. Single genome amplification (**SGA**) allowed assessment of minority variants in protease (**PR**), reverse transcriptase (**RT**), and integrase (**IN**) regions, and the nef 3'polypurine tract (3'PPT). SGA sequences were analyzed by Stanford HIVDR Database and 3'PPT was mapped to HIV-HXB2 to detect mutations.

Results: While awaiting study enrollment, all 4 women took EFV/3TC/TDF or EFV/FTC/TDF for 1-7 days; FIGURE. All infants breastfed and received nevirapine+/-zidovudine prophylaxis. Three cases of perinatal transmission occurred in mother-infant pairs randomized to DTG-ART and 1 to EFV-ART. A median of 18 viral templates (range 9-30) were sequenced for each HIV region. HIVDR to non-nucleoside RT inhibitors (**NNRTIs**) was selected (i.e., newly detected) in Mothers A and C. NNRTI HIVDR was detected in Infants A, B, and D at diagnosis; transmitted HIVDR potentially occurred in Infant A and was selected/acquired in B and D. IN, RT, and PR mutations were limited to those associated with low-level resistance except for M184V/I in 2 infants. 3'PPT A-to-G mutations were detected in 2 mothers at low frequencies.

Conclusion: High-level HIVDR to NNRTIs were observed. NNRTI mutations appear to have been acquired/selected in 2 mothers who switched from initial EFV- to DTG-based regimens likely due to the long half-life of EFV after excretion of other antivirals; and in 2 (possibly 3) infants from nevirapine prophylaxis (transmitted NNRTI resistance is possible in 1). While 3/4 cases of HIV transmission occurred from women randomized to DTG-ART, neither DTG HIVDR nor prevalent mutations in 3'PPT were detected. Our data show DTG-ART is associated with low rates of perinatal transmission and HIVDR; and similar to other studies, the majority of infants acquire NNRTI resistance; suggesting need infant prophylaxis regimens with a high barrier to HIVDR.

Mother and infants' plasma HIV RNA levels, genotypic resistance, and antiretroviral treatment



780 MATERNAL BROADLY NEUTRALIZING ANTIBODY ACTIVITY AND PERINATAL TRANSMISSION OF HIV-1

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Background: Over 150,000 children are infected with HIV-1 every year. Despite increased availability and access to antiretroviral therapy (ART), up to 5% of women with HIV still transmit the virus to their infants. While development of broadly neutralizing antibodies (bNAbs) through vaccination and therapeutic interventions are intended to prevent mother-to-child-transmission of HIV-1, recent evidence suggests that there may be limitations to bNAb-based approaches. Our group has demonstrated viral escape of variants in the presence of maternal plasma bNAbs targeting the V3 glycan site and a dominant bnAb specificity in postnatal transmitting women plasma. Thus, we hypothesize that HIV-infected women with bNAbs targeting a single epitope may be at high risk of viral escape that can lead to vertical transmission.

Methods: We acquired plasma from 15 perinatal transmitting women with HIV from the US-based, pre-ART era Mother-Infant Cohort Study (MICS). Plasma was collected at delivery and assessed for neutralization activity against a global HIV-1 panel. Additionally, we screened postnatal HIV-transmitting women from the Breastfeeding, Antiretroviral, and Nutrition Study (BAN) and Center for HIV/AIDS Vaccine Immunology 009 (CHAVI009) for plasma neutralizing activity (BAN: n = 21 and CHAVI009: n = 3 postnatal HIV-transmitting women). MICS and CHAVI samples were also screened against murine leukemia virus (MLV) and BAN samples against Vesicular Stomatitis Virus-G (VSV-G) for non-specific neutralization.

Results: Six out of 15 (40%) perinatal HIV-transmitting women from the MICS cohort neutralized over 50% of viruses of a heterologous, 10-virus global panel after correcting for non-specific neutralization activity (MLV). While this rate is higher than that reported in HIV-infected adults (20-30%), high neutralization breadth was also found among postnatal transmitting women with HIV in the BAN and CHAVI cohorts (18 of 24, 75%) indicating that transmission during perinatal and postnatal settings may involve a similar high rate of maternal bnAb responses that could lead to viral escape.

Conclusion: The finding of high plasma bnAb rates in perinatal HIV-transmitted, ART-untreated women is similar to that observed for postnatal HIV-transmitting women and might indicate role for viral escape of neutralization in perinatal transmission. Immune interventions involving multispecific bNAbs that are synergistic with ART may be key for bnAb-based strategies for ending the pediatric HIV epidemic.

781 RECONSTRUCTION OF THE ADCC ANTIBODY REPERTOIRE OF AN HIV-1 NON-TRANSMITTING MOTHER

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Background: Evidence from animal and human studies supports a role for Fc-mediated antibody (Ab) effector functions in protection from HIV acquisition and/or pathogenesis. In the setting of vertical transmission, passively-transferred Abs that mediate antibody-dependent cellular cytotoxicity (ADCC) correlate with reduced transmission, as well as improved clinical outcome in infants that acquire HIV. The characteristics of Abs that comprise the plasma ADCC response are not well understood. We isolated monoclonal Abs (mAbs) from an HIV non-transmitting mother to determine how these mAbs contribute to her plasma ADCC activity.

Methods: Memory B cells were sorted and cultured from a late pregnancy PBMC sample from Kenyan mother MG540, who did not transmit HIV to her infant during breastfeeding, despite high plasma and breastmilk viral loads. A targeted approach was used to identify wells with B cells producing HIV-specific Abs capable of ADCC. From these wells, mAbs were reconstructed and their epitopes defined using phage display or competition ELISA. ADCC was measured via the RFADCC assay. FcR-null (GRLR) variants were generated to determine how mAbs contribute to overall plasma ADCC activity.

Results: 18 mAbs, comprising 14 clonal lineages, were reconstructed. They all mediated ADCC and targeted various epitopes on the gp120 and gp41 subunits of HIV Envelope, including CD4-inducible epitopes recognized by prototypic mAbs A32, C11, and 17b, as well as the V3 loop and gp41 clusters I and II. Only the V3-specific mAbs were neutralizing, albeit weakly. In competition experiments, GRLR variants of gp120-specific mAbs individually reduced MG540 plasma ADCC by up to 10%, whereas combinations of 3-5 mAbs targeting distinct epitopes accounted for the majority of MG540 gp120-specific plasma ADCC (55%). GRLR variants of single gp41-specific mAbs accounted for up to 26% of gp41-specific plasma ADCC, with a combination of mAbs reducing plasma ADCC by 78%. GRLR variants of the MG540 mAbs recapitulated the passively-acquired ADCC activity of her infant, BG540, to a similar degree.

Conclusion: The isolated MG540 mAbs collectively accounted for the majority of contemporaneous MG540 plasma ADCC and the passively-acquired ADCC activity of her infant, whereas individual mAbs contributed only a small percentage of the activity. These Abs targeted several epitopes across gp120 and gp41, indicating this was a highly polyclonal ADCC response. These mAbs also provide tools for further probing of plasma ADCC responses.

782 PBPK MODEL PREDICTION OF LONG-ACTING CAB AND RPV CONCENTRATIONS IN PREGNANCY

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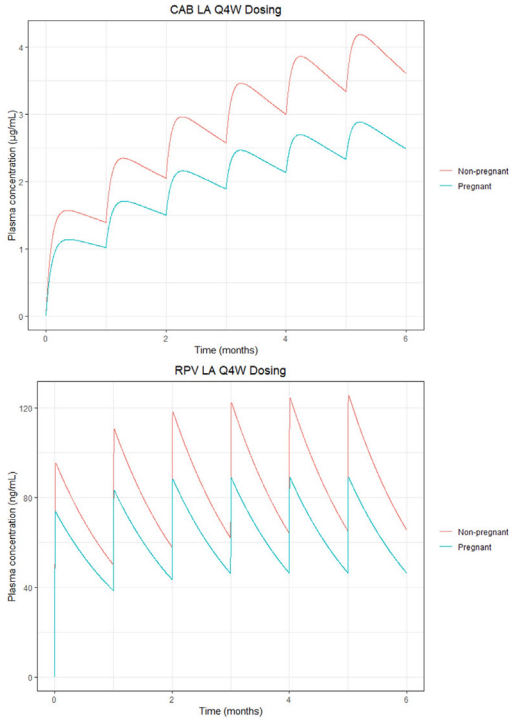
Background: The pharmacokinetics (PK) of cabotegravir (CAB) long-acting and rilpivarine (RPV) long-acting has not been prospectively studied in pregnancy. Physiologically-based pharmacokinetic models (PBPK) offer the ability to incorporate physiologic pregnancy-associated changes and drug specific characteristics to predict the concentration exposure during pregnancy.

Methods: We used a published maternal-fetal PBPK model by Dallmann et. al. in Open Systems Pharmacology to predict concentrations of Cabotegravir (CAB) and Rilpivirine (RPV) after long-acting injection (LAI) in nonpregnant cisgender women during their 2nd and 3rd trimesters of pregnancy. This model was previously used to predict the maternal PK of Dolutegravir and Raltegravir and to verify the induction of UGT1A1 and CYP3A4 during the 2nd and 3rd trimesters. We obtained drug specific parameters for CAB and RPV from the published literature and used published clinical PK data for CAB and RPV (oral and IM) in nonpregnant, cisgender women to validate the nonpregnant PBPK model. We then extended the validated model to pregnancy and the PBPK model was utilized to simulate dose sequences in nonpregnant and pregnant individuals, including a loading dose paradigm, with monthly dosing up to 6 months.

Results: The simulation result using the maternal-fetal PBPK model is shown in figure 1. According to the simulation results, the trough concentrations after the 1st injection were 29.5% and 23.0% lower during pregnancy compared to outside of pregnancy for CAB and RPV, respectively. The trough concentrations after the 6th injection were 31.1% and 29.2% decreased for CAB and RPV, respectively.

Conclusion: This maternal-fetal PBPK model predicts a reduction in plasma concentrations in the 2nd and 3rd trimesters for both CAB LA and RPV LA, attributed to the predicted induction of UGT1A1 and CYP3A4 during the 2nd and 3rd trimesters. Clinical trials of CAB LA and RPV LA in pregnancy populations are necessary to further evaluate the pharmacokinetics in the 2nd and 3rd trimesters.

Predicted PK of CAB LA and RPV LA in non-pregnant and pregnant patients



783 PHARMACOKINETICS AND VIROLOGIC OUTCOMES OF BICTEGRAVIR IN PREGNANCY AND POSTPARTUM

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Background: Bictegravir (BIC) is an HIV-1 integrase strand transfer inhibitor with potent antiviral activity. It is highly protein bound (~99.7%) and eliminated by UGT1A1 and CYP3A metabolism. Although protein binding and hepatic enzyme activity are altered during pregnancy, limited data exist on BIC pharmacokinetics (PK) in pregnancy. We describe preliminary BIC PK in pregnancy compared to postpartum and associated virologic outcomes.
Methods: IMPAACT 2026 is an ongoing, nonrandomized, open-label, parallel-group, multi-center phase-IV prospective study of antiretroviral PK in pregnant women with HIV. Intensive steady-state 24-hour PK sampling of oral BIC 50 mg once-daily (a component of Biktarvy®) and HIV viral load testing were performed during the 2nd and 3rd trimesters (2T, 3T), and 6-12 weeks postpartum (PP). Total BIC concentrations were measured by a validated LC-MS/MS assay, quantitation limit of 0.078 mcg/mL. Geometric mean ratios (GMR) with 90% confidence intervals (CI) were calculated between 3T vs. PP.
Results: Preliminary analysis, triggered by low PK exposures, included 17 participants, 16 from the United States and 1 from Thailand (9 Black, 3 white, 1 Native American/Alaskan Native, 1 Asian and 3 unknown; 41% Hispanic/Latina; median entry age 31.0 years [interquartile range 25.8, 36.7]). BIC PK data were available for 6, 13, and 5 participants in 2T, 3T and PP. Compared with paired postpartum data (n=5), BIC AUC_{tau} was 60% lower and C_{max} was 53% lower in 3T (Table 1). All C_{24} concentrations were above the estimated BIC protein-adjusted EC95 value of ~0.162 mcg/mL. Nine of 13 women had a 3T BIC AUC_{tau} < the prespecified target, the 10th percentile for non-pregnant persons (58.7 mcg*hr/mL). Viral suppression (< 40 copies/mL) was achieved in 5/6, 12/13, and 4/5 participants at 2T, 3T and PP, respectively. The same participant had detectable viral loads at all three timepoints despite exceeding the 10th percentile BIC AUC_{tau} for non-pregnant persons.
Conclusion: Total BIC exposures were lower during pregnancy compared to postpartum, yet all C24 concentrations were greater than the BIC EC95. Viral suppression was maintained in pregnancy and postpartum. As physiological changes during pregnancy can reduce drug protein binding, increased unbound BIC concentrations combined with the high potency of BIC may have contributed to observed viral suppression. Study enrollment is ongoing with collection of additional BIC PK results (including unbound concentrations), safety, and clinical outcomes.

Table 1. Bictegravir Pharmacokinetic Parameters by Noncompartmental Analysis, Median (IQR)

Parameter	2nd Trimester	3rd Trimester	Postpartum	GMR (90% CI): 3rd Trimester/Postpartum
	n = 6	*n = 13*	*n = 5*	*n = 5*
AUC_{tau} (mcg*hr/mL)	50.8 (32.4 – 53.8)	42.5 (34.3 – 60.6)	124.5 (120.7 – 139.5)	0.40 (0.25 – 0.64)
C_{max} (mcg/mL)	3.85 (2.75 – 4.02)	3.38 (3.04 – 4.08)	8.45 (7.61 – 9.39)	0.47 (0.37 – 0.60)
C_{24} (mcg/mL)	0.71 (0.49 –1.04)	0.95 (0.51 – 1.20)	3.21 (2.70 – 4.75)	0.24 (0.13 – 0.41)
CL/F (mL/hr)	984.3 (929.7 – 1668.5)	1176.5 (825.1 – 1457.7)	401.6 (358.4 – 414.3)	2.38 (1.56 – 3.63)
$T_{1/2}$ (hr)	9.4 (8.3 – 11.0)	11.0 (8.6 – 12.8)	17.7 (14.5 – 19.2)	0.53 (0.45 – 0.63)

Abbreviations: AUC_{tau}: Area under plasma concentration-time curve over the 24 hour dosing interval; C_{24}: Plasma concentration 24 hours post dose; CL/F: Apparent oral clearance; C_{max}: Maximum observed concentration; GMR (90% CI): Geometric Mean Ratio (90% Confidence Interval); IQR: Interquartile Range; $T_{1/2}$: Elimination half-life;
Only 2 participants had bictegravir data for both 2nd trimester and postpartum; GMR of 2nd trimester/postpartum is not reported

784 LONG-ACTING NANOFORMULATIONS REDUCE DOLUTEGRAVIR EXPOSURE TO EMBRYO BRAIN

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Background: Dolutegravir (DTG) is an integrase strand transfer inhibitor, which is currently recommended as part of first-line treatment regimens for HIV-1 patients worldwide. This is particularly due to its high potency, limited drug-drug interactions and intrinsic high genetic barrier to resistance. Nonetheless, concerns emerged for its usage in pregnant women. Notably, DTG-based regimens have been linked to neural tube defects and postnatal neurodevelopmental deficits when taken at conception. To this end, the need for intervention strategies that would maximize DTG's efficacy benefits while limiting adverse events cannot be overstated. Thus, we created and evaluated an intramuscularly administered long-acting nanoformulated DTG (NDTG). Our goal was to determine whether poloxamer coated NDTG would sustain therapeutic DTG levels in the mother's peripheral system with minimal drug exposure to the embryo brain during pregnancy.
Methods: Female C3H/HeJ mice were either treated orally every day with DTG at human therapeutic equivalent dosage (5 mg/kg) starting at gestation day (GD) 0.5, with a single intramuscular (IM) injection of NDTG (45 mg/kg) at GD 0.5 or with two NDTG (25 mg/kg) intramuscular injections, first at GD 0.5 and second at GD 9.5. DTG concentrations were measured in plasma of dams and in whole brain tissues of embryos at GD 16.5 and at GD 17.5, respectively, using mass spectrometry (LC-MS/MS).
Results: Single (45 mg/kg) or two (25 mg/kg) IM injections of NDTG achieved equivalent plasma DTG levels to daily oral DTG administration (5 mg/kg) in pregnant dams. In all the treatment groups, plasma DTG levels were between 4000-6500 ng/mL, which are comparable to therapeutic DTG concentrations from daily oral dosing in humans. However, significantly lower levels of DTG biodistribution in embryo brain was observed following NDTG injections in comparison to daily oral administration. For daily oral DTG administration, average DTG concentrations of 196 ng/g were recorded in the embryo brains compared to 34 ng/g and 45 ng/g for groups administered with single or two IM injections of NDTG, respectively.
Conclusion: This work demonstrates that long-acting DTG nanoformulations sustain therapeutic DTG levels in maternal plasma while limiting drug exposure to the embryo brain during pregnancy. Our preliminary work shows that novel drug delivery approaches could potentially minimize embryo brain DTG exposure and thus, potentially limit drug related neurodevelopmental toxicities.

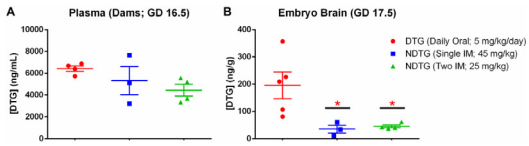

Figure 1. Significantly lower dolutegravir (DTG) biodistribution in embryo brain following long-acting DTG nanoformulations (NDTG) in comparison to daily oral DTG administration at human therapeutic dosage. DTG levels were measured in (**A**) plasma of dams and (**B**) embryo whole brain tissues in three treatment groups, Group 1 – Daily oral DTG (5 mg/kg/day, mouse weight) administration; Group 2 – Single NDTG intramuscular injection (45 mg/kg; mouse weight) at the day of conception (Gestation day, GD 0.5); Group 3 - Two NDTG intramuscular injections (25 mg/kg; mouse weight) first at the day of conception (GD 0.5) and second at GD 9.5. (**A**) DTG concentrations in plasma of dams. DTG levels were measured at gestation day (GD)16.5 to evaluate DTG levels in the mother's blood. (**B**) DTG concentrations in brain tissues of embryos. Whole brains from embryos were processed at GD 17.5 for measurement of DTG levels. (**A–B**) Each sample (plasma or tissue) represents distinct litter. For drug concentration quantitation in all samples, data are expressed as mean ± SEM, N = minimum 3 animals at each time point. (**B**) t test (two-tailed) was used to compare brain tissue DTG levels between daily oral DTG and either NDTG group(*P < 0.05).

785 DAPIVIRINE RING SAFETY AND DRUG DETECTION IN BREASTFEEDING MOTHER-INFANT PAIRS

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Background: Global guidance supports exclusive breastfeeding for infants up to six months of age, continued breastfeeding with the introduction of complementary foods. World Health Organization (WHO) guidance also supports provision of oral pre-exposure prophylaxis (PrEP) for breastfeeding people at substantial risk of HIV acquisition. In January 2021, WHO recommended the 25 mg dapivirine vaginal ring (DVR) as an HIV prevention choice as part of combination prevention approaches. However, data are limited on DVR safety and pharmacokinetics during breastfeeding, a period of increased risk for HIV acquisition.

Methods: Microbicide Trials Network (MTN)-043 was a phase 3b, randomized, open-label trial, with 12 weeks of exposure to monthly DVR or daily oral PrEP (200 mg emtricitabine [FTC]/300mg tenofovir disoproxil fumarate [TDF]). From September 2020 to July 2021, healthy, HIV-negative, exclusively breastfeeding, mother-infant pairs were enrolled 6-12 weeks after delivery at sites in Malawi, South Africa, Uganda, and Zimbabwe. Mother-infant pairs were randomized in a 3:1 ratio (DVR: PrEP). Adverse event data were collected for mothers and infants throughout product exposure and at two weeks following end of product use. Drug concentrations were measured in maternal plasma, maternal dried blood spots (DBS), breast milk, infant plasma, and infant DBS.

Results: We enrolled 197 mother-infant pairs (DVR: 148, PrEP: 49). Median infant age at enrollment was 9 weeks and >95% of visits were completed. No SAEs or ≥Grade 3 events in mothers or infants were deemed related to study product. Drug concentrations are presented in the Table. Results indicate high uptake of study product in both arms with extremely low concentrations of dapivirine (DVR arm) detected in infant plasma samples. In the oral PrEP arm, tenofovir diphosphate concentrations from infant DBS were all below the lower limit of quantitation.

Conclusion: In this first evaluation of DVR safety and drug detection during breastfeeding, few SAEs or ≥Grade 3 AEs occurred among mothers and infants and all infant AEs were deemed unrelated to study product. While dapivirine appears to concentrate in breastmilk, detection in infant plasma was low. This favorable safety profile, along with data demonstrating low dapivirine transfer to infants, supports updates to WHO and national guidelines to include breastfeeding people when recommending the DVR as an additional HIV prevention choice.

Drug concentrations in maternal plasma, maternal dried blood spots, breast milk, and infant plasma by study arm

	Dapivirine arm						Oral PrEP arm*			
	Maternal plasma		Breast milk		Infant plasma		Maternal DBS		Breast milk	
	Detection (%)	Mean (pg/ml)	Detection (%)	Mean (pg/ml)	Detection (%)	Mean (pg/ml)	Detection (%)	Mean (fmol/punch)	Detection (%)	Mean (ng/ml)
Week 1	99.3%	367.0	99.3%	698.3	--	--	100.0%	293.2	97.9%	7.0
Week 2	97.1%	374.6	98.6%	646.4	15.0%	14.5	100.0%	492.4	93.6%	5.3
Month 1	98.6%	320.0	98.6%	612.4	14.4%	12.4	95.7%	680.6	89.4%	4.5
Month 2	95.8%	340.6	97.2%	590.8	9.8%	11.8	100.0%	720.1	88.4%	5.1
Month 3	97.8%	314.3	97.8%	596.1	5.1%	10.7	100.0%	908.1	82.6%	3.6
2 weeks post-use	33.8%	26.6	66.2%	50.1	0%	BLQ	97.8%	505.7	6.5%	2.9

*Detection and concentration of tenofovir diphosphate (TFV-DP) reported for maternal/infant DBS and tenofovir (TFV) reported for breast milk.
Detection = a value above the lower limit of quantitation (LLOQ) for the assay. To summarize mean concentration, samples with concentrations below the LLOQ were assigned a value equivalent to half the LLOQ (see below for LLOQ for each assay). BLQ = below the lower limit of quantitation.
LLOQ for dapivirine in plasma = 20 pg/ml and breast milk = 10 pg/mL; LLOQ for TFV-DP in DBS = 31.3 fmol/punch; LLOQ for TFV in breast milk = 1 ng/mL.

786 PREGNANCY AND BIRTH OUTCOMES FOLLOWING ORAL PrEP USE BY OBJECTIVE LEVELS OF TDF/FTC

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Background: TDF and FTC have been evaluated for safety among pregnant and lactating people taking PrEP. Prior safety studies measured exposure using self-reported recent adherence, which may over or under-report actual use. This is one of the first studies to compare pregnancy and birth outcomes using objective levels of tenofovir diphosphate (TDF-DP) in dried blood spots (DBS) of women in the 2nd or 3rd trimester of pregnancy.

Methods: We enrolled pregnant women >15 years old without HIV at first antenatal care visit and offered them PrEP following HIV counseling. We quantified TDF-DP levels in DBS in pregnant women who reported taking PrEP in the past 30-days in the 2nd or 3rd trimester. We used logistic regression models with generalized estimating equations to evaluate pregnancy and birth outcomes by TFV-DP (any vs. none), adjusting for age, gestational age and gravidity.

Results: In 300 pregnant women, median age was 26 yrs (IQR=23-32yrs); gestation age at baseline was 16 wks (IQR=12-21wks). Overall, 7.3% had TFV-DP concentrations corresponding to 7 doses/wk (n=22); 27.3% of levels corresponded to 2-6 doses/wk (n=82); 27.3% of levels corresponded to < 2 doses/wk (n=82); 38% had levels below the limit of quantification (BLQ; n=114). Correlates of having TFV-DP concentrations corresponding with >2 doses/week included older age, higher education and condomless sex in past month. Comparing women with any TFV-DP in DBS (n=186; 62%) with those with no TFV-DP (n=114; 38%), 97% had live births (adjusted odds ratio [aOR] for any TFV-DP in DBS vs. BLQ= 1.35; 95%CI=0.45-4.02). There were no differences in pregnancy or birth outcomes by TFV-DP level (Table). The composite adverse pregnancy and birth outcome included pregnancy loss (miscarriage, stillbirth), neonatal death, pre-term (< 37wks gestation) and infants small for gestational age. Overall, 12% of women with TFV-DP had an adverse pregnancy or birth outcome, compared to 11% in women without any TFV-DP in their 2nd or 3rd trimester (aOR=0.98; 95%CI=0.47-2.07).

Conclusion: Our study is one of the first to compare objective PrEP use with birth outcomes. Pregnancy and birth outcomes did not differ by PrEP exposure per TFV-DP levels, including pregnancy loss, pre-term birth or small for gestational age. Our study provides further evidence that TDF is safe in pregnancy and highlights the importance of counseling women on the effective use and safety of TDF/FTC as PrEP in pregnancy. Limitation includes the differing time for TFV-DP collection in pregnancy.

Table 1. Pregnancy and birth outcomes in pregnant women who reported taking oral PrEP by TFV-DP level in 3rd trimester of pregnancy (n=300 women) in South Africa

Table 1. Pregnancy and birth outcomes in pregnant women who reported taking oral PrEP by TFV-DP level in 3rd trimester of pregnancy (n=300 women) in South Africa				
	Any TDF-DP present in DBS (n=186)	No TFV-DP present (BLQ) (n=114)	OR	aOR*
Total	186 (62%)	114 (38%)		
Live birth	180 (97%)	110 (96.5%)	1.55 (0.52, 4.58)	1.35 (0.45, 4.02)
Pre-term (<37 weeks)	7 (3.9%)	5 (4.5%)	0.71 (0.23, 2.18)	0.51 (0.09, 2.74)
Small for gestational age	16 (8.9%)	8 (7.2%)	1.24 (0.51, 3.01)	1.24 (0.50, 3.08)
Pregnancy loss	6 (3%)	4 (3.5%)	0.81 (0.19, 3.71)	0.54 (0.12, 2.54)
Miscarriage	1 (0.5%)	0 (0%)		
Stillbirth	3 (1.6%)	1 (0.9%)	1.97 (0.20, 19.33)	2.67 (0.32, 22.11)
Neonatal death	2 (1.4%)	3 (3%)		
Composite adverse pregnancy or birth outcomes	22 (11.8%)	13 (11.4%)	1.04 (0.45, 2.16)	0.98 (0.47, 2.07)
* adjusted for maternal age and gestational age at baseline, gravidity				
TDF-DP, tenofovir diphosphate; DBS, dried blood spots; BLQ, below limit of quantification; OR, odds ratio; aOR, adjusted odds ratio				

787 ANGIOGENIC BIOMARKERS OF POOR OUTCOMES IN PREGNANT WOMEN WITH HIV IN BOTSWANA

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Background: The Botswana-based Tsepamo study identified associations between dolutegravir (DTG)-containing antiretroviral therapy (ART) regimens initiated prior to conception and maternal hypertension (HTN) and infants born small for gestational age (SGA) using a comparison group of HIV-seronegative pregnant women and their infants. Early biomarkers of poor pregnancy outcomes to detect and intervene on pregnancies at elevated risk of poor fetal growth are needed.

Methods: The Botswana-based Tshilo Dikotla study enrolled pregnant women, those with and without HIV, between 16-36 weeks gestation and followed their infants. This analysis included 114 women (46 with HIV) with maternal plasma samples collected between 26-28 weeks gestation. Women with HIV were on DTG/TDF/FTC. Levels of angiopoietin 2 (Ang2), placental growth factor (PlGF), and soluble Fms like tyrosine kinase 1 (sFlt-1) were quantified by enzyme-linked immunosorbent assay. Differences in log-transformed values between groups were compared using Student's t-test. PlGF levels and sFlt-1:PlGF ratios were assessed using standard cut-offs, where a level < 12pg/ml or a value >85 respectively is indicative of a high-risk pregnancy. Proportions of women below or above cut-offs, as applicable, were compared by maternal HIV status using Chi-squared testing. Logistic regression models were fit to assess associations of each biomarker with maternal HTN and infant SGA (< 10th percentile), stratified by HIV status and adjusting for maternal BMI

Results: Log-transformed Ang2, PlGF, and sFlt-1 levels did not differ significantly between groups. Compared to women without HIV, a higher proportion of women with HIV had levels of PlGF < 12pg/ml and a sFlt-1:PlGF ratio >85 (PlGF: 17.4% vs 1.5%, p=0.002, sFlt-1:PlGF ratio: 19.5% vs 2.9%, p=0.0036). (Table 1) PlGF below and sFlt-1:PlGF ratio above cut-offs were significantly associated with maternal HTN at 26-28 weeks (PlGF: aOR 11.2 [2.4–51]; sFlt-1:PlGF aOR 7.8 [1.8–33]) and with infants born SGA (PlGF: adjusted odds ratio (aOR) 10.3 [95%CI 2.0–53] sFlt-1:PlGF: aOR 10.6 [95%CI 2.4¬–47]). Women with HIV were significantly more likely.

Conclusion: Angiogenic biomarkers known to be associated with placental dysfunction and adverse pregnancy outcomes, sFlt-1 and PlGF, were altered at higher prevalence in women with HIV on DTG-based ART than women without HIV. Larger studies are needed to validate these results and identify the mechanistic pathways of these clinical findings

Table 1

Characteristic	Women Living with HIV (N=46)	Women Living without HIV (N=68)	P-value
Maternal Age (years)	27.4 (24.0, 31.1)	25.8 (21.6, 29.4)	0.03
Body Mass Index (BMI)	26.6 (23.3, 32.4)	25.6 (23.0, 30.3)	0.52
Maternal HTN at 26-28weeks	6 (13%)	5 (7.6%)	0.35
Maternal HTN within 2y of enrollment	20 (43.4%)	21 (30.9%)	0.23
SGA infant	6 (13%)	6 (8.8%)	0.54
PlGF<12 pg/ml	8 (17.4%)	1 (1.5%)	0.002
sFLT-1:PlGF > 85	9 (19.5%)	2 (2.9%)	0.0036

788 DOLUTEGRAVIR EXPOSURE AND CONGENITAL ANOMALIES IN SUB-SAHARAN AFRICA

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IeDEA Multiregional MANGO Collaboration

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Background: Regional data eliciting associations between antiretroviral treatment (ART) use and adverse maternal and newborn outcomes, including congenital abnormalities (CAs), are limited. We explored the association between periconception dolutegravir (DTG) exposure and the risk of major CAs within the Measuring Adverse Pregnancy and Newborn Congenital Outcomes (MANGO) collaboration in Kenya and South Africa (SA).

Methods: In MANGO we ascertain delivery outcomes among pregnant women living with HIV (WLHIV) and not living with HIV (WNLHIV) in Eldoret, Kenya and Cape Town, SA. The Kenyan cohort consists of a prospective cohort (i.e., women followed during pregnancy through delivery) and a retrospective cohort (i.e., all women delivering at a tertiary referral facility). The SA cohort is prospective (i.e., all women followed during pregnancy at a primary care facility delivering at two referral facilities). Data from women delivering from 9/25/2020 to 8/17/2022 were stratified by HIV status and ART exposure at conception (i.e., WLHIV on dolutegravir [DTG]- versus non-DTG-containing ART). We used log-link regression models to determine factors associated with risk of major CAs detected at a birth surface exam.

Results: Among 17,235 deliveries, the median maternal age at delivery was 26.0 years, 16,823 (97.6%) were live births, and 2,229 (12.9%) were among WLHIV. Among 1,064 WLHIV with recorded ART exposure, 309 (29.0%) were on DTG-containing ART. Any CAs were detected in 226 births (23.4% polydactyly), and major CAs were detected in 123 births, in 111 (7.40/1000 births) among WNLHIV, 12 (5.38/1000 births) among WLHIV, 2 (6.47/1000 births) among WLHIV on DTG, 4 (5.30/1000 births) among WLHIV on non-DTG ART, and 6 (5.15/100 births) among WLHIV with unknown ART. Major CAs were detected in 1 (1.83/1000 births), 102 (8.64/1000 births), and 20 (4.10/1000 births) among the prospective Kenyan, retrospective Kenyan, and SA cohorts, respectively. Neither HIV status (aRR 1.0, 95% CI 0.53, 1.90) nor DTG exposure (aRR 1.46, 95% CI 0.24, 8.73) were associated with major CAs; the retrospective Kenyan cohort had a higher rate of major CAs detected, likely due to the referral facility receiving women for delivery with known complications.

Conclusion: We did not find any differences in the risk of major CAs detected by a birth surface exam based on HIV status or periconception DTG exposure. Pharmacovigilance programs need to continue monitoring adverse outcomes as new ARTs become available in HIV endemic settings.

Factors associated with any major congenital anomaly detected by a birth surface exam*, stratified by HIV status and dolutegravir exposure, from the IeDEA Multiregional MANGO Collaboration, September 2020 to August 2022

Table. Factors associated with any major congenital anomaly detected by a birth surface exam*, stratified by HIV status and dolutegravir exposure, from the IeDEA Multiregional MANGO Collaboration, September 2020 to August 2022

Variable	All women regardless of HIV status (n=17,235)		All WLHIV with known ART (n=1,064)	
	uRR (95% CI)	aRR[1] (95% CI)	uRR (95% CI)	aRR[2] (95% CI)
Maternal age at delivery outcome (per year)	1.003 (0.974-1.032)	1.007 (0.978-1.037)	1.031 (0.901-1.179)	1.030 (0.899-1.180)
Region/country (Kenya vs. South Africa)	2.033 (1.261-3.279)	2.053 (1.231-3.421)	0.631 (0.074-5.378)	0.545 (0.057-5.238)
HIV status (Positive vs. negative)	0.728 (0.402-1.318)	0.999 (0.525-1.902)	n/a	n/a
Periconception DTG exposure (vs. non-DTG exposure)	n/a	n/a	1.222 (0.225-6.636)	1.460 (0.244-8.732)

uRR=unadjusted risk ratio; aRR=adjusted risk ratio; ART=antiretroviral therapy; CI=confidence interval; DTG=dolutegravir; WLHIV= women living with HIV; WNLHIV=women not living with HIV
* All pregnancies; excluding women with missing delivery date, missing delivery outcome or unknown HIV status. All characteristics at delivery (including multiple pregnancies).
[1] Calculated with a log-link regression model with a log link among the cohort of WLHIV (regardless of ART exposure) and WNLHIV, adjusting for the other variables, as applicable, in the table.
[2] Calculated with a log-link regression model with a log link among the cohort of WLHIV on DTG and WLHIV on non-DTG ART, adjusting for the other variables, as applicable, in the table.

789 ALLOSTATIC LOAD AND SPONTANEOUS PRETERM BIRTH AMONG WOMEN WITH HIV IN LUSAKA, ZAMBIA

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Background: Maternal HIV is associated with preterm birth risk. In resource-rich settings among women without HIV, spontaneous preterm birth has been linked to biomarkers of stress. We examined the association between a composite allostatic load index (ALI) and spontaneous preterm birth among women with HIV in Lusaka, Zambia.

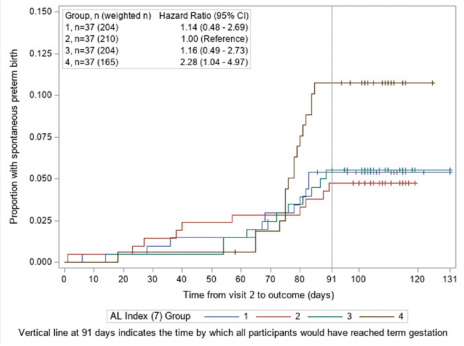
Methods: We conducted a nested case-cohort analysis using data from IPOP, a trial of weekly intramuscular progesterone to prevent preterm birth in women with HIV. Our primary outcome was spontaneous preterm birth (delivery before 37 weeks preceded by spontaneous labor or pre-labor rupture of membranes). We measured 15 biometric and circulating markers of allostatic load at the 24-week visit from 4 domains: cardiovascular, immune, metabolic, and neuroendocrine. Z-scores were calculated for each marker by standardizing for gestational age at collection to a mean of 0 and a standard deviation of 1; a composite ALI was calculated by summing individual component Z-scores from all 15 indicators (ALI-15) and from a subset of 7 (ALI-7) that met a prespecified criterion of difference in Z-scores between outcome groups of >0.1. ALI-15 and

ALI-7 were categorized into quartiles for risk assessment. We estimated time-to-event curves and hazard ratios associated with ALI quartiles and employed robust errors to account for the case-cohort design.

Results: From 2017-2019, 800 women were enrolled in the IPOP trial; 51 (6%) delivered spontaneously before term (cases). We randomly selected 107 participants for inclusion in the sub-cohort, 6 of whom were cases. We then selected all remaining cases of spontaneous preterm birth (n=45), yielding a final case-cohort population of 152. Z-score distributions of systolic blood pressure, maternal heart rate, high-density lipoprotein, triglycerides, hemoglobin A1C, albumin, and 25-OH Vitamin D met criteria for inclusion in the subset ALI. ALI-15 was not associated with spontaneous preterm birth. However, in time-to-event analysis between quartiles of ALI-7, participants in the fourth quartile had higher hazard of the primary outcome (HR 2.28, 95% CI 1.04-4.97) compared to those in the second quartile.

Conclusion: High allostatic load index among pregnant women with HIV was associated with spontaneous preterm birth. Early detection and preventive intervention among high-risk women with HIV could have a substantial public health benefit.

Figure 1. Incidence curves of spontaneous preterm birth over time by z-score quartile of allostatic load index



790 NEURAL TUBE AND OTHER BIRTH DEFECTS BY HIV STATUS AND ART REGIMEN IN ESWATINI

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Background: Dolutegravir (DTG) has improved viral efficacy and tolerance compared to efavirenz (EFV). Early data suggested a potential neural tube defect (NTD) safety signal in infants of women receiving DTG at conception. While recent evidence no longer finds an association and WHO recommends DTG-ART as preferred treatment, continued surveillance is needed to more definitively refute the signal among women of reproductive potential.

Methods: We evaluated birth outcomes of women delivering in 5 Government hospitals in 4 regions of Eswatini in September 2021-June 2022. Routine data on pregnancy history and HIV/ART status was collected from paper and electronic clinic records. Women of live or stillborn infants with birth defects were consented for interviews capturing detailed history and exposure data and photographs of newborns' birth defects. Blinded interview data and photographs were reviewed by a medical geneticist for confirmatory defect diagnosis. We aimed to describe rates and 95% confidence intervals (CI) for birth defects among infants by maternal HIV and ART status. Eswatini population NTD rate was unknown but estimated as 0.1%.

Results: Among 18,877 women enrolled with live (18,398) or stillbirths (479), 13,062 were HIV-negative, 5,806 HIV-positive and 9 were missing HIV status. Of HIV+ women, 3,629 (62.5%) were on DTG at conception, 865 (14.9%) EFV at conception, 758 (13.1%) not receiving ART at conception, 58 (1.0%) were on non-DTG/EFV ART, and 496 (8.5%) were missing regimen and/or timing information. Overall, 171 surface defects were identified (0.91%, 95% CI: 0.78-1.05); NTD comprised 9.9% of defects. NTD prevalence was 0.08% (0.02-0.24), 0.09% (0.05-0.16), and 0.23% (0.03-0.83) for women on DTG at conception, HIV-negative women and women on EFV at conception respectively. 10/17 NTDs (58.8%) were myelomeningocele/meningocele. The most common non-NTD major defect was varus foot malformation (30.3%, 23). Nearly all minor defects were polydactyly, postaxial hand or other/unspecified (97.5%, 79). Non-NTD major and minor defects were similar in HIV+ women on DTG at conception and HIV-negative women (major 0.36% and 0.42%; minor 0.55% and 0.41%, respectively).

Conclusion: There were similar rates of NTD and non-NTD defects between women on DTG at conception and HIV-negative women, which does not support an association of NTD with DTG at conception. The NTD rate among women on EFV at conception was higher but there were fewer EFV-exposed births and the rate had wide CIs.

Birth defects by HIV and ART status, rate and 95% CI

Women's HIV Status and Conception Regimen	Live/Stillbirth	NTD	Major non-NTD birth defects	Minor birth defects	Total birth defects
Total	**18877**	17 (0.09%, 0.05-0.14	76 (0.40%, 0.32-0.50)	81 (0.43%, 0.34-0.53)	171 (0.91%, 0.78-1.05)
HIV-negative	**13,062**	12 (0.09%, 0.05-0.16)	55 (0.42%, 0.32-0.55)	53 (0.41%, 0.30-0.53)	118 (0.90%, 0.75-1.08)
HIV-positive	**5806**	5 (0.09%, 0.03-0.20)	21 (0.36%, 0.22-0.55)	28 (0.48%, 0.32-0.70)	53 (0.91%, 0.68-1.19)
DTG at conception	3629	3 (0.08%, 0.02-0.24)	13 (0.36%, 0.19-0.61)	20 (0.55%, 0.34-0.85)	35 (0.96%, 0.67-1.34)
EFV at conception	865	2 (0.23%, 0.03-0.83)	4 (0.46%, 0.13-1.18)	7 (0.81%, 0.33-1.66)	13 (1.50%, 0.80-2.56)
No ART at conception (diagnosed with HIV during pregnancy)	758	0	4 (0.53%, 0.14-1.35)	1 (0.13%, 0.00-0.73)	5 (0.66%, 0.22-1.53)

791 VAGINAL INFLAMMATORY MARKERS ASSOCIATED WITH PRETERM BIRTH IN ZAMBIAN WOMEN WITH HIV

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Background: HIV infection is a known risk factor for adverse pregnancy outcomes, including preterm birth (PTB). There is a limited understanding of the maternal biological mechanisms that result in PTB, and how those mechanisms are impacted by HIV. We performed a targeted proteome analysis of vaginal samples to determine the association between HIV and preterm birth in Zambian pregnant women.

Methods: We conducted a case-cohort study that consisted of 160 Zambian women with and 136 women without HIV, of which 51 or 30, respectively, experienced PTB outcomes. Dry vaginal swabs collected at < 24 and 28 weeks of gestational age (GA) were subjected to a targeted proteomic analysis consisting of 17 key inflammatory, angiogenic, and immune biomarkers IL-1α, IL-1β, IL-1RA, IL-4, IL-6, IL-8, IL-10, IL-12, IL-23, IFNγ, IFNα2, TNFα, sTNF R1, and CXCL10 were measured using Abcam FirePlex-384 assays. sCD14 and LBP were measured using Luminex multiplex assays, and I-FABP was measured by ELSA. Concentrations were log-transformed before the results were analyzed using an unpaired t-test with Welch's correction using Graphpad Prism 9.

Results: At both timepoints, women with HIV who had term deliveries presented with higher levels of inflammatory mediators, including TNF-a, IL-12, IL-23 and sCD14, whereas vaginal IFN-g levels were lower compared to women without HIV (p values ranging from $p < 0.05$ to $p < 0.0001$). Compared to women with term birth, women without HIV and PTB had higher levels of IL-12 ($p < 0.01$), IL-23 ($p < 0.01$), and IFN-a2 ($p < 0.05$) at both visits, whereas women with HIV had increased vaginal levels of IL-6 ($p < 0.02$) or IL-1b ($p < 0.02$) at 24 or 28 wks. GA, respectively. Among all PTB cases, women with HIV had increased vaginal concentrations of sCD14 ($p < 0.03$) and IFAB ($p < 0.05$) and higher levels of IL-1b ($p < 0.01$) at both timepoints. In contrast, IL-4 ($p < 0.05$), IL-10 ($p < 0.03$), and IFNa2 ($p < 0.01$) were lower at 24 wks GA compared to women without HIV and remained lower at >28wks GA.

Conclusion: Even in pregnancy progression to term birth, the vaginal milieu in women with HIV is characterized by heightened inflammation compared to women without HIV. Vaginal inflammation was a common factor for PTB in women with and without HIV. However, among all PTB cases, increased levels of IL-1b and markers of microbial translocation appear to be associated with PTB and distinguish women with HIV from women without HIV.

792 MATERNAL ART USE AND PRETERM DELIVERY: THE IMPACT OF DATA SOURCES AND DATA QUALITY

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Background: Majority of studies investigating associations between maternal antiretroviral therapy (ART) and preterm delivery (PTD) are observational and subject to bias, which may contribute to heterogeneity in findings. We

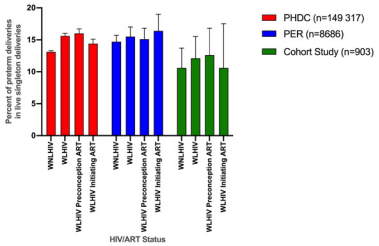
investigated the impact of participant selection, data source and data quality on observed associations between maternal ART and PTD.

Methods: Data from 3 related data sources from the same underlying population over same time-period (January 2017-July 2018) in Western Cape Province (South Africa) were compared. 1) Province-wide routine electronic health data on pregnant women (records linked across health services by the Provincial Health Data Centre (PHDC)); 2) facility-based pregnancy exposure registry (PER) (based on digitisation of patient-held booklet recording pregnancy-related clinical information); and 3) a purposely sampled cohort study (questionnaire-based data collection and clinical records abstraction). Data availability, detail and quality of baseline characteristics varied by data source. Associations between maternal ART and PTD were examined separately to assess impact of data source on the association. We compared PTD by HIV status (HIV+ vs HIV-) and ART status (initiation preconception vs during pregnancy).

Results: Median age (27y) was similar across data sources, however proportions of primigravid and HIV+ women differed: PHDC (n=183593), 53% primigravid, 19% HIV+ of whom 56% on ART preconception; PER (n=9476) 25% primigravid, 32% HIV+ of whom 66% on ART preconception; and cohort study (n=989) 21% primigravid, 48% HIV+ of whom 70% on ART preconception (82% TDF+FTC+EFV, 7% PI-based regimens). Among women with live singleton births, PTD deliveries differed by HIV/ART status in PHDC (population-level); differences were less pronounced in PER and cohort study (Figure). Increased PTD risk in HIV+ women (ARR1.15, 95% CI1.11-1.18) and women on preconception ART (ARR1.08, 95% CI1.01-1.14) was only observed in PHDC. Data availability and quality did not impact association estimates, however statistically significant differences by HIV/ART status were only detectable in the larger PHDC population.

Conclusion: With improvements in birth outcomes due to increased coverage of safer ART regimens, sample size considerations will be important to detect differences in obstetric outcomes by HIV status. Inclusion of both population level data and purposely sampled studies will remain important to leverage the benefits of both data sources.

Preterm delivery by HIV/ART Status



793 PREGNANCY HORMONAL DYSREGULATION CORRELATES WITH HIV-EXPOSED INFANT GROWTH OUTCOMES

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Background: Many hormones in pregnancy regulate fetal growth. Few data exist on fetal growth-related hormones in pregnancy in women living with HIV (WLHIV) and whether maternal hormonal alterations are associated with infant anthropometrics.

Methods: The Tshilo Dikotla study prospectively enrolled pregnant women in Botswana. WLHIV receiving dolutegravir/tenofovir/emtricitabine and HIV-seronegative (HIV-) women were included in this analysis. Levels of estradiol (E2), sex-hormone binding globulin (SHBG), cortisol, growth hormone 1 (GH1), insulin-like growth factor 1 (IGF-1), and insulin-like growth factor binding protein 1 (IGFBP-1) were measured by ELISA in plasma collected between 24-28 weeks gestation. Bioavailable E2 (bE2) was calculated using measured values of E2 and SHBG. Infant anthropometrics were converted to weight-for-age and length-for age Z-scores (WAZ, LAZ) at birth and 1 year-of-life. Data was normalised by log transformation. Generalized linear models were fit to evaluate associations between each hormone and 1) HIV status (model #1), 2) infant anthropometrics at birth and 12 months (model #2). The anthropometrics model included an interaction term between HIV status and each hormone to assess effect modification by HIV status.

Results: Plasma specimens were available from 114 women (46 WLHIV), of which 95 had a live birth while in the study. WLHIV were older (27 vs. 26 years), had higher gravidity (3 vs 1), and were less likely to breastfeed (78% vs. 100%) than HIV- women. Among WLHIV, median enrollment CD4 count was 494 cells/mm^3, and 90% had HIV RNA levels < 40 copies/mL at enrollment. After adjusting for maternal age, BMI, and gestational age of specimen draw, WLHIV had lower mean log bE2 (β: -0.22, p=0.028), cortisol (β: -0.22, p=0.001), and IGF1 (β: -0.81, p=0.007), but higher GH1 (β: 0.91, p=0.011) (Fig 1). Log bE2 was positively associated with birth WAZ (b 0.91 (95% Confidence Interval (CI) 0.41, 1.40, p< 0.001) for all infants. HIV status modified the associations of log GH1 (β:-0.22, p=0.05) and log IGF1 (β: 0.40, p=0.004) with infant WAZ at 12 months after adjusting for maternal age and BMI, duration of exclusive breastfeeding, and birth WAZ.

Conclusion: Growth hormone levels are dysregulated in WLHIV suggestive of impaired placenta function. The dysregulation, particularly of GH1 and IGF1, may influence growth in the first year of life among infants exposed to HIV.

Figure 1: Unadjusted & Adjusted Differences in Mean Log Hormone Concentrations by Maternal HIV Status

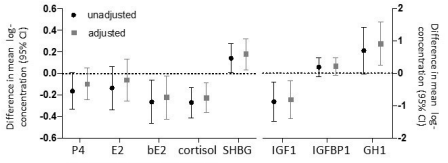

Figure: Differences in mean log concentration (with 95% confidence interval) of maternal hormones between WLHIV and HIV-seronegative women (ref). Unadjusted estimates are shown in black. Adjusted estimates are shown in grey and were adjusted for maternal age, maternal BMI, and gestational age at sample collection. P4, progesterone; E2, estradiol; bE2, bioavailable estradiol; SHBG, sex hormone binding protein; IGF1, insulin-like growth factor 1; IGFBP1, insulin-like growth factor binding protein 1; GH1, growth hormone 1.

794 SARS-CoV-2 ANTIBODY RESPONSES POST-INFECTION IN PREGNANCY BY VACCINATION STATUS

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Background: We evaluated SARS-CoV-2 antibody binding and neutralization responses at delivery among pregnant persons with prior SARS-CoV-2 infection by vaccine status.

Methods: We enrolled participants with evidence of prior SARS-CoV-2 infection detected in pregnancy (anti-nucleocapsid [anti-N] IgG+ on enrollment or prior RT-PCR+ or antigen+) and followed them through delivery. Maternal delivery and cord blood samples were tested for SARS-CoV-2 binding antibodies to spike (anti-S) (from vaccination and/or infection) and anti-N (from infection only) IgG by Abbott Architect followed by neutralizing antibodies (classified as neutralizing if serum dilution inhibited infection by 50% [ND50 heat] ≥20 and R^2 ≥0.9) if sample volume allowed. Positive IgG thresholds were Abbott index ≥1.4 for anti-N and ≥50 AU/mL for anti-S. Chi-squared test was used to compare differences in proportions between groups. Wilcoxon rank sum test was used to compare medians.

Results: Among 71 participants with delivery and cord samples, median age was 33 years (interquartile range [IQR] 30-35) and median gestational age was 31.7 weeks (IQR 18.0–37.9) at enrollment in pregnancy. By delivery, 17 (24%) participants were unvaccinated, 21 (30%) were partially vaccinated or had completed a primary series, and 33 (46%) were boosted. Median time from infection (RT-PCR+ or antigen+ result) to delivery was 16.7 weeks (IQR 9.7-24.3). At delivery, 33 (46%) of maternal (median 3.2 index) and 37 (52%) of cord samples (median 3.1 index) were anti-N IgG+.

Participants with ≥1 vaccine were more likely to be anti-S IgG+ than those unvaccinated (100% vs. 82%, p< 0.01), have higher median anti-S IgG+ (25,000 vs 1,019 AU/ml, p< 0.01), and have neutralizing antibodies (100% vs. 81%, p< 0.01) with higher median $\log_{10}$ neutralization (1:4.00 vs 1:2.41, p< 0.01) at delivery.

Similarly, cord blood from participants with ≥1 vaccine was more likely to be anti-S IgG+ than those unvaccinated (100% vs. 82%, p< 0.01), have higher

median anti-S IgG+ (25,000 vs 1,188 AU/ml, p< 0.01), and have neutralizing antibodies (100% vs. 75%, p< 0.01) with higher median log_{10} neutralization (1:4.00 vs 1:2.41, p< 0.01) at delivery.

Conclusion: Among pregnant people with prior SARS-CoV-2 infection detected during pregnancy, maternal and cord blood antibody binding and neutralization responses were higher among those receiving SARS-CoV-2 vaccination prior to delivery.

SARS-CoV-2 antibody binding and neutralization responses after infection during pregnancy in maternal delivery and cord blood by vaccination status, n=71 maternal infant pairs

	Total N=71	Unvaccinated N=17	≥1 Vaccine N=54*	p-value
	n (%) or median (IQR)			
Maternal delivery blood samples				
Anti-N IgG+†	33 (46)	9 (53)	24 (44)	0.54
Anti-N IgG (index) ‡	3.17 (1.85-4.84)	3.18 (2.76-5.85)	3.10 (1.74-4.28)	0.17
Anti-S IgG+	68 (96)	14 (82)	54 (100)	<0.01
Anti-S IgG (AU/ml)	25,000 (4368-25,000)	1,019 (448-1284)	25,000 (25,000-25,000)	<0.01
Neutralization (n=54)	51 (94)	13 (81)	38 (100)	<0.01
Log_{10} ND50 (heat)	1:3.84 (2.62-4.00)	1:2.41 (2.04-2.62)	1:4.00 (3.70-4.00)	<0.01
Cord blood samples				
Anti-N IgG+	37 (52)	8 (47)	29 (54)	0.63
Anti-N IgG (index)	3.10 (2.10-4.44)	4.29 (2.56-6.29)	3.02 (1.99-4.23)	0.17
Anti-S IgG+	68 (96)	14 (82)	54 (100)	<0.01
Anti-S IgG (AU/ml)	25,000 (8020-25,000)	1,188 (560-2170)	25,000 (25,000-25,000)	<0.01
Neutralization (n=52)	48 (92)	12 (75)	36 (100)	<0.01
Log_{10} ND50 (heat)	1:3.94 (2.83-4.00)	1:2.41 (2.16-2.65)	1:4.00 (3.75-4.00)	<0.01

*Partially vaccinated (n=1); completed primary series (n=20); boosted (n=33).
†Positivity thresholds: anti-N IgG+ Abbott index ≥1.4; anti-S IgG+ ≥50 AU/mL; pseudo-neutralization ND50 (heat) ≥20 and $R^2 \geq 0.9$.
‡Median values for anti-N IgG index, anti-S IgG (AU/ml) and neutralization (log_{10} ND50 [heat]) are among those who had positive samples.

795 SARS-CoV-2 SEROPREVALENCE TREND AMONG PREGNANT WOMEN IN ZAMBIA, 2021-2022

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Background: Confirmed COVID-19 case counts underestimate SARS-CoV-2 infections, particularly in countries with limited testing capacity. Pregnant women attending antenatal care (ANC) clinics have served as healthy population surrogates to monitor diseases like HIV and malaria. We measured SARS-CoV-2 seroprevalence among women attending ANC clinics to assess infection trends over time in Zambia.

Methods: We conducted repeated cross-sectional surveys among pregnant women aged 15-49 years attending their first ANC visits in 3 districts of Zambia during September 2021-September 2022. Up to 200 women per district were enrolled each month, completing a standardized questionnaire. Dried blood spot samples were collected for serologic testing for prior infection using the Tetracore® FlexImmArray™ SARS-CoV-2 Human IgG Antibody Test and HIV testing according to national guidelines. We calculated odds ratios (ORs) for SARS-CoV-2 seroprevalence by demographic characteristics, adjusting for the district.

Results: A total of 5,351 women were enrolled at 29 study sites between September 2021 and September 2022. Participants' median age was 25 years (interquartile range: 21-30), 530 (9.9%) tested positive for HIV, and 101 (1.9%) reported a prior positive COVID-19 test. Overall, SARS-CoV-2 seroprevalence was 67%, and rose from 49% in September 2021 to 85% in September 2022 (Figure 1). The greatest increase in seroprevalence occurred during the 4th wave caused by the Omicron variant (48% in December 2021 to 63% in January 2022). Seroprevalence was significantly higher among women living in urban districts (Chipata and Lusaka) compared to rural Chongwe District (Chipata OR: 1.2, 95% confidence interval [CI]: 1.1-1.4; Lusaka OR: 1.7, 95% CI: 1.5-2.0). The age group was not significantly associated with seroprevalence after adjusting for the district (aOR: 1.1, 95% CI: 1.0-1.2). Seroprevalence was significantly lower among women living with HIV than women living without HIV (aOR: 0.8, 95% CI: 0.6-0.9).

Conclusion: Overall, two-thirds of women in the three surveyed districts in Zambia had evidence of SARS-CoV-2 exposure, rising to 85% after the Omicron variant spread throughout the country. ANC clinics have a potential role in ongoing SARS-CoV-2 serosurveillance and can continue to provide insights into SARS-CoV-2 infection dynamics. Furthermore, they provide a platform for focused SARS-CoV-2 prevention messaging and COVID-19 management in pregnant women at higher risk of severe disease.

Figure 1: SARS-CoV-2 seroprevalence among pregnant women attending antenatal care clinics in Zambia by district, age group, and HIV status, September 2021-September 2022.

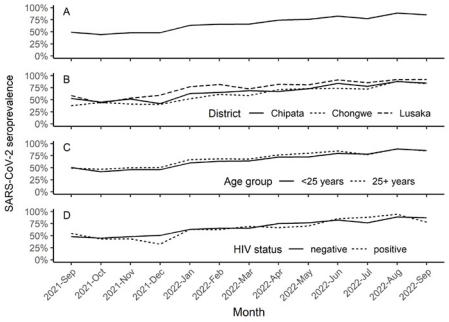

Figure 1. SARS-CoV-2 seroprevalence among women attending first antenatal care visits in three districts of Zambia, September 2021-September 2022. SARS-CoV-2 seroprevalence trends (A) overall, and by (B) district, (C) age group, and (D) HIV status.

795.5 SARS-COV-2 SEROPREVALENCE BY HIV STATUS AMONG PREGNANT WOMEN IN ZAMBIA, 2021-2022

Elizabeth Heilmann[1], Taniya Tembo[1], Sombo Fwoloshi[2], Kalubi Kalenga[1], Mpanji Siwingwa[2], Samuel Yingst[1], Julie Gutman[3], Victoria Seffren[3], Ruchi Yadav[3], Theodora Savory[1], Izukanji Sikazwe[1], Jonas Hines[1]

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Background: People living with HIV (PLHIV), though at no greater risk of SARS-CoV-2 infection, are at increased risk of severe COVID-19 and have been prioritized for COVID-19 mitigation strategies in Zambia. Evidence suggests that the natural and vaccine-derived immune response among PLHIV may be less durable compared to immunocompetent populations. We measured SARS-CoV-2 seroprevalence and COVID-19 vaccine coverage by HIV status among women attending antenatal care (ANC) clinics in Zambia.

Methods: We conducted a cross-sectional survey among pregnant women at 29 ANC clinics in Zambia between September 2021 and September 2022. Women completed a standardized questionnaire and were tested for HIV according to national guidelines. Dried blood spot samples were collected for serologic testing using the Tetracore® FlexImmArrayTM SARS-CoV-2 Human IgG Antibody Test, a multiplex assay targeting SARS-CoV-2 spike and nucleocapsid proteins. We calculated age-adjusted odds ratios (aORs) for SARS-CoV-2 seroprevalence and COVID-19 vaccination.

Results: We enrolled 4,971 women, 10% of whom tested HIV positive, and 67.4% tested SARS-CoV-2 positive (Table). PLHIV were older than women living without HIV (median age: 29 vs. 24 years, p< 0.001). COVID-19 vaccine coverage was higher among PLHIV (21% vs. 17%, p=0.003), while SARS-CoV-2 seroprevalence was lower (62% vs. 68%, p=0.007). After stratifying by COVID-19 vaccination status, SARS-CoV-2 seroprevalence only differed by HIV status among unvaccinated women (aOR: 0.67, p< 0.001). Among the small number of women who reported a prior positive COVID-19 test (91 [1.8%]), fewer PLHIV were SARS-CoV-2 positive compared to women without HIV (50% vs. 78%, p=0.09), although the difference was not statistically significant.

Conclusion: Overall, SARS-CoV-2 seroprevalence was high among women attending antenatal care in Zambia but lower among those with HIV. Although the sample size was small, PLHIV reporting prior COVID-19 had lower SARS-CoV-2 seroprevalence, potentially reflecting immune differences compared to women who are HIV-negative. Additionally, PLHIV might have been shielded from COVID-19 through a robust HIV care program, which offered health education, multi-month prescriptions, facemasks, and COVID-19 vaccines. The low vaccination coverage among pregnant women, regardless of HIV status, points to the need to increase COVID-19 primary series and booster vaccinations to help protect this population from COVID-19.

796 COVID-19 VACCINATED MATERNAL/CORD BLOOD DONT HAVE NEUTRALIZATION FOR OMICRON VARIANTS

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Background: Maternally derived antibodies are crucial for neonatal immunity. Understanding the binding and -cross neutralization capacity of maternal/cord antibody responses to COVID-19 vaccination during pregnancy can inform neonatal immunity.

Methods: Here we characterized binding and neutralizing antibody profile at delivery in 24 pregnant individuals following two doses of Moderna mRNA-1273 or Pfizer BNT162b2 vaccination. We evaluated the transplacental antibody transfer by profiling maternal and umbilical cord blood. We analyzed for SARS-CoV-2 multivariant cross-neutralizing antibody levels for wildtype Wuhan, Delta, Omicron BA1, BA2, and BA4/BA5 variants by enzyme-linked immunosorbent assay

Results: Our results reveal that current vaccination induced significantly higher ($p=0.003$) RBD-specific binding IgG titers in cord blood compared to maternal blood for both Wuhan and Omicron BA1 strain. Interestingly, binding IgG antibody levels for the Omicron BA1 strain were significantly lower ($P< 0.0001$) when compared to the Wuhan strain in both maternal and cord blood. In contrast to the binding, the Omicron BA1, BA2, BA4/5 specific neutralizing antibody levels were significantly lower ($P< 0.0001$) compared to the Wuhan and Delta variants. It is interesting to note that the BA4/5 neutralizing capacity was not at all detected in both maternal and cord blood.

Conclusion: Our data suggest that the initial series of COVID-19 mRNA vaccines were immunogenic in pregnant women, and vaccine-elicited binding antibodies were detectable in cord blood at significantly higher levels for Wuhan and Delta variants but not for Omicron variants. Interestingly, the vaccination did not induce neutralizing antibodies for Omicron variants. These results provide novel insight into the impact of vaccination on maternal humoral immune response and transplacental antibody transfer for SARS-CoV-2 variants and support the need for boosters as new variants emerge.

797 HIV-EXPOSED UNINFECTED (HEU) INFANTS DISPLAY UNIQUE PRO-INFLAMMATORY BIOPROFILES

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Background: HEU infants are at risk for adverse metabolic, infectious, and neurodevelopmental outcomes when compared to HIV unexposed uninfected (HUU) infants. However, the relationships between maternal immunity in pregnant women with HIV (PWWH) and their HEU infants are largely unexplored. Proinflammatory immune pathways from PWWH and their HEU infants were examined in comparison to pregnant women without HIV (PWWOH) and their HUU infants.

Methods: Archived plasma samples from 46 ART-treated PWWH prior to delivery and their HEU newborns enrolled in PACTG 316, *a Phase III Randomized, Double Blinded Study of Nevirapine for the prevention of maternal-fetal transmission in pregnant HIV-infected women* were evaluated. Age-balanced PWWOH (n=18) and their HUU infants served as reference groups. A panel of 21 immune biomarkers associated with germinal center formation, inflammation, and macrophage or lymphocyte activation were measured using Mesoscale Diagnostics multiplex assays. Manifold Approximation and Projection (UMAP) was applied to test for biomarker relatedness of study groups. Comparisons of individual biomarkers between HEU and HUU infants were performed by Mann-Whiney *U* test, and biomarker correlations between mothers and their babies were assessed by Spearman's rank test.

Results: Bioprofiles of HEU and HUU infants separated well from each other as well as from their mothers with distinct separation between mothers by HIV status. HEU infants compared with HUU infants displayed significantly higher plasma levels of biomarkers for germinal center development (APRIL, BAFF, IL-21), macrophage (sCD14, sCD163) or lymphocyte activation (sCD27, IFNγ, IL-22), and pro-inflammatory cytokines and chemokines (CXCL9, CCL4, TNFα, IL-1β, IL-1RA, IL-6). All mother-infant dyads, independent of maternal HIV status, showed positive correlations for BAFF, IL-21, sCD14, IL-17A and CXCL9. In addition, mothers with HIV and their infants showed unique significant positive correlations for APRIL, sCD163, IL-22, CCL4, CCL5, TNFα, IL-1β, IL-1RA and IL-6.

Conclusion: HEU infants have elevated inflammatory markers associated with innate and adaptive immunity that are distinct from HUU. Levels of some, but not all biomarkers in infants are positively correlated with the levels in their mothers, implying modulation by maternal immunity. Therefore, HIV-associated inflammation in mothers may have long-term implications for early immune development in their HEU infants.

Fig 1. Relatedness of study populations.

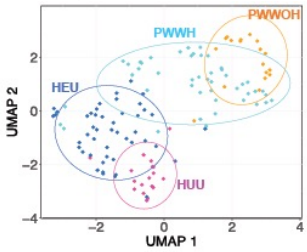

Fig 1. Relatedness of study populations. Immunological bioprofiles of HIV-exposed uninfected (HEU) and HIV-unexposed uninfected (HUU) newborns separated well from each other as well as from their mothers. The separation between mothers without (PWWOH) or with HIV-infection (PWWH) was also distinct.

798 NO EVIDENCE OF PERTURBATIONS OF THE BREAST MILK MICROBIOME BY ANTIRETROVIRAL THERAPY

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1077BF/1077FF PROMISE (Promoting Maternal and Infant Survival Everywhere) Team

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Background: Antiretroviral treatment (ART) has greatly reduced AIDS-related morbidity and mortality in women living with HIV (LWH) and has broken the chain of mother-to-child transmission (MTCT) of HIV-1 both peripartum and through breastfeeding. Breastfeeding has profound benefits including reducing infant mortality. Human milk contains over 200 beneficial factors including cells, antibodies, human milk oligosaccharides and microbes that are critical to infant immune development. Some data indicate that ART may alter the microbiome of people LWH. We investigated whether ART altered the breast milk microbiome.

Methods: In PROMISE[1], postpartum mother-infant pairs were randomized to receive either maternal ART (mART) with tenofovir, emtricitabine, and ritonavir-boosted lopinavir or infant nevirapine (iNVP) for prophylaxis of MTCT for the duration of breastfeeding. Longitudinal maternal samples at 6, 26, 50 and 74 weeks postpartum from a subset of participants matched on baseline maternal CD4 count, viral load, country, and date of study randomization were selected for 16S rRNA gene sequencing of V4 region. DADA2, decontam, and phyloseq were used for sequence inference, contaminant removal, and subsequent analyses. Differences in overall microbiome composition were assessed using permutational multivariate ANOVA (PERMANOVA) with Jenson-Shannon distances. To account for repeated measures, linear mixed effects models were used to identify specific taxa that differed between the treatment groups. All statistical analyses were performed using 'R' v4.1.3.

Results: Microbiome profiles were obtained for 196/200 samples following standard processing and filtering criteria from 50 women (25 mART, 25 iNVP). Overall, breast milk microbiomes were similar between women receiving ART and those whose infants were on NVP, with Streptococcus and Staphylococcus as the dominant members. PERMANOVA revealed that time since delivery and the microbiome were associated as expected ($R2=0.037$, $p< 0.001$), but maternal ART treatment was not a significant driver of overall microbiome variation ($R2=0.001$, $p=0.845$). No statistically significant differences in diversity at any of the four timepoints nor in genus- or species-level relative abundances between the treatment arms were observed when using a linear mixed-effects model.

Conclusion: We found no evidence that the breast milk microbiome is altered by ART in lactating women living with HIV compared with women LWH and not on ART.

799 RBC FOLATE CONCENTRATIONS IN MOTHERS/INFANTS RANDOMIZED IN PREGNANCY: DTG VS EFV

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Background: The Botswana Tsepamo Surveillance study found a possible association between dolutegravir (DTG) use at conception and increased risk of neural tube defects. To explore mechanisms of this early finding, we hypothesized that DTG may block cellular uptake of folate.

Methods: We conducted a substudy in IMPAACT 2010, a multicenter, open-label, randomized controlled phase 3 clinical trial that assigned pregnant women between 14-28 weeks of gestational age to initiate one of three antiretroviral treatment (ART) regimens: DTG+ emtricitabine (FTC)/tenofovir alafenamide (TAF), DTG+FTC/tenofovir distoproxil fumarate (TDF), or efavirenz (EFV)/FTC/TDF. Red blood cell (RBC) folate concentrations, normalized for hematocrit, were assessed at study entry and delivery in mothers and at birth in infants. Outcomes were: 1) maternal RBC folate from entry to delivery, 2) infant RBC folate and 3) ratio of infant-to-maternal RBC folate at birth/delivery. Generalized estimating equation models for the $\log_e$ of folate outcomes were fit to estimate the geometric mean ratio (GMR) and 95% confidence intervals (CIs) of each arm comparison, unadjusted and adjusted for precision variables. The estimated GMR trajectory of maternal RBC folate was compared between arms with a ratio (GMRT/C).

Results: 340 mothers had at least one RBC folate measurement available: 114 in each DTG arm and 112 in the EFV arm. 310 infants had a folate measurement. Median maternal age was 25 years (IQR 22, 30) with the majority from Africa (78%). Median CD4 count was 482 cells/mm^3 and median $\log_{10}$ HIV RNA was 3 copies/mL. At study entry, median gestational age was 22 weeks (IQR 17, 25), Overall, 90% of mothers received folic acid supplements and 90% lived in countries with folic acid fortification of food. RBC folate concentrations at entry were similar across arms. The estimated geometric mean trajectory of maternal folate was only 3% higher in the DTG+FTC/TAF arm than the EFV/FTC/TDF arm (aGMRT/C: 1.03, 95%CI 1.00, 1.06). The DTG+FTC/TAF arm had only an estimated 8% lower infant-maternal folate ratio (aGMR 0.92, 95%CI 0.78, 1.09) compared to the EFV/FTC/TDF arm. Results are consistent with no clinically meaningful differences between treatment arms in maternal RBC folate trajectory, infant RBC folate, or infant-to-maternal RBC folate ratio at birth/delivery.

Conclusion: Our findings suggest that cellular uptake of folate and transport of folate to the infant do not differ in pregnant persons starting DTG- vs. EFV-based ART (nor TAF vs. TDF).

Table. Geometric Means of Each RBC Folate Outcome by Treatment Arm and Comparisons of Maternal/Infant RBC Folate Outcomes Between Arms in the IMPAACT 2010 Study in Nine Countries from June 2018 to August 2019

RBC Folate Measurement	Treatment Arm	RBC Folate - nmol/L Geometric mean - (geometric SD)[1]	Model Estimates of the Geometric Mean Ratio (95%CI) of Each Arm Comparison for Each RBC Folate Outcome			
			RBC Folate Outcome	Treatment Arm Comparison	Estimate (95%CI)[2,3,4] Unadjusted	Adjusted
Maternal Entry / Delivery	DTG+FTC/TAF	751 (1.76) / 830 (1.68)	Maternal RBC folate trajectory	DTG+FTC/TAF vs. DTG+FTC/TDF	1.02 (0.98, 1.06) P=0.34	1.02 (0.99, 1.05) P=0.22
	DTG+FTC/TDF	746 (1.62) / 743 (1.67)		DTG+FTC/TAF vs. EFV/FTC/TDF	1.02 (0.98, 1.06) P=0.22	1.03 (1.00, 1.06) P=0.094
	EFV/FTC/TDF	731 (1.67) / 694 (1.78)		DTG+FTC/TDF vs. EFV/FTC/TDF	1.01 (0.97, 1.05) P=0.69	1.01 (0.98, 1.04) P=0.62
Infant at birth	DTG+FTC/TAF	907 (1.56)	Infant RBC folate at birth (nmol/L)	DTG+FTC/TAF vs. DTG+FTC/TDF	1.04 (0.90, 1.22) P=0.59	1.02 (0.88, 1.17) P=0.81
	DTG+FTC/TDF	869 (1.57)		DTG+FTC/TAF vs. EFV/FTC/TDF	1.07 (0.92, 1.24) P=0.44	1.08 (0.93, 1.24) P=0.36
	EFV/FTC/TDF	850 (1.70)		DTG+FTC/TDF vs. EFV/FTC/TDF	1.02 (0.88, 1.19) P=0.74	1.06 (0.92, 1.22) P=0.41
Infant-to-maternal ratio	DTG+FTC/TAF	1.16 (2.15)	Infant-to-maternal ratio	DTG+FTC/TAF vs. DTG+FTC/TDF	0.97 (0.81, 1.17) P=0.79	0.96 (0.82, 1.14) P=0.69
	DTG+FTC/TDF	1.19 (1.86)		DTG+FTC/TAF vs. EFV/FTC/TDF	0.95 (0.79, 1.14) P=0.62	0.92 (0.78, 1.09) P=0.36
	EFV/FTC/TDF	1.21 (1.76)		DTG+FTC/TDF vs. EFV/FTC/TDF	0.98 (0.82, 1.17) P=0.80	0.96 (0.81, 1.13) P=0.57

1. *The geometric standard deviations are on the multiplicative scale not the additive scale.*
2. *This was a complete case analysis.*
3. *Adjusted model of **maternal folate trajectories** - includes treatment arm, time from entry to delivery (weeks) treatment arm*weeks, and precision variables (country, use of folic acid supplements, use of folic acid antagonists, mandatory folate fortification in country, and season when folate sample collected)*
4. *Adjusted models of **Infant RBC folate at birth and infant-to-maternal RBC folate ratio** - include treatment arm and precision variables (time from entry to delivery, country, use of folic acid supplements, use of folic acid antagonists, mandatory folate fortification in country, and season when folate sample collected)*

800 EFFECT OF IN-UTERO HIV AND ANTIRETROVIRAL THERAPY EXPOSURE ON GROWTH DURING INFANCY

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Background: Exposure to HIV and antiretroviral therapy (ART) *in utero* may influence infant growth and development. Most available evidence predates the adoption of Option B+ (women with HIV are immediately offered ART, regardless of their CD4 count, in order to prevent vertical transmission). We compared growth and development in HIV-exposed uninfected (HEU) to HIV-unexposed (HUU) infants in a recent cohort.

Methods: This analysis used data from a prospective birth cohort of women with and without HIV infection, and their infants in Western Kenya. Women were enrolled during pregnancy and followed up until 24 months postpartum. We used multivariable linear mixed-effects models to compare growth rates (weight-for-age z-score [WAZ] and height-for-age z-score [HAZ]) and multivariable linear regression to compare overall development (assessed with caregiver-reported early development instruments [CREDI]) between HEU and HUU children.

Results: Among 355 infants, 184 (51.8%) were HEU infants, 3.9% (14/355) were low birthweight, and 8.5% (26/307) were preterm. Median maternal age (interquartile range [IQR]) was 25.0 (22.0-29.0) years; mothers of HEU children were older and had higher incomes. During pregnancy all mothers of HEU children received ART; 67.9% (125/184) started ART pre-pregnancy and 87.3% (158/181) received 3TC/FTC,TDF,EFV. longitudinal linear analyses, HEU children did not differ significantly from HUU in growth or development (p >0.05 for all). In the combined HEU/HUU children cohort, adjusted for potential confounders, higher maternal education was associated with significantly better growth and development: WAZ (β=0.18 [95% CI:0.01, 0.34]), HAZ (β=0.26 [95% CI: 0.04, 0.48], and development (β=0.24 [95% CI: 0.02, 0.46]). Breastfeeding was associated with significantly better HAZ (β=0.42 [95% CI: 0.19, 0.66]) and development (β=0.31 [95% CI: 0.08, 0.53]).

Conclusion: HEU children had a similar growth trajectory and development to HUU children. Breastfeeding and maternal education improved weight, height, and overall development of children irrespective of maternal HIV status.

801 IPT DURING INFANCY HAS NO ADVERSE EFFECT ON GROWTH AMONG HEU CHILDREN

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Background: Isoniazid preventive therapy (IPT) decreases risk of tuberculosis (TB) disease. It is challenging to evaluate the growth impact of infant IPT in observational studies because of confounding by indication - children who received IPT may differ from those who did not. In a recent randomized trial (RCT) we assessed IPT effects on infant growth without a known TB exposure.

Methods: The infant TB Infection Prevention Study (iTIPS) trial was a non-blinded RCT among HIV-exposed uninfected (HEU) infants in Kenya. Inclusion criteria for the parent RCT were age 6-10 weeks, birthweight >2.5 kg, and gestation >37 weeks. Infants in the IPT arm received 10 mg/kg isoniazid daily for 12 months while the control arm received no intervention; post-trial observational follow-up continued through 24 months of age. We used intent-to-treat linear mixed-effects models to compare growth rates (weight-for-age z-score [WAZ] and height-for-age z-score [HAZ]) between trial arms.

Results: Among 298 infants, 150 were randomized to IPT, 47.6% were females, median birthweight was 3.4 Kg (inter-quartile range [IQR] 3.0-3.7), and 98.3% were breastfed. During 12-month intervention period and 12-month post-RCT follow-up, WAZ and HAZ declined significantly in all children with more HAZ decline in male infants. There were no growth differences between trial arms, including in sex-stratified analyses. In longitudinal linear analysis, mean WAZ (β=0.04 [95% CI:-0.14, 0.22]), HAZ (β=0.14 [95% CI:-0.06, 0.34]), and WHZ [β=-0.07 [95% CI:-0.26, 0.11]) z-scores were similar between arms as were WAZ and HAZ growth trajectories. Infants in the IPT arm had higher monthly WHZ increase (β to 24 months 0.02 [95% CI:0.01, 0.04]) than the no-IPT arm.

Conclusion: IPT administered to HEU infants without known TB exposure did not significantly impact growth outcomes in the first two years of life.

802 IMPACT OF IN-UTERO EXPOSURE TO HIV AND LATENT TB ON INFANT HUMORAL RESPONSES

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Background: Latent tuberculosis (LTBI) is a common coinfection in people with HIV. How maternal HIV and LTBI influence the development of an infant's immune response is not well characterized. We hypothesized that maternal antibodies (Ab) may interact with the infants' immune responses to TB and BCG providing the basis for this study.

Methods: Frozen plasma from pregnant women with HIV (14-34 weeks gestation) (IGRA+: n=98, IGRA-: n=101) and their infants, aged 12 and 44 weeks, were obtained from the IMPAACT P1078 study. All women were on ART with median CD4 counts of 466 (IGRA-) and 499 (IGRA+). 6 mothers developed active TB disease (ATB), determined by AFB smear. Infants were HIV-exposed uninfected and received BCG at a median of 1 week after birth. Mother/infant (M/I) pairs were characterized by IGRA status as –/–, +/–, –/+, +/+. At 44 weeks, 9 infants had become IGRA+. M/I plasma was evaluated for the presence of TB- (PPD, ESAT6/CFP10, Ag85A, and LAM) and HIV-specific (GP120) IgG, IgA, and IgM using a bead-based Luminex assay with Flexmap 3D. Statistical analysis using a Mann-Whitney test was used to identify significant differences ($p< 0.05$) between mothers (IGRA- vs IGRA+ vs ATB) and infants (–/– vs +/– and IGRA– vs IGRA+).

Results: Maternal plasma from entry was evaluated for Ab based on antepartum IGRA status (IGRA- vs IGRA+ vs ATB). No significant differences were found between IGRA- and IGRA+ mothers. Mothers who developed ATB were evaluated at the time of diagnosis and had increased PPD, ESAT6/CFP10, and Ag85A IgG ($p=0.006$, $p=0.03$, $p=0.007$), ESAT6/CFP10 and Lipoarabinomannan (LAM) IgM ($p=0.049$, $p=0.055$), and PPD and ESAT6/CFP10 IgA ($p=0.01$, $p=0.001$). Infants (–/– vs +/–) showed no differences in TB-specific plasma Ab responses at 12 weeks. Infants (+/–) exhibited a trend ($p=0.09$) for lower IgG against LAM compared to (–/–) infants at 44 weeks. IGRA+ infants exhibited a trend for higher PPD- ($p=0.066$) and Ag85A-specific ($p=0.091$) IgG at 44 weeks compared to IGRA- infants.

Conclusion: Exposure to maternal LTBI *in utero* does not significantly differentiate the infant's Ab profile against TB and BCG, however, we observed a trend for reduced LAM-specific IgG responses at 44 weeks in (+/–) infants. Further evaluation of the function of these Ab and cellular immunity to BCG would provide greater insight into the effect HIV and TB exposure *in utero* has on the infants' responses to BCG and protection from TB.

IGRA- Infant Antibody Responses

IGRA- Infant Antibody Responses (Mean Fluorescence Intensity, mean (standard deviation))												
	IGRA- Infants/IGRA- Mothers 12 Wks (n=87)			IGRA- Infants/IGRA+ Mothers 12 Wks (n=83)			IGRA- Infants/IGRA- Mothers 44 Wks (n=84)			IGRA- Infants/IGRA+ Mothers 44 Wks (n=72)		
	IgG	IgM	IgA	IgG	IgM	IgA	IgG	IgM	IgA	IgG	IgM	IgA
HIV GP120	16892 (13707)	258.6 (200.6)	126.2 (16.69)	16990 (12994)	504.5 (2169)	126.1 (24.79)	313 (992)	1296 (2214)	130.5 (23.72)	1173 (5304)	1399 (1693)	141.8 (13.66)
PPD	235.7 (113.8)	328.3 (168.7)	141.9 (24.13)	227.2 (79.73)	326.7 (144.1)	139.3 (20.91)	395.2 (350.4)	870.5 (990.9)	153.4 (30.39)	344.9 (209.5)	865.5 (754.2)	157.2 (20.11)
ESAT6/CFP10	311.8 (296.5)	445.5 (391.9)	172.7 (34.30)	366.4 (526)	486 (864.0)	167.2 (23.78)	569.5 (735.3)	1624 (2076)	193.8 (68.34)	575.4 (963)	1645 (1729)	203.8 (57.42)
Ag85A	376.3 (693)	1808 (1784)	185.1 (73.83)	315.1 (192.1)	1876 (2255)	188.8 (94.49)	509.8 (383.6)	3214 (2752)	220.4 (130.2)	519.1 (451.8)	4103 (3614)	215.4 (55.29)
LAM	183.1 (76.19)	142.1 (37.80)	112.8 (15.06)	175.8 (60.83)	138.6 (34.58)	110 (14.31)	276.4 (195.9)	412.1 (444.9)	123.7 (24.89)	273.9 (326.3)	544.3 (1131)	128 (15.88)
Background (PBS control)	141.06 (23.236)	133.04 (16.956)	131.78 (18.886)	141.06 (23.236)	133.04 (16.956)	131.78 (18.886)	141.06 (23.236)	133.04 (16.956)	131.78 (18.886)	141.06 (23.236)	133.04 (16.956)	131.78 (18.886)

803 LOWER ACADEMIC PERFORMANCE AMONG CHILDREN WITH PERINATAL HIV EXPOSURE IN BOTSWANA

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Background: Higher risk of suboptimal neurodevelopment has been identified among children who are HIV-exposed but uninfected (HEU) compared to children born to women without HIV in some studies. However, academic performance of school-aged children by HIV exposure status has not been well studied.

Methods: The Botswana-based FLOURISH study is an ongoing prospective observational study re-enrolling mother-child pairs who previously participated in maternal-child health studies through the Botswana Harvard AIDS Institute Partnership and for which data on maternal HIV status, antiretroviral treatment (ART), obstetric history, and child HIV status and outcomes through at least 18 months-of-life had been prospectively collected. FLOURISH parents report their child's past school grades at enrollment. A Cochran-Mantel-Haenszel test was used to compare academic performance between children who are HEU vs. HIV-unexposed uninfected (HUU) and whose last grade completed was standard 3 or 4 (4th and 5th grade United States equivalence). Lower academic performance was defined as an overall grade for all coursework of "C" or lower (≤55%). Unadjusted and adjusted logistic regression models were fit to identify factors associated with lower academic performance.

Results: Of 160 children, 114 were HEU. 16 (14%) children HEU were born preterm (< 37 weeks gestation) compared to 4 (9%) children HUU. Among children HEU, 76% were exposed *in utero* to triple ART, 23% to only zidovudine, and 1% had no fetal antiretroviral exposure. Women with HIV were more often older at enrollment, a higher proportion had no or primary education only (16% versus 0%), and less likely to have breastfed (19% vs 100%). A higher proportion of children HEU had lower academic performance compared to their HUU peers (71% vs 48%; $p=0.013$). In adjusted analyses, children HEU remained significantly more likely to have lower academic performance (Adjusted odds ratio: 2.31 [95% Confidence Interval: 1.05, 5.11]; $p=0.04$) (Table 1).

Conclusion: In this small cohort in Botswana, primary school academic performance was lower among children HEU compared to children HUU. If confirmed, this could have significant human capital implications for countries, such as Botswana, where >20% of infants are born HEU. Identifying modifiable contributors is of paramount importance, as is the development of screening tools to identify children at risk of poor academic achievement and interventions to mitigate the risk well before initiation of formal education.

Table 1: Logistic Regression Model of Factors Associated with Lower Academic Performance in Children Completing Standard 3 or 4

	Unadjusted Model		Adjusted Model	
Covariates of Interest	Odds Ratio (95% CI)	p-value	Odds Ratio (95% CI)	p-value
HEU versus HUU	2.68 (1.32, 5.42)	**<0.01**	2.31 (1.05, 5.11)	**0.04**
Low Maternal Education[1]	3.01 (0.83, 10.89)	0.09	2.20 (0.58, 8.42)	0.25
Maternal Depression/Anxiety[2]	1.93 (0.51, 7.34)	0.33	1.68 (0.42, 6.76)	0.46
Maternal Income[3]				
>5P00 per month	REF		REF	
P101-P500 per month	3.68 (0.98, 13.84)	**0.05**	2.30 (0.57, 9.27)	0.24
P51 - P100 per month	7.20 (1.52, 34.14)	**0.01**	4.65 (0.92, 23.64)	0.06
P1 - P50 per month	5.14 (1.17, 22.69)	**0.03**	3.59 (0.76, 16.98)	0.11
None	3.50 (0.91, 13.48)	0.07	2.31 (0.55, 9.62)	0.25
Household Food Insecurity[4]	0.79 (0.38, 1.65)	0.53	0.72 (0.32, 1.60)	0.42
Male Child	1.72 (0.89, 3.30)	0.10	1.72 (0.84, 3.53)	0.14
Preterm Birth[5]	1.04 (0.39, 2.79)	0.93	0.99 (0.32, 2.98)	0.97

[1]Low maternal education defined as no or primary education only
[2]Maternal Depression was evaluated using the PHQ9 screening tool and anxiety via the GAD7 screening tool.
[3]Maternal income collected in Pula where $1 USD ~ P10
[4]Household food insecurity was defined as being present if a caregiver reported that in the last 12 months that the household ever had to cut the size of meals or skip meals because there was not enough food in the household.
[5]Preterm birth was defined as a gestational age < 37.0 week completed gestational age.
Abbreviations: HEU: HIV-exposed uninfected; HUU: HIV-unexposed uninfected; P=Pula
NB: Covariates in unadjusted analyses with a p-value ≤ 0.20 or those for which peer-reviewed literature has reported associations with neurodevelopment were included in the adjusted model.

804 PSYCHIATRIC DISORDERS IN HIV-EXPOSED UNINFECTED VS NON-HIV-EXPOSED CHILDREN

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Background: Psychiatric health of HIV exposed uninfected (HEU) children in the era of maternal antiretroviral therapy (ART) remain unclear. We aimed to

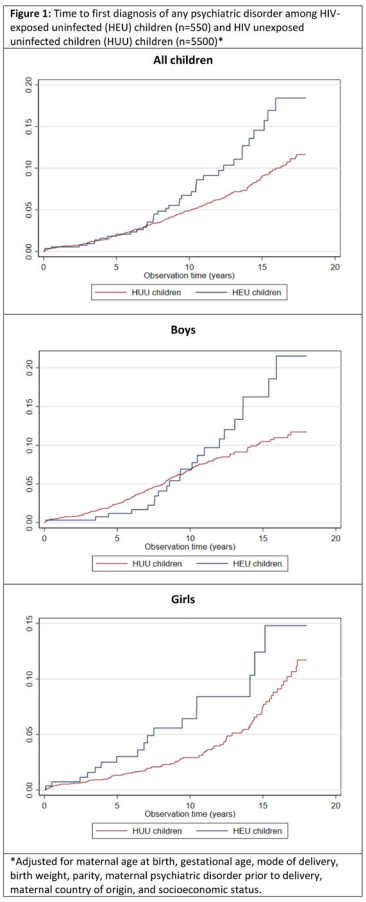
compare risk of psychiatric disorders among HEU children to a matched control group of HIV unexposed uninfected (HUU) children, born in Denmark.

Methods: In a nationwide register-based study we included all HEU children born in Denmark, 2000-2020. Each HEU child was individually matched by year of birth, maternal age at birth, and maternal immigration status to 10 HUU children. The primary outcome was risk of any psychiatric disorder (ICD-10 F00-F99). Incidence rate ratios were estimated using Poisson regression, both univariate and multivariate analysis adjusting for child and maternal confounders. Person-years at risk (PY) were calculated from birth until onset of outcome (incident diagnosis), emigration, death, or end of follow-up (December 31st, 2020). Analyses stratifying by age and sex were also conducted.

Results: In total, 550 HEU children and 5,500 HUU children were included. HIV-infected mothers were more likely to be of African origin (54% vs. 9%) and their infants were more likely to be born preterm (< 37 weeks) (12% vs 6%) and to be delivered by Caesarean Section (65% vs. 27%). At the time of delivery, all HIV-infected mothers were on ART and 87% had HIV RNA levels < 50 copies/mL. HEU children had an increased risk of any psychiatric disorder (IRR 1.45; 95% CI: 1.04 - 2.04) in the unadjusted analysis, but in the adjusted analysis, the risk was only significant for children aged 6-11 years (aIRR 1.85; 95% CI: 1.06 - 3.23) (Figure 1). Stratifying by sex, girls aged 6-11 years had an increased risk of any psychiatric disorder (aIRR 4.40; 95% CI: 1.71 - 11.36), while boys had an increased risk at age 12-20 years (aIRR 2.58; 95% CI: 1.13 - 5.90). Compared to HUU girls, HEU girls had an increased risk of anxiety (aIRR 4.00; 95% CI: 1.67 – 9.69) which was also the most common psychiatric disorder among HEU girls (n=10). The most common psychiatric disorder among HEU boys (n=8) was attention-deficit hyperactivity disorder (ADHD). However, there was no difference in risk of ADHD between the HEU and HUU boys (aIRR 0.61; 95% CI: 0.20 – 1.86).

Conclusion: In a high-resource setting, HEU children had an increased risk of any psychiatric disorder compared to HUU children, especially among the 6–11 years-old girls and the 12-20 years-old boys. These findings highlight the importance of addressing the mental health needs of HEU children and young adults.

Figure 1. Time to first diagnosis of any psychiatric disorder among HIV-exposed uninfected (HEU) children and HIV unexposed uninfected children (HUU) children



805 EVALUATING ASSOCIATIONS BETWEEN IN UTERO HIV/ART EXPOSURE AND PUBERTAL STATUS

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Pediatric HIV/AIDS Cohort Study

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Background: Many factors influence pubertal onset including *in utero* exposure to medications and infections. Few studies have evaluated the influence of *in utero* HIV/antiretroviral exposure on pubertal onset in children who are HIV-exposed and uninfected (CHEU).

Methods: CHEU in the Surveillance Monitoring for ART Toxicities study of the Pediatric HIV/AIDS Cohort Study and children who are HIV-unexposed/uninfected (CHUU) in the Bone Mineral Density Cohort with sexual maturity rating (SMR) assessments at age 9yr (±4mo) were included. Puberty was defined as SMR >2 separately by sex assigned at birth (girls: breasts and/or pubic hair; boys: genitalia and/or pubic hair). Weights were used to standardize sex and racial distribution of CHUU to CHEU. Log-binomial regression models were fit to estimate the adjusted relative risks (RR) for puberty at age 9 in CHEU vs. CHUU. Among CHEU, log-binomial regression models were fit to assess the association of puberty at age 9 with: 1) protease inhibitor (PI) exposure at ≤30wk gestation, 2) maternal CD4 ≤200 vs. >200cells/mm^3, 3) HIV viral load (VL) copies/mL, and 4) child body mass index (BMI) >95th percentile.

Results: 227 CHEU (113 boys, 114 girls) and 344 CHUU (162 boys, 182 girls) were included. CHEU boys were more likely to have reached puberty by age 9 compared to CHUU boys (15% vs 9.9% genitalia, 11.2% vs 3.7% pubic hair, 10.3% vs 2.5% both), with an estimated 2-fold higher (RR=2.07, 95%CI 0.89, 4.79) risk for genitalia and 3.5 fold higher risk (RR=3.55, 95%CI 0.92, 13.81) for pubic hair. Among girls, the presence of puberty at age 9 in CHEU and CHUU was 35.2% vs 23.1% for breasts, 32.4% vs 14.8% for pubic hair, 27.8% vs 8.8% for both) with similar risks for breast (RR=0.96, 95%CI 0.65, 1.41) and pubic hair (RR=1.10, 95%CI 0.70, 1.72). Among CHEU, 74% were exposed to PIs at ≤30wk gestation. Factors associated with CHEU having begun puberty by age 9 differed by sex (Table). Among boys, those with PI exposure at ≤30wk gestation had a lower risk of reaching puberty by age 9 for genitalia and pubic hair, while higher maternal VL in pregnancy increased the risk of both outcomes. For girls, high BMI was associated with a higher prevalence of SMR >2 breasts.

Conclusion: Male CHEU were more likely to have reached puberty by age 9 compared to CHUU. Higher maternal viremia in pregnancy was associated with higher risk and PI exposure with lower risk of presence of puberty at age 9 in males, but not in females. Further confirmatory and mechanistic studies are warranted.

Table: Adjusted associations of PI exposure, CD4 count, viral load in pregnancy, and child BMI with sexual maturity rating (SMR) greater than or equal to 2 for each indicator by sex for CHEU.

Exposure		Male genitalia			Male pubic hair		
		N	Adjusted RR/PR (95% CI)[4]	p-value	N	Adjusted RR/PR (95% CI)[4]	p-value
PI exposure ≤30 wk[1]	No	16	REF		16	REF	
	Yes	74	0.23 (0.05, 1.05)	0.06	74	0.18 (0.03, 1.12)	0.07
CD4 count in pregnancy[2]	>200 cells/mm^3	81	REF		81	REF	
	≤200 cells/mm^3	15	1.51 (0.37, 6.16)	0.56	15	3.11 (0.58, 16.54)	0.18
Viral load in pregnancy[2]	1-unit increase in log RNA	96	1.93 (1.11, 3.33)	0.02	96	2.00 (1.05, 3.79)	0.03
Child BMI[3]	≤95th percentile	69	REF		69	REF	
	>95th percentile	28	2.09 (0.75, 5.86)	0.16	28	2.65 (0.76, 9.27)	0.13
		Female breasts			Female pubic hair		
			Adjusted RR/PR (95% CI)[4]	p-value		Adjusted RR/PR (95% CI)[4]	p-value
PI exposure ≤30 wk[1]	No	18	REF		18	REF	
	Yes	70	0.85 (0.35, 2.06)	0.72	69	1.19 (0.47, 3.05)	0.71
CD4 count in pregnancy[2]	>200 cells/mm^3	81	REF		80	REF	
	≤200 cells/mm^3	13	0.88 (0.30, 2.59)	0.82	13	0.91 (0.31, 2.71)	0.87
Viral load in pregnancy[2]	1-unit increase in log RNA	94	0.87 (0.64, 1.19)	0.40	93	0.88 (0.64, 1.21)	0.42
Child BMI[3]	≤95th percentile	65	REF		64	REF	
	>95th percentile	30	1.65 (0.98, 2.78)	0.06	30	1.30 (0.73, 2.32)	0.37

[1] Adjusted for age at SMR assessment, race/ethnicity, maternal pre-pregnancy BMI, household income, and earliest CD4 count <30 wk gestation.
[2] Adjusted for age at SMR assessment, race/ethnicity, maternal pre-pregnancy BMI, and household income.
[3] Adjusted for age at SMR assessment, race/ethnicity, and household income.
[4]Relative risks were computed for outcomes by maternal PI, CD4 count, and viral load, and prevalence ratio for child BMI.
BMI=body mass index, CI=confidence interval, PI=protease inhibitor, RR=relative risk, PR=prevalence ratio

806 MORTALITY LINKED TO HIGHER INFLAMMATION IN PERINATALLY-INFECTED HIV+ KIDS

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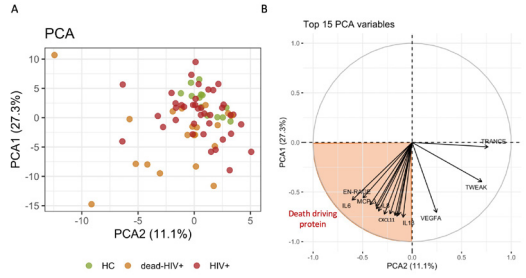
Background: Mechanisms underlying mortality in some early ART-treated HIV-perinatally infected children remain unclear. The prospective EARTH study (Early Anti-Retroviral treatment in HIV- infected children), enrolled in 6 African centers, 220 perinatally HIV-infected children collecting clinical data and peripheral blood (< 2weeks of age). Trying to identify biomarkers predictive of mortality risk at enrollment visit, we assessed the differential plasma concentration of pro-inflammatory molecules in 3 different groups: deceased (dead-HIV+), non-deceased HIV+ children (HIV+) and healthy control (HC) study participants.
Methods: Selection of patients was done using Nearest Neighbor matching 1:2. A propensity score distance was used to select 59 individuals (HIV+), within the EARTH cohort, with similar characteristics at entry (including CD4 count, HIV viremia, weight for height, ART adherence, age at enrollment, age at ART start, country of birth, and prematurity) to 20 deceased children. Plasma samples were analyzed using an Inflammation panel proximity extension assay (*Olink* platform; T96) and benchmarked to 13 HC HIV unexposed controls. Principal Component Analysis (PCA) was done to visualize patterns in proteomics.
Results: PCA analysis on proteomic data revealed a gradient in the distribution of samples with dead-HIV+ clustering separately from HC and matched HIV+ participants (FIG.1A). Top 15 loading proteins highlighted molecules as pro-inflammatory IL-6, CXCL11 (potent agonist of CXCR3, involved in activated T cells chemotaxis) and CCL7 (also known as MCP-3, important for the activation and chemoattraction of macrophages) as death driving proteins (Fig.1B). Differential analysis at the same time point, also revealed significant higher levels in the relative concentration (NPX) of these 3 molecules, with the plasma of those who died. Logistic regression model adjusted for gender and propensity score pair match, reveals that an increase of one NPX of IL-6, CXCL11, and MCP-3 is associated with a probability increase in death of 0.75, 0.80 and 0.87, respectively.
Conclusion: HIV+ children who prematurely died demonstrated higher concentrations of inflammatory molecules at enrollment, suggesting a possible role of inflammation in driving eventual mortality. Larger studies are needed to confirm early molecular correlates of mortality in HIV+ children which may identify actionable biomarkers and inform trials of novel immunomodulatory drugs to reduce mortality.

Figure 1. A) PCA showing the sample distribution among the groups: HIV+, dead-HIV+ and HC; B) Top 15 loading proteins contributing to samples distribution within PCA.



807 INFECTED NAIVE CD4+ T CELLS IN CHILDREN WITH HIV CAN PROLIFERATE AND PERSIST ON ART

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Background: We previously showed that HIV persists in perinatally infected children through clonal expansion of T cells infected before the initiation of ART. Although HIV primarily infects memory CD4+ T cells (T_{Mem}), recent studies in adults and SIV/SHIV-infected rhesus macaques have shown that naïve CD4+ T cells (T_{Naive}) harbor a higher proportion of intact HIV genomes. Little is known about the T_{Naive} HIV reservoir in early treated children. The aims of this study were to determine (i) if HIV infects T_{Naive} in early-treated children, (ii) the infection frequency relative to T_{Mem}, (iii) the proportion that are predicted intact, and (iv) if infected T_{Naive} can undergo cellular proliferation to form infected T cell clones.
Methods: The cohort consisted of 8 children aged 5-11 years who initiated ART at a median of 4 weeks of age (range 0-39) with suppressed viremia for a median of 8.5 years. PBMC were sorted into T_{Naive} (CD45RO-CD28+CD27+CD95-CCR7+CD45RA+) and T_{Mem}(CD45RO+ CD95+). Multiple displacement amplification (MDA) was performed on genomic DNA from 320,000 T_{Naive} and 106,667 T_{Mem} from each child and dispensed in 96-well plates at limiting dilution for HIV proviruses. To detect MDA wells containing an HIV provirus and to estimate the proportion of the HIV+ MDA wells with predicted intact proviruses, probe-based PCR methods were used to screen for HIV LTR, Psi, and RRE. Integration site analysis (ISA) was performed on T_{Naive} in the child with the highest T_{Naive} frequency of infection.
Results: FACS sorting resulted in purities of a median 96.6% (range 93-100%) for T_{Mem} and 97% (range 96.5–100%) for T_{Naive}. HIV-infected T_{Naive} were detected in all 8 children at a median of 37.5 infected cells/million (range 6–231), a mean of 11-fold lower than infected T_{Mem} in the same children. Of the 201 HIV LTR+ T_{Naive} detected in the 8 children, 4 were predicted intact (6.5% of proviruses with detectable Psi and/or RRE, 2% of LTR+). ISA identified 8 clones of infected cells in the TNaive subset. None of 8 infected cell clones were found to carry intact HIV proviruses.
Conclusion: We found that infected T_{Naive} persist in children with perinatal HIV on ART for 5-11 years. Some infected T_{Naive} can proliferate into clones of infected cells. Measurements adapted from the Intact Provirus Detection Assay, showed that 6.5% of infected T_{Naive} (2% of LTR+) are predicted to be intact. Our results demonstrate that T_{Naive} are an important HIV reservoir in perinatally infected children on ART.

808 LONGITUDINAL T CELL IMMUNE PROFILING IN HIV-EXPOSED INFECTED AND UNINFECTED INFANTS

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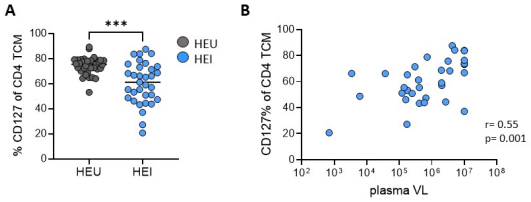
Background: In perinatal HIV infection, early ART initiation is now recommended but questions remain regarding infant immune responses to HIV as well as the impact of HIV on early immune development.
Methods: We conducted a longitudinal study in HIV exposed infected (HEI,n=33) and uninfected (HEU,n=35) infants from Maputo, Mozambique (TARA cohort). Although ART was prescribed at diagnosis (1-2mo), adherence was inconsistent with only 6/33 achieving suppression within 5 mo of starting ART and maintaining plasma virus load (VL) < 200 copies/ml for 2 yrs. T cell phenotypes were assessed at ages 1-2 mo. (entry, Pre-ART), 5, 10, and 18 mo. Expression of markers of activation and immune regulation (CCR5, CD127, CD25, CD28, CD31, CD38, CXCR5, HLA-DR, PD-1, TIGIT) were measured on CD4 and CD8 T cell subsets by flow cytometry. Median VL in HEI at entry was 5.7 logs (range 2.5-7 logs). Spearman correlation was performed to find associations between T cell phenotypic data and VL.
Results: Compared to HEU at entry, higher frequencies of cells expressing activation markers, HLA-DR, PD-1, CD38, and CD25 and lower frequencies of CD28 and CD127 (IL-7R) were noted in CD8 and CD4 T cells of HEI. At entry, CD127+ CD4 T central memory cells correlated positively with VL (r=0.53, p=0.002) and CXCR5+ CD4 T cells correlated negatively with VL (r=-0.54, p=0.001). Dynamic changes in surface receptor expression were evident from 1 to 18 mo. in HEU and HEI infants, with CXCR5, PD-1, and TIGIT increasing and CD127 and CD38 decreasing with age in CD4 and CD8 T cells. Thus, to identify age-independent immunological correlates of VL in HEI at different timepoints longitudinally, we excluded T cell parameters that showed significant correlations ($p< 0.05$) with all three of the following: age in HEU, age in HEI, and VL in HEI leaving 62/382 parameters (16%); of these, co-expression of HLA-DR and CD38 on CD8 T cells was a strong positive indicator of plasma VL levels ($r=0.44$, $p< 0.0001$).

Conclusion: Our results point to a role for IL7/IL7R signaling in early response to HIV infection in infants and suggests that the magnitude of IL-7 receptor downregulation on memory CD4 T cells in response to IL-7 levels could be a correlate of viral control. Further, we report the T cell developmental changes directly attributed to HIV burden and provide a strategy for identifying age-independent correlates of viral control in infants that may be important to guide the design of immune-based interventions, including vaccines, in early life.

Relationship of CD127 (IL7R) expression on CD4 T cells and Virus Load in Infants



Relationship of CD127 (IL7R) expression on CD4 T cells and HIV infection in TARA cohort. CD127 positive cell frequencies are shown for CD4 central memory T cell subset (Tcm; defined by CD3+CD4+CD45RO+CD27+CCR7+ Live lymphocytes). In **A)** comparison between Entry (1-2mo.) cell frequencies in HIV exposed uninfected (gray, HEU) and HIV exposed infected (blue, HEI). Unpaired t test was performed, *** indicates p<0.001. In **B)** X-Y plot showing correlation between CD127 expression on CD4 Tcm and Entry plasma VL measurement. Spearman correlation was performed, data shown on figure.

809 TORQUETENOVIRUS: MARKER OF IMMUNE RECONSTITUTION IN PERINATALLY HIV-INFECTED PATIENTS

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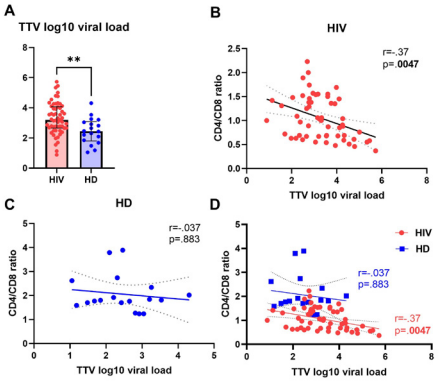
Background: Torque Teno Virus (TTV), a small, circular, single-stranded DNA virus, is an integral part of the human virome, whose implications in terms of immune response are barely understood. Recently, studies have suggested its potential use as an immunological marker in immunocompromised patients. The aim of this study was to measure TTV viral load in a cohort of perinatally HIV-infected patients (PHIV) and explore its association with immune reconstitution.

Methods: Chronic PHIV on stable antiretroviral treatment (ART) and with sustained undetectable HIV viral load were selected from the Spanish Cohort of PHIV (CoRISpe/FARO), and compared to a cohort of uninfected controls. Plasma samples and peripheral blood mononuclear cells (PBMCs) were obtained from the Spanish HIV BioBank. Plasma TTV detection and quantification was assessed by qPCR and T-cell phenotype was studied by multiparametric flow cytometry on PBMCs. Correlations with baseline CD4 and CD8 and long-term immune and HIV VL evolution were analysed.

Results: A total of 57 PHIV (44% males) were included and compared to 23 HIV-uninfected healthy donors (34% males) (HD). At baseline, PHIV were younger (20 [17-24] vs 26 [24-27] years, p< 0.001). Their median CD4-T cells was 736 [574-906] and had a median of 17 years [14-20.5] since ART initiation and 65 months [39-116] under virological control. TTV viral load in plasma was significantly higher among PHIV (Fig.A) and in males compared to females (p=0.02). TTV viral load correlated with CD4 and CD8 T-cell and the CD4/CD8 ratio (p=0.002; r=-0.39, p=0.037; r=0.277, p=0.005; r=-0.37 respectively) among PHIV (Fig.B-D), but not with CD4 nadir, age at ART initiation or time under HIV suppression. Among PHIV, TTV viral load positively correlated with the co-expression of HLA-DR/CD38 in CD4 T-cells (p< 0.01, r=0.39) and the soluble proinflammatory biomarker IL-6 (p=0.04, r=0.37). Baseline TTV viral load was higher in patients who lost HIV suppression during the follow-up (p< 0.05). After three and five years of follow-up, changes in CD4/CD8 ratio from baseline time-point, inversely correlated with TTV levels (p=0.09; r=-0.33 and p=0.06; r=-0.56 respectively).

Conclusion: TTV viral load was significantly higher among PHIV. Despite associations with T-cell activation and IL-6 were mild, TTV viral load strongly correlated with the CD4/CD8 ratio, suggesting its potential value as an immunological predictor.

TTV viral load in PHIV vs HD (A) and correlations with CD4/CD8 ratio in PHIV and HD (B-D).



810 HIGH MORTALITY IN AFRICAN INFANTS HOSPITALIZED WITH SEVERE PNEUMONIA AND ADVANCED HIV

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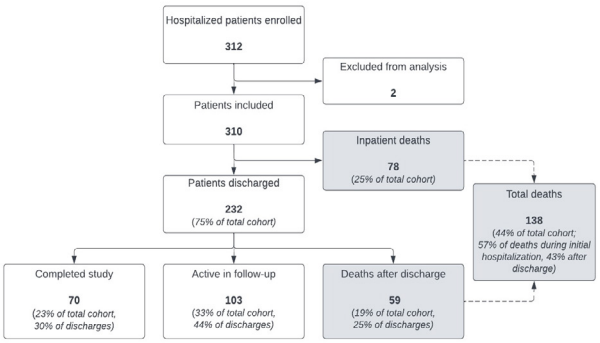
Background: Children with advanced HIV disease are known to have increased risk of mortality, but inpatient and post-discharge death rates for infants hospitalized with severe pneumonia are not well-described.

Methods: EMPIRICAL is an ongoing clinical trial (#NCT03915366) supported by EDCTP2 and the European Union (RIA2017MC-2013) enrolling infants 28-365 days age with HIV and severe pneumonia in 22 hospitals in Ivory Coast, Malawi, Mozambique, Uganda, Zambia, Zimbabwe. It is a Phase II-III, open-label randomized factorial (2×2) trial to assess the impact of empiric treatment against cytomegalovirus (CMV) and tuberculosis (TB). Infants are randomized (1:1:1:1) to (i) standard of care (SOC--antibiotics, therapeutic cotrimoxazole + steroids, and antiretroviral therapy (ART) by day 15), (ii) SOC+valganciclovir (Val), (iii) SOC+TB treatment (TBT), or (iv) SOC+TBT+Val. Confirmed TB or known TB contacts are exclusion criteria. The primary endpoint is all-cause mortality at 15 days and 12 months.

Results: In interim analysis, 312 infants were enrolled and 310 were included, with median follow-up of 2.7 months [IQR, 0.27-6.18]. Median age was 4.5 [IQR, 3.2-7.3] months and 155 (50%) were female. At recruitment 285 (92%) had chest indrawing, 199 (64%) had oxygen saturations < 90% and 84 (27%) had severe malnutrition. HIV was newly diagnosed in 226 (73%), there was history of maternal or infant prophylaxis for 119 (38%), and 93 (30%) were on cotrimoxazole prophylaxis (CPT). Median baseline viral load and CD4% were 6.3 logs cp/mL [5.8-7.0] and 14.4% [9.9-21.6], respectively. Overall, 137 infants (41%) died during follow-up at a median age of 5.4 months [IQR, 3.7-8.3], and at a median of 9 days [IQR, 2-35] after recruitment. A total of 43% of deaths occurred after discharge and 25% of discharged patients died during subsequent follow-up (Figure 1). The probability of survival at 15 days was 71% (95%CI: 66-76), and at 12 months was 50% (95%CI: 44-57). Pneumonia (48%) and sepsis (18%) were the most common causes of death.

Conclusion: Infants with HIV and severe pneumonia have extremely high mortality rates during hospitalization and after discharge. Urgent measures are needed to close gaps in PMTCT and early infant diagnosis programs, with timely linkage to CPT/ART and ongoing adherence support. For those infants that fall through the cracks and develop severe pneumonia requiring hospitalization, we will report on the impact of addition of CMV and TB treatment to the current standard of care at trial conclusion.

Recruitment, follow-up, and mortality



811 MORTALITY RISK AMONG CHILDREN < 5 YEARS OLD LIVING WITH HIV ON ART

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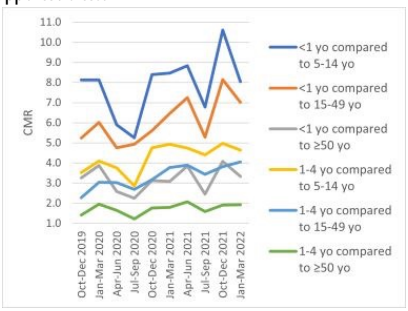
Background: Children living with HIV (CLHIV) < 5 years old (yo) not on antiretroviral treatment (ART) experience disproportionately high mortality. Mortality risk among those on ART is less clear. We aimed to describe and compare mortality risk among CLHIV < 5 yo on ART with that of older people living with HIV (PLHIV) ≥5 yo on ART.

Methods: We analyzed US President's Emergency Plan for AIDS relief (PEPFAR) Monitoring, Evaluation, and Reporting data collected quarterly from all PEPFAR-supported sites globally during October 2019-March 2022. We described the total number of deaths reported, proportion of those on ART who died (number of reported deaths in the current reporting quarter divided by the sum of PLHIV on ART in the previous reporting quarter and PLHIV started on ART in the current reporting quarter), and viral load suppression rates (VLS: proportion of PLHIV on ART with VL result reported who were virally suppressed [HIV RNA < 1000 copies/mL]). Crude mortality ratios (CMR) were calculated comparing proportion who died among CLHIV < 5 yo (stratified by < 1 and 1-4 yo to differentiate infants from other children < 5 yo) and PLHIV ≥5 yo (stratified by 5-14, 15-49, and ≥50 yo) on ART during Oct 2019-Mar 2022.

Results: From Oct 2019-Mar 2022, on average 123,636 CLHIV < 5 yo were on ART each quarter (n=14,152 < 1 yo and n=109,484 1-4 yo); in total 7,949 CLHIV < 5 yo on ART died (n=1,510 < 1 yo and n=6,439 1-4 yo) over this period. CLHIV < 1 yo on ART were more likely to die compared to PLHIV on ART 5-14 yo (CMR 7.6, range by quarter 5.2-10.6), 15-49 yo (CMR 6.0, range 4.8-8.1) and ≥50 yo (CMR 3.1; range 2.2-4.1). CLHIV 1-4 yo on ART were also more likely to die compared to those 5-14 yo (CMR 4.2, range 2.9-5.0), 15-49 yo (CMR 3.3, range 2.3-4.0) and ≥50 yo (CMR 1.7; range 1.2-2.1, Figure). Average VLS among CLHIV < 1 and CLHIV 1-4 yo were 78% and 72%, respectively, compared to 84%, 94%, and 96% of those 5-14, 15-49 and ≥50 yo, respectively.

Conclusion: PEPFAR program data suggest CLHIV < 5 yo on ART, specifically those < 1 and 1-4 yo, have higher risk of death compared to PLHIV 5-14, 15-49, and ≥50 yo on ART. Suboptimal VLS suggests inadequately treated HIV may be a factor. More granular data can help better understand confounding and causal factors related to mortality of CLHIV < 5 yo. These findings further highlight the health inequities that CLHIV < 5 yo experience and the importance of global efforts to improve their health.

Crude Mortality Ratios (CMR) comparing proportion who died among children <5 years old (yo) living with HIV on antiretroviral treatment (ART) and older people ≥5 yo living with HIV on ART during October 2019-March 2022 in all PEPFAR supported sites.



812 RELATIVE GAP IN HIV VIRAL LOAD SUPPRESSION IN YOUNGER CHILDREN IN ETHIOPIA

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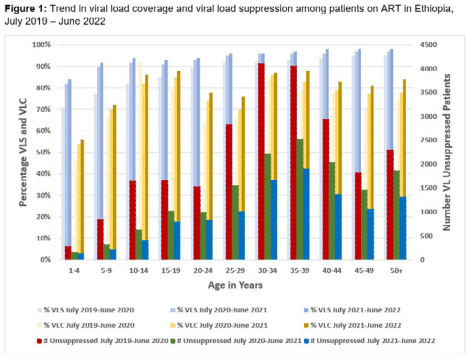
Background: Ethiopia adopted the 95-95-95 UNAIDS goal for controlling HIV by 2030. The country subsequently strengthened viral load (VL) testing services and implemented interventions to improve viral load suppression (VLS) among 95% of people on antiretroviral (ARV) treatment. We present the trend of VL coverage (VLC) and VLS by age-band in the past three years.

Methods: We used aggregate national VL data from Data for Accountability, Transparency, and Impact (DATIM) for 2019-2022. Annual trend analysis of VLC (number tested/total eligible on ART) and VLS (number suppressed/number tested) are presented. Percentage is computed to describe the trend in VLC and VLS and the absolute number of VL unsuppressed (>1,000 copies/ml) cases is also presented.

Results: At baseline (July 2019-June 2020), the VLS in the age group 1-4 and 5-9 years was in the lowest range, 71% and 77% respectively. The highest baseline VLS (95%) was reported among the age group 45-49 and 50+. The baseline VLC was relatively lower in the age group 1-4 (46%), 5-9 (66%), 20-24 (64%) and 25-29 (66%) while the VLC in the remaining age groups at baseline was above 70%. After two years, VLS in age group 1-4 and 5-9 showed a relative improvement (84% and 92% respectively) while all other age bands beyond 25 years exceeded the 95% target. The two years result showed that VLC increased modestly among younger children: 56% and 72% for 1-4- and 5–9-year-old respectively. In July 2021- June 2022, the only adult age groups with VLC less than 80% were 20-24 and 25-29 corresponding with their relatively lower baseline result. A total of 24,042 unsuppressed cases were reported in July 2019-June 2020 most of which (88.4%) were in the adult age group above 15 years of age. The number of unsuppressed patients significantly reduced over the three years in all age groups and reached at 10,739 in July 2021-June 2022 (reduced by 55.3% from the baseline) and the adult proportion was 92.9% with relative increase from the baseline.

Conclusion: Ethiopia is on track in achieving the UNAIDS third 95 target within all age groups in 2030 provided the VLS performance gap among younger children is addressed. Improving VLC among children and young adults is beneficial to distinctly understand their VL suppression status. Understanding the root causes of low VLC and VLS among children on ART and devising targeted interventions is very important. The progressive reduction in the absolute number of unsuppressed cases is an encouraging result.

Trend in viral load coverage and viral load suppression among patients on ART in Ethiopia, July 2019 – June 2022



813 FANMI: A RANDOMIZED TRIAL OF COMMUNITY COHORT HIV CARE FOR ADOLESCENT GIRLS, HAITI

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Background: Adolescent girls and young women are the epicenter of the global HIV epidemic and in need of multilevel interventions to improve their health outcomes.
Methods: FANMI, a randomized-controlled trial, evaluated the effectiveness of community-based cohort HIV care versus standard of care (SOC) among adolescent and young adults living with HIV (AYALH) in Haiti. Females, 16-24 years who were newly diagnosed with HIV at clinic or community HIV testing sites, or defaulted >6 months from care, were randomized 1:1 to FANMI vs SOC. FANMI was designed to improve convenience, social support and stigma by grouping AYALH in cohorts of 6-10 peers to attend monthly HIV care sessions in a community center with integrated clinical care, group counseling, and social activities led by the same provider. National guideline changes during the study included switching participants to dolutegravir regimens and expanding SOC visits to 6 months. The primary outcome was 12-month retention defined as any visit 9-15 months from enrollment. Secondary outcomes included viral suppression (< 1000 copies/ml), risk behaviors, and acceptability using interviews.
Results: 120 AYALH enrolled (60 per arm) between May 2018-January 2021. Median age was 21, 91% were newly diagnosed, and median CD4 count was 591 cells/mm^3 (IQR 399-788). A total of 78.3% (47/60) FANMI participants vs 85.0% (51/60) in SOC achieved the primary outcome (unadjusted RR=0.92 95%CI 0.78-1.09, p=0.35). Excluding 9 participants who never attended a FANMI/SOC visit after enrollment, 12-month retention was 88.7% (47/53) in FANMI vs 87.9% (51/58) in SOC (RR =1.01 95%CI 0.88-1.15, p=0.90). Participants who presented for HIV testing vs community testing and achieved the primary outcome: 95% vs 70% (FANMI) and 83% vs 88% (SOC). Viral suppression among those retained at 12 months: 44.6% (21/47) in FANMI and 37.3% (19/51) in SOC (RR 1.20 95% CI 0.74-1.9, p=0.45). There were no differences in pregnancy and risk behaviors. Providers preferred FANMI reporting increased time for counseling and peer support. FANMI participants reported high acceptability, decreased stigma, and increased social support with no confidentiality breaches. Limitations included interrupted study operations during the COVID-19 pandemic.
Conclusion: FANMI was not more effective for AYALH in Haiti but was preferred by providers and highly acceptable to participants. It offers promise as a complementary program for high-risk AYALH in low-income settings facing barriers to clinic-based care.

814 ECONOMIC STRENGTHENING INTERVENTION TO IMPROVE ART ADHERENCE IN HIV-INFECTED YOUTH

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Background: Adolescents living with HIV (ALHIV) have low antiretroviral therapy (ART) adherence and poor treatment outcomes. Poverty is a major threat to adherence, yet many interventions do not address poverty to improve adherence. In this cluster-randomized trial, we examined the impact of a multi-component asset-based economic empowerment intervention on ART adherence among ALHIV in Uganda.
Methods: In this study, we enrolled 702 ALWHIV aged 12-16 from 39 clinics (intervention=20, control=19) in Uganda between January 2014 and December 2015. Thirty-nine clinics were randomized into the control (n=344) or intervention arm (n=358). The intervention consisted of a long-term child development account (CDA), four micro-enterprise workshops, and 12 mentorship and educational sessions. Adherence was measured using unannounced pill counts, where good adherence was defined as taking 85% of prescribed pills. We used mixed-effects logistic regression analysis to examine the effect of the intervention on ART adherence, while controlling for clustering at the clinic. Study is registered at ClinicalTrials.gov (#NCT01790373).
Results: The mean age was 12.6 years, and 58% were females. **Intervention effect:** The intervention significantly improved ART adherence, OR=1.99 (95% CI: 1.09 – 2.96). **Main effect of time:** adherence gradually decline at every visit (except visit two); third visit OR=0.40 (95% CI: 0.26 – 0.64); fourth visit OR=0.35 (95% CI: 0.24 – 0.52); fifth visit OR=31 (95% CI: 0.22 – 0.43); and the sixth visit OR=0.27 (95% CI: 0.19 – 0.39). **Intervention-time effect:** we found significantly higher adherence in the intervention group at visit four OR=1.59 (95% CI: 1.00 – 2.54); visit five OR=1.67 (95% CI: 1.11 – 2.50); and visit six, OR=2.06 (95% CI: 1.41 – 3.00).
Conclusion: Our findings support the theory that economic strengthening interventions improve patient outcomes and should be in incorporated in the care packages for ALWHIV in resource-limited settings if the 95-95-95 targets are to be realized.

Effect of economic empowerment intervention on ART adherence among adolescents living with HIV

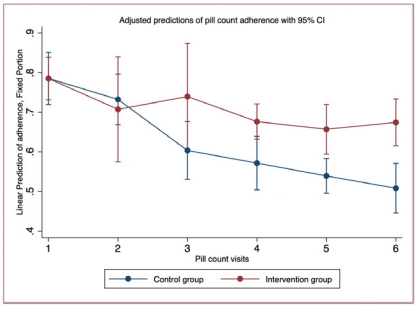

Figure 1: Graph showing the impact of the economic empowerment intervention on adherence to antiretroviral therapy among adolescents living with HIV in Uganda.

815 ORAL MICROBIOTA IN CHILDREN WHO STARTED ANTIRETROVIRAL THERAPY AT YOUNG AGES

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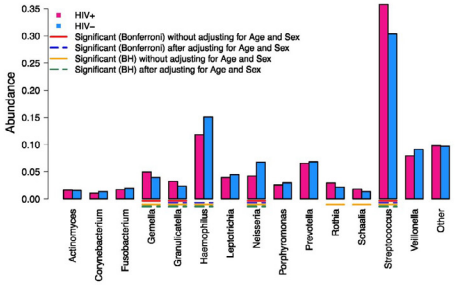
Background: Infancy is an important developmental period when the human microbiome is shaped. Given links between young age at antiretroviral treatment (ART) initiation and smaller persisting viral reservoirs, we hypothesized that earlier ART initiation may leave distinct microbial signatures in the oral cavity detectable in children living with HIV (CLWH).
Methods: Oral swab samples were collected from 477 CLWH and 123 children without HIV at two sites in Johannesburg, South Africa. CLWH had started ART < 2 years of age with 60% starting < 6 months of age. Most were well-controlled on ART at a median of 10 years of age when the swab was collected. Controls were age-matched and recruited from the same communities. Sequencing of the V4 amplicon of the 16S rRNA gene was done using established protocols. DADA2, decontam, and phyloseq were used for sequence inference, contaminant removal, and subsequent analyses. All p-values were adjusted for multiple testing using Benjamini-Hochberg false discovery rate method. Statistical analyses were performed with R.
Results: CLWH had lower alpha diversity than uninfected children (Shannon index p< 0.0001). Genus-level abundances of *Granulicatella*, *Streptococcus* and *Gemella* were greater and *Neisseria* and *Haemophilus* were less abundant

among CLWH compared to uninfected children. Associations were strongest among boys. There was no evidence of attenuation of associations with earlier ART initiation. In fact, decreased bacterial diversity and differences in taxa abundances in CLWH versus controls were consistent regardless of whether ART was started before or after 6 months of age. Shifts in genus-level taxa abundances relative to uninfected controls were most marked in children on regimens containing lopinavir/ritonavir; with few shifts seen if on regimens containing efavirenz.

Conclusion: A distinct profile of less diverse oral bacterial taxa was observed in school-age CLWH on ART versus uninfected age-matched children suggesting persisting interference of HIV and its treatments on microbiota in the mouth. Any effects of earlier ART initiation were not detectable at this age. Studies of treated adults with HIV have observed similar shifts in taxa abundances. Oral microbiota have been linked to salivary cytokine levels with associations between *Granulicatella* and IL-8 and *Neisseria* and IL-6. Declines in *Neisseria* abundances in oral samples have been associated with more severe outcomes in influenza and COVID-19.



Barplot of mean abundances for each of the 15 genus-level taxa among 476 children living with HIV (pink bars) and 123 children who are uninfected (blue bars) with significant differences between the groups marked with lines adjusting for age and sex.

816 IMMUNE ACTIVATION AND NEUROCOGNITION IN UGANDAN ADOLESCENTS LIVING WITH HIV

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Background: Immune activation is associated with neurocognitive problems in virally suppressed adults living with HIV. Less is known about this relationship in adolescents with perinatally acquired HIV (PHIV) residing in low-income countries with high burdens of PHIV. We examined this relationship in Ugandan adolescents with PHIV.

Methods: Eighty-two adolescents in Kampala, Uganda (28 virally suppressed [< 400 copies/mL] PHIV and 54 socio-demographically matched HIV- controls) completed 12 tablet-based neurocognitive tests. Control based test z-scores and a global/overall z-score were calculated. We measured plasma (soluble CD14 and CD163), monocyte (proportions of monocyte subsets), and T-cell (expression of CD38 and HLA-DR on CD4+ and CD8+) activation. Spearman correlations examined associations between test performance and immune activation.

Results: Median [IQR] age was 15[13-16] years, 40% were female. Median time on ART was 10[7-11] years for PHIV; 87% had viral load < 50 copies/mL. There were no sociodemographic or immune differences between groups. Compared to controls, global z-scores were lower among the PHIV group (p=0.05), and significantly worse on executive functioning and delayed recall tests (p≤0.05). Overall, monocyte activation significantly correlated with worse test performance: sCD163 with worse global z-score (r=0.22, p=0.04); sCD163 and non-classical monocytes with worse attention, processing speed, and motor speed (r=0.2-0.3, p≤0.01). T-cell activation (% CD4+ and CD8+ T cells expressing CD38 and/or HLA DR) was significantly associated with worse performance on learning, working memory, and executive functioning tests (r=0.2-0.4, p≤0.04). Similar associations were found by study arm, though among controls, T-cell activation and worse delayed recall were also significantly correlated (r=0.32, p=0.02).

Conclusion: PHIV with virologic suppression on ART showed evidence of worse neurocognition and similar levels of immune activation compared to controls. For the first time, we showed that monocyte and T-cell activation correlated with worse neurocognition in Ugandan adolescents with PHIV, extending findings from prior studies. However, controls also showed similar associations between immune activation and neurocognition. More research is needed to understand this relationship and its mechanisms in adolescents in low-income countries exposed to myriad sources of immune activation, as well as tremendous social and environmental adversity across neurodevelopment.

817 NEUROCOGNITIVE FUNCTION AMONG SCHOOL-AGED CHILDREN AFFECTED BY HIV IN BOTSWANA

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Ntemoga Study

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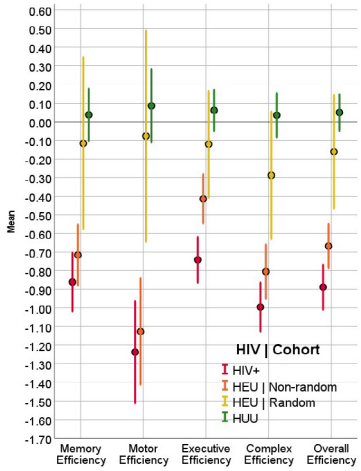
Background: Children living with HIV (HIV+) have higher rates of cognitive dysfunction, particularly in domains of attention, information processing speed, episodic memory, psychomotor, and executive functioning. HIV-exposed uninfected children (HEU) have been shown in some, but not all, studies to suffer from more neurodevelopmental delays than HIV-unexposed uninfected children (HUU). The Penn Computerized Neurocognitive Battery (PCNB) includes 14 tests that have been adapted for school-aged children in Botswana to assess memory, complex cognition, motor/processing speed, and executive function. We hypothesized that differences between HIV+, HEU and HUU children would be measurable using the PCNB.

Methods: We compared PCNB accuracy, speed, and efficiency scores in 628 children aged 7-< 18 years, ~1/3 of whom were in each of the following groups: a) HIV+, randomly selected from a clinic; b) HUU, randomly selected from public schools; and c) HEU, 18% of whom were randomly selected as part of the public school recruitment and 82% recruited HEU family members of clinic patients. Scores were age-normed using non-linear multiple regression. Multivariate normative comparisons were used to detect clinically relevant impairment (i.e., below the lower bound of the 95% confidence interval for HUU children) in individuals.

Results: All summary scores and domain scores (e.g., memory) were significantly lower for HIV+ children compared to HUU children, with medium-to-large effect sizes. In nine out of 15 comparisons, the means of the HIV+ and non-randomly selected HEU were contained within each other's confidence intervals (CIs), indicating some level of equivalence. By contrast, there were no comparisons in which the randomly selected HEU CIs included the HIV+ mean (or vice versa). HUU CIs included the randomly selected HEU mean in six of the 15 comparisons of accuracy, speed, and efficiency. (See Figure for efficiency data.) Multivariate normative comparisons flagged 27% of HIV+, 23% of HEU, and 9% of HUU children as clinically impaired. Of the HEU, 49 of 168 (29%) non-randomly selected and 6/36 (17%) randomly selected children were flagged as neurocognitively impaired.

Conclusion: HIV+ children showed worse neurocognitive function than HUU children in Botswana, supporting the validity of the PCNB in this setting. Interestingly, results also raise questions of whether previous findings of worse performance in HEU children were related to biased sampling or unmeasured confounding.

PCNB efficiency scores stratified by HIV status and cohort



818 TRAUMATIC EVENT EXPOSURE AND MENTAL DISORDERS IN YOUTH PERINATALLY AFFECTED BY HIV

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Background: Traumatic event exposure (TEE) is elevated amongst people living with HIV when compared to the general population and precedes negative outcomes such as mental illness, poor medication adherence, and viremia. Few studies have examined the impact of TEE on any of these outcomes in adolescents and young adults perinatally infected with HIV (PHIV) or perinatally exposed, but uninfected (PHEU). This largely urban and ethnically minoritized population bare a high burden of life stressors and mental illness and may be more vulnerable to TEE effects. This longitudinal analysis examines TEE prevalence experienced in childhood/adolescence among youth with PHIV (YPHIV) and PHEU (YPHEU) and assesses associations of cumulative TEE exposure with psychiatric or substance use disorders in young adulthood.
Methods: YPHIV and YPHEU, ages 9-16 years, were recruited in New York City and interviewed every 12-18 months over 5 follow-ups (FUs). Data come from the DISC-IV, a psychiatric interview. Lifetime TEE data come from youth report at enrollment (mean age=12), FU1 (mean=14), and FU2 (mean=17). Past year psychiatric and substance use disorder data come from FU5, when participants were young adults (mean age=23). Logistic regressions tested associations between cumulative counts of childhood/adolescent TEE and young adult psychiatric and substance use diagnoses.
Results: Among participants (N=237, 54% female, 59% African American, 51% Latinx), 39% endorsed ≥4 lifetime TEE; and 21% endorsed 0 or 1 during youth study visits. At FU5, 26% had a past-year psychiatric diagnosis, and 28% had a substance use disorder. Experiencing 4 or more lifetime TEEs vs. 0 or 1 TEE was positively associated with both past-year psychiatric and past-year substance use diagnoses in young adulthood. Those who had been in a situation where they thought someone would be seriously hurt or killed had higher odds of both outcomes; those who had been upset by seeing a dead body had higher odds of a substance use disorder. There were no HIV-status group differences.
Conclusion: YPHIV and YPHEU may be at high risk for TEE. TEE experienced in childhood/adolescence is associated with higher odds of psychiatric and substance use disorders in adulthood, which may lead to worse health outcomes in populations at risk for or living with HIV. Future work could investigate causal pathways between TEE and mental health and inform interventions to address long-term effects of TEE on health and mental health in youth affected by HIV.

819 MULTIFACETED PREMATURE AGING IN ADOLESCENT/YOUNG ADULT WITH PERINATAL-ACQUIRED HIV

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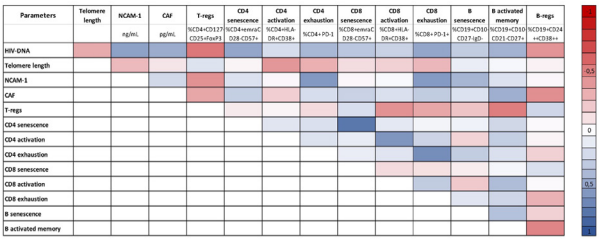
Background: HIV infection has become a chronic condition, due to antiretroviral treatment. Adolescents and young adults with perinatal acquired HIV (PHIV) are at risk of developing premature senescence and aging-associated illness. The assessment of aging biomarkers and their relation with the HIV reservoir becomes a priority to characterize and monitor these patients.
Methods: 41 PHIV adolescents/young adults (age 16 - 30 years) under antiretroviral therapy and with undetectable viremia for at least 10 years, and 23 aged-matched healthy controls were enrolled in this study. The immune aging profile (activated, senescent, exhausted and regulatory T and B cells) was studied by flow cytometry. Relative telomere length and HIV-DNA in PBMC were measured by real time PCR and ddPCR, respectively. Circulating denervation biomarkers NCAM-1 (Neural Cell Adhesion Molecule-1) and CAF (C-terminal Agrin Fragment), associated with aging and sarcopenia, were assessed by ELISA. Statistical analyses were performed using RStudio software and data were adjusted by age.
Results: Compared to healthy controls, PHIV subjects had significantly higher levels of immune senescence [%CD4emraCD28-CD57+: 8.14 (5.26-18.18) vs 3.73 (2.16-4.93), p< 0.000, % CD8emraCD28-CD57+: 6.86 (4.00-12.50) vs 3.45 (2.44-6.25), p= 0.003; %CD19+CD10-CD27-IgD-: 10.49 (8.36-14.62) vs 9.20 (4.81-11.82), p= 0.050], exhaustion [%CD4+PD-1+: 11.45 (7.81-13.58) vs 6.58 (5.58-9.52), p< 0.000; %CD8+PD-1+: 11.90 (8.20-13.85) vs 6.75 (4.46-7.36), p< 0.000] and denervation biomarkers [NCAM-1: 364.6 (284.7-575.0) vs 282.5 (241.0-374.2) ng/mL, p= 0.006; CAF: 2282.8 (1989.2-2865.8) vs 2119.5 (1662.9-2356.5) pg/mL, p=0.048]. HIV-DNA positively correlated with immune senescent, activated and exhausted T and B cells, and inversely correlated with regulatory T and B cells and telomere length. Notably, HIV-DNA was also significantly correlated with denervation biomarkers (Table).
Conclusion: These findings provide evidence for premature aging in PHIV adolescents and young adults, and reinforce the relationship between the HIV reservoir and immune senescence. In addition, these findings demonstrate for the first time that the HIV reservoir positively correlates with circulating denervation biomarkers, thus adding new tools for minimally invasive monitoring of biological aging in this population over time.

Spearman correlation plot. Colour scale represents Spearman's correlation coefficient. Blue and red correspond to positive and negative coefficient, respectively



820 CHILDREN WITH PERINATAL HIV EXHIBIT HIGH GDF15 LEVELS DESPITE ANTIRETROVIRAL THERAPY

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Background: Growth differentiation factor-15 (GDF15) is induced by myocardial inflammation to facilitate tissue repair. GDF15 levels were linked with cardiovascular disease (CVD) in adults living with HIV and echocardiographic abnormalities in children with perinatal HIV (CPHIV) >5 years old, but there is limited data in younger CPHIV. We investigated GDF15 in CPHIV ages 2 months to 20 years and their correlations with clinical parameters, immune activation and intestinal damage.
Methods: We quantified GDF15 plasma levels in 232 Kenyan children who were HIV unexposed (HU) or CPHIV and treatment naïve (ART-) or virally suppressed on treatment (ART+) aged 0-5 years ("0-5y" n=30 ART-, 30 ART+, 36 HU) and 5-20 years ("5-20y" n=43 ART-, 47 ART+, 46 HU). We assessed correlations between GDF15 and HIV viral load, CD4%, CD4:CD8, monocyte (sCD14, sCD163), T cell (CD38+HLA-DR+ CD4 and CD8 T cells) and systemic (CRP) activation markers and gut mucosal damage (intestinal fatty acid binding protein, IFABP). Plasma biomarkers were measured by ELISA (R&D Systems) and T cell activation by flow cytometry. Kruskall-Wallis test and Spearman's correlation were performed with GraphPad Prism.
Results: Compared to HU, ART- had higher GDF15 levels in 0-5y (p=0.001) and 5-20y (p=0.0002). In both age groups ART+ had higher GDF15 compared to HU (p< 0.0001). 5-20y ART+ had higher GDF15 levels than ART- (p=0.001). There was no correlation between GDF15 and age in HU or CPHIV. GDF15 in 0-5y CPHIV correlated with CD4% (p=0.04, r=-0.26), CD4:CD8 ratios (p=0.03, r=-0.31), IFABP (p=0.004, r=0.37), sCD14 (p=0.004, r=0.36), CRP (p=0.03, r=0.28) and CD38+HLA-DR+ CD4 T cells (p=0.005, r=0.39). In 5-20y CPHIV, GDF15 correlated with viral load (p=0.04, r=-0.21) and sCD14 (p=0.01, r=0.27). GDF15 correlated directly with age at ART initiation (p=0.02, r=0.41) and inversely with ART duration (p=0.03, r=-0.39) in ART+ 0-5y but not 5-20y.
Conclusion: CPHIV have elevated GDF15 levels compared with HU starting in early childhood regardless of age and treatment. In younger CPHIV, high GDF15 levels linked with advancing HIV and global inflammation. In older CPHIV, GDF15 levels were independent of inflammatory markers but higher in ART+ compared to ART-. Our data suggest that myocardial inflammation may begin early in perinatal HIV and continue despite ART in older children. Starting ART at younger ages may mitigate cardiovascular comorbidities in CPHIV but needs further study with clinical CVD measures.

821 48 MONTHS ANTHROPOMETRIC EVOLUTION OF ADOLESCENTS SWITCHING TO DOLUTEGRAVIR IN SPAIN

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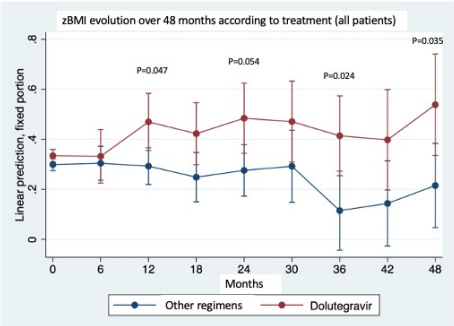
Background: Dolutegravir (DTG) is now recommended as a first-line treatment for people living with HIV. However, clinical trials among adults have risen concerns regarding DTG-associated weight gain, and real-life data addressing weight gain in adolescents are still scarce. Anthropometric changes are hard to evaluate and a concern, especially during adolescence, a period characterized by changes in body composition. We compare the evolution of a cohort of children and adolescents who switched to DTG-based regimens vs. those who maintained their previous regimens.

Methods: Retrospective study within the Spanish Cohort of Pediatric HIV. Patients < 18 years of age switching to a DTG-containing regimen before December 2020 and with at least 6 months of follow-up data were included. Patients under follow-up in the same cohort and not receiving DTG or bictegravir were included for comparison. The WHO growth charts were used to estimate zBMI. Linear mixed models were built to model the treatment effects on zBMI over 48 months.

Results: We included a total of 275 patients (135 switching to DTG), 49% female. The median age was of 13.6 ± 2.9 years (48% Caucasian, 28% Black, 9% Latino). DTG regimens mostly included abacavir plus lamivudine (75%). The third drug in the control group included protease inhibitors (45%) efavirenz (32%), or elvitegravir/raltegravir (21%). At baseline, the prevalence of overweight and obesity were 20% and 6.5%, respectively. Both groups were comparable regarding age, gender, ethnicity and zBMI. After controlling for age, sex, ethnicity and baseline zBMI as covariates, subjects switching to DTG experienced a greater adjusted zBMI increase than those remaining on their previous treatment (p=0.027) (Figure 1), with no significant changes in overweight/obesity. Subanalyses indicated that the effect was driven by participants of black ethnicity (n=76), in which the adjusted zBMI gain was especially marked while losing significance in the non-black population.

Conclusion: Our observational study shows an effect of DTG switch on zBMI, already significant at 12 months and maintained up to 48 months of follow-up, mainly affecting black adolescents. Despite the risk of residual confounders, our results are consistent with previous experience in adults suggesting a higher risk of weight gain in the black population. Larger studies are needed in order to analyze the long-term effects of DTG among children and adolescents, ideally including more precise assessments of body composition.

Figure 1. Anthropometric evolution according to treatment (all patients)



822 METABOLIC HEALTH AND BONE DENSITY IN YOUTH LIVING WITH PERINATAL HIV

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BONDY Study Research Group

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Background: Adverse metabolic profiles in adults living with HIV are associated with traditional risk factors, HIV viraemia and antiretroviral therapy (ART) with a paucity of data for youth living with perinatally acquired HIV (YPaHIV). As body mass index (BMI) impacts metabolic health and bone mineral density (BMD), we explored the relationship between markers of metabolic health, body fat distribution, hepatic steatosis and BMD in YPaHIV.

Methods: A longitudinal observational study examined bone and metabolic health in YPaHIV aged 15-24 years by total body dual-energy X-ray absorptiometry (DXA), liver fibroscan and fasting metabolic biochemistry. Associations of metabolic markers with DXA and fibroscan outcomes and by tenofovir alafenamide (TAF) use were made using two-sample t-tests and correlations investigated by Pearson's coefficient. Metabolic risk factors for lumbar spine (LS) BMD were assessed by linear regression.

Results: 85 participants; 49 (58%) male, 80 (94%) black/black African, median age 22 years (IQR 19-24), and CD4 count 645 (IQR 373-917) cells/ul, were followed for 26 months (IQR 25-28). Mean (SD) systolic blood pressure was 120 (12), fasting lipids (triglycerides 0.7 [0.9], HDL 1.4 [0.4]) and glucose 4.5 (0.5). Baseline BMI was 25.7 (5.4) increasing at 26 months by TAF (n=44) versus non-TAF (n=41) by +0.6 (2.7), +1.4 (2.6), (p 0.22) with weight gain of 2.2 (7.8) and 3.7 (6.3), (p 0.34) respectively. Correlation (p< 0.05) with BMD included BMI 0.23 (0.03), fasting lipids (total cholesterol -0.33 [0.002], triglycerides -0.23 [0.03], LDL -0.31 [0.004]), total body -0.26 (0.02) and gynoid -0.26 (0.02) fat. Correlation with controlled attenuation parameter (CAP) score included; BMI 0.27 (0.01), waist circumference 0.29 (0.007) and fasting glucose 0.33 (0.002) but not lipid or body fat parameters. Hepatic transaminases correlated with E score (ALT 0.56 [< 0.0001], AST 0.42 [0.0001]) but not CAP. Factors associated with BMD are shown in table 1. Metabolic factors according to TAF versus non-TAF differed only for total cholesterol; mean (SD) 4.4 (0.9) versus 4.0 (1.0), (p 0.03) with no differences seen for triglycerides, BMI, weight, waist circumference and body fat distribution.

Conclusion: Metabolic factors including obesity, gynoid fat distribution and abnormal lipid profiles were associated with adverse bone health in this youth cohort living with PaHIV. Effective interventions targeting traditional risk factors are required.

Linear regression of factors associated with lumbar spine bone mineral density

		Unadjusted			Adjusted		
		Beta	95% CI	P	Beta	95% CI	P
Gender	Male v Female	0.56	-0.10 0.06	0.56			
Age	Per year older	0.00	-0.02, 0.01	0.83			
CD4 count	Per 100 higher	-0.01	-0.02, 0.01	0.35			
BMI[a]	Per 1 higher	0.01	0.00, 0.13	0.08	0.00	-0.01, 0.01	0.53
Systolic BP[b]	Per 10 higher	0.03	0.00, 0.06	0.06	0.03	0.00, 0.06	0.10
Waist circ[c]	Per 10 higher	0.02	-0.01, 0.04	0.23			
Total Cholesterol	Per 1 higher	-0.06	-0.10, -0.02	0.004	-0.04	-0.09, 0.00	0.04
Triglycerides	Per 1 higher	-0.11	-0.19, -0.02	0.01	-0.08	-0.17, 0.00	0.06
Glucose	Per 10 higher	-0.46	-1.26, 0.33	0.26			
HbA1c[d]	Per 10 higher	0.01	-0.07, 0.10	0.78			
ALT[e]	Per 10 higher	0.00	-0.02, 0.01	0.52			
platelets	Per 100 higher	0.04	-0.01, 0.10	0.14	0.03	-0.03, 0.09	0.31

[a]Body mass index, [b]Blood Pressure, [c]Waist circumference, [d]glycosylated haemoglobin, [e]alanine transferase

823 THE BONDY STUDY: BONE DENSITY IN YOUTH LIVING WITH PERINATALLY ACQUIRED HIV

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Background: Youth living with perinatally acquired HIV (YPaHIV) have multiple risk factors for low bone mineral density (BMD); early years malnutrition, impaired growth, delayed puberty, and the cumulative effects of antiretroviral therapy (ART) including tenofovir disoproxil fumarate (TDF). Tenofovir alafenamide (TAF) is recommended as an alternative to TDF in those < 25 years due to an improved safety profile. We present longitudinal data on BMD accrual in YPaHIV on TAF vs non-TAF, non-TDF ART.

Methods: A longitudinal, observational study (London U.K.) evaluated bone health in YPaHIV aged 15-19 years (n=50), 20-24 (n=50) and 25+ (n=30) by dual-energy X-ray absorptiometry, bone biochemistry and turnover markers,

vitamin D and parathyroid hormone (PTH) with 2-year follow up evaluation in 15-19 years (n=42) and 20-24 (n=43). Abnormal BMD was classified as osteopenia (Z/T score < -1) or osteoporosis (Z/T score < -2). T-tests compared results between TAF and non-TAF ART. Linear regression identified factors associated with low BMD and 2-year BMD accrual.

Results: At baseline 74/130(57%) were female, 106(82%) black, median age 21(IQR 18-24) years and CD4 count 707(IQR 485-925) cells/μL. L2-4 and/or femur BMD matched for age, sex and ethnicity was abnormal in 13(26%) 15-19 years, 25(50%) 20-24 and 19(63%) 25+. Vitamin D was < 50nmol/l in 42(84%), 36(72%) and 21(70%) with high PTH (>7.2 pmol/L) in 12(24%), 24(48%) and 11(37%). 85 followed up at a median of 26(IQR 25-28) months; 44(52%) on TAF. Changes in BMD and bone mineral content (BMC) from baseline are shown (Table). There was no difference in BMC delta change with TAF, except for lumbar spine (LS) BMC in 15-19 years (Δ=0.70±0.48 TAF vs 2.18±0.48 non-TAF;p=0.038;all other p >0.25). Predictive factors of LS BMD change were baseline calcium (β=-0.16 per 1 higher;95% -0.32,-0.01;p=0.04); no association was seen with TAF use/duration, age, gender, BMI, mobility, bone markers (NTX, P1NP), PTH, vitamin D or alkaline phosphatase (ALP). LS BMC change was weakly associated with TAF duration (β=+0.04 per month longer;95%CI-0.01, +0.10;p=0.09) and ALP (β=+0.76 per 10 higher;95%CI+0.01,+0.15;p=0.04). In those 20-24 years, greater BMD hip change was associated with PTH (β=-0.01 per 10 higher;-0.02,0.00;p=0.01).

Conclusion: Reassuringly longitudinal BMD accrual was in keeping with an age, sex and ethnicity-matched population. We found limited evidence of a difference in BMD accrual favouring those receiving TAF-ART compared to non-TAF, non-TDF containing regimens.

Table. Mean and Standard deviation bone mineral density and bone mineral content of YPaHIV at baseline and 26 months, stratified by age group

Parameter	Timepoint	15-19 years (n=50 baseline; n=43 follow-up)	δ Δ	20-24 years (n=50 baseline; n=42 follow-up)	δ Δ	25+ years (n=30)
LS BMD (g/cm2)	Baseline	1.22±0.18	0.03±0.06	1.19±0.15	0.03±0.07	1.27±0.18
	Follow up	1.26±0.18	-	1.22±0.18	-	-
LS BMC (g)	Baseline	46.3±10.9	1.49±2.04	46.70±9.42	1.97±2.51	49.31±11.33
	Follow up	48.2±12.2	-	48.20±10.15	-	-
LS Z/T-score*	Baseline	-0.12±1.33	-0.15±0.44	-0.21±1.26	0.11±0.55	0.36±1.51
	Follow up	-0.30±1.38	-	-0.08±1.51	-	-
Hip mean BMD (g/cm2)	Baseline	-	-	1.07±0.15	-0.01±0.03	1.07±0.18
	Follow up	-	-	1.05±0.15	-	-
Hip T-score	Baseline	--	-	0.26±1.23	-0.10±0.47	0.28±1.24
	Follow up	-	-	0.055±1.22	-	-

Abbreviations: BMC bone mineral content; BMD bone mineral density; LS lumbar spine; δ Δ Delta change; Z-score for 15-19 years group; T-score for other groups

824 OUTCOMES IN CHILDREN LIVING WITH HIV WITH NON-SEVERE TUBERCULOSIS IN THE SHINE TRIAL

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Background: Children living with HIV (CLWH) are at high risk of developing tuberculosis (TB). Here we compare clinical outcomes between CLWH vs HIV-uninfected children with non-severe TB in the SHINE trial; and describe viral suppression among CLWH

Methods: SHINE was an open-label, randomized controlled trial conducted in 3 African countries and India. Children aged < 16 years of known HIV status, with smear-negative, non-severe TB were randomized to receive 4 vs 6 months anti-tuberculosis treatment (ATT) and followed for 72 weeks. Among CLWH, CD4 and viral load (VL) were measured at 24 and 48 weeks. Logistic regression and Cox proportional hazards models were fitted to investigate predictors of mortality, hospitalization and VL suppression

Results: Of 1204 enrolled, 127(11%) were CLWH and of similar age (median[IQR] 3.6 [1.2, 10.3] vs 3.5[1.5, 6.9] years), but more underweight (WAZ;-2.3 vs -1.0, p< 0.01) and anemic (hemoglobin 9.5 vs 11.5 g/dl, p< 0.01), and fewer had bacteriological confirmation of TB (6 vs 15%, p=0.01), compared to HIV-uninfected children. Baseline median CD4% and counts were 16% (10-26) and 719 (241-1134) cells/mm3, and 68(54%) were ART-naïve. The SHINE trial found no difference in TB outcomes between 4 vs 6 months of treatment by HIV status (NEJM 2022). There were 31(3%) deaths during the trial, many occurring early (median time to death; 4.5 vs 6.5 months in CLWH vs HIV-uninfected). Mortality risk in the trial was higher in CLWH (aHR [95%CI] 2.6 [1.2,5.8]). Age < 3 years (aHR 6.3 [1.5,27.3]), malnutrition (aHR 6.2 [2.4,15.9]) and anemia (Hb < 7g/dl) (aHR 3.8 [1.3,11.5]) independently predicted mortality. Overall, CLWH were more likely to be hospitalized (aOR=2.4 [1.3-4.6]) compared to HIV-uninfected children. Viral suppression was suboptimal with 45% and 61% with VL < 1000 copies/ml at week 24 and 48. Children initiating EFV-based ART were more likely to have VL suppression vs LPV/r-based by week 48 (71 vs 50%, p=0.056). There was no effect of randomized duration of treatment (4 vs 6 months ATT) on mortality and hospitalization by HIV-status

Conclusion: In children with non-severe TB, deaths occurred early during ATT with higher mortality in CALWH. Young age, malnutrition and anemia independently predicted mortality in both CALWH and HIV-uninfected children. Suboptimal viral suppression was common among CLWH, with worst suppression on LPV/r. There was no evidence that CALWH needed longer ATT than HIV-uninfected children, and therefore can receive 4 months ATT for non-severe TB

825 TUBERCULOSIS INCIDENCE AMONG ADOLESCENTS AND YOUNG ADULTS WITH HIV IN KENYA

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Background: There is a lack of data regarding the risk of TB among adolescents and young adults living with HIV (YWHIV), despite the observed increase in TB among this vulnerable age group.

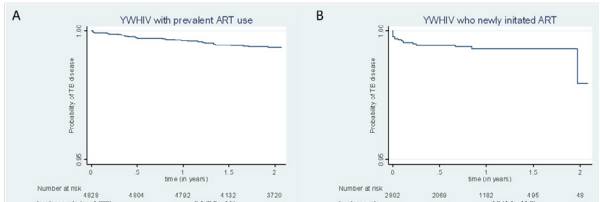
Methods: This study utilized medical records from 86 Kenyan HIV clinics from 1/1/2016 – 1/18/2018 to estimate incidence rates (IR) and evaluate individual characteristics associated with TB disease from date of antiretroviral therapy (ART) initiation (among new ART users) or from the start date of the study abstraction period (1/1/2016 among prevalent ART users). Univariate Cox proportional hazard regression was conducted to estimate hazard ratios (HR) separately among new ART initiators and those already on ART.

Results: Among 7,658 YWHIV assessed, median age at ART initiation was 18 years (IQR 11-21). Overall, 2,804 (37%) newly initiated ART after 1/2016 and 4,854 (63%) were already on ART (median duration 3 years) at 1/1/2016. Over the follow-up period, 47 YWHIV had a new TB diagnosis; TB incidence was 7.0/1,000 person years (PY) among YWHIV newly initiating ART vs. 3.1/1,000 PY those already on ART. YWHIV newly on ART had a significantly higher likelihood of TB than those already on ART (incidence risk [IR] difference: 4.0 [95% CI 0.40 – 7.21] p=0.01; Figure 1, Panels A & B). Time to incident TB was 21.3 and 295.1 days for YWHIV who newly initiated ART and prevalent ART users, respectively. YWHIV newly on ART included those diagnosed with TB concurrent with ART initiation (6[33.3%]) which contributed to the risk difference.

Among YWHIV newly on ART over the age of 18, those who had HIV treatment support had a lower risk of TB disease (HR 0.30 [95% CI 0.10-0.97] p=0.04). YWHIV with prevalent ART use had lower risk of TB disease if they received cotrimoxazole (HR 0.13 [95% confidence interval (CI) 0.02-0.96] p=0.05) or if they had a partner who tested for HIV at their baseline HIV clinic visit (among YWHIV over the age of 18; HR 0.17 [95% CI 0.05-0.64] p< 0.01).

Conclusion: YWHIV had a high incidence of TB, particularly among those newly initiating ART. Therapeutic (cotrimoxazole) and interpersonal (partner testing and treatment support) factors influenced TB incidence in this population. It is important to optimize TB prevention and case finding in this vulnerable population.

Figure 1. Kaplan Meier survival estimates for incident TB among (A) YWHIV with prevalent ART use and (B) YWHIV newly initiated ART



826 PK & SAFETY OF ABC/3TC DISPERSIBLE TABLETS & LPV/r GRANULES IN NEONATES: PETITE STUDY

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Background: No oral solid fixed-dose combination (FDC) antiretroviral dispersible formulations are available for HIV prevention or treatment from birth. Neonates could benefit from existing pediatric antiretroviral solid formulations. We evaluated the pharmacokinetics (PK) and safety of pediatric ABC/3TC dispersible tablets and LPV/r (2-in-1) granules in term neonates exposed to HIV, birth weights ≥2.0 to £4.0 kg.
Methods: The 'PETITE' study was a phase I/II, open-label, single arm, clinical trial in South Africa evaluating oral ABC/3TC (120/60 mg) dispersible tablets and LPV/r (40/10mg) granules. Neonates stratified by birth weight received 30/15 mg of ABC/3TC daily (¼ dispersible tablet) and 80/20 mg of LPV/r twice daily (2 sachets) from birth through 28 days. Two intensive PK sampling visits were performed: one at < 14 days of life and after ≥ 72 hours of treatment (PK1), and another 10-14 days later (PK2). Safety visits were performed 1-2 week(s) after each PK visit. Electrocardiograms (ECGs) were performed at baseline and during follow-up.
Results: Sixteen neonates (15 breastfed) started ABC/3TC + LPV/r within 3 days of life, median (range) birth weight was 3.1 (2.2-3.8) kg. PK1 and PK2 visits were performed between 6-14 and 19-24 days of life, respectively; 2 neonates did not complete PK2. ABC, 3TC doses were 9 (7-13), 4 (3-7) mg/kg once daily, LPV dose was 377 (307-480) mg/m2 twice daily. Geometric mean (GM, 90% CI) AUC0-24 of ABC, 3TC and LPV were higher at PK1 versus PK2 – Table 1. ABC exposures at PK1 crossed the upper target reference range but rapidly decreased to within range by 2-3 weeks of life. 3TC and LPV exposures were within the reported ranges for young infants. Geometric mean ABC, 3TC, and LPV AUC0-24 were also higher in neonates with birth weights 2-3 kg compared to 3-4 kg, 43.1 vs 31.5, 17.9 vs 11.2 and 63.4 vs 43.4 mg.hr/L, respectively. No Grade 2 or higher adverse events were related to study drug. All ECGs were normal except for a single Grade 1 prolonged QTcF interval which spontaneously resolved.
Conclusion: Initiating pediatric solid FDCs of once daily ABC/3TC dispersible tablets in combination with twice daily LPV/r granules from birth was safe and well tolerated. ABC and 3TC drug exposures were initially high but rapidly decreased. LPV exposures were lower than in adults but comparable to young infants receiving LPV/r liquid. This study supports giving solid dispersible FDCs from birth for HIV prevention and treatment in neonates.

Table 1: Geometric mean (90% CI) of ABC, 3TC and LPV PK parameters in neonates

	N	C_{max} (mg/L)	C_{tau} (mg/L)	AUC_{tau} (mg.hr/L)	AUC Reference Range[#]
ABC					
PK Visit 1	16	5.6 [4.8-6.6]	0.33 [0.21-0.53]	51.7 [42.8-62.3]	
PK Visit 2	14	4.3 [3.7-4.9]	0.02 [0.01-0.06]	25.0 [19.5-32.1]	
Overall	**30**	**5.0 [4.4-5.5]**	**0.09 [0.05-0.18]**	**36.8 [30.6-44.3]**	**6.3-50.4[#]**
3TC					
PK Visit 1	16	1.7 [1.6-1.9]	0.13 [0.08-0.20]	17.2 [14.6-20.4]	
PK Visit 2	14	1.5 [1.3-1.8]	0.03 [0.01-0.06]	11.3 [8.5-15.0]	
Overall	**30**	**1.6 [1.5-1.8]**	**0.06 [0.04-0.10]**	**14.2 [12.0-16.7]**	**6.3-26.5[#]**
LPV					
PK Visit 1	16	6.5 [5.0-8.4]	4.27 [2.85-6.41]	58.5 [42.4-80.8]	
PK Visit 2	14	5.3 [3.8-7.4]	2.70 [1.88-3.88]	46.4 [33.3-64.6]	
Overall	**30**	**5.9 [4.8-7.2]**	**3.45 [2.63-4.52]**	**52.5 [42.0-65.6]**	**27.9-62.6[#]**

[#] *IMPAACT 2019 Protocol: ^Chadwick et al PIDJ, 2009;28: 215–219 (IMPAACT P1030)*

827 TWICE DAILY 50 MG DOLUTEGRAVIR IN TUBERCULOSIS-HIV COINFECTED CHILDREN 20-35 KG

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Background: Indication for dolutegravir, dosed at 50 mg daily, have been extended to children 20-35kg. There are, however, limited data on safety and pharmacokinetics of twice daily 50 mg dolutegravir in children with HIV and tuberculosis (TB) co-infection.
Methods: We conducted an open-label, sequential non-randomised prospective study in children initiated on a rifampicin-based TB regimen and dolutegravir twice daily (BD) during TB treatment and once daily (OD) after stopping rifampicin (**NCT04746547**). Plasma samples were collected in steady-state at pre-dose, and at 1, 2, 3, 4, 6, and 12 or 24h post-dose and assayed with a validated LC-MS/MS method. Non-compartmental pharmacokinetic (PK) analyses were conducted using the ncappc package in R.The area under the concentration-time curve (AUC) was calculated using the linear-up log-down trapezoidal method. Extrapolation was done from the last measurement to 12 or 24h, using the elimination rate constant. Participants underwent frequent clinical and safety visits. Viral load was measured at weeks 8, 12, 24 and 48.
Results: We enrolled 13 children between August 2021 and September 2022 and report the preliminary analysis of all data collected up to November 2022; Median (IQR) age 10 (9-11) range [5-13] years; 54% males; 100% black race. The median (IQR) viral load and CD4 at baseline were 2.5 (1.6-5.0) log_{10}-copies/mL and 108.5 (76.5-385.2) cells/µl. Viral load was undetectable in all children completing the week 12 and 24 visits. There were two grade 3 adverse events and no SAEs. Data from 12 children were included in the preliminary PK analysis, contributing 12 profiles on twice daily dolutegravir and rifampicin and 2 profiles on once daily dolutegravir (total of 114 dolutegravir plasma concentration values). Median trough concentration (C_{Tau}) was 1.60 and 1.49 mg/L, while AUC_{0-24} was 33.55 and 36.67 h*mg/L for participants on BID dolutegravir with rifampicin and OD dolutegravir, respectively. All C_{Tau} were > 0.3 mg/L. Results are summarized in Table 1.
Conclusion: Preliminary data from children 20-35kg receiving twice-daily dolutegravir during TB treatment suggest this dosing is well-tolerated and achieves similar PK values to daily treatment for HIV-alone. VL suppression data are, similarly, promising.

Table 1. Dolutegravir (DTG) pharmacokinetic parameters and their unit presented for visit 1 and visit 2 in Median (Min, Max)

Table 1. Dolutegravir (DTG) pharmacokinetic parameters presented in Median (Min, Max).

Parameter (Unit)	Visit 1[a] DTG 50mg BD + RIF (n=12)	Visit 2 DTG 50mg OD (n=2)
T_{Max} (h)	2 (1, 4)	3.5 (3, 4)
C_{Max} (mg/L)	6.82 (3.87, 9.90)	10.1 (9.71, 10.4)
C_{Tau} (mg/L)	1.60 (0.457, 3.26)	1.49 (1.41, 1.57)
AUC_{0-12} (h*mg/L)	16.8 (8.69, 34.4)	
AUC_{0-24} (h*mg/L)	33.6 (17.4, 68.8)	36.7 (35.9, 37.4)
Half-life (h)	4.18 (3.01, 7.36)	7.55 (7.32, 7.78)
Clearance (L/h)	1.04 (0.648, 2.54)	0.431 (0.422, 0.440)

Table 1. ([a]) Two children were sampled twice during this treatment, the geometric mean was used to summarise their exposures before the summary. For children receiving 50 mg DTG BD with RIF, the AUC_{0-24h} was calculated by doubling the AUC_{0-12h} and the C_{Trough} concentrations (C_{Tau}), as a surrogate marker, were predicted at 12 hours for two children. While for children receiving 50 mg DTG OD without RIF, C_{Trough} was predicted at 24 hours and AUC_{0-24h} was calculated by extrapolating up to 24 hours, and C_{Tau} was predicted at 24 hours.

828 CAREGIVERS OF CHILDREN WITH HIV IN BOTSWANA PREFER MONTHLY IV bNAbs TO DAILY ORAL ART

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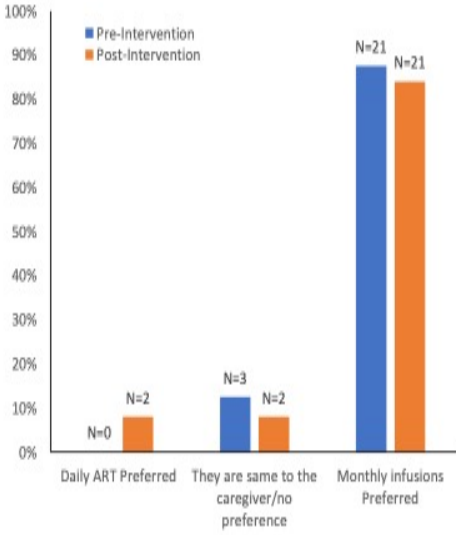
Background: Monthly intravenous infusion of broadly neutralizing monoclonal antibodies (bNAbs) may be an attractive alternative to daily oral antiretroviral treatment (ART) for children. Acceptability by caregivers remains unknown.
Methods: We evaluated monthly infusion of dual bNAbs (VRC01LS and 10-1074) as a treatment alternative to ART among children participating in the Tatelo Study in Botswana. Eligible children aged 2-5 years received 8-32 weeks of bNAbs overlapping with ART, and up to 24 weeks of bNAbs alone, at monthly intravenous infusion visits. Using closed-ended questionnaires, we evaluated the acceptability of each treatment strategy among caregivers prior to first bNAb administration visit (pre-intervention) and after completion of final bNAb administration visit (post-intervention).
Results: Twenty-five children completed all study phases, and acceptability data were available from 24 caregivers at both time points (1 primary caregiver was unavailable at pre-intervention visit). Responses were provided by the child's mother at both visits (60%), an extended family member at both visits (28%), or a combination of mother and extended family member (12%). Caregiver acceptance of bNAbs was extremely high both pre-and post-intervention, with 21/24 (87.5%) preferring bNAbs to ART pre-intervention, and 21/25 (84%) preferring bNAbs post-intervention (9/21 cared for a child who remained virally suppressed, 12/21 for a child with a viral rebound on bNAbs) (Fig 1). No caregivers preferred ART pre-intervention; however, 2/25 preferred it post-intervention (1 cared for a child who remained virally suppressed, 1 for a child with viral rebound on bNAbs). Pre-intervention, 3 (13%) caregivers

had no preference between bNAbs or ART, and 2 (8%) had no preference post-intervention. Pre-intervention, the most common reasons for preferring bNAbs over ART were "if infusions were better at suppressing the virus than ART" (n=10) and "if infusions continued to be once monthly compared to daily ART" (n=9). Post-intervention, no dominant reason for preferring bNAbs over ART emerged from caregivers.

Conclusion: Monthly intravenous bNAb infusions were highly acceptable to caregivers of children with HIV in Botswana and preferred over standard ART by most. Our findings suggest that caregiver acceptability is an unlikely barrier to bNAb uptake and eventual programmatic use for children living with HIV.

Figure 1. Pre- and post-intervention preferences by caregivers for monthly bNAb infusions vs. daily ART (if medical benefit were equal)



829 SIX-MONTH OUTCOME OF F/TAF COBICISTAT-BOOSTED DARUNAVIR IN CHILDREN 14 TO < 25KG

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Background: Emtricitabine/tenofovir alafenamide (F/TAF) is a preferred component of the pediatric ART regimen in the US guidelines and is on the WHO priority list for HIV treatment in children. Despite the increased worldwide use of INSTI-based regimens, PIs remain an important class when constructing the ARV regimen for children. There are limited data on the pharmacokinetics (PK) of F/TAF with boosted PIs in young children. We studied PK, safety and efficacy in virologically supressed children ≥3y weighing 14 to < 25kg taking the once-daily low dose tablet of F/TAF (120/15mg) and cobicistat-boosted darunavir (DRV/c).

Methods: Participants were enrolled in an open-label study evaluating F/TAF given with DRV/c (NCT02016924). The primary objective was to evaluate steady-state PK of DRV and TAF and safety of F/TAF and DRV/c. Participants had CD4 ≥200 cells/μL and estimated glomerular filtration rate ≥90 mL/min/1.73m^2 at screening and received F/TAF for at least 48 weeks, with a possible extension phase. All participants participated in an intensive PK visit, with regular HIV-RNA, adverse events (AEs), and laboratory tests assessments throughout the study. Continuous variables are presented as median (Q1, Q3), and PK parameters as geometric mean.

Results: Nine participants were enrolled from South Africa and Zimbabwe: age 4y (3, 6); 5 females. Baseline absolute and relative CD4 count were 1237 (844, 1490) cells/μL and 41% (35, 42). Duration of study drug exposure was 66 (63, 72) weeks. Steady state PK parameters for TAF, tenofovir (TFV) and DRV are presented in Table 1. At Week 24, 100% (7/7; missing=excluded analysis) had a viral load < 50 copies/mL, while CD4 percentage increased 0.8% (-1.4, 1.7). The only AEs observed in more than 1 participant were vomiting and anaemia. No participant experienced a Grade 3-4 AE. Creatinine remained within the normal range throughout follow-up, with an increase at W60 of 0.01 (-0.04, 0.09) mg/dL.

Conclusion: F/TAF LDT given with DRV/c showed acceptable exposures of TAF, TFV, and DRV in young children ≥3y weighing 14 to < 25 kg. The rate of maintained viral suppression is consistent with that observed in adolescents and adults after 24 weeks of treatment. The regimen was well tolerated. The results support continuing evaluation of F/TAF as an NRTI backbone in combination with boosted PIs in younger children with HIV; tablets for oral suspension of F/TAF and cobicistat have been developed for evaluation.

Table 1. Pharmacokinetics Parameters (Median) for TAF, TFV, and DRV

Table 1. Pharmacokinetics Parameters (Median) for TAF, TFV, and DRV

PK Parameter	TAF	TFV	DRV
AUC, h·ng/mL	325[1]	1194[2]	145565[2]
C_{max}, ng/mL	395	69	14,400
C_{tau}, ng/mL	BLQ	38.1	1680

[1] = AUC_{last}, area under curve until last detectable observation; [2] = AUC_{tau}, area under curve over dosing interval; C_{max} = maximum concentration; C_{tau} = trough concentration; BLQ = below the lower limit of quantification.

830 BIC/FTC/TAF IN FRENCH CHILDREN: FREQUENT VIRAL FAILURE BUT RARE ACQUIRED RESISTANCE

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Background: Bictegravir-50mg/Emtricitabine-200mg/Tenofovir alafenamide-25mg (BIC/FTC/TAF) is now approved for use in HIV+ children weighing ≥25 kg. However, published data about its efficacy in the paediatric population are limited to one clinical trial including only subjects with suppressed viremia at baseline, good adherence to treatment and short-term follow-up. This "real-life" study aimed to provide long-term data about the risk of viral failure (VF) and acquired genotypic resistance in children and adolescents receiving BIC/FTC/TAF and followed at Necker Hospital (Paris, France).

Methods: This retrospective monocentric study included 60 paediatric patients aged < 18 years who received BIC/FTC/TAF in 2019-2022. VF was defined as not achieving a plasma viral load (pVL) < 50 copies/ml within three months of BIC/FTC/TAF initiation or as experiencing viral rebound ≥50 copies/ml.

Results: Most of the individuals were antiretroviral experienced (93.3%), were previously exposed to INSTI (mainly dolutegravir, 85%), and displayed viral suppression at baseline (63.4%). Their median age was 11.1 years [IQR: 8.9-14.4]. In most ARV experienced subjects, BIC/FTC/TAF introduction reduced treatment burden compared to previous regimen, which contained multiple pills (61%) or syrups (30%), twice-daily dosages (43%) and/or larger pills size (4%). Genotypic susceptibility score of BIC/FTC/TAF was ≥2 in all cases. INSTI-associated resistance associated mutations (RAMs) were previously isolated in 8 patients: E157Q (n=3), L74I (n=5). Median follow-up was 29 months [IQR: 19-35]. VF occurred in 23 persons (38.3%), more frequently in case of baseline pVL ≥50 copies/mL (57.1% versus 28.2%, p< 0.05). Compared to children with sustained viral suppression, those with VF had higher median baseline pVL (4.5 versus 2.7 log_{10} copies/mL, p=0.02) and longer median duration of follow-up (33 versus 27 months, p=0.03). No emergence of RAMs was observed in patients with VF, despite a long duration of viraemia while on treatment (median 7.5 months [IQR: 6-23]). With reinforced measures to improve adherence, undetectable PVL was obtained at the last visit in 81.7% of patients without requiring ART change. None patient stopped BIC/FTC/TAF for drug-related side effect.

Conclusion: Because of its good tolerance, its high genetic barrier to resistance and small pill burden, BIC/FTC/TAF could be especially useful in the paediatric population, in which the risk of poor treatment adherence is high.

831 ADEQUATE DTG EXPOSURE IN INFANTS ON RIFAMPICIN TREATMENT RECEIVING TWICE-DAILY DTG

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EMPIRICAL clinical trial group

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Background: Dolutegravir (DTG) is recommended by WHO as first-line treatment option for children living with HIV. Rifampicin (RIF) interacts

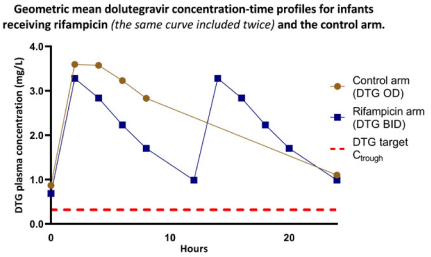
substantially with DTG by increasing DTG metabolism through induction of UGT1A1 and CYP3A4, thereby reducing its exposure resulting in potential treatment failure. Adapting the DTG dosing interval from once-daily (OD) to twice-daily (BID) was safe and effective in both adults and children. However, no pharmacokinetic (PK) data was available for children weighing < 14kg. The outcome of the RIF-DTG interaction may be different in infants as maturation of metabolic enzyme activity may not have been completed. PK data in infants receiving DTG and concomitant RIF is warranted and was identified as a knowledge gap by WHO. We evaluated plasma DTG concentrations in infants living with HIV receiving DTG BID with RIF-based TB-treatment.

Methods: This is a 2-arm PK sub-study of the EMPIRICAL randomized controlled trial (#NCT03915366) for severe pneumonia in infants living with HIV. Eligible infants aged 1-11 months, weighing ≥3kg, receiving DTG OD (control) or DTG BID with RIF-based TB-treatment, were recruited in Mozambique, Uganda, Zambia, and Zimbabwe. Infants received DTG following WHO weight-band dosing. Six blood samples were taken over 12 (BID) or 24 (OD) hours 30-90 days after start of RIF and at least 14 days after initiation of DTG. Relevant PK parameters and the proportion of infants with DTG C_{trough} below the PK target (0.32 mg/L) were summarised per treatment arm. This project is part of the EDCTP2 programme supported by the European Union RIA2017MC-2013.

Results: Of 30 enrolled infants, 27 had evaluable PK curves (Figure) of which 21 received concomitant RIF. The median (IQR) age was 7.1 (6.1 – 9.9) months, weight 7.1 (6.1 – 9.9) months, and 11/27 were female. DTG C_{trough}, AUC_{0-24h} and C_{max} GM(%CV) were 1.05(82) mg/L, 49.7(70) h*mg/L, and 3.36(65) mg/L for children on RIF, and 1.11(46) mg/L, 54.4(39) h*mg/L, and 3.86 (38)mg/L for children in the control arm, respectively. Only 1/21 infants in the RIF arm had DTG C_{trough} < 0.32mg/L vs none out of 6 in the control arm. Apparent oral DTG clearance was about 2-fold higher for infants receiving RIF.

Conclusion: Consistent with data from older children and adults, BID dosing of DTG when administered in infants on RIF resulted in adequate DTG exposure. These PK data support the use of DTG BID for infants living with HIV receiving RIF.

Geometric mean dolutegravir concentration-time profiles for infants receiving rifampicin and the control arm.



832 MODEL-INFORMED DOLUTEGRAVIR DOSE SELECTION IN PEDS WITH 1ST GENERATION InSTI-R

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Background: Dolutegravir (DTG) is an integrase strand transfer inhibitor (INSTI) approved for once-daily doing in INSTI-naive adults and children living with HIV. For adults with INSTI resistance (INSTI-r) based on certain substitutions or clinical suspicion, current recommendations are to double the standard 50 mg dose of DTG giving it twice daily (BID). However, dosing recommendations for children with INSTI-r have not been assessed. Our objective was to generate model-based population pharmacokinetic (PopPK) data to inform DTG BID dosing in 1st generation INSTI-r (raltegravir or elvitegravir) children (age ≥4 weeks and weight ≥3 kg), extrapolating efficacy and safety from adults to pediatric population based on drug exposures, in accordance with FDA and EMA guidance.

Methods: A PopPK model was developed using data from IMPAACT P1093 (NCT01302847) and PENTA ODYSSEY (NCT02259127) to predict exposures from BID dosing of DTG in pediatric patients. Clinical trial simulations were performed to evaluate predicted drug levels with different dosing strategies. Exposure metrics (AUC_{0-24}, C_{24} and C_{max}) were calculated for each dose within each weight band. The target PK exposures (C_{12h} geometric mean >1.97 µg/mL & AUC_{0-12h} >32.2 µg*h/mL) for pediatrics were selected based on this adult data. DTG C_{max} exposures were also evaluated for safety, with reference to existing adult and pediatric data.

Results: The BID dosing using the dose approved for once-daily dosing in INSTI-naive children exceeded C_{max} exposures in several weight-bands compared to existing adult and pediatric data. Among the several dosing strategies evaluated, the proposed BID dosing (Table 1) yielded predicted exposures within each weight band that were comparable to the pre-defined adult exposures. These proposed doses are expected to provide similar efficacy as observed in adults with 50 mg BID dosing.

Conclusion: The proposed BID dosing for children is predicted to achieve similar drug exposures to those in adults. While clinical PK data would form an ideal basis for dosing, recruitment of children with 1st generation INSTI-r is exceedingly challenging. These modeled data inform DTG dose selection for pediatric patients with 1st generation INSTI-r (raltegravir and elvitegravir). It is important to note that this dosing differs from guidance in adults (double standard dosing) and that BID dosing of DTG is not expected to be effective against viral resistance to DTG or bictegravir.

Table 1. Dolutegravir Model-Based BID Dosing Regimen in 1st Generation INSTI-r Pediatric Subjects

Weight Band (kg)	Dispersible Tablet BID Dose	Cmax (µg/mL)	AUC0-12h (µg*h/mL)	C12h (µg/mL)
≥3 to <6	5 mg	6.53 (3.06 – 14.22)	50.28 (22.12 – 115.5)	3.10 (0.94 – 9.15)
>6 to <10	10 mg	7.69 (3.64 – 16.73)	56.24 (23.70 – 131.95)	3.07 (0.82 – 9.97)
≥10 to <14	15 mg	6.89 (3.64 – 13.42)	47.56 (22.24 – 101.22)	2.30 (0.62 – 7.15)
≥14 to <20	15 mg	6.02 (3.14 – 11.66)	41.81 (19.40 – 90.05)	2.03 (0.55 – 6.33)
≥20 to <30	20 mg	6.97 (3.66 – 13.54)	48.65 (22.50 – 104.60)	2.40 (0.67 – 7.32)
≥30 to <40	20 mg	5.78 (3.00 – 11.29)	40.81 (18.96 – 86.44)	2.04 (0.57 – 6.13)

*PK parameters presented as Geometric Mean (90% Prediction Interval). The target GM AUC0-12h is 32.2 µg*h/mL and C12h is 1.97 µg/mL for each of the weight bands.*

833 IMPACT OF MALNUTRITION ON DOLUTEGRAVIR EXPOSURE AND ALTERNATIVE DOSING

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Background: Despite improvements in access to antiretroviral therapy (ART) worldwide, HIV/AIDS remains a major cause of child mortality, with 120,000 children dying of HIV-related illnesses in 2020. Among children receiving ART, malnutrition is associated with higher mortality. However, current dosing guidelines for many ARTs do not account for age or nutritional status. Thus children of healthy weight are often given the same dose as malnourished children of the same weight, irrespective of disparities in metabolic capacity due to their age differences. Low ART exposure may contribute to mortality in malnourished children with HIV. In order to assess the potential impact of nutritional status on ART exposures, we simulated pharmacokinetics (PK) for dolutegravir (DTG) in a real-world global population of children under 5 years of age.

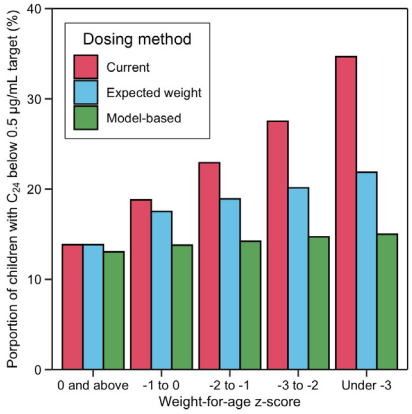
Methods: Anthropometric data from the 30 countries with the largest populations of children living with HIV were acquired from demographic health surveys. A population PK model was used to simulate DTG exposures. WHO guideline dosing was compared to: a) a modified algorithm which used expected weight for age (as opposed to actual weight) for malnourished children, and b) model-based dosing derived from individual PK parameters. Both alternative methods require only weight, age, and sex as inputs. Target geometric mean (GM) C_{24} was 0.995 µg/mL, with an acceptable individual minimum C_{24} of 0.500 µg/mL. Simulations were performed with NONMEM 7.4.3. Data analysis was done in R.

Results: In the anthropometric dataset, 389216 children aged 0-5 years were included, and 26% of those were underweight, defined as having a weight-for-age z-score (WAZ) below -2. Considering the estimated pediatric HIV incidence in each country, we predict that as many as 13,941 and 17,101 children under 5 could be brought above the individual minimum target by changing from guideline dosing to expected-weight and model-based dosing, respectively. Among underweight children, predicted GM C_{24} was 0.78, 1.03, and 1.29 µg/mL with guideline, expected-weight, and model-based dosing, respectively.

Conclusion: Current dosing guidelines, which are weight-based, may need to account for age and nutritional status to prevent under-exposure of first-line

ART drugs such as dolutegravir and improve outcomes in young, malnourished children with HIV.

Simulated DTG target attainment



834 NILMATREVIR-RITONAVIR TREATMENT IN CHILDREN WITH SARS-CoV-2 INFECTION

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Background: Children seem to experience a less severe form of COVID-19 disease than adults, nevertheless, cases of severe infection have been described in a small proportion of patients, requiring hospitalization in 5-10% of cases. Among COVID-19 deaths 0,4% occurred in children and adolescents under 20 years of age. Most hospitalized children with acute COVID-19 had underlying conditions. Moreover, some children with previous COVID-19 infection, may later develop Multisystem Inflammatory Syndrome in Children (MIS-C), a rare but serious condition associated with COVID-19. These data suggest that a specific therapy is necessary in high-risk pediatric population, in order to prevent severe COVID-19, especially in children with underlying conditions. Antiviral paediatric data are currently very few

Methods: We conducted a retrospective study on patients < 18 years of age who received Paxlovid (nirmatrelvir-ritonavir) for the treatment of mild-to-moderate COVID-19 at Bambino Gesù Children's Hospital from April 2022 to September 2022. Patients at high risk of progression to severe COVID-19 who had no need of supplemental oxygen received Paxlovid according to AIFA's indications for adults with the Informed Consent of relatives

Results: 40 patients aged 1-18 years with confirmed SARS-CoV-2 infection were treated with Paxlovid (Tab 1)The average symptom duration was 4.2 days. No patient developed severe COVID-19 r All patients were treated within 5 days of symptom onset, Four patients received a longer course treatment (10 days) due to the persistence of symptoms combined with the presence of severe comorbidities .The mean time of viral shedding was 12.7 days, with a patient being persistently positive for 56 days. After Paxlovid initiation, only 5 patients (12.5%) experienced adverse reactions:

Conclusion: Treatment with Paxlovid has proven to be safe. Further pharmacokinetic studies are required species for children < 5 years old

Adverse Reactions tab 1

	Total	0-6 years	7-12 years	13-18 years
Adverse reactions	5	1	2	2
Nausea and vomiting	2	1	1	0
Increased CPK and triglycerides	1	0	1	0
Metallic taste	2	0	0	2
Treatment interruption	2	1	1	0

835 COMORBIDITIES THAT INCREASE RISK FOR SEVERE ACUTE COVID-19 IN PEDIATRIC POPULATION

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EPICO, EPICO Colombia and ORCHESTRA

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Background: Little is understood about which comorbidities are associated with severe outcomes in children hospitalized with acute COVID-19. Some confusion lies especially for cancer or diabetes.

Methods: Data from 2 multicenter prospective cohort studies of hospitalized children (aged 0-18 years) with confirmed SARS-CoV-2 in Spain and Colombia were combined for this analysis. Data were obtained from 116 hospitals. Outcome was classified as (in decreasing order of severity): death, mechanical ventilation (MV), pediatric intensive care unit (PICU) admission, high flow/CPAP, oxygen therapy with nasal prong (NP) and hospitalization without respiratory support. Risk factors for severity, adjusting for age and gender, were identified using multinominal logistic regression and a backwards selection process.

Results: A total of 1,753 patients were included, 734 (41.8%) in Spain and 1,019 (58.1%) in Colombia. The most frequent comorbidities were asthma (9.0%), chronic neurological disorder (NRL) (7.4%), immunosuppressive medication (7.2%), malignant neoplasms (5.4%) and chronic lung disease (not asthma) (CLD) (4.5%). Comorbidities associated with the different endpoints are summarized in Figure 1.

Asthma was associated with a significantly increased risk of death (OR: 4.17; 95%CI 1.34-12.97), MV (OR: 7.94 (3.59-17.56)), PICU admission (OR: 3.37 (1.91-5.96)), high flow/CPAP (OR: 6.65 (2.69-16.46)), and NP (OR: 3.85 (2.57-5.77)) compared to hospitalization without respiratory support. NRL was associated with increased risk of death (OR: 7.34 (3.01-17.90)), MV (OR: 3.07 (1.20-7.82)) and high flow/CPAP (OR: 4.36 (1.68-11.29)).

CLD was associated with increased risk of death (OR: 6.22 [2.28-16.94]) and NP (OR: 3.1 (1.74-5.58)) and in addition, chronic cardiac disease was associated with increased risk of MV (OR: 5.21 (1.76-15.41)) and PICU (OR: 2.78 (1.27-6.08)).

Risks of death (OR: 4.49 (2.03-9.05)), MV (OR: 2.97 (1.52-5.81)), PICU (OR: 4.27 (2.89-6.33)), and NP (OR: 4.67 (3.64-5.99)) were higher in the Colombia Cohort.

Conclusion: Asthma, chronic neurological, cardiac and lung disease; and belonging to the Colombia cohort were consistently associated with multiple severe outcomes of COVID-19. Cancer and diabetes association with selected endpoints rather than with most endpoints may be more related to the baseline disease than with the actual COVID-19.

Multivariable association between comorbidities on the odds of each outcome (compared to hospitalization without respiratory support). Table 1. Color gradient across endpoints (red: risk factors, green: protective)

Comorbidity	Death n=XXX	MV	PICU	CPAP/High flow therapy	O2
Chronic cardiac disease	1.36 [0.29;6.49]	5.21 [1.76;15.41]	2.78 [1.27;6.08]	3.28 [0.87;12.32]	1.73 [0.92;3.26]
Chronic pulmonary disease	6.22 [2.28;16.94]	2.60 [0.73;9.22]	1.14 [0.41;3.17]	2.97 [0.83;10.59]	3.12 [1.74;5.58]
Asthma or recurrent wheezing	4.17 [1.34;12.97]	7.94 [3.59;17.56]	3.37 [1.91;5.96]	6.65 [2.69;16.46]	3.85 [2.57;5.77]
Chronic neurological disorder	7.34 [3.01;17.90]	3.07 [1.20;7.82]	1.52 [0.79;2.96]	4.36 [1.68;11.29]	1.10 [0.68;1.76]
Malignant Neoplasm	5.03 [2.09;12.12]	0.00 [-;-]	1.15 [0.59;2.21]	1.00 [0.22;4.41]	0.15 [0.06;0.37]
Chronic hematologic disease	2.67 [0.85;8.37]	1.44 [0.32;6.40]	0.68 [0.27;1.69]	0.75 [0.10;5.86]	0.35 [0.15;0.80]
Diabetes	2.99 [0.29;30.70]	0.00 [0.00;0.00]	5.67 [1.84;17.47]	0.00 [-;-]	1.19 [0.33;4.24]

836 PERSISTENT SYMPTOMS IN CHILDREN ADMITTED WITH COVID SIMILAR TO CONTROLS 1 YEAR LATER

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Background: The aim of this study was to describe the prevalence of persistent symptoms of COVID in hospitalized pediatric population one year after admission compared to a control group.

Methods: Prospective observational study conducted in 2 hospitals. We included patients aged 0-18 years hospitalized for acute COVID-19 more than a year ago and controls, matched by age and sex, hospitalized for causes other than COVID-19, and who had never COVID-19 at recruitment or during the follow-up. Families were contacted and a standardized survey was conducted. Persistent COVID/disease was defined as the presence of symptoms with onset in the first 3 months after COVID-19 and with persistence for more than 2 months.

Results: 50 cases and 46 controls were analyzed, 58.3% male, 36% <5 years. Families were interviewed a median of 1.89 years (interquartile range; 1.25-2.07) after hospitalization. The definition of persistent COVID-19/disease was met in 34% of cases vs. 37% of controls (p=0.767). Symptoms persisted ≥11 months in 24% (12/50) of cases vs. 13% (6/46) of controls (p=0.182), with no differences by age group. The most frequent symptoms at 1 year in cases were fatigue (8%), headache (6%), poor appetite (6%), abdominal pain (6%) and variations in heart rate (6%). In controls, persistent symptoms were mostly abdominal pain (6%) and poor appetite (6%). The number of readmissions was 11/50 (22%) and 6/46 (13%) (p=0.267), respectively. On emotional/behavioral items, 16/50 (32%) of cases reported that their emotional state was worse or much worse than before admission, compared to 16/46 (34.7%). No risk factors associated with the development of persistent symptoms were found, except the length of hospital admission (p=0.043).

Conclusion: In this study, the prevalence of persistent symptoms was not different in patients with and without COVID-19. 1-year persistence was higher in COVID-19 cases but did not reach significance. Persistence correlated with length of hospitalization.

837 PERSISTENCE OF SYMPTOMS ONE YEAR AFTER MULTISYSTEM INFLAMMATORY SYNDROME IN CHILDREN

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Background: Long term evolution of Multisystem Inflammatory Syndrome in children (MIS-C) is poorly understood. In this report, we described the frequency of persistent symptoms and sequels after one-year monitoring in a cohort of MIS-C patients.

Methods: This is a prospective observational study in under-18-aged patients diagnosed with MIS-C between October 2020 and April 2021 in a tertiary hospital. Data from initial episode was obtained from the Spanish national database and the medical history. A standardized phone questionnaire was done one year after the acute episode. As patients pared by age and sex were included with i) history of acute COVID-19, from the same national database, and ii) with peritonitis diagnosis in the electronic medical record. Data was collected using REDCap and analysed with R. Ethics committee approval was obtained.

Results: A total of 48 patients were included in the study, 16 in each group. Average age at hospitalization was 11,2 years old [IQR: 6,6-14,4] and 52% (23/48) were male. MIS-C patients presented high frequently 94% (15/16) cardiological complications during hospitalization, in contrast with 19% (3/16) of acute COVID-19 patients and 25% (4/16) of peritonitis group (p< 0.01). All of them resolved after a year except the ones associated to hypoxic ischemic encephalopathy in a patient with MIS-C that need ECMO assistance. Summary characteristics during acute episode are shown in Table 1.

After one-year follow-up, 88% MIS-C patients suffered one or more symptoms, more frequently: headache (44%), fatigue (38%), insomnia (38%) and concentration problems (38%). A total of 56% of COVID-19 patients presented persisted symptoms, mainly fatigue and concentration problems (19%), and 31% in peritonitis group (19% loss of appetite and abdominal pain), (p< 0.001). MIS-C patients visited more frequently the medical professionals due to emotional change, behaviour or interpersonal relationships after the disease [4/16 (25%) in MIS-C vs. 0/16 (0%) in both control groups, p= 0.028].

Conclusion: Majority of MIS-C patients have persistent symptoms one year after acute episode, even with the resolution of cardiological complications. Frequency of long term symptoms in MIS-C patients is significantly higher than in COVID-19 hospitalized and than in a control group of surgical peritonitis patients.

Summary characteristics during acute episode

Features		All N=48	MIS-C N=16	COVID-19 N=16	Peritonitis N=16	p
Days of Admission, (median, RIQ)		6,00 [4,00-11,0]	10,5 [8,00-12,0]	4,00 [3,00-6,00]	5,50 [4,75-10,2]	**0,001**
Inflammatory markers at entry	PCR (N=47)	12,4 [1,98-21,7]	18,8 [14,5-26,9]	0,85 [0,34-5,00]	11,6 [5,57-22,8]	**0,001**
Oxygen therapy	Yes (n, %)	14/48 (29,2%)	9/16 (56,2%)	3/16 (18,8%)	2/16 (12,5%)	**0,018**
	Days of oxygen therapy, (N=14) (median, RIQ)	4,00 [2,00-6,75]	5,00 [2,00-10,0]	2,00 [1,50-4,00]	4,00 [3,50-4,50]	0,629
PICU admission	Yes, (n, %)	17/48 (35,4%)	12/16 (75,0%)	1/16 (6,25%)	4/16 (25,0%)	**<0,001**
	Days of admission to PICU, (N=17) (median, RIQ)	5,00 [3,00-7,00]	4,50 [3,00-7,50]	2,00 [2,00-2,00]	6,00 [5,50-7,75]	0,185
Complications during admission	Yes, (n, %)	22/48 (45,8%)	15/16 (93,8%)	3/16 (18,8%)	4/16 (25,0%)	**<0,001**
	Pleural effusion (n, %)	7/48 (14,6%)	6/16 (37,5%)	0/16 (0,00%)	1/16 (6,25%)	**0,011**
	Cardiological (n, %)	14/48 (29,2%)	13/16 (81,2%)	1/16 (6,25%)	0/16 (0,00%)	**<0,001**
	Renal failure (n, %)	6/48 (12,5%)	5/16 (31,2%)	1/16 (6,25%)	0/16 (0,00%)	0,036
	Other complications (n, %)	6/48 (12,5%)	2/16 (12,5%)	1/16 (6,25%)	3/16 (18,8%)	0,859

838 PBMC IMMUNOPHENOTYPING AND PLASMA INFLAMMATORY PROFILE OF CHILDREN WITH LONG COVID

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Background: Long COVID can be developed by individuals after an infection with SARS-CoV-2 as described by the WHO. Although this condition is more commonly described in adults, it can occur in children and adolescents with a wide range of estimated prevalence of 1-25%. Little is known about the role of the immune system in long COVID. However, one of the main hypotheses about the underlying mechanism in long COVID is that there is an immune and inflammatory dysregulation that persists after the acute infection. The objective of this study is to compare immune cells populations, and inflammatory biomarkers in paediatric populations with and without long COVID.

Methods: We analyzed 55 blood samples from the pediaCOVID cohort (Hospital Germans Trias i Pujol), which includes more than 130 children diagnosed with long COVID and 23 controls. We measured different immune cell populations using spectral cytometry with a panel of 37 cellular markers, and 42 inflammatory markers using Luminex or ELISA. EdgeR was used for statistical analysis of the spectral data; p-values of inflammatory markers were calculated using the likelihood ratio test and they were corrected for multiple comparisons.

Results: The study cohort had a median age of 14.3 (IQR, 12.5-15.2) and 69.1% female. Patients had at least 3 symptoms associated with long COVID

(median [IQR]; 10 [7-16]). The most common symptom was asthenia/fatigue (98.2%). Compared to the control cohort, children with long COVID had increased numbers of $CD4^+CD8^+$ T cells, $IgA^+CD21^+CD27^+$ memory B cells, and $IgA^+CD21^-CD27^-$ memory B cells, while $CD4^+$ T_{EMRA} cells ($CD45RA^+$, $CCR7^-$), intermediate monocytes ($CD14^+$, $CD16^+$) and classical monocytes ($CD14^+$, $CD16^-$) were decreased (all $p< 0.05$; q=n.s.). None of the 42 inflammatory biomarkers showed significant differences between children with and without long COVID.
Conclusion: The results of this study suggest that specific populations of peripheral blood immune cells might be involved in the mechanisms underlying prolonged COVID in children and adolescents. The increase in both $IgA^+CD21^-CD27^-$ and $IgA^+CD21^+CD27^+$ memory B cells could be associated with the persistence of viral antigen in the gut and/or gut dysbiosis. Moreover, the decrease in $CD4^+$ T_{EMRA} cells could be related to autoantibodies against G-protein coupled receptors (GPCRs), since this cell population can express GPR56, and autoantibodies against GPCRs were previously reported to be elevated in adults with long COVID.

839 INFLAMMASOME BUT NOT IFN-I/III RESPONSE IS ALTERED IN CHILDREN WITH LONG COVID

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*Presented at CROI by a nonauthor colleague

Background: Severe COVID-19 is less common in children than in adults. Increasing evidence show that distinct immune-pathological changes can persist weeks or months after SARS-CoV2 infection, leading to "Long COVID (LC)". We investigated the systemic type I/III interferon (IFN-I/III) and inflammation response in peripheral blood mononuclear cells (PBMCs) of children with and without LC symptoms.
Methods: Blood samples were collected from children attending Umberto I hospital of Rome, within 3-6 months after a SARS-CoV-2 positive test and from control children. RNA was extracted from PBMCs for determining the levels of IFN-I (IFN-Alpha2, -Beta, -Epsilon and -Omega), IFN-III (IFN-Lambda1-3), NLRP3 and IL-1beta genes, and miR-141 expression by quantitative RealTime-PCR assays, normalized to housekeeping GUS gene and RNU6B, respectively.
Results: 28 participants (M 12.5y SD 3.0) with LC symptoms, 28 participants (M 11.8y SD 3.0) without LC symptoms and 18 children who've never had SARS-CoV-2 infection (M 10.5y SD 3.1) were enrolled. Comparing the three study groups, we found reduced levels of IFN-Lambda1, IFN-Lambda2 and IFN-Lambda3 ($p=0.006$, $p< 0.001$, $p=0.012$, respectively; *Kruskal–Wallis* (KW) test) mRNA in patients who have had SARS-CoV-2 infection as opposed to control group, whereas transcript levels of IFN-Epsilon ($p= 0.019$; KW test) were increased in the former with respect to the latter group; as well, remaining IFN-I genes analyzed showed a tendency to be up-regulated. As far as NLRP3 and IL-1beta levels was concerned, these genes were increased in LC patients ($p< 0.001$ for both genes; KW test). Additionally, miR-141, which has been reported to regulate inflammasome response, was overexpressed in LC patients ($p< 0.001$; *Mann–Whitney* test).
Conclusion: These results showed a decreased levels of IFN-III mRNAs and an overexpression of IFN-Epsilon in children after 3-6 months of SARS-CoV-2 infection regardless of development of LC symptoms, suggesting that SARS-CoV-2 could have caused dysregulation of IFN response through unknown mechanisms (e.g. epigenetic modifications). Also, we found an overexpression of miR-141, NLRP3 and IL-1beta mRNAs in LC patients, indicating that a prolonged activation of inflammasome pathways could be associated with the development of LC symptoms.

840 PROTECTION AGAINST HETEROLOGOUS CHALLENGE 1 YEAR AFTER INFANT SARS-CoV-2 IMMUNIZATION

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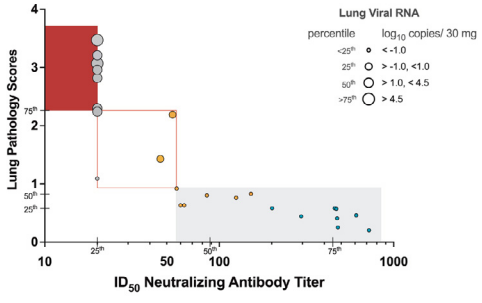
Background: Although mRNA SARS-CoV-2 vaccines have received emergency-use-authorization for infants age 6 months and older, vaccine uptake is slow, stressing that questions of safety and durability of vaccine efficacy remain prominent.
Methods: Infant rhesus macaques (RMs) (n=8/group) at 2 months of age, comparable to human toddler age, were immunized intramuscularly at weeks 0 and 4 with 30µg stabilized prefusion SARS-CoV-2 S-2P spike (S) protein (Washington strain) encoded by mRNA encapsulated in lipid nanoparticles (mRNA-LNP) or 15µg S protein mixed with 3M-052 in stable emulsion (Protein). At 1 year, vaccinated and age-matched unvaccinated RM (n=8) were challenged intranasally (10^6pfu) and intratracheally ($2x10^6$pfu) with B.1.617.2. Lung radiographs and pathology were blindly assessed, viral N gene RNA (vRNA) copies were measured by qPCR in pharyngeal swabs and lung, and neutralizing antibody and peripheral blood T cell responses were measured.
Results: At 1 year, D614G-specific neutralizing antibody (nAb) titers were still detectable in the Protein (ID_{50}=755; range: 359-1,949) and mRNA-LNP groups (ID_{50}=73; range: 41-240). Both vaccines also induced cross-neutralizing antibodies to B.1.617.2. Peripheral blood CD4+ T cell responses to the ancestral spike protein at week 52 did not differ between the groups. However, median CD8+ T cell responses were higher (p=0.002, Mann Whitney) in the mRNA-LNP group (2.8%; range: 0.9%-7.1%) compared to the Protein group (0.8%; range: 0.1%-1.6%). Control RMs had significantly higher median vRNA copies/ml ($1.4\pm2.7x10^8$) in day 4 pharyngeal swabs compared to Protein ($3.8\pm6.8x10^3$) or mRNA-LNP (4.4±9.7x105) vaccinated RMs. Severe lung pathology was observed in 7 of 8 controls compared to 1 of 8 or 0 of 8 RMs in the mRNA-LNP or Protein group respectively. Protection against lung inflammation was associated with nAb titers (r=-0.592, p=0.003) (Figure 1).
Conclusion: These results demonstrate that despite lower vaccine doses compared to adults, both protein and mRNA vaccines were safe, induced durable immune responses and provided comparable protective efficacy against infection with a heterologous SARS-CoV-2 variant in infants, implying that early life vaccination of human infants may lead to durable immunity.
Neutralizing ID50 antibody titers are a correlate of protection in infant RMs challenged with SARS-CoV-2



841 mRNA VACCINES INDUCES A HIGHER ANTIBODIES RESPONSE IN CHILDREN WITH PREVIOUS COVID-19

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Background: mRNA vaccines elicit a durable humoral response to SARS-CoV-2 in adults, whereas evidence in children is lacking. This study aimed to evaluate

the early and long-term immunological response after the BNT162b2 vaccine in children with or without a previous SARS-CoV-2 infection.

Methods: In a multicenter, prospective, observational study we profiled the immune response to the BNT162b2 vaccine in children aged 5-11 years attending the Pediatric Departments at the University of Padua and Bambino Gesù Children's Hospital in Rome (Italy). Forty-four healthy children (HC), 20 immune compromised (IC), and 18 children who previously developed MIS-C (MIS-C) were included in the study. Blood samples were collected pre-, 1, and 6 months after a 2-doses vaccination schedule. Neutralizing antibodies (NAbs) and anti-S-RBD IgG titers were analyzed through Plaque Reduction Neutralization Test (PRNT) and chemiluminescent immune-enzymatic assay (CLIA), respectively. B and T cell phenotypes were analyzed by flow cytometry. Geometric mean titers (GMTs) and 95% confidence intervals and median and interquartile range (IQR) of variables were evaluated according to pre-existing confirmed COVID-19.

Results: Eighty-two children were studied; 60 with a molecular-documented previous COVID-19 (Group A) and 22 without previous infection defined as the absence of antigen-specific antibodies before the vaccination (Group B). Overall, in Group A we observed higher NAbs GMTs, anti-S-RBD titers, and T- and B-reg cells than in Group A, at both 1 and 6 mo after vaccination (table); Nabs against the parental virus resulted to be greater in Group A than in Group B by a factor of 18 and 11, at 1 and 6 mo after vaccination, respectively.

Both Groups recorded a decrease in antibody titers of approximately 50-70% between 1 and 6 months. A significant difference for Omicron NAbs (p=0.02) and anti-S-RBD (p=0.07) titers decay was observed between Group A and B; in contrast, Parental NAbs titers appeared to have similar trends in the 2 groups (p=0.47). Comparable antibody titers at 1 and 6 mo. (p=0.37) were detected across the three categories of HC, IC, and MIS-C (table).

Conclusion: mRNA vaccination triggers a higher humoral response in children with a previous history of COVID-19, regardless of the immune deficiency or previous MIS-C, at least up to 6 mo, providing insight into boosting preexisting immunity with mRNA vaccines.

Table. Humoral and cell response comparison between groups A and B, overall, and stratified according to HC, IC, and MIS-C.

	Group A (N=60)			Group B (N=22)				
	1 mo.	6 mo.		1 mo.	6 mo.			
	Median (IQR)	Median (IQR)	p-value*	Median (IQR)	Median (IQR)	p-value*	p-value§-1 mo.	p-value§-6 mo.
S-RBD (kBAU/L)	4690,69 (2714.48-7514.72)	1629,81 (912.76-2897.2)	<0.0001	916,66 (377.14-3227.7)	349 (230.36-1134.03)	0.4386	0.0006	0.0068
	GMT (95% CI)							
Parental NAbs	5715,95 (4140.11-6571.35)	1669,45 (1227.73-2270.07)	<0.0001	276,41 (128.06-596.64)	151,54 (53.56-428.8)	0.2257	< 0.0001	0.0018
Omicron NAbs	895,51 (714.63-1132.22)	351,91 (250.58-494.22)	<0.0001	32,48 (16.07-65.62)	58,11 (24.48-137.96)	0.1289	<0.0001	0.0038
	Median (IQR)							
T-reg	3,74 (2.64-5.89)	2,75 (1.79-4.52)	0.0052	1,16 (0.64-2.28)	1,21 (0.54-2.94)	0.4609	0.0006	0.0119
B-reg	5,19 (3.37-6.65)	3,74 (2.71-6.62)	0.0269	3,62 (2.13-4.15)	2,25 (1.46-3.66)	0.4609	0.0141	0.0299
S-RBD (kBAU/L)	Median (IQR)	Median (IQR)	p-value‡	Median (IQR)	Median (IQR)	p-value‡		
HC	3130,16 (2338.63-7430.28)	1576,77 (943.51-2723.14)	0.8871	993,74 (853.01-5338.89)	850,85 (349-2194.01)	0.6068		
IC	4533,51 (980.31-27495.5)	1715,11 (329.51-14570.45)		1864,5 (377.14-3227.7)	277,77 (6.06-1134.03)			
MIS-C	5079,31 (2776.4-6581.6)	1823,58 (912.76-3605.59)						
Parental NAbs	GMT (95% CI)	GMT (95% CI)	0.3177	GMT (95% CI)	GMT (95% CI)	0.7115		
HC	6018,81 (4812.71-7527.15)	1650,39 (1160.03-2348.05)		570,18 (168.96-1924.08)	640 (110.9-3693.94)			
IC	4561,4 (182.63-113926)	2031,87 (81.35-50748)		246,86 (41.8-1457.91)	96,67 (16.97-550.62)			
MIS-C	2560 (894.57-7325.96)	1602,63 (742.94-3457.09)						
Parental NAbs	GMT (95% CI)	GMT (95% CI)	0.8417	GMT (95% CI)	GMT (95% CI)	0.4218		
HC	947,9 (152.63-1193.8)	355,06 (248.39-507.55)		31,75 (4.08-247.08)	201,59 (11.29-3598.86)			
IC	718,38 (8.29-62283)	201,59 (1.79-22671)		30,29 (8.04-114.02)	47,17 (14.19-156.86)			
MIS-C	761,09 (460.71-1257.32)	444,71 (200.36-987.04)						

* Intragroup comparison between antibodies and cells titers at 1 and 6 mo. stratified by infection
§ between-group comparison (Group A vs Group B) of antibodies and cells titers at 1 and 6 mo.
‡ between-group comparison of decrement of antibodies and cells titers from 1 mo. to 6 mo. stratified by infection

842 EFFECT OF BNT162B2 ANTIGEN DOSAGE ON PROTECTION AGAINST SARS-CoV-2 OMICRON INFECTION

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Background: Coronavirus Disease 2019 (COVID-19) vaccine antigen dosage may affect protection against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection, but direct evidence to quantify this effect is lacking.

Methods: A matched, retrospective, cohort study that emulated a randomized control trial was conducted in Qatar between February 3, 2022 and November 8, 2022, to provide a head-to-head, controlled comparison of protection induced by two antigen dosages of the BNT162b2 vaccine. The study compared incidence of omicron infection in the national cohort of adolescents 12 years of age who received the two-dose primary-series of the 30-µg BNT162b2 vaccine to that in the national cohort of adolescents 11 years of age who received the two-dose primary-series of the pediatric 10-µg BNT162b2 vaccine. Associations were estimated using Cox proportional-hazard regression models.

Results: Among adolescents with no record of prior infection, cumulative incidence of infection was 6.0% (95% CI: 4.9-7.3%) for the 30-µg cohort and 7.2% (95% CI: 6.1-8.5%) for the 10-µg cohort, 210 days after the start of follow-up. Incidence during follow-up was dominated by omicron subvariants including, consecutively, BA.1/BA.2, BA.4/BA.5, BA.2.75*, and XBB. The adjusted hazard ratio comparing incidence of infection in the 30-µg cohort to the 10-µg cohort was 0.77 (95% CI: 0.60-0.98). Corresponding relative effectiveness was 23.4% (95% CI: 1.6-40.4%). Relative effectiveness was -3.3% (95% CI: -68.0-27.5%) among adolescents with a record of prior infection.

Conclusion: Three-fold higher BNT162b2 dosage was associated with ~25% higher protection against infection in infection-naïve adolescents of similar age. These findings may inform design of future COVID-19 vaccines and boosters for persons of different age groups.

843 STUDY ON THE FREQUENCY OF DUAL INFECTIONS IN NEW HIV-1 DIAGNOSES IN SPAIN

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Background: Dual infections (DIs) with phylogenetically-distinct HIV-1 strains have been reported. DIs can lead to generation of novel recombinant strains and may be associated with faster disease progression. Here we estimate DI frequency in Spain among newly diagnosed HIV-1 infections and examine associated epidemiological, virological, and clinical factors.

Methods: Plasma samples were obtained from 498 patients with HIV-1, antiretroviral drug-naïve, and newly diagnosed in 2017-2020 in 6 Spanish regions. Reverse transcriptase (RT) and env V3 region fragments were amplified by RT-PCR/nested PCR from plasma-extracted RNA. Amplicons were sequenced with Illumina MiSeq 2x300 sequencing protocol. Ultra-deep sequencing (UDS) data were analyzed with a home-developed pipeline. Only samples with ≥500 sequences in both segments were used in further analyses. Sequences were grouped according to similarity (97%) in operational taxonomic units (OTUs). Phylogenetic trees were constructed including all OTUs and all RT (n=21,377) and V3 (n=8,268) Sanger sequences obtained in our laboratory. DIs were identified as those with OTUs branching separately in either RT or V3, interspersed among sequences from other patients, with sequences from the minor variant comprising ≥0.5% and ≥5 sequences. Clinical and epidemiological associations were evaluated using chi-square (categorical variables) and Mann-Whitney (continuous variables) tests, and logistic regression.

Results: DIs were detected in 23 (4.6%) patients, of which 10 were intrasubtype (9 B, 1 CRF02_AG) and 13 were intersubtype (all B+non-B). 14 DIs were detected in RT, 5 in V3, and 4 in both fragments. Non-subtype B infections and infections belonging to transmission clusters of ≥4 individuals were significantly associated with DIs. Mixed bases in protease-RT previously identified in Sanger sequencing were significantly more numerous in DIs (mean 20.1 vs 5.1). Age, gender, $CD4^+$ T-cell counts, and viral load were not significantly associated with DIs, and there was a marginally non-statistically significant tendency for more frequent DIs in men who have sex with men and persons who inject drugs.

Conclusion: Dual infections were detected in 4.6% of newly diagnosed HIV-1 infections in Spain, more frequently among non-B and clustering infections. To our knowledge, this is the largest reported study on dual infections based on UDS.Information on HIV-1 DIs may have important clinical, epidemiological, and public health implications.

844 EPIDEMIOLOGICAL AND MOLECULAR EVOLUTION OF THE HIV-1 CRF94: BIRTH OF CRF132

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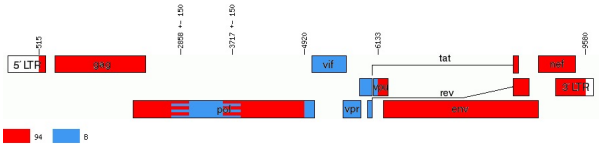
Background: In 2018 we reported the emergence of the new HIV-1 recombinant CRF94_02BF2 involved in a large transmission cluster of 49 French MSM mostly infected in 2016-2017. This CRF94 raised concerns of enhanced virulence. Prevention actions were undertaken in the area and population affected. This study reported the molecular and epidemiological evolution of this CRF94 until June 2022.

Methods: In 2021-2022, French sequence databases were screened for patients infected with HIV-1 subtype CRF94 or similar strain. HIV subtyping was confirmed by phylogenetic analysis of genes encoding both protease and reverse transcriptase (1070bps), and integrase (696bps) using IQ-Tree. Five whole genomes, related but distinct from CRF94, were obtained with the DeepChek® assay Whole Genome kits. Recombination breakpoints were estimated using RDP4 and SimPlot. Mann-Whitney and LogRank tests were used for statistical analyses to compare patients' characteristics.
Results: In June 2022, 49 new HIV-1 sequences were collected: 14 clustered with the 49 previous CRF94, 32 formed a new cluster next to but distinct from CRF94, and 3 strains could not be classified. Analysis of 5 whole genomes from the new cluster revealed a new recombinant, the CRF132_94B, mainly consisting of CRF94 which recombined with subtype B in the POL and accessory genes. Vif gene changed from the F2 to the B subtype. Both CRF94 and 132 clusters involved >95% of MSM, mostly infected < 1 year before diagnosis. However, there were differences: 97% were diagnosed in 2013-2019 for CRF94 vs 90% in 2020-2022 for CRF132. At time of diagnosis, 33% of patients infected with CRF94 knew the Prep vs 95% for CRF132. In the cluster CRF94, patients were older (34 vs 30 years, p=0.02), had higher viral loads (5.42 vs 4.42 log_{10} copies/Ml; p< 0.001), a lower CD4 cell counts (358 vs 508 /mm3, p=0.002). On treatment, the patients with the CRF94 reached viremia < 50 copies/Ml significantly later than those infected with CRF132 (p=0.0002). The prevention activities targeting the CRF94 cluster could explained the few patients infected with this strain after 2018. The CRF132 is mainly located in another Paris region area, but no specific transmission place has been identified.
Conclusion: After 2019, the CRF94 spread seems greatly slowed down but the very close CRF132_94B has given birth to a new highly active cluster in 2020-2022, despite the COVID social-distancing and a strong knowledge of the Prep. CRF132 appears to be less virulent perhaps due to the Vif gene change.
Identified breakpoints positions of the new HIV-1 CRF132_94B. GenBank accession numbers of the five references : ON901787 to ON901791



845 ACCURACY OF MOLECULAR EPIDEMIOLOGICAL INFERENCES IN A SIMULATED EPIDEMIC

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Background: Molecular Epidemiology is the 4th pillar of the Ending the HIV Epidemic plan, and it is hoped that the use of these analyses will lead to both prevention and treatment interventions in at-risk populations. Concern has been voiced that the inferences derived from molecular epidemiological (ME) analyses could be used in criminal and civil litigation. However, the level of concern is impacted by the accuracy of these analyses. Here we assessed the accuracy of ME analyses to identify correct transmission pairs and the correct direction of transmission in a simulated HIV epidemic.
Methods: An agent-based simulation based on the EpiModel software package was parameterized to fit the San Diego HIV epidemic among MSM. The simulated data, which included information of who transmitted to whom and time of transmissions, were used to simulate HIV genetic sequences for the corresponding individuals, incorporating time from infection to sampling. Both full length consensus and next generation sequences (NGS) were generated. These sequences were then analyzed to measure the ability of consensus and NGS to predict correct linkage and directionality. We then repeated the analyses varying sample fraction, portion of genome sequenced, human migration in and out of the region of interest, and the inclusions of assays for testing recency of infection when inferring who infected whom.
Results: Consensus sequences did not reliably predict correct directionality and linkage, regardless of sampling depth. See **Figure 1**. For NGS data, given the intense computation burden associated with analyzing these sequences, we chose pairs of individuals where the sequence data had a high likelihood of correctly identifying both linkage and transmission direction (infector probability >80%). Within this subset, we found a sensitivity that ranged from 67.5 to 77.5% and specificity from 89.9 to 92.3%.
Conclusion: The accuracy of inference of directionality and linkage in a large epidemic using molecular epidemiology is low when consensus sequences are used. However, accuracy increases considerably if additional epidemiologic data leading to a high pre-test probability are available, and NGS data are used.
Precision-Recall Curves with Varying Parameters

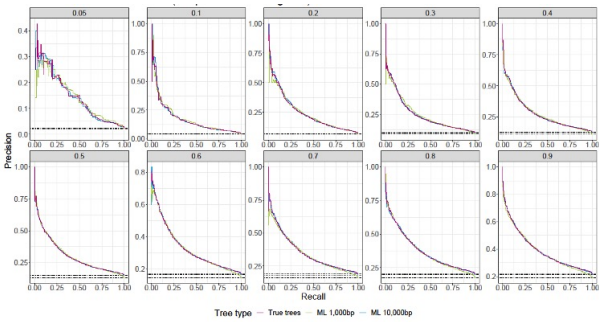

Figure 1. Example of precision-recall curves (chosen over ROC curve because of the large proportion of true negative results causing a skewed dataset) showing poor area under the curve regardless of portion of genome sequenced (10-100%) and sampling (5% to 90%). Top row includes only 1 migration event, and bottom row includes 250 migration events.

846 PRESENCE OF CXCR4-USING HIV-1 VIRUS IN NEWLY DIAGNOSED INDIVIDUALS IN NORTH CAROLINA

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Background: HIV-1 uses either CCR5 or CXCR4 as the coreceptor to enter host cells. Transmitted viruses are usually CCR5-using (R5 virus), and CXCR4-using (X4/dual) viruses emerge in the late stage of disease. In 2018 we implemented a statewide recency assay for HIV-positive tests conducted at the NC public health lab. This platform uses a UMI-based NGS approach to sequence portions of the HIV-1 genome including the *env* gene V3 region for co-receptor prediction. We assessed the prevalence of X4 viruses among people with newly diagnosed HIV-1 from 2018 to 2021.
Methods: Remnant diagnostic sera from people with new HIV-1 diagnoses were sequenced using the Multiplexed Primer ID MiSeq protocol targeting the HIV-1 *pol* gene and *env* V1-V3 region. Recent HIV-1 infections (within 9 months of infection) were estimated based on pairwise sequence diversity. Coreceptor tropism was predicted using Geno2Pheno algorithm using two false positive rate (FPR) cut-offs of 2% and 5.75%.
Results: A total of 726 people had sufficient sequence depth for the analysis. Overall, using the 2% and 5.75% cutoffs, we found that 10.3% and 21.5% had X4 variants, with a median abundance within the individual viral populations of 32.3% (IQR: 10.9-85.2%) and 53.3% (IQR: 11.5-97.6%), respectively. Using the 9-months recency cut-off, we found significantly more X4 variants in the chronically infected individuals (13.8 and 26.8%) than the recently infected (5.9 and 15.6%) using both FPR cut-offs (p< 0.01). Most of the X4 variants found in the recent infections had homogenous populations, with a median abundance greater than 95% at both cut-offs, suggesting they were transmitted X4 variants. Conversely, most chronically infected individuals had mixed populations of R5 and X4 viruses, consistent with a late diagnosis of infection. Among the recently infected patients, those with X4 variants had significantly lower CD4 counts using 2% FPR cut-off (p< 0.01). Carrying X4 variants was not associated with having significantly more DRMs at the pol region.
Conclusion: We previously observed that viruses with an FPR≤2% have an X4 entry phenotype while half of those with an FPR from 2% to 5.75% have an X4 entry phenotype. Thus, we estimate that the overall transmission rate of X4 viruses is approx. 10%. This is significantly higher than previously thought and may represent further maturation of the epidemic with an increased fraction of transmissions from chronically infected people not on therapy.

847 HOTSPOTS OF RECENT HIV INFECTIONS AMONG ADULT PEOPLE LIVING WITH HIV IN NIGERIA

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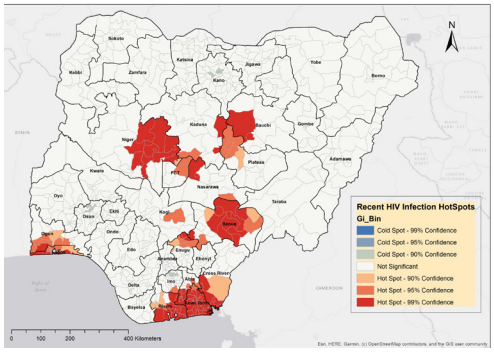
Background: In Nigeria, recency testing was introduced in 2020 to assist in identifying those who had recently acquired HIV infection between 4weeks and 12 months so that prevention programs can focus on preventing incident infections and ultimately break the chain of transmission to control the epidemic. This study aimed to identify the spatial distribution pattern of recent HIV infection among adult PLHIV, identify correlates of recent HIV infection and detect recent HIV infection hotspots.

Methods: This was an ecological descriptive and analytical design conducted between October 2019 and December 2021. We georeferenced recent HIV case reports from 197 of 774 Local Government Areas (LGAs) spread across all of Nigeria's six geographic regions. Percent of recent HIV infections among adult PLHIV was calculated from data extracted from the national Recency testing registers. Spatial autocorrelation of recent HIV infection was analysed via a Global Moran's I test. Hotspot analysis using Getis-Ord-Gi* statistics highlighted regions of significant clusters of recent HIV infection among neighbouring geographic regions, and Poisson regression model identified correlates of recent HIV infection in Nigeria.

Results: Among the 62,382 PLHIV tested for recent infection, 61% were females. Of the 4,077 (6.5%) PLHIV identified as having recent HIV infection, 1,499 (6.3%) were males and 2,578 (6.7%) were females. Females between the ages of 15-19 (10%) had the highest recent infection when compared to other female age groups, while males (16%) aged 50 and over were four times more likely than females (4%) in this age group to have recently contracted HIV. The global spatial autocorrelation Moran's I statistics (z-score=10.7, p< 0.0001, Moran's Index=0.104) revealed a clustered distribution of the spatial pattern of recent HIV infection. Hotspot analysis identified significant clusters of recent HIV infection that were confined to LGAs in the North Central, North East, South West, South East and the South South regions of the country. In the Poisson model, knowledge of HIV prevention (p< 0.0004) and ART coverage (p< 0.0001) were significantly associated with recent HIV infection.

Conclusion: Given the effect of knowledge of HIV prevention and ART coverage on recent HIV infection among adult PLHIV, adopting policies and strategies to enhance awareness and encourage people to seek early HIV testing and implementation of intensified community ART delivery services can break the transmission of HIV infection.

Hotspots of Recent HIV Infections, October 2019 and December 2021



848 PROGRAMMATIC IMPLICATIONS OF NATIONAL RECENT HIV INFECTION SURVEILLANCE IN CAMBODIA

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Background: National recent infection surveillance using the recent infection testing algorithm (RITA) is a tool to provide insights on epidemiological trends of recent HIV infections (i.e., individuals likely infected with HIV within the last year). We sought to compare risk factors for HIV infection diagnosis (i.e. diagnostic algorithm positive) and HIV diagnosis classified as recent (i.e. RITA-recent) amongst individuals tested for HIV infection in Cambodia.

Methods: Individuals who were tested for HIV from 1 August 2020–¬¬11 August 2022 in 68 public facilities across the 25 provinces in Cambodia were included. Those newly diagnosed HIV positive and ≥ 15 years of age who consented were tested for recent HIV infection using the Asanté ™ HIV-1 rapid recency® assay (Sedia Biosciences). Individuals testing recent on the assay were tested for viral load (VL) for final classification (VL ≥ 1000 = RITA-recent). Data was managed in the MySQL database. Risk factors involved in the odds for HIV diagnosis and testing RITA-recent were analyzed using multivariable generalized estimating equations (GEE) logistic regression models in R version 4.1.2. HIV-negative individuals were used as the comparator for both analyses. The GEE method was used to produce logistic regression estimates for clustered data using R geepack 1.3.3.

Results: During the first two years of national recent infection surveillance, 53,031 individuals were tested for HIV infection and 6,868 (13%) were diagnosed with HIV. Of these, 6,180 (90%) were tested for recent infection. Of 314 individuals who tested assay-recent, 237 were tested for viral load and 192 tested RITA-recent. We observed differences in odds for HIV diagnosis and testing RITA-recent by HIV testing client type, marital status, and age (Table). Compared with the general population, men who have sex with men, transgender people, and entertainment workers had higher odds for testing RITA-recent than for HIV diagnosis while people who use drugs had lower odds for testing RITA-recent than for HIV diagnosis.

Conclusion: National recent infection surveillance provides unique insights on HIV acquisition patterns compared to using new HIV diagnosis alone. These data have implications for prevention, testing, and key population programmes.

Multivariable odds ratios for HIV diagnosis and RITA-recent in comparison to testing HIV negative. All variables listed were included in the multivariable analysis.

Characteristic	aOR for HIV diagnosis (95% CI)	P-value	aOR for RITA-recent (95% CI)	P-value
Sex				
Female	REF	-	REF	-
Male	1.73 (1.62-1.86)	< .001	2.04 (1.21-3.42)	0.01
Age				
15-19 years	REF	-	REF	-
20-34 years	1.48 (1.30-1.68)	< .001	1.35 (0.64-2.83)	0.42
= 35 years	1.55 (1.35-1.78)	< .001	0.82 (0.38-1.76)	0.61
Marital Status				
Single	REF	-	REF	< .001
Married	0.74 (0.68-0.81)	< .001	0.76 (0.45-1.31)	0.33
Widow/-er	2.63 (2.31-2.98)	< .001	1.56 (0.82-2.96)	0.17
Education				
None	REF	-	REF	< .001
Primary	0.59 (0.52-0.65)	< .001	0.56 (0.29-1.09)	0.09
Secondary	0.49 (0.43-0.55)	< .001	0.52 (0.27-1.03)	0.06
High School	0.36 (0.32-0.41)	< .001	0.45 (0.23-0.88)	0.02
Above High School	0.16 (0.14-0.19)	< .001	0.18 (0.09-0.38)	< .001
Type of client				
General Population	REF	-	REF	-
Men who have sex with men	15.50 (14.00-17.16)	< .001	27.40 (15.53-48.33)	< .001
Transgender person	11.00 (9.50-12.75)	< .001	19.05 (9.58-37.88)	< .001
Persons who use drugs	26.34 (17.22-40.29)	< .001	13.93 (1.94-100.05)	0.01
Entertainment Worker	3.46 (2.88-4.16)	< .001	6.14 (2.47-15.28)	< .001

849 AN ANALYSIS OF HIV RECENT INFECTION SURVEILLANCE DATA AMONG YOUNG PEOPLE IN MALAWI

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Background: Malawi has made significant progress towards UNAIDS 95-95-95 targets, yet awareness of HIV status is at 88.3% and lowest among young people, 15-24-year-old (76.2%). Low awareness of HIV status may contribute to further transmission in the population, therefore there is a need to better understand HIV testing history and transmission in this age group.

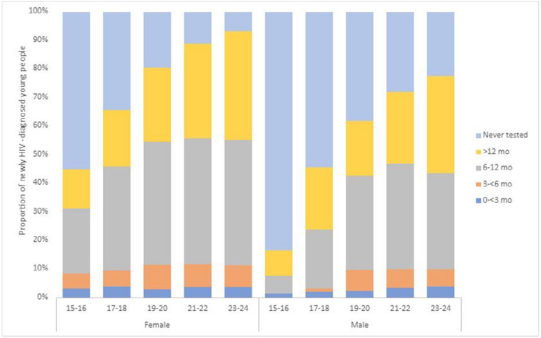
Methods: We analyzed pooled recent HIV infection data to describe testing history and recent HIV infection (< 12 months) status among 8,389 newly HIV-diagnosed 15-24-year-olds from 251 sites across Malawi, between September 2019 - March 2022. HIV recent infection classification was based on a positive rapid test for recent infection and a viral load ≥1000 copies/ml. We calculated the proportion of consenting newly HIV-diagnosed participants classified with

recent HIV infection by age, sex, residence, testing point, and self-reported testing history to describe differences related to risk and behavior.

Results: Most newly HIV-diagnosed young people were female (84.1%), aged 23-24 years-old (32.1%), rural residents (60.4%), and diagnosed at voluntary counselling and testing points (53.8%). A history of reported prior HIV testing was less frequent in younger age groups (Figure 1). Among 15-24-year-olds, 32.9% of males and 16.1% of females reported no previous HIV testing history. Overall, 4.9% of new HIV diagnoses were classified as recent infections, with the highest proportions observed in Mzimba (8.5%) and Machinga (6.9%) districts, among breastfeeding women (8.2%), persons tested at sexually transmitted infection clinics (9.0%), persons with a prior test within the past 6 months (11.9-13.5%), and 17-18-year-olds (7.3%).

Conclusion: These findings highlight gaps in HIV testing among young people by age and sex with the majority (>95%) potentially having been infected for >12 months. Tailored and innovative HIV prevention and testing strategies for adolescents, young males, and pregnant and breastfeeding women may be needed for HIV epidemic control. Routine data collection and analysis of recent HIV infection data and triangulating various surveillance data sources can be utilized to inform targeted HIV testing and preventive strategies for young people.

Figure 1: The age/sex disaggregated proportion of young people with a positive HIV test and their reported time of last HIV test.



850 HIV RECENT INFECTION IN SEXUAL AND GENDER MINORITIES IN BRAZIL AND PERU: ImPREP STUDY

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Background: HIV incidence estimation is critical for monitoring the HIV epidemic dynamics, transmission trends and effectiveness of public health prevention interventions. We aimed to identify HIV recent infection (RI) cases, its associated factors and to estimate annualized HIV incidence using recency testing among sexual and gender minorities (SGM) undergoing HIV testing in Brazil and Peru.

Methods: Cross-sectional multicenter study in HIV testing services in Brazil (6 cities) and Peru (7 cities) from Jan/21-May/22. Inclusion criteria: 18+ years, cisgender men who have sex with men (cis-MSM), transgender women (TGW) and other SGM. Exclusion criteria: HIV+, current PrEP/PEP use. Rapid HIV 4th generation test was used; dried blood spots (DBS) were obtained from the HIV+ cases. We identified HIV RI using the Maxim HIV-1 Lag-Avidity EIA assay as part of RI testing algorithm (RITA), which includes HIV-1 RNA < 400 copies/mL, CD4 count < 200 cells/mm^3, and prior/current ART use (to exclude long-standing infections). We assumed mean duration of recent infection of 214 days (95%CI: 193-237) and a false recent ratio (FRR) of 0%. Annualized HIV incidence was calculated per country using the WHO mathematical formula. Multivariable logistic regression models per country were used to estimate factors associated with HIV RI.

Results: Of 7362 individuals approached, 7116 (97%) were eligible and enrolled [Brazil: 4700 (66%); Peru 2416 (34%)]; 86% cis-MSM, 11% TGW, 3% other SGM. Median age was 27 years (IQR:23-34), 64% ≤ 30 years, 72%≤ secondary education, 74% low income. In the prior 6 months, 35% reported >5 sex-partners, 79% condomless sex, 20% STI symptoms, 14% sex work, 27% substance use and 57% binge drinking. HIV prevalence was 13.7% [N=971; Brazil: 470/4700 (10.0%); Peru: 501/2416 (20.7%)]. DBS were available for 959 (99%); 165 (17.2%) were classified as recently infected [Brazil: 81/4700 (1.7%), Peru: 84/2416 (3.5%)]. The overall annualized HIV incidence rate was 4.64% (95% CI: 4.11-5.17); Brazil: 3.30% (95% CI: 2.76-3.84); Peru: 7.59% (95% CI: 6.40-8.78). Multivariable models showed that in both countries engaging in condomless sex increased the odds of HIV RI and in Peru being 30 years or younger (see Table).

Conclusion: High levels of HIV prevalence, HIV RI and annualized HIV incidence among SGM in Brazil and Peru highlight the burden of the HIV epidemic among these populations. Public Heath policies and interventions to increase PrEP access in Latin America are urgently needed.

Factors associated with HIV recent infection among sexual and gender monorities from Brazil and Peru: ImPrEP Seroincidence Study.

	Brazil			Peru		
	HIV recent infection n/N (%)	Multivariable Model[1] aOR (95%CI)	p-value	HIV recent infection n/N (%)	Multivariable Model[1] aOR (95%CI)	p-value
Age						
≤30 years	63/3145 (2.0)	0.97 (0.61-1.57)	0.087	63/1437 (4.4)	1.93 (1.17-3.29)	0.012
>30 years	18/1555 (1.2)	Ref.		21/979 (2.1)	Ref.	
Condomless sex (prior 6 months)						
Yes	72/3642 (2.0%)	2.18 (1.14-4.72)	0.030	78/1931 (4.0)	3.51 (1.63-9.14)	0.004
No	9/1058 (0.9%)	Ref.		6/485 (1.2)	Ref.	

[1] Models adjusted for gender, race, schooling, income, ever testing for HIV, number of sex-partners, sex work, substance use, binge drinking and signs/symptoms of sexual transmitted infections (STI) (for all these variables, p>0.05.

851 HIV TIME-SPACE ALERTS AMONG PWID AND MSM IN THE UNITED STATES, 2018-2021

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Background: HIV time-space (TS) cluster detection is routinely conducted by CDC and by state and local health departments to identify U.S. counties where diagnoses are elevated compared with historical levels. These analyses generate "alerts" for review that may indicate clusters or outbreaks needing response. Previously, national TS cluster detection primarily focused on persons who inject drugs (PWID). Differences in the frequency, characteristics, and reoccurrence of alerts among men who have sex with men (MSM) versus alerts among PWID have not been previously described.

Methods: HIV diagnoses reported to the National HIV Surveillance System were analyzed quarterly during 2018–2021 to detect TS alerts using standard CDC methods. Each quarter, for each county, the number of HIV diagnoses during the preceding 12 months among the group of interest (PWID and MSM) was compared with the annual average from the preceding 3 years. An alert was generated if the number of diagnoses in the year of interest was >2 standard deviations and >2 diagnoses above the baseline number of diagnoses. Within each alert type — PWID and MSM — alerting counties were stratified by urban-rural classification. For counties with initial alerts during 2018–2019, reoccurrences of alerts during the following 8 quarters were identified.

Results: During 2018–2021, PWID alerts occurred in 154 (4.9%) counties and MSM alerts occurred in 445 (14.2%) counties (Table). PWID alerts occurred in a higher percentage of large central metro areas (41.2%) than other areas (0.3–14.2%). MSM alerts occurred in a higher percentage of large fringe (29.1%) and medium (27.4%) metro areas than other areas (3.7–19.6%). Multiple subsequent alerts were more common for PWID than for MSM alerts: 30% of counties with PWID alerts had ≥2 subsequent alerts in the following 8 quarters, compared with 19% of counties with MSM alerts.

Conclusion: The occurrence of PWID alerts in >41% of large central metro areas is concerning, as it might suggest expanding HIV transmission among PWID in these areas. Application of similar time-space alert criteria to assess TS clusters among MSM yields nearly three times as many alerts among MSM as among PWID. Compared with PWID alerts, a lower percentage of MSM alerts reoccur, suggesting that increases detected typically are not sustained. Additional work to refine TS cluster detection criteria, or to prioritize additional follow-up or investigation, is needed for MSM alerts.

Table. Urban-rural classification* of counties with time-space alerts, 2018–2021

Table. Urban-rural classification* of counties with time-space alerts, 2018–2021					
	Total counties	Counties with PWID alerts		Counties with MSM alerts	
	N	n	row %	n	row %
Total	3144	154	4.9%	445	14.2%
Large central metro	68	28	41.2%	9	13.2%
Large fringe metro	368	40	10.9%	107	29.1%
Medium metro	372	53	14.2%	102	27.4%
Small metro	358	19	5.3%	70	19.6%
Micropolitan (nonmetro)	641	10	1.6%	107	16.7%
Noncore (nonmetro)	1337	4	0.3%	50	3.7%

* Large central metro: central counties in metropolitan statistical area (MSAs) of ≥1M population. Large fringe metro: non-central counties in MSAs of ≥1M. Medium metro: counties in MSAs of 250,000–999,999. Small metro: counties in MSAs of <250,000. Micropolitan (nonmetro): counties in micropolitan statistical areas of 10,000–49,999 population. Noncore (nonmetro): counties not in micropolitan statistical areas.

852 EVOLUTION OF CLUSTERS TRANSMISSION PATTERNS IN FRANCE DURING THE LAST DECADE

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Background: The recent transmission clusters (RTCs) identified through phylogenetic approaches allow to describe the main transmission networks. This render possible to describe potential shifts among HIV transmission routes and populations and, in some cases, to specifically target prevention measures. Here we describe the evolution of RTCs over the last decade in a specialized laboratory serving centers from the entire French territory.

Methods: We extracted all the HIV reverse transcriptase sequences available between 01/01/2013 and 31/08/2022. The sequences dataset was studied overall and divided into three equal time periods: 2013-15, 2016-18, 2019-2021. The first sequences available for each patient were aligned and the trees were reconstructed by maximum likelihood using IQtree software. Clusters, defined by a maximum genetic distance < 4.5% and a branch support >90%, were extracted using ClusterPicker.

Results: Overall, 8591 sequences were included. Among them, 950 RTCs were identified including 2492 sequences (29%) and 68 large RTCs (>4 sequences) with 475 (5.6%) sequences. The mean duration of large RTCs (from the first to the last sequences) was 5.1 years [IQR: 4.1-7.1] and 34 were still active (including at least one sequence during the last year of the study period). 3640, 2897 and 2157 sequences were included for the 2013-15, 2016-18 and 2019-2021 periods, respectively. We identified 298 RTCs (19.5% of sequences), 249 (20.4%) and 226 (27.5%) among those periods, respectively. While the number of sequence pairs decreased from 2013-15 to 2019-21, the number of large RTCs increased steadily (see Table 1). During the period 2019-21, including the largest clusters, patients belonging to a RTC were more often male (68 vs 58%, p< 0.001) and younger (average age: 39 vs 44 years, p< 0.001) than non-RTC patients. This observation was even more marked for very large RTCs (see Table 2). It should be noted that the largest cluster (14 patients) was mainly composed of women and located in French overseas territories.

Conclusion: This study shows an evolution of the structure of HIV sequence clusters over time with a decreasing number of small RTCs but an increasing number of large RTCs. These trends can be explained by a better global control of transmission, due in part to TasP, but not preventing some super-transmitters networks, despite PrEP use and not only including MSM is some settings. The COVID period does not seem to have strongly prevented such large transmission networks.

Table. Numbers of recent transmission clusters identified among each tree, along with median age and sex ratio according to the inclusion into no cluster, a small cluster or large cluster in the tree including all sequences (2013-2022).

Type of clusters	Time periods (n clusters)				Median age (years)	Sex ratio % male
	2013-15	2016-18	2019-21	2013-22	2013-22	2013-22
Not in a cluster	-	-	-	-	44.3	57.5
Small cluster (2-4)	290	245	209	881	38.4	64.9
Large cluster (>4)	8	4	17	68	32.7	66.7

853 BEYOND FAST-TRACK CITIES: DYNAMIC OF HIV CLUSTERS IN A FRENCH REGION NEAR PARIS

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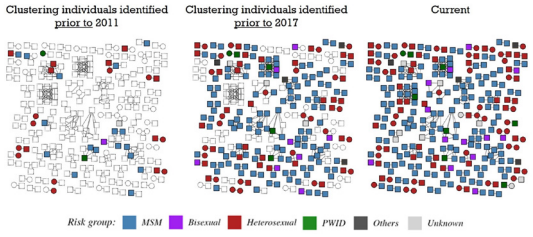
Background: The Loire Valley region is a low-density demographic and medical region with the second most elevated rate of positive HIV testing in France (1.4/1000 screening) after Paris, despite a low testing rate (60/1000 inhabitants). Among new HIV diagnoses, 40% are men having sex with men (MSM) and 43% are heterosexuals (HET) born abroad. We investigated the role and characteristics of transmission clusters in the HIV dynamics in this region close to the fast-track city of Paris for appropriate local response.

Methods: 1305 HIV *pol* gene sequences collected in Loire Valley region over a decade (2010-2020) were included in a phylogenetic analysis combined with epidemiological data. Putative transmission clusters were inferred using HIV TRACE methods (≤0.015 substitutions/site, Tamura Nei 93 substitution model). Risk factors of being part of a cluster were studied using an uni- and multivariate logistic regression model.

Results: Of the 1,305 participants, 44% (n=579) were born out of France, including 36% originating from Sub-Saharan Africa (SSA), 494 (38%) were women, 433 (33%) MSM, 694 (53%) HET. Migrants had lower CD4 cell count at diagnosis than those born in France (296 vs 443, p< 0.01), likely due to delayed time to diagnosis, and were mainly women (62%). A total of 86 clusters were identified (N=276 sequences, clustering rate of 21%) including 33 of N ≥ 3 linking 170 participants (3-16 per cluster), and 53 dyads (Figure 1). We identified risk factors of clustering: MSM born in France (OR 2.57, p< 0.01), higher viral load (OR 1.39, p< 0.01) and residency in one administrative division of the region (OR 3.17, p< 0.05). HET from SSA were at lower risk than those born in France (OR 0.01, p < 0.01). Among large clusters of N≥7, virological control was achieved in a median of 75% of people per cluster (IQR 74-87) vs 84% for the total cohort. Fourteen clusters were still growing after 2017 despite PrEP availability.

Conclusion: In Loire Valley region, we found that French-born MSM were part of local transmission networks but not HET migrants, suggesting a two-compartment HIV dynamic. Delayed diagnosis or infection before settling in the region could lead to under-representation of migrants in cluster analysis. Locally, epidemic control would require further implementation of PrEP and TASP in MSM to slow the dynamics of HIV clusters and generalized access to HIV screening for migrants. The same actions are promoted by the Paris Sans SIDA initiative and should be extended to neighboring territories.

Figure 1. HIV transmission networks in French Loire Valley region between 2010 and 2020. Circles represent women and squares represent men. The network is represented in 3 periods based on the date of diagnosis of each participant, with a focus on the years following PrEP implementation in France (>2017). The circles and squares are colored according to the risk group (see legend; white = yet to be sampled/diagnosed).



854 NOT ALL CLUSTERS ARE EQUAL: STATEWIDE MOLECULAR HIV CLUSTER DYNAMICS IN RHODE ISLAND

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Background: Molecular HIV clusters are assumed to have uniform patterns over time. We hypothesized that assessment of cluster evolution may reveal distinct cluster patterns, improving molecular characterization of the local HIV epidemic and informing public health.

Methods: Annual phylogenies were inferred by cumulative aggregation of partial *pol* sequences of all individuals with HIV-1 in Rhode Island (RI), diagnosed between 1990 and 2020. Molecular clusters were detected in annual phylogenies by strict and relaxed cluster definition criteria and the impact of annual newly-diagnosed cases to the structure and behavior of individual clusters were examined over time.
Results: Of 2,153 individuals representing a statewide epidemic, 31% (strict criteria) to 47% (relaxed criteria) were found in clusters. Longitudinal tracking of individual clusters identified three cluster types: *normal*, *semi-normal* and *abnormal*. Normal clusters (83%-87% of all identified clusters) showed predicted growing/plateauing dynamics, with ~3-fold higher growth rates in large (15%-18%) vs. small (~5%) clusters. *Semi-normal* clusters (1%-2% of all clusters) temporarily fluctuated in size and composition. *Abnormal clusters* (11%-16% of all clusters) demonstrated collapses and re-arrangements over time. Borderline values of cluster-defining parameters explained dynamics of non-normal clusters.
Conclusion: Comprehensive tracing of individual molecular HIV clusters over time in a statewide epidemic identified distinct cluster types, likely missed in cross-sectional analyses. Data suggest that not all clusters are equal, knowledge that could improve methodology of molecular surveillance of HIV epidemics to better inform public health strategies to disrupt HIV transmission.

855 HIV SEQUENCING AT DIAGNOSIS ENHANCES DETECTION OF CLUSTERS AND POTENTIAL CARE GAPS

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Background: HIV genetic sequencing enables identification of growing transmission clusters, but typically occurs after a person diagnosed with HIV is linked to care and undergoes drug resistance testing. Many surveillance systems utilize these sequences to assess for outbreaks but could miss members who have not engaged in clinical care. We assessed whether additional sequencing from remnant diagnostic specimens could enhance cluster detection and response activities in a statewide surveillance system.
Methods: We built an analysis platform to monitor HIV clusters in North Carolina (NC). To date, >20,000 pol sequences from routine "clinical" genotypes have been systematically reported to state surveillance from reference laboratories. From 2018 to 2021, we performed next-generation sequencing (NGS) on remnant diagnostic specimens from individuals with new HIV diagnoses at the NC State Laboratory for Public Health to augment molecular surveillance. We evaluated clinical and cluster characteristics of persons who had subsequent clinical sequences compared to those who only had NGS at diagnosis. Clusters were defined at < 1.5% genetic distance threshold between ≥2 sequences using the TN-93 model, including sequences from persons diagnosed prior to 2018.
Results: In total, 855 persons newly diagnosed with HIV had NGS from remnant specimens; 591 (69%) had a subsequent clinical sequence reported to surveillance and 264 (31%) had NGS only. Of persons with clinical sequences, 89% had at least one care visit (≥1 recorded viral load or CD4 cell count) and 73% were virally suppressed in 2021. Among persons with only NGS, 83% had linked to care since diagnosis, 69% had at least one care visit in 2021, and 55% were virally suppressed in 2021. Persons with only NGS were less likely to be identified in a cluster (62% vs. 74% with a subsequent sequence). There were 319 unique clusters (median size: 5 members [Range: 2-106]). 122 (38%) clusters included ≥1 newly diagnosed member with only an NGS (median: 1 member [Range: 1-5]). In 22 (7%) clusters (size: 2 [2-6]), all new diagnoses had only an NGS.
Conclusion: Almost a third of individuals newly diagnosed with HIV did not have a clinically reported HIV sequence following diagnosis. These persons were somewhat less engaged in care, and over half were linked to HIV clusters, including membership in over one-third of clusters. HIV sequencing at the time of diagnosis enhances cluster detection, highlighting areas where intervention and monitoring could be intensified.

Table 1. Clinical* and cluster characteristics among persons who received NGS at diagnosis followed by routine clinical sequencing compared to persons who received NGS only.

	NGS + Routine clinical sequencing (N=591)	NGS only (N=264)
Ever received care		
Yes	590 (99.8%)	219 (83.0%)
No	1 (0.2%)	45 (17.0%)
Received care in 2021		
Yes	527 (89.2%)	183 (69.3%)
No	63 (10.7%)	36 (13.6%)
Missing	1 (0.2%)	45 (17.0%)
Virally suppressed in 2021		
Yes	430 (72.8%)	144 (54.5%)
No	153 (25.9%)	64 (24.2%)
Missing	8 (1.4%)	56 (21.2%)
NGS recency category		
Recent	228 (38.6%)	101 (38.3%)
Indeterminant	73 (12.4%)	41 (15.5%)
Chronic	290 (49.1%)	122 (46.2%)
HIV diagnosis year		
2021	139 (23.5%)	56 (21.2%)
2020	93 (15.7%)	34 (12.9%)
2019	159 (26.9%)	89 (33.7%)
2018	200 (33.8%)	85 (32.2%)
Identified in a cluster		
Yes	436 (73.8%)	164 (62.1%)
No	155 (26.2%)	100 (37.9%)
Missing	0 (0%)	0 (0%)

*DEFINITIONS: (Ever received care): ≥1 recorded HIV viral load or CD4 cell count since HIV diagnosis; (Received care in 2021): ≥1 recorded HIV viral load or CD4 count in 2021, missing if never received care; (Virally suppressed in 2021): latest HIV viral load value in 2021 indicates ≤200 copies of HIV per mL blood, missing if never received care; (NGS recency category): recent if NGS estimated to have occurred within 9 months of infection; chronic if NGS estimated >9 months after infection

856 MOLECULAR CLUSTER TYPES SUSTAINING HIV SPREAD AMONG MSM IN QUEBEC: 2014-2020

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Background: HIV molecular network analysis can enhance our understanding of HIV transmission driving HIV spread in core Men having Sex with Men (MSM) and heterosexual populations. In this study, we characterized the role of clusters having 6+ members in HIV epidemic growth over the 2014-200 period.
Methods: HIV infections from newly infected persons (2002-2020) were stratified into three groups including, i) the subtype B epidemic in MSM (male-male clusters); ii) the subtype B heterosexual epidemic (female, mixed gender clusters); and iii) the non-B subtype epidemic MSM/HET epidemic introduced from persons born outside Canada. Molecular analysis of sequences from the Quebec genotyping program were analyzed using MEGA-10, RAxML, and Microbe-Trace methodologies to ascertain the linkage of viral sequences at 1.5%, 2.5%, and 4,5% genetic distance thresholds.
Results: Amongst MSM, there were 56%, 43% and 27% declines in singleton, small cluster (1-5 members) and large cluster networks (6-157 members) over the 2014-2020 period when compared to the 2007-2013 period, Epidemic growth from 2014-2020 was sustained by i) 10 newly-emerging clusters (n=128 infections) having a median of 12 members [10-16 IQR]; ii) 8 actively growing clusters (n=110 new infections in 2014-2020 linked to 87 pre-existing infections) adding 11.5 members [7-21 IQR] per cluster; and iii) 18 stable clusters experiencing 40% growth adding 395 new infections in 2014-2020, with a median of 14 new members (7-29 IQR) per cluster. Large cluster growth required relaxed 4.5% genetic thresholds to incorporate all members. Microbe-Trace at 1,5% and 2.5% genetic distance thresholds revealed multiple waves of episodic spread, including drug resistant outbreaks. Cluster size was associated with molecular recency of infection (% mixed base calls), younger age and higher viral load of cluster members.
Conclusion: HIV epidemic control amongst MSM remains challenging despite promising declines in HIV transmission in the 90-90-90 era. Incentivized testing, expanded ore-exposure prophylaxis, earlier initiation of treatment and treatment adherence is needed to avert early-stage transmission cascades, secondary outbreaks, and the persistence of more transmissible and stable variants.

857 CHANGING RISK OF HIV BEHAVIORAL AND DEMOGRAPHIC CLUSTERS IN RAKAI, UGANDA

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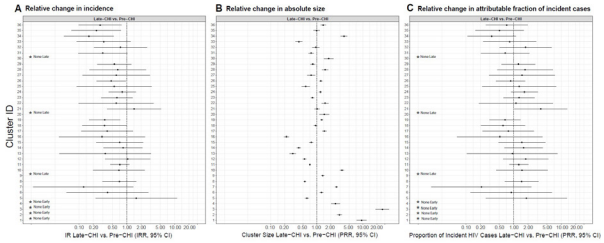
Background: New HIV infections have declined substantially in eastern Africa with the introduction of combination HIV interventions (CHI). However, it is unknown whether incidence has declined throughout the population or whether ongoing transmission is driven by sub-populations with high HIV incidence.

Methods: We used a machine learning algorithm applied to 12 survey rounds of data (1999-2016) from the Rakai Community Cohort Study (RCCS) in Uganda to identify population sub-groups with similar demographic and sexual behavioral characteristics. Sub-groups (i.e., clusters) were identified using k-means clustering agnostic to HIV status, with the number of clusters selected to optimize parsimonious prediction of HIV status. We assessed changes in cluster size, proportion of incident HIV cases accounted for, and within-cluster HIV incidence rates (IR) over time. Our algorithm supported 3- and 36-cluster solutions, depending on the fit statistic used (BIC vs. AIC). HIV incidence rate ratios (IRR) and 95% confidence intervals were calculated by visit and CHI epoch (pre CHI: 1999–2004; early CHI: 2005–2011; late CHI: 2011–2016) for each cluster. In the 3 cluster solution, we categorized clusters as low (0.38/100 person years [pys]), average (0.79/100 pys), and high (1.5/100 pys) risk based on pre-CHI HIV IRs.

Results: 33,866 individuals contributed 102,759 person-visits to the analysis. Most clusters with low pre-CHI incidence increased in size while the size of average and high-risk clusters decreased or remained unchanged. In the 3-cluster solution, the low-risk cluster increased from 8.7% of participants in 1999 to 20.0% by 2016, while the average-risk and high-risk clusters decreased in size from 50.9% to 45.5% and 40.3% to 34.5% respectively. IR per 100 py trended downwards in low and medium risk clusters, while significantly declining in the high-risk cluster (IRR 0.50, 0.29-0.86). In the 36-cluster solution, HIV IR declined in most clusters (Figure). The majority of incidence reduction (89%) could be attributed to within-cluster risk reductions, rather than changes in cluster size. Incidence did not concentrate among clusters with higher pre-CHI incidence over time.

Conclusion: In southern Uganda, HIV incidence has declined in nearly all population sub-groups with few exceptions and with no concentration of incidence in high-risk groups. More targeted strategies may be needed to reduce HIV risk in population sub-groups where incidence has remained stable or increased.

Changes in cluster incidence rate, size, and attributable fraction of incident HIV cases over time (36-Cluster Solution). Asterisks indicate clusters where there were zero incident cases in either the early or late-CHI period. Clusters are numbered in ascending order based on pre-CHI incidence levels (e.g., cluster 1 had the lowest pre-CHI incidence and cluster 36 the highest).



858 SEX DIFFERENCES IN NON-FATAL OVERDOSES: A POPULATION-BASED COHORT STUDY

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Background: Canada and the United States continue to face increases in both fatal and non-fatal overdoses. In Canada, the magnitude of the overdose crisis is most severe in British Columbia (BC), with sex disparities among people experiencing fatal overdoses higher than in any other province. However, little is known about sex disparities pertaining to non-fatal overdoses (NFODs) among people living with HIV (PLWH).

Methods: We used data from the Comparative Outcomes and Service Utilization Trends (COAST) study, a population-based longitudinal cohort study in BC, Canada. Administrative health records are available for all known PLWH and a 10% random sample of the HIV-negative population, all ≥19 years of age. Using data from January 1st, 2012 – March 31st, 2020, we identified 12,717 PLWH and 473,947 people living without HIV. We defined NFODs using ICD-9/10-CA codes in linked administrative data sets (i.e., hospital admissions, emergency department, and physician visits).

Results: Within COAST, 21.8% (n=2767) of PLWH and 49.7% (n=235,655) of the HIV-negative group are female. Among females living with HIV (FLWH), 18.3% (n=508) experienced at least one NFOD, compared to 10.7% (n=1069) of males living with HIV, 1.3% (n=3043) of females and 1.5% (n=3473) of males living without HIV. FLWH who experienced an initial NFOD had, on average, 2.5 recurrent NFODs; males living with HIV had, on average, 1.8. In contrast, males and females in the HIV-negative comparison group had < 1 recurrent NFOD. Overall, FLWH had the highest NFOD incidence (10.53/100 person-years (PY); 95%CI: 10.05, 11.03). These rates surpassed those of males living with HIV (4.86/100 PY; 95% CI: 4.69, 5.04), and females (0.37/100 PY; 95%CI: 0.36, 0.38) and males (0.44/1000 PY; 95%CI: 0.43, 0.45) living without HIV. In unadjusted analyses, FLWH were more likely to experience an NFOD than men living with HIV (incidence rate ratio (IRR): 2.17, 95%CI: 2.04, 2.30), whereas females living without HIV were less likely to experience an NFOD (IRR: 0.83; 95%CI: 0.80, 0.86) in comparison to males living without HIV.

Conclusion: Our analyses demonstrate that among PLWH, females experience a higher incidence of NFOD events. This sex disparity is important to explore further, given the potential for adverse health outcomes after NFODs. These findings have implications by suggesting the need for policies and programs oriented toward women to mitigate overdoses, especially those living with HIV.

859 TRANSGENDER WOMEN BASELINE PROFILE IN TRANSCITAR: TRANS-SPECIFIC COHORT IN ARGENTINA

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Background: Transgender women (TGW) are among the population most affected by the HIV epidemic in Argentina, despite a progressive legal framework. TransCITAR is a trans-specific cohort in Argentina that aims to assess physical and mental health among transgender and non-binary people (TGNBP). We present baseline characteristics of TGW.

Methods: TGW attending a trans-friendly clinic to receive HIV/STIs prevention/treatment, mental health care and/or gender-affirming hormone therapy (GHT) were invited to participate. Semiannual visits including clinical assessments, laboratory tests, and psychosocial interviews were performed. Oral PrEP was offered as part of a combined prevention strategy since September 2021.

Results: Between September/2019 and August/2022, 500 TGNBP were enrolled, 416 were TGW (median age: 30 years, IQR 25–37). High social vulnerability was observed (Table 1). Regarding trans-specific characteristics, 49.8% reported industrial silicone injections and 36.8% were receiving GHT. 76.9% were sex workers. Baseline STIs prevalence were: HIV 42.3% (10.2% diagnosed at enrolment), syphilis 40% (defined as positive nontreponemal test VDRL with titers of at least 1/8), past HBV 18.5%, chronic HBV 3.8%, HCV antibody positive 2.6%. Only 57% presented HBV protective antibodies titers (HBVsAb≥10UI/ml), 8 TGW were on PreP. For those with HIV, median CD4+ cell count was 602 cells/mm3 (IQR 378-933), 66.5% were on ART at enrolment (53.6% were virally suppressed) and 14.8% initiated at baseline. During 36 months of follow up, 4 TGW died (one AIDS-related and one COVID-19-related). Bivariate analyses showed that a positive HIV diagnosis was independently associated with migration, low level of education, unstable housing, silicone injecion and sex work, while was negatively associated with being on GHT. In multivariable logistic regression, only sociodemographic variables remain associated: migrant (aOR=.487, 95% CI=.304-.768); incomplete high school (aOR=.463, 95% CI=.300=.714); unstable housing (aOR=.614, 95% CI=.401-.940); and sex work (aOR=.324, 95% CI=.177-.593).

Conclusion: TGW from TransCITAR presented poor health outcomes: high prevalence of HIV/syphilis, high proportion with incomplete/no HBV vaccine and high levels of depression and violence. A comprehensive approach to care and addressing social determinants of health is pivotal to reduce HIV burden in this population.

Table 1. Baseline factors associated with HIV diagnosis.

Characteristics	Total n=416 n(%)	HIV no n=240(57.7%)	HIV yes n=176(42.3%)	p	OR(95% CI)
Migrant (yes)	127(30.5)	59(24.6)	68(38.6)	**.002**	.52(.34-.79)
Education (less than complete high school)	204(49)	163(67.9)	147(83.5)	**.000**	.42(.26-.68)
Unstable housing (yes)	172(41.3)	82(34.2)	90(51.1)	**.001**	.50(.33-.74)
Sex work lifetime (yes)	320(76.9)	161(57.1)	159(90.3)	**.000**	.22(.12-.39)
Depression (yes)[a]	134(32.2)	73(30.4)	61(34.7)	.360	
Current tobacco smoking (yes)	173(41.7)	93(38.8)	80(45.7)	.155	
Hazardous drinking (yes)[b]	80(19.3)	41(17.1)	39(22.3)	.185	
Drug abuse (yes)[c]	12(2.9)	7(2.9)	5(2.8)	.964	
Cocaine use last year (yes)	215(51.7)	120(50)	95(54)	.423	
Sexual violence, lifetime (yes)	86(20.7))	42(26.8)	44(31.2)	.393	
Physical violence, lifetime (yes)	159(38.2)	77(48.7)	82(55.8)	.218	
Silicone injection, lifetime (yes)	207(49.8)	101(43.2)	106(60.6)	**.000**	.49(.33-.74)
Hormone therapy, current (yes)	152(36.8)	100(41.8)	52(29.9)	**.013**	1.68(1.12-2.55)

Note: In bold, significant values ≤ .05. CI = Confidence interval; OR = odds ratio. [a]CES-D ≥16, [b]AUDIT ≥ 8, DAST[c] ≥ 6.

860 INTIMATE PARTNER VIOLENCE IN A COHORT OF PERSONS WITH HIV IN CARE

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Background: The prevalence of intimate partner violence (IPV) is estimated to be higher among persons with HIV (PWH) relative to the general population in the U.S. We examined prevalence of past-year IPV and associated health outcomes among PWH in care in a multi-site U.S. cohort.

Methods: PWH at 8 Centers for AIDS Research Network of Integrated Clinical Systems (CNICS) sites across the US reported on a 4-item scale of IPV experienced in the last 12 months in their patient reported outcomes and measures assessment between 6/2016-5/2022. We examined association with IPV and important health outcomes and behaviors using linear and logistic regression models adjusted for age, ethnicity, and site.

Results: 9748 PWH (mean age 49, 82% cisgender male/16% cisgender female/1% transgender female, 54% white/36% Black/15% Hispanic) reported on IPV, with 9.3% (n=905) reporting IPV in the past 12 months, of whom half reported psychological IPV with no physical IPV (n=453). In adjusted models, having any IPV was associated with recent viral load (VL) ≥ 75, a greater likelihood of reporting depression and anxiety with panic symptoms, concern for sexually transmitted infection (STI) exposure, unstable housing, and binge alcohol, cannabis, cocaine, opioids, or methamphetamine (MA) use. IPV correlated with a lower likelihood of attending their HIV medical visits in the past year (Table 1). Additionally, PWH who reported IPV had 10% lower quality of life score, 4.4% lower antiretroviral (ARV) adherence, 1.9 higher stigma score and 2.4 more HIV symptoms index symptoms than those without IPV. Of note, associations among PWH who experienced only psychological IPV were similar to those who experienced physical IPV, with the exceptions of current MA use, which was associated with a significantly greater odds of use among PWH reporting physical IPV, and concern for STI exposure, which was higher among those experiencing physical IPV.

Conclusion: Almost one in ten PWH reported experiencing any IPV in the prior year, which is associated with potentially poorer HIV outcomes. IPV is also associated with greater mental health and lower quality of life concerns and variable substance use depending on the type of IPV, suggesting the need to assess both psychological and physical IPV among PWH as part of routine care and provide appropriate healthcare intervention.

Table 1. Association of IPV with outcomes, logistic and linear regression, adjusted for age, race/ethnicity, site.

Note: The figure for this abstract was not legible as submitted

861 SYNERGISM BETWEEN VIOLENCE & HIV STATUS ON SUICIDAL IDEATION AMONG TRANSGENDER WOMEN

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NHBS-Trans Study Group

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Background: High rates of suicidality among transgender women (TGW) have been attributed to experiences of violence. Further threats to their mental health include the high burden of HIV and its corresponding stigma. This analysis aimed to explore the association between violence and suicidal ideation (SI) and moderation by HIV status. Better understanding of these relationships could inform health services and structural interventions tailored to lived experiences of TGW.

Methods: TGW were recruited via respondent-driven sampling (RDS) from 7 US cities, were interviewed, and offered HIV testing. Those aged 18 and above, assigned male or intersex at birth, self-identified as woman or TGW, not a previous participant, spoke English/Spanish, and who consented were included. Separate log-linked Poisson regression models were conducted to analyze the association between past-year experience of gender-based, physical intimate partner, or sexual violence (GBV, PIPV, or SV) and past-year SI. Models controlled for RDS design and confounders to generate adjusted prevalence ratios (aPR) and 95% confidence intervals (CI). Interaction terms for violence and HIV status were assessed for effect modification.

Results: Among 1549 TGW, 656 (42%) tested HIV-positive, 893 (58%) were HIV-negative, 865 (56%) reported GBV, 236 (15%) reported PIPV, and 232 (15%) reported SV. Of 276 (18%) TGW who reported SI, 203 (74%) reported GBV, 69 (25%) reported PIPV, and 81 (29%) reported SV. There was higher prevalence of SI among those who reported GBV (aPR 1.39, 95%CI 1.02-1.88), PIPV (aPR 1.42, 95%CI 1.16-1.73) and SV (aPR 1.52, 95%CI 1.15-1.99) than those who had not reported violence. There was significant interaction between HIV status and SV ($p < 0.05$). Among persons who did not report SV, the prevalence of SI was significantly lower among HIV+ persons compared to HIV- persons (aPR 0.64, 95%CI 0.47-0.87). However, HIV+ persons who *did* report SV had significantly higher prevalence of SI than HIV- persons who did *not* report SV (aPR 1.77, 95%CI 1.27-2.47).

Conclusion: Prevalence of SI and violence among TGW were high. Among those who did not report violence, HIV+ status was associated with lower SI prevalence, and may be attributed to care and support groups for HIV+ persons. However, GBV, PIPV and SV were associated with higher prevalence of SI, especially among HIV+ persons experiencing SV. An integrated approach to violence prevention and sexual and mental health could aid in addressing suicidality among TGW.

Association between past-year experience of sexual violence and suicidal ideation and effect modification by HIV status among transgender women participants in the NHBS-Trans in 7 U.S. Cities from June 2019 – February 2020

	No sexual violence in the past year		With experiences of sexual violence in the past year	
	N with / without suicidal ideation	aPR (95% CI)	N with / without suicidal ideation	aPR (95% CI)
HIV negative	141 / 607	1.00 (Ref)	54 / 91	1.52 (1.15-1.99)*
HIV positive	54 / 515	0.64 (0.47-0.87)*	27 / 60	1.77 (1.27-2.47)*

Measure of effect modification on multiplicative scale: ratio of PRs (95% CI) = 1.83 (1.18-2.82)*
*significant at $p < 0.05$
aPR – adjusted prevalence ratios; CI – confidence intervals
Adjusted for respondent-driven sampling design and confounding factors, including age, race/ethnicity, education, poverty, gender affirming hormonal therapy status, gender affirming surgery status, disability, incarceration, illicit drug use, homelessness, and perceived social support

862 PREVALENCE AND CORRELATES OF VIOLENCE AMONG PARTNERS OF PWID LIVING WITH HIV IN KENYA

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Background: In Kenya, people who inject drugs (PWID) have a higher HIV burden compared to the general adult population. Violence and its related HIV risk behaviors and low HIV service uptake are also more common among PWID living with HIV, which may increase HIV transmission among PWID and their sexual and/or injecting partners. Understanding the nature and correlates of violence may inform population-specific public health interventions and policy recommendations.

Methods: Using cross-sectional data from a prospective cohort study in Kenya, we identified the prevalence and correlates of violence among sexual and injecting partners of PWID living with HIV, whom we contacted through assisted partner services. Violence is defined as any physical harm (hit, slap, kick, physically hurt), threats with a weapon or mentally, or forced sexual acts inflicted on a person by anyone in the past year. We used a Chi-squared test and a two-sided Fisher's exact test to identify the socio-demographic characteristics associated with violence. Using the Woolf test for homogeneity, we conducted a stratified analysis to test effect modification by gender and HIV status.
Results: Among 3302 partners, 1439 (44%) experienced violence within the past year. Physical violence was the most common form of violence experienced (35%; 95% confidence interval [95%CI] 33.3%, 36.5%), followed by being threatened (23%; 95%CI 21.5%, 24.4%), and sexual violence (7%; 95%CI 6.2%,7.9%). Being male (Relative Risk [RR]=1.22; 95%CI 1.11, 1.33; p< 0.001), living in coastal Kenya (RR=1.53; 95%CI 1.41, 1.66; p< 0.001), having multiple sexual partners (RR=1.39; 95%CI 1.22, 1.6; p< 0.001), being divorced/ separated/ widowed (vs. single) (RR=1.24; 95%CI 1.13, 1.37; p< 0.001), not having stable housing (RR=1.14; 95%CI 1.03, 1.27; p=0.019), being both a sexual and injecting partner of a PWID (vs. injecting partner only) (RR=1.18; 95%CI 1.06, 1.32; p=0.005), being an active injection drug user not on methadone (vs. on methadone) (RR=1.53; 95%CI 1.04, 2.25; p=0.018), and, for men, having had sex with men (RR=1.36; 95%CI 1.21, 1.54; p< 0.001) were associated with experiencing violence. The stratified analysis identified that gender was an effect modifier while HIV status was not.
Conclusion: Study results highlight PWID partners at increased risk for experiencing violence, which may help to formulate and tailor effective public health interventions and policy recommendations for increasing HIV-related services among key populations in Kenya.

Table: Stratified analysis by Gender on the association between some partner characteristics and experiencing violence

Variable		Crude RR of violence (n=3302) RR (95% CI)	RR of violence among males (n = 2336) RR (95% CI)	RR of violence among females (n = 966) RR (95% CI)	P value for interaction
Region	Nairobi	1(Ref)	1(Ref)	1(Ref)	
	Coast	1.53 [1.41-1.66]	1.35 [1.23-1.48]	2.04 [1.75-2.39]	<0.001
Employment	Formal	1(Ref)	1(Ref)	1(Ref)	
	Informal	0.99 [0.81-1.20]	1.08 [0.86-1.36]	0.59 [0.35-1.01]	0.041
	Illegal	1.15 [0.95-1.39]	1.39 [1.08-1.77]	0.90 [0.66-1.23]	0.033
Partner type	Injecting	1(Ref)	1(Ref)	1(Ref)	
	Both sex & inject	1.18 [1.06-1.32]	1.79 [1.48-2.17]	1.02 [0.89-1.17]	<0.001
HIV status	Negative	1(Ref)	1(Ref)	1(Ref)	
	Positive	0.98 [0.89-1.09]	1.01 [0.89-1.16]	1.08 [0.91-1.28]	0.560

863 PERSISTENTLY HIGH HIV INCIDENCE AMONG MSM AND PWID ATTENDING CARE CENTRES IN INDIA

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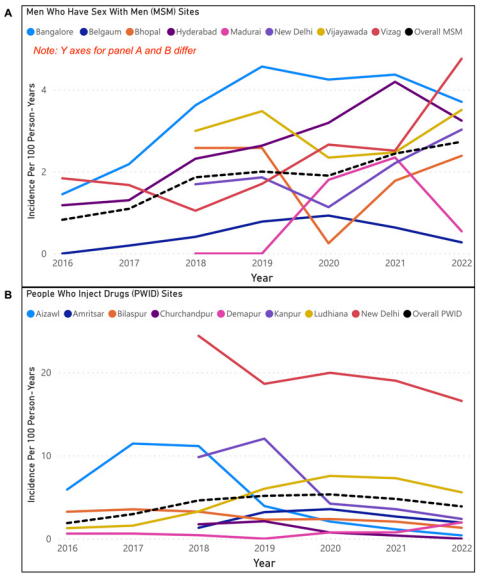
Background: Understanding temporal changes in HIV incidence among vulnerable populations is critical for understanding where to direct prevention efforts. Yet, due to logistical contraints there are few sources of longitudinal incidence data, particularly among key populations (KP).
Methods: Integrated care centres (ICCs), established 2014-2016 in 15 Indian cities, provide rapid onsite HIV testing as well as other population-specific services to men who have sex with men (MSM, 8 sites) or people who inject drugs (PWID, 8 sites). ICC clients are tracked and encouraged to return for repeat testing every 6 months. Client testing data were included in the analysis if they had ≥2 tests and not positive on the first test. Person-time was accrued between HIV test dates except for those with a positive result, for whom the seroconversion date was estimated as the midpoint between the last negative and first positive test and person-time was calculated accordingly. Incidence rates per 100 person-years (PY) were stratified by population group, city/site, and year. To visualize temporal trends in incidence, we used line graphs per population and city with a 2-year moving average for smoothing purposes.
Results: From June 2014-July 2022, 13,101 clients (5722 MSM, 7379 PWID) had ≥2 HIV tests with a median total follow-up time of 1.9 years (interquartile range 0.9-3.5). Median age at first test was 28 years and 7% of PWID were women. Among MSM, 66% had recent unprotected sex with a man at their first test. Among PWID, 63% were actively injecting and 39% recently shared injecting paraphernalia. There were a total of 1039 incident HIV infections. The overall incidence rate for MSM and PWID were 1.9/100 PY (95% CI: 1.7-2.2) and 4.1 (3.9-4.4), respectively. Among MSM sites, incidence ranged from 0.4 to 3.5 and in PWID sites from 0.6 to 19.1. Among MSM, incidence increased significantly each year (0.7 in 2015 to 2.9 in 2022). Among PWID, incidence increased significantly until a peak in 2020 and then significantly declined (1.8 in 2015, 5.6 in 2020, 3.8 in 2022). Across populations/cities these trends were generally similar though the magnitude of incidence was highly variable (**Fig 1**).
Conclusion: While there was substantial geographic variability, nearly all experienced high incidence (>2/100PY) despite being currently engaged in a community-based clinic where preventive services are free. This highlights the need to focus on KP in LMICs when considering novel strategies such as long acting PrEP to curtail incidence.

HIV incidence among MSM and PWID Intergrated Care Centre clients with a 2-month moving average, 2015-2022 in India



864 NOT GETTING TO ZERO HIV FOR PEOPLE WHO INJECT DRUGS, SAN FRANCISCO

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Background: From 2012 to 2021, new diagnoses for people who inject drugs (PWID) decreased by 14%, with an ***increase*** of 50% in the last 3 years. We examined data from the recently completed National HIV Behavioral Surveillance (NHBS) survey of PWID to characterize the status of the HIV epidemic for this population and progress toward the UNAIDS 95-95-95 targets in San Francisco.
Methods: Data are from NHBS which tracks HIV prevalence and related risk factors among populations at risk in major U.S. cities. The team sampled PWID using respondent-driven sampling. Eligibility criteria were age over 18 years, injected non-prescribed drugs in the last 12 months, San Francisco residence, and referral by another participant. HIV testing was done, and interviews collected demographics and HIV-related behavior. We present demographics, HIV-related behavior, and HIV test results collected from June to December 2022 with comparisons to 2018.
Results: Of 527 eligible PWID, 53% were non-White, 68% male, 73% heterosexual, 47% over 50 years old, and 67% experiencing homelessness. Although current HIV prevalence was identical to 2018 (11%), new HIV-positive test results increased by 33%. Participants with new HIV-positive test results in 2022 tended to be Black/African American (42%), male (50%), heterosexual (83%), and over 50 years old (50%). While 75% of PWID with a new HIV-positive test result had a healthcare visit in the last 12 months, only 22% of them were

offered an HIV test during a visit. More than half delayed healthcare due to injection drug use stigma (55%) and discrimination (54%) when accessing healthcare. With respect to 95-95-95 targets, 80% of PWID living with HIV were previously diagnosed, of whom 92% were on antiretroviral treatment, of whom 71% were virally suppressed.

Conclusion: San Francisco is not on course to get to zero HIV infections for PWID, progress toward 95-95-95 targets is slow, and stigma remains high. Our data corroborate citywide HIV case reporting suggesting recent increases in new HIV infections among PWID despite decreases in the epidemic overall. Our data point to a need for HIV testing in healthcare missed opportunities for early diagnosis, and challenges for retention in care and viral suppression. PWID-sensitive and focused programs are needed to increase HIV testing overall, sustain retention in care, and address stigma if San Francisco is to end the epidemic for all.

865 RACIAL DISPARITIES IN HIV PRE-EXPOSURE PROPHYLAXIS-RELATED OUTCOMES IN MALE VETERANS

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Background: Despite its known efficacy, human immunodeficiency virus (HIV) pre-exposure prophylaxis (PrEP) has had limited uptake in United States (US) Veterans at high risk for HIV acquisition. We hypothesized that Black US Veterans of minoritized sexual orientation (MSO) receive PrEP at comparable rates relative to other racial categories. However, we also hypothesized that higher rates of HIV acquisition would be associated with Black race, regardless of PrEP receipt.

Methods: A retrospective analysis was conducted for the period of July 12, 2012 through July 1, 2019, using a validated natural language processing system to derive a cohort of Veterans documented as MSO. HIV diagnosis was defined as the first appearance of the diagnosis in the electronic health record (EHR) as identified by an International Classification of Disease code. PrEP recipients were individuals with two or more pharmacy fills of emtricitabine/tenofovir disoproxil fumarate. Race was defined by structured categories available in the Veterans Affairs EHR. Chi-square tests evaluated the association between race and HIV acquisition stratified by PrEP use (α=0.05).

Results: A cohort of 67,299 HIV-negative male Veterans with MSO documentation was identified. In total, 2,375 received PrEP and 64,924 did not. Of the 11,181 Black Veterans, 459 (4.1%) received PrEP, while 1621 (3.2%) of the 50,336 White Veterans and 295 (5.1%) of the 5,782 Other Veterans received PrEP. For those who received PrEP, 10.5% of Black Veterans, 8.1% of White Veterans, and 6.8% of Other Veterans acquired HIV. The association between HIV acquisition and race was not statistically significant in PrEP recipients. For those who did not receive PrEP, 9.8% of Black Veterans, 2.8% of White Veterans, and 4.8% of Other Veterans acquired HIV. The association between HIV acquisition and race was statistically significant in PrEP non-recipients.

Conclusion: Rates of PrEP receipt in Veterans with MSO documentation were comparable across racial groups. HIV acquisition was lower in White and Other Veterans who did not receive PrEP, suggesting that patients and providers assessed their risk as lower than those who were offered and accepted PrEP. The lack of full protection in those receiving PrEP reinforces the real-world occurrences of gaps in adherence and persistence. For Black Veterans, rates of HIV acquisition were comparable for those who did and did not receive PrEP. These findings suggest a higher baseline risk for HIV acquisition independent of PrEP receipt.

HIV Acquisition by Racial Category for Veterans Who Did and Did Not Receive PrEP

		PrEP Recipients				
		Total N = 2375	Black N = 459	White N = 1621	Other N = 295	p-value
Diagnosed with HIV? N (percentage by race)	No	2,175 (91.6)	411 (89.5)	1,489 (91.9)	275 (93.2)	0.16
	Yes	200 (8.4)	48 (10.5)	132 (8.1)	20 (6.8)	
		PrEP Non-Recipients				
		Total N = 64,924	Black N = 10,722	White N = 48,715	Other N = 5,487	p-value
Diagnosed with HIV? N (percentage by race)	No	62,221 (95.8)	9,672 (90.2)	47,327 (97.2)	5,222 (95.2)	<0.0001
	Yes	2,703 (4.2)	1,050 (9.8)	1,388 (2.8)	265 (4.8)	

HIV, human immunodeficiency virus; PrEP, pre-exposure prophylaxis

866 BEHAVIOR CHANGE AMONG HIV-NEGATIVE MEN WHO HAVE SEX WITH MEN NOT USING PrEP IN THE US

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Background: HIV incidence is falling among US gay, bisexual and other men who have sex with men (MSM) as a result of HIV pre-exposure prophylaxis (PrEP) and HIV treatment as prevention; however, >20,000 diagnoses still occur among MSM each year. Considerable research has documented behavior change among MSM on PrEP. We know of no studies to consider such change among HIV-negative US MSM *not* using PrEP, even though they still comprise the majority of MSM and are presumably at greatest seroconversion risk. We hypothesized that such men may see increasing rates of condomless anal sex (CAS) either with partners believed to be on PrEP or suppressed (indirect protection), or more generally given changing norms around condom use. We also predicted that increases would be largest for young MSM and vary by race/ethnicity.

Methods: We used serial cross-sectional data from the American Men's Internet Survey (2014-2019), limited to the subsample enrolled in 2 consecutive years and reporting being HIV-negative and not using PrEP both years (HNNP-2, n=2,421). We estimated the proportion reporting CAS each year, and used one-sided McNemar tests to identify significant increases. We then disaggregated by partner HIV status (unknown, positive, negative). Among HNNP-2 respondents reporting 2+ CAS partners each year, we used Wilcoxon signed rank tests to identify significant increases in number of CAS partners in year 2.

Results: Overall, CAS increased by 2 percentage points (pp) from year 1 to year 2 (68-70%); increases were largest among younger (age 15-24, 5pp) and Hispanic/Latino (Latino) (5pp) respondents; especially among younger Latinos (13*pp*, from 68% to 81%). Increases were concentrated among those with perceived HIV-negative partners. Additional predictors included lower education and income, and residence on metropolitan fringe. Younger participants also had significant increases in the number of CAS partners year-over-year.

Conclusion: Among HIV-negative MSM *not* on PrEP, younger and Latino males are experiencing sizeable increases in CAS. Patterns suggest this is unlikely to represent effective reliance on indirect protection (partners on PrEP or suppressed). This signals a need to increase access to HIV prevention messaging specifically for these populations. Although efforts often focus on getting MSM on PrEP, it is also key to enhance counseling about risk among those who are unable or unwilling to initiate PrEP, as other prevention measures may be getting less visible in these communities.

867 REASONS FOR MIGRATION AND ASSOCIATIONS WITH HIV RISK AMONG SEXUAL MINORITY MEN

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Background: The U.S. population of immigrants has grown rapidly over the past two decades. Knowledge about reasons for migration and their association with HIV-related behaviors is limited. We explored patterns in reasons for migrating to the U.S. among cisgender gay, bisexual, and other sexual minority

men (SMM) and determined their associations with HIV risk and prevention behaviors.

Methods: Data were from the 2018-2020 cycles of the American Men's Internet Survey, an annual online survey of SMM in the U.S who report having sex with other men in the past year. We limited analyses to participants born outside the U.S. who reported reason(s) for migration and reported HIV-negative/unknown status. Participants selected from a list of reasons and could write in a reason. Latent Class Analysis (LCA) was performed to identify patterns in the reasons for migration. We used multivariate logistic regression controlling for demographic characteristics to assess class associations with the following in the past 12 months: condomless anal sex (CAS), illicit drug use, marijuana use, HIV testing, and PrEP use.

Results: Among 1,657 SMM, 21% were from Mexico, 18% from Europe, and 13% from South America; 29% spoke a primary language other than English. LCA identified 6 distinct patterns in reasons for migration: 1) Family and friends (14%); 2) Financial (17%); 3) Personal freedom related to being gay (10%); 4) Pursuit of opportunities while living openly as SMM (12%); 5) Educational purposes (18%); 6) Not my decision (29%). While HIV testing (range=57.6-65.4%) and PrEP use (15.6-21.4%) did not vary by class (p >0.05 for all), CAS and illicit drug use were significantly different (Table). SMM who migrated to pursue opportunities while living openly and whose reasons were not their decision had greater odds of CAS than SMM who migrated for educational purposes (adjusted odds ratio [aOR]:1.72, 95% confidence interval [95%CI]:1.15-2.59; 1.57, 1.13-2.19, respectively). SMM who migrated because of personal freedom related to being gay and for educational purposes had lower odds of illicit drug use than SMM who migrated due to family and friends (aOR, 95%CI: .57, .35-.93; .67, .45-1.00, respectively).

Conclusion: Reasons for migrating to the U.S. among SMM were associated with behaviors that can increase HIV risk. Push and pull factors related to migration matter when considering the HIV prevention needs of immigrant SMM.

Latent Class Analysis (LCA) Model: Comparisons of HIV Risk and Prevention Behaviors By Reasons for Migration Latent Classes

Table: Latent Class Analysis (LCA) Model: Comparisons of HIV Risk and Prevention Behaviors By Reasons for Migration Latent Classes

	Condomless Anal Sex[a]		Illicit Drug Use[a]		Marijuana Use[a]		HIV Testing[a]		PrEP Use[a]	
LCA Classes	aOR[b] (95% CI[c])	n(%)	aOR[b] (95% CI[c])	n(%)	aOR[b] (95% CI[c])	n(%)	aOR[b] (95% CI[c])	n(%)	aOR[b] (95% CI[c])	n(%)
Class 1: Family and Friends	0.74 (0.52-1.04)	141 (62.40)	1.27 (0.89-1.78)	83 (36.70)	1.19 (0.83-1.71)	70 (31.00)	1.00 (0.71-1.42)	135 (59.70)	0.79 (0.51-1.22)	36 (15.90)
Class 2: Financial Reasons	0.92 (0.66-1.29)	196 (68.80)	0.89 (0.63-1.25)	80 (28.10)	0.93 (0.65-1.32)	70 (24.60)	1.05 (0.77-1.45)	171 (60.00)	1.13 (0.77-1.66)	61 (21.40)
Class 3: Personal Freedom Related to Being Gay	0.90 (0.60-1.35)	111 (66.10)	0.72 (1.46-1.13)	35 (20.80)	0.64 (0.39-1.06)	26.00 (15.50)	0.70 (0.47-1.04)	87 (51.80)	0.67 (0.40-1.12)	30 (17.90)
Class 4: Pursuit of Opportunities while Living Openly as SMM[d]	1.10 (0.74-1.63)	137 (71.70)	0.97 (0.66-1.44)	53 (27.70)	1.05 (0.70-1.59)	047 (24.60)	1.30 (0.89-1.90)	125 (65.40)	1.01 (0.65-1.59)	40 (20.90)
Class 5: Educational Purposes	0.64 (0.46-0.89)	182 (59.90)	0.84 (0.59-1.19)	83 (27.30)	0.76 (0.52-1.11)	67 (22.00)	0.88 (0.63-1.22)	175 (57.60)	1.01 (0.65-1.59)	64 (21.10)
Class 6: It Was Not My Decision (ref)[e,f]	--	342 (70.80)	--	162 (33.5)	--	141 (29.2)	--	281 (58.2)	--	88 (18.20)

[a]Outcomes were reported for the past 12 months
[b]aOR: adjusted odds ratio; [c]CI: Confidence Interval; all models adjusted for age, education, country/region of birth, primary language, Census region of residence, urban-rural classification of residence, and health insurance status
[d]SMM: sexual minority men
[e] ref: Referent group, [f]Regression models were re-estimated in a sequential manner by rotating the referent LCA group (Not shown in table)

868 SEXUAL RISK AND ROLE OF LOW-LEVEL VIREMIA TO HIV TRANSMISSION IN SUB-SAHARAN AFRICA

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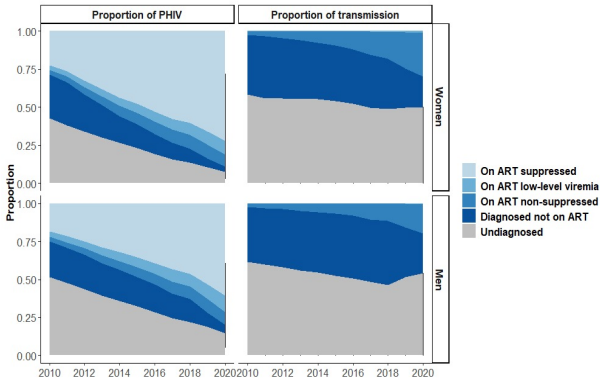
Background: Sexual HIV transmission can occur when people with HIV (PHIV) have detectable viraemia and unprotected sexual contact with susceptible partners. Low-level viremia (LLV) 51–999 viral copies/mL among PHIV on antiretroviral therapy (ART) can lead to HIV transmission even as ART coverage rises. We assessed differences in sexual risk behaviours and distribution of viral load (VL) at stages of the HIV cascade, including LLV, and modelled the contribution to transmission.

Methods: We analysed data for adults (≥15 years) from Population-based HIV Impact Assessment (PHIA) surveys conducted in 13 sub-Saharan African countries during 2015–2019, incorporating survey weights. We used log-binomial regression to estimate adjusted prevalence ratios (aPR) of HIV high-risk behaviours (multiple partners and condomless sex in past year) for five cascade categories: undiagnosed, untreated, on ART but non-suppressed (≥1000 copies/mL), on ART with LLV (51–999 copies/mL), and suppressed (≤50 copies/mL). We calculated the mean log_{10}-VL and transmission rate by cascade group and sex. A transmission equation incorporating the proportion of individuals, prevalence ratio of high HIV risk behaviour, and transmission rate was used to quantify the proportion of transmission from each subgroup.

Results: Compared to suppressed PHIV, reported high-risk behaviour was more likely among undiagnosed PHIV (aPR for women: 1.25, 95%CI: 1.06–1.48; aPR for men: 1.59, 95%CI: 1.32–1.93) and men diagnosed but untreated (aPR: 2.05, 95%CI: 1.32–1.93). There was no significant association between LLV and high-risk behaviour. The mean log_{10}-VL and estimated transmission rate was similar between those undiagnosed, diagnosed but untreated and those on ART but non-suppressed, but lowest among individuals with LLV. Undiagnosed and diagnosed but untreated PHIV contributed most to estimated transmission (73–92%), with low (≤1%) estimated transmission from those with LLV. Estimated transmission from individuals on ART but non-suppressed increased over time as awareness of status and ART coverage increased.

Conclusion: Undiagnosed and diagnosed but untreated PHIV account for the majority of transmissions in sub-Saharan Africa, highlighting a need for increased access to HIV testing and ART linkage services. Transmission from PHIV with LLV is low. In countries with high ART coverage, non-suppressed individuals on ART account for an increasing share of transmission, underscoring the importance of maintaining high viral suppression levels.

Figure. Pooled estimated proportion of PHIV across the 13 surveyed countries and estimated transmission proportion attributable to PHIV subgroups, 2010 to 2020. Data on proportion of PHIV outside survey years were obtained from UNAIDS country estimates.



869 REDUCTION OF HIV INCIDENCE AFTER ELIMINATION OF LYMPHATIC FILARIASIS

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Background: A general population survey from 2007 to 2011 in Southwest Tanzania previously revealed a 2.3-fold increased HIV incidence among individuals infected with *Wuchereria bancrofti* (WB), the parasite causing lymphatic filariasis. In 2007, the prevalence of filarial and HIV infections were 36.4% (385/1058) and 13.8% (162/1173), respectively, for individuals aged 14 to 65. A government program distributed the antifilarial drugs ivermectin and albendazole annually from 2009 to 2015. This intervention was evaluated in 2019 and a WB prevalence of 1.7% (22/1299) was found in 14 to 65 year olds. The impact of the quasi-elimination of WB on the HIV incidence is evaluated here.

Methods: Individuals who participated in the survey from 2007 to 2011 were re-visited in 2019 and screened for WB with a strip test detecting circulating filarial antigen and HIV using the government test algorithm.

Results: 1299 individuals from the first survey who were 14-65 years old at the current visit (2019) were able to participate in the screening. 116 (8.9%) of them had been HIV-infected at the end of the previous study in 2011. Among the 1183 participants without prior HIV, 57 new HIV infections occurred between 2011 and 2019. Among these 1183 participants, 372 (31%) had been previously

infected with *W. bancrofti* but were now cured. Between 2011 and 2019, 21 new HIV infections were seen in 2747 PY , HIV incidence 0.76/100 person years (PY). This is compared to 17 HIV infections in 890 PY (HIV incidence 1.9/100 PY) between 2007 and 2011, during which these individuals had been infected with *W. bancrofti*. The incidence rate ratio (IRR) of 0.39 was shown to be significant, p=0.0036 by using a Poisson regression and adjusting for age and gender.

Among the continuously filarial-uninfected 673 study participants, 38 HIV new infections occurred between 2011 and 2019 in 5915 PY (HIV incidence 0.64/100PY), as compared to 9 incident HIV infections between 2007 and 2011 in 1250 PY (HIV incidence 0.72/100PY, IRR of 0.92, p=0.815).

Conclusion: The increased HIV incidence of 1.9/100 PY seen in filarial-infected individuals from 2007 to 2011 dropped significantly to 0.76/100 PY between the 2011 and 2019 surveys, after years of effective antifilarial treatment. At the same time, the HIV incidence among the filarial-uninfected group declined only slightly from 0.7/100 PY in 2007 to 2011 to 0.64/100 PY between 2011 and 2019. These findings highlight that elimination of NTDs can lower the HIV incidence and help reduce the spread of HIV.

870 TRENDS IN MORTALITY IN PEOPLE LIVING WITH HIV IN AN INTERNATIONAL COHORT (RESPOND)

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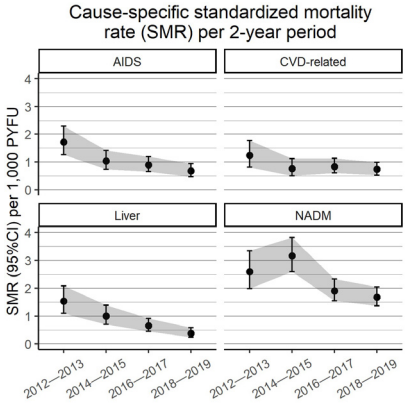
Background: Mortality rates in people living with HIV (PLWH) have declined in recent years due to effective antiretroviral treatment (ART). Aging, coinfections, and comorbidities among PLWH may drive further changes in mortality.

Methods: Mortality due to specific causes classified by the Coding Causes of Death in HIV (CoDe) methodology were investigated between 2012–19 among PLWH from the RESPOND cohort consortium. Age-standardized mortality rates were calculated over 2-year periods and age-adjusted Poisson models were used to compare mortality between periods. We also investigated all-cause mortality with multivariable Cox regression.

Results: Among 33642 PLWH with 170084 person-years of follow-up (PYFU) (median PYFU 4.9; IQR 3.1–8.0), 1702 (5.1%) died. Crude all-cause mortality per 1000 PYFU decreased from 13.0 (95%CI 11.8–14.4) in 2012–13 to 8.4 (95%CI 7.7–9.3) in 2018–19. Median age increased from 2012–13 (44 years IQR 36—51) to 2018–19 (49 IQR 40—56) as did median age at death from 52 (IQR 45—62) to 56 (IQR 48—65). The leading cause of death across the entire period was non-AIDS defining malignancy (NADM): 2.18 per 1000 PYFU (95%CI 1.96—2.41). Age-adjusted Poisson regression showed statistically significant decreases in mortality from 2012—13 to 2018—19 for deaths due to NADM, AIDS, cardiovascular disease (CVD), and liver disease (figure). The proportion of deaths due to AIDS (13.1% to 7.9%) and liver-disease (11.0% to 4.9%) declined from 2012—13 to 2018—19, and increased due to NADM (16.5% to 22.5%) and CVD (7.6% to 9.9%), but with concomitant increase in deaths due to unknown/missing causes (18.8% to 30.6%). In multivariable analysis, the strongest predictor of all-cause mortality was current CD4 ≤350 cells/mm3 + HIV viral load (VL) >200 cp/mL: adjusted hazard ratio (aHR) 10.4, 95%CI 8.8–12.3, vs. CD4 ≥500 cells/mm^3 + VL < 200 cp/mL. Other predictors were chronic kidney disease (aHR 1.45, 1.24—1.68), diabetes (aHR 2.32, 1.91—2.82), chronic untreated hepatitis C (HCV) (aHR 2.18, 1.88—2.54 vs. HCV antibody negative), and smoking (aHR 2.03, 1.71—2.39 current vs. never; 1.5, 1.25—1.79 previous vs. never).

Conclusion: In the RESPOND cohort, the leading cause of death was NADM. Age-adjusted mortality rates from AIDS, NADM, CVD, and liver-related causes declined, especially 2012—13 to 2016—17; the role of other contributing factors will be explored further. All-cause mortality was strongly associated with modifiable risk factors, indicating areas for improvement.

Cause-specific standardized mortality rate (SMR) per 2-year period



871 NON-AIDS DEFINING MALIGNANCY MORTALITY IN PEOPLE LIVING WITH HIV

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Background: Our aim was to evaluate rate and prognostic factors of mortality due to non-AIDS defining malignancies (NADM) among persons living with HIV (PLWH) from the cohort of the Spanish AIDS Research Network (CoRIS) during 2004-2020.

Methods: We included antiretroviral-naive individuals aged ≥ 20 years at enrolment, recruited during 2004-2020. NADM deaths were all deaths due to cancer, except those due to AIDS defining malignancies such as Kaposi sarcoma, certain types of non-Hodgkin lymphomas and cervical cancer. We estimated mortality rates and standardised mortality ratios (SMRs) using NADM mortality rates from the Spanish general population. We applied cause-specific Cox proportional hazard models, accounting for competing risk, and age as time-scale to identify prognostic factors for NADM mortality.

Results: Of the 17,329 study participants, 85% were men and median age was 35 years. The overall mortality rate was 1.53 (95% confidence interval: 1.32, 1.79) per 1,000 person-years (PY), 76% higher as that in the general population (SMR: 1.76, 95% CI 1.51, 2.06). The highest mortality rates were found for lung (0.56 per 1,000 PY; 95%CI 0.44, 0.73) and liver cancer (0.18 per 1,000 PY, 95%CI 0.12, 0.28). Mortality rates increased with age, whereas SMRs decreased from 3.42 (95%CI 1.63, 7.18) at ≤35 years to 0.92 (95%CI 0.56, 1.53) at ≥70 years.

Risk of NADM mortality was higher in participants that acquired infection through heterosexual contact (Hazard Ratio: 1.48; 95%CI 1.07, 2.03) and injection drug use (HR: 1.54 (0.87, 2.76), compared to men who have sex with men. Time-varying prognostic factors for NADM mortality were: active smoking (HR: 2.23; 95%CI 0.96, 5.18), presence of hepatitis C virus antibodies (HR: 1.74; 95%CI 1.09, 2.78) or hepatitis B surface antigen (HR: 2.02; 95%CI 1.12, 3.66) and decreasing CD4 count (HR: 8.49; 95%CI 5.46, 13.20 for CD4< 200 cells/µl, HR: 4.10; 95%CI 2.57, 6.55 for CD4 200-349 cells/µl;HR: 2.50; 95%CI 1.64, 3.80 for CD4 350-499 cells/µl compared to CD4≥500 cells/µl).

Conclusion: Mortality due to NADM in PLWH is higher than in the general population, mainly at younger ages. Smoking, viral hepatitis coinfections and immunosuppression independently increased risk of death due to NADM.

872 PROPORTION OF DEATHS OCCURRING OUTSIDE OF HEALTH FACILITIES ATTRIBUTABLE TO HIV/AIDS

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Background: Reliable and accurate mortality and cause-of-death data are lacking for deaths occurring outside health facilities in Malawi, including HIV/AIDS-related deaths. According to Malaria Vaccine Implementation Program (MVIP) data, over 70% of deaths in Malawi occur in the community. Malawi is piloting cause-of-death reporting in community using the 2016 World Health Organization (WHO) verbal autopsy (VA) tool. We used data from this pilot to estimate proportion of deaths occurring in the community that are due to HIV/AIDS in Malawi.

Methods: The pilot implementation is taking place in Kochilira and Nkanda clusters in Mchinji district where a community death registration system is already established and has an HIV prevalence of 5.4%. VA interviews are conducted with consenting "primary caregivers" of the deceased by trained mortality surveillance assistants using the 2016 WHO VA electronic questionnaire on OpenDataKit. Primary caregivers are persons who were with the deceased in the period leading to the death. Using InterVA5 software, we analyzed VA data collected between January and August 2022. We compared the VA data with health facility mortality data collected within the same period in the same district.

Results: 354 deaths were recorded in the two clusters, of which 54% (190/354) occurred in the community. Cause of death was assigned to 91% [(172/190) 95% CI: 90%-92%)] of community deaths vs 52% [(86/164) 95% CI: 45%-59%)] of health facility deaths. The median age of the deceased were 69 years (95% CI: 58-73) for community deaths and 44 years (95% CI: 24-57) for health facility deaths. The proportion of females was 45% [(77/172; 95% CI: 38%-52%] among the community deaths and 44% [(38/86); 95% CI: 34%-55%] among health facility deaths. For community deaths, HIV/AIDS was the second leading probable cause of deaths [17% (29/171) 95% CI 12%-23%]; after unspecified-cardiac-diseases [17% (30/171); 95% CI: 13%-24%]. For health facility deaths, HIV/AIDS was the third leading probable cause of death [8% (7/86) 95% CI: 4%-16%)].

Conclusion: Malawi is piloting the 2016 WHO VA tool with almost all deaths sampled from the targeted communities successfully assigned a cause of death. We found a higher proportion of deaths attributed to HIV/AIDS among community deaths than among health facility deaths. Scale up of VA may improve the accuracy of national cause-of-death and HIV/AIDS-related mortality estimates in Malawi.

873 MEASURING EXCESS MORTALITY ASSOCIATED WITH HIV: ESTIMATES FROM THE PHIA PROJECT

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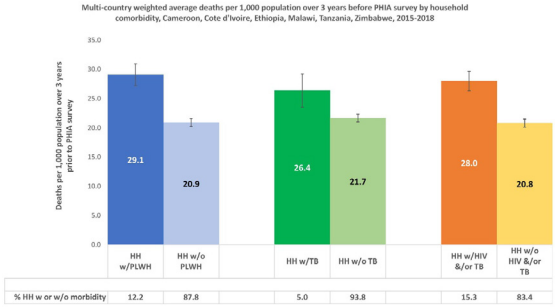
Background: Assessing national HIV epidemics requires accurate data on new HIV infections and HIV-related deaths. Mortality estimates are challenging in settings with incomplete vital statistics. We used unique survey data on household-level mortality and HIV status to estimate excess mortality associated with HIV epidemics. We compared mortality between individuals in households (HH) with and without people living with HIV (PLWH) and explored how a diagnosis of tuberculosis (TB) may modify mortality estimates.

Methods: We used publicly available data from 6 Population-based HIV Impact Assessment (PHIA) surveys conducted in Cameroon, Cote d'Ivoire, Ethiopia, Malawi, Tanzania, and Zimbabwe between 2015-2018. Heads of HH of randomly selected HH were asked to list all usual HH members and whether any usual HH members died in the 3 years before the survey. For each death reported, they indicated sex of the deceased, age at death and date of death. All consenting HH members answered questions about their TB status and provided blood for rapid HIV testing. We calculated the number of reported deaths per 1,000 for the 3-year period before the survey, and measured mortality differences associated with the presence of documented HIV and/or self-reported TB among HH members. Analyses included all usual HH members. Multi-country weighted deaths per 1,000 were calculated.

Results: The number of HH in each survey ranged from 8,983 in Cote d'Ivoire to 14,811 in Tanzania. The percent of HHs reporting any deaths in the prior 3 years ranged from 3.7%-12.9%. The estimated crude number of deaths in the prior 3 years ranged from 11.4 in Ethiopia to 32.7 per 1000 in Cameroon. In multi-country analyses, the number of weighted deaths per 1,000 were 29.1 (95% Confidence Interval (CI): 27.2-31.0) versus 20.9 (95% CI: 20.2-21.6) for individuals in HH with and without PLWH; 26.4 (95% CI: 23.5-29.2) versus 21.7 (95% CI:21.0-22.3) for those in HH with and without TB case(s); and 28.0 (95% CI: 26.3-29.6) versus 20.8 (95% CI: 20.1-21.5) for those in HH with HIV and/or TB versus without HIV or TB (Figure).

Conclusion: In this first description of mortality using PHIA data from 6 nationally representative surveys, HH with residents who had HIV and/or TB had significantly higher numbers of deaths compared to HHs with residents who had neither. These findings suggest a new approach, which captures indirect effects of HIV on mortality of HH members, to tracking progress towards zero AIDS-related deaths.

Multi-country weighted average deaths per 1,000 population over 3 years before PHIA survey by household comorbidity, Cameroon, Cote d'Ivoire, Ethiopia, Malawi, Tanzania, Zimbabwe, 2015-2018



874 ONE-YEAR MORTALITY OF PEOPLE WITH HIV AFTER INTENSIVE CARE UNIT ADMISSION

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Background: People with HIV (PWH) continue to experience opportunistic infections and critical illness, increasing their risk of, and mortality after, intensive care unit (ICU) admission. The literature-reported data on risk of death in and after discharge from ICU are limited. We describe trends in 1-year mortality among adult PWH (>18 years) admitted to ICU from 2000-2019 in an HIV-referral centre.

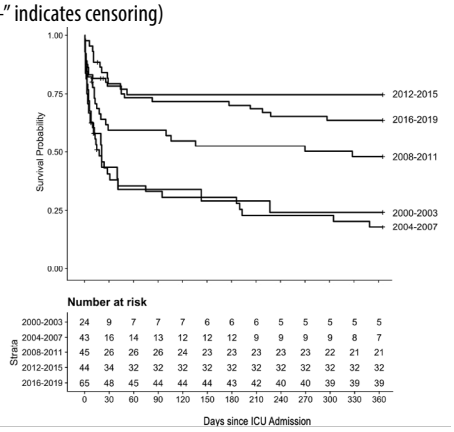
Methods: One-year mortality was calculated from index ICU admission to date of death; follow-up was right-censored at day 365 if the person was known to remain alive at 1 year, or day 7 after ICU discharge if known to be alive at hospital discharge but lost to follow-up. Between-group differences in characteristics at admission by calendar year (2000-3, 2004-7, 2008-11, 2012-15 and 2016-19) were explored using Kruskal Wallis/Cochrane Armitage tests, and 1-year mortality using Kaplan-Meier/log-rank tests. Cox regression described associations with calendar year (as a continuous covariate) before and after adjustment for characteristics at ICU admission: age, sex, Acute Physiology and Chronic Health Evaluation II (APACHE II), CD4+ T-cell count, and recent HIV diagnosis (within 3 months of ICU admission).

Results: 221 PWH were admitted to ICU (72% male, median [interquartile range (IQR)] age 45 [38-53] years) of whom 108 had died within 1-year (median survival: 349 days, cumulative 1-year survival: 50%). Those admitted in later years had a lower median admission APACHE II (29, 25, 17, 14, 13 respectively, $p< 0.001$) and were older (medians of 40, 44, 44, 46, 49 years, respectively, $p=0.03$), with higher median CD4+ T-cell count (98, 52, 169, 212, 128 cells/mm3, $p=0.002$), lower percentage with advanced HIV (CD4+ T-cell count < 200 cells/mm^3 and/or AIDS at admission to ICU; 95, 77, 66, 50, 66%, $p=0.01$) and greater percentage with HIV-RNA <50 copies/mL (17, 34, 59, 46, 53%, $p=0.02$). Cumulative survival increased in later years (Figure, $p=0.001$, log-rank test), with an 11% reduction in the hazard of 1-year mortality per later year (hazard

ratio (HR): 0.89 (95% confidence interval (CI): 0.87-0.93)). After adjustment, the annual decrease in 1-year mortality was reduced to 7% per year (adjusted HR: 0.93 (95% CI: 0.89-0.98)).

Conclusion: One-year mortality after ICU admission declined at our ICU. Whilst confirmation in other ICUs is needed, our finding emphasises that despite improvements in long-term survival, continued appropriate management of care both in and after discharge from hospital among PWH is critical.

Figure. Kaplan-Meier plot by 4-year ICU admission year group, 1 year of follow-up ("+" indicates censoring)



875 REGISTRY LINKAGE IMPROVES SURVIVAL ESTIMATION AMONG PEOPLE WITH HIV IN LATIN AMERICA

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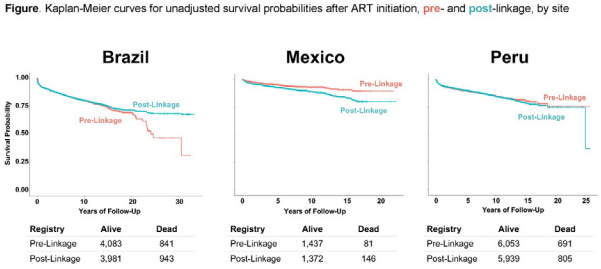
Background: Accurately describing the epidemiology of HIV requires robust outcome ascertainment. In Latin America, as in many regions, reliable mortality data may not be consistently available to clinical cohorts, particularly among those lost to care (LTC), leading to potential bias in survivorship measured in these populations. We therefore linked cohorts with vital status registries and assessed the impact on estimated survival among people with HIV (PWH) in Latin American countries where comprehensive registries exist.

Methods: Adult (≥18 years old) PWH in care at Caribbean, Central and South America network for HIV epidemiology (CCASAnet) sites in Brazil, Mexico, and Peru contributed data from antiretroviral therapy initiation date until the first of death date, cohort closure (Dec. 31, 2019), or date of last visit if LTC (i.e., no visit < 12 months before cohort close). Those LTC were matched with national or state mortality registries (Sistema de Informação de Mortalidade in Brazil, Sistema Epidemiológico y Estadístico de las Defunciones in Mexico, and National Registry of Identification and Civil Status in Peru) by probabilistic algorithms, using first and last name (Soundex), birth date, birth sex, as well as governmental identifiers and mother's maiden name, where available. Kaplan-Meier curves with cluster-corrected log-rank tests were used to compare survivorship in cohorts pre- vs. post-linkage.

Results: Among 13,186 eligible PWH, 4,924 (37.3%) contributed in Brazil, 1,518 (11.5%) in Mexico, and 6,744 (51.1%) in Peru; overall, 1,345 (10.2%) were LTC, 1,613 (12.2%) deceased, and 10,228 (77.6%) alive in-care, pre-linkage. Post-linkage, proportions LTC (9.4%) and alive (i.e., no death observed; 76.3%) both dropped, while deaths increased (14.3%). Though proportions newly ascertained deceased were small within sites (2.0% in Brazil, 4.3% in Mexico, and 1.7% in Peru), overall numbers and proportions were sizable (n=278 new deaths total; 15% of all deaths). Kaplan-Meier curves showed slight but significant differences in survival post- vs. pre-linkage at each site (cluster-corrected p< 0.01, each), though survival probabilities diverged differently across sites (**Figure**).

Conclusion: Though groups like the World Health Organization rely on weights derived from Sub-Saharan African populations to correct for mortality misclassification in Latin America, our results demonstrate that local registry linkage can be successfully used to reduce measurement error in survivorship for these populations.

Figure. Kaplan-Meier curves for unadjusted survival probabilities after ART initiation, pre- and post-linkage, by site



876 RACIAL/ETHNIC DISPARITIES IN TIMELY ANTIRETROVIRAL THERAPY INITIATION: 2007-2019

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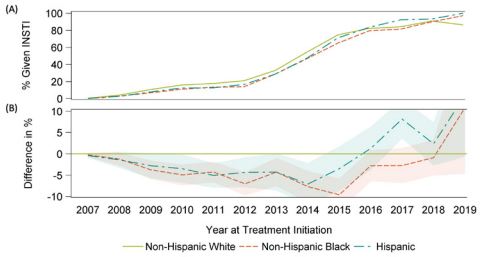
Background: Integrase inhibitor (INSTI)-containing antiretroviral therapy (ART) is currently the guideline-recommended first-line treatment for HIV. Delayed initiation of INSTIs may amplify racial and ethnic inequities in health outcomes among people with HIV. We therefore estimated racial/ethnic differences in ART initiation and INSTI prescription among adults newly entering HIV care in the United States from 2007-2019.

Methods: We conducted an observational study among 42,841 adults entering HIV care at over 200 U.S. clinical sites in the North American AIDS Cohort Collaboration on Research and Design (NA-ACCORD). Outcomes were the probability of initiating ART within 1 month of care entry and the proportion of patients prescribed an INSTI. For each outcome, we estimated overall (i.e., unadjusted) differences among non-Hispanic (NH) Black and Hispanic compared with NH White patients. Confidence intervals (CIs) around differences were estimated by the delta method; intervals that exclude 0 indicate a significant difference at α=0.05. We examined variation in racial/ethnic differences over time in relation to FDA approval of INSTIs, updated national guidelines on 'when to start' ART, and guidelines' inclusion of INSTIs as preferred initial ART.

Results: From 2007-2015, the probability of ART initiation within 1 month of care entry was 45% among NH White patients, 50% among Hispanic patients (difference: 5%; 95% CI 0, 9), and 47% among NH Black patients (2%; -4, 7). From 2016-2019, after guidelines strongly recommended treating all patients regardless of their CD4+ T-cell count, this probability increased to 68% among NH White patients, 68% among NH Black patients (0%; -8, 9), and 71% among Hispanic patients (3%; -6, 11). INSTIs were prescribed to 22% of NH White patients and only 17% of NH Black (-5%; -7, -4) and 17% of Hispanic (-5%; -6, -3) patients from 2009-2014, when INSTIs were FDA-approved as initial therapy but not yet guideline-recommended. Significant differences persisted for NH Black (-6%; -8, -4) but not Hispanic (-1%; -4, 2) patients from 2014-2017, when INSTIs were a guideline-recommended option for initial therapy; differences by race/ethnicity were not statistically significant from 2017-2019, when INSTIs were the single recommended initial therapy for most people with HIV.

Conclusion: Updates to national treatment guidelines corresponded with increased pharmacoequity among adults initiating HIV treatment in the United States.

(A) Percent of patients prescribed INSTIs and (B) racial/ethnic differences in percent of patients prescribed INSTIs by year at treatment initiation among persons entering HIV care from 2007-2019 (shaded bands indicate 95% CI)



877 IMPACT OF REDLINING ON TIME TO VIRAL SUPPRESSION AMONG PERSONS DIAGNOSED WITH HIV

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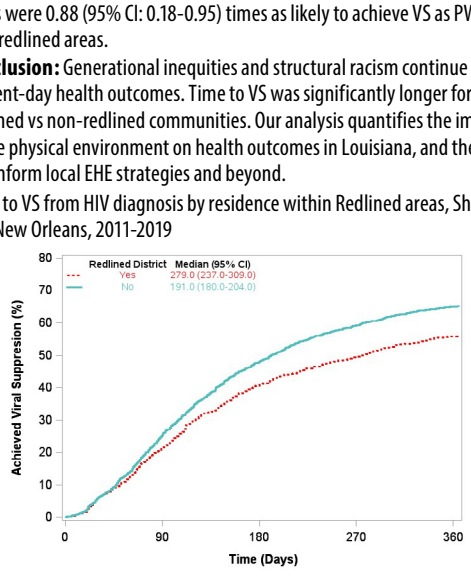
Background: Developed in the 1930s by the US government, Home Owners' Loan Corporation (HOLC) Security Maps classified residential neighborhoods with populations of 40000 or more into grades based on the alleged investment risk of resident borrowers. Grades ranged from A (mapped as green areas considered "Best") to D (or red areas that were poorer and predominantly Black neighborhoods considered "Hazardous"), the latter colloquially referred to as "Redlined". The ongoing impact of redlining on chronic diseases such as obesity and diabetes has been described previously. Similar associations with HIV outcomes could help direct local Ending the HIV epidemic (EHE) Initiatives. We seek to assess the association of structural racism through redlining policies on current time to viral suppression (VS) among people newly diagnosed with HIV in two cities in Louisiana, a state with one of the highest HIV incidence rates in the country.

Methods: City boundaries were defined by 2020 U.S. Census Bureau Zip Code Tabulation Areas and spatially joined with HOLC-graded neighborhoods. Redlined neighborhood residences of new HIV diagnoses from 2011-2019 were determined using Louisiana HIV surveillance data. Unadjusted and adjusted estimates for time to VS by redline status were calculated using Kaplan-Meier and Cox proportional hazard models, adjusted for age, race/ethnicity, sex at birth, mode of HIV transmission, and AIDS status at diagnosis (Stage 3 vs other).

Results: Of the 3227 PWH analyzed, 929 (28.8%) lived in a redlined neighborhood, 606 (18.8%) lived in A, B or C HOLC neighborhoods, and 1692 (52.4%) lived within the city but not in a HOLC graded area. In redlined areas, 74.1% of PWH were Black as compared to 63.5% in A, B, and C grade areas, and 78.3% in non-graded areas. The adjusted median time to VS among PWH in redlined areas was 262.0 days (95% CI: 219.0-294.0), compared to 195.0 days (95% CI: 182.0-207.0) among PWH in non-redlined areas. PWH in redlined areas were 0.88 (95% CI: 0.18-0.95) times as likely to achieve VS as PWH in non-redlined areas.

Conclusion: Generational inequities and structural racism continue to impact present-day health outcomes. Time to VS was significantly longer for PWH in redlined vs non-redlined communities. Our analysis quantifies the importance of the physical environment on health outcomes in Louisiana, and these findings can inform local EHE strategies and beyond.

Time to VS from HIV diagnosis by residence within Redlined areas, Shreveport and New Orleans, 2011-2019



878 MONITORING CARE AND VIRAL SUPPRESSION AFTER HIV DIAGNOSIS IN UNITED STATES: 2017-2020

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Background: The Ending the HIV Epidemic in the U.S. (EHE) initiative aims to significantly reduce HIV transmission in the United States by 2030. Key EHE strategies include rapid linkage to care and prompt delivery of antiretroviral treatment to people with HIV after diagnosis. We evaluated a jurisdictional proposal to use early HIV viral suppression as an outcome indicator for monitoring national progress in HIV care.

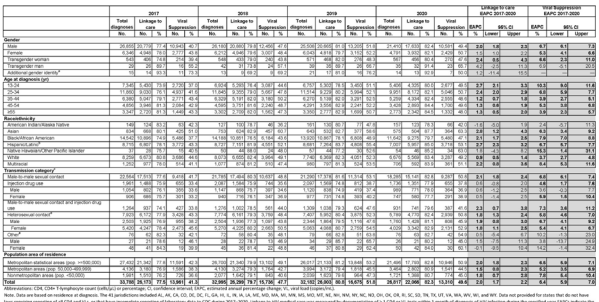
Methods: Data reported to the National HIV Surveillance System through December 2021 were used to determine linkage to HIV care (≥ 1 CD4 or viral load (VL) tests within 1 month of diagnosis) and early viral suppression (VL < 200 within 3 months of diagnosis) among persons aged ≥13 years with HIV diagnosed during 2017 (EHE baseline) through 2020. Data were analyzed by gender identity, age, race/ethnicity, HIV transmission category, population density of area of residence, and area of residence at diagnosis (not shown in table) for persons residing in 41 jurisdictions (40 states and the District of Columbia) with complete reporting of CD4 and VL results. Estimated annual percentage change (EAPC) and 95% CIs were calculated to assess trends, which were considered statistically significant if the EAPC confidence intervals (CIs) excluded 0.

Results: Overall, the percentage of persons linked to HIV medical care within 1 month of diagnosis increased 2.0% (CI: 1.7–2.2) per year from 2017-2020 (Figure 1). By subpopulation, increases ranged from 0.9% (CI: 0.5–1.4) among White persons to 2.8% (CI: 1.2–4.3) among Asian persons per year. Linkage to care increased in areas of all population densities and in 13 of the 41 jurisdictions (Table 1).

Overall, the percentage of persons with viral suppression within 3 months of diagnosis increased 6.4% (CI: 5.9-7.0) per year from 2017-2020 (Figure 1). By subpopulation, increases ranged from 3.7% (CI: 2.7–4.8) among White persons to 15.3% (CI: 1.4–31.1) among Native Hawaiian/other Pacific Islander persons per year. Viral suppression increased in areas of all population densities and in 22 of the 41 jurisdictions (Table 1).

Conclusion: Trends in prompt linkage to HIV medical care and early viral suppression showed progress overall; however, no changes since the baseline year of EHE were observed among some subpopulations and geographic areas. Accelerated efforts to increase access to HIV care and rapid start of treatment is urgently needed to meet national goals of reducing HIV transmission and eliminating disparities.

Linkage to HIV medical care within 1 month and viral suppression within 3 months of HIV diagnosis among persons aged ≥ 13 years during 2017–2020, by selected characteristics and area of residence - 41 jurisdictions



879 VIRAL SUPPRESSION AND COMMUNITY VIRAL LOAD AMONG MSM WITH HIV IN 23 US CITIES: 2017

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Background: ART adherence among MSM with HIV can lead to viral suppression (VS) in individuals and lower community viral load (CVL) in populations, reducing the potential for sexual transmission of HIV. Identifying

characteristics associated with VS and CVL can inform programs aiming to improve VS and prevent HIV transmission among MSM.

Methods: In 2017, MSM in 23 U.S. cities were recruited via venue-based sampling to participate in National HIV Behavioral Surveillance. Participants included in our analysis were assigned male sex at birth, identified as male, were aged ≥18 years, ever had oral or anal sex with another man, completed the survey and rapid HIV testing, had an HIV-positive test result, and provided dried blood spots (DBS). HIV RNA viral load (VL) was obtained from DBS. We defined VS as having a VL result < 1000 copies/mL. We then used multivariate log-linked Poisson regression models to obtain adjusted prevalence ratios (aPR) and 95% confidence intervals (CI). For CVL, when VL was below the lower level of quantification (LLOQ), we assigned a VL of one half of the LLOQ (832/2=416 copies/mL). We assessed CVL means, mean differences, and 95% CIs for key associations using a linear regression model on $\log_{10}$-transformed VL counts. Final models accounted for clustering by venue recruitment event and adjusted for city and key variables that were identified through a manual backwards elimination approach.

Results: VS was observed among 71.2% (1,530/2,149) participants. MSM who were Hispanic/Latino, had public health insurance, had private health insurance, and had an HIV care visit within the last 6 months were more likely to be virally suppressed (Table). VS was lower among those living below the federal poverty level. Estimated mean CVL was 2.90 log copies/mL and was lower among Hispanic/Latinos, those with public or private health insurance, and those who had an HIV care visit in the last 6 months. CVL was higher among those living below the federal poverty level and those with an unmet need for healthcare due to cost in the last year.

Conclusion: Access to health insurance, routine HIV care visits, and not living below the federal poverty level were associated with VS and lower CVL. Programs to support health insurance access, retention in regular HIV care, and assistance with healthcare and daily living costs may be useful in assisting MSM with HIV in being virally suppressed and reduce the potential for population HIV transmission.

Table. Characteristics associated with viral suppression and community viral load among MSM with HIV in 23 U.S. cities—National HIV Behavioral Surveillance, 2017, N=2,149

Table. Characteristics associated with viral suppression and community viral load among MSM with HIV in 23 U.S. cities—National HIV Behavioral Surveillance, 2017, N=2,149

	Viral Suppression[1]				Community Viral Load[2]		
	n	%	aPR[3]	95% CI	Mean (log copies/mL)	Mean difference[4]	95% CI
Race/ethnicity							
Black/African American	672	74.3	Ref		2.95	Ref	
Hispanic/Latino[5]	364	80.0	1.12	(1.04, 1.21)	2.87	0.10	(0.18, 0.02)
White	386	83.7	1.06	(0.99, 1.14)	2.82	-0.04	(-0.12, 0.03)
Other/Multiple	101	74.8	1.01	(0.91, 1.12)	2.95	-0.01	(-0.12, 0.10)
Below 2017 federal poverty level							
Yes	397	72.5	0.93	(0.87, 0.99)	3.00	0.12	(0.04, 0.20)
No	1173	80.5	Ref		2.86	Ref	
HIV care visit, past 6 mo.							
Yes	1259	82.4	1.20	(1.07, 1.34)	2.82	0.26	(0.38, 0.14)
No	102	67.6	Ref		3.11	Ref	
Unmet need for healthcare, past 12 mo.							
Yes	–	–	–	–	3.07	0.12	(0.02, 0.23)
No	–	–	–	–	2.88	Ref	
Health insurance							
No health insurance	137	62.0	Ref		3.14	Ref	
Public	698	79.4	1.17	(1.05, 1.30)	2.87	-0.18	(-0.30, -0.06)
Private	599	80.3	1.14	(1.02, 1.27)	2.87	-0.15	(-0.27, -0.03)
Other/multiple	94	82.4	1.14	(1.00, 1.30)	2.84	-0.14	(-0.29, 0.02)
Total	1530	71.2			2.90		

Abbreviations: aPR, adjusted prevalence ratio; CI, confidence interval; Ref, referent

[1]Defined as <1000 copies/mL in dried blood spot HIV viral load testing.

[2]Defined as the log10 transformed viral load count. When below the lower level of quantification (LLOQ), we assigned a viral load of one half the LLOQ (832/2=416 copies/mL) before log10 transformation.

[3]Based on log-linked Poisson multivariable model with robust standard errors that adjusted for city and listed variables and accounted for clustering by venue recruitment event.

[4]Based on linear multivariable model that adjusted for city and listed variables and accounted for clustering by venue recruitment event.

[5]Hispanics/Latinos can be of any race.

880 HOSPITAL READMISSIONS AMONG ADULTS LIVING WITH HIV IN THE US

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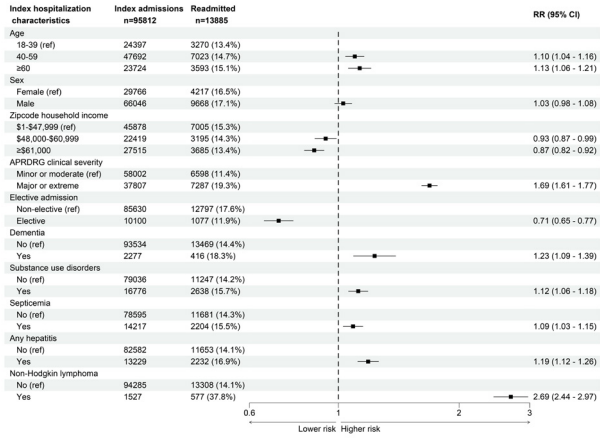
Background: Hospital readmission is a key indicator of quality-of-care. There are limited nationwide data characterizing readmissions among people living with HIV (PLHIV) in the era of universal HIV treatment. We described the contemporary risk of all-cause hospital readmission for adult PLHIV in the US.

Methods: Longitudinal data from the 2019 Nationwide Readmission Database, the largest public readmissions database which was developed by the Healthcare Cost and Utilization Project, were used to describe the risk of hospital readmissions among PLHIV. Adult PLHIV identified by ICD-10 codes who were discharged alive from their first recorded (index) hospitalization between January 2019 and November 2019 were included. We examined the probability of 30-day all-cause readmission since the discharge of index hospitalization. Age- and sex-adjusted risk ratios (aRR) of 30-day readmission were estimated by index admission characteristics (e.g., demographic, clinical and hospital factors) using modified Poisson regression models. Subgroup analyses were conducted stratified by sex. Survey weights were used to obtain nationally representative estimates.

Results: The weighted population included 95,812 HIV-related index hospitalizations, of which 68.9% were among males and the median age was 52 (IQR=39-59) years. The probability of 30-day readmission was 14.5% (n=13,848), and the top reason (except HIV) for readmission was sepsis (10.3%). Older age and living in a zip code with a median household income < $48,000 were associated with a higher risk of readmission (Figure). Males and females had a similar risk [aRR=1.03 (95%CI=0.98-1.08)]. PLHIV with a higher clinical severity (APRDRG scores), admitted for non-elective reasons (vs. elective), and with comorbidities (e.g., dementia, substance use disorders, septicemia, hepatitis, and non-Hodgkin lymphoma) at index admission had a higher risk of readmission. In sex-stratified analyses, septicemia index hospitalizations were associated with greater readmission risk among females [aRR:1.28 (95%C=1.17-1.42)], but not among males [aRR:1.01 (0.95-1.08)]. Pregnant females at index hospitalization had a lower readmission risk than non-pregnant females [aRR:0.44 (0.35-0.55)].

Conclusion: Over 1 in 10 hospitalized PLHIV who were discharged alive were readmitted within 30 days. Readmissions disproportionally occurred among those with older age, from lower-income areas, and with comorbidities. Efforts are needed to mitigate potentially preventable readmissions among PLHIV.

Figure. Age and sex adjusted risk factors of 30-day hospital readmissions among hospitalized PLHIV in the US



881 HIV AND THE VETERANS CHOICE ACT: A GEOSPATIAL ANALYSIS IN GEORGIA, 2020-2022

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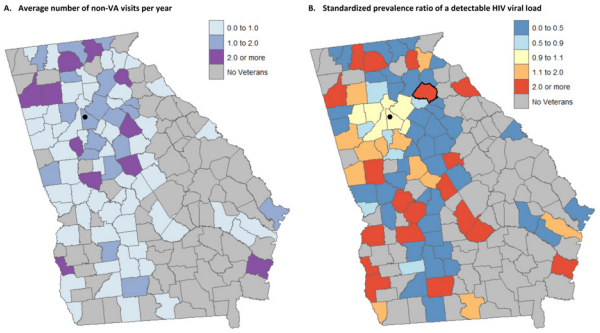
Background: One-quarter of all Veterans with HIV (VWH) – and three-quarters of rural VWH – live more than an hour's drive from the nearest HIV clinic in the Veterans Administration (VA). Rural VWH who do not receive HIV care have suboptimal outcomes across the continuum of HIV care. In response, the 2014 Veterans Choice Act was enacted to expand healthcare access, which is purchased by the VA but provided by non-VA providers. Our objective was to examine the geospatial distributions of non-VA visits and detectable HIV viral load, and their associations with distance from the Atlanta VA Medical Center (AVAMC) among VWH.

Methods: Veterans diagnosed with HIV after August 1, 2014, who have had >1 visit at the AVAMC since September 15, 2020, and who reside in Georgia were included. Non-VA visits include any healthcare purchased by the VA and provided by a non-VA provider. Detectable HIV viral load was defined as ≥50 copies/mL on the most recent measurement in the past two years. The average number of non-VA visits per year and the standardized prevalence ratio (SPR) of detectable HIV viral load were mapped by county. Spatial heterogeneity was assessed by chi-square tests. Data were fitted to Poisson regression models to estimate their associations with geodesic distance between each county and the AVAMC.

Results: 1,588 VWH met the inclusion criteria; of whom, 279 (18%) had a detectable HIV viral load. The number of non-VA visits exhibited significant spatial heterogeneity (χ^2=2030, p=0.002). VWH who reside outside of but surrounding Atlanta appear to have the highest average number of non-VA visits per year. However, for every 25-mile increase, it is estimated that the average number of non-VA visits decreases by 1.7 (p< 0.001). The SPR of detectable HIV viral load varied considerably but was statistically insignificant (χ^2=91, p=0.312). The observed prevalence of detectable HIV viral load is between two- and six-fold greater than what is expected in many parts of rural Georgia (e.g., SPR=4.3 in Jackson County, p=0.034). However, for every 25-mile increase, it is estimated that the number of detectable HIV viral load decreases by 1.5 (p< 0.001).

Conclusion: VWH who reside in counties adjacent to the Atlanta metro area are more likely to receive non-VA healthcare, likely due to the >40-mile eligibility requirement and availability of such care. Non-VA healthcare may be less accessible in rural Georgia due to fewer resources and unaccounted socioeconomic factors. Telemedicine may be able to bridge this gap.

Figure 1. Geospatial distribution of non-VA purchased care visits and detectable HIV viral loads among Veterans with HIV who reside in Georgia and receive care at the Atlanta VA Medical Center, 2020-2022. Data are limited to Veterans diagnosed with HIV after the enactment of the Veterans Choice Act in August, 2014, and who have had at least one HIV viral load test in the past two years. A. Average number of non-VA purchased care visits per year since HIV diagnosis; the purpose and type of care received during these visits vary. B. Standardized prevalence ratio of a detectable HIV viral load between September 15, 2020 and September 15, 2022; a HIV viral load of <50 copies/mL was considered undetectable; dark boundaries denote a statistically significantly higher standardized prevalence ratio than expected. No Veterans with HIV who met the inclusion criteria lived in counties that are grey in color.



882 INTERNALIZED HIV STIGMA AND MENTAL HEALTH/SUBSTANCE USE OVER TIME

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Background: Internalized HIV stigma (IHS) may have significant impact on people with HIV (PWH). Our prior work suggests associations between IHS and increased HIV viral load are mediated by depression. Herein, we describe longitudinal changes in IHS and associations with mental health and substance use.

Methods: The CFAR Network of Integrated Clinical Systems (CNICS) is a longitudinal, multisite, cohort of PWH in care who complete tablet-based care assessments. At two different timepoints (T1 and T2) 1 year apart (from 2016-2022), IHS was assessed by 4 Likert scale response questions (low 1-5 high), with mean score and dichotomized score at ≤2 (no stigma) vs >2 used as primary exposures. We estimated adjusted rate ratios (ARR) of the association between IHS, depression, anxiety, and substance use at T1 and T2, adjusting for plausible confounders using conditional logistic regression (CLR) for dichotomized and Poisson regression (PR) for mean IHS score. We also fit autoregressive (AR) models with IHS parameterized as none, decreasing, constant, or increasing stigma (≤2 to >2) from T1 to T2.

Results: 6123 PWH had complete IHS and outcome data at T1 and T2. Mean IHS was 2.01 at T1 and 1.93 at T2, with younger, non-gay identifying, and female PWH reporting higher IHS at T1 and T2 (p< 0.001). From T1 to T2, 2248 (37%) PWH had IHS score ≤ 2 (i.e., no stigma) and 694 (11%) had IHS >2 with no change in IHS, while 1737 (28%) had a decrease and 1444 (24%) had an increase in IHS score. Compared to those with no IHS at T1 and T2, PWH whose IHS changed or stayed high were in care for fewer years and were more likely to report heterosexual or bisexual than gay/lesbian identity (p< 0.01). Those with a decrease in IHS were more likely to be female and younger. Higher IHS was significantly associated with depression and recent anxiety attacks, methamphetamine and opioid use, and binge and at-risk alcohol consumption in CLR and PR (Table). In AR, these associations remained consistent for those reporting an increase in IHS compared to those with no IHS at either T1 or T2. Additionally, IHS >2 at both timepoints was associated with increased risk of depression and anxiety compared to no IHS.

Conclusion: We observed >30% prevalence of IHS at any timepoint, with consistent and concerning associations between IHS and depression, anxiety and substance use among PWH. There is a need for further causal inference analyses and future studies to support directionality of these associations and inform actionable interventions.

Table: Longitudinal associations between internalized HIV stigma (IHS) and substance use and mental health outcomes in different models (N=6123 for all models)

	Conditional Logistic Regression Stigma > 2	Poisson Regression Stigma score	Autoregression	
Outcome	ARR (95% CI)	ARR (95% CI)	Stigma Change T1 –> T2 (REF= No stigma T1 or T2)	RR (95% CI)
Depression	1.60 (1.39, 1.85)	1.36 (1.27, 1.45)	Decreased	1.19 (1.02, 1.41)
			Stayed high T1 & T2	1.88 (1.58, 2.23)
			Increased	2.02 (1.72, 2.36)
Anxiety attack past 4 weeks	1.34 (1.19, 1.50)	1.23 (1.16, 1.29)	Decreased	1.02 (0.90, 1.14)
			Stayed high T1 & T2	1.41 (1.24, 1.60)
			Increased	1.47 (1.31, 1.64)
Methamphetamine use	1.35 (1.12, 1.62)	1.22 (1.11, 1.34)	Decreased	0.88 (0.73, 1.06)
			Stayed high T1 & T2	1.10 (0.90, 1.35)
			Increased	1.26 (1.06, 1.50)
Cocaine use	1.13 (0.89, 1.44)	1.12 (0.99, 1.28)	Decreased	0.93 (0.73, 1.18)
			Stayed high T1 & T2	1.20 (0.93, 1.54)
			Increased	1.28 (1.02, 1.60)
Opioid use	1.50 (1.04, 2.16)	1.23 (1.03, 1.46)	Decreased	1.25 (0.86, 1.82)
			Stayed high T1 & T2	1.19 (0.75, 1.90)
			Increased	1.48 (1.01, 2.16)
Binge alcohol consumption	1.32 (1.12, 1.55)	1.20 (1.10, 1.30)	Decreased	0.88 (0.75, 1.03)
			Stayed high T1 & T2	1.03 (0.85, 1.25)
			Increased	1.16 (0.99, 1.36)
At risk alcohol use	1.15 (1.01, 1.31)	1.10 (1.03, 1.18)	Decreased	0.98 (0.86, 1.12)
			Stayed high T1 & T2	1.24 (1.07, 1.45)
			Increased	1.17 (1.03, 1.33)

All models adjusted for age and years in care, autoregression models also adjusted for outcome at T1

883 RANDOMIZED TRIAL OF BRIEF ALCOHOL INTERVENTION FOR VIRAL SUPPRESSION AND ALCOHOL USE

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Background: Unhealthy alcohol use is a major contributor to viral non-suppression among persons with HIV (PWH), and a significant source of morbidity globally. It is unknown whether brief behavioral interventions to reduce alcohol use can improve viral suppression among PWH with unhealthy alcohol use in sub-Saharan Africa (SSA).

Methods: As part of the SEARCH study (NCT04810650), we conducted an individually randomized trial in Kenya and Uganda of a brief, culturally-adapted skill-based alcohol intervention among PWH with HIV viral non-suppression (viral load [VL] ≥400 copies/mL), missed visits, or out of care, and with self-reported unhealthy alcohol use (Alcohol Use Disorders Identification Test – Consumption [AUDIT-C] in the prior 3 months: ≥3/female; ≥4/male). The intervention included in-person counseling sessions at baseline and 3-months, and booster phone calls every 3-weeks in the interim. The primary outcome was HIV viral suppression (VL < 400 copies/mL) at 24-weeks. Alcohol use at 24-weeks, assessed via self-report (AUDIT-C, prior 3 months) and phosphatidylethanol [PEth], an alcohol biomarker, was a secondary outcome.

Results: 400 persons (197 intervention, 203 in control; 57% in Uganda) were enrolled from April 2021 through September 2021, with 94% analyzed

at 24-weeks (6% moved from the study area). At baseline, 60% were virally suppressed. There was no difference in viral suppression between arms at 24-weeks: suppression was 83% in intervention and 82% in control arms (RR: 1.0, 95% CI: 0.93-1.10, p=0.40). Among PWH with baseline viral non-suppression (n=150), suppression was 73% in intervention and 64% in control arms (RR: 1.15, 95% CI: 0.93-1.43). Unhealthy alcohol use (AUDIT-C ≥3/female; ≥4/male or PEth≥50 ng/mL) declined from 100% at enrollment to 73% in intervention and 84% in control arms at 24-weeks (RR: 0.86, 95% CI: 0.79-0.94; p< 0.001). Effects on unhealthy alcohol use were stronger among women (RR: 0.70, 95%CI: 0.56-0.88; p=0.001) than men (RR: 0.93, 95%CI: 0.85-1.01; p=0.05). There were also intervention effects on high/very high-risk alcohol use (AUDIT-C≥6 or PEth >200 ng/mL; RR: 0.84, 95% CI: 0.74-0.94; p=0.001).

Conclusion: In a randomized trial of 400 PWH with unhealthy alcohol use, a brief alcohol intervention reduced alcohol consumption but did not affect short term viral suppression at 24-weeks. Brief alcohol interventions have the potential to improve the health of PWH in SSA by reducing alcohol use, a significant driver of HIV and associated co-morbidities.

884 12-MONTH CONSEQUENCES IN PEOPLE WITH HIV/SARS-CoV-2 COINFECTION: NATIONAL EHR COHORT

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Background: Long-term consequences of COVID-19 are well characterized in general populations. Yet it remains unclear how existing HIV infection attributes to the risks of long-term consequences in people with coinfection of HIV/SARS-CoV-2. This study aims to examine the long-term consequences of people living with HIV (PLWH) at 12 months after the first SARS-CoV-2 infection.

Methods: Using the National COVID Cohort Collaborative (N3C), Electronic Health Records (EHR) sampled from 50 states and over 75 healthcare systems in the US, we constructed a cohort of PLWH with COVID-19 between March 1, 2020 and January 15, 2021, a historical control group (HIV individuals without COVID-19 between March 1, 2018 and January 15, 2019, two years predating the pandemic), and a contemporary control group (PLWH without COVID-19 between March 1, 2020 and January 15, 2021) to mitigate time/selection biases. The time of HIV infection was before March 1, 2020 for the cases and contemporary controls and, before March 1, 2018 for historical controls. The date of the first COVID-19 infection marked the start of a 12-month follow-up in the COVID-19 group. The start of follow-up in the contemporary controls was assigned by matching the same distribution of start dates of COVID-19 cases. We used logistic regression to examine odds ratios of health consequences at 12 months post COVID-19 comparing against contemporary and historical controls, respectively.

Results: We identified 5,619, 41,791, and 24,240 patients for COVID-19 cases, contemporary controls, and historical controls, respectively. The COVID-19 group had significantly higher odds in acute respiratory distress syndrome [OR: 3.45, 95% CI (2.98, 3.99)], hypertension [OR: 1.41, 95% CI (1.29, 1.54)], congestive heart failure [OR: 1.36, 95% CI (1.14, 1.63)], myocardial infarction [OR: 1.51, 95% CI (1.22, 1.86)], and diabetes [OR: 1.62, 95% CI (1.42, 1.84)], compared to contemporary controls. Odds in these outcomes were significantly higher when compared to historical controls (Figure 1).

Conclusion: This sentinel study for the first time reported elevated risks of multi-system dysfunction (i.e., respiratory, cardiovascular, and metabolic) among PLWH at 12 months post COVID-19. To our knowledge, it is the largest EHR cohort study assessing long-term consequences in PLWH. Our findings call for immediate attention to the post-COVID care among PLWH, including follow-up guidelines, care planning, and health policy tailored for PLWH.

Figure 1. Risks of long-term consequences of COVID-19 at 12 months among people living with HIV.

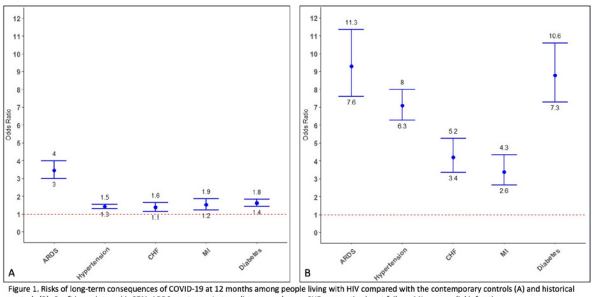

Figure 1. Risks of long-term consequences of COVID-19 at 12 months among people living with HIV compared with the contemporary controls (A) and historical controls (B). Confidence interval is 95%. ARDS: acute respiratory distress syndrome. CHF: congestive heart failure. MI: myocardial infraction.

885 TRENDS IN COVID-19 ADMISSIONS AND DEATHS AMONG PEOPLE WITH HIV IN SOUTH AFRICA

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Background: South Africa experienced five COVID-19 waves and over 90% of the population have developed immunity. HIV prevalence among adults is 19% and over 2 million people have uncontrolled viral loads, posing a risk for poor COVID-19 outcomes. Using national hospital surveillance data, we aimed to investigate trends in admission and factors associated with in-hospital COVID-19 mortality among people with HIV (PWH) in South Africa.

Methods: Data between March 5, 2020 and May 28, 2022 from the national COVID-19 hospital surveillance system, SARS-CoV-2 case linelist and Electronic Vaccine Data System were linked and analysed. A wave was defined as the period for which weekly incidence was ≥30 cases/100,000 people. Descriptive statistics were employed for admissions and mortality trends. Post-imputation random effect multivariable logistic regression models compared (a) characteristics of PWH and HIV-uninfected individuals, and (b) factors associated with mortality among PWH.

Results: 68.7% (272,287/396,328) of COVID-19 admissions had a documented HIV status. PWH accounted for 8.4% (22,978/272,287) of total admissions, and 9.8%, 8.0%, 6.8%, 12.2% and 6.7% of admissions in the D614G, Beta, Delta, Omicron BA.1 and Omicron BA.4/BA.5 waves respectively. The case fatality ratio (CFR) among PWH and HIV-uninfected was 24.3% (5,584/22,978) vs 21.7% (54,110/249,309) overall, and in the respective waves was 23.7% vs 20.4% (D614G), 27.9% vs 26.6% (Beta), 26.2% vs 24.5% (Delta), 18.2% vs 9.1% (Omicron BA.1) and 16.8% vs 5.5% (Omicron BA.4/BA.5). Chronic renal disease, malignancy and past TB were more likely, and hypertension and diabetes were less likely in PWH compared to HIV-uninfected individuals. Among PWH, along with older age, male sex and presence of a comorbidity, there was a lower odds of mortality among individuals with prior SARS-CoV-2 infection (aOR 0.6; 95% CI 0.4-0.8); ≥1 dose vaccination (aOR 0.1; 95% CI 0.1-0.1); and those admitted in the Delta (aOR 0.9; 95% CI 0.8-0.9), Omicron BA.1 (aOR 0.5; 95% CI 0.5-0.6) and Omicron BA.4/BA.5 (aOR 0.5; 95% CI 0.4-0.7) waves compared to the D614G wave. PWH with CD4< 200 had higher odds of in-hospital mortality (aOR 1.9; 95% CI 1.8-2.1).

Conclusion: In South Africa, mortality among PWH was less likely in the Delta and Omicron waves but PWH had a disproportionate burden of mortality during the two Omicron waves. Prior immunity protected against mortality, emphasizing the importance of COVID-19 vaccination among PWH, particularly PWH with immunosuppression.

Risk factors for in-hospital mortality among PWH admitted with COVID-19, South Africa, 5 March 2020-28 May 2022

Characteristic	Case Fatality Ratio n/N (%)	Adjusted Odds Ratio (95% CI)	p value
Age group (years)			
<20	51/540 (9.44%)	Reference	
20-39	1,277/8,283 (15.42%)	2.00 (1.47-2.72)	<0.001
40-59	2,859/10,876(26.29%)	4.27 (3.14-5.80)	<0.001
60+	1,397/3,279 (42.60%)	8.93 (6.52-12.24)	<0.001
Sex			
Female	3,204/14,637 (21.89%)	Reference	
Male	2,379/8,330 (28.56%)	1.10 (1.02-1.18)	0.011
Race			
White	27/93 (29.03%)	Reference	
Mixed	92/400 (23.00%)	0.93 (0.55-1.59)	0.811
Black	4,397/17,075 (25.75%)	0.98 (0.59-1.62)	0.948
Indian	18/71 (25.35%)	1.10 (0.50-2.41)	0.809
Other	11/35 (31.43%)	1.06 (0.41-2.73)	0.900
Comorbidity*			
No	568/3,386 (16.77%)	Reference	
Yes	1,094/3,609 (30.31%)	1.47 (1.35-1.60)	<0.001
Health sector			
Private sector	507/2,685 (18.88%)	Reference	
Public sector	5,077/20,293 (25.02%)	0.75 (0.61-0.92)	0.007
Province			
Western Cape	1,250/6,594 (18.96%)	Reference	
Eastern Cape	833/2,795 (29.80%)	1.96 (1.53-2.51)	<0.001
Free State	359/1,512 (23.74%)	1.45 (1.07-1.96)	0.016
Gauteng	782/3,084 (25.36%)	1.44 (1.09-1.89)	0.008
KwaZulu-Natal	1,308/5,236 (24.98%)	1.47 (1.15-1.87)	0.002
Limpopo	348/1,038 (33.53%)	2.22 (1.64-2.30)	<0.001
Mpumalanga	322/1,006 (32.01%)	2.02 (1.47-2.79)	<0.001
North West	299/1,465 (20.41%)	0.90 (0.61-1.33)	0.619
Northern Cape	83/248 (33.47%)	2.65 (1.56-4.52)	<0.001
Wave period			
D614G	1,292/5,450 (23.71%)	Reference	
Beta	1,626/5,834 (27.87%)	0.96 (0.86-1.07)	0.520
Delta	1,774/6,760 (26.24%)	0.87 (0.78-0.97)	0.014
Omicron BA.1	797/4,370 (18.24%)	0.51 (0.45-0.57)	<0.001
Omicron BA.4/BA.5	95/564 (16.84%)	0.52 (0.40-0.67)	<0.001
Prior SARS-CoV-2 infection	5,514/22,377 (24.64%)	Reference	
No	70/601 (11.65%)	0.57 (0.43-0.76)	<0.001
Yes			
COVID-19 vaccination			
No	5,287/16,666 (31.72%)	Reference	
Yes	297/6,312 (4.71%)	0.09 (0.08-0.11)	<0.001

886 A MULTICENTER STUDY OF COVID-19 INFECTION IN PEDIATRIC INTENSIVE CARE UNITS IN THE US

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Background: To describe characteristics of COVID-19 infection among patients requiring admission to pediatric intensive care units (PICU) in the USA.

Methods:

Observational surveillance study of COVID-19 infected patients admitted to PICUs in 27 US states between April 1, 2020 – May 1, 2021.

Results: Four hundred fifty-three patients were included; the majority were from institutions in the South and Midwest regions (40% and 34%). The population was mainly male (57%) and Hispanic (36%), with a median age of 10 years (IQR 4-15). 76% had 1 or more comorbidity.

Patient's or caregiver's reported sources for COVID-19 infection were household and community contacts (31% and 24%). One hundred sixty-seven (40%) individuals were diagnosed with the multisystem inflammatory syndrome in children (MISC) within 7 days of PICU admission. Compared to COVID-19 cases without MISC, gastrointestinal, mucocutaneous, and neurological signs and symptoms were more frequent at PICU admission.

Nasal cannula (20%) and high-flow oxygen (12.4%) were the most common respiratory support strategies at day 1 of admission, and mechanical ventilation by day 7. Overall, 104 (23%) and 8 (1.8%) individuals were placed on mechanical ventilation and extracorporeal membrane oxygenation (ECMO) within the interval of observation.

Steroids and remdesivir were the most delivered COVID-19 targeted therapies (60% and 33%), and only 3% of the patients received convalescent plasma; IVIG (86.8%) and anakinra (61%) were commonly used among individuals with MISC. The overall mortality proportion (MP) was 2.65 (n= 12), and mortality was more frequent among individuals > 2 years old. Of the 167 children with MISC, only 1 died, MP (0.6).

Conclusion: Mortality associated with pediatric COVID-19 infection is less frequent than in critically ill COVID-19-infected adults. Among pediatric/adolescent patients, children > 2 years are the most vulnerable to adverse COVID-19-associated outcomes. MISC cases were frequent, yet mortality was low.

887 IDENTIFICATION OF CLINICAL FEATURES ASSOCIATED WITH SARS-CoV-2 REINFECTIONS

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Background: Over 600 million of COVID-19 cases have been reported. A remarkable fragment of these cases are reinfections, which are mostly explained by the genomic variability of the SARS-CoV-2 variants. However, little is known about other factors fostering these reinfections.

Methods: We recorded clinical and demographic data from subjects (N=3303, March 2020 - March 2022) with at least 2 PCR+ events separated by ≥90 days, analyzed by the Microbiology Department, Northern Metropolitan Clinical Laboratory from Germans Trias i Pujol Hospital (Spain). Data collected included: age, sex, comorbidities, adjusted morbidity group (GMA), hospitalization, symptomatology, NAAT (PCR, TMA) tests, antigen tests, serology, and vaccination. Temporal data was encoded using Python, and demographic characterization was performed under R.

Results: We identified 2344 cases of confirmed reinfections, where the 2 PCR+ events were separated by ≥90 days and a negative test was obtained between episodes. 72.2% of reinfected subjects were females with a median age of 45 IQR [28-63] years. Age density analysis showed three peaks at 24, 45, and 85 years, probably mostly composed of young people, who usually are less cautious, healthcare workers, and people living in nursing homes, respectively, being all of them groups prone to be tested. Regarding health status, 86.2% of participants had at least one chronic condition, with 40.5% of patients having chronic conditions in ≥4 systems based on GMA assessment. Interestingly, 75.2% of reinfected subjects < 26 years had at least one chronic condition. 121 (4.2%) participants were hospitalized during a COVID-19 episode, highlighting 8.3% (N=10) of them hospitalized during the reinfection (half of them vaccinated before hospitalization), and 5% (N=6) of them during both infections. The severity of the second infection may be caused by a diminished acquired immunity after the first infection. Time between reinfections density analysis provided three peaks at ~200, ~400, and ~600 days, corresponding with time between waves. A decrease of reinfections was observed between 40 and 100 days after vaccination, which would be the period of highest protection against reinfection.

Conclusion: SARS-CoV-2 reinfections are more prevalent among women. Importantly, people with an undermined health status, independently of age, are more sensitive to reinfections, but in most of the cases no hospitalization was required. Finally, vaccination seems to have a short protective effect on reinfection.

888 ANEMIA AS A PREDICTOR OF POOR CLINICAL OUTCOME IN PATIENTS ADMITTED FOR COVID-19

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Background: In respiratory infections, anemia is both a consequence of acute inflammation [1] and a predictor [2] of poor clinical outcomes. There are few studies investigating the role of anemia in COVID-19, suggesting a potential role in predicting disease severity [3, 4]. In this study, we aimed to assess the association between the presence of anemia at admission and incidence of severe disease and death in patients hospitalized for COVID-19.

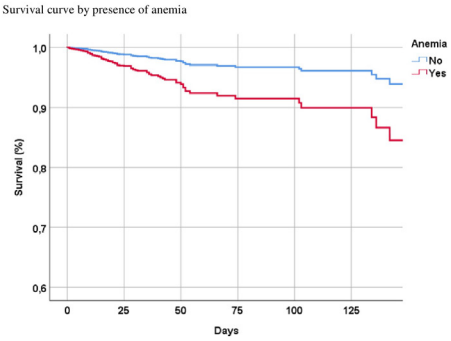
Methods: Data from all adult patients admitted for COVID-19 in University Hospital "P. Giaccone" (Palermo) and University Hospital of Bari, Italy, were retrospectively collected from 1st of September 2020 and 31 August 2022. The association between anemia (defined as Hb < 13 g/dl and < 12 g/dl in males and females, respectively), in-hospital mortality and severe COVID-19 was tested using a Cox's regression analysis. Severe COVID-19 forms were defined as admission to intensive or sub-intensive care unit or a qSOFAscore ≥2 or CURB65scores ≥3. P values were calculated using the Student's T-test for continuous variables and the Mantel-Haenszel Chi-square test for categorical

ones. The association between anemia and the mortality was made using a Cox's regression analysis, adjusted, in two models, for the potential confounders and using a propensity score.

Results: Among the 1562 patients included in the analysis, prevalence of anemia was 45.1% (95%CI 43-48%), and as shown in Table 1, were significantly older (p< 0.0001), reported more co- morbidities, and presented higher baseline levels of procalcitonin, CRP, ferritin and IL-6. As shown in Figure 1, patients with anemia reported a higher crude higher incidence of mortality compared to patients without this condition (Figure 1). Overall, the crude incidence of mortality was about four times higher in patients with anemia compared to those without. After adjusting for 17 potential confounders, the presence of anemia significantly increased the risk of death (HR=2.68; 95%CI: 1.59-4.52) and of risk of severe COVID-19 (OR=2.31; 95%CI: 1.65-3.24) (Table 2). The propensity score analysis substantially confirmed these analyses.

Conclusion: Our study provides evidence that, in patients hospitalized for COVID-19, anemia is both associated with a more pronounced baseline pro-inflammatory profile and higher incidence of in-hospital mortality and severe disease.

Figura 1. Survival curve by presence of anemia



Association between anemia at hospital admission a

		Anemia	
	No anemia	All sample	Propensity score
Mortality, incidence rate[1]	243 (135-439)	934 (610-1434)	-
Risk of mortality, model 1[2]	1, reference	3.19 (1.97-5.14)	-
Risk of mortality, model 2[3]	1, reference	2.68 (1.59-4.52)	1.91 (1.10-3.32)
Risk of severe COVID-19, model 1[2]	1, reference	6.59 (5.11-8.49)	-
Risk of severe COVID-19, model 2[3]	1, reference	2.31 (1.65-3.24)	1.77 (1.26-2.48)

Notes:

1. Data are reported as incidence rates (with 95% confidence intervals) per 100,000 persons-year.
2. The data are reported as hazard ratio for mortality and as odds ratio (with 95% confidence intervals) for severe COVID-19, adjusted for age, sex, center
3. The data are reported as hazard ratio for mortality and as odds ratio (with 95% confidence intervals) for severe COVID-19, adjusted for variables in Model 1 and presence of comorbidity, smoking status, oxygen saturation <92%, elevated procalcitonin, elevated D-dimer, elevated C reactive protein, elevated troponin, elevated transaminases, elevated IL-6, elevated LDH, presence of pneumonia at the CT or x-ray scan, low platelets levels, use of Venturi's mask during hospitalization, use of high flow oxygen.
4. Propensity score analysis included 388 patients with anemia matched for age, gender, presence of comorbidities, oxygen saturation <92%, elevated procalcitonin, elevated D-dimer, elevated C reactive protein, elevated troponin, elevated transaminases, use of Venturi's mask during hospitalization, use of high flow oxygen (all parameters with a p-value >0.10) with 388 patients without anemia.

889 CLINICAL OUTCOMES BY SARS-CoV-2 VARIANT AT A SINGLE ACADEMIC MEDICAL CENTER

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Background: SARS-CoV-2 continues to change over time due to genetic mutations and viral recombination.[1] Given the changing landscape of COVID-19 variants and availability of COVID-19 vaccinations, disease severity during acute infection has also been variable. However, most research related to COVID-19 to date has not focused on evaluating differences in outcomes by the dominant variant and the impact it might have on post-acute sequalae of COVID-19 (PASC).

Methods: We developed a data mart of electronic health record data pertaining to COVID-19 in a single North American metropolitan health system (RUSH University Medical Center). Patients were selected for analysis if they had at least one documented infection of COVID-19. Date ranges were established per dominant variant, and the date of diagnosis was matched to variant. Variants were determined by the most prominent variant of concern (VOC) circulating in the city of Chicago. Variants were categorized by the following by date ranges: Wildtype+D614G (3/7/20-3/20/21), Alpha (3/21/21-6/19/21), Delta (6/20/21-12/11/21), Omicron BA.1 (12/12/21-3/19/22), Omicron BA.2 (3/20/22-6/18/22), and Omicron BA.4/BA.5 (6/19/22-present (9/30/22). Subsequent clinical outcomes were examined, including hospitalization, intensive care unit admission, or death. We characterized our sample by conducting descriptive statistics including frequency and percent of outcome by variant.

Results: 44,499 patients were included in this analysis with 30.23% requiring hospitalization, 4.25% being admitted to intensive care unit (ICU), and 2.35% resulting in death. The greatest percentage of hospitalizations occurred with the Alpha variant at 41.88% (N=928), and the greatest percentage of ICU admissions (6.43%) and death (3.15%) occurred with the Delta variant. The latest Omicron variant (Wave 6) showed an increase in hospitalizations (35.18%), as compared to early Omicron waves (Wave 4 and 5) but maintained similar ICU rates. Death rates continued to decline during the Omicron waves (Table 1).

Conclusion: Although Alpha and Delta variants seem to have more severe outcomes compared to other variants, it is important to note that COVID-19 prevention, treatment access, and management continues to change, potentially influencing how outcomes may differ over time. Future work should determine factors to adjust for when examining variant-level differences.

Table 1 Outcomes by Dominant Variant

		Inpatient (%)	ICU (%)	Mortality (%)
Wave 1	Wildtype+D614G (3/7/20-3/20/21)	27.77	4.74	2.74
Wave 2	Alpha (3/21/21-6/19/21)	41.88	6.32	2.57
Wave 3	Delta (6/20/21-12/11/21)	40.40	6.43	3.15
Wave 4	Omicron BA.1 (12/12/21-3/19/22)	28.30	2.84	2.01
Wave 5	Omicron BA.2 (3/20/22-6/18/22)	28.53	2.20	0.81
Wave 6	Omicron BA.4/BA.5 (6/19/22-present (9/30/22))	35.18	2.66	0.68
Overall		**30.23**	**4.25**	**2.35**

890 EXCESS OF MORTALITY IN OLDER PEOPLE DURING THE COVID-19 PANDEMIC IN MOZAMBIQUE

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Background: The impact of COVID-19 pandemic was apparently less severe in African continents, probably underestimated due to the limited testing capacities and access to health facilities, particularly in rural areas. Hospital and community surveillance of COVID-19 was established in Manhiça District, rural Mozambique to understand the epidemic curve and natural history of SARS-CoV-2 including age-specific incidence of severe COVID-19 and reproduction number and effects of interventions through mathematical modelling

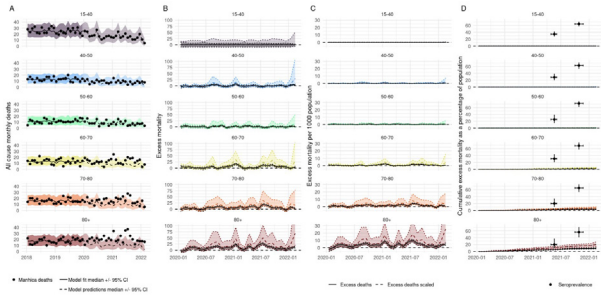
Methods: Suspected cases visiting the Manhiça District Hospital were screened for SARS-CoV-2 by qRT-PCR. Four age-stratified (0-19, 20-39, 40-59 and ≥60 years, n=300 each) community-based serosurveys were conducted (Apr 2021-Feb 2022) to estimate the prevalence of antibodies (Abs) against SARS-CoV-2. We fitted a statistical model within a Bayesian framework, to estimate the extent to which older people were over-represented in mortality data throughout the pandemic. This involved training the model on data from the pre-pandemic period and then using this model to generate estimates of the expected levels of mortality in the absence of COVID-19 in adults aged 40+ using data from our reference category (15-39 year olds).

Results: Between Dec 2020 and Aug 2022, 31.2% of 1332 swabs tested positive for SARS-CoV-2, with high proportion among people aged 50-59 years (62.1%, 36/58). Abs against SARS-CoV-2 were detected in 28% (180/666) of subjects enrolled in survey one, which increased two and tri-fold, in surveys 2 (64%, 595/936) and 3 (91%, 700/768); remaining stable (91.3%, 1023/1121) in 4. Age-specific analysis showed consistency on Abs detection over the surveys, including people non-eligible for vaccination (0-17 years) where >80% (165/188) had Abs detected. 93% (359/384) of subjected with Abs in survey 3, remained positive 3 months later. Shifting age-patterns throughout the pandemic are consistent with a high impact of the disease particularly in older ages. Depending on assumptions made in our modelling, we estimate a cumulative excess mortality rates in adults aged 80+ of between 8 and 17% with the largest peak coinciding with the peak in the delta variant wave.

Conclusion: Our data reveal that people in rural areas were widely exposed across including unvaccinated ones; and there was a signature COVID-19-like shift in mortality patterns towards older ages, suggesting substantial impact,

of the pandemic that is largely not reflected in patterns of confirmed COVID-19 deaths.

Quantitative estimates of shift in age-patterns throughout the pandemic. (A) Shows the fit of the model to age-patterns of mortality in the pre-pandemic period 2018-2020. This model is then used to generate the expected numbers of deaths in individuals aged 40+ throughout the pandemic (2020-2022). (B) excess deaths in the pandemic relative to the model, shown in (A), black lines and grey shaded regions show estimates assuming that declines in reported mortality in under 40s are due to declines in mortality (assumption 1), coloured show equivalent estimates assuming that declines in mortality in under 40s are due to declines in ascertainment (assumption 2). (C) Shows estimates from (A) as mortality per 1000 individuals within the age strata, (D) shows each excess mortality estimate as a proportion of the population within the age strata, with seroprevalence estimated from the first two cross-sectional surveys highlighted for reference



891 HIV VIRAL LOAD SUPPRESSION AND RACIAL DISPARITIES DURING THE COVID-19 PANDEMIC IN NYC

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Background: Antiretroviral therapy is highly effective in achieving HIV viral load suppression (VLS) but requires sustained engagement in care. The COVID-19 pandemic disrupted medical care, and its impact on engagement in HIV care and VLS remains unclear. Health information exchanges (HIEs) enable examination of patient care across multiple health systems. We sought to leverage HIE data to examine the effect of pandemic-related disruptions in HIV care on VLS and to explore racial/ethnic disparities in VLS.

Methods: We performed a retrospective observational study of people living with HIV (PLWH) using de-identified data from Healthix, an HIE encompassing >20 million patients and 8,000 healthcare facilities in the greater New York City (NYC) region, between 1/1/2018 and 7/14/2022. We identified PLWH based on HIV viral load (VL) tests and HIV diagnosis codes (ICD and SNOMED). We established two cohorts: PLWH engaged in care in 2020 with ≥1 VL test in 2019, 2020, and 2021(Group A) and PLWH not engaged in care in 2020 with ≥1 VL test in 2019 and 2021 but 0 VL tests in 2020 (Group B). HIV VLS outcomes were categorized as suppressed (< 200 copies/mL) or not suppressed (>200 copies/mL) using the last VL in 2019, first VL in 2021, and last recorded VL. We compared proportions using X^2-tests and fit a group-stratified logistic regression to examine the effect of race/ethnicity on VLS.

Results: We identified 711,358 VL tests representing 81,122 patients at 249 facilities. Of these patients, 36,199 met our definition of PLWH. Of those, 12,448 met the inclusion criteria for Group A, and 3,377 met the inclusion criteria for Group B. In 2019, Group B had a lower VLS proportion than Group A (85.9% vs 88.1%, $X^2 = 12.3$, $p < 0.0001$). In 2021, this gap increased; the proportion of VLS was 80.7% in Group B and 88.0% in Group A ($X^2 = 121.8$, $p < 0.00001$). Most recently, VLS in Group B had increased to 85.6%, but the inter-group gap in VLS had grown from 2.2% to 4.4%.

Within both groups, Black and Hispanic patients had lower odds of VLS than white patients. This disparity was greatest in Group B when they reengaged in care in 2021, with 72.0% of Black patients (OR 0.30, 95% CI 0.22-0.42), and 79.1% of Hispanic patients (OR 0.45, 95% CI 0.31-0.63), compared to 89.5% of white patients achieving VLS.

Conclusion: VLS remained high among PLWH who stayed engaged in care in 2020, dropped among PLWH who disengaged in care, and was lower in minoritized groups even after controlling for engagement in care.

Figure 1

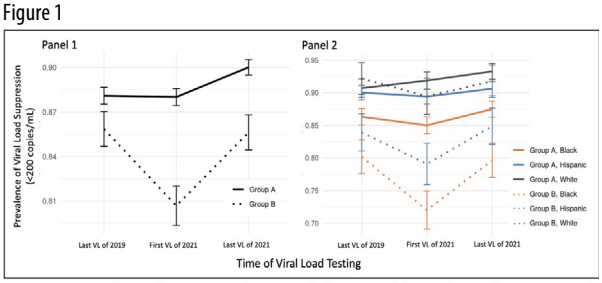

Figure 1: Prevalence of HIV viral load suppression (<200 copies/mL) among people living with HIV in the greater New York City region by group (Panel 1) and by race and group (Panel 2). All data is drawn from Healthix, a large regional health information exchange.

892 HIV AND CHRONIC COMORBIDITIES: MEDICATION ADHERENCE AND CLINICAL ENDPOINT COVARIATION

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Background: Evidence suggests negative monthly medication adherence trends during the COVID-19 era for patients with HIV (PWH) and multiple chronic conditions. However, it is unknown whether observed trends are associated with changes in outcomes of HIV care before and during the COVID-19 era.

Methods: Adult PWH with type 2 diabetes, hypertension, and/or hypercholesterolemia were identified in a US mid-Atlantic integrated health system. Multivariable population-averaged panel general estimating equations were used to assess the relationship between medication adherence [i.e., accepted dichotomous thresholds for optimal proportion of days covered (PDC)] for four medication groups: antiretrovirals [ART], diabetes medications [DMs], renin-angiotensin antagonists [RASMs], and statins [SMs] and their related clinical endpoints [i.e., viral load (VL; copies/mL), HbA1c, systolic and diastolic blood pressure (SBP, DBP; mmHg), and total cholesterol (TC; mg/dl)] during a 37-month longitudinal observation period [9/2018–9/2021]. Covariates included demographics, number of medication groups, COVID-19 era (starting 3/1/2020), and a COVID-19/PDC interaction term.

Results: The cohort [n=543] was predominantly 51-64y [59.30%], Black [73.11%], male [69.24%], and privately insured [65.38%]. All patients were prescribed ART with 75.32% co-prescribed SMs; followed by RASMs [42.73%]; and DMs [25.60%]. ART PDC≥0.9 was associated with decreased odds of VL≥200 copies/mL [aOR=0.77, 95% CI: 0.63-0.94]. For DMs, RASMs and SMS, PDC≥0.8 was not associated with the clinical endpoints of HbA1c≥7.0% [aOR=0.99, 95% CI: 0.94-1.04], SBP≥130 mmHg [aOR=1.03; 95% CI: 0.93-1.14], DBP≥80 mmHg [aOR=1.05, 95% CI: 0.94-1.16] or TC≥200 mg/dl [aOR=1.00, 95% CI: 0.96-1.04], respectively. The COVID-19 era [3/2020 to 9/2021] was associated with increased odds of SBP≥130 [aOR=1.22, 95% CI: 1.01-1.48], but not for DBP≥80 mmHg [aOR=1.05, 95% CI: 0.85-1.28], VL≥200 copies/mL [aOR=1.01, 95% CI: 0.67-1.52], HbA1c≥7.0% [aOR=0.99, 95% CI: 0.88-1.11], and TC≥200 mg/dl [aOR=0.95, 95% CI: 0.86-1.04]. No interactions between COVID-19 era and PDC on clinical endpoints were observed.

Conclusion: ART adherence was associated with viral suppression in PWH, but there were no observed associations between DM, RASM, and SM adherence and their respective clinical endpoints. With the exception of a direct relationship between the COVID-19 start date and SBP, the COVID-19 era was not associated with variations in VL, HbA1c, DBP, and TC clinical endpoints.

893 HIGH PANDEMIC-RELATED MORTALITY AMONGST PEOPLE WITH HIV IN SASKATCHEWAN, CANADA

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Background: Saskatchewan, a Canadian Prairie province, faces a complicated HIV epidemic characterized by high rates of transmission due to injection drug use (IDU) and disproportionate representation of younger persons, women, and persons of Indigenous ethnicity. HIV incidence in Saskatchewan in 2021 was 19.7 per 100,000, 4.5 times higher than the Canadian average.

Concurrently, during the COVID-19 pandemic, the recreational use of synthetic opioids such as fentanyl increased, leading to high numbers of overdose events & deaths.

We characterized the difference in cascade of care outcomes & mortality amongst people with HIV (PWH) living in southern Saskatchewan during the COVID-19 pandemic.

Methods: We conducted a retrospective cohort study for all PWH cared for in the Infectious Diseases Clinic (IDC) at Regina General Hospital between December 31/19 and June 10/22. Age, sex, ethnicity & primary mode of HIV acquisition were collected from the IDC database, along with cascade of care & mortality data. Deaths, including most likely cause of death were characterized via individualized case review.

Results: On December 31/19, IDC cared for 518 PWH. This increased to 585 by June 10/22. Amongst the current cohort, 245 (42%) were female, 163 (28%) were ≤ 35 years old, 306 (52%) were Indigenous, and 318 (54%) had acquired HIV through IDU.

Cascade of care indicators worsened during the COVID-19 pandemic. 58.1% of the cohort were retained in care & 76.1% virally suppressed (HIV RNA ≤ 200 copies/mL) in December 2019, decreasing to 51.3% retained (p=0.02) & 68.8% suppressed (p=0.06) by June 2022.

There were 80 deaths during the study period, representing 15.4% of the cohort from the end of 2019. Most deaths (49, 61.3%) were due to suspected or confirmed drug overdose. 10 (12.5%) additional deaths occurred due to complications from IDU (i.e., sepsis). No deaths were directly attributable to COVID-19. Most who died acquired HIV from IDU (69/80, 86%).

Conclusion: We describe intersecting epidemics of HIV and IDU disproportionately affecting high-risk populations, leading to significant morbidity & mortality during the COVID-19 pandemic. Contributing factors may have included disruption of safe opioid supply and disrupted access to harm reduction services due to COVID-19. Comprehensive population-level harm reduction and addictions management strategies are urgently needed to reduce morbidity & mortality from drug use amongst PWH in Saskatchewan.

894 IMPACT OF THE COVID-19 PANDEMIC ON MALARIA SERVICES IN UGANDA: A TIME SERIES ANALYSIS

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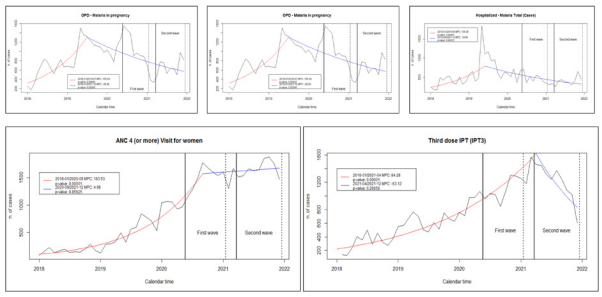
Background: Pregnancy is both a risk factor for P. falciparum infection and development of severe malaria and, in Uganda, its control relies heavily in the administration of intermittent preventive treatment with sulfadoxine-pyrimethamine (SP-IPTp) during antenatal care visits (ANC). COVID-19 pandemic severely impacted health systems globally. This study aims to assess trends in delivering malaria in pregnancy related healthcare services before and during Covid-19 in thirty health facilities in Northern Uganda.

Methods: Interrupted time series study comparing two periods: I) pre-Covid-19 (January 2018 to February 2020) and II) Covid-19 (from March 2020 to December 2021) period. Data were sourced from the District Health Information Management System II (DHIMS2) routinely collected indicators. Comparisons between the two periods were computed with a jointpoint regression model and Annual Average Percentage Changes (AAPC) were calculated.

Results: The study involved data collected by 30 health facilities, 30 health facilities in Northern Uganda – including one hospital - with a catchment area of 506,276 inhabitants and an estimated number of pregnancies ranging from 21,440 to 23,315. Covid cumulative cases and deaths for Oyam districts are reported in Figure 1. As shown in Figure 2, during COVID period we found a significant reduction in the number of women accessing to at least 4 antenatal care (ANC) visits and taking at least three doses of intermittent preventive treatment (IPT) with sulfadoxine-pyrimethamine. The total number of pregnant women receiving Artemether-Lumefantrine for nonsevere malaria or being hospitalized for severe malaria, along with the total number of institutional deliveries and stillbirths followed kept following the trend recorded prior to the pandemic.

Conclusion: The present study shows that, despite the international call for prioritization of maternal and reproductive health service delivery during COVID-19 pandemic, in Uganda, the essential care for malaria in pregnancy have been disrupted. This is concerning, as the failure to increase the delivery of SP-IPTp may impact malaria-related mortality.

Jointpoint regression model for selected indicator



895 NEW HIV DIAGNOSES IDENTIFIED FROM LINKAGE TO CARE AFTER MPOX INFECTION, TEXAS 2022

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Background: HIV surveillance collects data from laboratory reports submitted to the health department. Staff evaluate lab results to determine follow-up activities. Following the 2014 HIV Surveillance Case Definition, all persons whose lab results are indicative of a new HIV diagnosis are contacted for partner services while surveillance staff collect information from the diagnosing provider. Individual lab results are insufficient to make a case determination. Disease intervention specialists are dispatched to offer follow-up testing, but patients can decline. Patients are occasionally lost to follow-up with only a positive screening test reported. The first mpox case in Texas was identified on June 7, 2022, and the U.S Department of Health and Human Services declared mpox a public health emergency on August 4. Matching between the HIV/STD and mpox registries began in September. Matching mpox cases with the HIV registry enabled staff to identify persons with incomplete HIV case reporting and prioritize follow-up.

Methods: Match was conducted with all persons reported to Emerging & Acute Infectious Disease Unit (EAIDU) with confirmed and probable mpox. Person identifiers reported through routine electronic reporting were used for the match, including first and last name, birth date, birth sex, and address. Mpox cases reported to EAIDU thru November 28 were matched to the HIV registry. The HIV dataset included all persons diagnosed with HIV and with preliminary positive screening tests. Data was matched using statistical software SAS 9.4.

Results: Of the 2,826 mpox cases reported to DSHS thru November 28, 2022, 1,413 (50%) matched to the people who had a documented case of HIV meeting the 2014 case definition. During the 4 months of matches, a total of 51 new HIV cases were identified through matching mpox and HIV data. These people had preliminary HIV testing but did not have complete case reporting for HIV. After mpox linkage to care, they received public health follow-up confirming their HIV status and a complete an HIV surveillance report. People identified as comorbid cases had applications for AIDS Drug Assistance Program and Care Services expedited allowing clients to receive services.

Conclusion: Utilizing disease data sources other than HIV/STD can assist in identifying individuals who did not receive an HIV diagnosis, were lost to follow-up, or did not link to HIV care after diagnosis allowing prioritization for HIV/STD public health follow-up and resource assistance.

896 MPOX VIRUS IN THE PHARYNX OF MEN HAVING SEX WITH MEN: A CASE SERIES

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Background: The recent outbreak of monkeypox virus (Mpx) in Europe and North America was predominantly sustained by sexual transmission among men who have sex with men (MSM). Although vital virus has been recovered from sexual fluids, different sources of transmission are possible. Therefore, the dynamic of the virus in other organs and fluids, such as in the pharynx, merits to be investigated.

Methods: We describe a case series of patients with Mpx recruited in an urban STI center in Lombardy (Italy) between May and Aug 2022. We collected

data on demographics, transmission, and clinical presentation using a standardized form. Skin lesion and oropharyngeal swabs were collected from all patients at baseline and tested for the presence of the Mpx using the RealStar Orthopoxvirus PCR Kit 1.0 (Altona diagnostics). Since July, all patients with a positive swab underwent weekly test of skin lesions and oropharyngeal swabs until both tests resulted to be negative

Results: 15 patients, all MSM, 40% HIV-positive, were included. All patients but one reported recent unprotected sexual activity. Oropharyngeal symptoms (pharyngodynia or odynophagia) were reported only by one third of the patients and lesions in the oral cavity were present only in 20%. These and other characteristics are showed in Table 1.

Mpx was identified in 14/15 patients from skin lesions while in one patient it was identified only in the oropharyngeal swab. Overall, oropharyngeal swabs tested positive in 13/15 (86.7%) of the patients. Lower cycle threshold (Ct), indicating higher viral load, was measured in skin than in pharynx swabs (mean Ct 18.1 [95%CI 14.8-21.5] vs. 24.2 [21-27.5]). Nonetheless, among 7 patients followed prospectively until clinical and virological cure, Mpx PCR positivity persisted, on average, 5.3 days longer in pharynx than on skin. In one immunosuppressed patient (due to previous bone marrow transplantation), oropharyngeal swabs remained positive for 80 days (55 days beyond skin lesion resolution). No cases of transmission in the household, apart from one transmission to the cohabiting sexual partner, occurred.

Conclusion: Our findings suggest that Mpx can be recovered from the pharynx in absence of symptoms or signs of local involvement and that it can persist in the pharynx for long. Routine testing of the oropharyngeal swab among suspect cases and exposed indivuduals may contribute to increase diagnostic yield. Whether replication in the oropharynx may contribute to disease transmission needs to be assessed.

Table 1: Patient characteristics

Characteristic	N (%) or Median (IQR)
Male Gender	15 (100%)
Age (years)	36 (35-45)
Men having sex with men	15 (100%)
Immunodeficiency	
HIV-positive	6 (40%)
Bone marrow transplantation	1 (6.7%)
Diabetes	1 (6.7%)
None	87 (46.7%)
Vaccinated for smallpox	2 (13.3%)
Reporting recent unprotected sex	14 (93.3%)
Receptive anal intercourses	1 (6.7%)
Receptive anal and oral intercourses	2 (13.3%)
Only oral sex	2 (13.3%)
Unspecified sex with other men	9 (60%)
Other concurrent sexually transmitted infections	2 (13.3%)
Syphilis	1 (6.7%)
Chlamydia	1 (6.7%)
Neisseria	
Putative place of acquisition	
Locally	12 (80%)
Abroad	3 (20%)
Symptoms at onset	
Fever	12 (80%)
Lymphadenopathy	9 (60%)
Pharyngitis	5 (33.3%)
Rectal pain	10 (66.7%)
Skin/mucosal lesions	15 (100%)
Oral/perioral	3 (20%)
Genital	5 (33.3%)
Anal/perianal	6 (40%)
Number of lesions	
<5	2 (13.3%)
5-10	5 (33.3%)
>10	8 (53.3%)

897 MPOX AMONG MSM IN THE NETHERLANDS PRIOR TO MAY 2022, A RETROSPECTIVE STUDY

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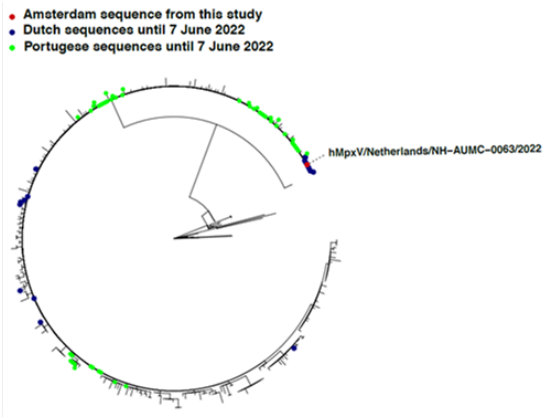
Background: Since May 2022 over 20.000 monkeypox (mpox) cases have been reported from 29 EU/EEA countries, predominantly among men who have sex with men (MSM). With over 1200 cases and a crude notification rate of 70.7 per million population, the Netherlands was in the top 5 European countries most affected. The first national case was reported from May 10th, yet potential prior transmission remains unknown. We therefor performed a retrospective study to elucidate whether undetected transmission of human monkeypox virus (hMPXV) occurred prior to the first reported cases in the two largest cities in the Netherlands, Amsterdam and Rotterdam.

Methods: Data from the two largest Centers for Sexual Health in the Netherlands were used. We retrospectively tested stored samples for hMPXV using an in-house developed and validated qPCR. Stored samples comprised anorectal samples that were positive for Chlamydia or Gonorrhoea (Ct/Ng) and all collected ulcer samples. Whole genome sequencing was performed for hMPXV positive samples. For phylogenetic analysis we used all available Genbank sequences and added the Dutch strains generated as part of this study.

Results: We tested 262 (169 in Amsterdam; 93 in Rotterdam) anorectal samples that were positive for Ct/Ng and 137 ulcer samples (125 Amsterdam, 12 Rotterdam) collected between February 14 and May 18, 2022 on the presence of hMPXV. Two hMPXV positive samples were identified, one from an anorectal sample and one from an ulcer sample, both collected in the first week of May (week 18), 2022. Both samples were from MSM, one had symptoms of proctitis and one had multiple ulcers. The anorectal hMPXV positive sample was successfully sequenced. This sequence, like all other Dutch sequences belonged to the clade IIb cluster (B.1) with a close relation to international strains of hMPXV (figure).

Conclusion: The first mpox cases in the Netherlands coincided with the first cases reported in the United Kingdom, Spain and Portugal. We found no evidence of widespread hMPXV transmission in Dutch sexual networks of MSM prior to May 2022. Likely, the hMPXV outbreak expanded across Europe within a short period in the spring of 2022 in an international highly intertwined network of sexually active MSM.



898 CHANGES IN SEXUAL BEHAVIORS DUE TO MPOX: A CROSS-SECTIONAL STUDY OF SGM IN ILLINOIS

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[1]Northwestern University, Chicago, IL, USA, [2]Stroger Hospital of Cook County, Chicago, IL, USA

Background: The spread of the mpox virus in 2022 primarily within the sexual networks of men who have sex with men (MSM) triggered a potentially stigmatizing public health response in the US. Despite mpox primarily spreading through skin-to-skin contact, most messaging has promoted abstinence and/or reduction in sexual risk behaviors. Persistent risk reduction may be necessary to prevent future surges; therefore, ongoing work is needed to investigate whether decreases in sexual risk behaviors continue among sexual and gender minority (SGM) youth and young adults (YYA), and what factors are associated with persistence of risk reduction behaviors.

Methods: The parent study, Keeping it LITE, examined HIV risk factors in young adults who reported sexual activity between 2017 and 2019 (n=3,444). A substudy of mpox was conducted between September 10th and 20th, 2022 for all active participants with Illinois residency (n = 469). Survey questions included demographic data and sexual risk reduction behaviors. Responses were aggregated, and an exploratory factor analysis (EFA) was utilized to investigate potential behavioral clustering using MPlus. Bivariate analyses were conducted with three outcome variables related to sexual risk-taking. Odds ratios (ORs) and 95% confidence intervals (CIs) were calculated for the dichotomous outcome of reporting sexual contact since June 1st. Generalized linear models (GLMs) with corresponding F-statistics were generated for both sexual risk reduction factors.

Results: Survey participation was 68.2% (322/469). Three-quarters of participants (82.6%) reported sexual activity since June 1st. Most sexually active participants (83.5%) reported adopting at least one sexual risk reduction behavior because of mpox. Black and Hispanic/Latinx participants were less likely to be sexually active, but more likely to report risk reduction behaviors (31.3% and 22.6%, respectively). Participants who received the mpox vaccine were more likely to report sexual activity.

Conclusion: SGM YYA in Illinois overwhelmingly reported reducing sexual contact due to the mpox outbreak. Vaccinated individuals were more likely to report sexual activity and a greater number of prophylactic activities. Thus, sex-positive and harm reduction messaging strategies are likely to be more effective than abstinence-only prevention, which may further stigmatize marginalized groups.

Demographic Characteristics and Bivariate Associations with Sexual Contact (n = 317).

	N (%)	Sexual Contact since 06/01/22		No Sexual Contact since 06/01/22		OR (95% CI)	Chi-Square (p-value)
		N	%	N	%		
Race/ethnicity							**Fisher's Exact Test (FET; 0.003)**
Non-Hispanic White	153 (48.3)	137	89.5	16	10.5	1.00 (--)	
Non-Hispanic Black	48 (15.1)	33	68.8	15	31.3	**0.26 (0.12, 0.57)**	
Non-Hispanic Asian	20 (6.3)	17	85.0	3	15.0	0.66 (0.18, 2.51)	
Multiracial	31 (9.8)	26	83.9	5	16.1	0.61 (0.21, 1.80)	
Hispanic/Latinx	62 (19.6)	48	77.4	14	22.6	**0.40 (0.18, 0.88)**	
Other	3 (1.0)	1	33.3	2	66.7	**0.06 (0.01, 0.68)**	
Age, Years (mean, SD)	29.9 (4.8)	30.2	4.7	28.4	4.8	**1.08 (1.02, 1.15)**	**t = -2.47 (0.014)**
Transgender Identity							1.51 (0.47)
Yes	47 (14.8)	36	13.7	11	20.0	0.63 (0.30, 1.34)	
No	260 (82.0)	218	83.2	42	76.4	1.00 (--)	
Not Sure	10 (3.2)	8	3.1	2	3.6	0.77 (0.16, 3.76)	
Gender							FET (0.78)
Man/Boy	257 (81.1)	214	83.3	43	16.7	1.00 (--)	
Woman/Girl	10 (3.2)	8	80.0	2	20.0	0.80 (0.17, 3.92)	
Genderqueer	11 (3.5)	10	90.9	1	9.1	2.01 (0.25, 16.1)	
Non-binary	30 (9.5)	23	76.7	7	23.3	0.66 (0.26, 1.64)	
Other	9 (2.8)	7	77.8	2	22.2	0.70 (0.14, 3.50)	
Sexual Orientation							**13.3 (0.004)**
Gay/Lesbian	226 (71.3)	193	85.4	33	14.6	1.00 (--)	
Bisexual/Pansexual	43 (13.6)	30	69.8	13	30.2	**0.40 (0.19, 0.83)**	
Queer	37 (11.7)	33	12.6	4	10.8	1.41 (0.47, 4.24)	
Other	11 (3.5)	6	54.6	5	45.5	**0.21 (0.06, 0.71)**	
Relationship Status: Single	163 (51.4)	120	45.8	43	78.2	**0.24 (0.12, 0.47)**	**19.1 (<0.0001)**
MPV Vaccine							**14.6 (0.0022)**
No	142 (44.8)	106	40.5	36	65.5	1.00 (--)	
Yes, Partial	88 (27.8)	78	29.8	10	18.2	**2.65 (1.24, 5.66)**	
Yes, Fully	77 (24.3)	71	27.1	6	10.9	**4.02 (1.62, 10.0)**	
Not Sure	10 (3.2)	7	2.7	3	5.5	0.79 (0.20, 3.23)	

899 SEXUAL BEHAVIOR REDUCTION DO NOT EXPLAIN DECREASED MPOX INCIDENCE AMONG PrEP USERS

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Background: The Italian monkeypox (MPX) outbreak involved essentially the Milan area starting from mid-June 2022. As observed in other European regions, new cases decreased significantly by October but no reasons for this epidemiologic trend have been established yet. We aimed to assess whether reduction in sexual activity and at-risk behaviors and/or vaccination might explain this finding in PrEP users attending a community-based service.

Methods: Milano Checkpoint provides assistance to the largest Italian cohort of PrEP users. At each visit clients are tested for sexually transmitted infections (STIs) and fill self-administered questionnaires about their behavior in the previous 3 months. Subjects with a visit in July to November 2022 were selected: overall and condomless sexual intercourses, chemsex practices, and STIs incidence were compared to what registered in the previous visit. Descriptive statistics and non-parametric tests (Pearson's Chi-square, Mann-Withney U, McNemar exact, and Wilcoxon signed-rank) were used to compare groups, while incidence rates of STIs and incidence rate ratio (IRR) were calculated. Logistic regression model was built to describe factors associated to change in sexual encounters.

Results: We selected 435 individuals: Table 1 describes features of study population. Smallpox vaccine was available from the second half of August and only a minority (26.2%) completed the full course. A reduction in the number of intercourses was observed in 174 (40.0%) PrEP users, but the majority did not change the number of sex acts during the MPX outbreak: the overall number of sexual contacts arose from 11 (IQR 5-25) to 12 (IQR 5-26) in the epidemic months (p=0.070). Condomless intercourses and use of chemsex did not change (p=0.459 and p=0.766, respectively). The incidence of STIs was 87.3 per 100 PYFU in the pre-epidemic versus 84.8 per 100 PYFU in the epidemic period (IRR 1.03, 95% CI 0.80-1.32, p=0.813). The only factor associated to reduction in sexual activity was a lower level of education (OR 0.69, 95% CI 0.54-0.86, p=0.001). Sexual behavior did not change after vaccination (p=0.593) nor a diagnosis of MPX (p=0.856).

Conclusion: Both reduction of risky sexual behavior and MPX vaccination do not explain the vanishing of epidemics. Saturation of high-risk groups or hesitancy to contact health facilities to avoid quarantining policies should be investigated.

Table 1. Demographic, clinical, and behavioral features of study population.

		Overall (N=435)	Decreased sexual activity (N=174)	No change in sexual behavior (N=261)	p
Age, years, median (IQR)		39 (33-46)	39 (34-46)	39 (32-47)	0.588
Italian origin, n (%)		379 (87.1)	155 (85.8)	224 (89.1)	0.320
Gender identity, n (%)	Males	423 (97.3)	168 (96.5)	255 (97.7)	**0.034**
	Females	8 (1.8)	2 (1.2)	6 (2.3)	
	TGW	4 (0.9)	4 (2.3)	--	
Length of PrEP, months, median (IQR)		14.7 (6.7-22.3)	16.1 (8.2-24.1)	13.9 (6.2-20.8)	**0.021**
Level of education, n (%)	Degree	295 (68.0)	134 (77.0)	161 (61.9)	**0.004**
	Secondary School	120 (27.6)	34 (19.5)	86 (33.1)	
	Lower level	19 (4.4)	6 (3.5)	13 (5.0)	
Occupied, n (%)		381 (87.8)	153 (87.9)	228 (87.7)	0.941
Any STI in the previous 3 months, n (%)		38 (8.7)	15 (8.6)	23 (8.8)	0.545
Number of sexual intercourses in the previous 3 months, median (IQR)		11 (5-25)	20 (10-33)	8 (3-16)	**<0.001**
Number of condomless sexual intercourses in the previous 3 months, median (IQR)		4 (0-12)	5 (1-15)	3 (0-9)	**0.003**
Number of condomless sexual intercourses in the previous 30 days, median (IQR)		2 (0-5)	3 (0-6)	1 (0-4)	**0.008**
Use of any recreative drug in the previous 4 weeks, n (%)		169 (38.9)	70 (40.2)	99 (37.9)	0.630
	Cocaine hydrochloride	42 (9.7)	12 (6.9)	30 (11.5)	0.112
	Cocaine freebase	16 (3.7)	5 (2.9)	11 (4.2)	0.467
	MDMA	27 (6.2)	10 (5.8)	17 (6.5)	0.746
	Crystal meth	14 (3.2)	1 (0.6)	13 (5.0)	**0.011**
	Mephedrone	29 (6.7)	9 (5.2)	20 (7.7)	0.308
	GHB/GBL	28 (6.4)	10 (5.8)	18 (6.9)	0.632
	THC	79 (18.2)	30 (17.2)	49 (18.8)	0.685
	Ketamine	21 (4.8)	5 (2.9)	16 (6.1)	0.121
	Popper	110 (25.3)	46 (26.4)	64 824.5)	0.652
	MDPV	18 (4.1)	5 (2.9)	13 (5.0)	0.280
	Heroine	10 (2.3)	1 (0.6)	9 (3.5)	**0.050**
Chemsex, n (%)		52 (11.9)	19 (10.9)	33 (10.6)	0.587
5PD inhibitors use, n (%)		86 (19.8)	35 (20.1)	51 (19.5)	0.883
Infected by MPX*, n (%)		32 (10.5)	13 (10.9)	19 (10.3)	0.856
Vaccinated against smallpox, n (%)	No vaccination	253 (58.2)	95 (54.6)	158 (60.5)	0.082
	During childhood	23 (5.3)	10 (5.8)	13 (5.0)	
	During childhood plus one boost	21 (4.8)	14 (8.0)	7 (2.7)	
	One injection	45 (10.3)	21 (12.1)	24 (9.2)	
	Two injections	93 (21.4)	34 (19.5)	59 (22.6)	

* Data available only for 304 subjects.

900 STIGMA RELATED TO HUMAN MPOX VIRUS AMONG MSM IN THE US, AUGUST 2022

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Background: Stigma related to identity, behavior, and HIV status can manifest in multiple domains of life. In the 2022 mpox outbreak, gay, bisexual, and other men who have sex with men (MSM) and non-Hispanic Black and Hispanic men have represented overly large proportions of reported cases. Because these groups also regularly face stigma in their lives, there was potential for messaging about the mpox outbreak to increase stigma for these already marginalized groups. However, CDC sought to promote non-stigmatizing, sex positive harm reduction messages from the beginning of the outbreak.

Methods: To understand prevalence and impact of mpox-related stigma amongst MSM in the United States, we conducted a study within the American Men's Internet Survey, which enrolled 824 cisgender MSM aged 15+ from August 5-15, 2022. We administered 10 mpox-related stigma items; we retained 9 after exploratory factor analysis and pooled these 9 into a binary variable for "any reported stigma" which was used in subsequent bivariate and multivariate logistic regression analyses.

Results: 1.9% (n=15) of participants felt excluded from their family because of fear they may have mpox, with 1.1% (n=9) unsure. 1.8% (n=14) of participants felt excluded from friends or were unsure 1.8% (n=14). Regarding discriminatory remarks or gossip from family, 3.5% (n=28) felt some level of discrimination, with another 3.8% (n=30) unsure. Overall, 1.3% (n=10) felt worried about going to their doctor because of being diagnosed with mpox. In total, 1.0% (n=8) of participants reported being verbally harassed because someone thought they had mpox, with another 0.6% (n=5) unsure. Overall, 6.6% (n=54) reported experiencing any mpox-related stigma. In bivariate analyses, reporting any mpox-related stigma was associated with knowing someone who tested for mpox (OR=4.15; 95% CI=1.99,8.69), knowing someone who was vaccinated for mpox (OR=1.97; 95% CI=1.12, 3.47), and having an unexplained rash in the 3 months prior to survey administration (OR=4.01; 95% CI= 2.05, 7.83). Multivariable logistic regression models with potential intersecting determinants such as race/ethnicity, age group, and region did not significantly affect the presented relationships.

Conclusion: There was low overall prevalence of mpox-related stigma among MSM in August 2022. These data suggest that messages developed by CDC and others about mpox and how to protect oneself from mpox infection did not lead to widespread stigma for this sample of MSM in the US.

901 HIGH LEVEL OF MPOX KNOWLEDGE AND STIGMA AMONG LGBTQIA+ COMMUNITIES IN BRAZIL

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Background: Globally in 2022, Brazil ranks second in number of mpox cases and deaths. Stigma and discrimination, against the LGBTQIA+ community, might result in structural barriers that impact access to health services, leading to undertesting and underreporting of cases. We aim to evaluate community knowledge of mpox, and describe sociodemographic and behavioral aspects according to self-reported mpox diagnosis.

Methods: Cross-sectional on-line survey conducted among adults (>18 years) living in Brazil through advertisements on Scruff, Grindr, Instagram, and Facebook. Questions addressed sociodemographics; mpox knowledge, symptoms, and diagnosis; sexual behavior; HIV testing; and STI diagnoses. For statistical comparison, we used chi-square and Kruskal-Wallis tests.

Results: From October to November 2022, 6236 participants completed the survey: 5686(91.2%) cis-man, 252(4.0%) non-binary, 247(4.0%) cis-women, 15(0.2%) trans-man and 15(0.2%) trans-women. Most were gay/bi/pansexual (6032; 96.7%), white (3877; 62.2%), had college education (4902; 78.7%), and low/middle income (4070; 73.0%). Most had heard of mpox (6044; 96.9%) and reported willingness to take mpox vaccine (5008; 95.1%). Overall, 324 (5.6%) reported a mpox diagnosis; 318 of them (98.1%) reported lesions, 178 (56.0%) local pain and 316 (99.4%) attended health facilities for investigation. Among participants who reported no mpox diagnosis (N=5912), 4974 (84.1%) reported knowledge of mpox, 288 (4.9%) had a suspicious mpox lesion, but only 54.9% of those (n=158/288) attended a health facility for investigation. Participants reporting mpox diagnosis compared to those not diagnosed were younger (median 34 [IQR:30-39.2] vs. 37 [IQR:31-44] years; p< 0.001), reported sex partners with suspicious/confirmed mpox (34.6% vs. 3.5%; p< 0.001) and more sexual contacts (Table). HIV testing in the prior 3 months (74.1% vs. 42.1%; p< 0.001), current PrEP use (47.8% vs. 24.4%; p< 0.001) and any STI diagnoses (25.0% vs. 10.6%; p< 0.001) were higher among those reporting mpox diagnosis. Participants reporting mpox diagnosis more frequently reported changes in sexual behavior after mpox onset. HIV prevalence differed by report of mpox diagnosis (37.7% vs. 22.9%; p< 0.001). The majority affirm that LGBTQIA+ communities are being stigmatized due to mpox (5258; 84.4%).

Conclusion: Our results show high rates of mpox knowledge in the LGBTQIA+ communities. Expand access to gender competent care is critical to avoid underdiagnosis and fight stigma and discrimination.

Sexual behavior since June 2022 according to mpox self-reported diagnosis

	No (n=5912)	Yes (n=324)	Overall (N=6236)	P-value
Median number of sex-partners (n=5121)	4 (1,10)	10 (5,20)	4 (1,10)	<0.001
Receptive anal sex (n=5193)	2874 (58.1)	187 (75.1)	3061 (58.9)	< 0.001
Insertive anal sex (n=5193)	2996 (60.6)	214 (85.9)	3210 (61.8)	< 0.001
Condomless sex (n=5193)	3535 (72.9)	215 (87.4)	3750 (73.6)	< 0.001
Frequented sex venues	2173 (36.8)	206 (63.6)	2379 (38.1)	< 0.001
Chemsex	1429 (24.2)	118 (36.4)	1547 (24.8)	< 0.001
Binge drinking before/during sex	1565 (26.5)	115 (35.5)	1680 (26.9)	< 0.001
Any change in sexual behavior	2878 (48.7)	186 (57.4)	3064 (49.1)	0.002
Reduced number of partners	2226 (37.7)	149 (46)	2375 (38.1)	0.003
Avoided sex parties	1596 (27)	122 (37.7)	1718 (27.5)	< 0.001
Inspected partners for mpox lesions	860 (14.5)	66 (20.4)	926 (14.8)	0.004

902 CHARACTERISTICS AND DISPARITIES AMONG HOSPITALIZED PERSONS WITH MPOX IN CALIFORNIA

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Background: In the 2022 outbreak of mpox, reported hospitalization rates have ranged from 2%-13%. Severe clinical manifestations have been reported in persons coinfected with mpox and HIV. However, data describing sociodemographic characteristics and comorbidities among hospitalized persons with mpox are limited. We compared demographic characteristics, highlighting socioeconomic disparities and clinical characteristics, including HIV infection, among persons with mpox who were and were not hospitalized in California.

Methods: We included mpox cases reported in California from May 17 through September 8, 2022. All analyses were stratified by HIV status. Census tracts of residence of mpox cases were matched to the California Healthy Places Index (HPI), which categorizes neighborhoods based on characteristics that influence health of residents, with lower scores relating to fewer opportunities for residents of these communities to lead healthy lives. Fisher's exact tests and Wilcoxon rank sum tests were used to compare groups.

Results: Of 3241 persons with mpox, 1317(41%) had HIV and 119(4%) were hospitalized. Among those with HIV 68(5%) were hospitalized and 51(3%) without HIV were hospitalized. Hospitalization was commonly for oropharyngeal (25(21%)) or rectal symptoms (19(16%)), and bacterial infections (19(16%)). Among those with HIV, more hospitalized than non-hospitalized persons lived in the lowest HPI quartile (26(42%) versus 279(23%), p=0.01); no difference was seen among those without HIV. In those with HIV, having CD4 < 200 cells/uL (9(14%) versus 46(4%)) or a non-suppressed (≥200 copies/mL) viral load (27(42%) versus 121(9%)) was associated with hospitalization (p-values< 0.01). For those with HIV who were hospitalized, 13(36.1%) with non-suppressed viral loads and 4(44%) with CD4< 200 cells/uL lived in the lowest HPI quartile. Among those without HIV, having diabetes (3(6%) versus 31(2%), p< 0.001) or exfoliative skin conditions (5(10%) versus 59(3%), p< 0.001) was associated with hospitalization.

Conclusion: Among persons with mpox and HIV, more hospitalized cases had uncontrolled HIV and lived in communities with fewer opportunities to lead healthy lives. Among persons with mpox and without HIV, more that were hospitalized had diabetes or exfoliative skin disorders. Vaccination and rapid access to testing and treatment should be prioritized in these groups.

Table 1: Characteristics of persons with mpox in California from May 17th 2022-September 8th 2022 (N=3241).

	With HIV			Without HIV		
Characteristics	Hospitalized n(%)	Not Hospitalized n(%)	P-value	Hospitalized n(%)	Not Hospitalized n(%)	P-value
Total	68(5.2%)	1249(94.8%)		51(2.7%)	1873(97.3%)	
Age (Median[IQR])	39(33-46)	38(32-46)	0.30	34(29-41)	34(29-41)	0.93
HPI Quartile			**0.01**			0.45
1	26(41.9%)	279(22.7%)		6(12.2%)	317(17.1%)	
2	12(19.4%)	354(28.8%)		10(20.4%)	437(23.6%)	
3	10(16.1%)	239(19.4%)		15(30.6%)	392(21.2%)	
4	14(22.6%)	359(29.2%)		18(36.7%)	705(38.1%)	
Missing	6	18		2	22	
Diabetes	0	14(1.1%)	0.60	3(5.9%)	31(1.7%)	**<0.001**
Atopic dermatitis or other skin condition	3(4.4%)	24(1.9%)	0.12	5(9.8%)	59(3.2%)	**<0.001**

903 CD4 COUNT < 350 CELLS/MM³ INCREASES RISK OF HOSPITALIZATION WITH MPOX IN PWH

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Background: Mpox is typically a self-limited infection; however, HIV-associated immunosuppression increases the risk of severe illness. For persons with HIV (PWH), correlates of risk for severe illness, such as illness severe enough to warrant hospitalization, have not been well characterized. Such data could help determine which PWH with mpox should be prioritized for close monitoring and care including early or empiric tecovirimat treatment.

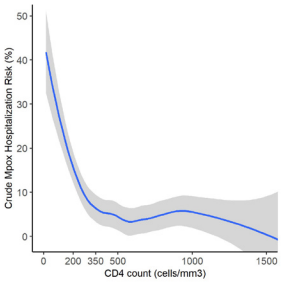
Methods: We characterized the HIV status of all reported cases of mpox in Georgia from 5/31/2022–10/31/2022 by linking surveillance data for mpox cases with HIV cases, including HIV laboratory results. We used a retrospective cohort design and a modified Poisson regression model with a log-link and robust variance estimates to calculate relative risks (RRs) for hospitalization with mpox. The predictor variable captured 1) most recent CD4 cell count (CD4) in the year prior (< 350 and ≥350 cells/mm³) and 2) engagement in care defined as any HIV laboratory results (CD4 or viral load) in the year prior to mpox onset.

Results: Among 1,921 mpox cases in Georgia, 1,851 (96%) were among cisgender men, and 1,124 (59%) were among PWH of whom 214 (19%) had a CD4 count < 350 cells/mm³ and 189 (17%) had an unsuppressed viral load (>200 copies/ml) in the year prior to mpox onset. Among 121 persons reported as hospitalized with mpox to GDPH, 84 (69%) were PWH, of whom 32 (26%) had CD4 < 350 cells/mm³ and 15 (12%) had no CD4 or VL results in the year prior. Common reasons for hospitalization included pain control (37%), breathing problems (13%), and treatment of a secondary infection (11%). Among PWH, persons with low CD4 count had increased risk of hospitalization starting around CD4 < 350 cells/mm³ [Figure]. Risk for hospitalization among PWH with

CD4 >350 cells/mm^3 was similar to that for persons without HIV (RR 1.0, 95% confidence intervals [CI] 0.6-1.5); however, PWH with CD4 < 350 cells/mm^3 were more likely to be hospitalized (RR 3.2, 95% CI 2.1-5.1). PWH without recent HIV laboratory results were also more likely to be hospitalized (RR 2.4, 95% CI 1.3-4.2).

Conclusion: PWH were more likely to be hospitalized with mpox if their most recent CD4 was < 350 cells/mm^3 or if they were not engaged in care (using laboratory criteria in the past year as a proxy). For PWH diagnosed with mpox who have CD4 < 350 cells/mm^3 or who are not engaged in HIV care, clinicians should closely monitor illness and consider early treatment with medical countermeasures such as tecovirimat.

Crude risk of hospitalization with mpox among persons with HIV by CD4 count produced with locally estimated scatterplot smoothing, shaded area is 95% confidence interval



904 MPOX VIRUS INFECTION IS MORE SEVERE IN PATIENTS WITH UNCONTROLLED HIV INFECTION

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Background: To date, information about the risk of severe monkeypox virus (MPXV) disease in PLWH is not well established. Therefore, the aim of this study was to assess the impact of HIV on the clinical course of MPXV infection.

Methods: National case-series study. Patients from 18 Spanish hospitals, with PCR-confirmed MPXV infection since April 27th to September 30th were included in this study. The duration of the clinical course was computed from the onset of symptoms until mucocutaneous lesions complete clearance or MPXV infection-related complications resolution. Disseminated disease was defined as the presence of mucocutaneous lesions involving 6 or more areas of the body surface. Severe complications included extensive superinfection of skin lesions without response to treatment, pain refractory to non-opioid analgesia, sepsis, odynophagia with obstructive sensation, myopericarditis, gastrointestinal bleeding, encephalitis, or ophthalmologic complications. The main outcome was the development of severe MPXV disease, defined as: i) duration of the clinical course ≥21 days, or; ii) disseminated disease, or: iii) emergence of severe complications, or iv) requirement of hospital admission.

Results: 1,028 individuals were included. Overall, 928 (90%) were MSM. 448 (43%) were PLWH, of whom 26 (2%) had a CD4 cell count < 350 cells/mm^3. HIV viral load ≥1,000 cp/mL was found in 19 (4%) PLWH. 18 of them (94%) were not on ART. Severe MPXV disease was observed in 16 (62%) PLWH with CD4 < 350 cells/mm3, 164 (41%) PLWH with CD4 ≥350 cells/mm^3 and 208 (40%); i.e, 61% PLWH and CD4 < 350 cels/mm^3 vs. 372 (40%), (p=0.032) of the remaining study participants showed severe MPXV disease. Regarding plasma HIV viremia, 14 (74%) PLWH with HIV-RNA ≥1,000 cp/mL showed severe disease vs. 174 (41%) PLWH with plasma HIV-RNA load < 1,000 copies/mL and 222 (38%) individuals without HIV infection (p=0.008). In multivariate analysis, adjusted by age, sex, CD4 cell count and HIV viral load at the time of MPXV infection, only plasma HIV-RNA ≥1,000 cp/mL was associated with a greater risk of developing severe MPXV disease among PLWH [adjusted OR= 5.6 (95% confidence interval 1.5-20.6), p=0.009].

Conclusion: PLWH, considered as a whole, are not at a greater risk of MPXV severe disease. However, those with uncontrolled HIV infection, due to lack of effective ART, develop more severe outcomes. Efforts should be done to increase HIV testing and to ensure linkage to HIV care services. In this setting, ART must be immediately started.

905 IMPACT OF HIV INFECTION ON MPOX-RELATED HOSPITALIZATIONS IN BRAZIL

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Background: Late presentation to care remains a major public health problem in Brazil, despite the country´s longstanding commitment to universal access to ART to all PLWH. The COVID-19 pandemic severely hit the country and further impacted the HIV care continuum, with worse disparities observed by gender and sexual orientation. By December 28th 2022, Brazil reported 10,493 and 14 mpox cases and deaths ranking second globall. Although mpox lethality is low, HIV-related immunosuppression may negatively impact mpox outcomes, increasing hospitalizations and fatalities. We aim to describe mpox hospitalization rates and explore the impact of HIV-infection on mpox-related hospitalizations and clinical outcomes.

Methods: Prospective, observational cohort study of individuals with confirmed mpox infection followed at the major mpox referral center in Rio de Janeiro, Brazil. Demographic and clinical data including reasons for hospitalization were systematically collected. Chi-squared or Fisher's exact tests for qualitative variables and the Moods median test for quantitative variables were used.

Results: From June 12 to December 12, 2022, 402 participants had a laboratory-confirmed mpox diagnosis. Median age was 34 years, 365 (91%) were cisgender men, and 197 (49%) were PLWH. Overall, 39 (10%) participants were hospitalized due to mpox-related causes; 20 (51%) were PLWH. All PLWH with CD4 counts< 200 cells/mm^3 required hospitalization. Compared to non-hospitalized PLWH, a higher proportion of hospitalized PLWH had concomitant opportunistic infections (4/20 [20%] vs. 1/177 [0.6%]; p< 0.001), were not virologically suppressed (7/20 [35.0%] vs. 22/177 [15.3%]; p=0.1) and were not on ART (4/20 [20%] vs. 15/177 [7.6%]; p=0.03). Among all hospitalized participants, PLWH were more frequently hospitalized due to severe proctitis than HIV-negative participants (12/20 [60%] vs. 5/19 [26.3%]; p=0.03), with no differences regarding hospitalizations for pain control (Table). PLWH accounted for all cases of hospitalized individuals who required intensive care support (n=4), had deep tissue involvement (n=3) and had a mpox related death (n=2).

Conclusion: Our findings suggest an association between worse outcomes in the HIV care continuum and mpox-related hospitalizations. Advanced immunosuppression (CD4< 200) contributed to more severe clinical presentations and death. Public health strategies to mitigate HIV late presentation and the negative impact of the COVID-19 pandemic to the HIV care continuum are urgently needed.

Sociodemographic and clinical characteristics of mpox cases according to HIV and hospitalization status

Table. Sociodemographic and clinical characteristics of mpox cases according to HIV and hospitalization status

	All mpox cases (n=402)	PLWH and mpox (n=197)	Not Hospitalized PLWH (n=177)	Hospitalized participants (n=39)			
				Overall (n=39)	*PLWH (n=20)*	*HIV-individuals (n=19)*	*p-value*
Median Age (IQR, years)	34 (29,40)	35 (31,41)	35 (31,41)	32 (29,41)	35 (31,44)	30 (26,36)	0.084
Cisgender Men	365 (90.8%)	186 (94.4%)	166 (93.8%)	36 (92.3%)	20 (100%)	16 (84.2%)	
Cisgender Women	29 (7.2%)	3 (1.0%)	4 (2.3%)	3 (7.7%)	0	3 (15.8%)	0.106
***Travesti* or Tansgender Women**	8 (1.7%)	7 (3.6%)	7 (3.9%)	0	0	0	
Hospitalized for Pain Control	-	-	-	36 (92.3%)	18 (90.0%)	18 (94.7%)	>0.999
Hospitalized due to Severe Proctitis	-	-	-	17 (43.6%)	12 (60.0%)	5 (26.3%)	0.034
Required Intensive Care Support during Hospitalization	-	-	-	4 (10.3%)	4 (20.0%)	0	0.106
Concomitant Opportunistic Infection	-	5 (2.5%)	1 (0.6%)	-	4 (20.0%)	-	
HIV RNA load > 200 copies/ml	-	29 (14.7%)	22 (15.3%)	-	7 (35.0%)	-	-
CD4 cell count < 200 cells/mm3	-	8 (4.1%)	0	-	8 (40.0%)	-	-
No ART[1]	-	15 (7.6%)	11 (6.2%)	-	4 (20.0%)	-	-

1 "No ART" category includes people for whom ART was never prescribed or who have not been on ART for the last 120 days

906 CHARACTERISTICS OF THE 2022 MPOX OUTBREAK IN A SOUTHEASTERN US CITY

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Background: In Atlanta, Georgia, the 2022 mpox outbreak disproportionately impacted people who are Black and people with HIV (PWH) compared to other areas. Here, we describe the demographic and clinical manifestations of mpox in Atlanta.

Methods: We performed a retrospective cohort study with manual chart abstractions of 180 individuals who tested positive for mpox at two academic medical centers in Atlanta between 6/1/2022 and 10/7/2022. We used descriptive statistics to summarize demographic and clinical characteristics and Fisher's exact tests to explore categorical associations between HIV indices, sexual behaviors, and mpox presentations.

Results: Of 180 people diagnosed with mpox, 175 (97.2%) were cisgender men and 5 (2.8%) were transgender women. 160 (88.9%) were Black, 9 (5.0%) Latinx, and 3 (1.7%) White. 152 (84.4%) were PWH. Of 113 PWH with a known HIV viral load (VL), 39 (34.5%) had VL >200 c/μL. Among 107 PWH with a known CD4 count, 15 (14.0%) were < 200, 30 (28.0%) were 201-350, and 62 (57.9%) were >350 c/μL. Of 152 persons with an identified suspected mpox exposure, 143 (94.1%) reported recent sexual contact and 97% reported sex with men. A concurrent syphilis diagnosis occurred in 34 (18.9%) and other sexually transmitted infections in 33 (18.3%). Common initial symptom(s) included: rash (71.7%), fever/chills (43.3%), lymphadenopathy (22.8%), and rectal pain (18.3%). Overall, 77 (42.8%) had mucosal lesions: 38 (21.1%) anorectal, 38 (21.1%) oropharyngeal, 14 (7.8%) urethral, and 2 (1.1%) ocular. PWH with CD4 < 200 c/μL were more frequently diagnosed with bacterial superinfection of mpox lesions (p=0.03) and delayed lesion healing >4 weeks (p=0.03). PWH with VL >200 c/μL had more frequent episodes of colitis and GI bleeding (p=0.05). 26 (14.4%) individuals required hospitalization for mpox or mpox complications [24 (92.3%) PWH and 2 (7.6%) people without HIV (PWoH)] and no deaths were observed. People with mucosal involvement (p=0.003) and PWH with VL >200 c/μL (p< 0.001) were more frequently hospitalized. Hospital length of stay ≥10 days occurred more frequently in PWH with CD4 < 200 c/μL (p=0.008).

Conclusion: Clinical presentation of mpox in Atlanta was similar to other reports; however, our cohort had a higher burden of HIV co-infection. Severe mpox disease was observed at higher frequency in individuals with uncontrolled HIV, indicating an urgent need to better understand the pathogenesis of HIV-mpox interactions and to develop better prevention and treatment options for PWH.

907 CLINICAL OUTCOMES AMONG IN- AND OUTPATIENTS WITH MPOX IN AN URBAN HEALTH SYSTEM

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Background: During the 2022 mpox outbreak, most patients were managed as outpatients, however many required hospitalization. We describe demographics, indications for hospitalization, therapeutic interventions and risk factors associated with hospitalization among patients with mpox in an urban health system.

Methods: Patients in the Johns Hopkins Health System (JHHS) with an mpox diagnosis from July 1 through December 15, 2022 were included. Demographic and clinical data were abstracted. Patients were stratified by location of care (outpatient (OP) vs inpatient (IP)). Characteristics were analyzed using Wilcoxon Rank Sum and chi-square tests. Logistic regression was performed to assess for factors associated with hospitalization, as well as a subset analysis among PLWH to assess the impact of CD4 and HIV-1 RNA.

Results: There were 85 patients identified with mpox during the study. Median age was 36 years, 61% were Black, 11% Latino, 97% assigned male sex at birth, 4% transgender women, 43% Medicaid or uninsured, 54% PLWH. Seventy (82%) were treated OP and 15 were IP (18%). There were no statistically significant differences between OP and IP in age, race, ethnicity, insurance status, HIV risk group, HIV status or obesity (Table 1). Among PLWH, CD4 < 350 was associated with IP (aOR 10.8 95% CI 1.1-108.3). There was a trend for increased IP among those with HIV-1 RNA >200 (aOR 10.0 [0.6-161.4], P=0.1).

The most common indication for hospitalization was pain control (66.7%). Fewer OP received tecovirimat than IP (19% vs. 93%), opiate pain control (5% vs 80%), and antibiotics (21% vs. 80%). Two IPs received vaccinia immune globulin (13%), two received cidofovir (13%) and two received trifluridine eye drops (13%). Among IP, the median LOS was 5 days (1-48). Forty percent of IP received surgical consultation. Two IP (13%) required ICU level care and ultimately died. Both deaths were in PLWH with CD4 < 50.

Conclusion: In this multi-hospital system, a significant proportion of mpox patients required hospitalization. Immunosuppression and HIV-1 viremia was associated with hospitalization for mpox. Achieving viral suppression and mpox immunization should be prioritized among those at risk.

Table 1

	NOT ADMITTED (N=70)	ADMITTED (N=15)	P-value
Age (Median, Range)	35.2 (19.0-65.6)	38.8 (25.3-56.8)	0.205 [1]
Men, Women, Transgender	94.3%, 2.9%, 2.9%	86.7%, 6.7%, 6.7%	0.579 [2]
Black or African American	60.0%	66.7%	0.675 [2]
Hispanic/Latino	11.4%	6.7%	0.576 [2]
MSM	90.7%	86.7%	0.816 [2]
Uninsured	6.2%	13.3%	0.341 [2]
Obesity	11.8%	26.7%	0.137 [2]
Persons Living With HIV (PLWH)	50.0%	66.7%	0.242 [2]
Median CD4 count among PLWH (cells/mm3)	587.5 (196-1417)	132 (4-881)	0.012 [1]
Viral suppression among PLWH (<200 copies/mL)	88.2%	44.4%	<0.01 [2]

1. Wilcoxon Rank Sum Test
2. χ^2 tests

908 HIV CARE AND PREVENTION CHARACTERISTICS AMONG PERSONS WITH MPOX AND HIV, TEXAS 2022

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Background: A public health emergency was declared for the mpox outbreak by the U.S. Department of Health and Human Services on August 4th, 2022. The Texas Department of State Health Services (DSHS) confirmed the first mpox case in Texas on June 7th, 2022. The objective of this analysis was to describe HIV care and prevention characteristics among persons with mpox and HIV infection in Texas.

Methods: The Texas DSHS conducted a match with the Enhanced HIV/AIDS Reporting System (eHARS) database and the state's integrated surveillance system to identify persons with mpox and HIV infection. Time from mpox diagnosis to HIV diagnosis and HIV laboratory data was examined to assess HIV care characteristics among persons with mpox and HIV infection. Mpox diagnosis date was estimated using the earliest date of either 1) rash onset, 2) illness onset, 3) positive laboratory result, or 4) health department notification.

Results: As of November 28th, 2022, there were 2,826 confirmed or probable mpox cases in Texas. 1,415 (50%) of persons with mpox had HIV infection. Of those, 55 (3.9%) were diagnosed with HIV infection after or within 30 days of mpox diagnosis, 86 (6.1%) between 30 days to 1 year, 72 (5.1%) between 1 to 2 years, 228 (16.1%) between 2 to 5 years, 418 (29.5%) between 5 to 10 years, and 556 (39.3%) more than 10 years ago. Of those with HIV laboratory testing in the 12 months prior to mpox diagnosis, 1,193 (84.3%) persons had CD4 count data and 1,067 (75.4%) had HIV viral load data. Among those with CD4 counts, 100 (8.4%) had a CD4 count of less than 200/μL cells, 313 (26.2%) had CD4 counts between 200-499/μL, 780 (65.4%) had CD4 counts greater than 500/μL. For persons with HIV viral loads, 890 (83.4%) were virally suppressed (< 200 copies/mL), 45 (4.2%) had viral loads between 201-1,000 copies/mL, and 132 (12.4%) had viral loads greater than 1,000 copies/mL.

Conclusion: Prevalence of HIV infection among persons with mpox was high, similar to other findings. The majority of persons with mpox and HIV infection were diagnosed with HIV more than 5 years ago and had HIV laboratory data signifying utilization of HIV care services in the past year. The disproportionate impact of mpox on those with HIV infection reinforces the importance of offering HIV screening testing to persons seeking care for mpox and focusing public health efforts on linkage or re-linkage to HIV care services as needed.

909 MPOX OUTBREAK IN PLWHA AND PrEP USERS IN A BRAZILIAN STI CENTER: DIFFERENT CHALLENGES

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Background: Since the beginning of the current MPOX outbreak, reports and case series have highlighted a significant distribution in people living with HIV (PLWHA) and also in pre-exposure prophylaxis (PrEP) users. Despite similar

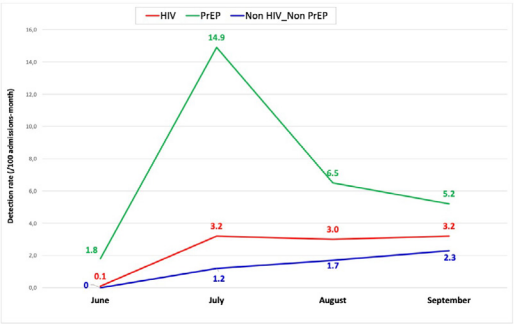
vulnerability behaviors, these populations are distinct from an immunological view. We evaluated the differences in clinical presentation between PLWHA and PrEP users.

Methods: We conducted an observational cross-sectional study among adults with suspected MPox in a public reference institution for the prevention and care of HIV infection and other sexually transmitted infections (STI) between 6/18/2022 and 9/22/2022. The data were obtained from the MPox notification database and supplemented by dispensing systems and electronic records. Multivariate analysis was performed using logistic regression models to compare clinical presentation between PLWHA and PrEP users.

Results: A total of 394 suspected cases were tested for Mpox RT-PCR, of which 304 (78.4%) were positive. The number of incident cases peaked in July/2022 (Figure 1). PCR-positive patients had a mean age of 33 years, 297 were male and MSM (97,7%) , 247 had anogenital lesions (82,3%). 167 (55%) were PLWH, and 97 (32%) were PrEP users, and no one died. In PLWHA, 85,2% were virologically suppressed patients, while 88,7% have CD4 >350 cells/mL. The patients with a positive PCR result, compared to patients with a negative result, were more likely to be in the 25-39 age group (OR 2.8; 95%CI 1.1-7.5), have fever (OR 4.7; 2.3-9.7), MSM/transgender women (OR 17,2;4,5-65,9), adenomegaly (OR 7.2; 3.8-13.7), multiple vesicular lesions (OR 4.2; 2.1-8.5) and have an STI concurrently (OR 3.2; 1.2-8.6). PLWHA, compared to PrEP users, were more likely to have extragenital involvement (26,3% vs 13,3%; p=0,016). The two groups did not exhibit any other significant differences in clinical presentation.

Conclusion: The Mpox outbreak in Brazil curbed in September, possibly as a result of the strong mobilization of the LGBTQIA+ community. The vast majority of our study participants were PLWHA and PrEP users. PLWA in our study presented more frequently with extragenital involvement than PrEP users, possibly due to a weakened immune response of PLWHA to contain the spread to distant areas.In low-incoming countries with limited diagnostic resources, the development of an epidemiological and clinical screening prioritizing testing in MSM, young ,with fever, adenomegaly and genital lesions, could be a strategy to be implemented.

MPOX DETECTION RATES (PER 100 ADMISSIONS-MONTH) FROM JUNE TO SEPTEMBER /2022 PER GROUP, CRT SAO PAULO



910 MPOX IN THE CONTEXT OF POPULATION-LEVEL HIV TREATMENT AND HIV PrEP PROGRAMS IN BC

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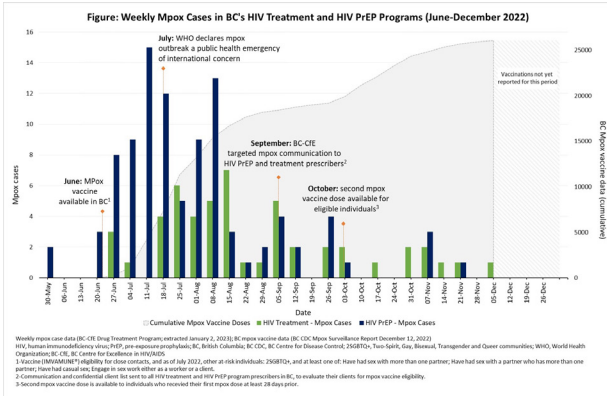
Background: On 23-Jul-2022 the World Health Organization (WHO) declared the global mpox outbreak a public health emergency, characterized by person-to-person contact and disproportionately affecting gay and bisexual men who have sex with men (gbMSM). In British Columbia (BC), 190 mpox cases were reported between June and December 2022. We describe mpox cases in BC's population-level HIV treatment (Tx) and PrEP programs.

Methods: We included adults aged ≥19 years, enrolled in the BC HIV Tx or PrEP programs who had program contact (based on drug dispensing and lab test results) on or after 1-May-2022. Mpox testing results reported between 1-Jun-2022 and 31-Dec-2022 were included. Mpox testing and cases over time, and client demographic and clinical characteristics are described.

Results: Of 16,471 program clients, a total of 148 (0.9%) mpox cases were diagnosed, including 51/8247 (0.6%) HIV Tx clients and 97/8224 (1.2%) PrEP clients. All mpox cases were cis-gender male, 87% were known gbMSM (risk group unreported in 13%), 99% were diagnosed in an outpatient or emergency room setting, and 84% resided in the populous Vancouver Coastal Health Authority. The median age of mpox cases was 42 years (Q1-Q3, 35-51) in HIV Tx and 36 years (Q1-Q3, 31-42) in PrEP (p< 0.001). Of HIV Tx mpox cases, the median CD4 count was 665 cells/μΛ (Q1-Q3, 450-920), two had CD4 count < 200 cells/mL, and based on dispensing records, 50/51 were on antiretroviral therapy at the time of mpox diagnosis (92% on INSTI-based regimens). Three clients were diagnosed with mpox within 6 days of a new HIV diagnosis. Overall, mpox testing was performed in 533 clients (166 HIV Tx and 367 PrEP), with testing frequency and % specimen positivity highest between July and September 2022, and 81% of mpox cases diagnosed during this period. A subsequent decline in infections has been observed thereafter (See Figure).

Conclusion: A high proportion of mpox cases in BC were prescribed HIV PrEP, consistent with overlapping risk behaviour and eligibility criteria for HIV PrEP with mpox transmission and vaccine eligibility. A smaller proportion of the more heterogeneous HIV Tx clients was similarly affected by mpox. The decline in mpox cases suggests a potential impact of mpox vaccine uptake and/or altered client behaviour. Cases of concurrent diagnosis of HIV and mpox emphasize the importance of screening for sexually transmitted infections, including HIV, in persons being evaluated for mpox.

Figure: Weekly Mpox Cases in BC's HIV Treatment and HIV PrEP Programs (June-December 2022)



911 MPOX IN AMSTERDAM: CROSS-SECTIONAL STUDY AMONG MSM AT THE CENTRE FOR SEXUAL HEALTH

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Background: In May, 2022 the first cases of mpox (Monkeypox) infection were reported in multiple European countries, predominantly among men having sex with men (MSM). Overlap in symptoms of mpox and other sexually transmitted diseases (STD) made triage for mpox testing challenging. With this study we aimed to identify characteristics of infection with mpox among MSM to further strengthen case definitions.

Methods: From 20 May 2022 to 15 September 2022 we tested MSM attending the Centre for Sexual Health in Amsterdam, the Netherlands for mpox (monkeypox) if they met the case definition, using an in-house developed and validated PCR using primers targeting the F3L and G2R G mpox specific genes. We compared socio-demographic and clinical characteristics, sexual behaviour, and STD diagnoses of MSM who tested positive for mpox, MSM suspected for mpox who tested negative and mpox unsuspected MSM visiting the Center for Sexual Health. In addition, in mpox positive MSM we compared Cycle threshold (Ct) values of the DNA positive mpox samples as a proxy for viral load by body location where the samples were obtained from.

Results: Of the 374 MSM tested, 135 (36%) tested positive for mpox. Comparing the mpox positive, mpox negative (n=239) and not tested MSM (n=6,932), the mpox positive MSM were older (median age respectively 36, 34, and 34 years, p=0.019) and more often lived with HIV (30% versus 16% and 7%, p< 0.001). Furthermore, mpox positive MSM more often reported receptive anal sex without a condom, reported more recent sex partners, and were more often diagnosed with bacterial STD (all p< 0.001), and more often engaged in sexualised drug use (p=0.01). PrEP use was comparable. Systemic symptoms and anogenital lesions were associated with mpox infection. For mpox positive

MSM anal (p=0.009) and skin lesion (p=0.006) samples showed significantly lower median mpox Ct values when compared to throat sample Ct values.

Conclusion: By December 2022, the number of new mpox positive visitors has dramatically decreased globally. Yet, according to the most likely scenarios, it is considered likely that mpox is still circulating. Centers for Sexual Health will continue to play an important role in the identification and management of mpox patients. Awareness creation and education of MSM at high risk for mpox infection, as well as offering prophylactic vaccination, will help to prevent infection and reduce transmission.

Table: Socio-demographic and sexual behaviour characteristics and STD of MSM diagnosed with mpox (monkeypox), those tested for mpox virus and negative, and those not tested for mpox, Center for Sexual Health, Amsterdam, the Netherlands, 20 May 2022 – 15 September 2022

	Mpox positive (n=135)		Mpox negative (n=239)		Not tested (6,932)		Overall
	n[1]	%[1]	n[1]	%[1]	n[1]	%[1]	p-value
Median age, years [IQR]	36	[31-44]	34	[27-42]	34	[28-44]	0.019
Number of sex partners[2], median [IQR]	10	[4-20]	8	[4-15]	6	[3-12]	<0.001
Receptive anal sex without a condom[3]	110	99%	171	92%	4,335	87%	<0.001
Sexualised drug use[3]	93	69%	139	58%	3,884	56%	0.010
Living with HIV	41	30%	39	16%	452	7%	<0.001
HIV negative, no PrEP or PrEP unknown	26	19%	75	31%	2,905	42%	
HIV negative and using PrEP[4]	68	50%	125	52%	3,575	52%	
Any bacterial STI at visit	43	32%	81	34%	1,239	18%	<0.001
Chlamydia at visit	22	16%	34	14%	643	9%	0.001
Gonorrhoea at visit	31	23%	49	21%	743	11%	<0.001
Syphilis at visit	0	0%	7	3%	6	0.1%	<0.001

1. Unless stated otherwise; 2.In the six months before current visit; 3. % of individuals reporting at least once in the six months before current visit; 4. PrEP use in the six months before current visit

912 CHARACTERISTICS OF PATIENTS HOSPITALIZED WITH MPOX DURING THE 2022 US OUTBREAK

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Background: During previous mpox outbreaks, severe manifestations of disease and poor outcomes have been reported among people with HIV (PWH), particularly those with AIDS. During the 2022 outbreak, Centers for Disease Control and Prevention (CDC) staff provided clinical consultations for providers caring for patients with mpox and seeking to discuss clinical management or to access therapeutics under the emergency investigative new drug protocol. In this analysis, we sought to characterize the manifestations, outcomes, and HIV care-related considerations of mpox in hospitalized patients to inform care and guide ongoing outbreak response efforts.

Methods: This descriptive analysis assessed characteristics of all hospitalized patients aged >18 years with confirmed mpox infection for whom CDC was consulted between August 10-November 22, 2022. CDC obtained data on patient demographics, clinical course, and outcomes during consultation with health departments or providers.

Results: Of 103 patients hospitalized with mpox infection, 100 (97%) were male, and the median age was 34.5 years (range = 20–61 years). Most patients were non-Hispanic Black (60%), and 22 (21%) were experiencing homelessness. Ninety (87%) had HIV infection; among these patients, 49 (58%) of 84 with a known CD4 count had < 50 CD4 cells/mm^3. Of patients with HIV infection, 14 (16%) were receiving antiretroviral therapy (ART) before mpox diagnosis. Manifestations included dermatologic involvement (96, 93%), severe mucosal lesions (76, 74%), and involvement of the lungs (21, 20%), eyes (23, 22%), gastrointestinal system (5, 5%), and brain or spinal cord (four, 7%). Twenty-three (22%) patients received ICU-level care and 20 (19%) died.

Conclusion: Mpox infection in the current U.S. outbreak has been associated with severe morbidity and mortality, particularly among persons with AIDS. The disproportionate burden of severe mpox among persons of color and persons experiencing homelessness echoes inequities seen in the continuum of care for PWH. Providers should test sexually active patients with suspected mpox infection for HIV and other sexually-transmitted infections as indicated at the time of mpox testing. Engaging all PWH in care remains a critical public health priority, with additional efforts in HIV outreach and care retention needed to reduce the population at risk for severe mpox.

Disseminated lesions on the back and hands of a patient with severe monkeypox. Note: Patient has consented to the publication of these photographs. (Photos credit: Alexandra Dretler)

913 EQUITY FOCUSED EVALUATION OF MPOX CARE METRICS IN KING COUNTY, WA

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Background: The 2022 mpox outbreak required rapid scale-up of testing and treatment, yet limited resources constrained access to care and may have contributed to disparities. We analyzed the characteristics of persons with mpox and tecovirimat (TPOXX) provision in King County, WA from May to October 2022.

Methods: Public health staff collected demographic, testing, and treatment data by interviewing patients, with mpox, reviewing laboratory and case report forms, and contacting medical providers. We analyzed patient demographics and time to testing and treatment (care metrics). We used chi-square testing (p< 0.05) to assess differences in TPOXX receipt by race/ethnicity or diagnosing site. We evaluated differences in care metrics over time using linear regression, and by race/ethnicity using Kruskal-Wallis testing.

Results: During 5/22-10/26/2022, 465 patients had laboratory-confirmed mpox. The median age was 37 years [interquartile range (IQR) 31-45 years. 205 (44%) identified as non-Hispanic White, 118 (25%) as Hispanic/Latinx, 45 (10%) as non-Hispanic Black, 26 (6%) as Asian, 16 (3%) as American Indian/Alaska Native; 55(12%) were other or unknown. 346 (74%) lived in Seattle. Of 420 patients with clinic site data, 159 (38%) were at the county sexual health clinic (SHC); 125 (30%) were at university-affiliated medical centers. Of 404 patients with treatment data, 311 (77%) started TPOXX. The proportion of patients treated within race-ethnicity groups was 73% (n=149) non-Hispanic White persons, 69% (n=82) Hispanic/Latinx, 69% (n=27) Black, 71% (n=17) Asian, and 85% (n=11) American Indian/Alaska Native persons (p=0.6). Of patients with data on both TPOXX status and clinic site, 126 of 159 (79%) at SHC received POXX, 109 of 120 (87%) at university-affiliated medical centers, and 62 (55%) of 113 at other sites combined (p< 0.001). Of 426 patients with clinical data, the median time from symptom onset to testing was 4 (IQR 2-7) days. Median time from testing to treatment was 2 (IQR 0-3) days. Both metrics decreased over time [p=0.0004 and p=0.0003, respectively (Table 1)] and did not vary by race/ethnicity (p=0.6 and p=0.5, respectively).

Conclusion: Public Health and healthcare organizations rapidly scaled-up mpox testing and treatment over the course of the 5-month epidemic allowing for most patients to receive TPOXX without significant racial disparities. Testing and treatment was largely dependent on a single sexual health clinic and university-affiliated sites.

Table 1: Median time to diagnosis and treatment by month in response, with significance by linear regression testing, Seattle—King County, May—October 2022

Table 1: Median time to diagnosis and treatment by month in response, with significance by linear regression testing, Seattle—King County, May—October 2022

Month in response	May	June	July	August	September	October	P-value, by linear regression	All
Time to diagnosis Median(IQR) (n=426)	6 days (6-6)	6 days (4-8.5)	5 days (3-7)	3 days (1-7)	4 days (2-6)	2 days (0.25-4.5)	0.0004	4 days (2-7)
Time to treatment Median(IQR) (n=404)	7 days (7-7)	4.5 days (2.25-6)	2 days (1-4)	1 days (0-2.5)	1 days (0-2)	0 days (0-0)	0.0003	2 days (0-3)

914 DEMOGRAPHIC AND CLINICAL CHARACTERISTICS OF MPOX WITHIN A NEW YORK CITY HEALTH SYSTEM

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Background: Since the global mpox outbreak began in Spring 2022, it has disproportionately affected gay and bisexual individuals. Mpox can cause serious illness, including painful mucosal lesions, superinfections, and ocular disease. Its presentation in hospitalized patients and those with HIV/AIDS and other immunocompromising conditions is not yet well described, nor is the efficacy of therapies such as tecovirimat. Here we describe the clinical characteristics and course of individuals diagnosed with mpox in a large New York City health system who were prescribed tecovirimat.

Methods: This retrospective study described clinical features of persons with mpox and the clinical outcomes amongst those who received tecovirimat. Data was obtained via chart review of patients prescribed tecovirimat in the Mount Sinai Health System in NYC during 7/1/2022 - 10/1/2022.

Results: 129 people diagnosed with mpox were prescribed tecovirimat between 7/1/2022 and 10/1/22. The median patient age was 37 years, 95% were men, and 95% identified as gay or bisexual. 25% of the cohort identified as Hispanic/Latinx, 48% White, 35% Black, 9% Asian, and 12% not reported/other. 62% had HIV, 49% of these with undetectable HIV viral loads and 11% with a CD4 cell count of < 200 cells/mL. Nearly all (96%) presented with rash, while 71% had anogenital lesions, 22% with oral mucosal lesions, and 4% had ocular involvement. Presenting symptoms included non-specific pain (76%), painful defecation (55%), and odynophagia (35%). Common systemic features included fevers/chills (49%), lymphadenopathy (35%), fatigue (26%), and myalgias (26%). Of those receiving tecovirimat with completed follow-up (N=85; 66%), 97% had recovery of lesions by time of post-treatment assessment (median of 8 days after finishing therapy). The median time for complete lesion resolution on tecovirimat was 10 days. Tecovirimat was well tolerated; there were no severe adverse effects attributable to the therapy. Hospitalized patients (n=16; 12% of total) were primarily admitted for superimposed bacterial infections (62%), with a median hospital stay of 4 days. 69% (n=11) of hospitalized patients had HIV; of these, 5 patients were severely immunocompromised, either due to AIDS or an additional immunocompromising condition.

Conclusion: In a diverse cohort of mpox patients, treatment with tecovirimat was well tolerated and associated with minimal adverse effects. The majority of hospitalizations occurred in patients with underlying immunocompromising conditions.

915 MPOX INFECTION IN WOMEN: A CASE SERIES FROM BRAZIL

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The INI-Fiocruz Mpox Study Group

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Background: Brazil ranks second in number of mpox cases globally, with 10,500 cases notified by December 27, 2022. Most of the current outbreak's cases are reported among gay, bisexual, and other cisgender men who have sex with men (MSM). Data from endemic countries show an increased risk of severe mpox among children, immunosuppressed individuals and pregnant women. This study aims to describe epidemiological and clinical aspects of mpox in women (cisgender and transgender) compared to men in Rio de Janeiro, Brazil.

Methods: We accessed an unidentified database with all confirmed mpox cases notified to the Rio de Janeiro State Health Department from June 12 to December 15, 2022. Gender identification of the female spectrum were included in the women category (cisgender or transgender), and gender identification of the male spectrum (cisgender or transgender) were included in the men category. Chi-squared test, Fisher's exact test and Moods median test were used for comparisons. We also provided behavioral and clinical characteristics of transgender women and non-binary individuals separately.

Results: A total of 1,306 confirmed mpox cases were reported, 1198 (91.7%) among men, 108 (8.3%) women (91.7% cisgender and 8.3% transgender) and 10 (0.8%) non-binary. Compared to men, women were more frequently older (40+ years: 34.3% vs. 25.1%; p< 0.001), reported more frequent non-sexual contact with a potential mpox case (21.4% vs. 10.0%; p=0.004), reported fewer sexual partnerships (10.9 vs. 54.7%; p< 0.001) and less physical contact with a partner with unknown mpox status (20.2% vs. 55.8%; p< 0.001) (Table). HIV prevalence was lower among women (2.2% vs. 46.3%; p< 0.001), with all cases among transgender women. Genital lesions were less frequent among women (31.8% vs. 57.9%; p< 0.001). Fewer women presented systemic mpox signs and symptoms (38.0% vs. 50.2%; p=0.015), including fever (43.5% vs. 58.7%; p=0.002) and adenomegaly (16.7% vs. 43.2%; p< 0.001).

Conclusion: We describe different epidemiological, behavior and clinical profiles of mpox among women and men. The milder mpox clinical presentation in women can be related to their lower HIV prevalence compared to men. Health services must provide a comprehensive clinical and epidemiological assessment that accounts for gender diversity to address the knowledge gaps regarding the impact of mpox on both cisgender and transgender women.

Table 1. Sociodemographic, behavioral and clinical characteristics of the mpox cases, according to gender (N=1,306), Rio de Janeiro State, Brazil.

	Women cases[1] (n = 108) n (%)	Men cases[2] (n = 1,198) n (%)	Overall (N = 1,306) n (%)	p-value	TGW (n=9)	Non-binary (n=10)
Sexual Partnership				0.025[a]		
With men	47 (90.3)	469 (73.5)	516 (74.8)		5/5	4/7
With men and women	3 (5.8)	79 (12.4)	82 (11.9)		0/5	3/7
With women	2 (3.9)	90 (14.1)	92 (13.3)		0/5	0/7
Cutaneous rash [b]				0.7[c]		
Localized	29 (39.7)	313 (37.5)	342 (37.7)		1/7	1/8
Disseminated	44 (60.3)	521 (62.5)	565 (62.3)		6/7	7/8
HIV Infection				<0.001[a]		
Yes	2 (2.2)	508 (46.3)	510 (42.9)		6/9	3/10
No	89 (97.8)	589 (53.7)	678 (57.1)		3/9	7/10
Hospitalization				0.3[c]		
Yes	8 (7.8)	61 (5.2)	69 (5.4)		0/9	0/10
Death						
Yes	0 (0)	5 (0.4)	5 (0.4)		0 (0)	0 (0)

[a] Fisher's exact test, [b] previous 21 days, [c] Chi-squared test.

[1] Cisgender or transgender women [TGW] and travesti. [2] Cisgender or transgender men and cases that self-identified as non-binary and also reported male sex assigned at birth

916 SARS-CoV-2 SEROPREVALENCE AMONG UGANDAN BLOOD DONORS: 2019-2022

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Background: COVID-19 in Africa was less severe with fewer reported cases, hospitalizations and deaths compared to other continents. However, the lack of adequate surveillance systems in Africa makes estimating the burden of infection challenging. Serosurveillance can aid in determining the frequency of infection within this population. This study is aimed to estimate SARS-CoV-2 seroprevalence, describe the SARS-CoV-2 antibody (Ab) levels, and examine associations of seroreactivity among Ugandan blood donors.

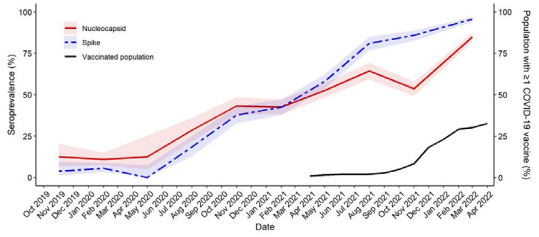
Methods: Samples were obtained from the Mirasol Evaluation of Reduction in Infections Trial (MERIT), a randomized, double blind, controlled clinical trial evaluating transfusion transmitted infections. MERIT blood donor samples (n=3,517) were collected from Kampala, Uganda between October 2019 to April 2022. Additional blood donor samples (n=1,876) were collected from around the country between November-December 2021. Samples were tested for Ab to SARS-CoV-2 nucleocapsid (N) and spike (S) using an electrochemiluminescence immunoassay assay (Meso Scale Diagnostics, Gaithersburg, MD) per manufacturer's protocol. Samples seroreactive to both N and S Ab were considered Ab positive to SARS-CoV-2. Seroprevalence among MERIT donors were estimated within each quarter. Factors associated with seroreactivity from November-December 2021 were assessed by chi-square test.

Results: SARS-CoV-2 seroprevalence increased from < 2.0% in October 2019-June 2020 to 82.5% in January-April 2022. Three distinct peaks in seroreactivity were seen in October-November 2020, July-August 2021, and January-April 2022 (see Figure). Among seroreactive donors, median N Ab levels increased

9-fold and median S Ab 19-fold over the study period. In November-December 2021, SARS-CoV-2 seroprevalence was higher among donors from Kampala (58.8%) compared to more rural regions of Hoima (47.7%), Jinja (47.9%), and Masaka (54.4%; p=0.007); S seroprevalence was lower among HIV+ donors (58.8% vs. 84.9%; p=0.009).

Conclusion: Blood donors in Uganda showed high prevalence of Ab to SARS-CoV-2 by March of 2022, indicating that the infection levels were similar to many other regions of the globe. Higher seroprevalence was observed in the capital compared to more rural areas in Uganda. Further, increasingly high antibody levels among seropositive donors may indicate repeat infections. The lower COVID-19 morbidity and mortality was not due to a lack of exposure of the virus, but other factors yet to be determined.

SARS-CoV-2 seroprevalence among Ugandan blood donors and COVID-19 vaccination in Uganda from 2019 to 2022



917 COVID-19 SEROPREVALENCE IN VACCINE-NAIVE POPULATIONS: DRC, GUINEA, LIBERIA, AND MALI

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Background: As part of an international multi-country study on COVID-19 vaccine immunogenicity (InVITE, NCT05096091), we sought to characterize baseline anti-Nucleocapsid (N) and anti-Spike (S) seropositivity by country and by self-report of prior positive SARS-CoV-2 test result.

Methods: 3063 vaccine-naive individuals from the InVITE study cohort, who received a COVID-19 vaccine as part of their country's national immunization programs at participating sites in Democratic Republic of Congo (DRC), Guinea, Liberia and Mali, were enrolled between August 2021 and February 2022. Demographic and baseline characteristics were collected at study enrollment. Blood was collected at baseline prior to initiation of the vaccine regimen. SARS-CoV-2 anti-S antibody and anti-N antibody levels were measured using Quanterix anti-S IgG semi-quantitative antibody and BioRad Platelia SARS-CoV-2 anti-N Total Ab assays, respectively. Demographic characteristics were assessed for association with positive anti-S and anti-N serology.

Results: Baseline demographics and serology results by country and overall are shown in the table.

Conclusion: Despite low numbers of prior self-reported positive SARS-CoV-2 test, the serology results in this cohort indicate prior infection in a significant proportion of the InVITE study participants prior to receipt of a first dose of COVID-19 vaccination. These results suggest widespread previous SARS-CoV-2 infections that were unrecognized possibly due to mild-no symptoms, poor access to/availability of testing and/or limited monitoring through surveillance.

Baseline Demographics and Serology Results

	Overall	DRC	Guinea	Liberia	Mali
N	3063	1099	500	664	800
Mean Age (sd)	31.6 (12.6)	36.7 (14.2)	28.1 (10.5)	30.8 (11.3)	31.4 (12.9)
% Female (%)	50.0	44.8	57.8	46.8	55.0
% BMI >= 30 kg/m^2	12.5	13.0	8.4	12.0	14.8
% Pregnant (%)	0.5	0.0	1.2	0.8	0.4
% HIV (%)	0.6	0.1	0.4	1.5	0.6
% Hypertension	5.9	6.2	4.8	3.2	8.4
% Reported positive SARS-CoV-2 test before enrollment	0.8	1.7	0.2	0.3	0.1
Anti-N positive n (%)*	1246/1981 (62.9%)	596/913 (65.3%)	6/10 (60.0%)	206/398 (51.8%)	438/660 (66.4%)
Anti-S positive* n (%)*	1602/1972 (81.2%)	730/913 (80.0%)	10/10 (100.0%)	320/398 (80.4%)	542/651 (83.3%)
Both Anti-N and Anti-S positive n (%)*	1184/1972 (60.0%)	567/913 (62.1%)	6/10 (60.0%)	199/398 (50.0%)	412/651 (63.3%)

*Performed to date

918 SARS-CoV-2 SEROPREVALENCE AND RISKS FACTORS IN AFRICAN WLHIV ON ART AND THEIR INFANTS

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Background: SARS-CoV-2 seroprevalence data in women living with HIV (WLHIV), their infants and associated risk factors in this subpopulation remain limited. We retrospectively measured SARS-CoV-2 seroprevalence from 09/2019-12/2021 among WLHIV and their children in the PROMOTE observational cohort in Uganda, Malawi, and Zimbabwe prior to widespread SARS-CoV-2 vaccination in those countries.

Methods: Sociodemographic, clinical data and blood were collected q6 months. Plasma stored during 3 waves of the COVID-19 pandemic in East/Southern Africa were tested for SARS-CoV-2 specific IgG antibodies (Ab) using serological assays that detect adaptive immune responses to SARS-CoV-2 spike protein. Modified-Poisson regression models were used to calculate prevalence rate ratios (PRR) and 95% confidence intervals (CI) to identify sociodemographic and clinical risk factors.

Results: Plasma samples from 979 PROMOTE mothers and 1332 children were analysed. We found no significant differences in baseline characteristics between participants testing positive (+) and negative (-) for SARS-CoV-2 Ab. Overall maternal SARS-CoV-2 seroprevalence was **57.6%** (95%CI: 54.5-60.7) and **39.3%** (95%CI: 36.7-41.9) for infants. The earliest + result was detected from a sample collected on 09/2019, in Malawi. Factors significantly associated with SARS-CoV-2 seropositivity were country of origin (reference Uganda, aPRR 1.45, 95%CI: 1.24-1.69) and non-breastfeeding mother (aPRR=1.22, 95%CI: 1.02-1.48). Children above 5 years had a 10% increased risk of SARS-CoV-2 seropositivity (aPRR=1.10, 95%CI: 0.90-1.34) when compared to younger children. We found no statistically significant association with sanitation, household density, distance to clinic, maternal employment, ART regimen or viral load. Mother/infant SARS-CoV-2 serostatuses were discordant in 373/865 (43.1%) families tested: mothers+/children- in 51.2%; mothers-/children+ in 12%; child+/sibling+ concordance was 21.4%.

Conclusion: These SARS-CoV-2 seroprevalence data indicate that by late 2021, about half of mothers and about a third of children in a cohort of HIV-affected families in eastern/southern Africa had been infected with SARS-CoV-2. Breastfeeding was protective for mothers, likely because of the need to stay home for young children. Discordant results between children within same families underscores the need to further understand transmission dynamics within households.

919 SARS-CoV-2 INFECTION AMONG PERSONS WHO INJECT DRUGS AND THEIR PARTNERS IN KENYA

Khai Hoan Tram[1], Bhavna H. Chohan[1], Cassia Wagner[2], Shradha Doshi[1], Hanley Kingston[1], Brandon L. Guthrie[1], Betsy Sambai[3], Loice W. Mbogo[3], Aliza Monroe-Wise[1], William Sinkele[4], Kibet Shikuku[5], Jared Mecha[5], David Bukusi[6], Carey Farquhar[1], Joshua Herbeck[1]
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Background: Despite increased social vulnerability and barriers to care, there has been a paucity of data on SARS-CoV-2 incidence among key populations in sub-Saharan Africa. We seek to characterize active infections and define transmission dynamics of SARS-CoV-2 among people who inject drugs (PWID) and their sexual and injecting partners from Nairobi and the coastal region in Kenya.

Methods: This was a nested cross-sectional study of SARS-CoV-2 infection from April to July 2021 within a cohort study of assisted partner services for PWID in Kenya. A total of 1000 PWID and their partners (500 living with and 500 living without HIV) were recruited for SARS-CoV-2 antibody testing, of whom 440 were randomly selected to provide self-collected nasal swabs for real-time

PCR testing. Whole genome sequencing (WGS) was completed on a limited subset of samples (N=23) with cycle threshold values £ 32.0. Phylogenetic tree construction and analysis was performed using the Nextstrain pipeline and compared with publicly available SARS-CoV-2 sequences from GenBank.

Results: A total of 438 (99.5%) participants provided samples for SARS-CoV-2 PCR testing. Median age was 37 (IQR 32-42); 128 (29.2%) were female; and 222 (50.7%) were living with HIV.

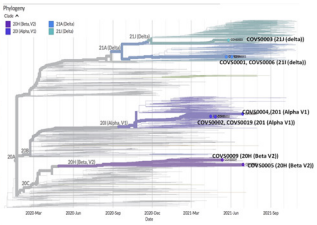
The overall prevalence of SARS-CoV-2 infection identified by RT-PCR was 86 (19.6%). In univariate analyses, there was no increased relative risk of SARS-CoV-2 infection related to positive HIV status, frequenting an injection den, methadone treatment, unstable housing, report of any high-risk exposure, or having a sexual or injecting partner diagnosed with COVID-19 or who died from COVID-19 or flu-like illness.

Eight samples were successfully sequenced via WGS and classified as WHO variants of concern: 3 Delta, 3 Alpha, and 2 Beta. Seven were classified into clades predominantly circulating in Kenya during 2021. Notably, two sequences were identical and matched identically to another Kenyan sequence, which is consistent with, though not indictive of, a transmission linkage.

Conclusion: Overall, the risk of SARS-CoV-2 infection in this population of PWID and their partners was not significantly associated with risk factors related to injection drug use. At a genomic level, the SARS-CoV-2 strains in this study were consistent with contemporary Kenyan lineages circulating during the time and not unique to PWID. Prevention efforts, therefore, must also focus on marginalized groups for control given the substantial amount of mixing that likely occurs between populations.

Predictors of active SARS-CoV-2 infection among PWID and their partners in Kenya & representative phylogenetic tree using Nextstrain

	Positive PCR (N = 86)	Negative PCR (N = 352)	Relative risk	p-value
Living with HIV (at enrollment)	49 (57.0)	173 (49.2)	1.29 (0.88-1.89)	0.196
Virally suppressed (n=148)	31 (70.5)	117 (72.2)	0.93 (0.53-1.66)	0.817
Currently on ART (n=214)	47 (95.9)	67 (97.1)	0.77 (0.23-2.55)	0.668
Frequented an injection den in the past week	76 (88.4)	289 (82.1)	1.52 (0.83-2.80)	0.179
Currently taking methadone	46 (53.5)	157 (44.6)	1.33 (0.91-1.95)	0.140
Reported stable housing	76 (88.4)	315 (89.5)	0.91 (0.51-1.64)	0.763
High-risk exposure in past 2 weeks?	5 (5.8)	15 (4.3)	1.29 (0.59-2.83)	0.525
Any sexual or injecting partners diagnosed with COVID-19?	6 (7.0)	12 (3.4)	1.75 (0.88-3.47)	0.108
Any sexual or injecting partners died from COVID-19 or flu-like illness since March 2020?	8 (9.3)	18 (5.1)	1.63 (0.88-2.99)	0.119
Any housing partners diagnosed with COVID-19?	3 (3.5)	8 (2.3)	1.40 (0.52-3.76)	0.501
Any housing partners died from COVID-19 or flu-like illness since March 2020?	1 (1.2)	12 (3.4)	0.38 (0.06-2.56)	0.323



Left: Predictors of positive SARS-CoV-2 PCR among PWID and their sexual and injecting partners in Kenya. **Right:** Phylogenetic tree built with Nextstrain. Tree available online at https://github.com/blab/ncov-kenya

920 SARS-CoV-2 SEROPREVALENCE AMONG PEOPLE WHO INJECT DRUGS IN BALTIMORE

Eshan U. Patel[1], Shruti H. Mehta[1], Owen Baker[2], Becky Genberg[1], Catherine Schluth[1], Jacquie Astemborski[1], Reinaldo Fernandez[2], Thomas C. Quinn[3], Greg Kirk[1], Oliver Laeyendecker[3]

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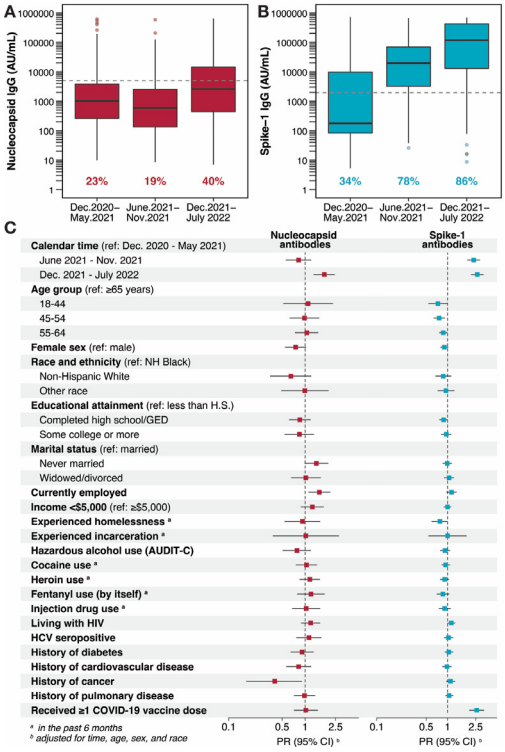
Background: People who inject drugs (PWID) may be at a greater risk of SARS-CoV-2 infection and COVID-19 due to socio-structural inequities, high-risk behaviors and comorbidities; however, PWID have been underrepresented in case-based surveillance due to lower access to testing. We characterize temporal trends and correlates of SARS-CoV-2 seroprevalence among a community-based sample of current and former PWID.

Methods: A cross-sectional study was conducted among participants in the AIDS Linked to the IntraVenous Experience (ALIVE) study—a community-based cohort of adults with a history of injection drug use in Baltimore, Maryland. Participants' first serum sample collected at routine study visits between December 2020 and July 2022 was assayed for antibodies to the nucleocapsid (N) (past infection) and spike-1 (S) (past infection and/or vaccination) proteins using the MSD V-Plex Panel 2 IgG SARS-CoV-2 assay. For each correlate, we estimated adjusted prevalence ratios (PR) via separate Poisson regression models adjusted for calendar time, age, sex and race.

Results: Of 561 participants, the median age was 59 years (range=28-77), 35% were female, 84% were Black, 36% were living with HIV (97% on ART), and 55% had received ≥1 COVID-19 vaccine dose. Overall, anti-N and anti-S prevalence was 26% and 63%, respectively. Prevalence of anti-N increased from 23% to 40% between December 2020-May 2021 and December 2021-July 2022, with greater increases in the prevalence of anti-S from 34% to 86% over the same period (Figure). Being employed (PR=1.53 [95%CI=1.11-2.11]) and never being married (PR=1.40 [0.99-1.99]) were associated with a higher prevalence of anti-N, while female sex (PR=0.75 [0.55-1.02]) and a history of cancer (PR=0.40 [0.17-0.90]) were associated with a lower prevalence of anti-N. Younger age, female sex (PR=0.90 [0.80-1.02]), and homelessness (PR=0.78 [0.60-0.99]) were associated with a lower prevalence of anti-S. Although HIV infection was not associated with anti-N, it was associated with a higher prevalence of anti-S (PR=1.13 [1.02-1.27]). Substance use was not associated with anti-N or anti-S.

Conclusion: Anti-N and anti-S levels increased over time, suggesting cumulative increases in SARS-CoV-2 incidence of infection and vaccination among PWID; however, disparities in seroprevalence remain. Younger and female PWID and those experiencing homelessness were less likely to be anti-S positive, suggesting programs should aim to improve vaccination coverage in such vulnerable populations.

Temporal trends and correlates of SARS-CoV-2 antibodies among people who inject drugs



921 QUANTIFYING POPULATION IMMUNITY TO COVID-19 IN WASHINGTON STATE AND OREGON

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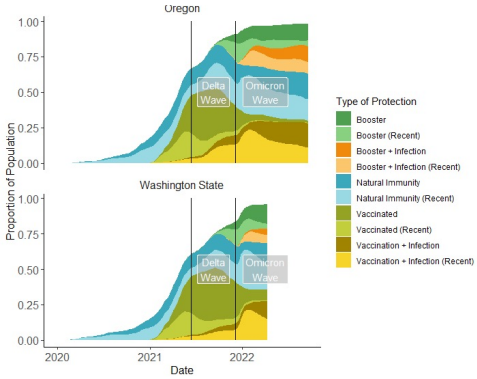
Background: Since early 2020, the novel SARS-CoV-2 virus has spread rapidly throughout the globe. Subsequently many individuals have developed some form of immunity due to either a prior infection, one or more vaccinations, or a combination of the two. Using local epidemic data and mathematical modeling, we enumerate the various immune populations in Washington State and Oregon and quantify the level of protection against infection and hospitalization.

Methods: We developed a compartmental model of ordinary differential equations, which stratifies the population by age (0-17 years, 18-49 years, 50-64 years, and 65+ years), region, type of immunity (naïve, infection-derived, vaccine-derived, booster-derived, hybrid immunity, etc), and recency of immune conferring event (recent and waned). To track the number of individuals in each category we combine 1) literature-based estimates of susceptibility to infection and severe disease by age, immune status, and variant, 2) calibration to the number of severe infections (hospitalizations and deaths) and number of vaccinations and 3) validation with serological surveys of the population.

Results: We estimate that by mid-April 2022 more than 95% of the populations of both Washington and Oregon had some immunity against COVID-19

infection and hospitalization. Younger age groups tended to have much higher rates of natural or hybrid immunity with 96% of 0–17-year-olds and 83% of 18–49-year-olds protected due to past infections. Overall, the population-level immunity against the Omicron variant reduced risk of infection by 59% (95% Credible Interval 54% – 62%) and risk of hospitalization by 79% (95% CI 77% - 81%) in Washington and 62% (95% CI 57% -66%) and 83% (95% CI 82% – 85%), respectively, in Oregon. There was similar population-level protection against Delta at the start of the Omicron wave in early December 2021, which reduced risk of infection by 60% (95% CI 56% - 63%) and risk of hospitalization 79% (95% CI 78% - 80%) in Washington and 66% (95%CI 63% - 70%) and 82% (81% – 83%), respectively, in Oregon.

Conclusion: Very large waves of new infections throughout 2021 and early 2022, in addition to high levels of vaccination and boosting among the older age groups in Washington and Oregon have greatly reduced population susceptibility to currently circulating strains. However even very high population immunity has allowed for emergence of novel variants that escape existing immunity, highlighting the need for continued develop of new variant-specific boosters.



922 WITHDRAWN

923 WITHDRAWN

924 RETROSPECTIVE ASSESSMENT OF THE ACCURACY OF MPOX CASE PROJECTIONS IN NEW YORK CITY

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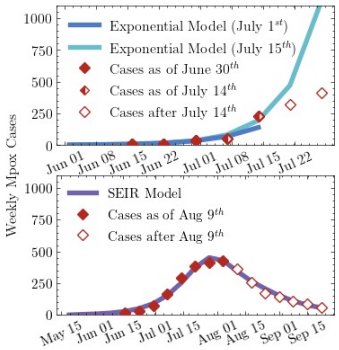
Background: In mid-2022, New York City (NYC) became the epicenter of the US mpox epidemic. Health authorities were in need of forecasts to anticipate the timing and magnitude of the outbreak. We provided mathematical model-based projections with methodologies that evolved alongside the epidemic. Here, we retrospectively evaluate our mpox case projections and reflect on potential reasons for accuracies and inaccuracies.

Methods: Early in the outbreak (July 1 – 15, 2022), when the size of the at-risk population was unknown, we performed short-term (2-week) forecasting using exponential regression. Once epidemic growth was no longer exponential (July 15 – Aug. 9), we consulted with the NYC Department of Health and Mental Hygiene regarding populations most-at-risk of mpox based on available epidemiological data. Modelers and epidemiologists collaboratively developed an estimate of 70,180 people at risk, informed by estimates of LGBTQ adults with male sex at birth who had 2+ partners in the last 3 months. We combined this with NYC case count data, NYC vaccination data, and global mpox natural history data to develop a Susceptible-Exposed-Infected-Recovered (SEIR) model, taking into account immunity accrued through vaccination and prior exposure, for longer-term forecasting.

Results: Initial exponential forecasts of the NYC mpox outbreak were only accurate for very short-term predictions (< 2 weeks) (Figure, top panel). Forecasts were more accurate after 1 week (mean absolute error: 83.0 cases/wk) than after 2 weeks (mean absolute error: 351.4 cases/wk). In contrast, the SEIR model accurately predicted the decline in cases through the end of Sept. 2022, when cases fell to < 70/wk. Over the period from Aug. 10 to Sept. 24 2022, the mean absolute error of the SEIR-based projection was 8.2 cases per week (Figure, bottom panel).

Conclusion: Model-based NYC mpox projections provided only short-term accuracy in the early epidemic, but long-term accuracy once the epidemic exited exponential growth and an SEIR model was developed. Cumulative cases and vaccinations when exiting exponential growth, and the epidemiology of those most-at-risk, provided evidence for the likely size of the most-at-risk population – a crucial input for an accurate SEIR model. The ability of the SEIR model to accurately forecast mpox cases was in part attributable to lack of vaccine or immune escape by mpox, in contrast to more rapidly-evolving viruses such as SARS-CoV-2.

Weekly Mpox Cases and Model Projections



925 MODELLING THE MPOX EPIDEMIC IN THE UK OVER MAY-AUGUST 2022

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*Presented at CROI by a nonauthor colleague

Background: The monkeypox epidemic in the UK began in May 2022. Unexpectedly and rapidly, rates of new cases declined during August 2022. Identifying the causes of this decline requires accurate estimates of the time-varying epidemic growth rate, which in turn depend upon the delay between symptom onset to healthcare presentation. In this paper, we utilise modelling and monkeypox data from the UK to quantify the changes in this delay and their effect on estimating the epidemic growth rate of monkeypox over the period May-August 2022 in the UK.

Methods: We developed a custom nowcasting Bayesian method which incorporates time-varying delays (EpiLine), simulating the growth rate of symptomatic cases and the parameters of delay distributions following Gaussian processes. We applied our model to the monkeypox data from the UK, sampling the posterior distribution of all parameters using Markov Chain Monte Carlo methods, to quantify the delay between monkeypox symptom onset to healthcare presentation and the growth rate over the study period.

Results: Our results suggest that the delay between symptom onset and healthcare presentation for monkeypox in the UK decreased from an average of 22 days in early May 2022 to 10 days by early June and 7 days in August 2022. When we account for these dynamic delays, the time-varying growth rate declined gradually in the UK over the May-September 2022 period. Not accounting for varying time delays would have incorrectly characterized the growth rate by a sharp increase followed by a rapid decline in monkeypox cases.

Conclusion: Our results highlight the importance of correctly quantifying the delay between symptom onset to healthcare presentation when charactering the epidemic growth of monkeypox in the UK. We show that reducing the delay in accessing healthcare is crucial as shorter delays can prevent onwards transmission, and allows prompt use of antivirals post infection. Hence, our study highlights the importance and need for public health agencies to focus on reducing delays from symptom onset to healthcare presentation early in an outbreak and when tailoring the optimal policy response.

926 MODELLING THE RISK OF FUTURE MPOX OUTBREAKS IN THE NETHERLANDS

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Background: Outbreaks typically occur when a pathogen is introduced into a population with little or no immunity. The 2022 mpox outbreak among men-who-have-sex-with-men (MSM) was a good example. In the Netherlands, smallpox vaccination ended in 1974. During summer of 2022, MSM who engage in high-risk sexual behavior were offered vaccination with the Imvanex vaccine. In September 2022, at the end of the outbreak, we measured an IgG seroprevalence against MPXV of 45% among MSM visiting the Center for Sexual Health in Rotterdam. Our study aims to predict whether the current seroprevalence levels can prevent future mpox outbreaks.

Methods: A modified stochastic SEIR model was developed. The model stratifies individuals based on vaccination status (unvaccinated, historically smallpox vaccinated and newly Imvanex vaccinated). Using literature estimates, vaccination is assumed to reduce infectiousness by 85% (range 75-95%) and 86% (83-90%) for historical and new vaccinations, respectively. Upon infection, individuals progress to an incubation period (4-12 days) and an infectious period (1-21 days). In our model, re-infections cannot occur. We assume that the outbreak was started by a super spreading event resulting in 15-100 initial infections. We calibrated the model to the exponential phase of the 2022 mpox outbreak in the Netherlands and to the total number of individuals (1,200-1,800), who were infected 120-180 days after the outbreak started. A new outbreak was modelled at a seroprevalence of at least 45% using all parameters and values from the calibrated model. The total number of infections was calculated as the number of secondary cases, excluding the initial infections starting the outbreak.

Results: The size and duration of a new mpox outbreak strongly decreased with increasing seroprevalence. At a seroprevalence of 45-55%, the average outbreak size was 108 cases (interquartile range, IQR, 60-147), with a peak after an average of 52 days (IQR 33–68). A seroprevalence of 70% would result in a further decrease to 20 cases (IQR 0-90) and a peak after 28 days (IQR 21-40), respectively. A new outbreak was unlikely at a seroprevalence of at least 85%.

Conclusion: Using stochastic modelling, we predict that increased seroprevalence during 2022 (by vaccination or infection) would strongly reduce the size and duration of future mpox outbreaks among MSM. Our findings emphasize the importance of vaccine-induced immunity in risk groups to prevent future outbreaks.

927 WHAT IMPACT WILL WORSENING AIR POLLUTION HAVE ON THE BURDEN OF COVID-19?

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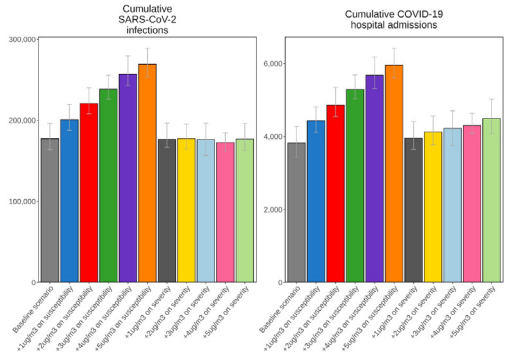
Background: Evidence suggests association between long-term exposure to air pollutants and increased risk of becoming infected with SARS-CoV-2, the causative agent of COVID-19, and increased severity of COVID-19. However, it remains unclear whether breathing more polluted air over many years affects susceptibility to infection or only affects disease severity, with uncertainty around the intensity of these associations. It has been estimated that anthropogenic emissions have contributed to over 10% of the over 660 million cases of SARS-CoV-2 and the over 7.5 million COVID-19 deaths reported worldwide over the course of the pandemic. Furthermore, as the world continues to warm and if air pollution levels increase, then so might the burden of respiratory infectious disease, including COVID-19.

Methods: Here we explore the potential impact of long-term exposure to increasing levels of particulate matter 2.5 microns or less in diameter (PM2.5) (+1 to +5 µg/m^3) assuming an association on either (1) SARS-CoV-2 susceptibility or (2) COVID-19 disease severity by projecting SARS-CoV-2 infections and COVID-19-related hospital admissions over a two-year period. Simulations were conducted using a SARS-CoV-2 transmission model in a global setting capturing age and comorbidity risk, considering seasonality, emerging variants, and vaccination and treatment options. We model linear, log, and $\log_{10}$ relationships between these associations.

Results: We show that if long-term exposure to higher levels of air pollution only affects COVID-19 severity, then as expected, the projected number of COVID-19-related hospitalisations would proportionally increase. However, if exposure directly affects the susceptibility of becoming infected, then while infections would be higher, hospitalizations would also be even higher due to the potential for onward transmission. This aligns with associations between air pollution and other respiratory infections and their associated health outcomes.

Conclusion: The anticipated additional impact air pollution is having on the public health burden of respiratory infectious disease, like COVID-19, should be considered in strategic action plans to mitigate and adapt to changing levels of air pollution. It is important to better understand at which point air pollution affects SARS-CoV-2 infection acquisition through to disease progression, to enable improved protection and to better support those most vulnerable.

Modelled impact of air pollution on COVID-19. The projected cumulative impact of long-term exposure to incrementally higher PM2.5 levels (+1 to +5 µg/m^3) affecting either SARS-CoV-2 susceptibility or COVID-19 disease severity on cumulative SARS-CoV-2 infections and COVID-19-related hospital admissions over a two-year period in a global setting of 100,000 people. Age and comorbidity risk are captured, seasonality considered, and it is assumed SARS-CoV-2 variants of concern (with 10% more infectious and 20% more immune-evading than the previous variant, and Omicron-level severity) emerge every six months, and COVID-19 vaccination and treatment (monoclonal-antibody PrEP and antivirals) are implemented for all those eligible. While the associations between PM2.5 exposure and either SARS-CoV-2 susceptibility or COVID-19 disease severity remains unclear and there is much uncertainty around estimated assumptions, here we show a modelled $\log_{10}$ relationship between these two potential associations. COVID-19: coronavirus disease 2019. PM2.5: particulate matter 2.5 microns or less in diameter. PrEP: pre-exposure prophylaxis. SARS-CoV-2: severe acute respiratory syndrome coronavirus 2.



928 WITHDRAWN

929 HIGH PERFORMANCE OF BLOOD-BASED HIV SELF-TESTS AT PRIVATE PHARMACIES IN KENYA

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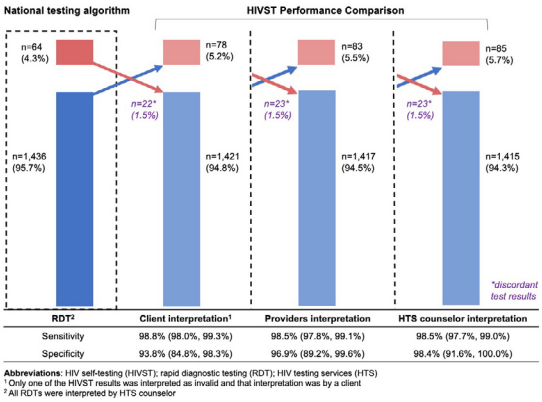
Background: HIV self-testing (HIVST) has the potential to support daily oral pre-exposure prophylaxis (PrEP) delivery in new community-based settings, but guidelines have not approved HIVST for PrEP dispensing. In Kenya, pharmacy providers are permitted to deliver HIVST, but to deliver rapid diagnostic testing (RDT), a certificate is required that few have. We sought to understand the performance of provider-delivered blood-based (BB) HIVST compared to RDT, the standard of care for PrEP delivery, at private pharmacies in Kenya to inform the possible use of HIVST for PrEP scale-up.

Methods: At 20 pharmacies in Kisumu County, we trained pharmacy providers (pharmacist & pharmaceutical technologists) on BB HIVST use and client assistance (if requested). We recruited pharmacy clients purchasing sexual and reproductive health-related products (e.g., condoms) and enrolled those ≥18 years with behaviors associated with HIV risk (e.g., partners of unknown HIV status). Enrolled clients received BB HIVST with associated provider counseling, followed by RDT by a certified HIV testing services (HTS) counselor. Pharmacy clients, providers, and HTS counselors independently interpreted the HIVST results prior to the RDT results (interpreted only by the HTS counselor). We calculated the sensitivity and specificity for BB HIVST compared to RDT.

Results: Between March and June 2022, we screened 1691 clients and enrolled 1500; 64% (n=954) were female and the median age was 26 years (IQR 22-31). We additionally enrolled 40 providers; 42% (n=17) were pharmacy owners and the median time in the profession was 6 years (IQR 4-10). The majority (79%, n=1190) of clients requested provider assistance with HIVST, and providers reported spending a median of 20 minutes (IQR 15-43) with each HIVST client. Compared to RDT, the performance of provider-delivered BB HIVST was high when interpreted by clients (sensitivity 98.8%, 95%CI 98.0%-99.3%; specificity 93.8%, 95%CI 84.8%-98.3%), providers (sensitivity 98.5%, 95%CI 97.8%-99.1%; specificity 96.9%, 95%CI 89.2%-99.6%), and HTS counselors (sensitivity 98.5%, 95%CI 97.7%-99.0%; specificity 98.4%, 95%CI 91.6%-100.0%), Fig. 1.

Conclusion: When compared to the national HIV testing algorithm, the performance of provider-delivered BB HIVST at private pharmacies in Kenya was high. These findings suggest that BB HIVST may be considered as a testing option to support PrEP initiation and continuation at private pharmacies and potentially other community-based delivery settings.

Fig. 1. Performance of blood-based HIV self-testing compared to rapid diagnostic testing at private pharmacies



930 REMOVAL OF A SUBSIDY FOR HIV SELF-TESTING KITS REDUCES ONLINE KIT SALES IN KENYA

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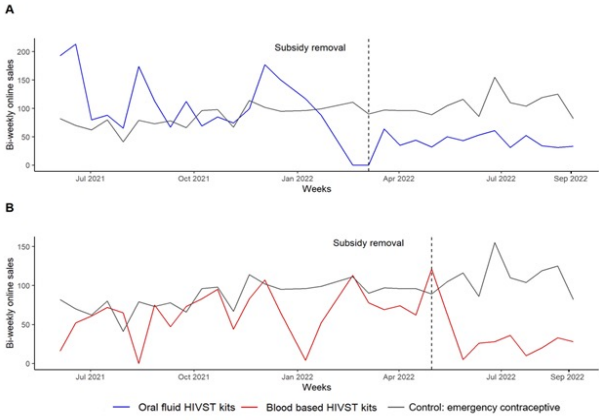
Background: HIV self-testing (HIVST) can enable individuals to learn their HIV status confidentially, without fear of stigma, which may result in an earlier linkage to prevention or treatment interventions. To help increase HIVST access, international donors and nongovernmental organizations partnered to subsidize HIVST kits in 50 low-income countries. In Kenya, this subsidy started in 2019 and ended in 2021. To understand the impact of this subsidy removal on online HIVST kit sales in Kenya, we used controlled interrupted time series (cITS) methods, a quasi-experimental approach.

Methods: For our analysis, we used bi-weekly sales data from MYDAWA, the first licensed fully online pharmacy in Kenya. During the subsidy period, both oral-fluid (OF) and blood-based (BB) HIVST kits were available via MYDAWA at 250 KES (~$2.3 USD) per kit. On March 3, 2022, MYDAWA ran out of subsidized OF HIVST kits and the price for these kits rose to 470 KES (~$4.3 USD); on May 25, 2022, the price of BB HIVST kits rose to 760 KES (~$6.9 USD) for the same reason. We conducted a cITS analysis to understand the impact of the subsidy removal on online OF and BB HIVST kit sales via MYDAWA, using sales of an emergency contraceptive product as a control.

Results: From June 2021 to September 2022, we had 32 bi-weekly time units of online sales data for HIVST kits and related products. For OF HIVST kits, we had 19 time units in the pre-subsidy and 13 time units in the post-subsidy period; for BB HIVST kits, we had 21 time units in the pre-subsidy and 11 time units in the post-subsidy period. When the subsidy was removed for OF HIVST kits, this reduced online bi-weekly sales by 273%, with 82 fewer kits (95% CI 47-117) sold bi-weekly compared to the control, **Fig. 1**. Then, when the subsidy was removed for BB HIVST kit sales, this reduced bi-weekly online sales by 690%, with 69 fewer kits (95% CI 49-89) sold bi-weekly compared to the control.

Conclusion: Removal of a subsidy for HIVST kits significantly decreased the online sale of both OF and BB HIVST kits in Kenya, resulting in potential missed opportunities for early HIV detection and linkage to prevention and treatment services. This evidence suggests that subsidies are effective at increasing the demand for HIVST and should be considered to increase HIV testing in Kenya and similar settings.

Fig 1. Bi-weekly MYDAWA online sales for oral fluid HIV self-testing (HIVST) kits, blood-based HIVST kits, and an emergency contraceptive product (i.e., the



931 VIRTUAL SUPPORT IMPROVES CLIENT EXPERIENCES WITH AN ONLINE HIV SELF-TESTING SERVICE

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Background: HIV self-testing (HIVST) has the promise to efficiently reach vulnerable populations who are hesitant or unable to visit healthcare locations for testing, especially as more affordable tests become available. We implemented a novel web-based HIVST service in India, which reached many who had never tested before and with high positivity. To understand how to scale HIVST and maximize efficiency, we assessed barriers and facilitators of the experience through a brief online survey.

Methods: The HIVST web-based service was launched in July 2021. HIVST kits were couriered to clients or picked up at select locations. Virtual counselors (VCs) were available to clients for pre/post-test counseling and assistance with using the kits, including interpreting and uploading results to the website, and linkage to appropriate services. For clients who agreed to be contacted later about their experiences, an automated WhatsApp message with a link to a web-based self-administered survey was sent. The survey included basic demographics and their experiences with ordering, taking the test, reporting results, and interactions with VCs.

Results: As of August 2022, 5014 clients ordered an HIVST, of whom 87% received the kit, 82% uploaded their result, and 5% screened positive; 74% were male, 64% 18-30 years of age, and 45% of kits were sent via courier. From October 2021-August 2022, 305 clients completed the survey; 85% of respondents were men and 81% had kits couriered. Nearly a quarter had ordered more than one kit and 5% had a verified positive HIVST result. A majority (87%) reported that it was easy using the website for ordering and receiving the kit. While most (85%) reported understanding the kit instructions and confidence about what to do with the result, the majority (81%) also reported receiving help completing the test - 76% from VCs and 14% from a friend. Most (88%) would recommend HIVST to others. Compared to those that did not get help from VCs, clients helped by VCs were more likely to understand kit instructions, complete the test, be confident in knowing what to do based on result, report the result, and recommend HIVST to others (**Table**).

Conclusion: Clients were able to easily order, receive, and use HIVST kits from a web-based service. However, it is notable that most had interaction with a VC who facilitated the process. Virtual support by trained counselors could improve efficiency, uptake, and linkage of both virtual and in-person HIV prevention and treatment services.

HIV self-test processes and experiences by whether clients received help from virtual counselors (VCs) among 305 respondents in India

Table HIV self-test processes and experiences by whether clients received help from virtual counselors (VCs) among 305 respondents in India

	Received help from VCs	Did not receive VC help
Understood test kit box instructions		
Difficult	9 (5.1)	7 (6.5)
Neutral	9 (5.1)	17 (15.7)
Easy	159 (89.8)	84 (77.8)
Completed test		
No	0 (0)	9 (7.7)
Yes	177 (100)	108 (92.3)
Confidence in knowing what to do based on result		
Not Confident	9 (5.1)	4 (3.7)
Neutral	8 (4.5)	21 (19.4)
Confident	160 (90.4)	83 (76.9)
Reported test result to website or VC	177 (100)	96 (88.9)
Likely to recommend HIV self-testing to others		
Will not recommend	1 (0.6)	11 (8.6)
Unsure	6 (3.4)	19 (14.8)
Will recommend	170 (96.0)	98 (76.6)

932 PEOPLE WHO INJECT DRUGS' WILLINGNESS TO USE AND DELIVER HIV SELF-TEST KITS TO PEERS

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Background: HIV self-testing (HIVST) kits, including their secondary distribution in social networks, promote HIV testing but remain understudied among people who inject drugs (PWID). To inform efforts to address barriers to standard facility-based HIV testing among PWID, we assessed willingness to use and distribute HIVST kits among PWID along the San Diego-Tijuana border.

Methods: From 2020-2021, 612 PWID in San Diego, USA, and Tijuana, Mexico, underwent HIV testing and completed interviewer-administered surveys. Modified Poisson regression examined associations between willingness to use and distribute HIVST kits and socio-demographics, sexual and substance use behaviors, HIV testing history, and social network characteristics.

Results: Among 539 HIV-negative PWID, median age was 43 years (IQR=35-52), 75% were male, 72% Latinx, 75% had ever tested for HIV, and mean social network size was 3.2 members. Overall, 81% were willing to use HIVST kits themselves, and 81% were willing to distribute them in their networks (79% to sex partners; 75% to drug use partners). Willingness to use HIVST kits oneself was associated with willingness to distribute them (prevalence ratio [PR]=8.4, 95% confidence interval [CI]: 4.9-14.2). At the individual level, prior HIV testing was positively associated with willingness to use (PR=1.3, 95% CI: 1.1-1.4) and distribute (PR=1.3, 95% CI: 1.2-1.5) HIVST kits, while perceiving oneself to be at higher HIV risk than other PWID was negatively associated with willingness to use (PR=0.8; 95% CI: 0.7-0.9) and distribute (PR=0.8; 95% CI: 0.7-0.9) HIVST kits. At the network level, willingness to distribute HIVST kits was positively associated with network size (PR=1.05 per network member, 95% CI: 1.01-1.08) and greater proportions of one's network being homeless (PR=1.6, 95% CI: 1.4-1.9), detained/arrested (PR=1.7, 95% CI: 1.5-2.0), and using heroin (PR=1.2, 95% CI: 1.1-1.3) and cocaine (PR=1.5, 95% CI: 1.3-1.7). Willingness to distribute HIVST kits was lower among those whose networks consisted of a greater proportion of persons they consider "very close" to them (PR=0.8, 95% CI: 0.7-0.9).

Conclusion: We found high levels of willingness to use and distribute HIVST kits among PWID, and high potential for secondary distribution to increase HIV testing among PWID who face the greatest barriers to standard testing. Efforts to bolster HIV knowledge and address fears of stigma from close peers may enhance the impact of HIVST among PWID.

933 OVERCOMING ACCESS BARRIERS TO VIRAL SUPPRESSION TESTING BY SELF-MICROCOLLECTED BLOOD

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Background: Structural and socio-behavioral barriers to clinic access for continuum of HIV care are major hurdles to medication adherence in areas of lower socioeconomic status. An important indicator of well-being for persons with HIV (PWH) is sustained engagement in care to support viral suppression (VS). Remote VS testing may be supported by self-collected blood in microcollection tubes (MCT), which has benefits over dried blood spots (DBS).

Methods: We developed a kit with instructions and procedure for remote VS testing using fingerstick blood in EDTA-preservative MCT (Microtainer®) and ambient temperature shipping with temperature monitoring. Separated plasma was used for semi-quantitative RNA testing in a 1:7 dilution protocol that, compared to DBS testing, allows for greater sensitivity (LOQ 210 cp/mL, 99% quantified at 350 cp/mL), requires less sample manipulation, and alleviates DNA contamination. MCTs from 90 participants from various HIV study cohorts willing to self-collect and mail specimens were assessed for allowable shipping time (≤4 days), transit temperature (≤35°C) and plasma volume (≥100 µL). Samples that met the criteria were HIV-1 RNA tested. For 28 participants, a same-day venipuncture sample was obtained for comparison to traditional viral load (VL).

Results: Of the 90 mailed MCTs, 12 (13%) were rejected on receipt: eight were below volume, three exceeded the temperature limit and one exceeded the shipping period. Four of six participants who obtained another self-collect kit after an unsuccessful fingerstick collection were able to obtain and mail an MCT sample. In total, 81% of persons who attempted self-collection provided a suitable specimen. Seventy-two persons documented to be on PrEP or who were virally suppressed had no viral target detected in the self-collected samples. The six individuals with a quantitated venipuncture VL also had RNA quantitated in MCT (VL range 273 -11,918 cp/mL). Results from the MCT were within 0.31 $\log_{10}$ cp/mL of the VL provided by venipuncture. Hemolyzed specimens were included as hemolysis did not affect test results.

Conclusion: Untrained individuals were able self-collect and ship sufficient blood volume to support remote viral suppression testing. Gained experience

with MCT collection would further increase the high proportion of usable samples. Offering remote VS testing to persons willing to self-collect could overcome recognized barriers to clinic access, support HIV telemedicine, and empower patients to remain in care.

934 RACIAL/ETHNIC DISPARITIES IN HIV TESTING EXPERIENCE BEFORE HIV DIAGNOSIS: 2014-2019

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Background: In 2019, Black/African American and Hispanic/Latino persons accounted for 13% and 18% of the US population, but 42% and 29% of HIV diagnoses. This analysis examines HIV testing prior to HIV diagnosis by race/ethnicity to describe trends in testing experience and identify which groups could benefit from increased testing and linkage to care.

Methods: We used National HIV Surveillance System data in 21 jurisdictions to assess trends [estimated annual percent change (EAPC) and 95%CIs] in HIV testing patterns among Black/African American, Hispanic/Latino and White persons aged ≥13 years with HIV infection diagnosed 2014–2019 by sex, age and transmission category.

Results: For all races/ethnicities, the percentage who ever had a previous negative HIV test before diagnosed HIV infection decreased from 2014 to 2019 [67% to 58%;EAPC=-2.6;95%CIs=-3.0,-2.2]. This decrease was highest in White [70% to 61%;EAPC=-2.9(-3.8,-2.0)], followed by Hispanic/Latino [64% to 57%;EAPC=-2.7(-3.5,-1.9)] and Black/African American [66% to 58%;EAPC=-2.5(-3.2,-1.8)] persons. Significant decreases occurred for males and females among Black/African American and Hispanic/Latino persons and males only among White persons. By age, significant decreases occurred for those aged 13-44 years among Black/African American, 13-54 years among Hispanic/Latino and all age groups among White persons. For Black/African American persons, significant decreases occurred for those with infection attributed to male-to-male sexual contact [70% to 62%;EAPC=-2.3(-3.1,-1.4)], male heterosexual contact [54% to 44%;EAPC=-3.8(-6.1,-1.4)], and female heterosexual contact [62% to 52%;EAPC=-3.7(-5.2,-2.2)]. For Hispanic/Latino persons, significant decreases occurred for those with infection attributed to male-to-male sexual contact [67% to 59%;EAPC=-3.0(-3.9,-2.1)] and male heterosexual contact [58% to 51%;EAPC=-3.1(-5.8,-0.3)]. For White persons, significant decreases occurred only for those with infection attributed to male-to-male sexual contact [73% to 63%;EAPC=-3.0(-4.0,-2.0)].

Conclusion: Further research is needed to determine whether decreases in HIV testing before diagnosis among persons in these racial/ethnic groups are associated with trends in uptake of HIV testing and prevention strategies in the general population. Annual HIV testing and tailored prevention strategies should be promoted among all persons with HIV risk factors to increase early detection and linkage for improving HIV care outcomes and reducing risk for HIV transmission.

935 CDC-FUNDED HIV TESTING AND UNDIAGNOSED HIV INFECTION IN ENDING THE HIV EPIDEMIC AREAS

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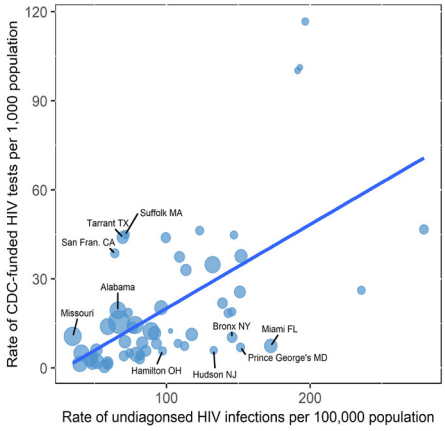
Background: HIV testing is a key component to diagnosing individuals and linking them to care. However, approximately 14% of persons with HIV (PWH) are unaware of their HIV status. To help reach the goals of the *Ending the HIV Epidemic in the U.S.* (EHE) initiative, it is important to understand the relationship between HIV testing rates and rates of undiagnosed HIV infection, particularly in areas with high HIV prevalence.

Methods: Using 2019 data from the National HIV Surveillance System and the National HIV Prevention Program Monitoring & Evaluation system, we calculated estimated undiagnosed HIV infection per capita (i.e., rate of undiagnosed HIV infections per 100,000 population) and CDC-funded HIV tests per capita (i.e., rate of CDC-funded HIV tests per 1,000 population) in Phase 1 EHE areas. We assessed the association between the two rates using Spearman's rank correlation. We also calculated a rank difference between the two rates for each EHE area to help understand which areas have greater unfilled needs for HIV testing.

Results: CDC-funded HIV tests per capita was positively associated with estimated undiagnosed HIV infection per capita (rho=0.59, p< 0.001). The EHE areas with the largest rank differences (i.e., higher undiagnosed HIV infection per capita and lower CDC-funded HIV tests per capita) were Miami-Dade County, FL; Prince George's County, MD; Hudson County, NJ; Bronx County, NY; and Hamilton County, OH. The EHE areas with the smallest rank differences were San Francisco County, CA; Tarrant County, TX; Suffolk County, MA; Missouri; and Alabama.

Conclusion: There is a significant association overall between CDC-funded HIV tests per capita and estimated undiagnosed HIV infection per capita, indicating that—in general—CDC-funded HIV testing is being conducted in areas with the greatest needs. However, some EHE areas had large discrepancies between CDC-funded HIV tests per capita and estimated undiagnosed HIV infection per capita. These aforementioned areas could use this information to identify barriers to their HIV testing services and improve or expand upon their HIV testing programs to help ensure that all PWH in their jurisdictions are diagnosed and linked to HIV medical care, prevention, and supportive services.

CDC-Funded HIV Tests per Capita by Estimated Undiagnosed HIV Infection per Capita, Ending the HIV Epidemic in the U.S. (EHE) Areas, 2019



Note: Areas with the greatest (below line) and lowest (above line) unfilled need for HIV testing labeled; bubble size represents size of jurisdiction population

936 FACTORS ASSOCIATED WITH HIV POSITIVITY UNAWARENESS AMONG TANZANIANS LIVING WITH HIV

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Background: The Tanzania HIV Impact Survey (THIS) 2016-2017 estimated that nearly four in every ten people living with HIV (PLHIV) aged 15 years and older were unaware of their HIV positive status. We assessed correlates of unawareness of HIV positive status among PLHIV in Tanzania.

Methods: We used data from the THIS 2016-2017, which was a cross-sectional nationally representative survey. In addition to self-reported HIV positive status, participants with detectable antiretrovirals (ARVs) in their blood were considered as aware. We used modified Poisson regression modeling to examine the associations of age, sex, residence, marital status, education, household wealth, condom use, and comprehensive HIV knowledge with unawareness of HIV-positive status.

Results: Among the 1,779 PLHIV in the sample, 39% were unaware of their HIV positive status after accounting for detectable ARVs in their blood. The risk of unawareness was 47% greater among males compared to females with adjusted prevalence ratio (aPR) of 1.47 [95% confidence interval (95%CI): 1.25-1.71]; 43% greater among young adults (15-24 years) compared to those who were at least 50 years old [aPR: 1.43; 95%CI: 1.05-1.95]; 42% greater among those who did not report condom use compared to those who did [aPR: 1.42; 95%CI: 1.19-1.71]; and 20% greater among those without comprehensive HIV knowledge compared to those with high knowledge [aPR: 1.20; 95%CI 1.03-1.40]. The risk of unawareness was 26% lower among those who were widowed compared to those who were married or living together [aPR: 0.74; 95%CI: 0.56-0.98].

Conclusion: Our findings suggest that, in Tanzania, the risk of unawareness of HIV positive status was greater among PLHIV who were males, young adults, those who did not report condom use and those who had low HIV knowledge.

These findings confirmed preliminary descriptive survey results which led to a review of Tanzania's identification strategies and reinforced targeted interventions to enhance HIV testing services by scaling up safe and ethical index testing, social network testing and HIV self-testing, focusing on at-risk populations including men and young adults.

937 OVER- AND UNDER-REPORTING IN HIV TESTING, STATUS, AND TREATMENT IN RURAL SOUTH AFRICA

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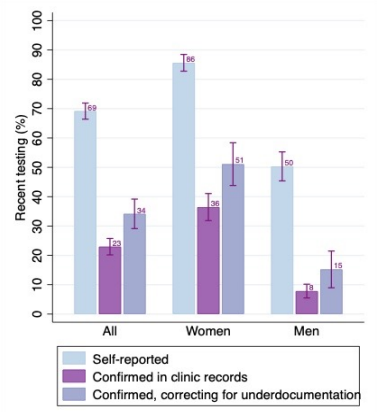
Background: Surveys are an important source of population-based indicators in tracking the HIV epidemic, including self-reported HIV status, testing history, and treatment adherence. Whether self-reported indicators are accurate has implications for epidemic monitoring but can be challenging to assess, particularly when collected without confirmatory biomarkers. We assess the accuracy of survey indicators by comparing self-reported testing, HIV status, and treatment responses in a population-based survey with clinical records in Bushbuckridge sub-district, South Africa.

Methods: We conducted a household-based survey of adults 18 – 49 years old in August – December 2018 with measures of HIV testing, test results, ART history, and source of health care. We drew from Agincourt Health and Demographic Surveillance System census records to link respondents to longitudinal clinical data from the 10 government facilities providing primary care in this area. We calculated indicators based on self-report and triangulated findings with data from clinic records. We adjusted testing estimates for known gaps in HIV test documentation and assessed individual and health system variables as predictors of reporting accuracy.

Results: Of 2089 survey participants, 1657 used a study facility and were eligible for analysis. Half of men and 84% of women reported an HIV test in the past year; 33% of reported tests could be confirmed in clinic data within 1 year and another 13% within 2 years. Confirmed tests were more common among women and younger adults. Accounting for documentation gaps, we estimated that 15% of men and 51% of women tested for HIV within the past year (Figure 1). Nearly half of those living with HIV did not report positive status: HIV prevalence was 16.2% based on self-report vs. 27.6% including clinic documentation. 238 of 250 (95.2%) of those self-reporting HIV diagnosis indicated current ART use; incorporating clinic documentation, current ART use would be 68% overall or 87.6% limited to those with a documented clinic record.

Conclusion: Prevalence of recent HIV testing was substantially higher on self-report while reported prevalence of HIV was 10 percentage points lower than estimates including clinical records. Self-report overestimated current ART by at least 7 percentage points. Discrepancies were higher for men. While clinical records are imperfect, survey-based measures should be interpreted with abundant caution in this rural South African setting.

Figure: Prevalence of HIV testing within 12 months based on self-report and with clinic record confirmation



938 SIGNS OF LATE HIV DIAGNOSIS AND OUTBREAKS IN TRANSMISSION NETWORKS IN JAPAN

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Background: In Japan, approximately 30% of newly diagnosed HIV-infected individuals were identified after the onset of AIDS symptoms, suggesting that many people living with HIV (PLHIV) remain undiagnosed. Understanding factors that are associated with late HIV diagnosis (LHD), which is a major concern worldwide, is essential in achieving the 95-95-95 goal in Japan. Recently, we found that LHD in Japan was associated with a transmission clustering pattern. We present the possibility of identifying LHD-involving clusters in transmission-network analysis using our large-scale monitoring of domestic transmission clusters (dTCs) in Japan.

Methods: We monitored the dynamics of HIV-1 dTCs in Japan using cases collected by the Japanese HIV Drug Resistance Surveillance Network. dTCs dynamics and the network structure of newly diagnosed cases in Japan were monitored by our search program for HIV nationwide clusters by sequence (SPHNCS), which identifies the transmission link with the genetic distance estimated by the protease-reverse transcriptase sequences. We recruited 9,722 newly diagnosed cases between 2003 and 2021 from our surveillance network, and identified their dTC affiliation, network structure, and chronological tree. The relationship of the transmission network patterns to LHD and outbreak involvements, which were recognized by the CD4 count and chronological tree, were investigated.

Results: At the end of 2021, 566 subtype B and 105 CRF01_AE dTCs were registered in SPHNCS. Of these, seven and 30 clusters were recognized as LHD and outbreak involved clusters, respectively. At least 5,594 (57.5%) of newly diagnosed PLHIV in Japan were cases of LHD. Individuals in dTCs were more likely to be LHD cases than those not in dTCs (aOR, 0.80; $p< 0.01$). While mature transmission networks usually follow the power law with the lower degree being more frequent, outbreak clusters were characterized by the opposite degree distribution of the graph. In the degree distribution of the graph containing LHD, we observed a spike indicating a node at the center of the star-like structure in the network.

Conclusion: Our results indicated that the graph structure of HIV transmission networks may imply involvements in late HIV diagnosis and outbreaks. This suggests the possibility that monitoring dTCs dynamics using network analysis can quickly identify a local population where an outbreak occurred or testing was delayed, to promote preventive measures.

939 PATTERNS OF HIV-1 RECENT INFECTION AMONG GENERAL AND KEY POPULATIONS IN NIGERIA

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Background: HIV-1 Recent Infection Testing Algorithm (RITA) is increasingly applied to population-based surveys in numerous countries for population level estimates of HIV incidence. Nigeria commenced implementation of recency surveillance in 2020 and preliminary data for estimating state and national level HIV incidence is becoming available. The aim of the study is to understand the patterns of HIV-1 recent infection from inception of the implementation of HIV-1 recent infection surveillance in four states of Nigeria.

Methods: The study was a 30-month descriptive analysis of patterns of HIV-1 recent infection among newly diagnosed people living with HIV (PLHIV) who are 15 years old and above, who received RITA testing integrated into routine HIV Testing and Services (HTS) at activated sites. Data for Gombe, Kaduna, Kogi, and Lagos States were retrieved from the Nigeria Data Repository (NDR) between March 2020 and August 2022.

Results: A total of 33, 820 eligible PLHIV were newly diagnosed of HIV, of which 16, 625 PLHIV (49%) received HIV recent infection testing over the 30-month period. Only 477 (3%) of those tested had recent HIV infection, 282 (59%) of which were female. The proportion of RITA recent ranged from 0.4% in Kogi to 4.1% in Lagos. RITA recent infection was largest among the 25-29 year age band (25%) and lowest in the 15-19 age-group (3%). Overall, 62% of female

between 20 and 44 years of age were recently infected with HIV compared with 38% of male within same age group. Similarly, 64% of males between ages 45 years and above were recently infected with HIV compared to 36% of their female counterpart. Recent infection rate was higher in the key population (3.8%; n=6,069) compared to the general population (2.7%, n=10,556). Disaggregating by sex, the rate of recent infection was higher among female (66%) in the general population compared to male (34%). However, the sex distribution of RITA recent was comparable among key population (51% in male versus 49% in female).

Conclusion: HIV-1 recent infection is higher in the key population, however, there is sex disparity in general population with female being more affected when compared to key populations. In general, recent infection rate may be higher among younger women and older men. The HIV response should prioritize preventive interventions targeting younger female at risk of HIV infection.

940 NO INCREASED VIOLENCE VICTIMIZATION AFTER RETURN OF RECENCY TEST RESULTS IN RWANDA

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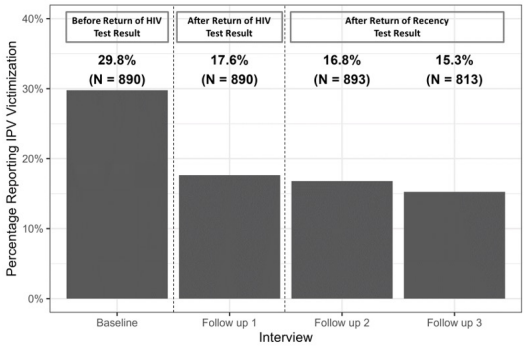
Background: The U.S. President's Emergency Plan for AIDS Relief does not recommend returning HIV recent infection results to newly diagnosed persons living with HIV (PLHIV) due in part to lack of safety evidence that return of results does not increase experience of intimate partner violence (IPV). We evaluated if IPV is more likely to increase as a result of return of recent infection results among newly diagnosed PLHIV in Rwanda.

Methods: We conducted a prospective cohort study of newly diagnosed PLHIV who underwent a rapid test for recent infection with baseline viral load from August 2021–October 2022 in 60 health facilities selected using probability sampling in all 5 provinces in Rwanda. Interviewer-administered questions on self-reported experiences of control, economic, emotional, physical, or sexual violence from a current partner 4 weeks prior to the interview were used to collect data at 4 study visits over a 6-month period. We compared 1. IPV prevalence using Fisher's exact test before/after return of HIV diagnosis (baseline vs. 1st follow up visit) and before/after return of recent infection test result (1st vs. 2nd/3 follow up visits) and 2. IPV experiences between recent (RT) and long-term (LT) cases, using generalized linear mixed models to estimate the mean difference (MD) in counts of IPV events. We included a subject-specific random effect, and adjusted for sex, age, marital status, living in Kigali, reported violence at baseline, and by multivariable propensity score.

Results: Of 932 newly diagnosed PLHIV with IPV data from ≥1 visits after return of recent infection test results, 849 (91%) had LT infection and 83 (9%) had RT infection. Prevalence of IPV was higher at baseline before HIV diagnosis compared to after HIV diagnosis (29.8% vs. 17.6%, p< 0.001). Prevalence of IPV did not increase after return of HIV recent infection test result (17.6% vs. 16.1%, p=0.4). Return of RT infection result was not associated with increased IPV relative to return of LT infection result in univariate analysis (MD=0.14, 95% CI -1.13–1.41), and after bivariate (MD=0.09, 95% CI -1.18–1.36) and multivariable propensity score adjustment (MD=0.13, 95% CI -1.15–1.41).

Conclusion: IPV victimization did not increase after return of recent infection test results—RT or LT result—compared to return of HIV diagnosis in a context with high baseline IPV. Programs returning results can adopt strategies to mitigate IPV risks and ensure access to violence response services.

Figure. Percentage Reporting IPV Victimization by Follow Up Visit in Rwanda, 2021-2022



941 NON-HIV ENTRY POINTS TO DELIVER HIV SERVICES TO TRANSGENDER WOMEN IN INDIA

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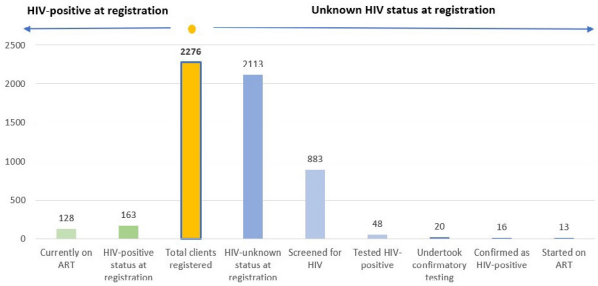
Background: Transgender (TG) women in India have a 14 times higher burden of HIV compared to the general population. They also face substantial societal challenges with access to HIV prevention and treatment services. Further, for most transwomen access to hormone replacement therapy (HRT), cosmetology, and social entitlements take precedence over HIV services. Consequently, we established a comprehensive care model for the TG community including HIV and non-HIV services.

Methods: As part of a PEPFAR-funded program, three comprehensive community-led trans clinics ("Mitr Clinics") were established in the Indian cities of Hyderabad, Pune and Thane since February 2021. These clinics provided HIV prevention and testing services with referral to the government program for free antiretroviral therapy (ART). The clinics also provided free consultation for HRT, cosmetology, and assistance with access to social protection schemes. Diagnostics for syphilis and nucleic acid testing for *C trachomatis* and *N gonorrhoeae* were offered free of cost on-site. Client data was routinely collected at all sites and correlates of uptake of HIV testing were explored using logistic regression.

Results: Between February 2021-July 2022, 2276 individuals were registered across the 3 clinics. The majority (54%) had never received services as part of the government's targeted interventions (TI) program. Median age was 26 years and 87% self-identified as a transwoman; 29% reported a history of transactional sex. The most utilized service was laser therapy (56%), followed by HIV services (54%). Of the total clients, 163 (7%) were aware of their HIV status at entry and 128 were currently on ART. 883 clients were screened for HIV at the clinics. HIV screening was significantly more common among those who visited the clinic for HRT (aOR 2.35; 95% CI: 1.66, 3.33) or condoms (aOR 2.25; 95% CI: 1.5, 3.37). 48 clients newly screened HIV-positive at the clinics, of whom 20 completed confirmatory testing and 13 initiated ART (Figure). Additionally, 336 clients were tested for syphilis, 79 for CT and NG with a prevalence of 9%, 4%, and 0%, respectively.

Conclusion: These data highlight the role of integrating non-HIV services as entry points to generate demand for facilities from communities previously unreached by HIV programming. Integrating essential HIV and other STI services including confirmatory testing, ART and PrEP into such facilities will promote a "person-centric" approach to HIV care to this marginalized, vulnerable community.

Figure - Clients' HIV Status and Testing Cascade



942 DIRECTED SCREENING FOR HIV INFECTION IN EMERGENCY SERVICES: VIHGILA STUDY

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Background: About 10 cases of HIV infection are diagnosed daily in Spain. Despite being a preventable disease, he trickle of new infections is incessant, in an infection that has been hidden for many years. It's fundamental establish various strategies aimed at identifying the infected population.

Up to 30% of patients diagnosed with HIV could have been identified earlier if in a Emergency Department (ED) a diagnostic test would have been performed in a consensual medical context. The recent "SEMES-GESIDA 2020" consensus recommends performing HIV serology tests in EDs in 6 very specific clinical scenarios: presence of STDs, post-exposure prophylaxis (PEP), practice of chem-sex (CS), sdme. mononucleoside (SMN), community pneumonia (NC) in those under 65 years, herpes zoster (HZ) in those under 65 years. This study analyzes the results of the implementation of the mentioned consensus, through a directed protocol (HIVGILA-SOCMUE Project).

Methods: 10 EDs from hospitals in Catalonia are included. Specific training of staff is carried out in all hospitals medical, nursing and microbiology service: explaining the details and concrete way to apply the consensus. In each of the EDs has a doctor and nurse responsible for implementing the protocol, carrying out a control strict of all procedures. Data is updated weekly with centralized monitoring.

Results: After 60 weeks of follow-up (June 1, 2021-August 30, 2022), 5959 HIV serologies have been performed and diagnosed 54 new patients with HIV (0.9%). 33/54 (61%) of new diagnoses occur in the 6 scenarios described: 5 HIV cases out of 1,211 PPE (0.4%), 7/796 STDs (0.8%), 13/694 NC (1.8%), SMN 5/257 (1.9%), CS 2/35 (0.7%), HZ 1/149 (0.6%), patients with other pathologies 21/2817 (0.7%).

Conclusion: The application of the SEMES consensus shows a high diagnostic efficiency: almost 1% of the serologies are positive for HIV. These percentages are 10 times above the percentages considered efficient (>0.1%) for the performing a screening. Performing serology on patients with NC and SMN shows a very high level of efficacy, close to 2%. In light of these results, EDs appear to be an optimal place to screen and diagnose infection for HIV. It is necessary to train health teams to implement HIV detection protocols in EDs.

943 HIV TEAMS AS A TOOL TO IMPROVE HIV INDICATOR CONDITION-GUIDED TESTING

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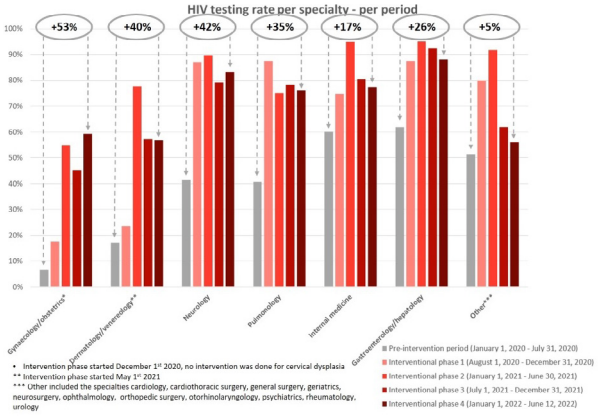
Background: The majority of patients newly diagnosed with HIV in the Netherlands are late presenters and had multiple prior missed opportunities to test for HIV. To stop the HIV epidemic, adequate identification of people unaware of their HIV diagnosis is necessary. A proven key strategy, recommended by (inter)national guidelines, is indicator condition-guided testing. The aim of this study is to evaluate the impact of HIV teams on HIV indicator condition-guided testing in hospitals.

Methods: A single center prospective implementation project was conducted at Erasmus University Medical Center Rotterdam. A two-step approach was used to identify possible HIV indicator conditions by automatic ICD-10 screening, followed by cross-comparing with standardized health insurance (DBC) codes. Data were collected on all patients ≥ 18 years who entered care between January 1st 2020 and June 12th 2022. Flagged indicator conditions were systematically reviewed by the HIV team. Multi-angle intervention started at August 1st 2020 and included proactive testing recommendations from the HIV team for physicians treating patients with HIV indicator conditions. We evaluated HIV indicator condition prevalence and the impact of HIV teams on HIV testing rate overall, per interventional phase and per specialty.

Results: During the study period, a total of 218,211 diagnoses were newly registered. Of these, 18,743 (8.6%) were flagged as possible HIV indicator conditions. After manually reviewing, 2,026 HIV indicator conditions were identified. The overall HIV testing rate was 61.4% (1,244/2,026). In the pre-intervention period, the HIV testing rate was 43%, while after implementing HIV teams, the HIV testing rate was 52.1%, 80.7%, 68.7% and 70.4% for interventional phase 1, 2, 3 and 4, respectively. The overall HIV positivity rate was 0.7% (9/1,244) (pre-implementation 0.4% and post-implementation 0.8%). Looking further at HIV test rates per specialty an increase in HIV testing rate was seen in all specialties with a peak in the first or second interventional phase (figure 1).

Conclusion: Implementing HIV teams increased the HIV testing rates with continued clinical benefit after an initial peak. Our data confirms a gap between indicator condition identification and HIV testing, even after proactive HIV testing advice. Future studies should focus on improving this gap and evaluate the barriers to test for HIV after HIV testing advice is given.

HIV testing rate per specialty - per period



944 IMPACT OF MPOX OUTBREAK ON HIV TESTING IN A LARGE INTEGRATED HEALTHCARE SYSTEM

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Background: People living with HIV (PLwH) were disproportionately impacted by the 2022 Mpox outbreak, with 40-60% of Mpox cases in PLwH. Due to this and substantial rates of sexually transmitted infection (STI) in patients diagnosed with Mpox we implemented a protocol for coinfection testing which included HIV testing at time of Mpox testing in 17 emergency departments (EDs) and 44 urgent cares (UC) across our large integrated healthcare system. As this HIV testing initiative overlayed an existing ED HIV testing program and EDs and UCs were the highest volume site for STI testing in our healthcare system, we examined the impact of the Mpox outbreak on HIV testing and diagnosis.

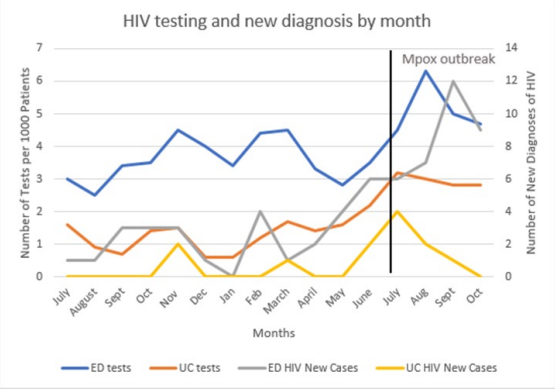
Methods: This is a retrospective observational study of HIV testing and diagnosis before and during the 2022 Mpox outbreak. We examined rates of HIV testing standardized by ED and UC visits during the Mpox outbreak from July

1,2022 through October 31,2022 compared to the prior 12 months: July 1, 2021 through June 30, 2022. We also compared total numbers of new HIV diagnosis during those time frames. T-tests were utilized to compare means of the tests and diagnoses before and during the outbreak. All analyses were conducted using SAS 9.4.

Results: The average number of HIV tests sent per month increased from 2.3 tests per 1000 patient visits per month prior to the Mpox outbreak to 3.8 tests per 1000 patient visits per month on average during the outbreak (p=.01). There was an average of 1.4 new cases of HIV diagnosed per month in our healthcare system's EDs and UCs prior to the Mpox outbreak and an average of 3.9 new HIV diagnosis per month for the 4 months of the outbreak (p=.02). A higher number of tests per patient encounters occurred and more new HIV diagnosis were made in EDs compared to UCs both before and during the Mpox outbreak but testing and new diagnosis increased at both locations (see Figure). Of the 41 new cases of HIV diagnosed during the Mpox outbreak, 16 had testing sent concomitant with Mpox testing.

Conclusion: Significantly increased rates of HIV testing and new HIV diagnosis were observed during the Mpox outbreak in our healthcare system. This may have been the result of increased awareness of need for testing with increased provider education provided as part of the Mpox outbreak response. Further opportunities exist for strengthening coinfection testing for HIV and Mpox and identifying undiagnosed cases of both viruses.

Figure: Number of HIV tests per 1000 patient encounters and new HIV diagnosis by site and month



945 DNA-CONFIRMATION OF HIV-1&2 COINFECTIONS AMONG DUALLY-REACTIVE WEST AFRICAN PATIENTS

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The EDIMARK-2 Study group
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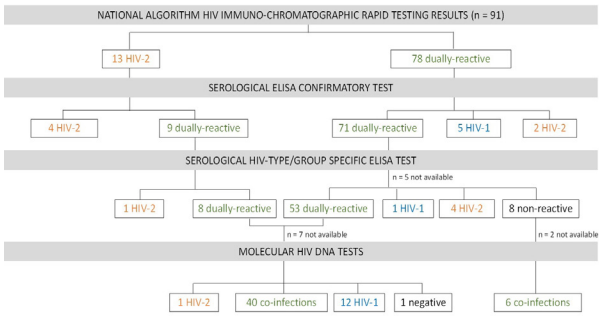
Background: West Africa is characterized by the co-circulation of HIV-1 and HIV-2, leading to co-infections with both viruses. ART-naïve patients co-infected with both viruses were reported to experience a higher mortality rate compared to HIV-2 mono-infected patients. The accurate diagnosis of this co-infection remains challenging for the national HIV testing algorithms of West African countries, mainly due to limited access to DNA PCR technique. The aim of this study was to confirm HIV-1 and HIV-2 co-infection among patients serologically dually-reactive, DNA PCR testing.

Methods: A cross-sectional survey was conducted from April 2016 to October 2017 in the biggest HIV clinics of Côte d'Ivoire and Burkina Faso.
A first serological confirmation was done in the referral laboratory using an in-house, indirect immuno-enzymatic essay allowing the qualitative detection of both HIV-1 and HIV-2 antibodies. In order to separately detect anti-HIV-1 and anti-HIV-2 antibodies, a type/group specific enzyme-immuno assay (HIV-GSEIA) was used. To confirm the co-infections, HIV-1 and HIV-2 DNA-qualitative PCR assays were performed.

Results: A total of 91 patients were enrolled in the study and provided blood sample for HIV type confirmatory testing including 13 (14.3%) HIV-2 mono-reactive and 78 (85.7%) HIV-1/HIV-2 dually-reactive based on the HIV testing National Algorithms. The first serological ELISA confirmatory test performed showed that 80 (78.9%) of the 91 participants were dually-reactive. The HIV-GSEIA performed on these 80 serum samples retrieve 61 HIV-1/HIV-2 dually-reactive samples. HIV-1 and HIV-2 DNA PCR were performed on 54 of the 61 HIV-1/HIV-2 dually-reactive samples and 46 out of 61 (75.4%) samples were found HIV-1/HIV-2 dually infected.

Conclusion: The contribution of type/group specific enzyme-immuno assay to accurately identify HIV-1/HIV-2 coinfections remain suboptimal, emphasizing the need for molecular diagnosis platforms in West Africa, to avail HIV DNA PCR test for the confirmation of HIV-1/HIV-2 co-infections

Study flow of characterization of HIV1&2 dually infected patients



946 EVALUATION OF A NOVEL MULTIPLEX IMMUNOASSAY: IMPROVEMENT FOR HTLV-2 DETECTION

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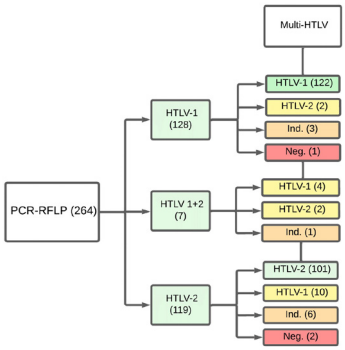
Background: Despite the high sensitivity and specificity by confirmatory serological tests for HTLV infection, numerous cases with untyped or indeterminate results are reported, mainly for HTLV-2 infection. New approaches are urgently needed, especially among volunteer blood donors and individuals co-infected with some persistent viruses. Therefore, the aim of this study was to analyze a new Multiplex-ELISA (Multi-HTLV/InfYnity Biomarkers) confirmatory serological methodology for HTLV-½.

Methods: For this purpose, we performed a comparative analysis between the molecular methodology of PCR-RFLP and Multiplex, with 254 plasma samples.

Results: In molecular assays (nested-PCR for HTLV-½), 128 samples were identified as positive for HTLV-1, 119 for HTLV-2 and 7 for co-infection of both types (HTLV-1+2). Among the samples confirmed as HTLV-1 by the gold standard methodology, 122/128 (95%) showed positive validation and reactivity to HTLV-1 discriminating proteins by the Multiplex; 4% (4/128) had indeterminate or differently typed results to RFLP and only 0.78% (1/128) showed false-negative results. However, for the HTLV-2+ cases by molecular assays, 85% (101/119) were positive and correctly discriminated. Approximately 13% had indeterminate or incorrectly discriminated results and two cases (2/119; 1.7%) had false-negative results. For the co-infected samples (HTLV-1+2), the multiplex did not yield any results according to PCR-RFLP. Of these, 57.14% (4/7) showed reactivity to discriminatory proteins for HTLV-1, 29% (2/7) for HTLV-2 proteins and 14% (1/7) had indeterminate results.

Conclusion: It is important to emphasize that the molecular PCR-RFLP techniques performed by this study showed better efficacy for the diagnosis of HTLV-2 when compared to Multi-HTLV. However, studies show that confirmatory serological results, such as the Western Blot, when compared to the same diagnostic technologies, present similar results, or even lower to the Multiplex/ELISA for this group of individuals. Becoming the closest serological technique to the effectiveness of molecular tests, considered "gold standard" for diagnosis of this infection. Discrepant results need to be further investigated to align serology with PCR techniques.

FIGURE 1: Comparative flowchart between PCR-RFLP results and Multi-HTLV results. PCR-RFLP: polymerase chain reaction-restriction fragment length polymorphism; Multi-HTLV: Multiplex-ELISA/Infynity Biomarkers.



947 HIV DETECTION IN WASTEWATER AS A NEW EPIDEMIOLOGICAL TOOL

Austen Terwilliger[1], Justin Clark[1], Visanthi Avadhanula[1], Karen Feliz[1], Eric Murphy[1], Loren Hopkins[2], Pedro Piedra[1], Anthony Maresso[1], **Thomas P. Giordano**[1]

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Background: Wastewater represents a broad, immediate, and unbiased accounting of the pathgens in the population. We aimed to develop methods to track HIV in wastewater utilizing a viral detection pipeline adapted from platforms developed to track SARS-COV-2.

Methods: We used samples from 6 wastewater treatment plants in the Houston area. We focused on regions of higher prevalence and lower prevalence. First, employing wastewater processing and nucleic acid extraction methods described by our group to detect SARS-COV-2, we tested a single high and low prevalence site in triplicate with all 3 primer sets. nucleic acid extracts from HIV and SIV cell culture supernatants were used as controls. Next, in subsequent samples, RT-PCR reactions with detections were subjected to gel electrophoresis to determine the amplified product sizes. To further confirm HIV detection, we sequenced the RT-PCR products and compared the proportion of reads which mapped to the expected amplified product. In a later set of studies, we fractionated samples into supernatant and pellet. We further tested HIV presence by performing whole virome sequencing on the extracts from some samples that produced detections and mapped reads to published genomes. A crAssphage genome was used as a negative control.

Results: Samples from all sites resulted in signal detection at least once. Only reactions with gag and pol primers appeared to amplify the expected product. Products from the HIV positive control mapped almost exclusively to the HIV genome (97-100% of reads), with a fraction of reads from the SIV negative control doing the same (16-18% of reads). The *ltr* and *pol* products did not map the HIV genome while gag products did (34-44% of reads). Among the fractionated sample, in total, 6 supernatant fractions produced no detection compared to 7 of 8 pellet fractions. The whole virome sequencing produced reads that mapped to the HIV genome with at least 8X depth coverage. The sample with the lowest Ct detection (26) yielded HIV coverage several logs greater than those samples with higher Ct detection (37). Reads from all samples mapped to at least 20% of the HIV genome.

Conclusion: This work provides the first evidence that HIV can be detected in municipal wastewater systems and has the potential to be developed into a new public health tool.

948 CLINICAL DIAGNOSIS IS HIGHLY PREDTIVE OF LAB-CONFIRMED MPOX IN A SEXUAL HEALTH CLINIC

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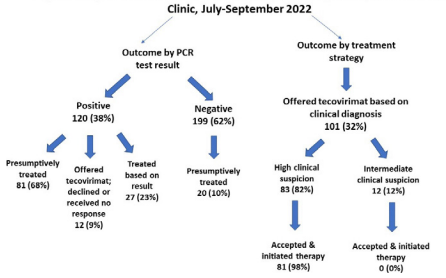
Background: Sexual health clinics (SHC) played a central role in the diagnosis, prevention, and treatment of mpox throughout the 2022 epidemic. From June to October 2022, Public Health-Seattle & King County's SHC diagnosed 44% of all mpox cases in King County, most of whom met tecovirimat treatment criteria. In July 2022, clinicians in our SHC began offering patients empiric tecovirimat therapy based on a clinical diagnosis of mpox or an intermediate clinical suspicion for mpox in a patient for whom arranging follow-up treatment based on mpox polymerase chain reaction (PCR) results would be challenging. We evaluated the accuracy of this approach and the extent to which it allowed us to rapidly initiate presumptive tecovirimat therapy.

Methods: Using data collected between July 29, 2022, and September 30, 2022, we estimated the sensitivity and positive predictive value (PPV) of the clinical diagnosis of mpox using mpox PCR positivity as a gold standard to define true infection. Additional analyses assessed the proportion of all mpox patients who received presumptive therapy and the proportion of presumptively treated patients who had a positive mpox test.

Results: Clinicians evaluated and sent lesion specimens for mpox testing for 320 patients, of whom 120 (38%) tested positive (Figure). Clinicians offered 101 (32%) of the 320 patients tecovirimat at their initial visit based on a clinical diagnosis. Clinical suspicion was high for mpox in 83 (82%) patients, 81 of whom elected to initiate empiric therapy. Clinical suspicion was only intermediate for mpox in 12 (12%) patients; all 12 patients were also offered tecovirimat, but none ultimately initiated. An additional 27 patients were offered tecovirimat after receipt of positive PCR results, of whom 26 (96%) initiated treatment. A total of 81 of the 101 patients with a clinical diagnosis of mpox tested PCR positive (PPV for clinical diagnosis = 80%), and clinical diagnosis was 79% sensitive (95 offered tecovirimat/120 total positives). All 12 patients with an intermediate clinical suspicion for mpox who were offered empiric tecovirimat tested PCR positive. Overall, 108 (90%) of all mpox patients initiated tecovirimat, 81 (75%) of whom started treatment on the day of their initial evaluation.

Conclusion: Clinical providers working in a high-volume, public SHC were able to accurately identify most patients with mpox to provide them with empiric tecovirimat, with 80% of presumptively treated patients ultimately testing positive for mpox.

Figure: 320 patients evaluated & tested for mpox at King County Sexual Health Clinic, July-September 2022



949 WITHDRAWN

950 MPOX TESTING AMONG MEN WHO HAVE SEX WITH MEN WHO REPORTED RECENT HIV OR STI TESTING

Yasmin Ogale[1], Alison Ridpath[1], Travis H. Sanchez[2], Marissa Hannah[2], Kevin Delaney[1], Stefan Baral[3], Patrick S. Sullivan[4], Thomas Carpino[3], Kaitlyn Atkins[3], Eboni Galloway[1], Bruce Furness[1], **Laura H. Bachmann**[1], Winston Abara[1]
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Background: In the current outbreak, mpox is mostly spread through close or intimate contact, and gay, bisexual, and other men who have sex with men (MSM) are disproportionately affected. Integrating mpox testing with HIV/STI testing might be an opportunity to increase case finding. We describe HIV/STI and mpox testing among an online sample of sexually active MSM in the United States, including prevalence and access and barriers to testing.
Methods: We analyzed data collected during August 2022 from the American Men's Internet Survey—Mpox Survey, a cross-sectional, online behavioral survey of 824 MSM in the United States. We calculated the prevalence of no mpox testing among MSM who reported any HIV or STI testing in the past 3 months and any unexplained rash. We described factors associated with not being tested for mpox and reported barriers to testing.
Results: Of 501 participants who reported any HIV or STI testing in the past 3 months, 52 (10%) reported any unexplained rash; of these, 47 (90%) reported no mpox testing. Most who reported no mpox testing were aged ≥40 years (25/47 [53%]) and non-Hispanic White (32/47 [68%]); many reported not living with HIV (37/47 [79%]), ≥2 sex partners (35/43 [81%]), and condomless anal sex in the past 3 months (35/47 [74%]). Overall, 53% (25/47) of participants who reported no monkeypox testing reported low confidence in accessing testing; among these, barriers to testing included not knowing where to get tested (79%), difficulty getting an appointment (58%), and difficulty testing at their doctor's office (47%).
Conclusion: Despite being eligible for testing and presenting for care, the majority of sexually active MSM with rash who reported recent HIV/STI testing did not report mpox testing. These individuals represent missed opportunities for testing; efforts to integrate mpox within HIV/STI testing and reduce testing barriers are recommended.

951 ACTORS ASSOCIATED WITH MPOX SYMPTOMS AND TESTING AMONG MSM IN THE US, AUGUST 2022

Kaitlyn Atkins[1], Thomas Carpino[1], Amrita Rao[1], Travis H. Sanchez[2], O. Winslow Edwards[2], Marissa Hannah[2], Patrick S. Sullivan[3], Yasmin Ogale[4], Winston E. Abara[4], Kevin Delaney[4], Stefan Baral[1]
[1]The Johns Hopkins Bloomberg School of Public Health, Baltimore, MD, USA, [2]Emory University, Atlanta, GA, USA, [3]Emory University, New York, NY, USA, [4]Centers for Disease Control and Prevention, Atlanta, GA, USA

Background: The recent human monkeypox virus (mpox) outbreak in the United States has disproportionately affected gay, bisexual, and other men who have sex with men (MSM). Uptake of mpox testing may be related to symptomology.
Methods: We conducted an online mpox survey from August 5-15, 2022 among cisgender men 15 and older who participated in the 2021 American Men's Internet Survey. We estimated the prevalence of mpox-related symptoms (fever or rash/sores with unknown cause in the last 3 months) and uptake of mpox testing. We calculated adjusted prevalence ratios (PRs) and 95% confidence intervals (CIs) for associations between participant characteristics and mpox symptoms, and summarized characteristics of MSM reporting mpox testing. Among MSM with symptoms who did not test, we examined testing self-efficacy, barriers, and facilitators.
Results: Of 824 MSM, 126 (15.3%) reported at least one mpox-related symptom in the last 3 months; 58 (46.0%) with rash/sores, 57 (45.2%) with fever, and 11 (8.7%) with both. Increased prevalence of mpox symptoms was associated with condomless anal sex (CAS; aPR 1.53, 95% CI 1.06-2.20). Mpox testing was reported by 9/824 MSM (1.09%), including 5 with symptoms. Most MSM reporting mpox testing were non-Hispanic white (7/9 vs 1 Black, 1 Hispanic/Latino) and all 9 lived in urban areas. Most reported having an STI test (8/9), two or more partners (8/9), CAS (7/9), and group sex (6/9) in the last 3 months. Three were living with HIV; the remaining 6 not living with HIV reported current PrEP use. Of MSM with symptoms who didn't report mpox testing but reported on mpox testing efficacy, 47/105 (44.8%) disagreed with the statement that they could get an mpox test if they wanted one. The most common barriers to testing were not knowing where to get tested (40/47, 85.1%) and difficulty getting appointments (23/47, 48.9%). Among those with high testing self-efficacy (58/105, 55.2%), the most common facilitators to testing were knowing where to test (52/58, 89.7%), convenient site hours (40/58, 69.0%), and low-cost testing (38/58, 65.5%).
Conclusion: Messages and interventions promoting testing awareness and community-based testing to increase access to convenient, low-cost services and improve mpox testing uptake are needed. An mpox neutral approach could integrate mpox testing and vaccination within PrEP and STI programs and incorporate targeted outreach to reduce barriers to mpox services for MSM in rural areas, Black and Hispanic/Latino MSM, and MSM living with HIV.

952 UTILITY OF A VIRAL VESICULAR PANEL MULTIPLEX PCR ASSAY FOR THE DIAGNOSIS OF MPOX

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Background: The ongoing Mpox outbreak is notable for its global reach and atypical presentations with significant variation in time of prodromal symptoms, staging and distribution of rash, and varied syndromic presentations (e.g., proctitis, pharyngitis). The overlap of the clinical presentation with common sexually transmitted infections and the high prevalence of co-infections (e.g. herpes simplex virus [HSV], varicella zoster virus [VZV]) highlights a need for improved diagnostic methods. A diagnostic test able to detect and differentiate Mpox from its common close mimics will be useful however, there are no multi-panel assays for vesicular and/or ulcerative lesions approved for clinical use. We evaluated a commercially available "research use only" multiplex PCR assay to detect Mpox virus, HSV, and VZV in clinical specimens.
Methods: Residual specimens collected during routine clinical care were tested using the multiplex panel (Qiagen, Germantown, MD, USA). This panel is a single-use automated multiplex real-time RT-PCR assay commercially available in the United States for "research use only" to detect Mpox virus Clade 1 (MPXV1), Mpox virus Clade 2 (MPXV2), HSV1, HSV2, HHV6, HEV, and VZV.

Reference testing was done by a commercial laboratory as part of routine care. Performance of the test assay was measured by calculating positive percent agreement and negative percent agreement with 95% confidence intervals using the efficient-score method (vassarstats.net).

Results: We tested 47 specimens from 40 unique patients (Table 1). The multiplex panel detected MPXV2 in 36/47 specimens whereas the reference standard detected MPXV2 in 37/47 (PPA 97.3%, 95% CI: 84.2-99.9%). The multiplex panel did not detect Mpox in any specimen that was negative for the reference test (NPA 100%, 95% CI: 65.5-100%). Other viruses beyond Mpox were detected by the multiplex panel in 11 samples, eight of which were co-infections with Mpox according to the reference method.

Conclusion: We report the first validation in the clinical context of a commercially available multiplex PCR assay for the detection of Mpox virus. The multiplex assay was highly accurate for the detection of Mpox and offers several advantages over current assays; short turn-around-time, ease of use, detection of other pathogens. Wider availability of Mpox testing could shorten time to treatment and improve infection control interventions. Finally, multiplex assays that can detect Mpox have utility in both disease surveillance and outbreak response.

Figure 1

		Reference Standard		
		Positive	Negative	Total
QIAstat	Positive	36	0	36
	Negative	1	10	11
	Total	37	10	47
	Positive % Agreement	97.3% (84.2-99.9%)		
	Negative % Agreement	100 % (65.5-100%)		

953 MPOX VIRAL LOAD BY SPECIMEN TYPE AND DIAGNOSTIC TESTING IN A CLINICAL LABORATORY

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Background: Unprecedented person-to-person transmission of MPOX (monkeypox virus) occurred in multiple countries in 2022, raising demand for diagnostic testing and generating uncertainty regarding optimal specimen types. A qualitative real-time PCR assay for the detection of MPOX DNA was validated and implemented in our clinical virology laboratory in August 2022, serving a high-risk population in both outpatient and inpatient settings.

Methods: The assay targeting the J2L/J2R gene (LightMix Modular Monkeypox Virus, TIB Molbiol), using MagnaPure96 for nucleic acid extraction and LightCycler 480 for amplification (Roche), was validated for swabs (skin lesions, rectal, genital, throat/oral) using reference specimens provided from a public health laboratory; all other specimen types were accepted but non-validated. All clinical specimens received for MPOX testing from Aug to mid-Dec 2022 were retrospectively analyzed for cycle threshold (Ct) values correlating with approximate MPOX viral load, percent positivity, and turnaround time.

Results: A total of 229 specimens were received from 144 unique patients (90.3% male, age range 4 to 83 years). Among patients testing positive for MPOX by any one specimen at first presentation (n=33), the mean Ct value and percent positivity varied by specimen type: Ct 22.3 for genital swabs (7/7, 100%), 22.4 for skin lesion swabs (16/16, 100%), 25.8 for rectal swabs (16/17, 94.1%), 30.3 for throat/oral swabs (12/13, 92.3%), 30.4 for urine (4/4, 100%), 35.0 for whole blood EDTA (6/7, 85.7%), and 36.3 for nasal/nasopharyngeal swabs (1/1, 100%). 29.2% of patients (42/144) had more than one specimen type submitted at the time of initial presentation; of those with confirmed MPOX infection (n=17), only 3 patients (17.6%) had one of their specimens test negative for MPOX DNA (1 blood, 1 throat, and 1 rectal swab). The average turnaround time from specimen receipt to result was < 24 hours (20h:12m). The overall positivity rate and testing volumes decreased from 34.7% (51/147 specimens) in Aug-Sep 2022 to 19.0% (8/42 specimens) in Nov-Dec 2022.

Conclusion: Swabs of skin lesions, particularly genital lesions, demonstrated the highest approximate MPOX viral load compared to other specimen types. Submitting multiple specimen types from patients did not improve diagnostic yield when skin lesions were otherwise present. Performing MPOX testing locally in a clinical laboratory enabled prompt turnaround times for timely diagnosis, clinical management and public health intervention.

954 MPOX VIRUS (MPXV) OUTBREAK IN BERLIN: IMPLEMENTATION OF MOLECULAR DIAGNOSTICS

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[1]Medizinisches Infektiologiezentrum Berlin, Berlin, Germany, [2]Praxis an der Kulturbrauerei, Berlin, Germany

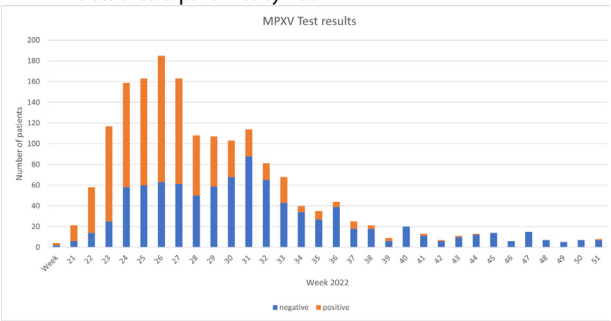
Background: In May 2022 an increasing number of MPXV infections has been reported throughout Europe. With increasing requests for MPXV diagnostics we implemented a multiplex PCR assay testing for Orthopox-Virus (OPV) and Monkeypox-Virus. For quality assessment an internal control and a cell control were included. The assay was validated against the national reference laboratory with more than 100 patient samples.

Methods: Outpatients with contact to confirmed cases or showing symptoms of MPXV infection were tested since end of May 2022 until mid of September. Samples consisted of swabs from lesions, genital, rectal and oro-pharyngeal swabs. To reduce the potential of false negative results we decided for a dual target approach including not only a PCR specific for MPXV but also including OPV. PCR primers and probe for OPV, MPXV and internal control (PhHV-1) from TIB Molbiol (Berlin) were combined with primers and probes for ß-globin in one multiplex PCR. On a Biorad Cfx96 cycler using the TaqPath™ ProAmp™ Multiplex Master Mix run duration was 1:14 h.

Results: 2002 samples were tested for MPXV with 827 positive results. Turn around time was below 24 hours for more than 95% of the samples. The lower limit of detection was confirmed on an EQA panel to be below 60 cop./ml. Most of the positive results were detected in June and July with decreasing rates of tested samples in August and September (see figure). In some cases, with low concentration of MPXV DNA only one of the target genes could be detected (either MPXV or OPV). These cases were all confirmed by additional testing from a new swab. In 28 of the samples neither MPXV-DNA nor cellular DNA could be detected.

Conclusion: We developed a rapid multiplex PCR system to improve patient care and allow better management of infection control. Despite information and vaccination campaigns since July 2022 we still detect new cases of MPXV infection including four cases of vaccination breakthroughs (single dose of vaccine) with high viral loads of up to 4 Mio. Copies/ml. High sensitivity of the assay is of great importance as quality of the swabs is divergent.

MPXV molecular tests performed by week



955 PERFORMANCE OF A DUAL TARGET MPOX VIRUS REAL-TIME PCR ASSAY

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Background: In May 2022 an increasing number of Monkeypox virus (Mpox) cases in non-endemic countries, including the United States, was noted. This outbreak of Mpox has primarily affected men who have sex with men who have reported recent sex with new or multiple partners. This study describes the performance of a single-well dual-target real-time PCR (RT-PCR) test for the detection of Mpox without the need for tiered testing.

Methods: Lesion swabs collected in viral transport media (VTM) were extracted and tested by RT-PCR using a non-variola *Orthopoxvirus* target (E9L-NVAR) and an Mpox virus clade II (West African) target (MPXV-WA). We assessed analytical sensitivity, specificity, precision, accuracy and specimen stability

during storage. RT-PCR cycle threshold (Ct) distributions were determined for specimens submitted for clinical testing.

Results: Analytical sensitivity was 100 copies/mL from swabs in VTM. Intra- and inter-assay precision had a %CV of < 4.9 across 3 target levels. Analytical specificity was 100% when tested among unrelated pathogens including herpes simplex virus (HSV) and varicella zoster virus (VZV), which can also cause lesions. An Mpox-positive clinical specimen diluted in negative swab media was stable for 24 hours at room temperature, 7 days refrigerated and 30 days frozen. Most (96.8%) Mpox-positives were obtained from males with a median age of 35 [IQR: 30-43; range: 3 - 81]. Although Ct values for both RT-PCR targets were highly correlated (Spearman rho 0.995), 12 specimens had undetectable Cts for MPXV-WA in spite of detectable Cts for E9L-NVAR. Six specimens submitted for sequencing harbored the recently described Mpox *crmB* gene deletion. While a single swab was typically collected, multiple swabs were collected from 26.3% (6,577/24,981) of the patients. Ct values from patients with multiple swabs that demonstrated both Mpox-positive and negative results had values that were 4.2 Cts (95% CI: 3.4-5.5) higher than Ct values for patients with exclusively Mpox-positive swabs (Table).

Conclusion: A sensitive, dual-target, RT-PCR assay to enable Mpox diagnosis without tiered testing demonstrated excellent performance in clinical specimens. The inclusion of 2 targets in a single well improved throughput relative to multi-well tests and reduced the risk of false negatives resulting from genomic deletions. Higher Ct values noted for patients with discordant positive and negative swabs may be associated with variability in lesion stage and swabbing efficiencies.

Demographics for patients having positive, mixed and negative Mpox tests

category[1]	sex	N	%	age median [IQR]	age (range)	Ct value median [IQR][2]
positive	M	6179	96.8%	34.0 [26.0-44.0]	1 - 99	
	F	153	2.4%	31.0 [22.0-46.8]	1 - 96	
	U	51	0.8%	33.0 [25.0-44.3]	1 - 71	
						20.3 [17.9-24.7]
mixed	M	266	91.7%	35.0 [29.9-42]	1 - 70	
	F	22	7.6%	30.5 [24.8-46.1]	16 - 92	
	U	2	0.7%	32.5 [32.0-33.0]	32 - 33	
						25.5 [20.0-33.7]
negative	M	10712	58.5%	35.0 [30.0-43.0]	3 - 81	
	F	7492	40.9%	32.0 [25.0-38.3]	1 - 77	
	U	104	0.6%	33.0 [29.2-42.0]	21 - 63	
						NA

[1] positive: positive Mpox test from patients submitting a single specimen or multiple specimens that were all positive for Mpox; mixed: specimens from patients submitting multiple specimens with both positive and negative Mpox tests; negative: all specimens submitted for Mpox testing yielded a negative result.

[2] Median and interquartile ranges for the *crmB* gene target. Hodge-Lehman shift: 4.2 [95% CI: 3.4-5.1]; p<0.0001.

956 COVID-19 SELF-TESTING AMONG HEALTHCARE WORKERS AND GENERAL POPULATION IN MALAWI

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Background: COVID-19 testing is critical for identifying cases to prevent transmission. SARS-CoV-2 self-testing has the potential to increase diagnostic testing capacity and to expand access to hard-to-reach areas in low-and-middle-income countries. We investigated the feasibility and acceptability of COVID-19 self-sampling and self-testing using SARS-CoV-2 Ag-Rapid Diagnostic Tests.

Methods: Between July 2021 to February 2022, we conducted a mixed-methods cross-sectional study examining self-sampling and self-testing using Standard Q and Panbio COVID-19 Ag Rapid Test Device in Urban and rural Blantyre, Malawi. Health care workers and adults (18y+) in the general population were systematically sampled.

Results: Overall, 1,330 participants were enrolled of whom 674 (56.0%) were female with 664 for self-sampling and 666 for self-testing. Overall mean age was 30.7y (standard deviation [SD] 9.6). Self-sampling usability threshold for Standard Q was 273/333 (82.0%: 95% CI 77.4% to 86.0%) and 261/331 (78.8%: 95% CI 74.1% to 83.1%) for Panbio. Self-testing threshold was 276/335 (82.4%: 95% CI 77.9% to 86.3%) and 300/332 (90.4%: 95% CI 86.7% to 93.3%) for Standard Q and Panbio, respectively. Agreement between self-sample results and professional test results was 325/325 (100%) and 322/322 (100%) for Standard Q and Panbio, respectively. For self-testing, agreement was 332/333 (99.7%: 95% CI 98.3 to 100%) for Standard Q and 330/330 (100%: 95% CI 99.8 to 100%) for Panbio. Odds of achieving self-sampling threshold increased if the participant was recruited from an urban site (odds ratio [OR] 2.15 95% CI 1.44 to 3.23, $P < .01$. Compared to participants with primary school education those with secondary and those with tertiary achieved higher self-testing threshold OR 1.88 (95% CI 1.17 to 3.01), $P = .01$ and 4.05 (95% CI 1.20 to13.63), $P = .02$, respectively.

Conclusion: One of the first studies to demonstrate high feasibility of self-testing using SARS-CoV-2 Ag-RDTs in low- and middle-income countries potentially supporting large scale-up.

Table 1. Self-sampling and Self-testing accuracy

Table 1. Self-sampling and Self-testing Accuracy

	Standard Q					Panbio				
	N	n	%	95% CI		N	n	%	95% CI	
Met self-sampling threshold[a]	333	273	82.0	77.4	86.0	331	261	78.8	74	83.1
Met self-testing threshold	335	276	82.4	77.9	86.3	332	300	90.4	86.7	93.3
Agreement with professional test										
Self-sampling	322	322	100	99	100	325	325	100	100	100
Self-testing	333	332	99.7	98	100	330	330	100	100	100

957 INTEGRATION OF SARS-CoV-2 RAPID ANTIGEN TEST IN HEALTH SERVICES IN KENYA AND CAMEROON

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Background: Early diagnosis of COVID-19 is key to prevent severe cases and poor outcomes in vulnerable populations, including pregnant women and people living with HIV or infected with tuberculosis (TB). The feasibility of integration of SARS-CoV-2 antigen rapid diagnostic testing (Ag-RDT) into maternal neonatal, and child Health (MNCH); HIV; and TB clinics is unknown.

Methods: We analyzed data from a SARS-CoV-2 screen and test program implemented in 50 health facilities (25 in Kenya and 25 in Cameroon), integrating SARS-CoV-2 Ag-RDT in MNCH, HIV, and TB clinics between May and October 2022. Clients aged two and older attending MNCH, HIV, and TB clinics were offered SARS-CoV-2 screening, and those eligible were tested using SARS-CoV-2 Ag-RDT. Routine SARS-CoV-2 program data were captured through dedicated paper forms in Cameroon or an electronic medical record (EMR) interface in Kenya and transferred to a database for analysis. We estimated the proportion of clients screened and tested and the SARS-CoV-2 positivity rates.

Results: Overall, 527,184 attendee visits were reported in Cameroon (282,404) and Kenya (244,780), with screening for COVID-19 symptoms and exposure performed in 256,033 (48.5%) with substantive variations between countries (62.6% in Cameroon and 32.4% in Kenya). Among the 256,033 screened, 19,058 (7.4%) were eligible for testing (9.0% in Cameroon and 3.9% in Kenya), of whom 12,925 (67.8%) were tested for SARS-CoV-2 with substantial variation in testing rates between countries (61.9% in Cameroon and 97.9% in Kenya) and clinics (59.9% in MNCH, 68.7% in HIV, and 92.8% in TB clinics). A total of 390 (3.0%) positive tests were identified (329 (3.3%) in Cameroon and 61 (2.0%) in Kenya). The estimated case detection rate was 1.26 (95% CI=0.76–1.75) per 1,000 attendee visits in Cameroon and 0.49 (95% CI=0.12–0.86) per 1,000 attendee visits in Kenya. Country integration strategy, facility level, setting, and clinic were independently associated with screening (Table 1) and testing.

Conclusion: Integration of SARS-CoV-2 Ag-RDT in HIV, TB, and MNCH clinics was feasible in both countries despite challenges with low screening rates in Kenya and low testing rates in Cameroon. Decentralization of SARS-CoV-2 testing at different facility clinics allowed detection of SARS-CoV-2 cases among vulnerable populations. Integration strategies should consider facility settings (rural compared to urban) and additional human resources in high volume facilities to improve screening and testing rates.

Factors associated with COVID-19 screening

Characteristic	Unadjusted OR (95% CI)	Adjusted OR (95% CI)	p-value
Country:			
Cameroun	1	1	
Kenya	0.27 (0.27 – 0.28	0.12 (0.12 – 0.13)	<0.01
Health Facility setting:			
Urban	1	1	
Semi-urban	0.60 (0.59 – 0.61)	1.71 (1.68 – 1.74)	<0.01
Rural	1.07 (1.05 – 1.10)	4.74 (4.62 – 4.86)	<0.01
Health Facility level:			
Primary	1	1	
Secondary	1.01 (0.99 – 1.02)	1.08 (1.06 – 1.10)	<0.01
Tertiary	0.65 (0.64 – 0.66)	1.02 (1.00 – 1.04)	0.10
Clinic:			
HIV clinic	1	1	
MNCH clinic	1.05 (1.04 – 1.06)	1.98 (1.96 – 2.01)	<0.01
TB clinic	0.98 (0.96 – 0.99)	1.13 (1.11 – 1.15)	<0.01

958 IMPACT AND COST-EFFECTIVENESS OF COVID-19 RAPID SELF-TESTING STRATEGIES IN SCHOOLS

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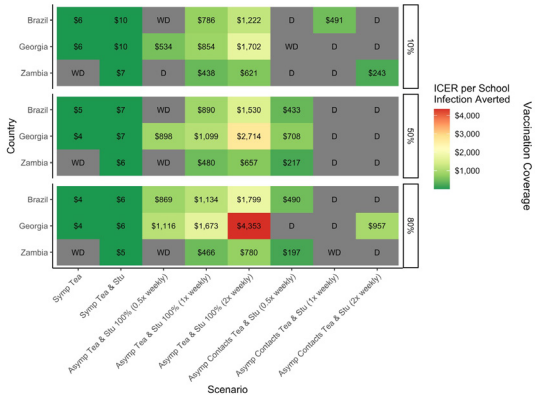
Background: Despite widespread vaccination and increasing population immunity from previous infections, community transmission of COVID-19 continues, and testing may continue to be an important component of our response particularly with the proliferation of new variants of concern. Strategic deployment of SARS-CoV-2 antigen-detection rapid diagnostic (AgRDT) self-tests to settings with increased transmission potential can reduce the viral burden within the specific settings, such as in K-12 schools, and may have spillover benefits for broader community transmission.

Methods: Using a previously developed agent-based simulation model, parameterized to three distinct country archetypes (Brazil, Georgia, Zambia), we analyzed 11 different self-testing strategies within the school-going population at three testing frequencies under 24 different epidemic conditions (Rt, vaccination coverage/effectiveness), comprising a total of 696 scenarios per country. Strategies included symptomatic testing, and in addition, asymptomatic testing at 5, 20, 40 or 100% of schools, or asymptomatic contact testing. These were all targeted to either only teachers or teachers and students. Then, with the cost to offer a COVID-19 self-test in schools at USD 2.50, we performed an economic analysis with all scenarios to identify the most cost-effective strategies by country.

Results: Routine asymptomatic testing of teachers and students at 100% of schools reduced the greatest number of infections across contexts, but at the greatest cost. However, with respect to both the reduction in infections and total cost, symptomatic testing of all teachers and students appears to be the most efficient strategy. Symptomatic testing can prevent up to 69.3%, 64.5%, and 75.5% of school infections in Brazil, Georgia, and Zambia, across all epidemic conditions. Additionally, it can prevent up to 77,200, 80,900, 107,800 symptomatic days per 100,000 teachers and students in each country, respectively, over the course of a 90-day epidemic wave. The incremental cost-effectiveness ratios for strategies that consistently appeared on the cost-effectiveness frontier across countries and epidemic conditions are shown in Figure 1 for an Rt of 1.2.

Conclusion: If financial resources are limited, symptomatic testing of teachers and students has the potential to be cost-effective while reducing a substantial number of infections and the amount of time lost from the classroom, making it a feasible strategy for implementation in a variety of settings.

Incremental cost-effectiveness ratios of COVID-19 self-testing strategies in schools by country at Rt 1.2 and vaccination effectiveness 30%



959 COST-EFFECTIVENESS OF WORKPLACE COVID-19 SELF-TESTING: A MATHEMATICAL MODELING STUDY

Ethan Klock[1], Alvin X. Han[2], Joshua M. Chevalier[1], Megan A. Hansen[1], Hiromi Pandithakoralage[1], Tom Ockhuisen[2], Sarah Girdwood[3], Nkgomeleng Lekodeba[4], Alexandra de Nooy[2], Helen E. Jenkins[1], Colin A. Russell[2], Brooke Nichols[5]
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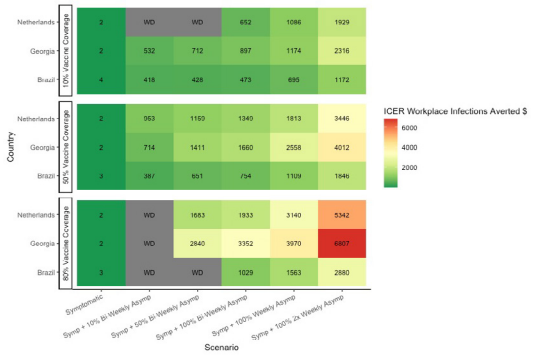
Background: As COVID-19 cases persist, one potential intervention to reduce absenteeism in the workplace due to COVID-19 is to use rapid antigen diagnostics to mitigate the spread of SARS-CoV-2. Furthermore, routine testing in the workplace offers an avenue to reaching a large proportion of the population which could lead to a greater community impact beyond solely mitigating transmission events that occur in the workplace. We sought to identify the most cost-effective workplace testing strategies at the community level and within individual workplaces.

Methods: We used two models to understand how SARS-CoV-2 AgRDTs could best be implemented within the workplace to mitigate the spread of COVID-19. In our community-level dynamic transmission model, PATAT, we evaluated the impact of symptomatic testing and asymptomatic testing of a fixed proportion of the formally employed workforce on broader community transmission. We stratified runs by asymptomatic testing frequency, vaccine coverage, vaccine effectiveness, and Rt. Simulations were informed using demographic data from Georgia, Brazil, and the Netherlands. We conducted a cost-effectiveness analysis using the results from each country and assumed a $2.50 total cost per test.

Results: We observed a substantial decrease in the number of infections occurring in both the workplace and community when a SARS-CoV-2 AgRDTs strategy was implemented. Under all conditions, mandatory symptomatic testing and related quarantine from the workplace averted up to 72%, 79%, and 74% of community infections in Brazil, Georgia, and the Netherlands respectively. Limiting tests to symptomatic workers was always on the cost-effectiveness frontier, regardless of the vaccine coverage, efficacy, or Rt of the virus (Figure 1), at $2-$4 per workplace infection prevented. While asymptomatic testing was on the cost-effectiveness frontier, it would cost an additional $500-$6700 to prevent one additional workplace infection. The added benefit of routine asymptomatic testing was minimal until 100% of the workforce was reached.

Conclusion: We found self-testing with AgRDTs for the formally employed workforce is both efficient at reducing workplace and community infections as well as cost-effective when targeting symptomatic individuals. Willingness to pay to avoid workplace absenteeism may differ by country, individual workplaces, and the perceived economic value of several workdays missed. If there is a higher willingness to pay, routine asymptomatic screening may be considered.

Cost-Effectiveness of Workplace Testing Strategies at Rt = 1.2 With Low Vaccine Efficacy by Workplace Infections Averted



960 HOME VERSUS FACILITY SARS-CoV-2 TESTING AMONG OLDER ADULTS IN NEW YORK CITY

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Background: While nationwide SARS-CoV-2 testing in the United States shifted from facility- to home-based in 2021, less is known about testing behavior of older adults who live at home. We analyze characteristics of older adults who reported facility-based testing with those who tested only at home or at both locations.

Methods: Adults 70 years and older living at home with a landline in New York City were selected using random digit dialing and completed a COVID-19 survey from February 2022 – March 2022. We conducted descriptive statistics using survey weights and bi-variable and multivariable analyses.

Results: Overall, 237 of a total of 294 (81%) participants had tested for SARS-CoV-2 in the prior year. Among those who tested, 81% had tested only at a facility, 4% only tested at home, and 15% tested at both locations (home and facility). White participants more often reported testing at both locations (27%) compared to Black (7%), Latinx (7%) or participants of another race (11%; p-value: 0.004). Those with college education or higher were less likely to rely solely on facilities for testing (75%) compared to those with less education (91%; p-value: 0.02) and 38% of those who reported currently working had tested both locations compared to only 12% of those who were not working (p-value: 0.002). There were no differences in testing by age, sexual orientation, or self-reported mobility. A multivariable logistic regression model that compared those who only tested at a facility with those who tested at both locations or only at home found that when adjusting for working status, age group and education, compared to White participants, Black participants had a third (0.33) the odds of white participants of testing at home or at both locations (p-value: 0.026).

Conclusion: In this sample of urban older adults, using a facility for SARS-CoV-2 testing was more frequently reported than testing at home, indicating the need to retain facility-based testing for this population. However, White participants, more educated participants and those who were working more frequently reported home-based testing compared to other groups suggesting that social constraints may limit access to home testing among the latter group of older adults.

Socio-demographic profile by testing location among older New York City adults

	Facility only	Home only	Both	P-value
Age				0.16
70-79	77.7	4.1	18.2	
80+	88.2	3.1	8.7	
Race and ethnicity				0.004
Black	92.1	1.2	6.7	
Latinx	91.6	2.6	5.7	
White	65.6	7.8	26.6	
Another Race	88.3	0	11.7	
Education				
Less than college	90.9	<1%	8.2	0.02
College and higher	75.1	5.6	19.3	
Employment status				0.002
Currently working	58.4	3.6	38.0	
Not currently working	84.1	3.8	12.1	
Physical activity				0.38
Not limited	82.3	5.0	12.7	
Limited	80.5	2.3	17.2	

961 ANTIBODIES TO SARS-CoV-2 VARY DUE TO ORDER AND FREQUENCY OF VACCINATION OR INFECTION

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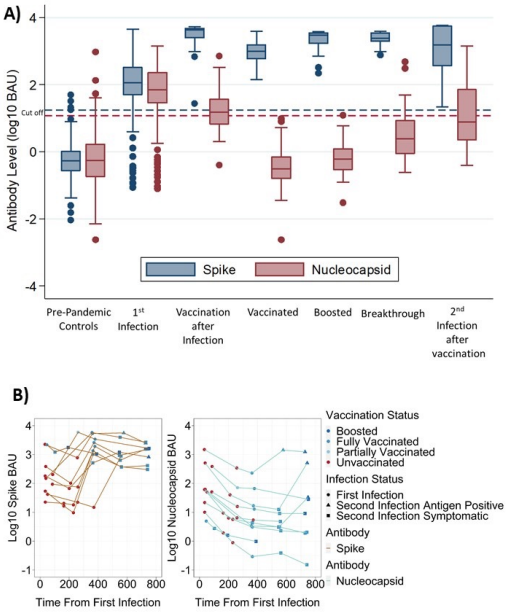
Background: Sero-studies of SARS-CoV-2 have used antibody (Ab) responses to spike (S) and nucleocapsid (N) antigens to differentiate mRNA vaccinated (S+/N-) from infected (S+/N+) individuals. We performed testing on well-characterized subjects to determine how repeated vaccination or infection, and time from those exposures, influence these Ab levels.

Methods: Samples from individuals with known infection status: pre-pandemic negative controls n=462; first-time infected n=237 (~45 days post); vaccinated after infection n= 34 (~40 days post-vaccination and ~180 days post-infection); fully vaccinated n=158 (~50 days post); boosted n=31 (~30 days post); breakthrough n=18 (~14 days post-infection); reinfected n=10 (varied). Longitudinal samples (n=51) from subjects with evidence of reinfection (symptoms and/or positive rapid antigen test), were tested to determine the impact of the order of infection and/or vaccination on the magnitude of the anti-S and anti-N IgG Ab detected in the blood. Testing was performed with MesoScale Diagnostics (Gaithersburg, MD) assay. Outcomes are presented in WHO International Binding Antibody Units (BAU/mL). The cutoff for a positive result was 18 BAU for S and 12 BAU for N.

Results: The median amount of Ab (IQR) in BAU for each group (**Figure A**) was: pre-pandemic negative controls S 0.53(0.27,1.03), N 0.55(0.18,1.67); first-time infected S 114(51,328), N 70(29,229); vaccinated after infection S 4367(2479,4837), N 15(7,35); fully vaccinated S 998(586,1529), N 0.31(0.16,0.68); boosted S 2988(1768,3522), N 0.59(0.32,1.03); breakthrough S 2429(2032,3413), N 2.5(0.93,8.6); reinfected S 1533(486,4643), N 7.8(2.6,62). For the breakthrough and second infections 17% and 40% were seropositive to N, respectively. Longitudinal analysis (**Figure B**) of those with multiple infections showed that all those with a positive rapid antigen test for their second infection had an increase in N Ab.

Conclusion: The prevalence of antibodies to nucleocapsid cannot be used to determine the proportion of individuals infected to SARS-CoV-2 in a vaccinated population. Booster, repeated, and breakthrough infections are associated with IgG Ab levels to S >400 BAU/mL. A majority of breakthrough infections did not elicit an Ab response to N. For those with repeated infection, a minority elicited antibody responses to N. This could be related to misdiagnosis or the burden of infection, as only those who were positive by rapid antigen assay (indicative of a high viral load) had an increase in N Ab.

Figure: Longitudinal levels of antibody against SARS-CoV-2 spike and nucleocapsid antigen in reinfected individuals.



962 SARS-CoV-2 REPLICON SYSTEM FOR THE PHENOTYPIC EVALUATION OF NSP GENE SUBSTITUTIONS

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Background: Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is the cause of the current global pandemic of the COVID-19, which has persisted partly through the emergence of new variants. A non-infectious, convenient, and reproducible *in vitro* system is needed to assess drug susceptibility of new variants of concern and potential drug resistance mutations.

Methods: The SARS-CoV-2 replicon protocol was adapted and optimized based on {Zhang 2021}. The replicon RNA was produced by *in vitro* transcription of full-length replicon DNA assembled by ligation of plasmid fragments encoding for the SARS-CoV-2 non-structural proteins (Nsps), nucleoprotein and gaussia luciferase reporter protein. Wild-type and mutant replicon RNAs were transfected into Huh7-1CN cells by electroporation and treated with remdesivir (RDV). To determine EC_{50} values, luciferase activity was determined at 48 hours post transfection. A recombinant SARS-CoV-2 virus rescue system {Xie 2020} was used to generate matching Nsp mutants for comparison with the replicon system.

Results: The selected substitutions reflective of Omicron BA.5 sub-lineage BF.7 variant: the triple mutants (Nsp12 (P323L) +Nsp13 (R392C) + Nsp14 (I42V), and a single Nsp12 L247F mutant as well as several specific Nsp12 mutations identified by *in vitro* resistance selection with RDV or RDV parent nucleoside analog GS-441524 were cloned into the replicon and tested for susceptibility to RDV. RDV inhibited the SARS-CoV-2 wild-type replicon with a mean EC_{50} value of 14.7 ± 3.5 nM (N=9). The Nsp12 P323L substitution, a common polymorphism in all major variants of concern including Omicron, was fully susceptible to RDV with a 0.6-fold change in EC_{50} from the wild-type. The Omicron BF.7 triple mutants and L247F were also fully susceptible to RDV with 0.5- and 0.4-fold changes, respectively. Nsp12 substitutions F480L, V557L, V792I, S759A+V792I, and C799F resulting from *in vitro* resistance selections with RDV showed minimal to moderate levels of reduced susceptibility to RDV (1.8 to 18.3-fold change) (Table 1). The RDV EC_{50} fold changes correlated between the non-infectious replicon and recombinant infection virus system (Table 1).

Conclusion: The replicon system is a convenient and reproducible model to test the susceptibility of SARS-CoV-2 mutant variants to RDV and potentially other antivirals. The common Nsp12 polymorphisms in all variants including the highly transmissible Omicron variant were fully susceptible to RDV.

Table 1. Correlation of EC_{50} fold changes between the SARS-CoV-2 replicon and recombinant virus system

Table 1. Correlation of EC_{50} fold changes between the SARS-CoV-2 replicon and recombinant virus system

Nsp12	RDV EC_{50} in nM, Average ± s.d. (N ≥ 2) (Fold-change relative to WT)	
	Recombinant virus system	Replicon
WT	57 ± 11 (1)	14.7 ± 3.5 (1)
P323L	44 ± 2 (0.8)	8.4 ± 2.1 (0.6)
F480L	118 ± 26 (2.1)	26.9 ± 0.8 (1.8)
V557L	112 ± 27 (2.0)	29.4 ± 2.8 (2.0)
V792I	171 ± 70 (3.7)	53.7 ± 6.9 (3.6)
S759A+V792I	1170 ± 53 (11.7)	269.3 ± 38.2 (18.3)
C799F	199 ± 58 (3.5)	49.9 ± 2.4 (3.4)

963 USE OF Ag-RDTs TO REDUCE SARS-CoV-2 INFECTIONS AT RELIGIOUS GATHERINGS IN LICS & MICS

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Background: Throughout the COVID-19 pandemic, it was evident that many SARS-CoV-2 infections occurred at mass gathering events. In many LMICs and LICs, places of worship serve as a venue for mass gatherings, and therefore a potential source of large-scale transmission events. Mass gatherings at places of worship also serve as an opportunity to distribute Ag-RDTs to a significant proportion of the community at regular intervals, disrupting transmission within the event and potentially impacting community spread of SARS-CoV-2.

Methods: We used an agent-based community assessment model, Propelling Action for Testing and Treatment, to estimate how various strategies of asymptomatic Ag-RDT self-testing of a fixed percentage of persons attending large religious gatherings (10%, 20%, 40%, 100%), in addition to the general underlying level of ongoing symptomatic testing in the population, would impact community transmission of SARS-CoV-2 in 3 contexts (Brazil, Georgia, Zambia). These testing strategies were analyzed with bi-weekly and weekly asymptomatic self-testing in a population with varying levels of vaccine efficacy (low/high), vaccine coverage (10%, 50%, 80%), and reproductive numbers (0.9, 1.2, 1.5, and 2.0) to simulate varying stages of the COVID-19 pandemic. We then performed an economical evaluation of the results from the model to understand the impact and cost-effectiveness of each self-testing strategy at places of worship.

Results: In each of the epidemic conditions modeled, testing of symptomatic persons at weekly and biweekly frequencies can avert 2%-16% of Brazilian community infections and 31%-45% of infections occurring in places of worship in Brazil. The same is true in Georgia (1%-6% of total infections and 28%-45% place of worship-related infections) and Zambia (2%-21% of total infections and 29%-45% of place of worship related infections) despite differences in the proportion of populations regularly attending places of worship in the 3 countries. Asymptomatic self-testing in 100% of places of worship in a country result in the greatest percent of infections averted and consistently lands on the cost-effectiveness frontier yet requires a budget 520-1550x greater than that of symptomatic testing alone.

Conclusion: Testing of symptomatic persons attending regular religious gatherings have a significant impact on the spread of SARS-CoV-2 in places of worship and can significantly reduce community spread in contexts where population level attendance at religious gatherings is high.

Cost-effectiveness analysis from Brazil, Georgia and Zambia modelling results with infections averted within places of worship and total community infections averted assuming a total cost per self-test of $2.50 USD.

Scenario	Percent total infections averted (%)	Incremental cost per total infection prevented (USD $)	Percent place of worship infections averted (%)	Incremental cost per infection prevented within place of worship (USD $)	Total Cost (USD $)
Brazil					
Symptomatic testing only	2-16	3-42	31-45	74-175	$17,600-$451,800
Asymptomatic self-testing 100%	3-34	161-11,838	52-82	2889-57,457	$7.4 million-$13.4 million
Georgia					
Symptomatic testing only	1-6	3-37	28-46	85-303	$2,700-$155,000
Asymptomatic self-testing 100%	1-10	165-18,693	53-80	2,995- 470,245	$2.3 million-$4.2 million
Zambia					
Symptomatic testing only	2-21	3-38	29-45	69-119	$43,200 - $711,200
Asymptomatic self-testing 100%	5-52	202-2,020	49-85	2,854-101,580	$12.3 million - $22.6 million

964 Ag-RDT MASS TESTING IN LARGE GATHERINGS TO IDENTIFY SARS-CoV-2 INFECTIONS IN KENYA

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Background: In Africa, the 9.3 million COVID-19 cases and 174,993 related deaths reported between 2020 and 2022 are underestimated given the limited testing and reporting capacity. Mass testing with antigen-detecting rapid diagnostic tests (Ag-RDTs), including testing of asymptomatic individuals, is expected to improve the identification of SARS-CoV-2 infections and enable immediate clinical management, isolation of patients, contact tracing, and quarantining of contacts. We offered mass Ag-RDT testing in large gatherings to determine the SARS-CoV-2 case detection rate, acceptance of mass testing, the prevalence of circulating variants, and the cost of implementation.

Methods: In 49 high-attendance facilities in Kiambu County identified as possible points of community-based transmission, individuals two years old and older were offered COVID-19 testing and vaccination. Those accepting testing were enrolled in the study after providing written informed consent. A questionnaire was administered and a nasopharyngeal swab was collected. Those testing positive and those testing negative but with COVID-19 symptoms were referred for PCR testing and genome sequencing. Data were analyzed using descriptive statistics. The total cost of implementing the community

testing was estimated from a health system perspective using a micro-costing method.

Results: From June-September 2022, 4,062 individuals were offered testing (mean age 39 years, 2,114 (58.6%) were male). The testing acceptance was 78.1% (3,174/4,062) 95%CI, 76.9%-79.5%). The case detection rate was 34/3,174 (1.07%: 95%CI 0.7%-1.4%). Table 1 shows the testing and case detection rates by facility type. Of the 34 positive cases, 11 (32%) were asymptomatic. A PCR result was available for 27 Ag-RDT positive participants and 13 Ag-RDT negative participants with SARS-COV-2 symptoms and was positive in 24 (88.9%) and 4 (30.8%) respectively. Circulating variants were identified in 11 participants (Omicron 22A: 36% and 22B: 64%); 15 samples could not be sequenced due to CT values >35. Community mobilization was the major cost driver (26%) followed by the purchase of SARS-CoV-2 Ag-RDT (20.5%). The total cost of the intervention was US$50,538; the cost per individual tested was US$15.89 and US$1,484 per new COVID-19.

Conclusion: Targeted mass community testing using SARS-CoV-2 Ag-RDT is a feasible and affordable strategy in identifying priority areas for vaccination and early treatment for individuals with COVID-19.

Table 1. Testing and case detection rates in the different venue types

Table 1. Testing and case detection rates in the different venue types

Venue type	Number offered testing (average per day)	Number tested (average per day)	Percentage tested among offered testing (95% CI)	Number of Ag-RDT positive (average per day)	Percentage of positive among tested (95% CI)
Market/shopping centre (n=31)	2591 (83.6)	1998 (64.5)	77.1 (75.4-78.7)	24 (0.8)	1.2 (0.8-1.8)
Chief's camp (n=5)	328 (65.6)	242 (48.4)	73.8 (68.7-78.5)	2 (0.4)	0.8 (0.1-3.0)
Bus parks (n=6)	397 (66.2)	293 (48.8)	73.8 (69.2-78.1)	8 (1.3)	2.7 (1.9-5.3)
Stadium (n=2)	148 (74)	109 (54.5)	73.6 (65.8-80.5)	0 (0)	0
Others (n=6 /5*)	598 (99.7)	532 (88.7)	89.0 (86.2-91.4)	0	0
Overall (n=50)	**4062 (81.2)**	**3,174 (63.5)**	**78.1 (64.8-76.8)**	**34 (0.7)**	**1.07 (0.7-1.4)**

965 SARS-CoV-2 WASTEWATER SURVEILLANCE IN A US JAIL: CORRELATION, FEASIBILITY, NEXT STEPS

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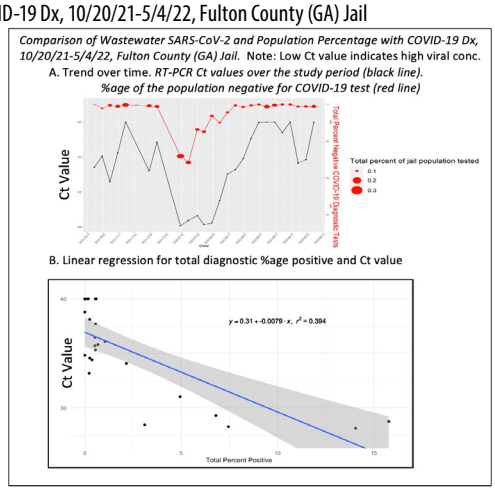
Background: Jails house vulnerable persons. Crowded conditions, restricted access to medical care, and limited resources facilitate infectious disease outbreaks, particularly for airborne, highly transmissible diseases like COVID-19 (C19). Wastewater-Based Surveillance (WBS) is a low-cost, highly sensitive, non-invasive method that can provide an early warning of C19 surges in communities. We examined the value of SARS-CoV-2 WBS for a mega-jail.

Methods: 28-week study period: 10/20/21- 5/5/22. Wastewater samples were collected x 25 weeks; SARS-CoV-2 RNA was measured using RT-qPCR. We sampled one manhole serving multiple housing units. C19 rapid test data on jail entrants were summarized daily by the jail; 16 mass PCR screenings using self-collected nasal swabs were conducted by the study team. Individual diagnostic tests were collated and analyzed on a weekly basis. Data were summarized by % of the tested jailed individuals found infected. The Spearman correlation coefficient between weekly SARS-CoV-2 RNA in wastewater and % of positive (pos) C19 diagnostic tests were calculated; we also used linear regression to assess the predictability between paired Ct values and weekly % of pos diagnostic tests.

Results: Weekly WBS coupled with periodic mass testing of jailed individuals was feasible. The efficiency of gathering individual nasal swabs increased to 3 tests collected per minute through a CQI process. PCR signal strength for SARS-CoV-2 RNA in jail wastewater correlated with the % of jail residents tested who had C19. The mean RT-qPCR Cycle threshold (Ct) value was 35.2. Overall, 3.4% of nasal swabs were pos. A strong inverse correlation was observed between % nasal swab pos and WBS Ct value (Figure.) The Spearman correlation coefficient was r= 0.628; linear regression likewise showed a similar correlation.

Conclusion: Weekly WBS results for C19 correlated with the proportion of C19 individual test results. WBS proved to be a practical strategy to surveil for C19 in this jail setting. We are developing means to identify exact source, by housing unit, of wastewater with positive signal. Future studies will explore WBS for Mpox and HIV in correctional facilities. HIV RNA can be found in wastewater specimens; whether WBS for HIV in congregate facilities is feasible remains an open question.

Comparison of WWastewater SARS-CoV-2 and Population Percentage with COVID-19 Dx, 10/20/21-5/4/22, Fulton County (GA) Jail



966 DISABILITY AND COVID-19 TESTING: A CROSS-SECTIONAL RADx-UP STUDY

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Background: Nearly 26% of adults in the U.S. live with disability and are more likely to experience chronic health conditions, barriers to healthcare, and severe COVID-19 illness. Therefore, COVID-19 testing of adults living with disability is important to consider. The purpose of this study was to explore relationships between disability and COVID-19 testing, infection, and related challenges.

Methods: A Rapid Acceleration of Diagnostics–Underserved Population (RADx-UP) project in Miami, FL determined disability with a modified version of the Washington Group General Disability Measure. HIV serostatus and COVID-19 vaccination were confirmed with medical records. COVID-19 testing and infection history were self-reported. Statistical analyses included chi-squared tests and multiple binary logistic regression; variance inflation factors were calculated to ensure absence of collinearity.

Results: A total of 1,689 RADx-UP participants with an average age of 55±12.3, 51% male, 49% Black non-Hispanic, 23% living with HIV (86% virally suppressed), and 76% received at least one dose of a COVID-19 vaccine. Nearly 40% were disabled, 37% reported employment disability, and 21% were functionally disabled (disability that interferes with performance of daily activities). Despite recruitment from the same sources, PLWH, compared to those without HIV, were more likely to be disabled (52% vs 36%; p< 0.0001), report employment disability (63% vs 30%; p< 0.0001), and report functional disability (29% vs 18%; p< 0.0001). Those with employment disability were less likely to have ever been tested for COVID-19 compared to those without (81% vs 85%; p=0.026). Employment disability was also associated with lower odds of having ever tested positive for COVID-19 after adjustment for demographics, health insurance, HIV, COVID-19 vaccination, smoking, and lung disease (aOR, 0.62; 95% CI, 0.43-0.90; p=0.013). Disability was associated with greater odds of transportation challenges (aOR, 2.33; 95% CI, 1.76-3.08; p< 0.0001), illicit drug use (aOR, 1.92; 95% CI, 1.49-2.47; p< 0.0001), and smoking (aOR, 1.74; 95% CI, 1.39-2.17; p< 0.0001). Compared to those without, those with transportation challenges (14% vs 40%; p< 0.0001) and illicit drug use (18% vs 30%; p=0.001) were more likely to postpone medical care.

Conclusion: Lower COVID-19 testing rates may contribute to underestimated COVID-19 positivity rates in adults living with disability. Challenges with transportation and substance abuse contribute to less engagement in care.

967 COST-EFFECTIVENESS OF THE DUAL PREVENTION PILL FOR CONTRACEPTION AND HIV PROPHYLAXIS

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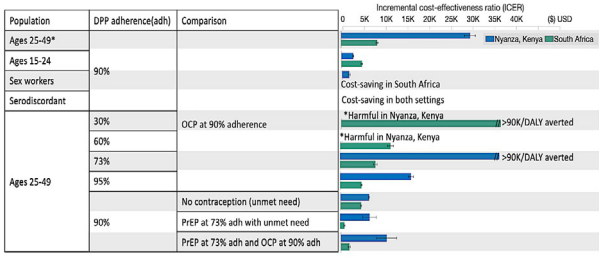
Background: Women in sub-Saharan Africa (SSA) experience the world's highest rates of both HIV infection and unintended pregnancy. The Dual Prevention Pill (DPP) co-formulates PrEP and oral contraception into a single daily pill and may be preferred by women with dual prevention needs. However, most countries in SSA face severe healthcare resource constraints. Research is needed to assess whether, in what populations, and in what use cases the DPP would be cost-effective.
Methods: We augmented an agent-based SSA HIV model with maternal health parameters including unintended pregnancy, abortion, and maternal mortality. Based on a previous market analysis, we assumed a primary DPP user population of current oral contraceptive users ages 25-49, and alternative user populations with different risk profiles (ages 15-24, sex workers, serodiscordant couples) and product use profiles (unmet need for contraception, oral PrEP use, and condom use). For each population and use case, we estimated the HIV infections averted, pregnancies averted, disability-adjusted life-years (DALYs) averted, and incremental cost-effectiveness ratio (ICER) over a 30-year time horizon, 3% annual discount rate, and assuming equivalent adherence to DPP as to oral contraceptives. Sensitivity analyses explored different adherence levels, unit costs, time horizons, economic discount rates, and SSA settings.
Results: The DPP is likely to be cost-effective in current oral PrEP users with high (73%) adherence and cost-saving in PrEP users with low (30%) adherence. It is also likely to be cost-saving in sex workers and serodiscordant couples not on PrEP, whether they have unmet need for contraception or are currently using oral contraception. DPP is unlikely to be cost-effective in oral contraceptive users ages 25-49 and would be net harmful if it reduced contraceptive adherence, depending on the setting. Results were robust to a range of time horizons or discount rates.
Conclusion: DPP is more likely to be cost-effective in settings and populations with higher HIV incidence. There is a risk that DPP could be net harmful for current oral contraceptive users if it led to substantial reductions in contraceptive adherence. DPP implementers should consider monitoring DPP adherence and promoting uptake in high-risk populations.

Cost-effectiveness of the dual prevention pill for contraception and HIV prophylaxis in Kenya and South Africa



968 POTENTIAL IMPACT & COST-EFFECTIVENESS OF WIDELY ACCESSIBLE TLD IN SUB-SAHARAN AFRICA

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Background: Post-exposure prophylaxis (PEP) offers protection from HIV after unanticipated condomless sex, but is not widely available in a timely way in sub-Saharan Africa (SSA). We propose consideration of making tenofovir-lamivudine-dolutegravir (TLD) widely and freely locally available in communities without prescription (e.g. where condoms are made available, along with HIV self-test kits and emergency contraception), with community ownership and education, to enable PEP use within 24 hours of sex. Giving unrestricted access would mean drugs might also be used as PrEP, and as ART for people with HIV, without engagement in care, the net effects of which are uncertain.
Methods: We used an existing individual-based model (HIV Synthesis). Beneficial effects of community TLD modelled: (i) higher PEP/PrEP coverage of new sex partnerships (ii) greater likelihood of HIV-diagnosed people being on ART (iii) some use of ART in people who have never been tested by the health care system, due to self-testing / self-starting ART; negative effects: (i) lack of initial / 3- monthly HIV testing in some PrEP users (ii) increase in proportion of people on ART who are not in care and not monitored (iii) increased risk of IRIS in people with starting ART without assessment of AHD (iv) some use of ART in people without HIV or a risk for HIV. Through sampling of parameter values we create "setting-scenarios" reflecting uncertainty in assumptions and a range of settings similar to those seen in SSA. For each setting scenario, we compare outcomes from 2022 between policies of (i) continuation of oral TDF/FTC PrEP availability only, and (ii) community availability of TLD/PEP. We assume a full 3 month (time step of the model) cost of TLD for 3-month periods in which PEP is used, and that TLD has no greater efficacy as PrEP than TDF/FTC.
Results: The modelled effects of community TLD availability result in a median (90% range over setting scenarios) reduction in incidence of 48% (23%-71%) over 20 years. Incidence in 20 years is < 1/100 person years in 50% of setting scenarios with community TLD/PEP. Overall, community availability of TLD has health benefits and is cost-saving. It is cost-effective in 84% of setting scenarios.
Conclusion: Community availability of TLD/PEP has potential to be impactful and cost-effective, providing impetus for pilot evaluations to understand whether this potential can indeed be realized in practice. We provide a framework to allow results from such evaluations to inform policy.

Table. Modelled effect of community TLD/PEP across settings scenarios in sub-Saharan Africa

	No community TLD/PEP	Community TLD/PEP	Comparison
	Mean (90% range over setting scenarios)		
Short term effects (5 years)			
Percent of people with PEP/PrEP indication who take PEP/PrEP	37 (22-52)	64 (44-82)	+27 (18-34)
Proportion of people with HIV on ART (men/women)	79 (67-89) / 86 (78-92)	84 (74-91) / 89 (82-94)	+5 (+2- +9) / +3 (+1- +6)
Outcomes (20 / 50 years)			
HIV incidence age 15-49 (over 20 years)	0.49 (0.13-1.29)	0.27 (0.05-0.77)	48% reduction (23% - 71%)
HIV incidence age 15-49 <0.1/100 pyrs (in 20 years)	10% of setting scenarios	51% of setting scenarios	+41%
Difference in DALYs per year over 50 years (1000s)	-----	-----	-18.2 (-71.4 – +30.0)
Difference in annual cost over 50 years	-----	-----	-$13.6m (-46.8 - +1.2)

Restricted to setting scenarios with HIV incidence in 2022 of > 0.2 / 100 person-years
Short term effects reflect assumptions over uptake.
For cost effectiveness analysis: $500 per DALY averted cost-effectiveness threshold, 3% per annum discount rate. DALYs costs in context of adult population of 10 million.

969 POPULATION IMPACT OF EXPANDING PrEP USAGE IN SOUTH AFRICA: MODEL COMPARISON ANALYSIS

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Background: Long-acting injectable cabotegravir (CAB-LA) demonstrated superiority to daily oral tenofovir disoproxil fumarate/emtricitabine (TDF/FTC) for HIV pre-exposure prophylaxis (PrEP) in two clinical trials. It is recommended by WHO as an additional prevention choice for people at substantial risk of HIV infection. HIV Modeling Consortium and HPTN Modeling Center conducted a comparative modelling analysis of the potential impact of expanding PrEP coverage by offering CAB-LA to men and women in South Africa.
Methods: Three independent age- and risk-stratified HIV transmission models (Synthesis, EMOD and Thembisa) were parameterised and calibrated to local data from South Africa. Expanding population PrEP coverage to 5 or 10% after 5 years were simulated by recruiting additional users based on model-specific targeting of PrEP use by risk. Models assumed 95% CAB-LA effectiveness based on HPTN 083 and model-specific TDF/FTC effectiveness. Population impact and efficiency of PrEP expansions were evaluated over 20 years compared to base-case scenarios assuming negligible TDF/FTC use.
Results: In the base-case scenarios with no PrEP expansion, median overall PrEP coverage in South Africa is currently < 1% and is modelled to remain < 1% by 2042. Achieving 5% PrEP coverage with CAB-LA by 2027 may avert 45% of new infections between 2022-2042 when use is assumed to be available to all

but concentrated amongst people in periods of substantial risk (Synthesis), 35% of new infections when targeted to high risk groups (EMOD), and 11% of new infections if CAB-LA is available to all but more likely to be used by high-risk individuals (Thembisa). Increasing CAB-LA coverage to 10% under the same conditions may avert 50% (Synthesis), 42% (EMOD), and 18% (Thembisa) of new infections. A 5% expansion with oral TDF/FTC instead of CAB-LA would be expected to reduce the impact by 18 percentage points (pp) (Synthesis), 21pp (EMOD), and 2pp (Thembisa) due to lower assumed TDF/FTC effectiveness. With better risk targeting, PrEP expansions would require only 18 (Synthesis) and 14 (EMOD) additional person-years (PYs) on CAB-LA to prevent one infection, compared to 67 PYs if CAB-LA is less risk-targeted (Thembisa).

Conclusion: Our analysis suggests that offering CAB-LA in South Africa may impact the HIV epidemic substantially if it results in higher PrEP coverage and is adequately used by people at high risk of acquiring HIV. Expanding PrEP could be highly efficient if predominately used during periods of substantial risk.

Percentage infections averted over 20 years with 5 and 10% population PrEP coverage achieved by 2027.

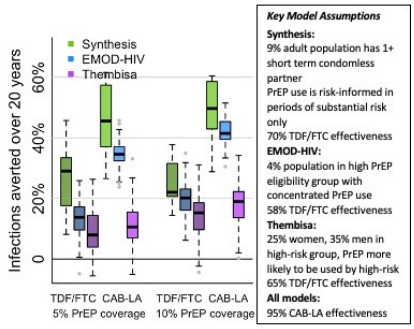

Figure: Percentage infections averted over 20 years with 5 and 10% population PrEP coverage achieved by 2027 with the Synthesis (green), EMOD-HIV (blue), and Thembisa (purple) models. Darker shades show oral PrEP (TDF/FTC) use and lighter shades show CAB-LA PrEP use. PrEP coverage refers to proportion of entire population covered.

970 RANDOMIZED EVALUATION OF THE IMPACT OF STI POINT-OF-CARE TESTING ON PrEP INITIATION

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Background: Pre-exposure prophylaxis (PrEP) programs present a platform for integrating curable sexually transmitted infection (STI) testing and treatment. Point-of-care (POC) STI testing has been hypothesized to influence PrEP use, but data are few, especially in pregnancy. We evaluated the impact of POC STI testing compared to standard-of-care (SOC) STI syndromic management on PrEP initiation and persistence among pregnant women in antenatal care in Cape Town, South Africa.

Methods: We enrolled consenting pregnant (≤34 weeks), HIV-negative women (aged ≥18 years) in Cape Town at their regular antenatal visit. Eligible women were randomised (1:1) to either the SOC (syndromic STI management in antenatal care) or intervention (POC STI testing) arm. Women were offered oral PrEP at baseline and asked to return after 1 month for PrEP counselling and dried blood spot (DBS) collection for tenofovir disphosphate (TDF-DP) analysis. Women in the intervention arm self-collected vaginal swabs that were tested for *Chlamydia trachomatis*, *Neisseria gonorrhoeae* and *Trichomonas vaginalis* using a Cepheid GeneXpert test and offered same-day treatment if diagnosed. We evaluated the proportion of women initiating PrEP and PrEP persistence at 1-month (through self-report and DBS) by study arm.

Results: Between November 2021 and July 2022, we enrolled and randomized (1:1) 272 pregnant women (median age 27 years; median gestation 22 weeks). Twenty-seven percent of women in the intervention arm were diagnosed with ≥1 STI vs. 23% of women who were treated for STI symptoms in the SOC arm (p=0.83). Overall, 64% of women initiated PrEP at baseline (62% in SOC; 67% in intervention arm; p=0.43); increasing to 72% among STI diagnosed/symptomatic compared to undiagnosed/asymptomatic women (76% among intervention [p=0.17] and 68% among SOC [p=0.46] arm). Among 152 women that reported PrEP persistence data, 55% reported taking 7 doses/week (51% in SOC, 44% in POC arm; p=0.42) in the last 30 days. Among 142 women with DBS results (93%), 58% had detectable levels of tenofovir at 1-month (60% among intervention and 56% among SOC; p=0.67).

Conclusion: The proportion of PrEP initiating or persisting (through self-report or DBS) women did not differ by POC vs syndromic STI management. A higher proportion of STI diagnosed and symptomatic women initiated PrEP compared to negative or asymptomatic women, suggesting that STI testing and/or treatment may influence PrEP initiation in pregnant women.

Characteristics of pregnant women randomized to point-of-care STI testing or standard syndromic STI management in antenatal care, Cape Town, South Africa, 2021–2022

Table. Characteristics of pregnant women randomized to point-of-care STI testing or standard, syndromic STI management in antenatal care, Cape Town, South Africa, 2021–2022

	Total (N=272)		Intervention: Offer point-of-care STI testing during antenatal care (N=135)		Standard-of-care: Syndromic STI management (N=137)		p-value
	N	(%)	N	(%)	N	(%)	
Maternal age (years; median IQR)	27	(23–32)	27	(23–32)	27	(23–33)	0.96
Gestational age (weeks; median, IQR)	22	(18–26)	22	(18–27)	21	(17–26)	
Reported ≥1 STI symptom	64		33	(24.4)	31	(22.6)	0.72
Reported vaginal discharge	37		23	(8.5)	14	(5.2)	
Reported pain during intercourse	25		12	(4.4)	13	(4.8)	
Reported pain during urination	23		10	(3.7)	13	(4.8)	
Reported vaginal bleeding	1		1	(0.4)	0	(0.0)	
Reported genital sore/ulcers	6		3	(1.1)	3	(1.1)	
Reported other^ STI symptom(s)	3		0	(0)	3	(2.2)	
Diagnosed with ≥1 STI (NG/CT/TV)			37	(27.4)			
Diagnosed with *Neisseria gonorrhoeae*			10	(7.4)			
Diagnosed with *Chlamydia trachomatis*			26	(19.3)			
Diagnosed *Trichomonas vaginalis*			14	(10.4)			
Initiated HIV pre-exposure prophylaxis	175	(64.3)	90	(66.7)	85	(62.0)	0.43
Provided DBS sample at one-month visit	142	(81.1)	74	(82.2)	68	(80.0)	0.14
Detectable tenofovir disphosphate levels in dried blood spot at one-month after PrEP initiation	82	(57.7)	44	(59.4)	38	(55.9)	0.67

^Other refers to 2 cases of vaginal itchiness and 1 case of vaginal cysts and pain

971 SEXUAL BEHAVIOR AND STI INCIDENCE DURING THE FIRST 4 YEARS OF PrEP USE AMONG MSM

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Background: A prospective demonstration project in Amsterdam (AMPrEP) provided pre-exposure prophylaxis (PrEP) to people vulnerable to HIV in 2015-2020. Data on long-term trends in sexual behavior and incidence of STIs during PrEP use are needed to inform future PrEP programs. Therefore, we assessed sexual behavior and incidence rates of STIs among MSM and transgender women on PrEP over four years.

Methods: AMPrEP participants chose between oral PrEP daily (dPrEP) or event-driven (edPrEP) at baseline and could switch regimens at each 3-monthly study visit. They were tested for STIs at these visits and if necessary in between. Follow-up began at PrEP initiation and continued until 48 months of follow-up or was censored at March 15, 2020 (start COVID-19), whichever occurred first. We assessed changes over time in incidence rates (IR) of chlamydia, gonorrhea, and infectious syphilis using Poisson regression. We estimated the IR of Hepatitis C (HCV) diagnoses per consecutive year. We described the number of HIV diagnoses, and sexual behavior (i.e. number of sex partners, condomless anal sex acts with casual partners [CAS]).

Results: A total of 367 (365 MSM) started PrEP and contributed 1249 person-years of observation. IRs of any STI was 87[95%CI 82-93]/100PY. There was no change in the IR of any STI and infectious syphilis over time on PrEP. We observed a slight decrease in incident chlamydia and gonorrhea in daily PrEP users (Table). Two incident HIV cases were diagnosed in the first year of follow-up. IRs for HCV were 1.5[0.6-3.6], 2.5[1.3-5.0], 0.7[0.2-2.7], and 0.4[0.1-2.8]/100PY, per consecutive year on PrEP.

Median number of sex partners per 3-month period decreased from 16[IQR 8-34] and 12[6-25] (dPrEP and edPrEP, respectively) at baseline, 15[7-30] and 8[3-16] at 24 months, and 12[6-26] and 5[2-12] at 48 months. Median number of CAS acts with casual partners were respectively 7[3-15] and 4[1-9] at baseline, 14[5-25] and 4[1-12] at 24 months, and 12[4-25] and 4[1-9] at 48 months.

Conclusion: Over the first 4 years of PrEP use overall STI incidence was high and stable. Chlamydia and gonorrhea incidence declined slightly in daily users. Numbers of sex partners seemed to decrease in both dPrEP and edPrEP users. Number of CAS acts with casual partners appeared to increase first, and then stabilized. Notably, this did not result in increased incidence of STIs. Regular

testing and treatment of STIs remain a priority among PrEP users. Biomedical prevention of STIs can be examined in this context.

Table. Characteristics of pregnant women randomized to point-of-care STI testing or standard, syndromic STI management in antenatal care, Cape Town, South Africa, 2021–2022

	Total (N=272)		Intervention: Offer point-of-care STI testing during antenatal care (N=135)		Standard-of-care: Syndromic STI management (N=137)		p-value
	N	(%)	N	(%)	N	(%)	
Maternal age (years; median IQR)	27	(23–32)	27	(23–32)	27	(23–33)	0.96
Gestational age (weeks; median, IQR)	22	(18–26)	22	(18–27)	21	(17–26)	
Reported ≥1 STI symptom	64		33	(24.4)	31	(22.6)	0.72
Reported vaginal discharge	37		23	(8.5)	14	(5.2)	
Reported pain during intercourse	25		12	(4.4)	13	(4.8)	
Reported pain during urination	23		10	(3.7)	13	(4.8)	
Reported vaginal bleeding	1		1	(0.4)	0	(0.0)	
Reported genital sore/ulcers	6		3	(1.1)	3	(1.1)	
Reported other* STI symptom(s)	3		0	(0)	3	(2.2)	
Diagnosed with ≥1 STI (NG/CT/TV)			37	(27.4)			
Diagnosed with *Neisseria gonorrhoeae*			10	(7.4)			
Diagnosed with *Chlamydia trachomatis*			26	(19.3)			
Diagnosed *Trichomonas vaginalis*			14	(10.4)			
Initiated HIV pre-exposure prophylaxis	175	(64.3)	90	(66.7)	85	(62.0)	0.43
Provided DBS sample at one-month visit	142	(81.1)	74	(82.2)	68	(80.0)	0.14
Detectable tenofovir disphosphate levels in dried blood spot at one-month after PrEP initiation	82	(57.7)	44	(59.4)	38	(55.9)	0.67

*Other refers to 2 cases of vaginal itchiness and 1 case of vaginal cysts and pain

972 PEP-IN-POCKET (PIP): LONG-TERM FOLLOW-UP OF ON DEMAND HIV POST-EXPOSURE PROPHYLAXIS

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Background: Pre-exposure prophylaxis (PrEP) and post-exposure prophylaxis (PEP) are two established methods to prevent HIV acquisition. However, the suitability of these tools for individuals with infrequent, higher-risk HIV exposures might be limited due to cost, high pill burden, or barriers to care. HIV post-exposure prophylaxis-in-pocket (PIP) involves prospectively identifying individuals with a low frequency of high-risk exposures and providing them with 28 days of PEP medication before an exposure occurs, along with instructions on when to initiate medications and how to follow up with care. We present long-term follow-up of a cohort of patients provided with PIP for HIV prevention.

Methods: We conducted a retrospective evaluation of the clinical characteristics and outcomes of patients who used PIP as their primary HIV prevention method. Patients referred for PrEP or PEP care were offered the option of PIP if they reported an ongoing risk of low frequency (0-4 per year), high-risk HIV exposures of any type. Importantly, HIV prevention method was chosen based on shared decision-making between patients and clinicians and was outside the realm of this study. Typical PIP regimens prescribed include Biktarvy® and tenofovir disoproxil fumarate/emtricitabine plus dolutegravir. Patients were followed at regular 4-6 months intervals. Demographic and clinical information was collected from two large HIV-prevention and care centers in Toronto, Canada between January 2016 and June 2022.

Results: PIP was prescribed to 109 patients, who were followed for a total of 168 patient-years. The average age was 37 years-old (range 20-69), with 106 (97.2%) patients assigned male at birth. Thirty-three (30.3%) patients self-initiated a total of 59 courses of PIP during the observation period. Patients fluidly transitioned between HIV prevention modalities as circumstances warranted: 34 (31.2%) changed from PIP to PrEP, and 32 individuals (29.4%) changed from PrEP to PIP.. There were 13 episodes of bacterial sexually transmitted infections in 9 individuals (8.3%) using PIP. No HIV seroconversions were detected.

Conclusion: PIP is an innovative and useful HIV prevention modality for individuals with a low frequency of higher-risk HIV exposures. Patients may transition between PIP and PrEP based on evolving HIV risk. PIP may be included with PEP and PrEP as a biomedical HIV prevention option for HIV-negative individuals at risk for infection.

973 ACCEPTABILITY AND FEASIBILITY OF A NEW URINE-BASED TENOFOVIR ADHERENCE TEST IN KENYA

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Background: Objective measures of oral pre-exposure prophylaxis (PrEP) adherence – especially point-of-care (POC) measures that enable real-time assessment, intervention, and feedback – have the potential to improve adherence. Our team previously developed and validated a novel urine-based POC measure of PrEP adherence. In this study, we sought to determine whether this urine assay for real-time adherence monitoring is acceptable and feasible among women taking PrEP and PrEP providers in Kenya

Methods: We conducted semi-structured in-depth interviews with 17 women on PrEP who were enrolled in the POC assay arm of the PUMA trial (NCT03935464) and their seven providers in Thika, Kenya. Interviews were conducted after the 12-month study follow-up period. Interview guides explored acceptability, feasibility, and perceived benefits of and concerns about POC urine adherence testing for PrEP among participants and providers. Transcripts were analyzed using rapid qualitative analysis approaches with memo-writing and data tables used to synthesize key themes.

Results: Most participants reported that the POC test improved their PrEP adherence since they wanted to receive positive results. For example, one woman said, "I don't skip drugs as [I did] before to avoid negative results". Positive adherence results also led to less worry of acquiring HIV. Women liked that the POC test was clinic-based because subsequent counseling and interpretation of results was aided by clinic providers. The providers reported that having real-time adherence results enabled them to tailor counseling to individual needs, what some referred to as 'evidence-based counseling'. Concerns expressed by participants included perception of lack of trust among providers and embarrassment associated with providing a urine sample. Provider concerns included the POC test not measuring long term adherence and potentially affecting retention of women with adherence challenges. The initial interpretation of results was challenging for providers, although they reported improvements with more familiarity with the test. Additionally, providers reported that the POC test would be more feasible if the kits were widely available and marketed for clinical use.

Conclusion: Our findings suggest that the POC urine TFV adherence test is highly acceptable and feasible for women on PrEP and their providers. Future studies should evaluate the impact of this novel test on adherence patterns over time in diverse populations.

974 WITHDRAWN

975 RANDOMIZED TRIAL OF DYNAMIC CHOICE PREVENTION AT OUTPATIENT DEPARTMENT IN EAST AFRICA

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Background: Dynamic choice models for delivering HIV prevention may increase coverage for persons at risk. Data are limited on actual product choices made by clients and the impact of choice-based delivery models on prevention coverage. Outpatient departments (OPD) in health facilities in rural sub-Saharan Africa account for a high proportion of new HIV diagnoses, but are an understudied entry point to biomedical HIV prevention, including dynamic choice models.

Methods: We conducted an individually randomized trial of a dynamic choice HIV prevention (DCP) intervention vs. standard-of-care referral to prevention services (SOC) among adults with current or anticipated risk of HIV exposure seen at OPD clinics in rural Kenya and Uganda (SEARCH; NCT04810650). DCP included 1) product choice (daily oral PrEP [TDF/XTC] or post-exposure prophylaxis [PEP]) with option to switch over time, 2) service location choice, 3) HIV self-testing option, 4) 24/7 phone access to clinician, and 5) provider training on client-centered care. Primary outcome over 48 weeks was biomedical covered time (proportion of follow-up covered by PrEP/PEP), assessed via self-report; secondary outcomes included coverage during periods of retrospectively self-assessed HIV risk.

Results: We enrolled 403 participants from April-July 2021, (197 DCP, 206 SOC): 61% women, 37% ages 15-24 years, 25% serodifferent partner, 88% HIV status unknown partner, 7% with prior PrEP or PEP use. In the DCP arm, 86% ever chose PrEP, 13% PEP over 48 weeks; selection of HIV self-testing increased from 26% to 51% and of out-of-facility visits from 8% to 52% during follow-up. Among 376/403 (93%) with outcomes ascertained, mean biomedical covered time was higher in DCP (47%) vs. SOC (18%); a difference of 29.2% (95% CI 22.7-35.7%; p< 0.001). Effect sizes were similar among men and women (28% and 31% higher coverage in the intervention arm, respectively). Intervention effect on coverage during periods at risk of HIV was larger; mean at-risk covered time was 65% in the DCP arm vs. 26% in SOC (difference 38.6%; 95%CI: 31.0-46.2%; p< 0.001).

Conclusion: In this randomized study, a dynamic choice prevention intervention with choice of PrEP/PEP, visit location, and HIV testing, plus client-centered care resulted in two-fold greater time covered by a biomedical prevention option compared to SOC among both men and women at elevated risk of HIV seen in a general outpatient department.

976 INCREASED UPTAKE OF BIOMEDICAL HIV PREVENTION BY YOUTH THROUGH COMMUNITY-BASED SRH

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Isisekelo Sempilo Research Group

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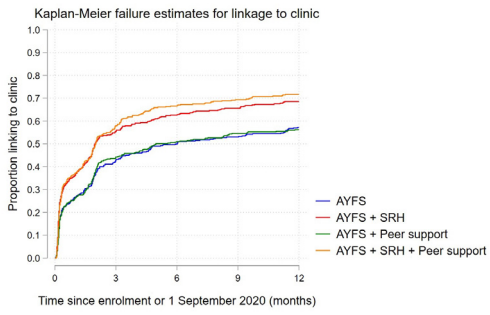
Background: Despite free and efficacious biomedical HIV prevention, including universal HIV test and treat (UTT) and Pre-Exposure Prophylaxis (PrEP), 200,000 South Africans acquired HIV in 2019. Incidence was highest among adolescents and youth, so strategies to improve HIV prevention are needed.

Methods: We conducted a 2x2 factorial trial (*Isisekelo Sempilo*) between March 2020 and August 2022. 2301 eligible 16-29-year-olds, randomly selected from a population surveillance area in rural KwaZulu-Natal, were randomly allocated to four arms: 1) enhanced Standard of Care (SoC): access to study-organized mobile adolescent youth friendly services (AYFS) for differentiated HIV prevention (condoms, UTT, PrEP if eligible); 2) Sexual and Reproductive Health (SRH): baseline self-collected specimens for sexually transmitted infection (STI) testing and referral to AYFS for differentiated HIV prevention integrated with SRH; 3) Peer-support: referral to a peer navigator for needs assessment to tailor health and social support, condom provision and facilitation of AYFS attendance for differentiated HIV prevention; 4) SRH + peer-support. Co-primary outcomes:1) the proportion of individuals with transmissible HIV (HIV viral load >400 copies per ml) measured from dried blood spots (DBS) collected at 12 months; 2) linkage to study AYFS for differentiated HIV prevention and care within 60 days of enrolment. NCT04532307

Results: 1743 (76%) eligible contacted individuals were enrolled and randomised; 1168 (67%) provided a DBS at 12 months. Baseline characteristics and outcome ascertainment were similar by arm. At 12 months 227 (19%) tested ELISA-positive for HIV, of which 185 (82%) had a HIV viral load < 400 copies/ml. Overall 41 (3.5%) of all who provided DBS had transmissible HIV. After adjustment for age, sex and rural/urban area there was no difference in transmissible HIV by either intervention: SRH: aOR 1.12; 95%CI:0.6-2.11; peer-support aOR 1.03; 95%CI:0.55-1.94. Overall 732 (42.6%) linked to AFYS by 60 days, Those randomised to SRH were significantly more likely to link (aOR 1.61; 95%CI:1.32-1.95) but peer-support had no effect unless combined with SRH.

Conclusion: In this representative sample of adolescents and youth in rural South Africa, STI testing and SRH (but not peer support) increased uptake of differentiated HIV prevention. While the UNAIDS target of 90:90:90 was exceeded in all arms, neither SRH nor peer support reduced transmissible HIV compared to AYFS.

Time to linkage to AFYS for differentiated HIV prevention, including PrEP/ART amongst n=1743 16-29 year olds



977 EFFECTS OF 6-MONTH PrEP DISPENSING WITH HIV SELF-TESTING ON SEXUAL BEHAVIORS IN KENYA

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Background: Six-month PrEP dispensing supported with interim HIV self-testing (HIVST) was shown to be non-inferior compared to 3-month PrEP dispensing with clinic-based HIV testing, the standard of care (SOC), for PrEP continuation outcomes in Kenya. We assessed the effects of this differentiated service delivery (DSD) model for PrEP on sexual behaviors.

Methods: The JiPime-JiPrEP trial (NCT03593629) was a randomized non-inferiority implementation trial in Thika, Kenya among HIV-negative adults ≥18 years who had been using PrEP for 1 month. Participants were randomized 2:1 to: 1) 6-month PrEP dispensing with interim HIVST and biannual clinic visits, or 2) SOC 3-month PrEP dispensing with clinic-based HIV testing and quarterly clinic visits. Participants reported the following sexual behaviors at every visit: any inconsistent condom use and number of sex partners, both in the past month. We conducted complete case analyses and used binomial regression models to estimate risk differences (RDs) for our binary outcome and linear regression models to estimate differences in means (DMs) for our continuous outcome. We adjusted all models for sex, HIV serodifferent partner status, and the corresponding baseline measure.

Results: From May 2018 to February 2020, we enrolled 495 participants (intervention: 329; SOC: 166), of whom 67% were women and 60% were in a serodifferent partnership. The median age was 33 years (interquartile range 27-40). Retention was similar across arms at both 6 months (intervention: 84.3%, SOC: 84.2%) and 12 months (intervention: 89.1%, SOC: 91.0%). Inconsistent condom use did not differ significantly between intervention and SOC arms at either 6 months (intervention: 90% vs. SOC: 87%; RD 3.1%, 95% CI -3.4%, 9.6%) or 12 months (intervention: 91% vs. SOC: 94%; RD -1.0%; 95% CI -5.8%, 3.8%). Additionally, the mean numbers of sex partners for participants were very similar in both arms at 6 months (intervention: 1.1 vs. SOC: 1.1; DM 0.0, 95% CI -0.3, 0.2) and 12 months (intervention: 1.0 vs. SOC: 1.0; DM 0.0, 95% CI -0.1, 0.2).

Conclusion: In this randomized implementation trial in Kenya, 6-month PrEP dispensing supported with interim HIVST did not significantly change participants' sexual behaviors compared SOC 3-month PrEP dispensing with clinic-based HIV testing. These findings further emphasize that this DSD model of PrEP, featuring fewer follow-up clinic visits and interim home-based HIVST, is safe, supporting its use to help simplify PrEP delivery in Kenya and similar settings.

978 PHARMACY-BASED PrEP DELIVERY IN KENYA: FINDINGS FROM A PILOT STUDY EXTENSION

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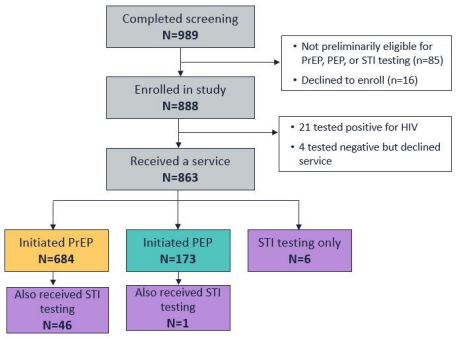
Background: To increase access to daily oral HIV pre-exposure prophylaxis (PrEP), policy makers and implementors are seeking evidence on whether and how PrEP can be delivered with high quality in non-clinical settings, including private pharmacies. Following a 12-month pilot study of pharmacy provider-initiated and managed PrEP, we conducted a 6-month extension to evaluate a modified version of this model that additionally offered post-exposure prophylaxis (PEP) and sexually transmitted infection (STI) testing.

Methods: We piloted the modified delivery model in 12 private pharmacies in Kisumu and Kiambu Counties. Pharmacy providers were trained to administer an HIV risk assessment screening tool; assess medical safety; assist clients with HIV self-testing; counsel; consult a remote clinician about complex cases and, if needed, refer to nearby public health facilities; and dispense. Eligible clients (≥18 years) received all services for free. Client and provider perceptions of model acceptability were assessed using Likert-type items derived from the Theoretical Framework of Acceptability.

Results: From January to July 2022, we screened 989 clients and initiated 863 (87%) on PrEP (n=684), PEP (n=173), and/or STI testing (n=53), **Fig. 1**. Among these 863 clients, 46% were male (n=400), 46% were < 25 years (n=399), and 78% were unmarried (n=670). Most PrEP clients (n=684) reported inconsistent condom use (86%, n=587), not knowing partners' HIV status (67%, n=459), and having multiple partners (62%, n=425). PrEP continuation at one month was 71% (484/684), and 18% (32/173) of PEP clients transitioned to PrEP upon PEP completion. STI positivity rate was 26% (14/53); the most prevalent STI was gonorrhoea (8/14). Model acceptability was high, with the majority (70-100%) of clients and providers reporting that they liked getting/delivering PrEP/PEP at the pharmacy and that getting/delivering PrEP/PEP at the pharmacy was not hard.

Conclusion: Our findings suggest that, when trained, pharmacy providers are capable of initiating and managing clients on PrEP in accordance with national guidelines and that additionally offering PEP and STI testing is a promising strategy for engaging clients in PrEP services. If this model were scaled up in Kenya, the rates of PrEP uptake and continuation might match or exceed those seen in public health facilities. More research is needed to identify business models (e.g., cost-sharing options) capable of sustaining pharmacy-delivered PrEP services in the long-term.

Figure 1. Study flow diagram



979 PREDICTIVE VALUES OF URINE PrEP (TFV) TEST SHOW STRONG CLINICAL AND RESEARCH UTILITY

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Background: Pharmacologic metrics of PrEP adherence predict effectiveness in clinical trials. Self-report is suboptimal but used in clinical and many research settings due to the expense and delay of laboratory-based tests (e.g. dried blood spots (DBS) or hair measures via liquid chromatography tandem mass spectrometry (LC-MS/MS)). A urine rapid point-of-care (POC) tenofovir (TFV) antibody-based test has compared well to LC-MS/MS of urine. To inform clinical and research utility, we calculated predictive values against self-reported recent PrEP use and previously validated measures of recent and longer-term adherence from DBS via LC-MS/MS.

Methods: Participants who reported currently taking PrEP in the RADAR community-cohort study of young men and transgender women who have sex with men were invited to this sub-study. At 3 monthly visits, participants completed a survey of daily PrEP use in the prior 7 days and provided DBS and urine samples. DBS samples were tested for TFV-diphosphate (TFV-DP) to estimate average dosing over the prior month and emtricitabine-triphosphate (FTC-TP) to assess recent dosing (past 2-3 d). A urine POC TFV test qualitatively assessed recent adherence (past 4–7 d) was performed.

Results: A subset of 74 PrEP-users contributed 131 observations. Self-reported adherence was over-reported (86% for 4+ doses in last 7 days), versus urine TFV (68%), DBS FTC-TP (66%), and DBS TFV-DP (53%). The two objective metrics of short-term adherence performed similarly well in predicting longer term adherence via TFV-DP, and better than self-report which overestimated (see Table for predictive values). Self-report was better for short term adherence metrics, but poorer than the urine assay. In multivariable logistic regression

analyses, the urine assay was a significant predictor of DBS TFV-DP (OR = 14.1, p < .001); self-report did not add significantly to prediction.

Conclusion: The urine POC TFV assay had excellent predictive values and self-report did not add significantly to prediction of adherence. The POC assay provides results in several minutes to enable same-visit counseling/intervention, requires no specialized training, and is projected to be low-cost. It could also be used for research where objective short term adherence metrics are needed.

Positive and negative predictive values for PrEP adherence

	DBS TFV-DP		DBS FTC-TP	
	Positive predictive value	Negative predictive value	Positive predictive value	Negative predictive value
DBS FTC-TP	77%	93%		
Urine	74%	90%	96%	95%
Self-report (4+ doses in prior 7 days)	60%	89%		
Self-report (1+ dose in prior 2 days)			75%	88%

980 ORAL AND INJECTABLE PrEP USE IN THE UNITED STATES, 2013 TO 2022

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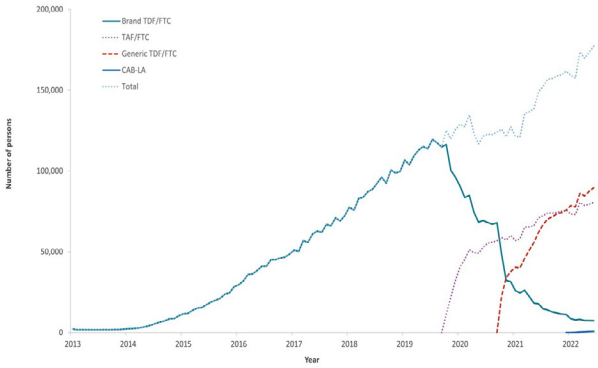
Background: Three oral PrEP drugs have been approved by the FDA: branded tenofovir disoproxil fumarate and emtricitabine (TDF/FTC) in July 2012, branded tenofovir alafenamide and emtricitabine (TAF/FTC) in October 2019, and generic TDF/FTC in July 2020. Long-acting injectable cabotegravir (CAB-LA) was approved in December 2021. We estimated trends in prescriptions for these PrEP drugs.

Methods: We analyzed IQVIA Real-World Data — Longitudinal Prescription Database (IQVIA) using a validated algorithm to identify persons prescribed antiretroviral drugs for PrEP. We estimated the number of persons prescribed branded TDF/FTC, TAF/FTC, generic TDF/FTC, or CAB-LA by month from January 2013 through June 2022. We estimated the proportions of prescriptions in June 2022 by type of PrEP drug. Among persons with an initial CAB-LA prescription from January through May 2022, we estimated the proportion who received a second prescription one month later. Among persons prescribed PrEP from January through June 2022, we estimated their demographic characteristics stratified by a prescription for oral PrEP or CAB-LA.

Results: We found that the number of persons prescribed branded TDF/FTC increased from January 2013 until October 2020 and then decreased markedly each month after TAF/FTC and generic TDF/FTC became available (Figure). Beginning in December 2021, the number of persons prescribed generic TDF/FTC exceeded the number prescribed TAF/FTC each month. In June 2022, 177,293 persons were prescribed PrEP; 89,654 (50.6%) were prescribed generic TDF/FTC and 80,754 (45.5%) TAF/FTC; only 804 (0.5%) were prescribed CAB-LA. From January through May 2022, among 800 persons who picked up their CAB-LA prescription 633 (79.1%) received a prescription for a second dose. During January through June 2022, women comprised 11.5% of persons prescribed CAB-LA compared with 6.4% of persons prescribed oral PrEP.

Conclusion: Most PrEP users were prescribed generic TDF/FTC and very few were prescribed CAB-LA since its recent approval. The increasing proportion of generic TDF/FTC prescriptions compared with TAF/FTC is encouraging and can result in lower healthcare expenditures for PrEP, yet a large proportion of prescriptions were for the more expensive TAF/FTC. Better understanding is needed of reasons for low uptake of CAB-LA, including of operational barriers to its implementation. Studies are also needed to understand factors associated with CAB-LA use among women to inform implementation efforts.

Figure. Persons prescribed PrEP by type of PrEP drug, IQVIA Real-World Data — Longitudinal Prescription Database — United States, January 2013 through June 2022



981 BREAKTHROUGH HIV-1 INFECTION IN SETTING OF LONG-ACTING CABOTEGRAVIR FOR PrEP

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Background: Long-acting cabotegravir (CAB-LA) is highly effective as HIV PrEP and superior to daily oral F/TDF in sexually active adults. We report a 28-year-old gender diverse patient assigned male at birth who acquired HIV-1 91 days after transitioning from F/TAF to CAB-LA despite on-time dosing.

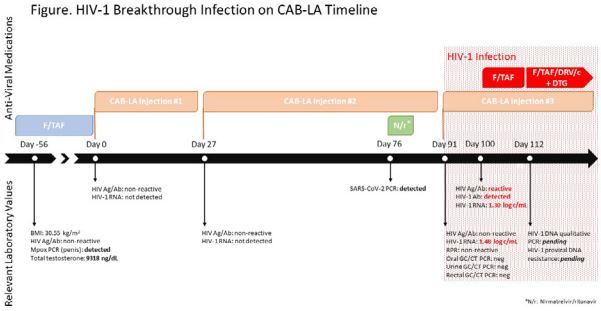
Methods: Electronic medical records were reviewed to assess patient history and CAB-LA administration details. Plasma 4th generation HIV-1/2 Ag/Ab combination immunoassay and HIV-1 RNA quantitative PCR were performed at each injection visit.

Results: Patient was on daily F/TAF for ten months prior to CAB-LA with acceptable adherence, missing 1 dose per week. Their medical history included hypothyroidism on levothyroxine and unconfirmed hypogonadism with illicit use of IM testosterone cypionate complicated by significantly elevated total testosterone levels. They were sexually active with cisgender men, endorsing condomless oral and anal sex with one primary partner and 20-30 unique partners per month. In the past 6 months, patient was diagnosed with syphilis and mpox. Patient was given 600mg of CAB-LA into their left gluteal medius on Day 0, 27, and 91. Day 0 and 27, plasma HIV 1/2 Ag/Ab was non-reactive and HIV-1 RNA PCR was not detected. Patient reported flu-like illness on Day 76 with positive SARS-COV-2 PCR; they completed a five-day course of nirmatrelvir-ritonavir with rapid resolution of symptoms. At the third injection of 600mg CAB-LA on Day 91, their plasma HIV 1/2 Ag/Ab was non-reactive but the HIV-1 RNA PCR test was detected at 1.48log c/mL. On repeat testing on Day 100, plasma HIV 1/2 Ag/Ab was reactive with HIV-1 Ab detected on differentiation assay and HIV-1 RNA PCR was detected at 1.30 log c/mL. Patient's primary partner was living with HIV resistant to NRTIs (65R, 118I) and INSTIs (92G) with undetectable plasma HIV-1 RNA for the past 24 months. Patient's viremia was below the threshold to perform standard HIV-1 sequencing; HIV-1 DNA qualitative PCR and HIV-1 proviral DNA resistance testing are currently pending. Patient ultimately started on F/TAF/DRV/COBI and DTG on Day 112.

Conclusion: This patient's history suggests HIV-1 infection despite on-time and appropriate CAB-LA injections. To our knowledge, this is the first case of CAB-LA PrEP failure outside the setting of a clinical trial and highlights the diagnostic and management challenges that may arise with such breakthrough infections in the real world.

HIV-1 Breakthrough Infection on CAB-LA Timeline

Figure. HIV-1 Breakthrough Infection on CAB-LA Timeline



982 ASSOCIATION OF METH USE AMONG GBMSM ON HIV PRE-EXPOSURE PROHPYLAXIS CARE ENGAGEMENT

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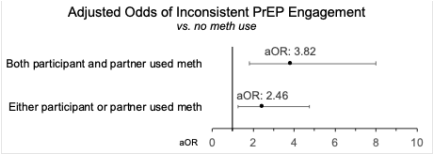
Background: There are limited quantitative studies describing the association between meth use in the context of male-male sexual partnerships and PrEP care engagement. We assessed the longitudinal relationship between individual and partnership level meth use with inconsistent PrEP engagement among young gay, bisexual and other men who have sex with men (GBMSM) in Los Angeles.

Methods: The mSTUDY (Men Who Have Sex with Men and Substance Use Cohort at UCLA Linking Infections, Noting Effects) is a cohort of GBMSM between the ages of 18 and 52 in Los Angeles. The primary outcome, PrEP engagement, had two levels. We defined consistent PrEP engagement as 18 consecutive months (3 study visits) of reported PrEP care. Inconsistent PrEP engagement was defined by 6 months of PrEP care followed by either 12 months of non-engagement or 6 months of non-engagement and 6 subsequent months of engagement. The primary exposure was meth use at the partnership level with a ternary variable (neither partner nor participant used meth, either used meth, or both used meth). We measured sexual risk characteristics including STI test positivity. Generalized estimating equations were used to assess odds of inconsistent PrEP engagement at different levels of partner-participant meth use, adjusting for age at visit, number of recent male partners and partner intimacy.

Results: The sample included 149 unique participants (n=602 visits), of whom 48% were Black/African American, 36% were Hispanic/Latinx and 9% were white. There were 447 continuous PrEP events and 155 inconsistent PrEP events. Among inconsistent PrEP engagement, 61% (vs 79.5% continuous) reported that neither they nor their partner used meth, 22% (vs 18%) reported that either partner or participant used meth and 17% (vs 8%) reported that both partner and participant used meth (P< 0.01). Positive gonorrhea test was higher among inconsistent PrEP engagement (13.2%) vs. consistent (5.4%, P=0.04). There were increased odds of inconsistent PrEP engagement when both partner and participant reported meth use (aOR: 3.82; 95%CI: 1.83-7.99) and when either partner or participant reported meth use (aOR: 2.46; 95%CI: 1.28-4.75) (Figure).

Conclusion: Meth use plays an important role in consistent PrEP engagement among GBMSM in mSTUDY. Odds of inconsistent PrEP engagement were higher when meth use was reported by either participant and partner or both. PrEP users who use meth with partners may benefit from integrated interventions addressing both meth use and PrEP engagement.

Adjusted odds of inconsistent PrEP engagement versus no meth use. Model also controls for age at visit, partnership assessment score and number of male partners.



983 NO IMPROVEMENT IN PREEXPOSURE PROPHYLAXIS USE AMONG PWID: SAN FRANCISCO, 2018-2022

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Background: The Ending the HIV Epidemic initiative aims to reduce new HIV infections by 90% by 2030. San Francisco is achieving progress toward this goal among men who have sex with men (MSM), with new HIV infections decreasing by 28% from 2019 to 2021. This period coincides with high and rising pre-exposure prophylaxis (PrEP) use in the last year, from 60% to 70%. Yet HIV infections among people who inject drugs (PWID) rose by 48% during this period, now accounting for 27% of new HIV diagnoses in San Francisco. In 2018, only 2.9% of PWID used PrEP in San Francisco. We examined PrEP cascade indicators among PWID in San Francisco, comparing data from 2018 to 2022.

Methods: Data originated from the National HIV Behavioral Surveillance (NHBS) study, which comprises serial cross-sectional surveys to assess HIV prevalence in key populations at risk in the US. Data were from PWID, who resided in San Francisco between June and December of 2018 and 2022. Respondent-driven sampling was used for recruitment. This analysis compared PrEP cascade indicators from 2018 to 2022 among PWID who self-identified as HIV-negative or unknown.

Results: Of 479 HIV-negative/unknown PWID, more than half had a usual source of care (76.6%) and healthcare visits in the past 12 months (75.3%). Only 54.9% were aware of PrEP, 5.9% discussed PrEP with healthcare providers (HCP), and 1.5% used PrEP in the past 12 months. PrEP indicator estimates were comparable to or significantly worse than those of 2018: 54.1% (p=0.796), 12.9% (p< 0.001), and 2.9% (p=0.003), respectively. Factors associated with low PrEP awareness among PWID in 2022 were Black/African American race/ethnicity (OR 0.50 vs. Whites, p=0.001, 95% CI 0.33-0.76), household income below the federal poverty level (OR 0.35 vs. above, p=0.017, 95% CI 0.15-0.83), and not testing for HIV (OR 0.43 vs. testing, p< 0.001, 95% CI 0.30-0.63), HCV (OR 0.48 vs. testing, p< 0.001, 95% CI 0.33-0.70) or sexually transmitted diseases (STDs) (OR 0.44 vs. testing, p< 0.001, 95% CI 0.30-0.66) in the past 12 months.

Conclusion: PrEP discussions with HCP and PrEP use were significantly lower among PWID in 2022. Lack of PrEP awareness was associated with social determinants of race/ethnicity, income, and sexual health testing. Public health interventions to increase HIV testing and PrEP discussions from HCP to PWID may have the greatest potential to improve PrEP awareness and use among PWID, particularly among Black/African American residents and PWID with low income.

984 EFFECT OF INTIMATE PARTNER VIOLENCE ON ART & PrEP ADHERENCE IN SERODIFFERENT COUPLES

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Background: Experiences of intimate partner violence (IPV) are associated with reduced adherence to antiretroviral (ART) and pre-exposure prophylaxis (PrEP) nonadherence, increased risk of HIV acquisition and poorer engagement in HIV care. There is limited evidence describing the ways in which exposure to violence and other maladaptive relationship dynamics may influence ART and PrEP adherence for both individuals in committed serodifferent partnerships.

Methods: Using longitudinal data from a stepped-wedge cluster randomized trial, we evaluated the effect of IPV exposure on ART and PrEP adherence for both partners in serodifferent unions. The primary outcome was PrEP or ART adherence—a derived variable determined via self-reported or, when available, quantified tenofovir diphosphate (for PrEP) or HIV viral load (for ART) biomarker data. The primary predictor, IPV exposure, was evaluated using a modified Conflict Tactics Scale to identify exposure to physical or sexual IPV since the last visit. As a secondary predictor, we used the Sexual Relationship Power Scale to assess perceived relationship dynamics. Outcome and predictor data were evaluated at 1-month and quarterly visits. We used generalized

estimating equations to assess the association between IPV exposure and ART/PrEP adherence.

Results: From June 2018 to December 2020, we enrolled and followed both partners in 149 heterosexual serodifferent couples. The median age at enrollment was 28 years [IQR: 24 - 33]. The partner living with HIV was female in 65% of couples. At enrollment 19% of male and 20% of female partners reported having experienced sexual or physical IPV in the past year. Recent IPV exposure was not significantly predictive of PrEP or ART adherence (OR: 1.27, 95% CI 0.52 – 3.16). Compared to their counterparts living with HIV, IPV-exposed HIV-negative partners had similar levels of PrEP adherence (OR: 0.77, 95% CI 0.19 – 3.14). Compared to their counterparts living with HIV, HIV-partners who reported more imbalanced relationship power dynamics had odds trending towards higher adherence (OR: 1.06, 95% CI 0.99 – 1.13).

Conclusion: We found that IPV was not predictive of adherence to PrEP or ART. These findings contribute to the evidence base outlining the association between IPV and ART/PrEP adherence in HIV serodifferent couples. Future research should leverage event-level analyses to further evaluate the circumstances and manners in which distinct types of IPV influence HIV treatment and prevention outcomes.

985 DETERMINANTS OF PRE-EXPOSURE PROPHYLAXIS RETENTION AMONG TRANSGENDER WOMEN

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Background: Transgender women (TW) face unique challenges staying engaged with HIV prevention services, including pre-exposure prophylaxis (PrEP). To inform efforts to increase PrEP retention among TW, we examined barriers to and facilitators of PrEP retention among TW in Southern California.

Methods: We used a mixed methods sequential explanatory approach with 2 phases. In Phase 1, we used quantitative data from a PrEP demonstration project (iMPrEPT) that included PrEP provision among 170 TW to evaluate 24-week retention by sociodemographics, engagement in sex work, substance use, and hormone replacement therapy (HRT) use. In Phase 2, we conducted 15 in-depth interviews with PrEP experienced TW purposively sampled to include TW who engaged in sex work based on Phase 1 findings. We then used thematic analysis to explain Phase 1 findings and integrated them in the presentation of Phase 2 themes.

Results: In Phase 1, a greater proportion of participants who were not retained at 24 weeks reported engaging in sex work than those who were retained (18% vs 7%). In Phase 2, two subcategories of sex work engagement emerged. The first was characterized as engaging in "non-survival sex work" – these TW had little difficulty staying in PrEP care, sought clients from online sources, had stable housing, accessed HRT through providers, and exchanged sex primarily for money. The second was characterized as engaging in "survival sex work" – these TW struggled to stay in PrEP care, had street-based clients, were unstably housed, used black market hormones, and more frequently exchanged sex for drugs. In Phase 1, a smaller proportion of participants not retained at 24 weeks reported HRT than those who were retained (56% vs 71%). In Phase 2, participants consistently prioritized HRT over PrEP, describing HRT as a basic necessity and life-saving, yet many also described the bidirectional benefits of accessing HRT and PrEP. In Phase 1, a greater proportion of participants who were not retained at 24 weeks reported substantial or severe drug use than those who were retained (18% vs 8%). In Phase 2, participants reported drug use as a barrier to PrEP, often in the context of sex work.

Conclusion: TW who engage in "survival sex work" experience barriers to PrEP retention (e.g., unstable housing, drug use) which may require supportive resources to stay engaged with PrEP care. The reciprocal benefits of HRT and PrEP suggest that co-location of services may be an optimal strategy for enhancing PrEP retention among TW.

Table 1. Sociodemographics of in-depth interview participants (N = 15).

Gender	Female/woman, N (%)	5 (33)
	Trans female/trans woman, N (%)	7 (47)
	transfeminine, male to female, transgender, or transsexual woman, N (%)	4 (27)
Race and ethnicity	Black or African American, N (%)	3 (20)
	Latina/x, N (%)	6 (40)
	White, N (%)	9 (60)
	Spanish or multiracial, N (%)	2 (13)
Currently on PrEP, N (%)		10 (67)
Sex work experienced, N (%)		9 (60)
Age, mean (standard deviation)		35.8 (9.7)

986 PrEP PRESCRIPTIONS AMONG PERSONS WITH MEDICAID BY RACE AND ETHNICITY: UNITED STATES

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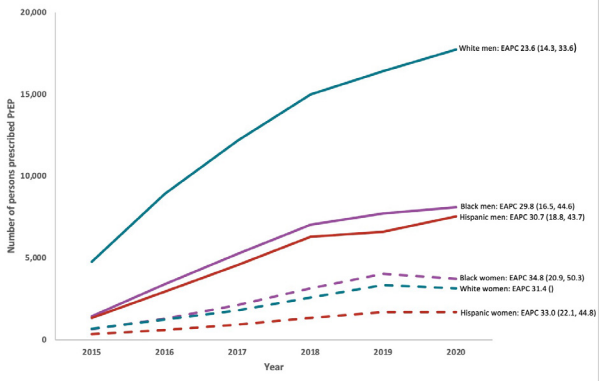
Background: Black/African American (Black) and Hispanic or Latino (Hispanic) populations have high HIV incidence but low coverage of preexposure prophylaxis (PrEP) prescriptions among those with PrEP indications. Pharmacy data are used to monitor the effectiveness of programmatic activities to decrease racial/ethnic disparities in PrEP use. These data are missing race/ethnicity variables for about 70% of persons so race/ethnicity at the national level must be imputed. Medicaid data includes the most complete race/ethnicity information among health services databases and can be useful to understand national trends in PrEP use by race/ethnicity.

Methods: We analyzed Centers for Medicare and Medicaid Services data for all 50 U.S. states and the District of Columbia to estimate the number of Medicaid enrollees prescribed PrEP from 2015–2020 by sex, age group, and race/ethnicity. We used a validated algorithm that excluded persons prescribed antiretroviral drugs for HIV treatment, hepatitis B treatment, or HIV postexposure prophylaxis. We calculated estimated annual percentage changes (EAPCs) and 95% confidence intervals (CIs) in the number of persons prescribed PrEP from 2015–2020. We also estimated the trend in PrEP prescriptions among men and women by race/ethnicity from 2015–2020.

Results: The number of Medicaid enrollees prescribed PrEP increased from 11,396 in 2015 to 52,907 in 2020 (EAPC 28.4%, 95% CI 18.0, 39.8). In 2020, 37,467 (71.9%) of enrollees prescribed PrEP were aged 16-39 years, 10,021 (18.9%) women, 11,825 (22.3%) Black, 9,235 (17.5%) Hispanic, and 20,854 (39.4%) White. The rate of increase in PrEP prescriptions was similar among White (EAPC 23.6% (14.3, 33.6)), Black (EAPC 29.8% (16.5, 44.6)), and Hispanic men (EAPC 30.7% (18.8, 43.7)) but the disparity in the number of White men prescribed PrEP compared with Black or Hispanic men increased from 2015–2020 (Figure). Only 3,735 Black women were prescribed PrEP in 2020.

Conclusion: The number of persons prescribed PrEP increased in all populations but continuing racial/ethnic disparities were observed and worsened among men. Black women had a similar trend compared with White women despite disproportionately higher rates of HIV diagnosed among Black women. Interventions designed to support PrEP implementation for Black and Hispanic gay, bisexual, and other men who have sex with men and Black women can support reducing HIV disparities and reaching goals of the Ending the HIV Epidemic in the U.S. initiative.

Figure. Trend in PrEP prescriptions among male and female Medicaid beneficiaries by race/ethnicity, United States, 2015-2020



987 BONE DENSITY CHANGES WITH CAB-LA OR TDF/FTC PrEP IN MSM AND TGW IN HPTN 083

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HPTN 083 Study Team

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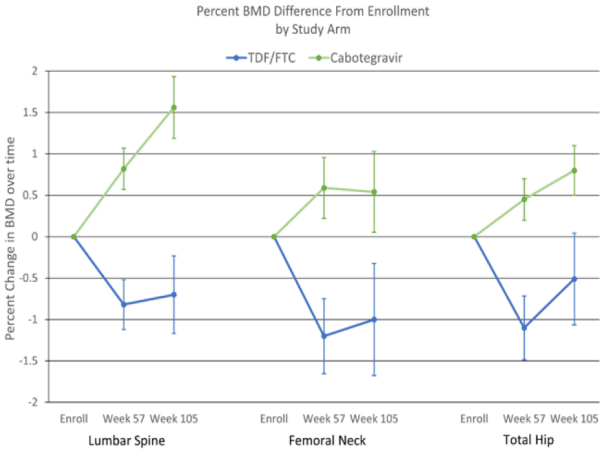
Background: Bone mineral density (BMD) loss has been a concern for HIV pre-exposure prophylaxis (PrEP) containing tenofovir disoproxil fumarate (TDF). Long-acting cabotegravir (CAB-LA) was superior to TDF/emtricitabine (FTC) for HIV prevention in two clinical trials, but the relative bone safety of these regimens is unknown.

Methods: HPTN 083 conducted a bone safety sub-study to compare BMD changes over 105 weeks with CAB-LA and TDF/FTC in cisgender men who have sex with men (MSM) and transgender women (TGW) at risk for HIV infection from 22 international sites. BMD was measured at the lumbar spine (LS), femoral neck, and total hip by dual-energy x-ray absorptiometry (DXA) at baseline, 57 weeks, and 105 weeks. Percentage BMD change at each anatomic site was compared between the two randomized arms by two-sample, independent t-tests in those who received at least 10 bi-monthly injections over 18 months from enrollment (n=254).

Results: At baseline the median (Q1, Q3) age was 27 (23, 35) years, 9.4% TGW, and 47.2% white. The proportion of those with low BMD at baseline (Z-score at any anatomic site £ -2.0) was 15%. At the LS, the median percentage change in BMD was 0.82% in the CAB-LA arm and -0.82% in the TDF/FTC arm (between arm difference (95% confidence interval [CI] –1.6% [-2.4, -0.87], p< 0.01) at 57 weeks (n=248). This difference persisted at 105 weeks (n=203) with a between-arm difference in percentage BMD change of -2.3% (95%CI: -3.4, -1.1%; p< 0.01). Similar results were observed at both the femoral neck and total hip (Figure).

Conclusion: Among MSM and TGW receiving CAB-LA versus TDF/FTC HIV PrEP, bone mineral density trajectories over two years were different, with BMD gain in the CAB-LA arm and BMD loss in the TDF/FTC arm. For individuals with low BMD or other fracture risk factors, CAB-LA PrEP may confer benefits related to bone health compared to TDF-containing PrEP.

Percent BMD Difference From Enrollment by Study Arm



988 PHASE 1 TRIAL OF CAP256V2LS AND VRC07-523LS ANTIBODIES AMONG WOMEN IN SOUTH AFRICA

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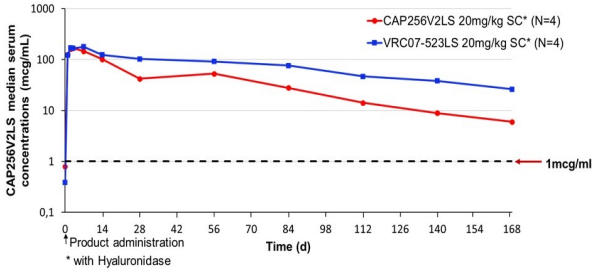
Background: Young women in sub-Saharan Africa continue to bear a high burden of HIV infection. Combination anti-HIV monoclonal antibodies are a potential HIV prevention technology that may overcome adherence challenges of daily oral pre-exposure prophylaxis. CAPRISA 012B, a first-in-human dose-escalation phase 1 trial evaluated the safety, pharmacokinetics and neutralization activity of the monoclonal antibody CAP256V2LS alone and in combination with VRC07-523LS in young HIV-negative women in Durban, South Africa.

Methods: From 13 July 2020 to 13 January 2021, 42 healthy women, aged 18-45 years, were enrolled. Groups 1 and 2 were open-label and CAP256V2LS was administered at 5mg/kg and 10mg/kg intravenously; and 5mg/kg, 10mg/kg and 20mg/kg subcutaneously. In Group 3 participants were randomized to receive a combination of CAP256V2LS and VRC07-523LS at 10mg/kg and 20mg/kg subcutaneously co-mixed with a recombinant human hyaluronidase. Neutralizing activity was measured using env-pseudotyped viral particles in the TZM-bl assay. A quantitative electrochemiluminescence sandwich immunoassay was performed to determine antibody concentrations.

Results: There were no serious adverse events or dose-limiting toxicities. Most commonly reported symptoms following intravenous administration were headaches [7/8 (88%)] and nausea [4/8 (50%)]. Commonly reported symptoms following subcutaneous administration were headaches [31/34 (91%)], chills [25/34 (74%)] and malaise/fatigue [19/34 (56%)]. Adverse events included transient lymphocytopenia [8/42 (19%)], proteinuria [9/42 (21%)], elevated aspartate aminotransferase [10/42 (24%)] and alanine aminotransferase [5/42 (12%)]. At 6 months, the median serum concentration of CAP256V2LS and VRC07-523LS in participants who received 20mg/kg, was 6µg/mL and 26µg/mL respectively. Overall, the estimated half-life was 43 days for CAP256V2LS and 66 days for VRC07-523LS. Neutralization data showed that both antibodies retained their functional activity post-administration.

Conclusion: CAP256V2LS and VRC07-523LS administered subcutaneously alone and in combination with recombinant hyaluronidase was safe and well tolerated, with detectable antibody concentrations up to 6 months post administration. CAP256V2LS is one of the most potent antibodies described to date and in combination with VRC07-523LS is predicted to provide significant coverage of global HIV strains. These data support further assessment in larger clinical studies.

Figure 1: Median concentrations of CAP256V2LS and VRC07-523LS through 168 days post study product administration observed in the CAPRISA 012B trial.



989 VAGINAL PrEP EFFICACY OF BIODEGRADABLE ISLATRAVIR IMPLANTS IN MACAQUES

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Background: Islatravir (ISL), a nucleoside reverse transcriptase translocation inhibitor, is in development for long-acting pre-exposure prophylaxis (LA PrEP) as a monthly pill and subdermal implant. ISL is on clinical hold after lymphopenia was observed in clinical trials. Here we investigated in macaques ISL implants with varied release rates and assessed safety, pharmacokinetics, and vaginal efficacy for LA PrEP.

Methods: Biodegradable polycaprolactone implants loaded with 86 mg or 45 mg of ISL and *in vitro* release rates of 705 µg/d (ISL-705) or 83 µg/d (ISL-83), respectively, were implanted subcutaneously in the arms of female pigtailed macaques. Macaques received one ISL-705 implant (n=6) or two ISL-83 implants (1/arm) for a cumulative release of 176 µg/d (n=6). Implant-site reactions were graded weekly using a modified Draize scale (range: 0-5). Plasma ISL was measured weekly by LC/MS-MS. Macaques with two ISL-83 implants were exposed vaginally to SHIV162p3 twice-weekly at weeks 5-11 post-implantation (12 total challenges). Infection outcome was compared with 6 untreated animals (2 real-time and 4 historical controls). Blood was collected at each challenge to monitor plasma ISL and SHIV RNA.

Results: ISL-705 and ISL-83 implants reached steady-state by day 21 with median [range] plasma ISL levels of 25.4 [23.0- 28.4] and 5.2 [2.3-6.6] nM, respectively. All macaques with ISL-705 implants had adverse implant-site reactions (Draize score 1-3) that persisted for 8 weeks, at which point the implants were removed. In contrast, no implant-site reactions were observed in animals with two ISL-83 implants (n=12 implants) over the 12-week study period (144 observations). Macaques with two ISL-83 implants (176 µg/d) remained uninfected during a cumulative of 72 SHIV exposures, while the 6 controls were infected after a median of 2.5 challenges [range 1-5] resulting in 100% efficacy. Median [range] plasma ISL levels during SHIV challenges were 4.0 nM [1.2-7.0].

Conclusion: We show that release rates from ISL-705 implants may impact local toxicity. In contrast, we identified ISL-eluting implants (ISL-83) with a cumulative *in vitro* release rate of 176 µg/d that did not result in implant-site reactions and fully protected macaques against repeated vaginal SHIV exposures. We also defined clinically relevant plasma concentrations of 1-7 nM that were associated with complete vaginal protection. These data will inform the selection of safe and effective biodegradable ISL implants for HIV LA-PrEP in women.

990 EXTENDED POST-EXPOSURE PROTECTION AGAINST SHIV VAGINAL INFECTION WITH TAF/EVG INSERTS

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Background: On-demand HIV prevention modalities used before or after vaginal sex may be a desirable alternative to daily oral pre-exposure prophylaxis (PrEP) for women with infrequent or clustered sexual activity. CONRAD has developed inserts containing tenofovir alafenamide fumarate (TAF) and elvitegravir (EVG) that were safe, well accepted, and showed good pharmacokinetics and pharmacodynamics in a clinical trial (CONRAD A18-146) after vaginal administration. We recently showed that TAF/EVG inserts fully protected macaques against repeated SHIV vaginal exposures when administered as post-exposure prophylaxis (PEP) 4h after virus exposure. Here, we sought to define the window of PEP activity by applying inserts 8 or 24 hours after SHIV exposure.

Methods: Cycling pigtailed macaques were challenged with low-dose SHIV162p3 and dosed 8 or 24h later with a TAF/EVG (20 mg/16 mg) insert (n=6 per group) or placebo insert. Animals were challenged once weekly for 13 weeks. Infection was monitored by plasma virus load using RT-qPCR. Due to the small sample size, efficacy and 95% confidence intervals were calculated with Fisher's exact test. Survival analysis was conducted to compare time to infection in 8h and 24h treated arms relative to 9 placebo controls (n=2 for 8 and 24h, n=5 historical controls) using the Log-Rank test (LRT) in SAS Proc Lifetest (SAS 9.4).

Results: At 8h PEP, only 1/6 treated animals became infected (at exposure 11), resulting in high calculated efficacy of 94.41% (95% exact CI =57.03%, 99.27%) and a significant difference in the time to infection compared to placebo controls (p=0.0063, LRT). Extending the window of PEP to 24h resulted in 3/6 animals becoming infected at exposures 2, 2, and 13, thus decreasing the efficacy to 77.23% (95% exact CI =20.00%, 93.52%) and leading to the loss of significance in time to infection (p=0.1154, LRT) when compared to the controls. The median time to infection for the control group was 3 challenges.

Conclusion: These data extend the window of high post-exposure protection by a single TAF/EVG insert to 8h and define a reduction in efficacy at 24h post-exposure. The study supports the clinical development of the TAF/EVG insert as an on-demand PEP option for women and informs its dosing modality.

991 PHARMACOKINETICS AND XRAY IMAGING OF LONG-ACTING CABOTEGRAVIR IN SITU FORMING IMPLANT

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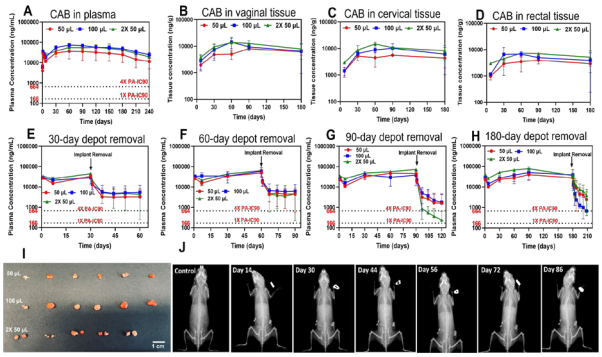
Background: Long-acting injectables (LAIs) for HIV PrEP can increase adherence and reduce stigma. Current LAIs are not removable and present a pharmacokinetic (PK) tail. To overcome these limitations, we developed an ultra-long-acting (ULA) biodegradable and removable *in situ* forming implant (ISFI) with cabotegravir (CAB). Here, we performed a PK study evaluating injection volume (IVOL), drug concentration in plasma and tissues, PK tail, and implant visualization with full-body x-ray imaging (FBXI).

Methods: PLGA-based ISFIs were comprised of 500 mg/mL CAB in a stable suspension. Female BALB/c mice (n=6/IVOL) were injected subcutaneously (SC) with 50, 100, or 2´ 50 µL of CAB ISFI formulation. Plasma, and vaginal, cervical, and rectal tissues samples were collected longitudinally to quantify drug concentration over ≥180 days. At day 30, 60, 90, and 180 post injection, depots were removed via a small skin incision to quantify residual CAB and determine PLGA molecular weight (MW) decrease over time. Plasma samples were collected 30 days post-depot removal to assess the PK tail. Additional CAB ISFI formulations were made with 10 wt% barium sulfate ($BaSO_4$) to generate a radiopaque implant. Mice (n=3) were injected with 50 µL of CAB/$BaSO^4$ ISFIs (right flank) and 50 µL of placebo/$BaSO_4$ ISFIs (left flank). Mice underwent biweekly FBXI to assess implant visualization post-injection.

Results: ULA CAB ISFIs elicited concentration in plasma for all IVOLs well above the 4× PA-IC_{90} for 240 days (Fig A) and high tissue concentrations for 180 days (Fig B-D). CAB concentration in all matrices was not significantly different across IVOLs. Significant decrease in plasma CAB was achieved post depot removal with ~9-, 13-, 29-, and 11-fold decrease for depots removed at d30, 60, 90, and 180 respectively (Fig E-H); however, complete elimination of CAB was not achieved 30 days post depot removal, likely a result of CAB accumulation in the SC tissue and/or incomplete depot removal. ISFIs were retrievable after 180 days post-injection (Fig I) with ~25% CAB remaining and ~85% decrease in PLGA MW for all IVOLs. ISFIs with BaSO4 maintained visualization via FBXI for 86 days (Fig J).

Conclusion: ULA CAB ISFI is the first injectable for HIV PrEP that is biodegradable and removeable, only if needed, elicited plasma and tissue PK for ≥180 days and is visualized for several months by FBXI. This comprehensive study further characterized the formulation and future directions include similar studies in non-human primates.



(A) Plasma concentration of CAB ISFIs at 50, 100, and 2X 50 µL injection volumes for 240 days. (B-D) CAB concentration in vaginal, cervical, and rectal tissue, respectively. (E-H) CAB concentration in plasma after implant removal at 30, 60, 90, and 180 days, respectively. (I) CAB ISFIs removed from mice 180 days post-injection. (J) Full-body x-ray imaging of mice subcutaneously injected with 50 µL of 10 wt% $BaSO_4$/CAB ISFIs into the right flank and 10 wt% $BaSO_4$/placebo (CAB-free) ISFIs into the left flank for 86 days. Control mouse did not receive ISFI injection.

992 LENACAPAVIR PROTECTS AGAINST RECTAL SHIV ACQUISITION IN MACAQUE MODEL

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Background: Pre-exposure prophylaxis (PrEP) is an important strategy for HIV prevention among people at risk. Long-acting antiretroviral agents circumvent the requirement for daily dosing to achieve maximal protection and represent an alternative to daily oral regimens. Lenacapavir (LEN) is a long-acting HIV capsid inhibitor recently approved in the European Union for the treatment of multi-drug-resistant HIV infection in combination with other antiretrovirals. Here, we assessed the relationship between LEN plasma concentration following a single subcutaneous (SC) administration and PrEP efficacy using a single high-dose SHIV rectal challenge macaque model.
Methods: LEN antiviral activity against SHIV and HIV was measured in activated PBMCs and adjusted for plasma protein binding. The SHIV stock was titrated over 8 cycles of escalating (0.625 to 100 $TCID_{50}$) rectal challenge (n=8 macaques/cycle) to define a suitable high-dose inoculum. Twenty naïve rhesus macaques received a single SC injection of LEN at 5, 10, 20, 50 or 75 mg/kg (n=4/group). Eleven animals with LEN exposures above its $paEC_{95}$ were challenged rectally with SHIV 7 weeks post-dose. Blood was collected weekly through study week 25 for the evaluation of drug levels, viral loads, and p27 ELISA.
Results: LEN inhibited SHIV replication in rhesus PBMCs with an EC_{50} of 390 pM, resulting in a projected 4.4-fold lower LEN activity against SHIV *in vivo* in rhesus as compared to HIV in humans (rhesus and human PBMC $paEC_{95}$ values of 8.8 and 2.0 nM, respectively). A SHIV inoculum resulting in 10 infections out of 16 rectal challenges of untreated macaques (62.5 % infection per challenge) was selected for the LEN efficacy study. Animals dosed with LEN exhibited a dose proportional increase in plasma C_{max} and AUC and a half-life ranging from 17-53 days. Of 11 SHIV-challenged animals, 3 became infected and 8 remained protected as confirmed by plasma PCR, cell-associated proviral DNA assay, and serology. Adjusting for the 4.4-fold LEN potency difference between HIV and SHIV, we computed protection above and below the clinical efficacy target LEN plasma concentration in this model (70 nM). In animals with LEN above this target, LEN demonstrated complete protection and was superior to the untreated group (p=0.012, one-tailed Fisher's exact test).
Conclusion: These data demonstrate effective SHIV prophylaxis in a stringent macaque model at clinically relevant LEN exposures and support the ongoing clinical evaluation of long-acting LEN for HIV PrEP.

993 EFFECTIVENESS OF HIV PRE-EXPOSURE PROPHYLAXIS AMONG FEMALE SEX WORKERS IN RWANDA

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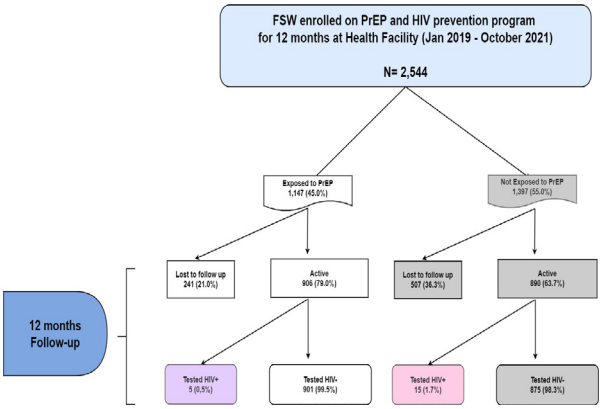
Background: Recent epidemiological analyses showed that the Rwandan HIV epidemic is mixed, with pockets of high HIV prevalence in specific high-risk populations such as Female sex workers, contributing to up to 46% of all new HIV infections. WHO Guidelines in 2015, recommend the use of tenofovir-based Pre-Exposure Prophylaxis (PrEP) in individuals at substantial risk of HIV, such as FSWs, as part of prevention programs. We aimed to evaluate the effects of the provision of PrEP to FSWs within a health program in urban settings of Rwanda.
Methods: This is a retrospective cohort study of HIV negative female sex workers who were exposed or not exposed to PrEP in 22 out of 59 health facilities of the city of Kigali. We included eligible HIV negative FSWs aged 18 years and older who consented to taking PrEP for life (exposed) and compare them to those who did not consent to taking PrEP (unexposed). Data were extracted in a csv format for analysis from an anonymized electronic database. We built logistic regression model the risk of HIV seroconversion at twelve months of follow-up after weighting the inverse probability treatment using a propensity score to control for confounding and reduce imbalance across different treatments.
Results: From January 2019 to October 2021; 2,544 HIV-negative FSW were followed-up in PrEP providing facilities. The majority of FSW 51.9% (1,322/2,544) was aged 18-29 years, 63.0% (1,604/2,544) lived alone and 73% (1,856/2,544) had only attended basic school. In total, 45.1% (1,147/2,544) of FSW participated in the PrEP program while 54.9% (1,397/2,544) were not. At 12 months of follow-up 78.9% (906/1,147) and 63.7% (890/1,397) of FSW were retained in PrEP and in the HIV prevention program, respectively. At 12 months' follow-up, 0.56% (5/906) of FSW in the PrEP program and 1.69% (15/890) of FSW in program without PrEP became HIV-positive. We estimated 69% lower risk of HIV infection among FSW actively followed-up at 12 months' participation in the PrEP program compared to participation in the pre-existing prevention program (adjusted odds ratio 0.31, 95% confidence interval :0.11-0.87)
Conclusion: In this pilot study incidence of HIV infection at 12 months was lower in FSW who were retained in the PrEP program compared to FSW who were ineligible or did not consent to participate. We recommend further longitudinal studies to estimate patient's long-term outcomes and scale-up to other high risk groups.

Figure 1: Participants' care continuum on Pre-Exposure Prophylaxis



994 PRE-EXPOSURE PROPHYLAXIS PRODUCT CHOICE IN US PARTICIPANTS IN HPTN 083

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Background: HPTN 083 demonstrated superiority of long-acting injectable cabotegravir (CAB-LA) compared to daily oral tenofovir disoproxil fumarate-emtricitabine (TDF/FTC) for HIV pre-exposure prophylaxis (PrEP) in cisgender men and transgender women (TGW) who have sex with men. At a planned interim review, an independent data safety and monitoring board recommended the study be unblinded. The protocol was then amended to continue as an open-label extension (OLE) in which participants without contraindication were offered the choice of open-label CAB-LA or to complete study participation with daily oral TDF/FTC. United States (US) participants

completed transition to the OLE before other regions, and therefore this analysis is limited to US participants.

Methods: US participant characteristics, including gender, race, ethnicity, age, education, and original randomized regimen were compared between participants choosing TDF/FTC or CAB-LA using chi-squared tests. We also described participants' reported reasons for choice of regimen.

Results: Regimen choice data were available for 803 participants, of whom 770 (95.9%) chose CAB-LA and 33 (4.1%) chose TDF/FTC. Of these 803, 65 (8.1%) were TGW, 418 (52.1%) were Black or mixed race including Black, 140 (17.4%) were Hispanic/Latinx, 613 (76.3%) had completed college or higher level of education, 229 (29.8%) were less than 25 years of age, and 415 (51.7%) were originally randomized to CAB-LA. Among those initially randomized to CAB-LA, 13 (3.1%) chose TDF/FTC and 402 (96.9%) chose CAB-LA, and among those initially randomized to TDF/FTC (n=388), 20 (5.2%) chose TDF/FTC and 368 (94.8%) chose CAB-LA; choice differences by original randomized study arm were not statistically significant, nor were there any significant differences in product choice by other subgroups. Reasons and proportions of participants choosing CAB-LA or TDF/FTC are listed in the Table.

Conclusion: Nearly all HPTN 083 US participants chose CAB-LA over daily oral TDF/FTC upon transition to the OLE phase of the study; no specific subgroup drove this choice disparity. General preference for either pills or injections largely dictated participants' choice of regimen. A limitation of this analysis is that individuals preferring an oral PrEP regimen may not have chosen to enroll in HPTN 083. Data from the non-US participants in HPTN 083 will provide important insights into regional/cultural differences in product preference.

Reported reasons for choosing an HIV PrEP regimen at the time of HPTN 083 open label extension entry, US participants only (n=803)

Table. Reported reasons for choosing an HIV PrEP regimen at the time of HPTN 083 open label extension entry, US participants only (n=803)

	N (%)
Reason for choosing CAB-LA (n=770)	
Prefer injection and/or don't like pills	541 (70.3)
CAB-LA shown to be superior to TDF/FTC for HIV prevention	112 (14.5)
CAB more convenient, discreet, or easier to adhere to	37 (4.8)
Want to avoid side effects of TDF/FTC	32 (4.2)
Contribute to research or research-dependent Issue	16 (2.1)
Curious to try something new	12 (1.6)
More than one response	5 (0.6)
Other	15 (2.1)
Reason for choosing TDF/FTC (n=33)	
Don't like injections and/or prefer pills	17 (51.5)
The potential side effects of TDF/FTC are better understood or preferable to those of CAB-LA	4 (12.1)
Concerned about resistance if injectable PrEP fails	4 (12.1)
Scheduling constraints/difficulties with visits	4 (12.1)
Undecided or not yet ready for CAB	2 (6.1)
Prior injection site reactions	1 (3.0)
Does not like long-term commitment of injections	1 (3.0)

HIV, human immunodeficiency virus; PrEP, pre-exposure prophylaxis; HPTN, HIV Prevention Trials Network; US, United States; CAB-LA, long-acting cabotegravir; TDF/FTC, tenofovir/emtricitabine

995 OPTIMIZING PRE-EXPOSURE PROPHYLAXIS WITH TDF-FTC AND TAF-FTC FOR INSERTIVE SEX

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Background: Simplifying pre-exposure prophylaxis (PrEP) dosing will facilitate implementation. On demand PrEP has not been evaluated in sub-Saharan Africa, young adults nor using TAF-FTC. Dose needed for insertive sex remains unknown. The CHAPS trial addressed these gaps of knowledge and pre-clinically assessed post-exposure prophylaxis (PEP) in foreskin.

Methods: Phase 2 open-label, randomised controlled trial in Uganda and South Africa. 144 HIV-negative men aged 13-24yrs, randomized to one of nine arms receiving: i) different doses of TDF-FTC or TAF-FTC, or no PrEP ii) different timing of circumcision in relation to PrEP iii) with/without PEP applied 20h post-challenge to foreskin explants. Foreskin explants and PBMCs were exposed to HIV-1_{BaL} at high or more biologically relevant, low viral titre. PEP without PrEP was evaluated with dosing at 1, 24, 48 or 72h post-challenge. Infection was assessed by p24 ELISA of culture supernatants. TFV-diphosphate (TFVdp) and FTC-triphosphate (FTCtp) concentrations were measured using LC-MS in PBMCs, foreskin tissue and CD4+T cells isolated from foreskin. PrEP effect on foreskin proteomics was assessed by western blot evaluation of tight junction proteins and inflammatory cytokines by Luminex.

Results: Compared to control arm, all PrEP dosing arms significantly decreased p24 levels after *ex vivo* HIV-1_{BaL} challenge of foreskin tissue (all $p < 0.0001$) and PBMCs (p 0.002 to < 0.0001) with no differences between drugs (TDF-FTC or TAF-FTC) or timings observed. *Ex vivo PEP* dosing did not increase protection in tissue but further reduced p24 levels in PBMCs. There was no difference in time to, or duration of protection between PBMCs and explants. Higher levels of TFPdp were obtained with TAF-FTC than TDF-FTC in foreskin and PBMCs ($p \leq 0.0001$). Foreskin CD4+ cell TFVdp levels were 42.7|10.9 fmol/10^6 cells (TAF|TDF: p=ns). PEP protection was lost with dosing after 48h exposure; TAF-FTC was significantly more protective than TDF-FTC at every time point. Tight junction proteins were not significantly affected. TDF-FTC significantly reduced IL-1a levels in foreskin.

Conclusion: Oral on demand PrEP with TDF-FTC or TAF-FTC provides *ex vivo* protection of foreskin and PBMCs. TAF-FTC provided higher TFVdp levels in foreskin and PBMCs, and better PEP activity than TDF-FTC in foreskin. PEP protection decayed after 48h post exposure.

996 INTERACTION BETWEEN TAF-BASED PrEP AND HORMONE THERAPY IN TRANSGENDER WOMEN: iFACT 3

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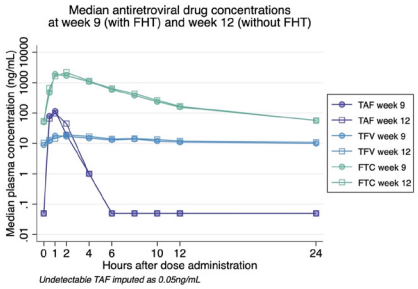
Background: Feminizing hormone therapy (FHT) is common among transgender women (TGW) receiving PrEP. To evaluate the potential drug-drug interaction (DDI) between FHT and emtricitabine (FTC)/tenofovir alafenamide (TAF)-based PrEP, we assessed the pharmacokinetics (PK) of FTC, TAF, tenofovir (TFV) and estradiol (E2) among TGW receiving FHT in Thailand.

Methods: Twenty TGW who had not undergone orchiectomy and had not received injectable FHT within 3 months were enrolled between January and February 2022. FHT (estradiol valerate 2 mg and cyproterone acetate 25 mg) was prescribed to participants at baseline until week 9, while PrEP (FTC 200 mg/TAF 25 mg) was initiated at week 3 until week 12. Intensive PK sampling was performed at weeks 3 (FHT only) and 9 (PrEP and FHT) for E2; and weeks 9 (PrEP and FHT) and 12 (PrEP only) for plasma FTC, TAF, and TFV. Blood bioavailable testosterone, FSH, and LH were also measured.

Results: 18/20 participants completed the PK visits and were included in this analysis. Median (interquartile range [IQR]) age and body mass index were 28 (23-32) years and 20.8 (19.9-21.9) kg/m^2, respectively. The area under the curve (AUC) and maximum concentration (C_{max}) geometric mean ratios (GMRs) (90%CI) at week 3 (reference) and week 9 for E2 were 0.80 (0.72-0.90, p=0.002) and 1.11 (0.94-1.31, p=0.23), respectively. The AUC and C_{max} GMRs at week 9 and week 12 (reference) were as follows: FTC, 0.92 (0.88-0.97, p=0.009) and 0.93 (0.84-1.03, p=0.24); TAF, 1.05 (0.83-1.33, p=0.73) and 1.14 (0.85-1.52, p=0.46); and TFV, 0.92 (0.88-0.97, p=0.01) and 0.97 (0.89-1.05, p=0.50) (*Figure*). No significant changes in bioavailable testosterone, FSH, and LH between weeks 3 and 9 were observed (bioavailable testosterone, median [IQR] 0.031 [0.025-0.120] vs 0.024 [0.006-0.122], p=0.17; FSH, 0.75 [0.6-1.3] vs 0.85 [0.4-1.6], p=0.24; and LH, 0.52 [0.21-0.86] vs 0.44 [0.25-0.79], p=0.95. No participants discontinued the study due to a reported adverse event. There were no significant changes in creatinine clearance and alanine aminotransferase levels over the study period.

Conclusion: Plasma E2, FTC and TFV exposures trended lower when FTC/TAF was administered with FHT; however, the AUC and C_{max} GMRs of FTC and TFV were within the bioequivalence range, indicating no clinically significant DDI from FHT towards FTC/TAF-based PrEP. Intracellular and tissues rectal measurements of TFV-DP and FTC-TP levels are ongoing.



997 PrEP USE AMONG US VETERANS USING VETERAN HEALTH ADMINISTRATION SERVICES: 2017-2021

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Background: The number of persons prescribed HIV preexposure prophylaxis (PrEP) in the United States has been estimated at the national-, state-, and county-levels using a large commercial pharmacy database. These data are used to calculate a quarterly PrEP coverage indicator to monitor progress towards the goals of the Ending the HIV Epidemic in the U.S. (EHE) initiative. This pharmacy database includes prescriptions from >90% of the U.S. retail pharmacies, but PrEP prescriptions from the Veteran Health Administration (VHA) system were not included. To address this gap, we analyzed VHA data to examine the trends in PrEP use among veterans receiving health services in the VHA system.

Methods: We analyzed 2017-2021 PrEP prescription data extracted from the VHA system. We reported the total annual number of persons aged ≥18 years prescribed PrEP each year, stratified by sex, age, race/ethnicity, and region. We assessed trends in the number of persons prescribed PrEP by calculating estimated annual percent change (EAPC) and 95% confidence intervals (CIs) using Poisson models.

Results: The number of veterans prescribed PrEP increased from 1,910 in 2017 to 4,847 in 2021 (EAPC: 24.0% [95% CI, 19.0–29.3]). In 2021, 4,847 veterans had PrEP prescriptions and 96.0% were men, 54.1% were aged 25–44 years, 52.3% were white, 24.6% Black/African American (Black) and 13.4% Hispanic or Latino. Majority of the 2021 PrEP prescriptions were in the South 2,050 (42.5%), 1,676 (34.7%) in the West, 620 (12.8%) in the Midwest, and 486 (10.1%) in the Northeast. The number of female veterans prescribed PrEP increased during 2017-2021 with an EAPC of 29.0% and the proportion of women who comprised PrEP users increased from 3.2% in 2017 to 4.7% in 2021. Similarly, the number of Black veterans prescribed PrEP increased with an EAPC of 29.3% and the proportion of Black persons who comprised PrEP users increased from 19.5% to 24.6% (Table).

Conclusion: VHA data fill a gap in monitoring PrEP use in the United States. We observed an increasing trend in the number of veterans prescribed PrEP similar to the trends among persons with commercial or public health insurance. An increasing proportion of Black veterans prescribed PrEP over the study period can help to decrease racial/ethnic disparities in receipt of HIV prevention services. Less than 5% of PrEP users were female veterans although women comprise 9.5% of U.S veterans. Interventions that support more equitable PrEP service implementation for women is needed.

Table. Number of persons prescribed PrEP by characteristic, U.S. Veteran Health Administration data, 2017-2021

	2017		2018		2019		2020		2021		
	No.	(%)	No.	(%)	No.	(%)	No.	(%)	No.	(%)	EAPC* (95% CI)
Total	1,910		2,738		3,616		4,145		4,847		24.0 (19.0, 29.3)
Sex											
Male	1,849	(96.8)	2,636	(96.3)	3,454	(95.5)	3,966	(95.7)	4,651	(96.0)	23.8 (19.0, 28.8)
Female	61	(3.2)	102	(3.7)	162	(4.5)	179	(4.3)	196	(4.7)	29.0 (18.1, 41.0)
Age (years)											
18-24	29	(1.5)	42	(1.5)	71	(2.0)	73	(1.8)	73	(1.5)	23.4 (12.4, 35.5)
25-34	579	(30.3)	798	(29.1)	986	(27.3)	1,109	(26.8)	1,264	(26.1)	19.7 (15.3, 24.3)
35-44	480	(25.1)	719	(26.3)	976	(27.0)	1,155	(27.9)	1,405	(29.0)	28.1 (22.9, 33.6)
45-54	426	(22.3)	585	(21.4)	756	(20.9)	810	(19.5)	928	(19.1)	19.4 (14.7, 24.4)
≥55	396	(20.7)	594	(21.7)	827	(22.9)	998	(24.1)	1,177	(24.3)	28.8 (22.8, 35.0)
Race/ethnicity											
White	1,132	(59.3)	1,527	(55.8)	1,966	(54.4)	2,211	(53.3)	2,537	(52.3)	20.8 (16.7, 25.1)
Black/African American	373	(19.5)	624	(22.8)	830	(23.0)	991	(23.9)	1,190	(24.6)	29.3 (21.7, 37.3)
Hispanic or Latino**	249	(13.0)	361	(13.2)	491	(13.6)	562	(13.6)	648	(13.4)	24.7 (18.9, 30.7)
Other	156	(8.2)	226	(8.3)	329	(9.1)	381	(9.2)	472	(9.7)	29.5 (24.6, 34.7)

EAPC = Estimated annual percent change; CI=confidence interval.
*EAPC was calculated based on number of persons prescribed from 2017-2021 using Poisson models.
**Hispanic/Latino persons can be of any race.

998 ALIGNMENT OF PrEP USE WITH HIV RISK IN YOUNG WOMEN AND MEN IN UGANDA

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Background: Oral daily pre-exposure prophylaxis (PrEP) uptake has been high but discontinuation is very common and often happens soon after initiation. Whether discontinuation among young women and their male partners aligns with potential exposure to HIV is unknown.

Methods: Young women ages 16-25 and their male partners were enrolled in separate but linked longitudinal studies in Kampala, Uganda from 2018-2021. Women could recruit ≥1 of their male partners to enroll. Data on sexual behaviors (self-reported), PrEP use (dispensing records), and STI positivity (diagnostics for *Chlamydia trachomatis* (CT), *Neisseria gonorrhea* (GC), and HIV) were collected at enrollment and quarterly follow-up visits. Potential HIV exposure was defined as having any STIs, condomless vaginal sex in the past 3 months, or multiple sex partners in the past 3 months. GEE regression with a Poisson link was used to examine the alignment between potential HIV exposure and PrEP use by young women and their male sex partners.

Results: We included 125 male partners of 88 young women in this analysis. The median age at enrollment was 24 (IQR 21-26) and 20 (18-21) years for male and female participants, respectively. At baseline, 27 participants (13%) had a positive test result for CT or GC (15 men, 12 women). One female participant was diagnosed with HIV infection at enrollment. In women and men, PrEP dispensation was more common when they or their partners reported multiple sex partners (adjusted prevalence ratio, in women: her multiple sex partners: 1.60 (1.03-2.49), his multiple sex partners: 1.36 (1.00-1.86); in men: his multiple sex partners, 1.69 (1.04-2.75), her multiple sex partners, 1.51 (1.01-2.28)). Condomless sex trended towards alignment with PrEP use without statistical significance (in women: her condomless vaginal sex: 1.24 (95% CI 0.87-1.75), his condomless vaginal sex: 1.27 (0.83-1.94); in men: his condomless vaginal sex, 1.47 (0.77-2.80), her condomless vaginal sex, 1.28 (0.90-1.83)).

Conclusion: Among young adults, PrEP use was more common when they or their partners self-reported multiple sex partners. These results are reassuring in light of the high occurrence of PrEP discontinuation among young people.

999 A PILOT RCT ASSESSING UPTAKE OF PrEP AND CONTRACEPTION IN HAIR SALONS IN SOUTH AFRICA

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Background: Half of unintended pregnancies in sub-Saharan Africa occur among women ages 15-24, who also have high HIV incidence. Women congregate regularly without partners in hair salons; these may be useful venues for family planning and HIV prevention services. Our objective was to assess the uptake of contraception and PrEP in hair salons in South Africa.

Methods: We conducted a pilot randomized trial to evaluate uptake of a stylist-initiated, nurse-supported intervention offering contraception (oral and injectable) and tenofovir-emtricitabine for PrEP in 3 salons in urban KwaZulu-Natal. Rapid HIV testing was performed at enrollment and each time PrEP was dispensed. Women could receive contraception and/or PrEP at the initial visit or opt in at a later visit during the 12-month study. We defined uptake as the proportion of eligible women who accepted salon-based PrEP and/or salon-based contraception (first-time and new users). Control salon participants were surveyed and referred to clinic for services. We assessed predictors of PrEP uptake among intervention participants using logistic regression, including self-perceived risk of HIV, partner ≥5y older, primary sex partner having other partners, intimate partner violence, and history of or current bacterial STI at enrollment.

Results: Among 85 participants in intervention salons, median age was 25y (IQR 22-29). 69% reported going to the salon at least every 2 months and 42% reported spending at least 2 hours. 32% were taking contraception at time of PrEP uptake. 26% reported having moderate or greater chance of getting HIV in the next year, 36% think their primary sex partner has other partners, and 67% did not use condoms in the past month. 9% reported intimate partner violence.

87% opted for salon-based contraception; 39% initiated PrEP during the study. Adjusting for age, uptake of salon-based PrEP was associated only with reporting any intimate partner violence (aOR 14.5, 95% CI 1.6, 100+).

Conclusion: Young women in urban hair salons in South Africa found receipt of family planning and HIV prevention services in a salon acceptable, with uptake of contraception (87%) higher than that of PrEP (39%). Apart from gender-based violence, risk factors including self-perceived HIV risk, age-disparate relationships and partner having other partners were not associated with PrEP uptake. Hair salons are a novel venue for reaching young women who may not perceive themselves at risk for unplanned pregnancy and HIV.

1000 DISPARITIES IN MPOX VACCINATION UPTAKE IN SAN FRANCISCO AMONG PLWH AND PEOPLE ON PrEP

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Background: In response to the 2022 global mpox outbreak, the San Francisco Department of Public Health launched a rapid mpox vaccination rollout. To identify disparities in vaccine uptake among populations disproportionately affected by mpox and to guide future vaccine campaign strategy, we assessed the proportion vaccinated among people who are either living with HIV (PLWH) in San Francisco (SF) or who are receiving HIV pre-exposure prophylaxis (PrEP) through the municipal STI clinic in SF.

Methods: Data were obtained from two sources: the statewide HIV case registry and the SF STI clinic database. The study population was limited to men and non-binary individuals who have sex with men (MSM) and transgender women (TGW) who were SF residents. PLWH diagnosed prior to 6/1/2022 and people receiving PrEP as of 6/1/2022 were included. The study population was matched to mpox case and vaccination data between 6/1/2022-10/15/2022 and to the STI case registry. All individuals who had received at least one dose of the mpox vaccine were considered vaccinated. Chi-square and Fisher's tests were used to compare vaccination rates by demographic and clinical characteristics and STI history. Record linkage was conducted in SQL Server Management Studio and statistical analysis was performed in SAS 9.4.

Results: Overall, 286/9167 (3%) of PLWH and 23/512 (5%) of people on PrEP had a diagnosis of mpox as of 10/15/2022. Of those without an mpox diagnosis, 42% of PLWH and 65% of people on PrEP at the STI clinic were vaccinated. Among PLWH, TGW (31%), Black people (34%), and people experiencing homelessness (PEH) (24%) were less likely to be vaccinated (see table). Among people on PrEP at the STI clinic, there were no significant differences in vaccination by gender identity, race/ethnicity or age. Within each cohort, those who had had an STI in the past year were more likely to be vaccinated than those who had not (66% vs. 38% among PLWH and 71% vs. 58% among those on PrEP, respectively.)

Conclusion: In SF, a considerable proportion of MSM and TGW PLWH and those on PrEP remain susceptible to mpox infection. Though uptake of mpox vaccine among people on PrEP at the STI clinic was high across racial/ethnic groups, significant disparities remain among PLWH. Efforts to integrate mpox vaccine into routine sexual health services, and to ensure equitable access and uptake, will be important for preventing future outbreaks.

Mpox Vaccination Among PLWH, 06/01/2022-10/15/2022

Mpox Vaccination Among PLWH, 06/01/2022-10/15/2022 (n = 8881)			
	Vaccinated	Unvaccinated	p value
Age (median, IQR)	54 (44-61)	57 (46-65)	
Gender (n, row %)			< 0.0001
Cis male	3562 (42%)	4924 (58%)	
Trans female	117 (31%)	258 (69%)	
Nonbinary	13 (65%)	7 (35%)	
Race (n, row %)			< 0.0001
White	1981 (41%)	2836 (59%)	
Black	308 (34%)	606 (66%)	
Hispanic	934 (44%)	1166 (56%)	
Asian	276 (49%)	285 (51%)	
Other/Unknown	193 (39%)	296 (61%)	
Homeless (n, row %)	82 (24%)	267 (76%)	< 0.0001

1001 ESTABLISHING AN OBSERVATIONAL MPOX VACCINATION STUDY WHILE THE OUTBREAK EVOLVES

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*Presented at CROI by a nonauthor colleague

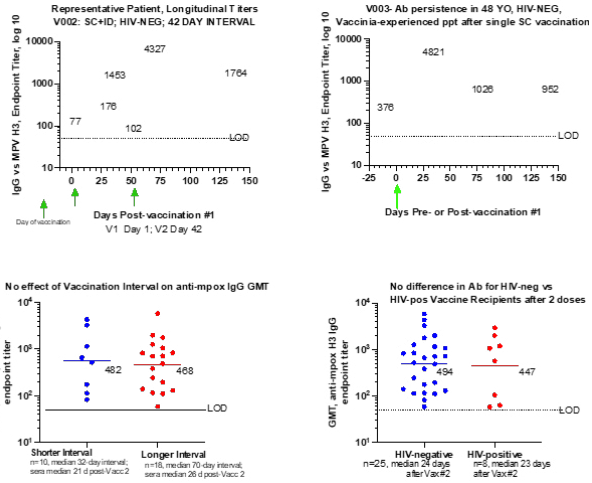
Background: The mpox outbreak of 2022 disproportionally and rapidly affected men, the LGBTQ+ community, and people living with HIV (PLWH). NYC was declared the nation's epicenter, with 3,816 cases reported as of December 26, 2022. NYC rolled out a Jynneos™ vaccination program, initially subcutaneously (SC) as a full dose then intradermally (ID) as a low dose; of note, ID route previously has not been evaluated in PLWH. This study was developed to assess the immunity, tolerability, and safety of SQ and ID mpox vaccinations in those with and without HIV.

Methods: A longitudinal, observational study of adults (PLWH and HIV-) who have received the JYNNEOS vaccine or with history of mpox infection in NYC was rapidly established. Immunogenicity endpoint is measured as the GMT of serum neutralization of mpox live virus; mpox-specific binding IgG titers are a secondary endpoint. Tolerability is assessed through a reactogenicity diary. Safety is monitored by capturing adverse events (AE) and serious AE (SAE). Vaccine acceptability is measured via a knowledge, attitudes, and practices (KAP) survey. Up to 300 participants will be enrolled.

Results: As of January 3, 2023, 54 participants have been enrolled, median age is 39 years, 31% are PLWH (median CD4 count 790), most identify as male (87%) and as LGBTQ+ (92%), with diverse ethnic backgrounds (61% White, 17% Asian, and 22% Black/African American, Native, or other races; and 28% Hispanic or Latino ethnicity). SC followed by ID has been the most common route of administration (45%). Preliminary immunogenicity data (see Figure) shows no significant differences in mpox-specific binding IgG antibody titers between shorter vs longer interval or between PLWH and HIV- participants regardless of the route of administration (by non-parametric Kruskal–Wallis multiple comparisons). Reactogenicity is higher with ID vs SC, with redness (53% ID vs 15% SC) the most common reaction. No SAE have been reported.

Conclusion: Rapid implementation of vaccine studies that respond in real-time to epidemics and include disproportionally-affected populations are an integral part of the public health response. The data resulting from this study will fill knowledge gaps, inform public health practices, guide policymakers, and address community concerns regarding the absence of data for low-dose ID vaccinations in PLWH. Preliminary antibody data suggest PLWH with preserved CD4+ T cell counts respond well to the vaccine.

Preliminary Immunogenicity Data



1002 EVALUATING THE USE OF DOSE-SPARING VACCINATION STRATEGIES FOR MPOX

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Background: The 2022 monkeypox outbreak had over 80,000 cases globally with most of them in gay, bisexual, and other men who have sex with men (MSM). In response to vaccine shortages, several countries implemented dose-sparing vaccination strategies, stretching a full-dose vaccine vial in up to 5 fractional-dose vaccines. Recent studies have found mixed results regarding the effectiveness of the monkeypox vaccine, raising the question of the utility of dose-sparing strategies.

Methods: We used an age- and risk-stratified mathematical model of an urban MSM population in the United States with approximately 12% high-risk MSM to evaluate potential benefits from implementing dose-sparing vaccination strategies in which a full dose is divided in 3.5 fractional-doses. We simulated a low (34% absolute VE) and high (68% absolute VE) fractional-dose vaccine effectiveness (VE). scenarios, corresponding to retaining 40% or 80% of the effectiveness the full-dose vaccine (see Table). Population impact was evaluated over 6-month period.

Results: We found that results strongly depend on the fractional-dose vaccine effectiveness (VE) and vaccine supply (see Table). With very limited vaccine available, enough to protect with a full-dose approximately one-third of the high-risk population, dose-sparing strategies are more beneficial provided that fractional-dose preserved at least 40% of full dose effectiveness (34% absolute VE), projecting 13% (34% VE) to 70% (68% absolute VE) fewer infections than full-dose strategies. In contrast, if vaccine supply is enough to cover the majority of the high-risk population, dose-sparing strategies can be outperformed by full-dose strategies. Scenarios in which fractional-dosing was 34% efficacious result in almost three times more infections than full-dosing.

Conclusion: Our analysis suggests that when monkeypox vaccine supply is limited and fractional-dose vaccination retains moderate effectiveness, there are meaningful health benefits from providing a smaller dose to a larger number of people in the high-risk population

Comparison of monkeypox vaccine full-dose to dose-sparing strategies for different public health scenarios

	Full-Dose Vaccination Strategy	**Dose-Sparing Vaccination Strategy** (% Incremental difference compared to full-dose)	
MSM population size [number high risk MSM]	**65,000 [7924]**		
Number of MSM vaccinated	**2500**	**8,750** (+250%)	
Vaccine effectiveness (VE)	**85%**	Low VE **34%**	High VE **68%**
Peak weekly number of new MPX infections over 6 months	745	736 (-1.2%)	170 (-77.1%)
Cumulative number of new MPX infections over 6 months	5424	4743 (-12.6%)	1679 (-69.0%)
Number of MSM vaccinated	**7,500**	**26,250** (+250%)	
Vaccine effectiveness (VE)	**85%**	Low VE **34%**	High VE **68%**
Peak weekly number of new MPX infections over 6 months	115	655 (+465%)	122 (+5.3%)
Cumulative number of new MPX infections over 6 months	1420	4147 (+193%)	1358 (-4.3%)

1003 IDENTIFYING DISPARITIES IN MPOX VACCINATION IN A SOUTHEASTERN ACADEMIC HIV CLINIC

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Background: Most cases of human mpox occur in men who have sex with men, and persons with HIV (PWH). A two dose vaccine series to prevent mpox has been approved and was first deployed in the United States (US) in mid-2022. Equitable vaccine deployment may have been impeded by barriers to healthcare including structural racism and insurance coverage, preventing targeted vaccination of high risk patients. We sought to evaluate vaccination disparities by race, insurance status, and mpox risk in our Southeastern academic HIV clinical practice.

Methods: The Duke electronic medical record interface was used to systematically identify PWH attending our clinic between 07/01/2021-11/30/2022 and mpox vaccination status. If a patient tested positive for gonorrhea or chlamydia, or had a positive rapid plasma reagin (RPR) during this period, we deemed them "high-risk" for acquiring mpox. Kruskall-Wallis test was used to compare timing of vaccination across groups. Multivariable logistic regression was performed to establish odds of vaccination among groups of interest.

Results: We identified 2,066 PLWH. 224(10.8%) received at least one vaccine for mpox. Among the 344(16.7%) that were high risk for mpox only 97(28.2%) received a vaccine for mpox. Among patients not at high risk for mpox, 127(7.4%) were vaccinated. Of those vaccinated, 99.6% were male, 92.9% were non-Hispanic, and 54% were Black; 71.4% had private insurance, 14.7% were self-pay, 6.3% had Medicaid, and 6.7% had Medicare. In multivariable logistic regression, patients who were White had higher odds of receiving a vaccine for mpox compared to those who were Black (OR 1.46, 95%CI 1.06-2.00). Additionally, patients who had private insurance (OR 2.03, 95%CI 1.13-3.65) or were deemed high risk for mpox (OR 4.86, 95%CI 3.59-6.59) also had higher odds of vaccination. Among all patients vaccinated, race was not associated with time to vaccination, but those who had private insurance were vaccinated earlier (median 42 days earlier compared with self-pay, $p < 0.0001$).

Conclusion: Among PWH followed at an infectious diseases clinic in the south-eastern US, patients who were White, had private insurance, or were at high-risk for acquiring mpox had higher odds of receiving a vaccine for mpox. Efforts to reduce racial, ethnic, and socioeconomic disparities with equitable access to vaccination, particularly in the setting of rapidly evolving public health emergencies, are urgently needed.

1004 MPOX AWARENESS, RISK REDUCTION, AND VACCINE ACCEPTANCE AMONG PWH IN WASHINGTON, DC

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The DC Cohort Executive Committee
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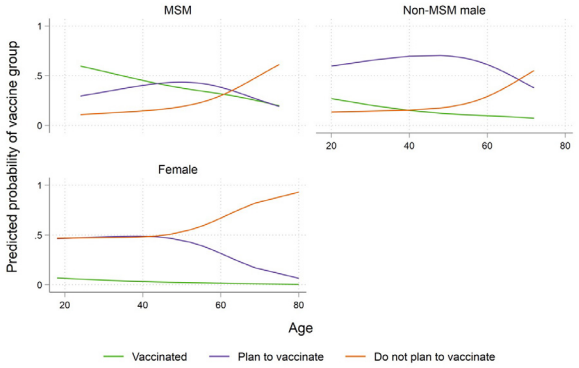
Background: PWH are disproportionally affected by mpox and at high risk for severe complications. The recent mpox outbreak response included increasing awareness, encouraging behavioral changes and pre- and post-exposure vaccination. We assessed knowledge and perceptions of mpox, adoption of preventive behaviors, and attitudes towards vaccination among PWH in Washington, DC.

Methods: Data from a cross-sectional mpox survey were collected between August and December 2022 from PWH enrolled in a longitudinal HIV cohort, the DC Cohort. We conducted uni- and bivariable analyses comparing participants by vaccination status (vaccinated, plan to vaccinate, no plan to vaccinate) and by HIV risk group (MSM vs. non-MSM). We conducted multinomial regression to identify factors associated with vaccine acceptance.

Results: Among 178 PWH completing the survey (median age 55; 71% male, 81% non-Hispanic Black, 37% MSM), 162 (91%) had heard of mpox. Among 159 PWH who had heard of mpox and answered vaccination questions, 21% (n=33) were vaccinated, 43% (n=69) planned to vaccinate and 36% (n=57) did not plan to vaccinate. Comparing the 3 groups, significant differences were observed by age, gender, education, income, HIV risk group, and level of worry about mpox (all $p < 0.01$). Viral suppression, prior COVID and influenza vaccination, access to STI services, and STI diagnoses in the last year were not associated with vaccine status. Behaviorally, a higher proportion of vaccinated participants reported limiting their number of sexual partners ($p < 0.001$) and using more preventive behaviors (e.g., limiting gatherings, increased condom use, avoiding skin-to-skin contact; $p=0.034$) in response to mpox. A higher proportion of MSM reported limiting their number of sexual partners compared to non-MSM (33% vs 7%, $p < 0.0001$) and were more likely to be vaccinated or plan to vaccinate vs non-MSM ($p < 0.001$). In adjusted multinomial regression models comparing vaccinated PWH and those planning to vaccinate to those not planning to vaccinate, age ($p = 0.0231$) and HIV risk factor/gender ($p < 0.0001$) were significantly associated with vaccination status with younger PWH and MSM more likely to vaccinate (Figure).

Conclusion: High levels of mpox awareness were observed among this cohort of PWH in Washington, DC with more MSM employing risk reduction behaviors and vaccination as mpox prevention strategies. Ensuring that all PWH, regardless of gender, sexual orientation, or age, understand the risks of mpox may improve vaccination uptake.

Figure. Predicted Probability of mpox Vaccine Group by Age and HIV Risk/Gender



1005 LONG-TERM COVID-19 BOOSTER EFFECTIVENESS AND IMMUNE IMPRINTING

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Background: Long-term effectiveness of COVID-19 mRNA boosters in populations with different prior infection histories and clinical vulnerability profiles is inadequately understood.

Methods: A national, matched, retrospective, target trial cohort study was conducted in Qatar to investigate effectiveness of a third mRNA (booster) dose, relative to a primary series of two doses, against SARS-CoV-2 omicron infection and against severe COVID-19. Associations were estimated using Cox proportional-hazards regression models.

Results: Booster effectiveness relative to primary series was 41.1% (95% CI: 40.0-42.1%) against infection and 80.5% (95% CI: 55.7-91.4%) against severe, critical, or fatal COVID-19, over one-year follow-up after the booster. Among persons clinically vulnerable to severe COVID-19, effectiveness was 49.7% (95% CI: 47.8-51.6%) against infection and 84.2% (95% CI: 58.8-93.9%) against severe, critical, or fatal COVID-19. Effectiveness against infection was highest at 57.1% (95% CI: 55.9-58.3%) in the first month after the booster but waned thereafter and was modest at only 14.4% (95% CI: 7.3-20.9%) by the sixth month. In the seventh month and thereafter, coincident with BA.4/BA.5 and BA.2.75* subvariant incidence, effectiveness was progressively negative reaching -20.3% (95% CI: -55.0-29.0%) after one year of follow-up. Similar levels and patterns of protection were observed irrespective of prior infection status, clinical vulnerability, or type of vaccine (BNT162b2 versus mRNA-1273).

Conclusion: Boosters reduced infection and severe COVID-19, particularly among those clinically vulnerable to severe COVID-19. However, protection against infection waned after the booster, and eventually suggested an imprinting effect of compromised protection relative to the primary series. However, imprinting effects are unlikely to negate the overall public health value of booster vaccinations.

1006 RESIDENTIAL SEGREGATION AS A BARRIER TO COVID-19 BOOSTER COVERAGE IN DEEP SOUTH

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Background: Coronavirus disease 2019 (COVID-19) had been a stronger hit in Deep South compared with other developed regions in the United States, and vaccination remains a top priority for all eligible individuals. However, there are limited data regarding the progress of booster coverage in the Deep South and how the coverage varies by county and age group, which is of critical importance for future vaccine planning. Racial/ethnic disparities were found in the COVID-19 vaccination, but the vast majority of evidence was generated from studies at the individual level. There is an urgent need for evidence at the population level to reveal and evaluate the booster coverage in racial/ethnic minority communities, which could identify vulnerable communities and inform future healthcare policymaking and resource allocation. We evaluated county-level COVID-19 booster coverage by age group in the Deep South and examined its relationship with residential segregation.

Methods: We conducted an ecological study at the population level by integrating COVID-19 vaccine surveillance data, residential segregation index, and county-level factors across the 418 counties of five Deep South states from December 15, 2021 to October 19, 2022. We analyzed the cumulative percentages of county-level COVID-19 booster coverage by age group (e.g., 12 to 17 years old, 18 to 64 years old, and at least 65 years old) by the end of the study period. We examined the longitudinal relationships between residential segregation, interaction of time and residential segregation, and COVID-19 booster coverage using the Poisson mixed model.

Results: As of October 19, 2022, among the 418 counties, the median percentage of booster coverage was 40% (interquartile range [IQR]: 37.8—43.0%). Compared with elders, youth and adults had lower percentages of booster uptake. There was geospatial heterogeneity in the COVID-19 booster coverage. Results of the Poisson mixed model found that as time increased, higher segregated counties had lower percentages of booster coverage. Such relationships were consistent across the age groups.

Conclusion: The progress of county-level COVID-19 booster coverage in the Deep South was slow and varied by age group. Residential segregation precluded the county-level COVID-19 booster coverage across age groups. Future efforts regarding vaccine planning should focus on youth and adults. Healthcare facilities and resources are needed in racial/ethnic minority communities.

Residential segregation and COVID-19 booster coverage by age group in the 418 counties across the five Deep South states from December 15, 2021 to October 19, 2022

Table. Residential segregation and COVID-19 booster coverage by age group in the 418 counties across the five Deep South states from December 15, 2021 to October 19, 2022†

Model 1	Main effects				
	Overall‖	12-17 years old‡	≥ 18 years old	18-64 years old	≥ 65 years old
Time	-0.058 (-0.078, -0.038)	0.055 (0.037, 0.074)	-0.051 (-0.072, -0.031)	-0.053 (-0.079, -0.027)	-0.028 (-0.044, -0.012)
Residential segregation	-0.066 (-0.086, -0.045)	-0.009 (-0.039, 0.020)*	-0.067 (-0.088, -0.047)	-0.074 (-0.099, -0.049)	-0.044 (-0.060, -0.028)
Model 2	**Main effects and interaction**				
Time	-0.082 (-0.100, -0.064)	0.044 (0.026, 0.061)	-0.077 (-0.095, -0.058)	-0.080 (-0.102, -0.058)	-0.051 (-0.068, -0.034)
Residential segregation	-0.073 (-0.094, -0.052)	-0.016 (-0.046, 0.014)*	-0.075 (-0.096, -0.053)	-0.083 (-0.109, -0.058)	-0.049 (-0.065, -0.032)
Time*residential segregation	0.054 (0.040, 0.069)	0.031 (0.018, 0.044)	0.057 (0.042, 0.072)	0.065 (0.049, 0.082)	0.047 (0.032, 0.062)

†: Unless otherwise noted, study period was from December 15, 2021 to October 19, 2022.
‡: The first record for the group of 12 to 17 years old was available on January 27, 2022. For other groups, the first record was available on December 15, 2021.
‖: From December 15, 2021 to January 26, 2022, the overall population referred to people at least 18 years old. Since January 27, 2022, it referred to people at least 12 years old.
Confounders: Gini index, proportion of people with public assistance, proportion of people in low working class, proportion of people with low education, proportion of noncitizen, household size, primary care provider rate, proportion of adults that report fair or poor health, proportion of households without car access
*: Model 1: P=.55; Model 2: P=.30.

1007 SARS-CoV-2 VACCINE EFFECTIVENESS IN A COHORT OF ACTIVE-DUTY US MILITARY PERSONNEL

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Background: The US Defense Dept launched its COVID-19 vaccination program in Dec 20. The VIRAMP study was designed to address knowledge gaps in US military personnel including vaccine effectiveness against asymptomatic infection, viral carriage and transmission, and durability of protection.

Methods: Military members who had received ≥1 dose of an FDA-authorized COVID-19 vaccine were enrolled at 3 sites in Texas May 21-Mar 22 and followed for up to 24 months after first dose. Study activities comprised of three in-person study visits and remote data collection: weekly and monthly questionnaires, self-collection of blood (monthly) and saliva twice weekly (more frequently if symptomatic). Participants shipped self-collected specimens for Ab analyses and SARS-CoV-2 PCR and sequencing. We report an interim analysis on data collected through May 22.

Results: Participants included 957 military members (60% male, 40% female), with 69% identifying as White, 15% Black/African American, 23% LatinX. Participants were Officers (38%) and Enlisted (62%); 54% were healthcare workers. The majority (92.5%) received the Pfizer/BioNTech monovalent A/Wuhan COVID-19 vaccine; 30% of participants received one booster dose. One or more breakthrough infections (bti), defined as positive saliva SARS-CoV-2 PCR, were detected in 228 (24%) participants (36 Delta, 192 Omicron). No differences were detected in rates of symptomatic vs asymptomatic bti by variant or time since last vaccine. Mean age was greater for participants with bti vs those without (35.4 (+/- 7.7) years vs 32 (+/- 8.2) years; p< 0.0001), but no differences were noted by sex, race, or ethnicity. Symptomatic infections (defined as ≥2 symptoms) were detected in 43% of participants, whereas 35%

of bti were asymptomatic; there were no hospitalizations or deaths. A trend towards reduced duration of saliva positivity was noted in Omicron infections in the 4 months following booster dose compared to infections in the 4 months following primary series (5.3 days vs 12.4 days; p=0.0645).
Conclusion: Approximately 1/4 of participants had bti in the first year, spanning the evolving epi and vaccination landscape of the pandemic, with about 1/3 demonstrating asymptomatic infection. A trend towards shorter duration of viral carriage following booster dose was noted in Omicron infections. The VIRAMP study demonstrated that prospective surveillance in a large, diverse cohort of US military members utilizing remote specimen and questionnaire collection is operationally feasible.

1008 EFFECTS OF PUBLIC HEALTH INTERVENTIONS AGAINST COVID-19 IN FRANCE

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Background: Non-pharmaceutical interventions (NPIs) and vaccines have been used by many countries to manage the dynamics of the COVID-19 pandemic. Despite numerous studies, considerable uncertainty remains about the effects of these public health interventions due to data quality issues and methodological challenges to estimating effects. However, producing accurate and precise estimates of the effects of these interventions is of utmost importance for the preparedness of any new epidemic.
Methods: We developed a population-based mechanistic compartmental model that includes the effect of NPIs on SARS-CoV-2 transmission and the effect of vaccination on the transmission and the rate of hospitalization. Our statistical approach estimated all parameters in one step, thus accurately propagating uncertainty, and representing spatial heterogeneity. We fitted the model to all available epidemiological data (hospital admissions and occupancy, cases, and deaths) from March 2020 to October 2021 in France. Hence, we estimated the time-varying transmission rate, and derived the effect of NPIs through an integrated regression model. We simulated counterfactual scenarios of the interplay of NPIs and vaccine availability and rollout with the same model.
Results: We found that the first lockdown reduced transmission by 84% (95% CI [83-85]) and was more effective than the second and third lockdowns (reduction of 75% [72-77] and 9% [6-13], respectively). A 6pm curfew was more effective than an 8 pm curfew (transmission reduction of 69% [67-70] vs. 50% [48-53]). School closures had a smaller effect on transmission (15% [12-19]). By the end of the study period, the protection conferred by vaccines against hospitalization and against infection, considering viral variants and population vaccine coverage, ranged between 69-92% and 29-40%, respectively. In a scenario without vaccines, we predicted 209% (95% PI [34-520]) more deaths and 346% [101-798] more hospitalizations throughout the study period. Conversely, if an effective vaccine had been available after 100 days, 65% [36-80] deaths and 72% [45-84] hospitalizations could have been averted.
Conclusion: Our results provide reliable effect and uncertainty estimates of each NPI and demonstrate that NPIs and vaccination synergistically reduced COVID-19 transmission, hospitalization, and deaths. This emphasizes the importance of stringent NPIs and a high vaccination rate to prevent further epidemic resurgences and control other emerging respiratory infectious diseases.

1009 EQUITY-BASED OPTIMIZATION FOR COVID-19 VACCINE ALLOCATION

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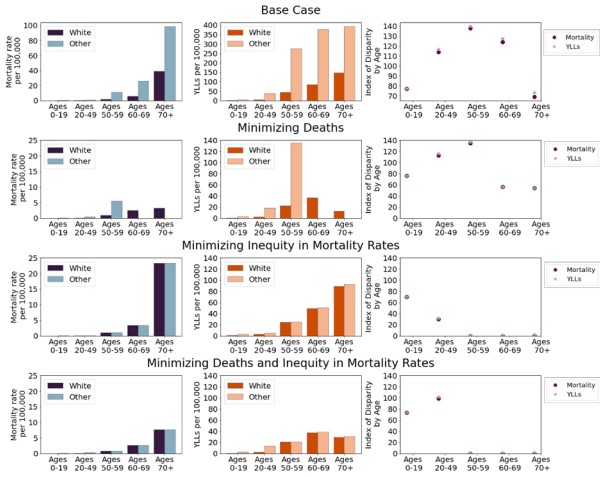
Background: Despite the development of safe and effective vaccines and antiviral treatments against COVID- 19, marginalized racial/ethnic groups in the United States continue to be disproportionally burdened by COVID-19. In response to this inequity, public health officials in several states designed, usually in an ad-hoc manner, policies aimed to be more equitable in both access and distribution of COVID-19 interventions.
Methods: We constructed an age- and race-stratified mathematical model of SARS-CoV-2 transmission and COVID-19 vaccination. We fit our model to data from Oregon at the beginning of 2021. Next, we explored counterfactual scenarios where we determined the optimal use of limited amounts of vaccine over the first 4 months of 2021 with the goal of minimizing 1) number of deaths or Years of Life Lost (YLL), 2) the inequity in mortality or YYL between race groups, 3) a combination of both. We compared them to a base-case scenario without vaccination.
Results: When vaccine supply is very limited (enough to cover 10% of the population), there is a trade-off between minimizing mortality or minimizing inequity (Fig.1). For minimizing mortality, it is optimal to allocate vaccine to the oldest age group, irrespective of race. To minimize inequity, vaccine needs to be allocated first to the marginalized populations in the young- and middle-aged groups, incurring significantly more deaths in all groups, including the marginalized ones, compared to minimizing mortality (Fig.1). When minimizing both deaths and inequity, the optimal vaccination strategy achieved a significant reduction in inequity while preserving most of the reduction in mortality (Fig.1). When minimizing YYL and inequity, the optimal allocation resulted in a more equitable distribution of resources and outcomes across race groups.
Once vaccine supply was enough to cover 20% of the population, our results suggest that it is possible to minimize both mortality (or YYL) and inequity, by protecting marginalized communities and the oldest populations at the same time.
Conclusion: With low vaccine supply, there is a trade-off between being more equitable and reducing mortality. This is true because COVID-19 related mortality is concentrated in the oldest population while marginalized populations are predominately young. This trade-off quickly disappears when more vaccine is available. An interdisciplinary approach is needed to address the inequitable distribution of resources and outcomes in public health.

Mortality rate (left), Years of Life Lost (center) and Indices of Disparity (right) with no vaccination (top row), minimizing deaths (2nd row), inequity (3rd row) or both (4th row) with enough vaccine to cover 10% of the population.



1010 VACCINE UPTAKE IN A PREDOMINANTLY BLACK AND LATINX COHORT HOSPITALIZED FOR COVID-19

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Background: Vaccine uptake has been notably lower in minoritized populations in the United States. The impact of previous infection with SARS-CoV-2, disease severity, and persistent symptoms on the uptake of COVID-19 vaccines and boosters in predominantly Black and Latinx communities has not been examined. We aimed to describe correlates of vaccine uptake in a minoritized cohort hospitalized for COVID-19 during the first pandemic wave in New York City, and investigate whether those with more severe initial COVID-19 and persistent symptoms would be less likely to get vaccinated.
Methods: This retrospective cohort study included the electronic medical records of the first 894 consecutive adult patients who survived hospitalization for COVID-19 at a large quaternary care medical center in Northern Manhattan between 1 March and 8 April 2020. We abstracted data regarding demographics, comorbidities, oxygen requirements during hospitalization, persistence of symptoms at 3- and 6-months after admission, COVID-19 vaccinations through November 2022, and influenza vaccination during the 2018-2019 through 2021-2022 seasons. Unadjusted and adjusted logistic regression analyses were conducted to describe the predictors of COVID-19

vaccination, delayed vaccination (first dose after 6 May 2021), and receipt of a booster vaccine. Statistical analyses were performed using R V.4.2.1.
Results: The cohort of 894 patients was predominantly Latinx (54%) and Non-Hispanic Black (15%). 41% received at least one influenza vaccine pre-COVID, and 67% had at least one comorbidity. 22% (199/894) remained COVID-19 unvaccinated. Of the individuals who received at least one dose of COVID-19 vaccine, 57% (397/695) received at least one booster. Exactly 31% (212/695) delayed vaccination. 25% (27/106) of unvaccinated individuals reported persistent generalized symptoms compared to 18% (78/436) of vaccinated individuals. Multiple logistic regression showed that Hispanic/Latinx ethnicity, age 35-64, and concurrent influenza vaccination were associated with increased COVID-19 vaccine uptake. No association was found between vaccine uptake and disease severity or persistence of symptoms.
Conclusion: Achieving a deeper understanding of the factors driving vaccine hesitancy is critical to increasing and sustaining acceptance of COVID-19 vaccination especially in communities with historically low uptake of annual vaccines.

1011 PREVALENCE AND CORRELATES OF SARS-CoV-2 VACCINE HESITANCY AMONG US PEOPLE WITH HIV

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Background: People with HIV (PWH) have a higher risk of COVID-19 morbidity and mortality. SARS-CoV-2 vaccination is highly effective in preventing severe COVID-19, although medical mistrust may contribute to vaccine hesitancy among PWH.
Methods: PWH from 8 sites in the Centers for AIDS Research Network of Integrated Clinical Systems (CNICS) completed the clinical assessment of patient-reported outcomes including a vaccine hesitancy instrument as part of routine care from 2/21-4/22. Participants were defined as vaccine hesitant if they had not yet received the SARS-CoV-2 vaccine and would probably or definitely not receive it. We assessed factors associated with SARS-CoV-2 vaccine hesitancy using logistic regression, and adjusted for demographics, unsuppressed viral load >200 copies/mL, calendar month and time on ART.
Results: Overall, 3,278 PWH with a median age of 55 responded; 19% were female sex at birth; 93% were virally suppressed. At the time of survey, 27% reported they had not received the SARS-CoV-2 vaccine, of whom 27% (n=242; 7% overall) reported vaccine hesitancy. Of these 242, 82% expressed concerns about vaccine efficacy; 86% about side effects; 38% reported distrust of healthcare, 53% reported concerns about vaccine contents (i.e. trackers, live virus); and 24% did not perceive risk from COVID-19. Factors associated with vaccine hesitancy included female sex (Adjusted Odds Ratio [AOR] 2.0; 95% Confidence Interval (CI): 1.5-2.8; **Table**), Black vs. White race (AOR 1.8; 95% CI: 1.3-2.5), age< 30 years (AOR 2.8; 95% CI: 1.5-5.2), South/Midwest vs. Northeast region (AOR 1.7; 95% CI: 1.2-2.4), years on ART (0.8; 0.7-0.9) and unsuppressed viral load (AOR 2.2; 95% CI: 1.4-3.5). Hesitancy decreased over time (AOR 0.9 per month; 95% CI: 0.8-0.9). Vaccine side effects were the primary concern for women; vaccine contents for Black PWH and those who were unsuppressed; and lack of perceived COVID-19 risk for youth.
Conclusion: Vaccine hesitancy was reported by approximately 7% of a U.S. multi-site cohort of PWH, and it was more prevalent among Black PWH, women, youth, those with unsuppressed viral loads, and residents of the South/Midwest. The association between virologic non-suppression and vaccine hesitancy highlights the intertwined challenge of medical mistrust for both HIV and COVID-19. Although vaccine hesitancy decreased over time, renewed efforts will be needed to address concerns of PWH about the COVID-19 vaccine, given the ongoing need for revaccination with the evolution of the pandemic.

Factors Associated with SARS-CoV-2 Vaccine Hesitancy in U.S. HIV Clinics

Factor	Adjusted Odds Ratio	95% Confidence Interval	p-value
Female sex at birth	2.04	1.48-2.81	<0.001
Black vs. White Race	1.78	1.28-2.49	0.001
Age< 30 years	2.79	1.49-5.24	0.001
Region vs. Northeast (ref): West	1.23	0.84-1.81	0.29
South/Midwest	1.73	1.23-2.44	0.002
Unsuppressed Viral Load (>200 copies/mL)	2.20	1.41-3.45	0.001
Years on ART (per 5 years)	0.79	0.69-0.86	<0.001
Study month	0.88	0.84-0.93	<0.001

Analyses were adjusted for age, birth sex, race/ethnicity, site, time on ART, viral suppression, and study month.

1012 SAFETY OF HETEROLOGOUS mRNA-1273 BOOST AFTER Ad26.COV2.S PRIME IN SOUTH AFRICA

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Background: Given the paucity of data on safety and effectiveness of mRNA COVID-19 booster vaccinations in lower income settings with high HIV prevalence, we evaluated a heterologous mRNA-1273 (Moderna) boost after priming with 1 or 2 doses of Ad26.COV2.S (Janssen, Johnson & Johnson) vaccine among health care workers (HCWs) in South Africa.
Methods: SHERPA is an open-label, phase 3 mRNA-1273 booster study, nested in the Sisonke Phase 3b implementation trial, that vaccinated ~500000 HCWs with 1 or 2 doses of Ad26.COV2.S from Feb and Dec 2021. Sisonke participants were offered mRNA-1273 boosters between 23 May and 12 Nov 2022 (median 17 and 8 months after 1 and 2 Ad26.COV2.S, respectively), with data cut-off on 12 Dec 2022. Reactogenicity and adverse events (AEs) were self-reported via an online data entry link shared by SMS with participants 1, 7 and 28 days after boosting. Using national databases analyses are underway to compare effectiveness against COVID-19 infections and severe disease with Sisonke participants who did not receive the booster.
Results: 12188 HCWs (79.5% female, 28.6% with self-reported previous COVID-19 diagnosis) received a mRNA-1273 booster, of whom 44.6% and 55.4% had received 1 and 2 prior Ad26.COV2.S vaccines in Sisonke, respectively. 3056 (25.2%) reported being HIV positive, more among those receiving only 1 previous Ad26.COV2.S (26.8% vs 23.9%), and 1.4% reported not being on antiretroviral therapy. 17.0% of participants reported hypertension and 6.4% diabetes mellitus. 262 participants (2.1% of women, 2.5% of men) reported 234 reactogenicity events and 95 AEs post-vaccination, with more reported by those with prior COVID-19 infection (3.5% vs 1.6%), HIV negative status (2.5% vs 1.2%) and those who received 2 prior doses of Ad26.COV2.S (2.4% vs 1.8%) (**Table**). Among 159 (1.3%) reporting injection site reactions the commonest were pain (59.7%), swelling (42.1%) and induration (20.1%). Of 177 (1.5%) systemic reactogenicity events (all grade 1 or 2 severity), the commonest were myalgia (69.5%), headache (67.8%) and fever (37.9%). 14 participants had AEs of special interest or serious AEs, of which 4 (all AESIs of ageusia or anosmia) were deemed related to the booster. 13 COVID-19 infections occurred a median of 125 days post booster vaccination (IQR 90–154) after 3477 person-years of follow up.
Conclusion: A mRNA-1273 booster administered after 1 or 2 doses of Ad26.COV2.S was well tolerated regardless of HIV status, other chronic conditions or prior COVID-19 infection.

Multivariable logistic regression model of local/systemic reactions adjusted for age and gender

	n/N (%) reporting AE/reacto	Unadjusted OR (95% CI)	Adjusted OR (95% CI)
Prior COVID diagnosis			
No	141/ 8696 (1.6%)	Reference	
Yes	121/ 3486 (3.5%)	2.18 (1.70 - 2.79)	2.15 (1.68 - 2.76)
HIV status			
No	224/ 9056 (2.5%)	Reference	
Yes	38/ 3056 (1.2%)	0.50 (0.35 - 0.70)	0.54 (0.38 - 0.77)
Prior vaccination			
1_Ad26.COV2.S	100/ 5437 (1.8%)	Reference	
2_Ad26.COV2.S	162/ 6751 (2.4%)	1.31 (1.02 - 1.69)	1.32 (1.02 - 1.70)

1013 REACTOGENICITY AMONG PEOPLE LIVING WITH HIV AFTER mRNA-1273 VACCINE IN UBUNTU STUDY

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CoVPN 3008 Ubuntu Study Team

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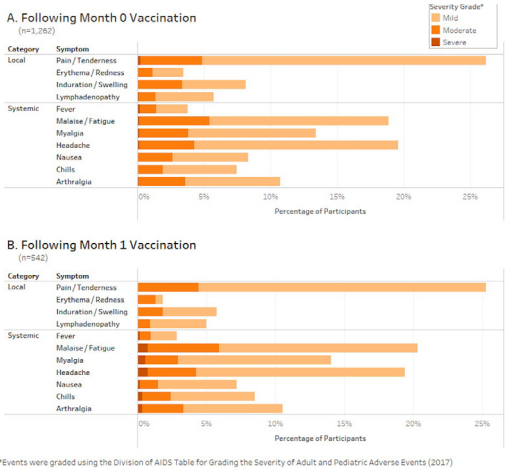
Background: The tolerability of mRNA COVID-19 vaccines among people living with HIV (PLWH) has been understudied in vaccine trials. CoVPN 3008 (Ubuntu) is the largest multicenter Phase 3 efficacy trial of mRNA vaccines in sub-Saharan Africa.

Methods: We enrolled adults age ≥18 years living with HIV or another comorbidity associated with severe COVID-19. Previously vaccinated individuals were excluded. Baseline testing included HIV, CD4 count and HIV viral load (VL) (if HIV+), anti-SARS-CoV-2 antibodies, and nasal swab SARS-CoV-2 nucleic acid amplification test (NAAT). All participants receive vaccinations at months 0 and 6, and SARS-CoV-2 seronegative individuals also receive vaccination at month 1. This analysis includes mRNA-1273 vaccinations at months 0 and 1. Reactogenicity (solicited adverse events [AEs]) was assessed among a representative subset of participants (Safety Subset, SS) for 7 days post-vaccination. Baseline characteristics associated with moderate/severe reactogenicity events were assessed by univariate and multivariate logistic regression.

Results: 14002 participants were enrolled in the trial (1510 into the SS) at 46 sites from 2 Dec 2021 to 9 Sep 2022. At baseline in the SS, 71% (1065) were female, median age 38 years (IQR 32-46), and median BMI 25.0 (IQR 20.7-30.2). 73% (1108) were SARS-CoV-2 seropositive, and 8.7% (131) had a positive nasal NAAT swab. 16% (197) had a history of tuberculosis. 84% (1267) were PLWH, with median CD4 count of 614 cells/μL (IQR 414-861); 7.8% had CD4 count < 200. 21% (238) had detectable HIV VL (≥50 copies/mL), with median VL 1660 (IQR 182-23932). 14% (172/1262) and 12% (64/542) of PLWH reported moderate/severe reactogenicity after the 1st and 2nd vaccination (Figure), with no hospitalizations. Female PLWH and CD4 count >500 had 35% (p=0.03) and 44% (p=0.04) increased odds of moderate/severe reactogenicity, respectively. Other baseline characteristics were not associated with the odds of reporting moderate/severe reactogenicity among PLWH after 1st vaccination. Similar trends were seen after the 2nd vaccination, but none reached statistical significance. In multivariate models, female sex remained associated with increased odds of moderate/severe reactogenicity after the 2nd vaccination.

Conclusion: Similar to observations in HIV-negative populations, mRNA-1273 was well tolerated by PLWH with more reactogenicity in females. Impaired inflammatory responses among participants with CD4 counts < 500 cell/μL may explain less moderate/severe reactions.

Solicited adverse events after 1st and 2nd mRNA-1273 vaccination in PLWH



*Events were graded using the Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events (2017)

1014 COVID-19 VACCINATION IN PERSONS WITH AND WITHOUT HIV: VETERANS AGING COHORT STUDY

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Background: COVID-19 vaccination is effective at preventing symptomatic infection, hospitalization, and death from COVID-19, but many people have experienced barriers to receiving this life preserving intervention. A study examining COVID-19 vaccination in New York state found that persons with HIV (PWH) were less likely to be vaccinated than the general population. We examined whether PWH are less likely to be vaccinated than persons without HIV (PWoH) in the Veterans Affairs (VA) Healthcare System.

Methods: We examined COVID-19 vaccination receipt by HIV status in the Veterans Aging Cohort Study (VACS), an open cohort of PWH and 1:2 age-, race/ethnicity-, sex-, and site-matched PWoH. Among participants with a VA encounter from 10 December 2020 to 12 September 2022, we calculated the proportion of individuals who were fully vaccinated and boosted. Fully vaccinated was defined as: 14 days after second dose of mRNA vaccine (either Pfizer BNT162b2 or Moderna mRNA-1273) or single dose of a viral vector vaccine (Janssen Ad26.COV2.S). Boosted was defined as an additional vaccination at least 180 days after full vaccination. We assessed differences using chi-square tests.

Results: Among 109,421 participants, PWH (n=31,337) were more likely than PWoH (n=78,084) to be fully vaccinated (77.6% vs 68.7%, p< 0.001) and boosted (71.1% vs 63.0%, p< 0.001) (**Table**). Most people received an mRNA vaccine with 6.9% of fully vaccinated PWH and 7.5% of fully vaccinated PWoH receiving the Janssen vaccine. Among PWH, having an undetectable HIV viral load was more common in those fully vaccinated than those not fully vaccinated (79.4% vs 72.0%, p< 0.001).

Conclusion: In a matched cohort of veterans with and without HIV in VA care, we found that PWH were more likely than PWoH to be fully vaccinated and boosted. These findings contrast with a New York state study which found lower COVID-19 vaccination rates in PWH, possibly due to differential healthcare access; all patients in our cohort have access to VA care. Further studies are needed to understand differences in vaccine acceptance and receipt to prevent COVID-19 hospitalizations and deaths.

COVID-19 Vaccination in People with HIV (PWH) and People without HIV (PWoH) - Veterans Aging Cohort Study, as of 12 September 2022

		PWH		PWoH	
Eligible* participants		31,337		78,084	
Number who received any vaccine		25,152		55,640	
Number fully vaccinated	(% of all eligible)	24,327	77.6%	53,658	68.7%
Number boosted	(% of fully vaccinated)	16,437	71.1%	32,019	63.0%
Vaccine type					
Pfizer	(% of fully vaccinated)	12,106	49.8%	24,886	50.0%
Moderna	(% of fully vaccinated)	10,533	43.3%	24,746	46.1%
Janssen	(% of fully vaccinated)	1,688	6.9%	4,026	7.5%

*Alive and had a visit in the VA during 10 December 2020 to 12 September 2022

1015 THE CHANGING IMPACT OF VACCINES IN THE COVID-19 PANDEMIC: A MODELING STUDY

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Background: Much of the world's population had already been infected with COVID-19 by the time that the Omicron variant emerged at the end of 2021, but the scale of the Omicron wave was larger than any that had come before or since, and left a global imprinting of immunity which changed the COVID landscape. In this study, we explore the changing value of vaccines in a landscape of dynamic immunity and rapidly evolving variants of concern.

Methods: We use Covasim, an established agent-based model of COVID-19 enhanced with detailed intra-host dynamics. First, we simulate a vaccine trial over March 2020 – April 2022 within a population resembling that of South Africa, and estimate how both vaccine efficacy (reduction in the risk of severe disease for vaccinated vs unvaccinated individuals) and efficiency (number of doses needed to avert a death) change as the population experiences waves of wild-type, Beta, Delta, and Omicron infections. Next, we introduce six

hypothetical variants starting from February 2022 and evaluate the impact of (a) the existing set of vaccines, and (b) vaccines specifically targeted to the new variants.

Results: We estimate that within our simulated population, vaccine efficacy against severe disease decreased from 80% to 20% in the wake of the first wave of wild-type COVID-19, then increased back to ~70% over the latter half of 2020 as population immunity waned. This pattern repeated following each subsequent wave of infections, with vaccine efficacy falling to its lowest (10%) in the immediate wake of the Omicron wave in December 2021. The efficiency of vaccination decreases over time at an increasing rate: at peak efficiency, fewer than 100 doses would have been required to avert a single death, but by the end of January 2022, we estimate that nearly 4,000 doses would be required to avert a single death.

We find that variant-chasing vaccines will only add value above pre-existing vaccines if we can shorten the window between variant introduction and vaccine deployment to under three weeks, an impossible time-frame without significant NPI use.

Conclusion: Although the vaccines have proven to be remarkably effective, our work demonstrates that the population immunity acquired over the first two years of the pandemic significantly reduced the impact per dose of doses delivered after this time. Next-generation vaccines to fight future COVID variants and/or other respiratory diseases must be delivered rapidly at scale for vaccine strategies to be maximally effective.

1016 HIV VIRAL LOAD AND TIME-TO-COVID-19 VACCINATION AMONG PEOPLE WHO INJECT DRUGS

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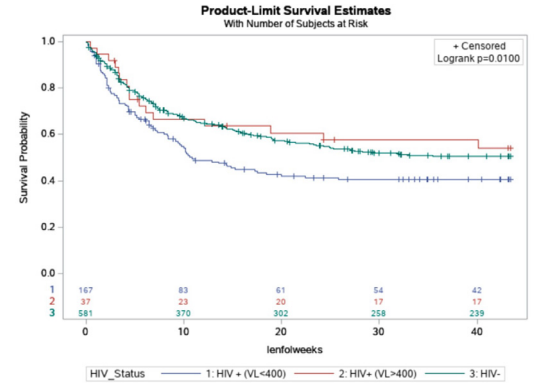
Background: Structural barriers to care among people who inject drugs (PWID) raise concerns about disproportionate access to essential services like COVID-19 vaccination. Given the heightened risk of serious complications resulting from SARS-CoV-2 infection, particularly among people living with HIV (PWH) with unsuppressed viral load, its critical to understand the role of HIV care among other factors associated with timely vaccination. We aimed to assess the role of HIV care on COVID-19 vaccination uptake among PWID.

Methods: We included 960 adult PWUD participating in the ALIVE (AIDS Linked to the Intravenous Experience) longitudinal study in Baltimore, Maryland, who were alive and in follow up as of April 2020. We abstracted COVID-19 vaccination data from electronic medical records linked to participants via the regional health information exchange. We conducted survival analysis to estimate time from broad vaccine eligibility (April 6, 2021) to completion of the COVID-19 vaccination primary series by HIV status (uninfected, virally suppressed PWH [HIV-RNA< 400 copies/mL], unsuppressed PWH [HIV-RNA >400 copies/mL]) and Cox Proportional Hazards regression to adjust for potential confounding by health status and substance use variables.

Results: Our sample (N=960) was primarily black (77%) and male (65%) with 31% reporting recent injection drug use. Among 265 people living with HIV (PWH) in our sample (27%), 84% were virally suppressed. As of February 22, 2022, 539 (56%) completed the primary series, 131 (14%) received a single dose of mRNA vaccine and 290 (30%) remained unvaccinated. Compared to PWID without HIV, virally suppressed PWH were significantly more likely to complete the primary series (Adjusted Hazard Ratio [AHR]:1.23,95% Confidence Interval [95%CI]:1.07,1.50), while PWH with higher viral loads were less likely (AHR:0.72,95%CI:0.45,1.16). Sensitivity analyses with a subsample restricted to PWH confirmed significant differences in time to vaccination by viral load status (log-rank p-value: 0.016) and modeling with an origin of Dec. 12, 2020, yielded similar adjusted results.

Conclusion: Among PWID with HIV, viral suppression is associated with quicker vaccination uptake, likely due to HIV care engagement. Alongside interventions targeting social determinants (e.g. low income, homelessness) and substance use behaviors (e.g. active injecting, stimulant use), targeted improvements along the HIV care continuum and other efforts to engage PWID may bolster vaccine uptake.

Figure 1. Kaplan-Meier survival curve demonstrating time-to-vaccination (completion of COVID-19 primary series) in weeks by HIV status accounting for viral load (HIV-, HIV+ [VL ≤ 400 cells/μL], HIV+ [VL > 400 cells/μL]), including results for Log-rank tests for homogeneity among strata (p-value).



1017 COVID-19 VACCINE COVERAGE AMONG PEOPLE WITH HIV IN THE VACCINE SAFETY DATALINK

Rulin Hechter[1], Lei Qian[1], In-Lu Amy Liu[1], Lina Sy[1], Denison Ryan[1], Joshua Williams[2], Laura Hurley[2], Nicola Klein[3], Robyn Kaiser[4], Elizabeth Liles[5], Hung Fu Tseng[1]

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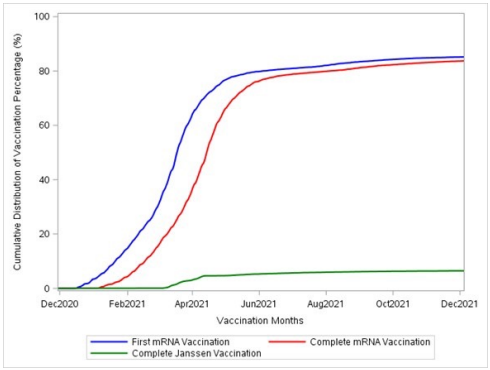
Background: People with HIV (PWH) may be at increased risk for severe COVID-19 outcomes compared with people without HIV. However, COVID-19 vaccination coverage among PWH is largely unknown, especially among those with advanced HIV or comorbidities.

Methods: We conducted a cohort study to evaluate coverage of the initial COVID-19 vaccine primary series and factors associated with the completion in adult PWH (≥18 years) enrolled in 8 healthcare organizations participating in the Vaccine Safety Datalink (VSD) project during December 1, 2020- December 31, 2021. Completion of two doses of the Pfizer-BioNTech or Moderna mRNA COVID-19 vaccines or one dose of the single-dose Janssen COVID-19 vaccine was assessed. Multivariable analysis was conducted using a robust Poisson regression model to estimate the rate ratio (RR) for factors associated with primary series completion, accounting for follow-up time.

Results: A total of 22,063 PWH were identified, among which 89% were male and 93% were viral suppressed (viral load, VL ≤200 copies/ml). Chronic comorbid conditions were prevalent, with 25% having a Charlson comorbidity score of 1-2 and 13% having a score of 3 or greater. About 23% were overweight and 17% were obese. The majority (90%) completed the primary series and 1,782 PWH (8%) did not receive any dose during the study period. A rapid uptake was achieved within the 6 months after the national COVID-19 vaccination program launched on December 14, 2020. (Figure 1) PWH who received one dose of mRNA vaccine (i.e., partially vaccinated) were excluded (n=314) from the analysis for the primary series completion. Having received an influenza vaccination in the past 2 years was the strongest predictor of completion (RR=1.17, 95%CI: 1.15, 1.20). Males (RR= 1.06, 95%CI: 1.04-1.08) and those of Asian race (RR=1.05, 95%CI: 1.03-1.06, vs. White) were more likely to complete the primary series. However, PWH with baseline CD4 counts < 200 (RR=0.97, 95%CI: 0.94-0.99) and those failing to achieve viral suppression (VL= 201-10k: RR= 0.89, 95%CI: 0.85-0.94; VL >10k: RR= 0.92, 95%CI: 0.87-0.98) were less likely to complete the primary series. Body mass index, Charlson comorbidity score, and neighborhood household income level were not associated with completion.

Conclusion: Coverage of the COVID-19 vaccine primary series was high in adult PWH in the VSD. However, targeted vaccination outreach is warranted for PWH with low CD4 counts and uncontrolled HIV viral load.

Figure 1. Cumulative proportion of PWH who received the initial COVID-19 vaccine primary series, by vaccine type and dosage over time during December 2020- December 2021.



1018 CORRELATES OF COVID-19 VACCINE UPTAKE IN MALAWIAN ADULTS

Hannah Whitehead[1], John Songo[2], Pericles Kalande[2], Khumbo Phiri[2], Eric Lungu[2], Sam Phiri[2], Joep J Van Oosterhout[2], Agnes Moses[2], **Risa Hoffman**[1], Corrina Moucheraud[1]

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Background: COVID-19 vaccine uptake has been suboptimal in many low-income countries. In Malawi, as of end-2022, just over 3.1 million adults have been fully vaccinated, representing ~21% of the adult population. We sought to identify correlates of COVID-19 vaccination among adults in Malawi to inform evidence-based policies and programs.

Methods: A survey was administered among adult (aged ≥18) clients at 32 health facilities across Malawi (May-June 2022). We asked about COVID-19 vaccination history and about hypothesized correlates per the WHO Behavioural and Social Drivers of Vaccination model: what people think and feel, social processes, and practical issues. We assessed correlations between these and vaccination status, adjusting for age, HIV status, sex, educational attainment, household wealth, and urban-rural classification using multivariable logistic regression.

Results: Surveys were conducted with 837 people, median age 39 (IQR 30-49), 56% female, 51% living with HIV and on ART. 33% were up-to-date on COVID-19 vaccination per Malawi guidelines (1 dose for J&J; 2 doses of AstraZeneca or Pfizer vaccines), 61% were unvaccinated, and 6% were overdue for a second dose, with no difference by HIV status, religion, or urban-rural classification. Up-to-date individuals were older than those who were not (45 vs 38 years, $p< 0.001$). The strongest correlates of up-to-date vaccination were believing the vaccine is important and safe, believing vaccination's benefits outweigh its risks, and perceiving social support for vaccination (Table). Of 510 unvaccinated respondents, 54% had been offered the vaccine; the most commonly reported reasons for being unvaccinated were concerns about vaccine side effects (56%) and access-related barriers, such as travel time or cost (19%). Among the unvaccinated, 54% were eager or willing to be vaccinated, 29% were ambivalent, and 18% were opposed. Those opposed were less concerned about COVID-19 infection, did not feel the vaccine is important, and were less confident in the vaccine's safety.

Conclusion: Up-to-date COVID-19 vaccination status was associated with positive attitudes about its importance and safety and perceiving pro-vaccination social norms. Concerns about vaccine side effects were common, but over half of unvaccinated respondents were willing to get vaccinated. Disseminating messages about vaccine safety and ensuring local availability of the vaccine may help address concerns and access barriers, and thus help increase COVID-19 vaccination in Malawi.

TABLE: Correlates of up-to-date COVID-19 vaccination status

TABLE: Correlates of up-to-date COVID-19 vaccination status	Adjusted odds ratio	95% confidence interval	p-value
A little, moderately, or very concerned about getting COVID-19 (vs. not at all) *(currently for unvaccinated, or before got vaccine for vaccinated)*	4.94	(3.24-7.54)	<0.001
Know anyone who has died due to COVID-19 (vs. no, don't think so)	1.88	(1.28-2.75)	0.001
Vaccine very important for own health, household health, and community health (vs. moderately or less important for any)	11.47	(5.83-22.56)	<0.001
Very confident in vaccine safety (vs. somewhat, not too, or not at all confident)	6.05	(4.15-8.83)	<0.001
Vaccine benefits outweigh risks (vs. risks and benefits are equal, or risks outweigh benefits)	4.81	(2.85-8.13)	<0.001
Agree or strongly agree that others in my community are/have been vaccinating against COVID-19 (vs. disagree or strongly disagree)	2.55	(1.61-4.04)	<0.001
Agree or strongly agree that my friends are getting vaccinated against COVID-19, or will do so when it is available to them (vs. disagree or strongly disagree)	2.53	(1.45-4.4)	0.001
Agree or strongly agree that it is/was expected of me that I should vaccinate against COVID-19 (vs. disagree or strongly disagree)	2.52	(1.53-4.15)	<0.001
Agree or strongly agree that my family/spouse believes vaccinating against COVID-19 is a good idea (vs. disagree or strongly disagree)	4.01	(2.25-7.12)	<0.001

Covariates in adjusted models include age, gender, HIV status, educational attainment, household income (categorical variable assessing whether allowed for saving), and urban-rural classification.

1019 SAFETY OF Ad26.COV2.S AND AZD1222 COVID-19 VACCINES AMONG ADULTS IN MALAWI

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*Presented at CROI by a nonauthor colleague

Background: The safety profiles of the Ad26.COV2.S and AZD1222 COVID-19 vaccines have not been described in a general population in Malawi. We present self-reported adverse reactions (AE) following receipt of these vaccines in Malawi as part of a phone-based syndromic surveillance survey.

Methods: We conducted phone-based syndromic surveillance surveys among adults (≥18 years) with verbal consent from July 2020 to April 2022. We used secure tablets through random digit dialing to randomly select mobile phone numbers and electronic data collection forms. Survey questions included whether the respondent had received at least one dose of the COVID-19 vaccines, whether they had experienced any AE following vaccination, and the severity of the AE. We used multivariable analysis to identify factors associated with self-reported adverse reactions post-COVID-19 vaccination.

Results: A total of 11,924 (36.0%) out of 33,150 participants reported receiving at least one dose of either Ad26.COV2.S or AZD1222 between July-December 2021; 65.1% were female. An estimated 49.2% of the vaccine recipients reported at least one AE, 90.6% of which were mild, and 2.6% were severe. About 16.9% (n=656) of respondents who received the first dose of AZD1222 had AE, while 50.2% (n=2,823) of those who received the second dose of AZD1222 and nearly all individuals (n=2,385) who received Ad26.COV2.S reported AE. Joint pain (45.5%), fever (26.7%), headache (26.1%), pain at the injection site (24.4%), and fatigue (16.6%) were among the commonly reported AE. Males were less likely to report an AE compared to females [Adjusted Odds Ratio (AOR) 0.81 95% confidence interval (CI) 0.75-0.88]. Older age was associated with reduced odds of an AE compared to those aged 18-24 years: 65 years+ (AOR 0.62, 95% CI 0.50-0.77). The likelihood of reporting AE increased with education level: tertiary education AOR 2.63 95% CI 1.96-3.53. Respondents who thought COVID-19 vaccines were not safe were more likely to report post-vaccination adverse reactions than those who thought it was very safe (AOR 1.44, 95% CI 1.30-1.61).

Conclusion: Ad26.COV2.S and AZD1222 vaccines are well-tolerated, with primarily mild and few severe AE among adults living in Malawi. Self-report of AE following COVID-19 vaccine receipt is associated with gender, age, education, and concern about the safety of the vaccines. Recognizing these associations is key when designing and implementing COVID-19 vaccination communication messages to increase vaccination coverage.

1020 COMPARISON OF THE EFFECTIVENESS OF DIFFERENT COVID-19 VACCINES AMONG PLWH

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National Taiwan University Hospital, Taipei City, Taiwan (Republic of China)

Background: Previous studies have demonstrated promising serologic responses in PLWH receiving a third dose of vaccine against SARS-CoV-2. However, real-world clinical effectiveness, especially during the pandemic caused by B.1.1.529 variant, remains less investigated.

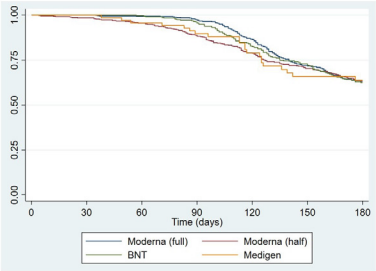
Methods: PLWH seeking HIV care at our hospital from 2021/6 to 2022/6 were included and advised to receive the third dose of COVID-19 vaccine. Individuals were excluded from this study if they had been previously diagnosed with COVID-19. Different types of COVID-19 vaccines were available in the vaccination program, including BNT162b2, mRNA-1273 (either 50 or 100 μg), MVC-COV1901 and NVX-CoV2373 vaccines. PLWH were screening for the occurrence of COVID-19 through the reporting system of notifiable diseases of Taiwan CDC, and were tested for anti-nucleocapsid (anti-N) IgG every 1 to 3 months. Participants were followed for 180 days until the fourth dose of COVID-19 vaccination, occurrence of SARS-CoV-2 infection, seroconversion of anti-N IgG, death, or loss to follow-up, whichever occurred first.

Results: 1,496 PLWH were included: 631 (42.2%) receiving 100 μg mRNA-1273 vaccine, 468 (31.3%) 50 μg mRNA-1273 vaccine, and 328 (21.9%) BNT162b2 vaccine, 65 (4.3%) MVC-COV1901 vaccine, and 4 (0.3%) NVX-CoV2373 vaccine for the third dose of SARS-CoV-2 vaccination. 297 (19.9%) PLWH were diagnosed with COVID-19 during the follow-up period, including 92 (14.6%) who received

100 µg mRNA-1273, 111 (23.7%) 50 µg mRNA-1273, 79 (24.1%) BNT162b2 and 15 (21.7%) either MVC-COV1901 or NVX-CoV2373; in addition, 98 PLWH had seroconversion of anti-N IgG during follow-up, including 23, 50, 19 and 6 PLWH who received 100 µg mRNA-1273, 50 µg mRNA-1273, BNT162b2, and either MVC-COV1901 or NVX-CoV2373, respectively. Similar rates of new infection with SARS-CoV-2 or seroconversion of anti-N IgG were demonstrated regardless the vaccine type of the third dose (log-rank test, p=0.46). Factors associated with a diagnosis of SARS-CoV-2 infection and seroconversion of anti-N IgG included an age >50 years (aOR, 0.67; 95% CI, 0.49-0.91) and newly infected with hepatitis C virus (HCV) (aOR, 1.41; 95% CI, 1.09-1.83).

Conclusion: Our study demonstrated that clinical effectiveness of the third dose of different vaccines available to PLWH was similar in preventing SARS-CoV-2 infection or seroconversion of anti-N IgG Taiwan. PLWH aged less than 50 years and those with newly diagnosed HCV infection were at higher risk of acquiring COVID-19.

Kaplan–Meier survival curve for acquiring COVID-19 or seroconversion of anti-N IgG in PLWH receiving different COVID-19 vaccination of the third dose (log-rank test, 4 groups, p = 0.46)



1021 COMPARISON BETWEEN HIV+ WOMEN TRANSITIONING THROUGH MENOPAUSE AND MEN OF SIMILAR AGE

Hachfeld Anna[1], **Andrew Atkinson[1]**, Catrina Mugglin[1], Petra Stute[1], Alexandra Calmy[2], Philip Tarr[3], Katherine Darling[4], Baharak Babouee-Flury[5], Christian Polli[6], Leila Sultan-Beyer[7], Irene Abela[8], Chloe Pasin[9], Andri Rauch[10], Karoline Aebi-Popp[11]

Swiss HIV Cohort Study (SHCS)

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Background: Not much is known on differences in treatment -adherence, psychiatric health and HIV-viral control between women transitioning through menopause and men of similar age, risk group and treatment history. With this study, we aimed at closing this knowledge gap.

Methods: We identified 1,437 HIV-positive women with menopause onset between 01/2010 and 12/2021, and 1,094 men of similar age from the same time period in the Swiss HIV Cohort Study (SHCS). We considered data on HIV-viral load, depression and/or being in psychiatric care and self-reported treatment adherence between the ages of 41 and 60. Non-adherence was defined as any person self-reporting missing one dose once every 2 weeks, or more often.

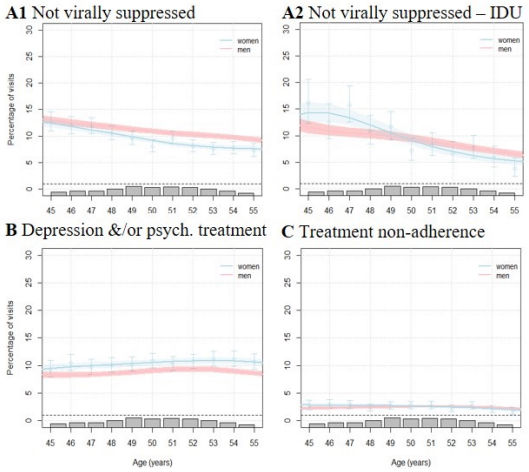
We fitted log-binomial interrupted time series (ITS) regression models to estimate the trajectory for the respective events over the age range and compared outcomes between men and women. We adjusted for differences in risk group (heterosexual, injection drug users [IDU]), time on ART and year of visit between men and women using inverse probability weighting (IPW), and calculated sandwich-type standard errors as patients have many clinical visits.

Results**:** 2,531 people living with HIV attending 90,310 clinical visits were included, of which detectable HIV-RNA (>50 copies/ml) was observed in 9.4% of women and 10.7% of men. 10.1% of women (men 8.6%) were depressed and/or in psychiatric care, and 2.3% of women (men 2.3%) self-reported treatment non-adherence.

Women had fewer visits with detectable HIV-RNA compared to men, but there was little overall difference between the ages of 48 and 52 (p=0.7, Figure **A1**). Women were slightly more likely to be depressed and/or in psychiatric care (IPW adjusted incidence rate ratio for women 1.26 (reference: men), 95% confidence interval [1.12, 1.41], p< 0.001, Figure **B**), but there was no difference in terms of treatment adherence (p=0.9, Figure **C**). Women IDU exhibited a slight increase in detectable HIV-RNA during peri-menopause (Figure **A2**).

Conclusion: There were no differences between men and women in terms of both detectable HIV-RNA and treatment adherence, but a slightly higher rate of being depressed and/or in psychiatric care for women of 48-53 years. Apart from women with IDU as the probable mode if HIV acquisition, there were no significant increases in viral events during peri-menopause.

Figure: Percentage of visits with detectable HIV-RNA (A), psychiatric treatment and/or depression (B) and treatment non-adherence (C) for women (blue) and men (red); age at menopause histogram on the x-axis.



1022 DISTINCT EFFECT OF SEX HORMONE INTAKE ON IMMUNITY IN CIS AND TRANS WOMEN WITH HIV

Chloe Pasin[1], David Garcia Nuñez[2], Katharina Kusejko[3], Hachfeld Anna[4], Karoline Aebi-Popp[5], Hélène Buvelot[6], Matthias Cavassini[7], Lauro Damonti[8], Christoph Fux[9], Begoña Martinez de Tejada[6], Julia Notter[10], Alexandra Trkola[1], Huldrych F. F. Günthard[3], Roger D. Kouyos[1], Irene A. Abela[1]

Swiss HIV Cohort Study

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Background: Sex and gender differences in immunity have been widely observed and could be partly due to the immune-modulatory effect of sex hormones. So far, the effect of sex hormones on the dynamics of HIV immune markers has not been extensively studied. Little is known on the immune effect of sex hormone intake in trans women (TW), and concerns on drug-drug interactions between antiretroviral treatment (ART) and hormones might limit hormone prescription in cis women (CW) and TW. We quantified how sex hormones affects the immune system by comparing key HIV biomarkers in subgroups of women living with HIV: CW under hormone intake (CW-H) or not (CW-NH), and TW under hormone intake (TW-H) or not (TW-NH).

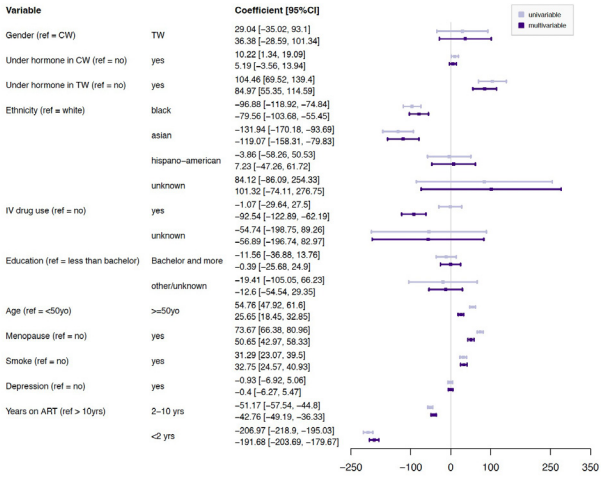
Methods: The Swiss HIV Cohort Study (SHCS) is a prospective multicenter cohort study enrolling people living with HIV in Switzerland. We considered longitudinal laboratory measurements from CW and TW from 2015, when systematic report of most comedications intake started. Measurements taken during pregnancy or while not on ART were excluded. We classified measurements into those sampled during hormone intake (oestrogens, progestogens, and/or anti-androgens) or not. CD4, CD8 counts and CD4:CD8 ratio were modeled with linear mixed effects adjusted on time on ART and other potential confounders; adherence, viral load, and co-infections were added in sensitivity analyses. We tested for an interaction term between “gender” (CW, TW) and “under hormones” (yes, no). Proteomics measurements were realized on samples from 35 CW and 35 TW before and after hormone intake to assess the immune stimulatory and inflammation environment.

Results: We included 3079 CW and 82 TW, with a total of 608 TW-H, 696 TW-NH, 4225 CW-H, and 45113 CW-NH measurements. Sex hormone intake was associated with increased CD4 counts of 85 (55-115, p< 0.001) in TW but not CW (Fig). Similarly, cis men had lower CD4 counts than CW. CD8 counts were

increased in TW-H (p=0.001) but not CW-H. Longitudinal measurements from 27 TW confirmed our finding as a significant change of slope in CD4+ T cell dynamics occurred after the start of sex hormone intake (p< 0.001). Proteomics analysis revealed activation of innate immunity pathways (MCP-2, MCP-4, CCL3, CCL4) in CW-H but not TW-H.

Conclusion: Sex hormone intake is associated with distinct modulations of the immune system in CW and TW, which could potentially be due to differences in dosing, combination of hormones taken, and/or mechanisms of actions of hormones on the immune system in CW and TW.

Forest plot showing factors (parameters and 95% confidence intervals) associated with CD4 counts.



1023 ACCEPTABILITY OF EMERGENCY CONTRACEPTION IN ACTG A5375

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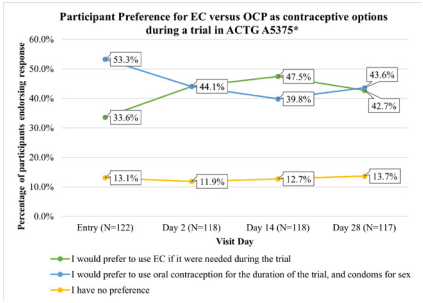
Background: Contraceptive requirements are a barrier to participation in clinical trials for people capable of pregnancy. Offering access to emergency contraception (EC) could increase trial participation of persons who are not sexually active or not using contraception for other reasons. EC is part of medical management post sexual assault, an experience of many women living with HIV. ACTG trial A5375 examined the PK and safety of dose-adjusted levonorgestrel (LNG) EC combined with efavirenz-based ART or rifampicin-containing TB therapy. We assessed acceptability and practicality of EC.

Methods: Participants did not require EC at entry and received a single dose of LNG on Day 0. Interviewer-administered questionnaires on Days 0, 2, 14 and 28 assessed attitudes and experiences with EC, recent contraceptive use, and contraceptive preference during clinical trials participation. Responses were summarized using descriptive statistics.

Results: A5375 enrolled 122 cisgender women (median [IQR] 34 [27,41] years) in 7 countries between May 2019- November 2020. The majority (66.4%) were Black (27.0% Asian; 4.9% White, 0.8% multiple races); 9.0% were Latina. Participants reported contraceptives used within 120 days of entry; 22% (N=27) reported abstinence and of the rest (N=95), 85.2% reported condoms and/or other methods (23.1%). Most (79.5%) had never used LNG EC prior to entry. When asked about preference for daily oral contraceptive pills (OCP) or episodic EC as needed, 53.3% preferred OCP, 33.6% preferred EC as needed, and 13.1% had no preference at Entry. At Day 28, there was a +9.1% absolute change in the preference for EC [Figure 1]. At entry, participants reporting that the option of EC as a contraceptive choice would make them more likely to participate in a trial was high (63.9%), and increased to 70.6% at Day 28. In abstinent participants, this percentage remained stable from Day 0 to 28 (66.6%). More participants knew where to access EC for routine clinical use at follow up visits compared to the entry visit (84.2% vs 77.0%, respectively).

Conclusion: EC was acceptable to participants and increased after receiving a single dose of LNG for EC during the trial. EC as a contraceptive option in clinical trials could address a barrier to women's participation, particularly as a second option when two methods are required or for women not having sex that could lead to pregnancy. Additional implications exist for promoting survivor autonomy during the provision of comprehensive sexual assault services.

Figure 1: Participant-reported preferences for EC versus OCP as contraceptive options in ACTG A5375



1024 THE EFFECT OF FP EDUCATION ON KNOWLEDGE AND USE OF FP IN UGANDAN FISHING COMMUNITIES

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Background: Family planning knowledge is poor and use is low in Ugandan fishing communities. We compared the effectiveness of enhanced family planning (FP) education with routine counseling on FP knowledge and use.

Methods: Individuals aged 15–49 years were randomly assigned to intervention or control arm. The intervention constituted enhanced FP education based on a simplified handout extracted from the WHO FP guidance tool called, "Family planning: A global handbook for FP providers" which participants took home for additional reading. The control arm constituted FP counseling following Uganda Ministry of Health guidelines. FP knowledge score and contraceptive prevalence rate (CPR) were compared between trial arms at baseline and at 12 months. Negative binomial regression models were used to estimate the effect of the intervention on FP knowledge and use.

Results: Overall, 1410 participants were screened to enroll 1,004 (502 per study arm, 48.5% women). Subsequently, 384 (76.5%) and 383 (76.3%) completed the 12 months' follow-up in the intervention and control arms respectively. At baseline, a median FP knowledge score of 8 and a < 70% FP knowledge score was observed for all participants with a CPR of 36.8%. At month 12, the median FP knowledge score improved in both arms, higher in the intervention arm than the control arm (46 vs 30; p< 0.001). In the intervention arm, 304 (79.2%) had a score of ≥70 compared with 21 (5.5%) in the control arm (p< 0.001). In the negative binomial regression model, the change in FP knowledge score was 47% higher in the intervention arm than in the control arm (score ratio: 1.47, 95%CI: 1. 43-1.51, p< 0.001). The change in CPR was 16% higher in the intervention arm than in the control arm (Prevalence ratio: 1.16, 95%CI: 1.01-1.34, p< 0.040).

Conclusion: Enhanced FP education using a simplified FP education handout was more effective in increasing FP knowledge and use compared to routine FP counseling for people living in fishing communities. Innovative FP education interventions are recommended for improving FP knowledge and optimizing uptake in remote-rural settings where literacy levels are low.

1025 INCREASED HIV, HCV & STIS AMONG ADULTS REPORTING SEX WORK IN ALABAMA: 2008-2022

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Background: The U.S. South represents 38% of the U.S. population, but as of 2020 more than 50% of new U.S. HIV diagnoses occurred in the region. HIV and other health-related outcomes are poorer in states considered the "Deep South," including Alabama. Relative to other states, Alabama has higher rates of HIV and other STIs, and 17% of people with HIV in Alabama are unaware of their status. Throughout the Deep South, HIV and STI epidemics are in part driven by

socioeconomic vulnerability, and sex work may play a role. However, few studies have estimated the prevalence or effects of sex work in Alabama or the Deep South.

Methods: We estimated the history of sex work (exchanging sex for money, drugs, or something of need in the last 5 years) among clients (ages 15-64) receiving services at a Birmingham, Alabama-based AIDS Service Organization from 2008-2022. We used chi-square tests to assess sex work's association with diverse drug use (injection and non-injection) and sexual risk behavior. We used logistic regression to examine the association between sex work and new HIV, hepatitis C (HCV), and STI (chlamydia, gonorrhea, syphilis, trichomoniasis) diagnoses. Analyses adjusted for age, race/ethnicity, and gender identity, with stratification to examine differences among gay, bisexual and other men who have sex with men (MSM, n=4,784).

Results: Across 20,673 visits, history of sex work was reported at 950 visits (4.6%). Sex work was associated with older age (p=0.002), being a cisgender woman or gender minority, identifying as non-Hispanic white, increased diverse drug use, and increased sharing of non-injection drug equipment (p< 0.001). Compared to other clients, those reporting sex work had increased odds of syphilis (aOR 3.42, p=0.05) and HCV diagnosis (aOR 1.76, p< 0.001). MSM with history of sex work had increased odds of diagnosis with HCV (aOR 4.57, p=0.005) and HIV (aOR 2.49, p=0.02), compared to other MSM.

Conclusion: Using 14 years of community-based data, this study is among the first to estimate the relationship between sex work and HIV, HCV, and STIs in the Deep South. We document converging sex work and diverse drug-related risks, which may act synergistically to influence poorer health outcomes and reinforce existing health inequities. Differences in HIV and HCV diagnosis between sex workers and other clients were even greater among MSM, suggesting a need for tailored interventions with this group.

Logistic regression of new HIV, HCV, and STI diagnosis on sex work history (adjusting for age, race/ethnicity, and gender identity) across 20,673 visits, 2008-2022.

Table. Logistic regression of new HIV, HCV, and STI diagnosis on sex work history (adjusting for age, race/ethnicity, and gender identity) across 20,673 visits, 2008-2022.

	All Respondents (n=20,673)			MSM respondents (n=4,784)		
	aOR	95% CI	p-value	aOR	95% CI	p-value
HCV	1.76	1.33-2.33	<0.001	4.57	1.58-13.20	0.005
HIV	1.93	0.96-3.85	0.063	2.49	1.17-5.30	0.018
Chlamydia (CT)	0.93	0.51-1.70	0.81	0.79	0.31-2.00	0.61
Gonorrhea (GC)	1.20	0.67-2.15	0.55	0.97	0.41-2.30	0.94
Trichomoniasis (TV)	0.70	0.21-2.29	0.55	Non-convergent due to small cell sizes		
Syphilis	3.42	1.00-11.67	0.050	Non-convergent due to small cell sizes		

1026 PREVALENCE OF CHLAMYDIA AND GONORRHEA AMONG ADOLESCENTS IN KISUMU, KENYA

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Maneno Yetu Study Team

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Background: The national diagnostic algorithm for sexually transmitted infections (STIs) in Kenya is based on syndromic management. This approach, however, underestimates STI prevalence as asymptomatic cases go undiagnosed and untreated. We conducted screening for *Chlamydia trachomatis* (CT) and *Neisseria gonorrhoeae* (NG) for adolescents participating in a sexual and reproductive health study in Kenya.

Methods: The *Maneno Yetu* study recruited adolescents aged 15 to 19 residing in the informal settlements of Kisumu, Kenya. Urine screening for CT and NG was offered to 1238 participants who reported having ever engaged in sex, of whom 1167 accepted and 1159 had interpretable results. Urine specimens were screened using the molecular Xpert CT/NG test. Associations were assessed by Chi-square tests.

Results: Of the 1159 adolescents, 53% were girls and 74% were 18 to 19 years of age. Overall, 55% of adolescents were worried about acquiring an STI, 24% had ever experienced STI symptoms and 5% had a prior STI diagnosis. Girls were more likely than boys to report experiencing symptoms (29% vs. 18%; p< 0.001). STI prevalence was 9.6% overall and was higher among girls than boys (12.5% vs. 6.3%; p< 0.001). Of the 111 adolescents (76 girls and 35 boys) who tested positive, 102 had CT, 15 had NG, 6 had CT/NG co-infection, and 66% did not report experiencing symptoms. Ninety-two adolescents (83%) were successfully linked to care and received STI treatment. Among our sample, 33% of adolescents had engaged in transactional sex and 34% had experienced forced sex. STI prevalence was higher among adolescents who had engaged in transactional sex (13.0% vs. 7.9% OR=1.74; p=0.006) and those who had experienced forced sex (12.2% vs. 8.2%; OR=1.56; p=0.028) compared to adolescents who did not.

Conclusion: Two-thirds of adolescents diagnosed with an STI in our study did not report any previous symptoms, and thus would most likely have gone undiagnosed and untreated based on the syndromic management diagnostic algorithm. Undiagnosed or misdiagnosed STIs can result in onward transmission and significantly impact the reproductive health of adolescents, including pelvic inflammatory disease and infertility in females. In addition, STIs are associated with an increased risk of HIV infection. Our findings lend support for offering STI screening to adolescents who report having engaged in transactional sex or experienced forced sex to enhance sexual and reproductive health and HIV prevention services.

1027 PATTERNS OF STI AMONG TRANSGENDER WOMEN LIVING WITH AND WITHOUT HIV IN THE US

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American Cohort To Study HIV Acquisition Among Transgender Women (LITE) Study Group

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Background: Transgender women (TW) bear a disproportionate burden of HIV and other STIs. There are limited data comparing the epidemiology of STIs between TW with HIV and TW without HIV. We describe the prevalence and patterns of STIs among TW in 6 eastern and southern US cities by HIV status.

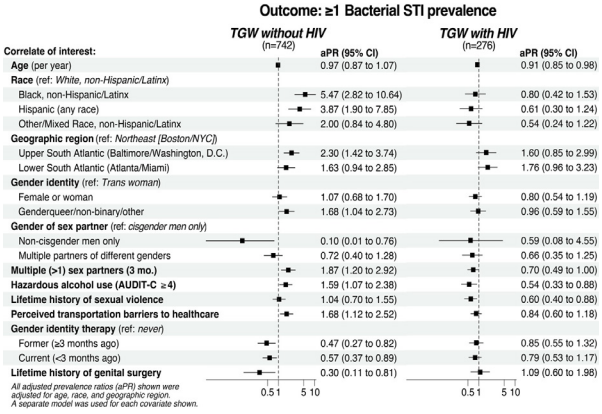
Methods: We analyzed baseline data collected between March 2018 and August 2020 among adult TW across 6 US cities screened for the LITE study (N=1,018). Participants completed a sociobehavioral survey, oral HIV screening, and self-collected urine, anal, and neovaginal specimens for *Chlamydia trachomatis* (CT) and *Neisseria gonorrhoeae* (GC) testing, and provided sera for treponemal syphilis testing and rapid plasma reagin (RPR) testing with quantitative RPR titers. Sera were assayed for herpes simplex virus type 2 (HSV-2). The primary outcome was ≥1 bacterial STI (BSTI). We examined the association of HIV status with BSTI and conducted HIV-stratified analyses to identify correlates of BSTI. For each covariate of interest, we estimated adjusted prevalence ratios (aPR) via separate modified Poisson regression models adjusted for age, race, and geographic region.

Results: Compared to TW without HIV (n=742), TW with HIV (n=276) had a higher prevalence of ≥1 BSTI (11% vs. 33%; aPR=1.96 [95%CI=1.43-2.70]). BSTI prevalence included 4% CT, 2% GC, and 6% syphilis among TW without HIV, and 8% CT, 4% GC, and 28% syphilis among TW with HIV. Compared to TW without HIV, TW with HIV also had a higher prevalence of HSV-2 antibodies (30% vs. 82%; aPR=1.53 [95%CI=1.33-1.75]). Among TW without HIV, a higher prevalence of ≥1 BSTI was associated with living in the Upper South Atlantic region (vs. Northeast), identifying as Black and/or Latinx (vs. White), identifying as gender nonbinary/genderqueer (vs. trans woman), reporting >1 sex partner, hazardous alcohol use, and having safety concerns regarding transit to healthcare (Figure). Receipt of gender-affirming medical services (e.g., psychotherapy, surgery) was associated with lower BSTI prevalence. Among TW with HIV, older age, hazardous alcohol use, and a lifetime history of sexual violence was associated with lower BSTI prevalence.

Conclusion: TW had a high prevalence of bacterial and viral STIs. STI prevalence was significantly higher in TW with HIV, and the correlates of BSTI prevalence differed by HIV status. Elucidating the drivers of STIs unique to TW with and

without HIV will be key to informing tailored interventions and reducing sexual health-related inequities among TW.

Figure. Correlates of Bacterial STI prevalence stratified by HIV status.



1028 SEXUALLY TRANSMITTED INFECTIONS AMONG YOUNG ADULTS AFFECTED BY PREINATAL HIV

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Background: As young people living with perinatally-acquired HIV (YPHIV) become sexually active, they become susceptible to sexually transmitted infections (STI). Because of their HIV status, YPHIV may more frequently receive advice to use condoms consistently to protect their partner(s) from HIV, hence may be at lower risk of STIs than those HIV uninfected. The objective of this study was to compare STI incidence rates between YPHIV and a comparator group of young adults living with perinatal HIV exposure but uninfected (YPHEU).

Methods: YPHIV and YPHEU participating in the U.S.-based Pediatric HIV/AIDS Cohort Study (PHACS) network had test results for chlamydia (CT), gonorrhea (GC), and trichomonas (TC) abstracted annually from medical charts. Additionally, participants were tested annually by Hologic Aptima^{tm} assay for CT, GC, TC. Women were also tested for human papillomavirus (HPV) via Aptima^{tm} assay. These research samples were sent for testing in batches to a centralized laboratory. Incidence rates of first positive test in AMP Up were calculated for CT, GC, and TC over person-time of follow-up s of January 1, 2020. HPV incidence rates were calculated among those with an initial negative HPV test result. Poisson regression with robust standard errors was used to calculate incidence rate ratios (IRR) and 95% confidence intervals (95% CI) comparing rates by HIV status, age at first STI test, sex at birth, race, and ethnicity.

Results: Among 579 AMP Up participants (83% PHIV; 62% female) YPHIV were older than YPHEU at first STI test (mean age 22.9 vs 19.1 years). Incidence rates of CT, GC, and TV were similar by HIV status and age. However, incidence of HPV was higher among women with PHIV compared to those PHEU. Rates of most STIs were higher for women than men, for those of Black (vs White/other) race, and non-Hispanic than Hispanic participants (Table).

Conclusion: Rates of CT, GC and TV were similar between YPHIV and YPHEU, underscoring the need for better STI prevention strategies among YPHIV, including promotion of condom use. The higher rate of HPV in women with PHIV than PHEU is consistent with the well-documented vulnerability of those with HIV for HPV and underscores the need for HPV-associated cancer surveillance. Confirmation of HPV vaccine status will be a critical next step to understanding HPV vaccine effectiveness in this group.

Incidence (per 1000 person-years) and Incidence Rate Ratios (95% confidence Intervals) of first positive STI test result during AMP Up follow-up by demographic characteristics

Incidence (per 1000 person-years) and Incidence Rate Ratios (95% confidence Intervals) of first positive STI test result during AMP Up follow-up by demographic characteristics

STI		PHIV vs PHEU (ref)	Age at first test 21+ vs 18-20 (ref)	Women vs Men (ref) (based on sex at birth)	Black vs White/other race (ref)	Non-Hispanic vs Hispanic ethnicity (ref)
Chlamydia	IR per 1000 PY IRR (95% CI)	76.6 vs 78.5 1.0 (0.6, 2.9)	68.5 vs 97.2 0.7 (0.5,1.1)	85.6 vs 62.8 1.4 (0.9, 2.1)	92.7 vs 47.8 1.9 (1.2, 3.2)	88.1 vs 50.0 1.8 (1.1, 2.9)
Gonorrhea	IR per 1000 PY IRR (95% CI)	34.2 vs 29.9 1.1 (0.5, 2.6)	26.8 vs 49.6 0.5 (0.3, 1.0)	39.1 vs 24.1 1.62 (0.8, 3.1)	46.8 vs 10.0 4.7 (1.7, 13.1)	39.1 vs 21.0 1.9 (0.9, 4.0)
Trichomonas	IR per 1000 PY IRR (95% CI)	56.6 vs 30.6 1.85 (0.8, 4.3) 2.1 (0.8, 5.6)	56.7 vs 39.5 1.44 (0.8,2.7)	68.4 vs 23.3 2.93 (1.5, 6.0)	78.8 vs 5.5 13.5 (3.3, 55.6)	73.4 vs 8.9 8.28 (2.6, 26.3)
HPV among females	IR per 1000 PY IRR (95% CI)	243.8 vs 117.3 2.1 (0.8, 5.6)	229.7 vs 205.8 1.1 (0.6, 2.1)	-	290.4 vs 159.0 1.8 (1.0, 3.3)	295.0 vs 115.6 2.6 (1.3, 5.1)

PY: person-years. IR: incidence rate; IRR: incidence rate ratio. CI: confidence interval

1029 INCREASED BURDEN OF ANAL HPV-RELATED POTENTIALLY PRECANCEROUS LESIONS IN HIV+ WOMEN

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Background: Women living with HIV (WLH) show increased risk of HPV related anal cancer. WLH are routinely screened to prevent HPV related cervical cancer, through research and treatment of potentially precancerous lesions, but screening for the prevention of HPV related anal cancer lacks in this population. In the present study we aimed to compare prevalence of anal HPV infection and anal dysplasia in WLH and women without HIV infection (WWH).

Methods: Since genital HSIL is a risk factor for anal dysplasia, women with previous or current cervical, vaginal or vulvar HSIL were excluded. 74 WWH and 26 WLH were enrolled in the present study. All participants underwent anal HPV DNA test, anal cytology and high resolution anoscopy (HRA). Data regarding genital HPV DNA and genital dysplasia (cytology and/or histology) were also collected. None of participants completed HPV vaccination course prior to enrollment.

Results: Median age of participants was 45 years in both groups. WLH showed lower prevalence of genital high-risk HPV (HR-HPV) (33% vs. 78%; p=0.01) and similar prevalence of low-risk HPV (LR-HPV) (40% vs. 22%; p=0.67) compared to WWH. 27% of WLH showed negative genital HPV. Screening for cervical dysplasia showed LSIL in 40% WLH and 35% WWH. Absence of dysplasia was observed in 60% WLH and 65% WWH.

Prevalence of anal HR-HPV was higher among WLH (34% vs. 14%; p=0.049), on the other hand prevalence of LR-HPV was similar between WLH and WWH (26% vs. 45%; p=0.1). Similar proportion of WLH and WWH showed negative anal HPV DNA (40% vs. 41%; p=0.8).

Cytological LSIL was observed in 40% WLH and 12% WWH (p=0.017), normal anal cytology was found in 54% WLH and 86% WWH (p=0.01).

All participants underwent HRA, biopsies were performed according to clinical evidences (53% WLH and 51% WWH). Biopsy proven HSIL was more frequently observed in WLH than WWH (20% vs. 4%; p=0.01). Prevalence of LSIL was similar between the two groups (33% vs. 22%; p=0.23).

HIV infection was associated with increased risk for histology proven anal HSIL (odds ratio 5.6; 95% CI 1.2-25.6). Receptive anal intercourse and smoke were not associated to increased risk of HSIL.

Conclusion: WLH show increased burden of HPV related anal dysplasia and potentially precancerous anal lesions in respect to WWH.

In WLH, despite similar prevalence of anal and genital HR-HPV, anal canal seems more prone to develop severe dysplasia.

WLH should be considered as a high-risk population and therefore should undergo screening for the prevention of anal cancer.

1030 EFFICACY OF LATE HPV VACCINATION IN YOUNG HIV+ MSM

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Background: Men who have sex with men (MSM), and in particular HIV+ MSM, show the greatest risk of anal HPV infection and the highest incidence of anal cancer. HPV vaccine should be ideally administered at an early age, before the first sexual intercourse. Since routine administration of HPV vaccine to young boys has begun only in recent years, currently the majority of immunized adult MSM individuals underwent vaccination after sexual debut. In the present study we aimed to evaluate vaccination rate and prevalence of anal HPV infection and

anal dysplasia (squamous intraepithelial lesion, SIL) in HIV+ and HIV- MSM aged < 45 years that received HPV vaccination after the first sexual intercourse.
Methods: 142 MSM, 110 HIV+ and 32 HIV-, younger than 45 years were included in the present study. All enrolled subjects underwent anal HPV DNA test for HPV identification and genotyping. The presence of anal dysplasia was assessed trough anal cytology or anal histology from anal biopsies collected during high resolution anoscopy.
Results: Vaccination rate was similar between HIV+ and HIV- participants (20% vs. 31.3%; p=0.169). 76.3% of HIV+ participants and 57.1% of HIV- participants tested positive at anal HPV DNA test (p=0.042). Anal SIL of any grade was observed in 76.3% of HIV+ individuals and 53.6% of HIV- subjects (p=0.017).
The prevalence of anal HPV infection was similar between vaccinated and unvaccinated HIV+ subjects (72.7% vs. 77.3%; p=0.864).
Among vaccinated participants, HPV DNA tested positive in 72.7% of HIV+ and 33.3% of HIV- subjects (p=0.041). On the other hand, 77.3% of HIV+ unvaccinated and 68.4% of HIV- unvaccinated individuals showed a positive HPV DNA test (p=0.415).
Among HIV+ participants, anal SIL was observed in 54.4% of vaccinated and 81.8% of unvaccinated individuals (p=0.01).
Among vaccinated participants, the presence of anal SIL was detected in 54.5% of HIV+ and 33.3% of HIV- vaccinated participants (p=0.283). In unvaccinated participants SIL was detected in 81.8% of HIV+ and 63.1% of HIV- subjects (p=0.073).
Being unvaccinated (OR 1.6; CI 95% 1.1-2.4), living with HIV (OR 2.8; CI 95% 1.2-6.6) and anal HPV infection (OR 6.7; CI 95% 2.9-15.4) were associated to an increased risk of anal dysplasia at multivariate analysis.
Conclusion: Even if administered after sexual debut, vaccination against HPV is useful in reducing the risk of anal dysplasia in HIV+ MSM aged < 45 years. Immunization against HPV should be encouraged, particularly in this population.

1031 HIGH PREVALENCE OF HPV, OTHER STI, AND ANAL LESIONS AMONG MSM IN TOGO

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Background: High prevalence of STI is a critical issue in Africa, especially in key populations such as MSM. Here, we present the baseline results of a 2-years longitudinal cohort study (ANRS DEPIST-H 12400) enrolling both HIV-positive and negative MSM.
Methods: MSM were included in Lomé (Togo) between June and december 2021, half of them living with HIV. High risk HPV (hrHPV) (Seegene) and HSV-1/2 (Altona) detection was performed on anal smears. Syphilis and HBs antigen were tested on sera samples on site. *Chlamydia trachomatis* (CT) and *Neisseria gonorrhoeae* (NG) were tested (Cepheid) from urine, pharyngeal and anal swabs. A clinical genital examination was carried out by trained physicians.
Results: 200 MSM with a median age of 23 years (IQR=21-29) were enrolled. Prevalence of each STI is shown in Table 1. Only 1.5% of paticipants were positive for HBs antigen, while no HCV nor syphilis infection was detected. The prevalence of CT and NG was 6.5% and 3.0% in urine, 26.0% and 22.0% in anal swab, and 5.0% and 19,0% in oropharyngeal area, respectively. Anal herpes simplex virus (HSV) infection were detected in 9 (4.5%) of MSM (1 HSV-1 and 8 HSV-2). Overall, a high prevalence of anal hrHPV was detected (75.9%) and was significantly higher among HIV-positive MSM (84.0% vs 67.7%, p=0.008). The prevalence of hrHPV 16, 35, 51, 52, 58, 59 types was >15%. HPV35 and HPV52 were the most prevalent types (24%) among HIV-infected MSM. Multi-infections (>2 hrHPV) tended to be more common in HIV-infected MSM (69.0% vs 55.2%, p=0.08). Two-thirds of hrHPV-positive MSM were infected with at least one hrHPV covered by the nonavalent vaccine. This proportion corresponded to 75% of HIV-infected MSM. More than a third of MSM (36.2%) presented an HPV-6 or -11. Anal lesions were detected at examination in 43.0% of MSM, with 19.5% of condylomas, 17.5% of marisks, 3.0% of anal fissures while anal ulcerations, gluteal abcess, hemorrhoid related pathology and anal fistula were diagnosed in 2.0% or less of participants. No anal cancer has been diagnosed.
Conclusion: These first data of the ANRS DEPIST-H emphasize the high burden of STIs among the key population of MSM in Togo. It also confirms the unusual distribution of HPV types in western Africa, with HPV35 being a highly prevalent hrHPV type non-covered by the nonavalent vaccine. A national strategy regarding STI screening and HPV vaccination in this key population is needed.

Patients characteristics at baseline of the ANRS 12400 DEPIST H cohort study

	All participants (n = 200)	MSM living with HIV (n = 100)	MSM negative for HIV (n = 100)	p-value
Age – years	23 (21–29)	27 (23–30)	21 (20–25)	p<0.0001 (Mann Whitney test)
IIDV (Agrifiix)	3 (1.5%)	3 (3.0%)	0 (0%)	p=0.15
Positivity for *Chlamydiae trachomatis*				
Urine sample (n, %)	13 (6.5%)	5 (5.0%)	8 (8.0%)	p=0.4 (Chi-2)
Anal swab (n, %)	52 (26.0%)	23 (23.0%)	29 (29.0%)	p=0.3 (Chi-2)
Oropharyngeal swab (n, %)	10 (5.0%)	5 (2.5%)	5 (2.5%)	p=1.0 (Chi-2)
Positivity for *Neisseria gonorrhoeae*				
Urine sample (n, %)	6 (3.0%)	1 (1.0%)	5 (2.5%)	p=0.1 (Chi-2)
Anal swab (n, %)	44 (22.0%)	22 (22.0%)	22 (22.0%)	p=1.0 (Chi-2)
Oropharyngeal swab (n, %)	38 (19.0%)	25 (25.0%)	13 (13.0%)	p=0.03 (Chi 2)
HSV anal infection				
HSV 1/2 positivity on anal smear	9 (4.5%)	7 (7.0%)	2 (2.0%)	p=0.09 (Chi 2)
HPV anal infections				
HPV16 or HPV18 positivity on anal smear (n, %)	46 (23.0%)	27 (27.0%)	19 (19.0%)	p=0.6 (Chi-2)
Anal smear positive for at least one hrHPV (n/N, %)	151/199 (75.9%)	84/100 (84.0%)	67/99 (67.7%)	p=0.008 (Chi-2)
Number of hrHPV in positive anal smears (median, [IQR])	2 [1-3]	2 [1-3]	2 [1-3]	
hrHPV multi-infections (> 2 hrHPVs) (n, % among hrHPV+ smears)	95 (62.9%)	58 (69.0%)	37 (55.2%)	p=.0.08 (Chi-2)
A least one hrHPV covered by the nonavalent vaccine (n,% among hrHPV+ smears)	101 (66.9%)	63 (75.0%)	38 (56.7%)	p=.0.02 (Chi-2)
HPV6 or HPV11 (n, % overall)	72 (36.2%)	40 (40.0%)	32 (32.3%)	p=0.24 (Chi 2)
Clinical examination of anal lesions (n, %)				
At least 1 anal lesion	86 (43.0%)	47 (47.0%)	39 (39.0%)	p=0.25 (Chi-2)
Anal condylomas	39 (19.5%)	15 (15.0%)	24 (24.0%)	p=0.11 (Chi-2)
Anal marisk	35 (17.5%)	24 (24.0%)	11 (11.0%)	p=0.02 (Chi-2)
Anal fissure	6 (3.0%)	3 (3.0%)	3 (3.0%)	p=1.0 (Chi 2)

1032 METHYLATION MARKERS ON ANAL SMEARS ARE ASSOCIATED WITH HIGHER ANAL CANCER RISK

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COAIN3 national cohort
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Background: Currently, there is no consensus about anal cancer screening. Molecular markers stratifying anal cancer risk are needed. Host cell DNA methylation markers (ZNF582 and ASCL1) have been associated to AIN3 and anal carcinoma in a cross-sectional study on biopsies from HIV-infected men.
Methods: This is an ancillary prospective study of the French COAIN3 cohort, which included patients with an AIN3 history. Cytology, high-risk HPV (hrHPV), p16/ki67 and methylation markers ZNF582 and ASCL1 on anal smears were compared with Wilcoxon tests. Association between anal cancer risk and methylation was evaluated in univariate Cox models. C/D time dependent AUC was estimated to assess discrimination of methylation markers. Similarly to Youden Index, methylation thresholds were determined for a one year follow-up. Methylation levels were expressed in $\log_2(\Delta\Delta ddct)$.
Results: Methylation analyses were successful for 424 patients with 60% of male, 59 years-old of median age and 45% of HIV-positive patients overall, 91% of them being men. Median follow-up was 36 months [32-40] in this sub-study. Twenty out of 424 patients evolved through anal cancer in the study period. A higher methylation rate of each gene was significantly associated with HSIL cytology, HPV16 or hrHPV detection and p16/ki67 positivity (p< 0.01 for all) on the same anal smear. Higher methylation levels were associated with higher anal cancer risk, in univariate analysis (HR = 1.34 [1.15-1.56], p< 0.001 for ZNF582 and HR=1.35 [1.12-1.63], p=0.002 for ASCL1). In our study, C/D AUC at one year were 82% [82-95] and 80% [64-99] for ZNF582 and ASCL1 respectively. On our dataset, thresholds of 0.62 and 1.95 could be defined for ZNF582 and ASCL1, respectively, with corresponding sensitivities of 86% and 78% and specificities of 63% and 67%. Regarding cancer risk, ZNF582 methylation >0.62 had a HR=5.02 [1.67-15.1] and ASCL1 methylation >1.95 a HR=5.02 [1.67-15.1]. At least one methylation marker above the corresponding threshold was associated with higher risk of cancer in univariate analysis with a HR 4.19 [1.39-12.6], p=0.011.
Conclusion: To our knowledge, this is the first study evaluating the potential role of methylation markers for anal cancer risk stratification in a real-life cohort on non-invasive sample such as anal smears. Further study are needed to confirm the prognostic value of these markers, notably in a less "at risk" population, with longitudinal follow-up of methylation, to define methylation thresholds that can be generalized.

1033 MPOX AND SEXUALLY TRANSMITTED INFECTION AMONG MEN WHO HAVE SEX WITH MEN

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Background: The majority of mpox cases in the United States have occurred among males, with a sizeable proportion reporting male-to-male sexual contact. In an effort to inform mpox testing and vaccination efforts, this study quantified the association of mpox infection in the first 100 days of the outbreak with a recent history of a nationally reportable sexually transmitted infection (STI), current use of pre-exposure prophylaxis for HIV (PrEP), and HIV diagnosis among gay, bisexual, and other men who have sex with men (GBMSM).
Methods: A case-control study was conducted among 229 GBMSM aged 18 years or older tested for mpox in a large, diverse safety-net health system in Denver, Colorado between May 25, 2022 and September 1, 2022. Dates of syphilis treatment and laboratory confirmed gonorrhea and chlamydia were used to determine whether an STI occurred in the preceding year, 6 months, or concurrently with (±30 days) the mpox test. Patients with current PrEP use were identified through electronic health records, medication dispense dates, and negative HIV serostatus.
Results: A larger proportion of cases than controls were over the age of 35, non-White, used PrEP, and were not living with HIV. Mpox infection was not associated with HIV diagnosis (odds ratio 0.62, 95% CI 0.35-1.11). After adjusting for age group and race/ethnicity, an STI in the preceding year increased the odds of mpox infection by 82% (adjusted odds ratio [aOR] 1.82, 95% CI 1.02-3.24) and an STI in the preceding 6 months increased the odds by 100% (aOR 2.00, 95% CI 1.04-3.84). Patients with mpox infection were 2.4 times more likely to have a concurrent STI compared to those without mpox (aOR 2.40, 95% CI 1.34-4.30). Among those without a HIV diagnosis, current PrEP use increased the odds of mpox infection by 130% (aOR 2.30, 95% CI 1.13-4.70).
Conclusion: This analysis demonstrated that there is a temporal relationship between mpox positivity among GBMSM and a recent history of STI as well as current PrEP use. These results offer several actionable implications. For healthcare providers, it is crucial that routine STI testing be offered when testing for mpox given the association between mpox infection and a concurrent STI. For public health agencies, this analysis suggests that mpox vaccine eligibility be universally expanded to include GBMSM with current PrEP for HIV use. Finally, health systems positioned to do so should consider proactively identifying GBMSM with a recent history of STI and current PrEP use for vaccine outreach.

CRUDE ASSOCIATIONS BETWEEN MPOX INFECTION AND SEXUALLY TRANSMITTED INFECTION, PRE-EXPOSURE PROPHYLAXIS USE, AND HIV DIAGNOSIS

Factor	Cases n (%) n=103	Controls n (%) n=126	OR (95% CI)
Living with HIV			
Yes	25 (24.3)	43 (34.1)	0.62 (0.35-1.11)
No	78 (75.7)	83 (65.9)	Ref.
Current PrEP Use			
Yes	47 (60.3)	35 (42.2)	2.08 (1.11-3.90)
No	31 (39.7)	48 (57.8)	Ref.
STI ≤1 Year			
Yes	41 (39.8)	34 (27.0)	1.79 (1.03-3.12)
No	62 (60.2)	92 (73.0)	Ref.
STI ≤6 Months			
Yes	30 (29.1)	21 (16.7)	2.06 (1.09-3.87)
No	73 (70.9)	105 (83.3)	Ref.
Concurrent STI			
Yes	45 (43.7)	31 (24.6)	2.38 (1.36-4.17)
No	58 (56.3)	95 (75.4)	Ref.

1034 HIV AND SEXUALLY TRANSMITTED INFECTIONS AMONG MPOX CASES, TEXAS 2022

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Background: Syphilis, Chlamydia, Gonorrhea (STD) and HIV are reportable conditions in Texas. Men who have sex with men (MSM) and racial minority populations are disproportionately impacted by these conditions. The first mpox case in Texas was identified on June 7, 2022, and the U.S Department of Health and Human Services declared mpox a public health emergency on August 4, 2022. Due to the disproportionate impact of mpox on the same populations, Texas Department of State Health Services (DSHS) began conducting routine HIV/STD/mpox matches in September 2022.
Methods: The data match was conducted with all persons reported to the DSHS Emerging and Acute Infectious Disease Unit with confirmed and probable mpox. Data elements and person level identifiers reported through routine electronic reporting were used for the match, including first and last name, date of birth, sex at birth, and patient address. Mpox cases reported to DSHS thru November 28, 2022, were matched to the HIV registry and the STD registry. All persons living with HIV/AIDS (PLWHA) were included in the HIV dataset, and all persons diagnosed with an STD within the previous 12 months were included in the STD dataset. Match processes were completed using SAS 9.4 and Link Plus.
Results: Of the 2,826 mpox cases reported to DSHS thru November 28, 2022, 1,413 (50%) matched to the HIV case registry. Among the 2,826 mpox cases, 1,945 (69%) were either PLWHA or diagnosed with an STD. Men were disproportionately impacted by mpox, 2,733 cases (98%), compared to women, 93 cases (2%). There are large differences in the rate of coinfection with HIV/STDs, 70% of men (n=1,920) diagnosed with mpox had an HIV/STD coinfection, while only 27% of women (n=25) had a coinfection. Among people in the 50-59 age range diagnosed with mpox, 73% had a coinfection (n=163), followed by the 30-39 age range at 72% (n=845). Among PLHWA and mpox cases, 1,323 (94%) had a documented risk history of sex with gay or bisexual men. Black and African American people living with HIV were more likely to be diagnosed with mpox 594 (61%) compared to White (42%) or Hispanic (47%) PLWHA.
Conclusion: Even as mpox, HIV and STDs disproportionately impact MSM and racial minority populations, the distribution of that impact is not uniform across age, sex, race or geographic regions of the state. Prevention for all diseases should be focused on populations experiencing higher burden of disease.

1035 CONCURRENT STI TESTING AMONG PATIENTS TESTED FOR MPOX AT DUKE UNIVERSITY HEALTH

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Background: Male-to-male intimate contact was a significant driver of the 2022 mpox outbreak. Co-infection with sexually transmitted infections (STIs) and mpox is common, and mpox disproportionately infected people living with HIV. Comprehensive testing for incident STIs, including HIV, should be concurrently performed with mpox testing during this outbreak; whether this is being performed in routine practice is unknown. We aimed to evaluate the proportion of concurrent STI/mpox testing within our health system in the Southeastern US.
Methods: The Duke electronic medical record interface was used to systematically identify patients tested for mpox in the Duke Health System between 07/01/2022-11/30/2022 and to assess concurrent STI testing during the same encounter using laboratory data. Chi-square test was used to examine the hypothesis that concurrent STI testing would differ by where patients presented for care.
Results: We identified 225 patients tested for mpox during the study period. Of those tested, 159 (70.7%) were male, 182 (80.9%) were non-Hispanic, 95 (42.2%) were Black or African American, and 34 (15.1%) had a known diagnosis of HIV. 71 (31.6%) patients tested for mpox were also tested for concurrent gonorrhea/chlamydia, 123 (54.7%) for syphilis, and 63/191(33%) of those not living with HIV were tested for HIV. When gonorrhea/chlamydia testing was done, 47 (66%) patients only had urine testing and 3% had concurrent urine, oral and pharyngeal testing. 114 (51%) were tested at urgent care facilities, 62 (28%) in emergency departments, 34 (15%) at primary care facilities, and 15 (7%) at other settings. Concurrent STI screening did not differ by setting except for HIV testing, which was done in 54% of ED visits vs. 26% of visits to other sites (p=0.0016). 52/225 (23.1%) patients tested positive for mpox, 19 (36.5%) of whom had known HIV. Only 10/173 (5.8%) patients who tested negative for mpox were diagnosed with a concurrent STI. Whereas 11/52 (21.2%) patients with mpox were diagnosed with a concurrent STI: 2 had gonorrhea, 1 chlamydia, 5 syphilis, 1 new HIV, 1 both gonorrhea and chlamydia, and 1 both syphilis and new HIV.

Conclusion: Although concurrent STIs among patients with mpox were common when testing was performed, most patients tested for mpox in our health system were not comprehensively tested for STIs. Electronic health record-based strategies to promote concurrent mpox/STI testing are needed.

1036 WITHDRAWN

1037 INEQUITIES IN TRAVEL-TIME TO HIV TREATMENT IN AFRICA: A 3 COUNTRY COMPARISON

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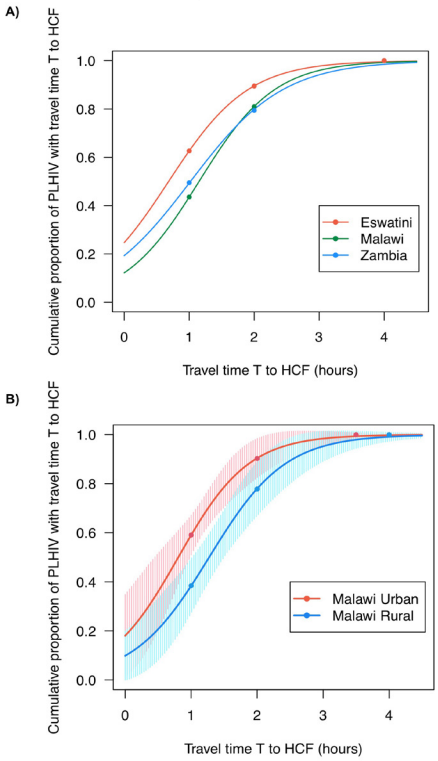
Background: UNAIDS has recently announced a new strategy "End Inequalities. End AIDS. Global AIDS Strategy 2021-2026". Increased travel-time to health facilities has been associated with decreased treatment initiation and retention. We analyze data from the nationally representative Population-Based HIV Impact Assessment (PHIA) surveys from Eswatini, Malawi, and Zambia to identify inequities in travel-time to treatment.

Methods: Data were collected in 2015/16 in Malawi, and 2016 in Eswatini and Zambia. The PHIAs collect questionnaire data and blood samples (used to identify the HIV status of each individual and detect the presence of antiretrovirals). People living with HIV (PLHIV) who reported being on antiretrovirals were asked to specify travel-time to receive treatment: < 1 hour, 1 to 2 hours, or > 2 hours. We first determined epidemic severity, and treatment coverage among adults aged 15-59. We then fit the observed travel-time data using Logistic cumulative distribution functions.

Results: Eswatini has the most severe epidemic: 28% prevalence, similar in urban (30%) and rural (27%) areas. Prevalence was 11% in Malawi, 12% in Zambia, and higher in urban than rural areas (14% to 10% [Malawi], 15% to 9% [Zambia]). Zambia has a predominantly urban epidemic: 58% of PLHIV in urban areas. Malawi and Eswatini have predominantly rural epidemics: 63% and 69% of PLHIV in rural areas. Eswatini had 77% treatment coverage, Malawi 70%, and Zambia 62%. Both Eswatini and Malawi had higher coverage in rural than urban areas: 78% vs. 73%, 71% vs. 66%. In Zambia, coverage was higher in urban (66%) than rural (57%) areas. The cumulative proportion of PLHIV on treatment is an increasing function of travel time (Figure); on average, PLHIV in Eswatini had the shortest travel time, PLHIV in Malawi had the longest. A fairly high percentage of patients traveled over 2 hours for treatment: 21% in Zambia, 19% in Malawi, and 11% in Eswatini. In all three countries, we found substantial urban-rural differences: a greater proportion of patients in rural areas, in comparison with urban areas, travelled for over 2 hours. Even in urban areas, quite a few traveled for over 2 hours to reach treatment: 11% (Zambia), 10% (Malawi), and 6% (Eswatini).

Conclusion: We have identified substantial inequities in access to treatment in Malawi, Eswatini, and Zambia when coverage levels were fairly high. As coverage has increased, it is important to determine whether inequities still exist and, if so, identify strategies to eliminate them.

Differences in travel time: country-specific and urban-rural



1038 EVALUATION OF MEDICAL DRONES FOR ANTI-RETROVIRAL DELIVERY IN AN ISLAND POPULATION

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Background: The Kalangala district is comprised of 84 islands in Lake Victoria. These island-dwelling communities have the highest HIV prevalence (27%) and lost to follow up from HIV care (50%) in Uganda. Delivery of anti-retroviral therapy (ART) is a challenge due to the geography and the nomadic nature of the community. In September 2021 we commenced delivery of ART to people living with HIV(PLHIV) using unmanned ariel vehicles (medical drones).

Methods: This study evaluated the feasibility of medical drone ART delivery to peer support groups as part of differentiated service delivery (DSD) implementation. Two DJI Matrice 300 drones flew from the island location of Bufumira health centre (BHC) to 5 remote landing sites previously receiving ART through outreaches by boat. The impact on PLHIV was assessed using surveys to PLHIV at baseline and those who received ART by drone in the 12th month after ART delivery commenced. PLHIV at Mazinga Health Centre(MHC) on another

island were interviewed as a control group. Routinely collected data from BHC and MHC was analysed.

Results: 150 PLHIV at BHC and 100 at MHC were interviewed at baseline. In September 2021, medical drone flights delivery commenced to 43 PLHIV on three landing sites served by BHC. Each delivery carried 7 bottles of 90 days of tenofovir, lamivudine and dolutegravir combined preparation. By October 2022 226 flights were completed, 115 PLHIV received ART by drone, and 63 had received 12 months of ART by medical drone. Average flight time was 9.3min, boat trip was 35 min; average distance was 6.6m. At 12 months there was 100/100 retention of PLHIV at receiving ART by drone at BHC and 63/100 at MHC. Viral suppression increased to 92% from 70% for PLHIV receiving ART delivery by drone at BHC and to 52% from 51% at MHC.

Conclusion: This proof of concept study provides encouraging results on the feasibility and early indications of positive impact of using medical drones for last mile delivery of ART in hard to reach areas. It showed increased access to ART and improved viral suppression in PLHIV receiving ART nearer to home thus avoiding expensive and dangerous boat travel.

Impact of medical drones ART delivery on outcomes in PLHIV at Bufumira HC compared to Mazinga HC

	Baseline				12 month follow up			
	Mazinga HC	%	Bufumira HC	%	Mazinga HC	%	Bufumira HC	%
	Control		Medical drone ART delivery		Control		Medical drone ART delivery	
Number surveyed	100		150		100		100	
Number receiving more than one ART delivery by drone					0		99	
On anti-retroviral therapy	58	58.0%	132	87.4%	63	63%	100	100%
Missed ART appointment in last 12 months	23	39.7%	37	28.0%	20	20.0%	2	2%
Reporting running out of ART in last 12 months	19	32.8%	31	23.5%	5	5%	1	1%
Viral load sample taken in last 12 months	88	88.0%	145	96.7%	61	61%	97	97%
Viral load result undetectable (<1000c/ul)		51%*		70%*	52	52%	92	92%
Dead					1		2	
Lost to follow up					39		0	

**health centre data*

1038.5 A LOW-COST, RAPID URINE TEST FOR TFV INCREASES ART ADHERENCE AND VIRAL SUPPRESSION

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Background: Innovative approaches are needed to achieve the third UNAIDS 95-95-95 target, to sustain virologic suppression (VS) in patients on ART. Tenofovir (TFV)-dolutegravir (DTG)-lamivudine (TLD) is first-line ART recommended by the World Health Organization (WHO). Virologic failure in patients on TLD is likely due to non-adherence because of DTG's high barrier to resistance. Identifying non-adherence to TLD with an objective measure of adherence may help patients achieve VS, while saving on costly repeated viral load (VL) testing and more expensive second-line ART. We integrated a low-cost, point-of-care (POC) urine test to detect TFV into standard enhanced adherence counseling (EAC) to improve VS in adults with high VL on first-line TLD in Namibia.

Methods: Patients on TLD with persistent non-VS (VL >1000 copies/mL) even after completing 3-months or more of EAC were enrolled from 38 clinics across Namibia. At each monthly ART pick-up, participants completed the POC urine test and received EAC informed by POC test results. After 3 months, participants received a VL test. If VS (the primary outcome) was not achieved, a second round of POC urine testing with EAC was provided. Acceptability of the urine assay was assessed via oral surveys administered to participants and providers.

Results: Of 127 participants enrolled (median age 33 years, interquartile range 22-46, 61% female) with virologic failure, 109 achieved the primary outcome with the urine assay: VS at month 3 (86%, $p< 0.001$). An additional 2 participants achieved VS at month 6 (87%). Positive TFV in urine increased from 81% to 97% in clients that achieved VS and 31% to 50% in those who did not. Overall, 86% of participants and 91% of 51 interviewed providers agreed/strongly agreed that the urine test should be incorporated into clinical care.

Conclusions: Nearly 90% of patients on TLD who were not virally suppressed at baseline despite counseling achieved VS within 3 months following EAC that incorporated feedback from a urine-based POC TFV test. While EAC alone did not achieve VS in this group, EAC that incorporated an objective patient-viewed metric of adherence in the clinic was successful for the vast majority of participants. Encouraging results of this pre-post intervention should be rigorously tested in a future randomized clinical trial. Given the cost of VL and resistance testing in lower-and middle-income countries, this POC urine test has great potential to help achieve the third 95-95-95 target in a low-cost, scalable manner.

1039 DOES TYPE OF PICK-UP POINT INFLUENCE 12-MONTH VIROLOGIC SUPPRESSION IN SOUTH AFRICA?

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Background: South Africa's Central Chronic Medicine Dispensing and Distribution (CCMDD) Program allows people living with HIV who are clinically stable the choice of collecting antiretroviral therapy (ART) at community pick-up points to increase convenience. Our objective was to assess the impact of community pick-up (vs. clinic-based 'fast-track' pick-up) on rates of virologic suppression 12 months after CCMDD enrollment.

Methods: We enrolled an observational cohort of adults (≥18 years) who met CCMDD clinical eligibility criteria (not pregnant, on ART for ≥1y, and virologically suppressed) in 7 public sector clinics in Umlazi, KwaZulu-Natal. We assessed CCMDD effectiveness using virologic suppression at 12 months (range 6-18 months) following CCMDD enrollment using data from the National Health Laboratory Service database. In addition to age and gender, we identified other potential predictors of virologic suppression in univariate models with $p< 0.2$ and fit a multivariable logistic regression model.

Results: Among 1642 participants, 67% were female, with median age 36 years (IQR 44-76), and median duration on ART prior to CCMDD enrollment of 2 years (IQR 1-5). 919 (56%) opted for community ART pick-up at enrollment. Among 1289 with viral load data available, 1112 (86%) were virologically suppressed at one year. In addition to type of pick-up point, variables included in the multivariable model were year of HIV diagnosis, distance to clinic, baseline self-efficacy, and HIV treatment beliefs. No predictors of virologic suppression were statistically significant. In particular, opting for clinic-based pick-up point (vs. community-based) was not associated with achieving 12- month virologic suppression (aOR 1.12, 95 CI 0.79-1.58).

Conclusion: In this multi-site study of the CCMDD program in South Africa, choice of pick-up point (community- vs clinic-based) was not associated with virologic suppression 12-months after enrollment in the CCMDD program. These results suggest that provision of community-based ART pick-up points has not reduced continued viral suppression in a population enrolled in the CCMDD program.

1040 AN ADAPTIVE INTERVENTION TRIAL TO SUPPORT VIRAL SUPPRESSION AMONG FEMALE SEX WORKERS

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Siyaphambili study team

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Background: Structural, network and individual barriers result in poor HIV treatment outcomes for female sex workers (FSW) living with HIV. The Siyaphambili trial tested two adaptive interventions to identify efficient pathways to viral suppression, including a nurse-led decentralized treatment program (DTP) using a mobile van vs. FSW-peer led individualized case management (ICM) consisting of face-to-face visits and calls.

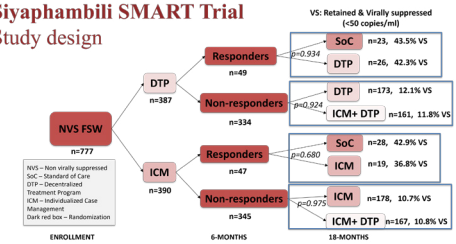
Methods: Non-pregnant, adult cisgender FSW living with HIV were recruited by TB HIV Care at its drop-in center and FSW venues in Durban, South Africa for a sequential multiple assignment randomized trial (SMART). Non-virally suppressed (>=50 copies/ml) FSW were randomized to DTP vs. ICM interventions, then re-randomized at 6-months per viral load responsiveness to continue vs. receive both interventions if non-virally suppressed, or continue vs. return to standard care (SOC) if virally suppressed. The re-randomized strategy was continued until 18-months; the primary endpoint was an intention-to-treat 18-month combined retention and viral suppression outcome in DTP vs. ICM.

Results: Overall, 1391 FSW were enrolled from June 2018-March 2020 (median age:31 [IQR:27-37]); 519/1391 (38%) were virally suppressed at enrollment. 777 non-virally suppressed FSW were randomized across the adaptive interventions. At 18-months, 117/777 (15.1%) of FSW were retained and virally suppressed.

There was no difference across arms, 16.0% DTP vs. 14.1% ICM (p=0.455); nor in those stepping up or stepping down interventions (Figure). Among FSW with sustained viremia at 6- and 12-months who returned for further bloodwork, 74/80 (92.5%) were resistant to first-line ART. In a non-randomized TB HIV Care program comparator arm of non-virally suppressed FSW engaged in HIV care during the enrollment period, 4/86 (5%) were retained and virally suppressed at 18-months.

Conclusion: No differences in treatment outcomes were observed between study arms. However, FSW who responded early were the most likely to be suppressed, even if stepped down after six months to the standard of care. While outcomes appear modestly improved over SOC, they are extremely sub-optimal and high rates of drug resistance were observed. These results reinforce the urgent need to improve treatment outcomes among FSW in South Africa to end new HIV infections by 2030.

Siyaphambili Study Design and Outcomes



1041 TRENDS IN PERSISTENT HIV VIREMIA DURING UNIVERSAL TEST-AND-TREAT SCALE-UP IN UGANDA

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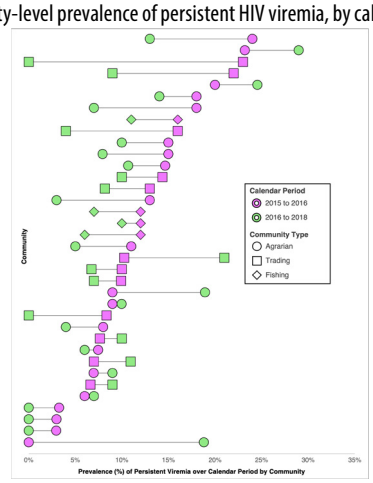
Background: Universal Test and Treat (UTT) has expanded antiretroviral therapy (ART) access globally, but population-based studies of longitudinal HIV treatment outcomes following UTT are rare. We characterized population-level trends in durable HIV viral load suppression (VLS) and persistent and intermittent viremia after UTT scale-up in Rakai, Uganda.

Methods: We ascertained viral load status among Rakai Community Cohort Study participants in 4 hyperendemic fishing villages and 36 lower-prevalence inland communities across 3 survey rounds (2015 to 2020), coinciding with UTT rollout. For each participant, viral load was assessed over 2 study visits (i.e., visit-pair, ~1.8-year interval between visits), and classified as follows: persistent viremia (≥1,000 copies/ml across visits), durable VLS (< 1,000 c/ml across visits), new/renewed VLS (≥1,000 c/ml at index visit only), or viral rebound (≥1,000 c/ml at follow-up only). Prevalence estimates for viral load outcomes in each visit-pair were assessed over calendar time and by age and gender. Individual- and community-level predictors of persistent HIV viremia were also identified using multivariable robust Poisson regression with generalized estimating equations, reported as adjusted risk ratios (aRR) with 95% confidence intervals (95%CI).

Results: Overall, 3,080 persons (mean age: 34 years, 62% women) contributed 4,604 visit-pairs to the analysis. One-fourth of visit-pairs exhibited any viremia, of which 42% were persistently viremic, and 10% had viral rebound. Among visit-pairs with persistent viremia, 21% were in persons reporting ART use for >1 year. Significant increases in durable VLS prevalence over time (71% to 80%) accompanied declines in persistent viremia (12% to 8%); however, the magnitude of these declines varied substantially across communities (**Figure 1**). Persistent viremia was significantly higher among youth (≤29 vs. 40-49 years: aRR 2.96, 95%CI 2.21–3.96), men (aRR 2.40, 95%CI 1.87–3.07), and individuals reporting inconsistent condom use with non-stable partners (aRR 1.38, 95%CI 1.10–1.74) and hazardous alcohol use (aRR 1.09, 95%CI 1.03–1.16).

Conclusion: Durable VLS increased with UTT, but 42% of viremic visit-pairs, nearly one-fourth of which were in persons on ART, remained unsuppressed for >1 year. Given the concentration of viremia in groups with known barriers to HIV care and elevated risks of onward HIV transmission, UTT alone may be insufficient to optimize clinical outcomes and achieve HIV epidemic control in this setting.

Community-level prevalence of persistent HIV viremia, by calendar period



1042 USAGE PATTERNS AND OUTCOMES IN A LARGE COMMUNITY ART PROGRAMME IN SOUTH AFRICA

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Background: Differentiated antiretroviral therapy (ART) delivery programmes are being rolled out globally but there is little data on long term implementation and outcomes for people living with HIV (PLHIV). We describe patterns of exposure to community ART delivery and associated treatment outcomes in the South African Centralized Chronic Medicines Dispensing & Distribution programme over 3.5 years.

Methods: We performed a retrospective cohort study among PLHIV on first-line ART who were referred for community ART delivery between Oct 2016 - Mar 2019 from 56 clinics in KwaZulu-Natal, South Africa. Follow up ended in Mar 2020. We used group-based trajectory modelling to characterize patterns of exposure to community ART following referral, and survival analyses to measure the association between time-varying exposure to community ART and time to loss-to-care, defined as no clinic visit for >365 days. We used logistic regression with generalized estimating equations to quantify the association between proportional exposure to community ART 12 months prior to viral load measurement and viraemia (>50 cps/mL) among those in care. Models of loss-to-care and viraemia adjusted for baseline patient age, gender and time on ART.

Results: Among the 37,596 patients referred to community ART, 68.6% were female with a median (interquartile range (IQR)) age of 38 (32-45) years, and 99.3% were on tenofovir-based regimens. Median (IQR) follow-up time was 656 (430-841) days. Time spent in community ART varied during follow-up; ~40% remained consistently in community ART following referral, ~ 20% returned to clinic-based care after their first referral visit while the remaining 40% oscillated between community ART and clinic-based care. The incidence of loss-to-care was 4.46 per 100 person-years and community ART exposure was associated with a 41.1% (95% confidence interval (CI): 34.1%-47.3%) reduction in the hazard of loss-to-care after adjusting for other covariates. Among those with at least one viral load measured after referral (N=33,378), 5.4% became viraemic. A 10% increase in the proportion of time spent in community ART in the 12-month period before viral load measurement was associated with a 4% (95% CI: 2%-5%) reduction in the adjusted odds of viraemia.

Conclusion: Community ART exposure patterns vary considerably after referral into the programme. Promoting consistent programme adherence will reduce clinic burden and the likelihood of patients being lost to care, whilst sustaining viral suppression.

1043 HIGH COVERAGE OF HIV TREATMENT, LOW COVERAGE OF PREVENTION SERVICES AMONG KP IN INDIA

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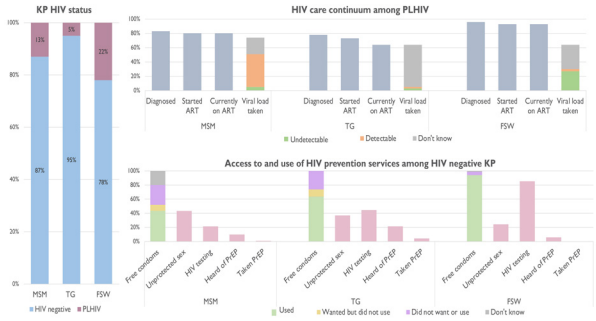
Background: Over the past decade, India has greatly expanded access to HIV services such as testing and treatment, resulting in declines in general population prevalence. However, key populations continue to experience a high burden of HIV and may have unique challenges with accessing critical HIV services.

Methods: We used respondent-driven sampling (RDS) to separately recruit members of key populations (KP) – men who have sex with men (MSM), transgender persons (TG), and female sex workers (FSW) – in Pune, India. People were eligible to enroll if they were a KP member, ≥18 years, and had a valid RDS referral coupon. Study participants completed rapid onsite HIV testing and completed an interviewer-administered survey covering demographics, behaviors, and health service utilization. By KP, we describe the uptake of HIV prevention, care, and treatment services. We assessed correlates of HIV testing in the prior 12 months (excluding known positives) and diagnosis of HIV infection (among all those living with HIV [PLHIV]) using logistic regression.

Results: As of September 13, 2022, we recruited 387 MSM, 432 TG, and 225 FSW. Median age was 28 (MSM), 26 (TG), and 40 years (FSW). HIV prevalence was 13% (MSM), 5% (TG), and 22% (FSW). Among negative KPs, FSW had high utilization of free condoms (94%) and HIV testing (85%) compared to MSM and TG (**Figure**). TG were most likely to be aware of PrEP (21%) but use was negligible across all KP. For HIV outcomes among PLHIV, 83% MSM, 78% TG, and 96% FSW were previously diagnosed. Current ART use was relatively high - 80% (MSM), 64% (TG), and 93% (FSW) but a history of viral load testing was low (44% MSM, 29% TG, 32% FSW) and many did not know the result. Among PLHIV, 33% (MSM), 56% (TG), and 24% (FSW) had been offered partner testing. Correlates of recent HIV testing included older age, higher education, and being FSW or TG. Correlates of diagnosis were older age and residing in the district for more than 5 years.

Conclusion: Treatment coverage among PLHIV is approaching UNAIDS targets, however utilization of prevention services is low, alongside high HIV prevalence among most KP. This leads to missed opportunities – particularly in HIV testing – to identify untreated PLHIV and reduce ongoing transmission.

HIV prevalence, care continuum, and prevention service utilization among key populations in Pune, India



1044 ACHIEVING THE EHE INCIDENCE REDUCTION GOALS AMONG AT-RISK POPULATIONS IN THE SOUTH

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Background: Antiretroviral therapy (ART) coverage remains sub-optimal in much of the United States, particularly the Sothern region, and Non-Hispanic Black or African American persons (NHB) continue to be disproportionately impacted by the HIV epidemic. The "Ending the HIV Epidemic in the U.S." (EHE) initiative seeks to reduce HIV incidence nationally by focusing resources towards the most highly impacted localities and populations. This study evaluates the impact of hypothetical improvements in ART and preexposure prophylaxis (PrEP) coverage to estimate the levels of coverage needed to achieve EHE goals in the South.

Methods: We developed a stochastic, agent-based network model of 500,000 individuals to simulate the HIV epidemic and hypothetical improvements in ART and PrEP coverage.

Results: New infections declined by 78.6% at 90%/40% ART/PrEP and 94.3% at 100%/50% ART/PrEP from 2022-2030. Declines in annual incidence rates surpassed 75% by 2025 with 90%/40% ART/PrEP and 90% by 2030 with 100%/50% ART/PrEP coverage. Increased ART coverage among NHB gay, bisexual, and other men who have sex with men (MSM) was associated with a linear decline in incidence among all MSM. Declines in incidence among Hispanic/Latino and White/Other MSM were similar regardless of which MSM race group increased their ART coverage, while the benefit to NHB MSM was greatest when their own ART coverage increased. The incidence rate among NHB women declined by over a third when either NHB heterosexual men or NHB MSM increased their ART use respectively. Increased use of PrEP was associated with a decline in incidence for the groups using PrEP. MSM experienced the largest absolute declines in incidence with increasing PrEP coverage, followed by NHB women.

Conclusion: Our analysis indicates that it is possible to reach EHE goals. The largest reductions in HIV incidence can be achieved by increasing ART coverage among MSM and all race groups benefit regardless of differences in ART initiation by race. Improving ART coverage to > 90% should be prioritized with a particular emphasis on reaching NHB MSM. Such a focus will reduce the largest number of incident cases, reduce racial HIV incidence disparities among both MSM and women, and reduce racial health disparities among persons with HIV. NHB women should also be prioritized for PrEP outreach.

1045 PROGRESS ON UNAIDS 95-95-95 TARGETS AMONG KEY POPULATIONS IN 3 TANZANIA REGIONS

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Background: Key populations (KP) such as female sex workers (FSW) and people who inject drugs (PWID) have high burden of HIV. The Tanzania HIV Impact Survey 2016-2017 estimated that 61% of people living with HIV (PLHIV) in the general population were aware of their status, 94% of diagnosed PLHIV were on antiretroviral therapy (ART), and 87% of ART clients achieved viral load suppression (VLS). UNAIDS estimates that 88% of PLHIV are now aware of their status in Tanzania in 2021; however, estimates of these targets among KP are unavailable. We measured progress towards the UNAIDS 95-95-95 targets among FSW and PWID in Mwanza, Mbeya, and Dodoma regions of Tanzania.

Methods: We conducted a bio-behavioral survey (BBS) using respondent-driven sampling (RDS) between March and May 2022. HIV serostatus among participants was determined based on the national HIV testing algorithm. HIV viral load was measured for HIV-positive participants using plasma samples. In RDS-adjusted analysis, we calculated the proportion of HIV-positive FSW and PWID who were aware of their status, diagnosed FSW and PWID who received ART, and ART clients with VLS (< 1000 copies/mL). FSW and PWID who self-reported not knowing their HIV-positive status but achieved VLS were considered aware. Diagnosed FSW and PWID who self-reported not on ART but achieved VLS were considered on ART.

Results: Across the three regions, we surveyed 1,247 FSW with HIV prevalence of 22.4% [95% confidence interval 18.4%-26.9%] and 1,252 PWID with HIV prevalence of 9.8% [7.8%-12.3%]. Among the 294 HIV-positive FSW, 83.7% [77.1%-88.6%] were aware of their status. Of the FSW who were aware of their HIV-positive status, 99.2% [96.0%-99.8%] were on ART. VLS among FSW on ART was 94.9% [90.7%-97.2%]. Among the 115 HIV-positive PWID, 74.3% [95% CI 63.3%-82.9%] were aware of their status. All PWID who were aware of their HIV-positive status were on ART. VLS among PWID on ART was 98.9% [96.0%-99.8%]. The estimates for FSW and PWID were not statistical significantly different across the three regions.

Conclusion: Our findings suggest that HIV burden continues to be disproportionate among FSW and PWID compared with the general population in the study regions. Substantial progress has been made in diagnosing HIV among FSW and PWID. Targeted and enhanced outreach is needed to reach the first 95 target. The second and third 95 targets have been met or exceeded suggesting that once KP know their status, with appropriate services, they can and do access ART and achieve VLS.

1046 INCREASING IN LIFE EXPECTANCY OF THAI LIVING WITH HIV IN THE ERA OF TREAT ALL

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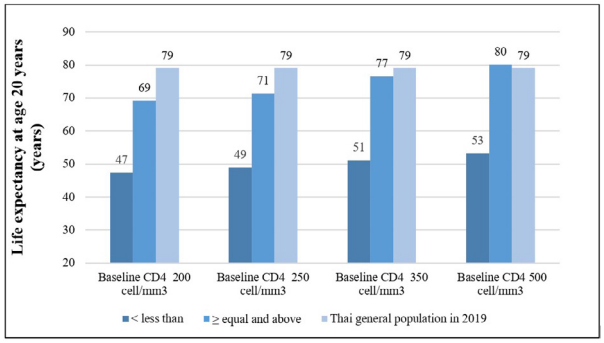
Background: In the era of 'treat all at any CD4 count', life expectancy among people living with HIV (PLHIV) has steadily increased. Here, we present recent estimates of life expectancy trends from 2008 - 2019 among PLHIV based on a National AIDS Program (NAP).

Methods: All Thai PLHIV aged ≥15 years initiating antiretroviral therapy (ART) from 2008 to 2019 were analyzed. Life expectancy (LE) was defined as additional years of life from age at starting ART; vital status was confirmed by Death Registry linkage. We used Chiang's method of abridged life tables to estimate life expectancy by period of ART initiation (2008–13 and 2014–19), overall and by sex and CD4 cell count at ART start (baseline). Segmented interrupted Poisson regression analysis was used to demonstrate mortality trends among PLHIV accounting for changing CD4 thresholds in treatment guidelines in 2010 (< 350) and 2014 (any CD4).

Results: A total of 321,786 PLHIV, with 1,813,110 person-years were included and median duration on ART was 5 (IQR 3-8) years. Median baseline CD4 was 191 (IQR 67-363) cells/mm^3, median age was 36 (IQR 28-43) years, and 175,341 (61%) were male. Overall LE starting ART aged 20 years was 32.1 (95% CI, 32.0-32.2) years and 25.6 (95%CI 25.5-25.7) years aged 35. Male LE aged 20 years was 29.4 (95%CI 29.3-29.5) and 37.0 (95%CI 36.9-37.2) for females aged 20. LE at baseline CD4 cell count ≥ 350 cells/mm^3 was 56.5 (95%CI 56.3-56.8) years at age 20, and 46.2 (95%CI 46.0-46.5) years at age 35, close to LE in the general Thai population (Figure 1). From 2008–13 to 2014–19, overall life expectancy at 20 years increased from 30.8 (95%CI 30.6–30.7) years to 33.5 (95%CI 33.4-33.6) years. Male LE at age 20 years significantly increased from 27.5 (95%CI 27.3-27.6) years to 31.2 (95%CI 31.0-31.3) years. Female LE slightly increased from 36.6 years (95%CI 36.4–36.8) to 37.8 years (95%CI 37.5–38.0), respectively. No LE trends were apparent for PLHIV starting ART aged 35 years after stratifying by sex and period of ART initiation. Guideline changes to treat all at any CD4 count in 2014 were associated with an additional monthly mortality decrease of 0.4% compared to starting ART at lower CD4 thresholds.

Conclusion: LE among PLHIV starting ART significantly improved after guidelines recommended staring ART irrespective of CD4 cell count. This finding further supports the recommendation of rapid ART initiation; early case finding will further improve life expectancy and reduce mortality.

Figure 1 Life expectancy of Thai people with HIV receiving ART at age 20 years by baseline CD4



1047 REACHING THE THIRD 95 IN UGANDA AFTER LOWERING HIV VIRAL LOAD SUPPRESSION CUTPOINTS

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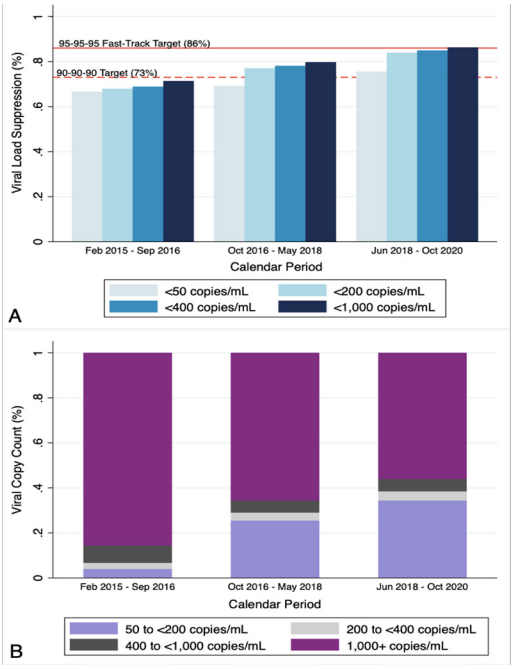
Background: Per UNAIDS 95-95-95 Fast-Track targets, reaching the "third 95" requires 86% of people living with HIV to achieve viral load suppression (VLS), defined by UNAIDS and WHO as < 1,000 HIV RNA copies/ml. Emerging evidence linking persistent lower-level viremia to HIV drug resistance has prompted calls to redefine VLS using lower cutpoints. However, it is unclear how lowering VLS cutpoints might impact achievement of the Fast-Track targets or resources required for delivering HIV treatment.

Methods: We used data from a prospective population-based survey in rural south-central Uganda, the Rakai Community Cohort Study, to assess the impact of lowering VLS cutpoints on estimated progress towards the 95-95-95 VLS target. We estimated VLS by calculating the proportion of serologically confirmed HIV cases with undetectable plasma viral loads or exhibiting viremia below specific cutpoints measured over 3 survey rounds in 40 communities (2015 to 2020). We ascertained differences in population VLS estimates across 4 routinely used VLS cutpoints: < 1,000, < 400, < 200, and < 50 copies/ml. We also assessed the relative increase in the fraction of viremic persons living with HIV if VLS cutpoints were lowered.

Results: Overall, 5,814 people living with HIV (mean age: 33 years, 63% women) contributed 10,418 observations to the analysis. In the final survey (2018–2020), estimated population VLS (86%, 95% confidence interval [95%CI] 85–87%) met the 95-95-95 Fast-Track target using a cutpoint of < 1,000 copies/ml (Figure 1A). However, when using the more conservative cutpoints of < 200 and < 50 copies/ml, population VLS fell to 84% (95%CI 83–85%) and 76% (95%CI 74–77%), respectively. Among persons with detectable viral load, lowering the VLS cutpoint from < 1,000 to < 200 copies/ml increased the proportion of people living with HIV who were viremic by 17% (Figure 1B).

Conclusion: Lowering VLS cutpoints may substantially impact Fast-Track target achievement, requiring countries and subnational units to reframe progress towards HIV epidemic control goals. It may also markedly increase programmatic resources needed for the clinical management of persons living with HIV who exhibit lower-level viremia.

Viral load suppression prevalence (Panel A) and the distribution of viral copy counts among viremic (>50 copies/ml) persons living with HIV, by calendar period



1048 GETTING TO ZERO: ACHIEVEMENT OF 95-95-95 AND DECLINING HIV INCIDENCE IN ESWATINI

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Background: Achieving UNAIDS global 95 targets among people living with HIV (PLHIV) is key to HIV epidemic control. Eswatini, a country with one of the severest HIV epidemics, has implemented an aggressive national HIV response with comprehensive HIV prevention and treatment services. We assessed progress towards these targets in the high HIV disease burden setting of Eswatini.

Methods: We compared 95-95-95 indicators and HIV incidence from two sequential Population-based HIV Impact Assessment (PHIA) surveys conducted in Eswatini in 2016 and 2021. These PHIAs were similarly designed as nationally representative household surveys among individuals 15 years and older. Respondents completed interviews and provided blood samples for HIV rapid testing (Determine and Unigold), antiretrovirals (ARV) testing, and viral load (VL) measurement. The first 95 (diagnosed PLHIV) was assessed by self-report or detectable ARVs; second 95 (on treatment) by self-report or detectable ARVs among diagnosed PLHIV, and third 95 (VL suppression, VLS) as VL < 1,000 copies/mL among PLHIV on treatment. Annual HIV incidence was estimated from recent infections (classified by HIV-1 LAg avidity assay, VL and ARV detection) using the formula recommended by the World Health Organization Incidence Working Group. Survey weights accounting for sample selection probabilities and adjusted for nonresponse and noncoverage were applied.

Results: The 11,199 adults in the 2021 PHIA were at 94-97-96, while the 10,934 adults in the 2016 PHIA were at 87-89-91, a statistically significant increase of 5-10% in all 95 indicators (see Table). Target achievement varied by sex, but all 95 indicators improved among men (92-96-97 in 2021 vs 80-90-91 in 2016) and women (95-98-96 in 2021 vs 91-88-91 in 2016). Overall annual HIV incidence declined by 45% from 1.13% in 2016 to 0.62% in 2021 (p = 0.055). Annual HIV incidence in 2021 was nearly seven times higher among women (1.11%) than among men (0.17%).

Conclusion: These findings reflect substantial progress toward HIV epidemic control, a remarkable achievement in the context of health, social and economic disruptions and challenges associated with the COVID-19 era. The 2021 data highlight remaining gaps in knowledge of HIV status, particularly among men, and HIV incidence reduction, particularly among women.

Table: Comparison of 95 indicators and HIV incidence between 2021 and 2016 among adults 15 years and older in Eswatini

	2021 PHIA			2016 PHIA			Comparison of 2021 Total vs 2016 Total	
	Men N=4,654	Women N=6,545	Total N=11,199	Men N=4,506	Women N=6,428	Total N=10,934	Relative risk	p value
First 95: diagnosed % (95% CI)	91.6 (89.6,93.5)	94.9 (93.8,96.0)	93.7 (92.7,94.7)	80.1 (77.4,82.8)	90.7 (89.1,92.1)	87 (85.7,88.3)	1.08 (1.06,1.10)	<0.001
Second 95: on treatment % (95% CI)	95.9 (94.4,97.4)	98.1 (97.3,98.8)	97.3 (96.6,98.1)	90.2 (87.8,92.7)	88.1 (86.3,90.0)	88.8 (87.2,90.4)	1.10 (1.07,1.12)	<0.001
Third 95: VLS % (95% CI)	96.7 (95.5,97.9)	95.9 (94.9,96.9)	96.2 (95.4,97.0)	90.5 (88.1,93.0)	91.8 (90.4,93.1)	91.4 (90.3,92.5)	1.05 (1.04,1.07)	<0.001
Annual HIV incidence % (95% CI)	0.17 (0.00, 0.41)	1.11 (0.53, 1.68)	0.62 (0.31, 0.93)	0.85 (0.34, 1.35)	1.41 (0.78, 2.04)	1.13 (0.73, 1.53)	0.55 (0.30,1.01)	0.055

1049 EARLY CASE-FINDING IS STILL NEEDED IN THE HIV TEST-AND-TREAT ERA TO PREVENT MORTALITY

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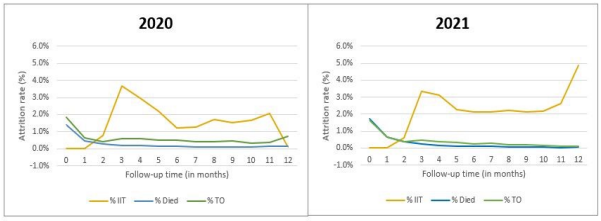
Background: Universal test and treat (UTT) for all people living with HIV (PLHIV) was recommended in 2016 by the World Health Organization and adopted by Kenya's national HIV program in 2017. We analyzed data from Kenya's HIV case surveillance (CS) system to determine mortality and interruptions in treatment (IIT) among PLHIV who initiated antiretroviral therapy (ART) after scale-up of UTT.

Methods: CS system is a repository of sentinel events among PLHIV (HIV diagnosis, linkage and retention on ART) derived from the Kenya National Data Warehouse (NDW) of electronic medical record containing data from over 80% of PLHIV on ART. We extracted data on outcomes in the first 12 months after enrollment among PLHIV enrolled in care between January to December in 2020 (97,176) and 2021 (84,103). Outcomes were: died, IIT, transfer-out (TO), and active on care. Clients who had IIT did not return for a clinic visit or ART refill for more than 90 days from the last scheduled visit. TO was a client who transferred out of a facility without a record of transfer-in (TI) to another facility. Clients without either a recorded death, IIT or who had a recorded TI after TO during the follow-up period were active on care. We used descriptive statistics to calculate monthly average and cumulative death, IIT and TO, accounting for censoring at the end of each month.

Results: Monthly average rate of death, IIT and TO in the first 12 months from enrollment for each cohort are shown in figure 1. Monthly attrition was similar in the two cohorts. While death and TO rates were highest in the first month from enrollment, IIT rates peaked between months three and five. Cumulatively, 3,044 (3.5%) and 2,859 (3.7%) of clients died in the first year of enrollment in 2020 and 2021, respectively. IIT accounted for the greatest cumulative rate of attrition in both cohorts. In the 2020 and 2021 cohorts, 19.1% (15,046) and 27.6% (14,021) of clients experienced treatment interruption, respectively. Cumulative rates of TO were 7.8% (6273) in 2020 and 5.0% (3.684) in 2021.

Conclusion: HIV CS data in Kenya shows high levels of attrition in the first 12 months of enrollment, with concerning trends in mortality and IIT. These findings suggest early diagnosis of HIV, before the onset of advanced disease, with intensive clinical management and adherence support to PLHIV newly initiating ART continue to be key areas for program strengthening. Examination of causes of death and IIT could identify additional areas for program improvement.

Figure 1: Monthly death, interruptions in treatment and transfer-out among PLHIV who initiated ART in 2020 and 2021, Kenya National HIV Case Surveillance



IIT: Interruption in treatment

TO: Transfer out

1050 RE-NORMING OF HIV TESTING IN TB CONTACT INVESTIGATION: A RANDOMIZED CONTROLLED TRIAL

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Background: HIV status awareness and linkage to care are critical for ending the HIV epidemic and preventing tuberculosis (TB), especially for close contacts of patients with TB, for whom HIV greatly increases the risk of incident TB and death. However, up to half of household contacts decline HIV test offers during contact investigation. We evaluated a brief social-behavioral norming strategy to increase acceptance of HIV testing during TB household contact investigation compared to standard strategies.

Methods: We carried out a household-randomized, controlled trial to evaluate the effect of the norming strategy among household contacts of pulmonary TB patients in Kampala, Uganda (ClinicalTrials.gov #NCT05124665). Community health workers (CHW) visited homes of TB index patients to screen contacts for TB symptoms and offer free, optional, oral HIV testing. Households were randomized to standard-of-care or intervention services. Contacts were eligible for inclusion if they were ≥15 years, self-reported not to be living with HIV, and living in a multi-contact household. The primary outcome, proportion of contacts accepting HIV testing, was analyzed using an intention-to-treat approach and a mixed-effects model to account for clustering by household. We assessed HIV testing yield as a proportion of all contacts tested.

Results: 328 contacts in 99 index patient households were randomized to the intervention and 224 contacts in 86 index patient households were randomized to the standard-of-care arm. In the intervention arm, 285 (87%) contacts met eligibility criteria. In the control arm, 187 (92%) contacts met eligibility criteria. Completion of HIV testing was higher in the intervention arm (98% versus 92%, difference +6%, 95%CI +2% to +10%, p=0.004). Yield of HIV testing was 2.1% in the intervention arm and 0.6% in the control arm (p=0.22).
Conclusion: A norming intervention significantly improved uptake of HIV testing among household contacts of patients with TB.

1051 MODELED IMPACT OF HIV SELF-TESTING FOR PrEP SCALE-UP ON DRUG RESISTANCE IN KENYA

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Background: Community-based oral pre-exposure prophylaxis (PrEP) provision has the potential to expand PrEP access. HIV self-testing (HIVST) can facilitate scale-up of PrEP delivery; however, HIVST can have lower field performance than standard provider-administered testing, potentially leading to inappropriate PrEP provision to persons with HIV and contributing to the development of drug resistance. The impact of using HIVST in PrEP scale-up is not well understood.
Methods: We parameterized an agent-based network model, EMOD-HIV, to project the impact of PrEP scale-up in western Kenya using either 1) provider-administered nucleic acid technique (NAT), 2) provider-administered rapid diagnostic tests detecting antibodies (Ab RDT), 3) capillary whole blood-based HIVST, or 4) oral-fluid HIVST, compared with a counterfactual of no PrEP. We assumed individuals 18-49 years entering a heterosexual partnership had a 75% probability of initiating PrEP (and continuing quarterly thereafter).
Results: In all HIV testing scenarios, the average estimated PrEP coverage was 29%, which was projected to avert 50% of HIV infections and 14% of HIV-related deaths over 20 years. Of an estimated 45 million PrEP initiations, the number of individuals with acute HIV infection who were inappropriately initiated on PrEP were 4,028 and 4,488 in the blood and oral HIVST scenarios respectively, compared to 988 in the Ab RDT and 92 in the NAT scenarios. The number of individuals with chronic HIV inappropriately initiated on PrEP were 7,645 and 13,653 in the blood and oral HIVST scenarios respectively, compared to 1906 in the Ab RDT and 141 in the NAT scenario. HIV infections with PrEP-associated nucleoside reverse transcriptase inhibitor (NRTI) resistance were 0.5% and 0.7% in the blood and oral HIVST scenario respectively, compared to 0.2% and 0.1% in the Ab RDT and NAT scenario, respectively. Accounting for background NTRI resistance, we found similar proportions of resistance across all scenarios (1.3% compared to 1.4% in the no PrEP scenario).
Conclusion: Increasing PrEP coverage has the potential to avert half of new HIV infections over 20 years. We project a low number of persons with HIV inappropriately initiated on PrEP due to the small number of acutely infected individuals. The population prevalence of NRTI resistance was similar across scenarios, largely due to the reduction in HIV (and thus HIV-related drug resistance) in the PrEP scenarios compared to the counterfactual of no PrEP.

1052 PREDICTORS OF PLWH NEWLY PRESENTING TO CARE WITH VIRAL SUPPRESSION IN LUSAKA, ZAMBIA

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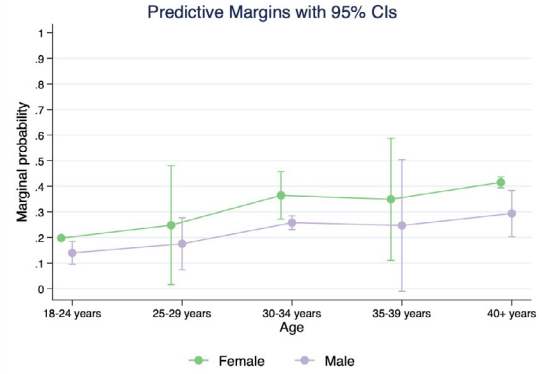
Background: As HIV treatment access in sub-Saharan Africa has expanded, it has become increasingly important to follow people living with HIV (PLWH) across multiple healthcare facilities to fully describe their HIV care journey. In Zambia, following PLWH across HIV care sites may be complicated by silent transfer. As part of a parent study on recent HIV infection, we measured viral load at baseline among PLWH newly presenting to care at two high-volume clinics in Lusaka, Zambia, and assessed predictors of potential silent transfer.
Methods: We conducted this sub-study using socio-demographic, clinical, and behavioral data from a cohort enrolled in the parent study from 2 June 2021–24 February 2022. We measured baseline HIV viral load as part of the national recent infection testing algorithm, and, for this analysis, used results to identify and describe PLWH newly presenting to care with viral suppression (i.e., potential silent transfers). We used mixed effects Poisson regression models to estimate prevalence ratios for viral suppression (at ≤1,000 copies/ml and ≤60 copies/ml) at presentation to care, and to construct marginal probability estimates by age category and sex.
Results: We included 248 individuals among whom 66 (27% [66/248]) had viral suppression defined at ≤1,000 copies (c)/ml and 53 (21% [53/248]) at ≤60 c/ml thresholds, respectively. Participants reporting widowed marital status had a significantly lower adjusted prevalence of baseline viral suppression (adjusted prevalence ratio [aPR]:0.28; 95% confidence interval [CI]:0.10, 0.83) compared to married participants, while participants age 40+ years had a significantly higher adjusted prevalence of suppression (aPR:2.10; 95% CI:2.08, 2.13) compared to participants aged 18-24 years. Participants reporting no formal education had a significantly higher adjusted prevalence of baseline viral load ≤1000 c/mL (aPR:1.63; 95% CI:1.52, 1.75). Finally, adjusted marginal probability for potential silent transfer was highest among older (40+ years) females (41.8%, 95% CI:39.3, 43.3%).
Conclusion: With a high proportion of PLWH newly presenting to care with baseline viral suppression, silent transfer is potentially a major issue in routine HIV programs. Our observations suggest characteristics of patients who may engage in silent transfer, allowing for program improvement to better identify and support these PLWH.

Figure 1: Marginal probability of new client being suppressed at presentation to HIV care by sex. Note: estimates based on model adjusted for marital status, educational attainment, month of testing, and facility; CI – confidence interval



1053 LATE PRESENTATION IN OLDER PWH IS ASSOCIATED WITH MORTALITY AND POOR IMMUNE RESPONSE

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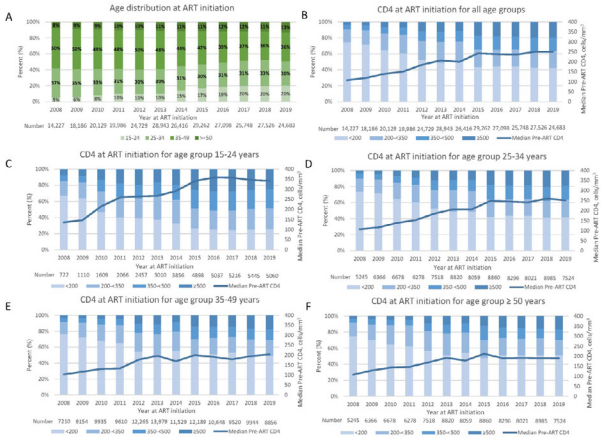
Background: HIV late presentation is increasingly observed among older people, although their healthcare access may be easier versus younger people. Data are limited regarding the burden of late presentation in older people in resource-limited settings, including whether they are at risk of poor HIV treatment outcomes.
Methods: We included people living with HIV (PWH) ≥15 years of age at ART initiation in the Thai National AIDS Program (NAP) from 2008 - 2019. Age and CD4 distributions in a 6-month window before ART initiation were assessed. Late presentation to care was defined as CD4 < 200 cells/mm3 at ART start. Immunological response (IR) was defined as achieving CD4 >350 cells/mm3 after ART initiation. Death was confirmed by National death registry linkage. We used Cox regression to investigate the association of age at ART initiation, late presentation to care and other demographic characteristics with IR and all-cause mortality.
Results: A total of 286,933 PWH (39% female) were included. Median (IQR) age at ART initiation was 36 (28-43) years; 18%, 26%, 29% and 27% started ART during years 2008-2010, 2011-2013, 2014-2016 and 2017-2019, respectively. Median CD4 at ART initiation was 191 (IQR 67-363) cells/mm^3. In 2019, the percent of late presentation was 26%, 42%, 49% and 52% in PWH aged 15-24, 25-34, 35-49 and ≥50 years, respectively. Median CD4 was lowest among PWH

aged ≥50 years over the time (**Figure 1B-F**). Median time from ART start to IR was 12 (IQR 6-27) months. PWH aged ≥50 years at ART start had a lower risk of IR (adjusted hazard ratio [aHR]: 0.81, 95%CI 0.79-0.82) after adjusting for CD4 at ART start, sex, within country residential region, HIV stage, ART duration and type. Over 1,669,397 person-years of follow-up (PYS), 37496 (13%) died. The crude death rate was 2.25 (2.22-2.27)/100 PYS; the median of time from ART initiation to death was 1.9 (IQR, 0.5-4.5) years. Starting ART aged ≥50 years (aHR: 2.59, 95%CI 2.48-2.71 vs. 15-24 years) and late presentation (aHR: 4.02, 95%CI 3.81-4.24) were significantly associated with higher mortality risk

Conclusion: Despite recent increases in HIV diagnoses among younger individuals, particularly young MSM in Thailand, the increasing proportion of older PWH who present late to care is concerning. The association of poor HIV outcomes in older PWH with late presentation signals an urgent need for implementation of targeted HIV testing to improve early diagnosis, and linkage to care for this vulnerable group.

Age and CD4 distribution at ART initiation



1054 POTENTIAL IMPACT OF LONG-ACTING ANTIRETROVIRAL THERAPY ON LOCAL HIV INCIDENCE

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Background: Long-Acting Antiretroviral Therapy (LAART) has demonstrated efficacy in virally suppressed people with HIV (PWH), and clinical trials are ongoing to evaluate its use in ART-naïve and ART-experienced, unsuppressed PWH. LAART has the potential to reduce non-adherence and promote retention in HIV care, but its potential effects on local HIV epidemics remain unclear.

Methods: We used the Johns Hopkins HIV Epidemiologic and Economic Model (JHEEM), a model of local HIV epidemics, to simulate the potential impact of rolling out LAART in four US cities: Atlanta, Baltimore, Los Angeles, and Miami.

We simulated LAART roll out at two levels for three separate indications, separately and in combination: (1) Transitioning either 25% or 50% of "durably suppressed" PWH (suppressed for ≥ 2 years on oral ART) onto LAART; (2) starting either 25% or 50% of ART-experienced PWH who were unsuppressed on LAART yearly; and (3) starting either 25% or 50% of ART-naïve PWH on LAART (instead of oral ART).

All interventions ramped up from 2025 to 2028 and continued through 2035. We assumed LAART had equivalent efficacy to oral ART, but randomly allowed LAART to range from equally as likely to keep PWH engaged in care to twice as likely across simulations.

Our primary outcome was the reduction in the projected number of incident HIV infections from 2025 to 2035. Secondary outcomes included proportion of PWH in care with resistance to antiretroviral medications after LAART.

Results: Simulations with no LAART projected incidence reductions ranging from 34% in Los Angeles to 65% in Baltimore between 2025 and 2035 (Table). Switching 50% of durably suppressed PWH yielded an additional reduction ranging from 1.2 percentage points in Los Angeles to 1.7 percentage points in Atlanta. Starting 50% of unsuppressed, ART-experienced PWH on LAART yearly yielded an additional reduction ranging from 1.3 percentage points in Atlanta to 3.4 percentage points in Los Angeles. Starting 50% of ART-naïve PWH on LAART yielded additional reductions ranging from 4.1 percentage points in Baltimore to 16.6 percentage points in Atlanta. Across all simulated interventions, the projected proportion of PWH in care in 2035 who would have ART resistance after LAART ranged from 0% to 2%.

Conclusion: LAART has the potential to modestly reduce HIV incidence in local epidemics. Its effect will depend strongly on the degree to which LAART promotes engagement in HIV care, particularly among unsuppressed PWH.

Table: Reduction* in HIV Incidence from 2025 to 2035 Under Interventions Rolling Out Long-Acting Antiretroviral Therapy for Different Indications Among People with HIV in Care

	No LAART	Proportion of Durably Suppressed PWH on LAART by 2028		Proportion of ART-Experienced, Unsuppressed PWH Started on LAART Yearly by 2028		Proportion of ART-Naive PWH Started on LAART Yearly by 2028		Combined Intervention	
		25%	50%	25%	50%	25%	50%	25%	50%
Atlanta-Sandy Springs-Alpharetta, GA	54% (47%-59%)	55% (48%-61%)	56% (49%-62%)	55% (48%-60%)	56% (48%-61%)	65% (59%-70%)	71% (65%-76%)	67% (61%-71%)	74% (67%-79%)
Baltimore-Columbia-Towson, MD	65% (61%-69%)	66% (62%-70%)	66% (62%-71%)	66% (62%-70%)	67% (62%-70%)	67% (63%-72%)	69% (65%-73%)	69% (64%-73%)	72% (67%-76%)
Los Angeles-Long Beach-Anaheim, CA	34% (25%-43%)	35% (27%-45%)	37% (28%-46%)	36% (29%-44%)	38% (31%-46%)	40% (31%-50%)	44% (35%-54%)	43% (35%-52%)	49% (41%-58%)
Miami-Fort Lauderdale-Pompano Beach, FL	43% (37%-48%)	44% (38%-49%)	44% (38%-50%)	44% (38%-49%)	44% (39%-49%)	48% (43%-52%)	51% (46%-56%)	49% (43%-54%)	54% (48%-59%)

*We report the mean and 95% credible interval across simulations

1055 IDENTIFYING PREFERRED PROGRAM DELIVERY ATTRIBUTES FOR LONG-ACTING INJECTABLE ART

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Background: As long-acting injectable antiretroviral therapy (LAI-ART) enters clinical practice, it is crucial to incorporate patient preferences into the design of LAI-ART delivery programs, especially among underserved people living with HIV (PLWH).

Methods: Using formative qualitative research, we developed a tablet-based discrete choice experiment (DCE) for administration in three urban HIV clinics (UCSF's Ward 86, Emory/Grady, University of Chicago), sampling for ≥100 patients per site and by care engagement status (less well engaged defined as detectable HIV RNA or no past-year HIV RNA with < 2 primary care visits). The DCE presented two hypothetical LAI-ART programs over 10 choice sets, including an 'opt-out' option. Designs were characterized by six attributes: injection visit location, extra visit with your HIV doctor at the injection, extra support services, visit length, extended hours on nights/weekends, and cost. Analyses were performed using the Hierarchical Bayes model to estimate zero-centered part-worth utility scores across all 13 attribute levels and generate mean attribute relative importance scores (RIS). We also examined preferences by population segments: age, gender, race/ethnicity, sexual orientation, housing status, past-month substance use, and care engagement status.

Results: From December 2021-May 2022, 370 patients completed the DCE with median age 46, 34% cis-female/gender minority, 59% Black, 13% Latinx, 44% heterosexual, 34% homeless/unstably housed, 19% with substance use, and 27% less well-engaged. Overall, cost (RIS 30.04%) and injection visit location (RIS 29.81%) were the most influential program design attributes, with preferred features being no cost and receiving injections at their HIV clinic. A cost of $40 and the mobile clinic option were the least preferred. Preferences for population segments were similar, except a slightly increased secondary preference for 'place where you stay' visit location was observed among those with substance use, 'Other' race/ethnicity, and the Emory site.

Conclusion: Assessing preferences of PLWH can inform a patient-centered approach to LAI-ART delivery. Among this predominantly racial/ethnic minority population, prioritizing that LAI-ART remains affordable and available at their HIV clinic could facilitate optimal uptake and delivery of this innovative treatment. However, sub-populations may further benefit from tailored approaches that provide injection visit location flexibility.

Table 1. Part-worth utilities (zero-centered values)a and relative importance scores (RIS) of LAI-ART delivery attributes and levels.

Table 1. Part-worth utilities (zero-centered values)[a] and relative importance scores (RIS) of LAI-ART delivery attributes and levels.

Attributes and Levels	Total Sample (n=370)	RIS (%) [sum to 100%]
Cost		*30.04%*
No cost	75.20	
$20	1.01	
$40	-76.21	
Visit Location		*29.81%*
Your HIV clinic	65.30	
Pharmacy separate from clinic	-6.98	
Place where you stay	0.66	
Mobile clinic that rotates locations	-58.98	
Extra Visit with My HIV Doctor		*13.77%*
Available	36.46	
Not available	-36.46	
Visit Length		*11.32%*
15 min	22.57	
45 min	6.58	
90 min	-29.15	
Extra Support Services		*9.00%*
Available	25.00	
Not available	-25.00	
Extended Hours		*6.06%*
Available	14.33	
Not available	-14.33	
None [b]	-195.65	

Notes:
a: Zero-centered part-worth utility scores imply the positive or negative magnitude of the participant's preference for the level choice in relation to the other level options within the same attribute. RIS (%) reflect the magnitude of influence that each attribute has on the respondents' decision-making process.
b: The "*None*" parameter represents the positive or negative magnitude in which a respondent is likely to select "None" (not willing to take LAI-ART in any scenario despite program configuration)

1056 UPTAKE AND OUTCOMES OF FIRST-LINE DOLUTEGRAVIR IN A LARGE SOUTH AFRICAN COHORT

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Background: South Africa has been introducing dolutegravir (DTG) into its large ART programme. We aimed to evaluate uptake and outcomes of first-line DTG, particularly in the context of initial safety concerns for women of child-bearing potential.

Methods: We analyzed de-identified, routine data from two separate cohorts at 59 primary care clinics in eThekwini Municipality, South Africa, from DTG introduction in Dec 2019 to Feb 2022. In the 'initiator' cohort, we used multivariable Poisson regression models with robust standard errors to evaluate the likelihood of being initiated on DTG vs non-DTG ART, and of attrition (loss to follow up/death) and viraemia >50 cps/mL, at 12 months post-initiation. For the 'transition' cohort we used multivariable Cox proportional hazards models to assess the transition from non-DTG to DTG-based first-line ART.

Results: Of 33,533 adults initiating ART, 21,362 (63.7%) were women, median age was 32 years (IQR 26-38), and 23,445 (69.9%) initiated DTG. Overall, DTG initiation was lower in women vs men (adjusted risk ratio [aRR] 0.77, 95% CI 0.75-0.79). While this difference by gender was largest in younger people (e.g. 15-24 years: women vs men aRR 0.68, 95% CI 0.0.62-0.74), it was not present in older age groups (≥55 years: aRR 0.94, 95% CI 0.80-1.09). Lower DTG initiation in women vs men occurred early in the rollout (Dec 2019-Feb 2020: aRR 0.30, 95% CI 0.27-0.34), disappearing by Jun-Aug 2021 (aRR 0.94, 95% CI 0.87-1.03). Among people with 12-months of follow-up, attrition (aRR 0.88, 95% CI 0.81-0.97) and viraemia (aRR 0.84, 95% CI 0.77-0.93) was lower in DTG initiators.

Of 177,082 adults already receiving first-line ART in Dec 2019, 122,004 (68.9%) were women and median age was 38 years (IQR 32-45). Median time on ART was 4.2 years (IQR 2.3-6.8) with the majority receiving efavirenz (98.6%) based first-line ART. By Feb 2022, 73.8% (118,253/160,171) of those remaining in care were transitioned to first-line DTG. Transition to DTG was lower in women (adjusted hazard ratio [aHR] 0.61, 95% CI 0.61-0.62) and in pregnancy (aHR 0.50, 95% CI 0.45-0.55). Again, the effect of gender on DTG transition was only evident in younger people, and before Jun-Aug 2021.

Conclusion: In this first, large analysis of first-line DTG use and outcomes in South Africa, pregnancy safety concerns likely led to young women being particularly disadvantaged, early in the rollout. As initiation with DTG was associated with better treatment outcomes, efforts to increase DTG use should be renewed.

Table: Univariable and multivariable analysis of DTG initiation and associations with 12-month attrition and viraemia, adjusted for potential confounders

Variable	Levels	LTF/Died	aRR (95% CI)	VL >50	aRR (95% CI)
DTG	Non-DTG regimen	1797 (20.8)	1.00	960 (17.5)	1.00
	DTG regimen	1685 (17.8)	0.88 (0.81- 0.97)	1026 (15.9)	0.84 (0.77 - 0.93)
Gender	Male	1307 (19.9)	1.00	846 (19.1)	1.00
	Female, not pregnant	1715 (18.2)	0.81 (0.74- 0.89)	951 (15.1)	0.84 (0.77 - 0.92)
	Female, pregnant	460 (22.1)	0.90 (0.79- 1.03)	189 (15.5)	0.85 (0.73 - 0.99)
Age (years)	55+	71 (14.5)	1.00	53 (14.8)	1.00
	45-54	210 (13.2)	0.83 (0.62- 1.11)	183 (15.7)	1.11 (0.84 - 1.48)
	35-44	829 (17.4)	1.08 (0.83- 1.41)	592 (17.8)	1.25 (0.96 - 1.62)
	25-34	1636 (20.0)	1.26 (0.97- 1.62)	854 (16.2)	1.29 (1.00 - 1.67)
	15-24	736 (23.8)	1.58 (1.21- 2.06)	304 (16.8)	1.56 (1.19 - 2.05)
TB at ART initiation	No TB	3240 (19.0)	1.00	1820 (16.2)	1.00
	Known TB	242 (22.6)	1.25 (1.07- 1.46)	166 (23.4)	1.10 (0.95 - 1.27)
Initiation CD4 count (cells/μL)	<200	575 (18.0)	1.00	547 (24.4)	1.00
	200-349	591 (17.9)	1.00 (0.89- 1.12)	403 (17.8)	0.73 (0.66 - 0.81)
	350-499	542 (18.9)	1.03 (0.90- 1.17)	269 (14.1)	0.60 (0.53 - 0.68)
	>=500	815 (18.4)	1.03 (0.91- 1.17)	325 (11.2)	0.47 (0.42 - 0.53)

1057 SEX DISPARITIES IN THE ROLLOUT OF DOLUTEGRAVIR IN LATIN AMERICA AND THE CARIBBEAN

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CCASAnet

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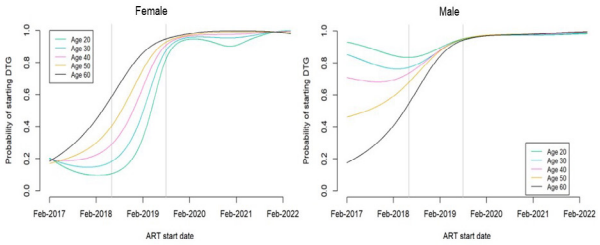
Background: The global warning of potential teratogenicity associated with antiretroviral therapy containing dolutegravir (ART-DTG) issued in May 2018 may have exacerbated sex inequalities in access to DTG, though this warning was later rescinded in July 2019. Therefore, we evaluated ART-DTG uptake by women with HIV in Latin America and the Caribbean (LAC), and its potential impact on HIV-1 viral load (VL).

Methods: ART-naive adult (≥16 years old) persons with HIV (PWH) receiving care at Caribbean, Central and South America network for HIV epidemiology (CCASAnet) sites, and starting ART after local DTG availability in Brazil, Chile, Haiti, and Honduras, were included. Estimated prevalence risk ratios of DTG use and VL suppression (< 50 copies/mL) during the first year after ART initiation were calculated using multivariable modified Poisson regression models adjusted for site, baseline tuberculosis, prior AIDS illness, and birth sex-age-calendar period interactions.

Results: Overall, 4115 PWH initiated ART after local DTG rollout (Brazil: 859, Chile: 578, Haiti: 2605, Honduras: 73). Among these, 1693 (41%) were female, and median age at ART initiation was 34 years (interquartile range 27-42). PWH starting ART before, during, and after the DTG warning numbered 313 (8%), 1191 (29%), and 2611 (63%), respectively. Overall, 3390 (82%) started ART-DTG. Prior to or during the DTG warning period, younger (age< 50) female was much less likely to start ART-DTG than younger male (aRR=0.75, 95% confidence interval (CI): 0.70-0.80) and older women (aRR=0.79, 95% CI: 0.71-0.87). In the post-DTG warning period, younger female was still slightly less likely to start ART-DTG than younger male (aRR=0.96, 95% CI: 0.94-0.98). Overall, of 2362 PWH with ≥1 year of follow-up and ≥1 VL test after ART initiation, 1953 (83%) were on ART-DTG and 2078 (88%) achieved VL suppression. Starting ART-DTG was associated with a higher likelihood of VL suppression (aRR=1.12, 95% CI: 1.05-1.19). In the post-DTG warning period, younger female had a similar likelihood of VL suppression as younger male (aRR=0.99, 95% CI: 0.94 -1.03), which was unchanged after controlling for DTG use (aRR=0.99, 95% CI: 0.95-1.04).

Conclusion: Despite the updated guidelines recommending DTG for all PWH, younger female in LAC continue to experience discrepancies in ART-DTG uptake, potentially impacting treatment outcomes. Therefore, assuring sex-equitable access to ART-DTG is needed in LAC.

Adjusted probability of starting a DTG based regimen by date and age for women and men



1058 MONITORING HIV DUAL-THERAPY IMPLEMENTATION AS REGIMEN SIMPLIFICATION POLICY IN BRAZIL

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Background: Long-term exposure to three-drug regimens has been associated with toxic effects such as renal and bone toxicity related to tenofovir (TDF), cardiovascular and metabolic disorders for other ITRN. Since 2019, to minimize toxicity, Brazil recommends two-drug regimens (2-DRs) (3TC+DTG or 3TC+DRVr) for those already on antiretroviral therapy (ART), with undetectable viral load (VL) and for whom the use of tenofovir is contraindicated. Using real life data, we aimed to describe 2-DRs user profile and analyze the virological response among people living with HIV (PLHIV) in use of dual-therapy.

Methods: We obtained MoH electronic records, from 2019 to 2021, on ART prescription, HIV viral load (VL) and demographic (age, sex, geographic region and ethnicity) data. We used descriptive statistics to quantify the use of 3TC+DTG and 3TC+DRVr and access VL suppression during HIV dual-therapy.

Results: From 2019 to 2021, 22,401 PLHIV used 3TC+DTG or 3TC+DRVr regimens, of which 99% were ART-experienced. Of those starting 3TC+DTG, 72% was previously using DTG-containing regimens; while among those starting 3TC+DRVr, 50% was taking DRVr-based ART. Undetectable VL (VL ≤ 49 copies/mL) before starting 2-DRs was observed in 96% in 2019, 97%, in 2020 and 99%, in 2021. Up to 94% of those under 2-DRs were 30 years or older, 50% white/yellow, 29% black, and 58% lived in the Southeast region. Sex ratio (M/F) raised from 1.8 in 2019 to 2.0, in 2021. 3TC+DTG regimen was the preferred choice, representing 72% of first 2-DRs dispensations in 2019, and 91% in 2021. From 2019 to 2021, viral suppression raised from 92% to 97% when in use of 3TC+DTG; and 85% to 93%, for 3TC+DRVr.

Conclusion: Dual-therapy regimens containing 3TC plus DTG or DRVr given to ART-experienced PLWHIV, with undetectable VL, provides a reasonable option for simplifying regimens, reaching satisfactory levels of viral suppression. This study further illustrates how monitoring of HIV care indicators is an effective way to validate and/or qualify health policies to guarantee proper health care for PLWHIV.

1059 A NATIONWIDE OPTIMIZATION STRATEGY USING SECOND GENERATION InSTIS IN MEXICO

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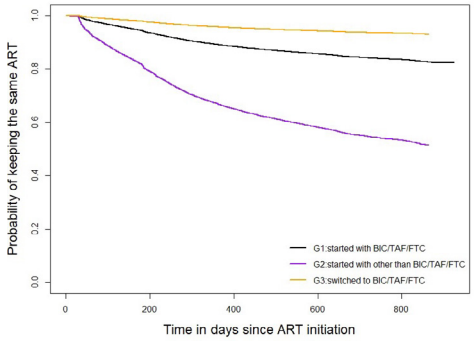
Background: In Mexico until 2018, first line antiretroviral therapy (ART) was mainly based on either efavirenz-containing regimens (despite reports of high pre-treatment resistance levels); or on other regimens with drugs no longer considered optimal -protease inhibitors (PIs), nevirapine, maraviroc and first-generation integrase inhibitors (InSTIs)- all of them amenable to be switched to 2nd generation INSTIs as a single tablet regimen (STR). We aimed to evaluate a national optimization strategy through a rollout program using second-generation INSTI-based STR both for ART initiation and switch.

Methods: SALVAR (National System for Antiretroviral Surveillance and Administration) database was used for the analysis. We included adults registered in SALVAR, who started on ART or switched to BIC/TAF/FTC, from June 1st 2019 to June 30th 2021. We categorized them as "started BIC/TAF/FTC" (G1), "started other than BIC/TAF/FTC" (G2) or "switched to BIC/TAF/FTC" (G3). We calculated the proportion of participants with viral suppression (VS) (< 40 copies/ml) at 6 months after ART initiation by group. We described VS and ART change by group at end of follow-up and fitted a Cox model to compare durability by group, sex and age. Durability was defined as maintaining the same ART versus changing ART regimen, LTFU or death.

Results: A total of 74,137 PLWH were included in the analysis and followed for a median of 1.6 years (IQR: 0.8-2.1), 23,786 (31%) were classified as G1, 5352 (7%) as G2 and 44,999 (61%) as G3. Of those classified as G2: 2543 (47.5%) were started on NNRTI's, 2021 (37.7%) on other INSTIs and 602 (11.2%) on PIs. The last regimen before switch in G3 group, was based on NNRTI's in 67%, PI's in 19%, other INSTIs in 10% and other regimens 4%. VS at 6 months after initiation or switch was observed in 87% individuals in G1, 80% in G2 and 98% in G3. At end of follow-up, 80% of those in G1, 56% in G2, and 87% in G3 remained with VS; < 1% of individuals changed to a different regimen in G1, 4% in G2 and 1% on G3. Durability of ART regimen by group is shown in Figure 1. At initial evaluation, 31% of all individuals were on a STR regimen, vs. 96% at the end of follow-up.

Conclusion: In this real-life analysis, we observed that second generation INSTIs represent an effective and durable option for treatment optimization in the Mexican National treatment program.

Figure 1.- Durability of the same ART regimen by group.



1060 PEOPLE FAILING FIRST-LINE REGIMENS REMAIN AT RISK FOR ADVERSE SECOND-LINE OUTCOMES

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Background: People living with HIV (PLH) who have trouble maintaining adherence to 1st line regimens may develop virological failure requiring a regimen switch, but continued poor adherence remains a challenge. We assessed 2nd line treatment outcomes in the Thai National AIDS Program (NAP).

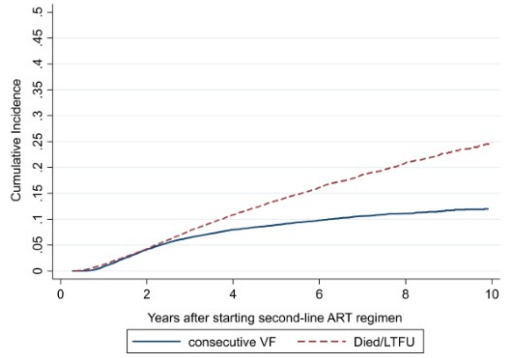
Methods: PLH aged ≥ 18 years starting 1st line (non-nucleoside reverse transcriptase inhibitor-based) ART from 2008 to 2019, who subsequently switched to 2nd-line protease-inhibitor (PI)-based ART after virological failure were studied. Virological failure (VF) after 2nd-line switch was defined as viral load ≥1000 copies/mL, two consecutive times after switch. Competing risks regression was used to calculate the VF cumulative incidence, and sub-distribution hazard ratios (SHR), for associations between individual characteristics and VF, with lost to follow-up (LTFU) and death as competing events. LTFU was defined as not attending clinic >12 months; mortality was confirmed by National death registry linkage.

Results: Of 299,261 people initiating ART, 29,061 (9.7%) switched to a 2nd line regimen after 1st line failure. Most (61%) were male with median age of 37 (IQR 31-44) years, median switch CD4 cell count of 149 (IQR 49-300) cells/mm^3 and median 1st line ART duration of 3.6 (IQR 1.8-5.8) years. 2nd line regimens were ritonavir booster lopinavir (LPV/r) (96%), atazanavir (2%) or darunavir (DRV/r) (2%). Overall attrition after 2nd-line switch was death: 4,606 (16%) and LTFU: 5,316 (18%). The cumulative incidence of VF in 25,696 PLH with viral load testing after switch was 0.85% (95% CI 0.74-0.97%), 4.15% (95% CI 3.90-4.41%), 7.96%

(95% CI 7.60-8.34%) and 12.10 (95% CI 11.42-12.74), at 1, 2, 4 and 10 years, respectively (Figure). VF was more common in females (aSHR 1.70 (95% CI 1.56-1.86)), younger PLH (aSHR in those aged 18 to < 25 years 2.84 (95% CI 2.33-3.47 vs >50 years)), and lower time-updated CD4 cell count. Compared to those with CD4 ≥350 cells/mm^3, the aSHR 10.35 (95% CI 9.29-11.53) in those with CD4 < 200 and 3.25 (95% CI 2.83-3.73) in those with CD4 200 - < 350. VF in those taking DRV/r was less likely compared to LPV/r-based regimens.

Conclusion: VF rate after switching to 2nd line PI-based regimens was approximately 12% at 10 years, but rates of death and LTFU were high. VF switch was more common in younger adults and females, possibly due to non-adherence/intolerance to LPV/r. A multidisciplinary support system is needed for this population.

Cumulative incidence of second-line ART regimen failure (consecutive VF)



1061 PREDICTORS OF TRANSITIONING TO A FIRST-LINE DOLUTEGRAVIR REGIMEN IN WEST AFRICA

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IeDEA West Africa Collaboration

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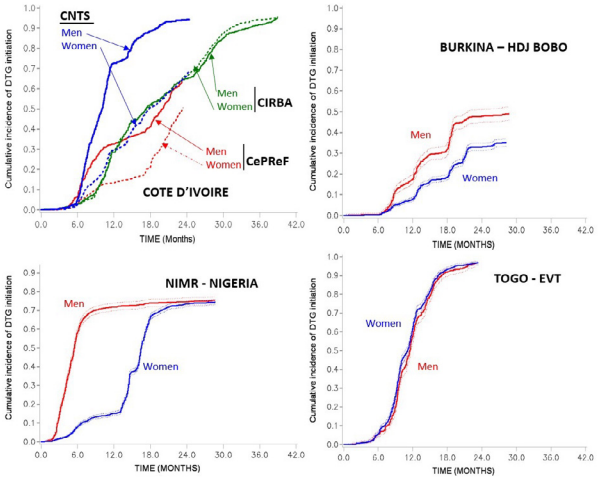
Background: Since 2019 Dolutegravir (DTG)-based antiretroviral therapy (ART) is recommended by the world health organization for all adults living with HIV (ALHIV) because of his tolerability and high barrier to drug resistance. Initial safety concerns in women of child bearing age have resulted in an initially lower transition in women. As most West African countries have transitioned to DTG, longer term predictors are not well documented. We describe the incidence and predictors of DTG transition (DT) in ART experienced ALHIV in West Africa.

Methods: We included all ALHIV from 6 adult cohorts in the IeDEA West Africa collaboration in Côte d'Ivoire (CePReF, CNTS & CIRBA), Burkina, Togo, and Nigeria with at least one documented visit since January 2019. Baseline follow-up was defined as the date of the DTG introduction at site-level (DISL). Patients were followed until database closure. We computed the cumulative incidence functions for DT over the follow-up period by sex in each cohort. Predictors of DT were explored using cause specific Cox proportional hazard models (with transfer, death, or loss to follow-up as competing risk). The overall follow-up time was divided into two periods (2 cox models) considering proportional hazard assumptions for sex [Early period: baseline to month 15 (P1) and late period: month 15 to database closure date (P2)].

Results: A total of 23,455 ART experienced ALHIV were included; 31% were men. Median age at DISL was 45 years (IQR: 39-52) and median follow-up was 8 years (IQR: 4-11). Overall, 14,529 (63%) DT occurred, 70% in men and 58% in women. DTG transition was heterogeneous between and within countries; characterized in some cohorts (CePReF, CNTS, NIMR) by an early steep increase in men compared to women followed by catch-up in later period among women, a persistent gap in Burkina while no difference between sex was observed in others cohorts (CIRBA, EVT-TOGO) (fig.1). Adjusted for cohort, age, ART regimen and virologic status; being a man was associated with a higher probability of DT (aHR : 2.2, 95%CI : 2.1-2.3) in P1 and a lower probability in P2 (aHR for men : 0.8, 95%CI : 0.7-0.9). In addition, DT was higher in younger (< 50 years) and virologically suppressed ALHIV during both periods.

Conclusion: In West Africa, early sex differences in DTG transition most likely related to the perinatal safety signal is gradually closing despite heterogeneity according to HIV cohorts. A continued monitoring of DT will contribute to universal and equal access to ART.

Figure 1. Cumulative incidence function of Dolutegravir initiation by sex according to participating cohorts & countries. The IeDEA West Africa Collaboration 2019-2022



1062 TRANSITION TO DOLUTEGRAVIR-BASED ART IN LOW- AND MIDDLE-INCOME COUNTRIES IN IeDEA

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International Epidemiology Databases to Evaluate AIDS (IeDEA) Consortium

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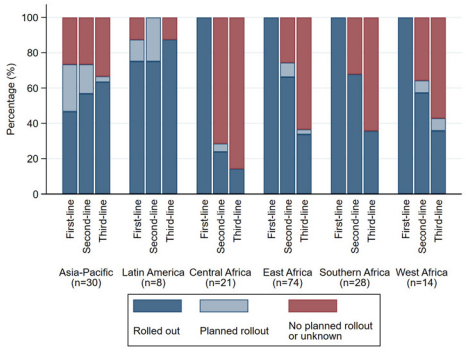
Background: The World Health Organization recommended dolutegravir (DTG)-based antiretroviral therapy (ART) for first-, second-, and third-line regimens in mid-2019 due to its tolerability and increasing levels of resistance to other ART regimens. The proportion of HIV treatment sites in low- and middle-income countries (LMICs) that have rolled out or plan to roll out DTG-based ART is unknown.

Methods: Between September 2020 and March 2021, the International epidemiology Databases to Evaluate AIDS (IeDEA) research consortium surveyed 179 HIV treatment sites in 35 LMICs to document the transition to DTG-based ART regimens and related clinical testing practices. Descriptive statistics were stratified by region.

Results: Ninety-eight percent (175) of sites completed the survey, of which 78% (137) were from 21 countries in Africa, 17% (30) from 8 countries in the Asia-Pacific, and 5% (8) from 6 countries in Latin America. DTG-based ART rollout or planned rollout by 2021 for first-, second-, and third-line regimens was reported by 95% (166), 68% (119) and 42% (73) of sites, respectively. 37% (64) of sites reported rollout or planned rollout for all three ART regimen lines; 31% (42) in Africa, 53% (16) in the Asia-Pacific, and 75% (6) in Latin America. While 97% (170) of sites reported routine viral load (VL) monitoring for patient care, 79% (139) reported that switching to DTG-based ART was based on VL testing [83% (114) in Africa, 60% (18) in the Asia-Pacific, 88% (7) in Latin America], with 70% (97) of these sites relying on VLs obtained in the prior 6 months, 20% (28) within 12 months, and 10% (14) reporting criteria that varied by patient group. 79% (139) of sites reported that HIV-1 genotypic drug resistance testing was available for routine patient care [78% (107) in Africa, 87% (26) in the Asia-Pacific, 75% (6) in Latin America], however, only 15% (26)

reported performing drug resistance testing at the time of switch to DTG-based ART [12% (16) in Africa, 30% (9) in the Asia-Pacific, 13% (1) in Latin America].
Conclusion: Although global HIV treatment guidelines recommend DTG-based ART for first-, second-, and third-line ART to mitigate increasing drug resistance levels, fewer than half of sites in our large global HIV consortium had or planned to fully implement these recommendations, with substantial regional variation. Incomplete rollout of DTG-based ART and suboptimal drug resistance monitoring may impede efforts to reduce HIV drug resistance, particularly in high HIV-burden settings.

Proportion of sites that have rolled out or plan to roll out dolutegravir-based antiretroviral therapy by 2021 for first-, second- and third-line ART in low- and middle-income countries in IeDEA.



1063 NATIONAL TRENDS IN ART REGIMENS FILLED FOR PEOPLE WITH HIV ON MEDICARE: 2013-2019

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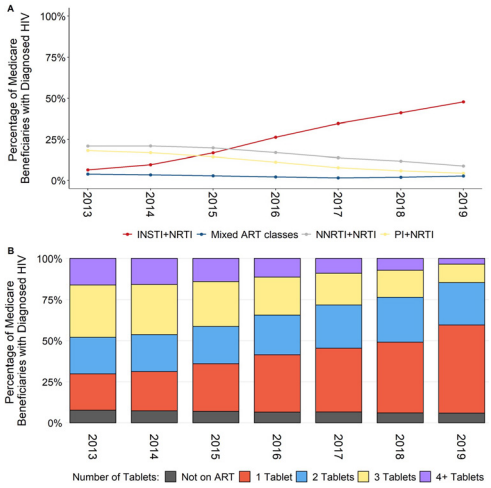
Background: Substantial improvements in ART regimens have occurred over the past decade, contributing to improved viral suppression and outcomes among PWH. Despite national attention on the rapidly evolving field of HIV therapeutics, empirical evidence on changes to the types of ART regimens filled by PWH over the past decade are unknown at a national level. Medicare claims data offer a unique approach to evaluate changes in prescribing patterns over time, which is increasingly important as PWH continue to age into the Medicare program.
Methods: Using a 20% sample of Medicare fee-for-service claims data (2013-2019), we identified PWH using the validated Medicare Chronic Condition Data Warehouse algorithm. We next used the Medicare Part D file to confirm filled ART prescriptions in each year. We identified individual ART regimens and grouped brand names with generics if they existed. We also categorized ART regimens into 1-, 2-, 3-, or 4+-tablet regimens. For PWH who switched regimens within a calendar year, we assigned them to the ART regimen that was filled for the most months during the year. We evaluated trends in the proportion of PWH who filled specific ART regimens and number of tablets in the regimen. We also identified PWH who did not fill ART prescriptions in a calendar year.
Results: Between 2013 to 2019, there were 36,955 unique Medicare beneficiaries with HIV in the study sample. The most common ART regimens in 2013 were EFV/FTC/TDF (15.9%), ATV+RTV+TDF/FTC (8.0%), and DRV+RTV+TDF/FTC (6.0%), which declined substantially by 2019 to 3.5%, 0.1%, and 0.4%, respectively (Figure). In 2019, the most common ART regimens among Medicare beneficiaries were INSTI-based: BIC/FTC/TAF (15.8%), ABC/DTG/3TC (11.1%), and EVG/COBI/FTC/TAF (10.6%). The proportion of PWH on 1-tablet regimens increased from 22.1% in 2013 to 53.5% in 2019, while the proportion of PWH on 4+-tablet regimens declined from 16.1% to 3.3%. The proportion of PWH who filled no ART prescriptions declined from 7.8% (2013) to 6.0% (2019).
Conclusion: Among PWH in Medicare, a major shift in ART regimens occurred rapidly within a seven-year period, with the majority of Medicare beneficiaries on INSTI-based ART and 1-tablet regimens by 2019. However, more than 5% of PWH with Medicare had no ART regimens filled under Part D despite recommendations for universal ART.

National Trends in Filled ART Prescriptions Among Medicare Beneficiaries with HIV: (A) Categories of ART Regimens and (B) Numbers of Tablets in ART Regimen



1064 NEW HIV DIAGNOSES IN THE SETTING OF PUBLICLY FUNDED PrEP IN BRITISH COLUMBIA, CANADA

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Background: In British Columbia (BC), Canada, antiretrovirals (ARVs) for HIV treatment and prevention are publicly funded and centrally distributed. In January 2018, tenofovir-emtricitabine based PrEP became available to eligible BC residents deemed at high risk of HIV infection. We characterize new HIV diagnoses in the first 4.5 years of the BC PrEP cohort.
Methods: Eligible persons enrolled in the PrEP program between 1-Jan-2018 and 30-Jun-2022 and subsequently diagnosed with HIV were included (followed to 31-Jul-2022). Client demographics, HIV risk, PrEP dispensing, HIV testing, viral load (pVL), genotypic resistance testing, and ARV treatment (ART) were described. New HIV diagnosis rate in clients dispensed PrEP at least once was calculated.
Results: Of 9737 clients enrolled in the PrEP program, 32 (0.3%) were diagnosed with incident HIV. All 32 were cis-men who have sex with men (MSM) with median (Q1-Q3) age 30 years (25-35), 28 (88%) resided in Greater Vancouver, 31 (97%) reported a HIRI-MSM score ≥10 [median 25 (19-30)] and 31 (97%) were prescribed daily (vs. on-demand) PrEP. Median (Q1-Q3) time from enrolment to HIV diagnosis was 374 days (291-790) with a gap from prior HIV test to diagnosis of 190 days (89-314). Of 27 clients diagnosed after ≥1 PrEP dispensing, median (Q1-Q3) proportion of days covered by PrEP was 36% (14-60), with 240 days (96-326) terminal lapse in PrEP supply (based on daily dosing). The new HIV diagnosis rate in 9441 clients ever dispensed PrEP was 0.13 per 100 person-years (PY) (95% CI, 0.08-0.18) in 20,578 PY of follow-up.
Of the 32 new HIV diagnoses, 10 were acute infections, median (Q1-Q3) time to ART initiation was 7 days (4-12) with 18 starting 4-drug ART (PI,INSTI, 2NRTI) and 14 with 3-drug ART (12 INSTI-based, 2 PI-based). Median (Q1-Q3) baseline CD4 was 600 cells/μL (432-765), fraction 32% (28-38), and pVL was >100,000 copies/mL in 53%. Mutations conferring reduced susceptibility to NRTI (n=2) or NNRTI (n=7) were detected in 9 of 31 tested. All NRTI resistance was due to M184V mutations in clients with active PrEP prescription at HIV diagnosis. Of the 29 new diagnoses with follow-up >60 days, 26 (90%) achieved pVL< 40 copies/mL within 6 months.
Conclusion: New HIV diagnoses in a centralized, publicly funded, eligibility-based PrEP program remain low. To date, no cases of emergent PrEP-related tenofovir resistance have been observed within our cohort. Centralized HIV treatment and prevention facilitated rapid ART initiation in PrEP clients with new HIV diagnosis.

1065 ESTIMATING THE EPIDEMIOLOGICAL IMPACT OF FLORIDA'S INTEGRATED HIV CARE PLAN IN MIAMI

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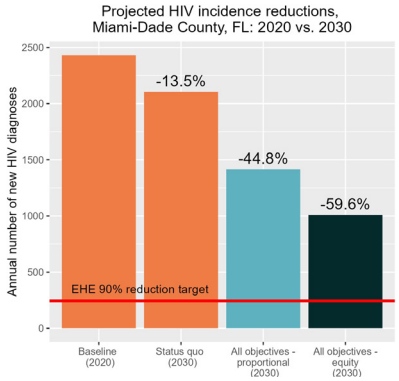
Background: The US Ending the HIV Epidemic (EHE) initiative has set goals to reduce national HIV incidence by 90% by 2030 and to address the disproportionate burden of HIV among Black and Hispanic/Latinx populations. The statewide HIV planning body for Florida recently released its 2022-2026 "Integrated HIV Prevention and Care Plan", which lists strategies to increase access and uptake of HIV prevention and treatment interventions to reach the national EHE goals. Using a case study, we estimate and compare the epidemiological impact of achieving targets individually and jointly and sustaining them from 2022-2030.

Methods: We adapted an HIV transmission model calibrated to Miami-Dade County and adjusted the scale of HIV testing, PrEP, and ART interventions to simulate the effects of reaching targets that could be modeled from Florida's 2022-2026 integrated plan. We defined a comparator scenario based on estimates of current population characteristics and health service access levels in Miami and set 2020 as a reference point to match the EHE timeline. Multiplicative factors were applied to reach the rate changes specified by the plan's current and target data indicator values. Resulting increases to service access were assumed (a) proportional to existing access levels across White, Black, and Hispanic/Latinx populations, and (b) equitably redistributed across racial/ethnic groups according to their numbers of new diagnoses in 2019. The primary outcome for each approach was HIV incidence reduction from 2022-2030.

Results: Compared to 2,432 infections in 2020, incidence reductions in 2030 from sustaining each of the targets in Miami would range from 1,018 (-41.8%) cases under the proportional approach to 1,423 (-58.5%) with the equitably redistributed approach (Figure 1). The single most influential strategy was reducing new HIV diagnoses in Hispanic/Latinx men who have sex with men via increased PrEP uptake, which dropped 2030 incidence to 1,537 (-37%) cases. Achieving the current integrated care plan goals would not achieve the EHE incidence reduction target (< 243 new cases in 2030).

Conclusion: Achieving the goals of Florida's current integrated care plan would reduce HIV incidence dramatically in Miami, however further efforts are required to achieve EHE targets by 2030. Structural changes in service delivery and a focus on effective implementation of available interventions, particularly among Black and Hispanic/Latinx populations, will be crucial to overcoming the HIV epidemic in Miami, Florida.

Figure 1. Projected HIV incidence reductions, Miami-Dade County, FL: 2020 vs. 2030



1066 AN RCT OF HOME-BASED CARE TO REDUCE POSTHOSPITAL MORTALITY IN SOUTH AFRICA: HOMELINK

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*Presented at CROI by a nonauthor colleague

Background: In sub-Saharan Africa 23% of people living with HIV (PLWH) die 6 months after discharge from a hospital. Failure to engage in care post-hospitalization is associated with mortality. We evaluated whether a series of structured post-hospitalization home visits would reduce mortality among recently discharged PLHIV in South Africa.

Methods: We designed a home visit package with up to 6 home visits starting 1-week post-hospitalization and every 2 weeks as required thereafter. The home visit team consisted of a professional nurse and a counsellor; they used a structured assessment algorithm to evaluate participants' social and medical needs, obtained direction from a doctor for further guidance, collected specimens for laboratory testing, or referred the participant for further evaluation. We compared this intervention to care as usual in a pilot randomized trial conducted at a single hospital in South Africa. The primary goals of the study were to determine feasibility and acceptability and identify opportunities to improve the home visit intervention. We report effectiveness for PLWH based on the primary outcome of all-cause mortality 6 months after discharge from hospital.

Results: We enrolled 125 PLWH who were randomized 1:1 to home visit intervention or care as usual; 14 were late exclusions because they died prior to discharge (n=13) or had a prolonged hospital stay (n=1). In the 111 PLHIV included in the analysis, the median (interquartile range [IQR]) age was 39 (33, 48) years, 69% were women, the median duration of the index hospitalization was 7 (3, 12) days, and primary reasons for the index hospitalization included TB (31%), heart and/or lung related diseases (22%), non-TB/COVID infections (25%), and anemia (15%). Most [96% (n=53/55)] intervention arm participants received ≥1 home visits. By six months 14 (13%) participants died: 4 (7%) in home visit intervention arm and 10 (18%) in the care as usual arm (p=0.09). A similar proportion of readmissions occurred by arm: 20 (36%) in the home visit arm and 22 (39%) in care as usual.

Conclusion: Home visits done after discharge from hospital provided care services to an extremely vulnerable group of PLWH at very high mortality risk . We demonstrated both feasibility and preliminary efficacy of delivering post-hospital visits. Structured home visits appear to be a promising approach that would benefit PLWH. Larger studies in diverse populations with cost effectiveness components are required.

1067 IMPROVING RE-INITIATION IN CARE AMONG MEN WITH HIV IN MALAWI: TWO RANDOMIZED TRIALS

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Background: Treatment interruption (TI) is a major contributor to poor HIV outcomes among men living with HIV (MLHIV). We report and compare results from two trials examining the impact of male-specific counseling (MC) and home ART on ART (re-)initiation in Malawi.

Methods: We implemented the ENGAGE and IDEaL randomized trials in 22 Malawian health facilities (ClinicalTrials.gov#NCT04858243 and # NCT05137210). Trials have the same eligibility criteria and recruitment strategy: MLHIV; >15 years; and disengaged from HIV care (defined as never initiated or currently experiencing TI after initiation); were recruited through community tracing. In ENGAGE (10 facilities), randomization was 1:1 to MC + monthly home ART distribution for 3-months, or standard of care (SOC) counseling + routine facility ART. In IDEaL (12 facilities), randomization was 1:1:1 to MC + routine facility ART, MC + one-time home ART distribution, or stepped services every two-weeks until clients achieved primary outcome, starting with MC + advanced psychosocial counseling + one-time home ART. Primary outcome for this analysis is ART (re-)initiation at 2-months. We conducted protocol driven analyses to compare outcomes within each trial, using intention-to-treat

analysis. We then conducted ad-hoc analyses to compare interventions from IDEaL to SOC from ENGAGE. In-depth interviews were conducted with a subset of men.

Results: 1149 MLHIV out of treatment were enrolled in IDEaL (n=515) and ENGAGE (n=634) between August 2021-September 2022. In ENGAGE, (re-) initation was significantly higher in the MC+Home ART (3-month) vs SOC arm (RR:1.28 [95%CI 1.19-1.36]). In IDEaL, (re-)initiation was equally high across all intervention arms with no significant differences (94-98%). In ad-hoc analyses, compared to ENGAGE SOC, (re-)initiation was significantly higher across all IDEaL intervention arms: MC+Facility ART (aRR:1.28 [95%CI 1.16 -1.42]); MC+Home ART (1-month) (aRR:1.28 [95%CI 1.14 -1.42]); and Stepped intervention (aRR:1.30 [95%CI 1.03-1.88]) (Table). All interventions had high satisfaction (~96%) and low unwanted disclosure (~1%). Men in interviews (N=45) valued being active participants in HIV services and desired ongoing relationships with healthcare workers. To promote retention men requested longer drug dispensing and increased privacy at facilities.

Conclusion: Male-specific counseling alone and combined with home-based ART improved men's ART (re-)initiation in Malawi. Longer term outcomes will indicate if ART gains will be sustained.

HIV outcomes for MLHIV with treatment interruption across interventions in Malawi: reported by MLHIV (n=1149)

	ENGAGE Trial		IDeAL Trial		
	SOC n (%)	MC+ Home ART (3-month) n (%); aRR (95% CI)^	Male Counseling (MC) n (%); aRR (95% CI)^^	MC+ Home ART (1-month) n (%); aRR (95% CI)^^	Stepped MC + Home n (%); aRR (95% CI)^^
N	311	323	179	172	164
Demographics					
Median Age (IQR)	39 (32-46)	39 (31-47)	39 (31-46)	39 (32-46)	38 (33-45)
Previously initiated ART	297 (95.5)	304 (94.4)	163 (91.1)	156 (90.7)	156 (95.1)
Study Outcome					
Initiated	234 (75.2)	310 (96) 1.28*** (1.19-1.36)	173 (96.6) 1.28*** (1.16-1.42)	161 (93.6) 1.28*** (1.14-1.42)	160 (97.6) 1.30*** (1.17-1.43)
Unwanted status disclosure[t]	4 (1.3)	3 (0.9)	4 (2.2)	1 (0.6)	2 (1.2)
Potential mediating factors					
Disclosure to Others	68 (21.9)	88 (27.2) 1.25 (0.95 - 1.64)	59 (33) 1.51** (1.10 - 2.07)	47 (27.3) 1.25** (1.02-1.52)	50 (30.5) 1.39** (1.03-1.88)
Internalized Stigma	150 (48.2)	139 (43) 0.89 (0.75 - 1.06)	59 (33) 0.68 (0.43 - 1.10)	46 (26.7) 0.89 (0.78 - 1.02)	57 (34.8) 0.72 (0.44 - 1.17)
Satisfaction with HCW interaction		307 (95)	178 (99.4)	169 (98.3)	161 (98.2)

[t]randomized comparison with SOC arm from ENGAGE Trial; ^^non-randomized comparison with SOC arm from ENGAGE Trial. adjusted for facility-level clustering
* p-value <0.01; ** p-value <0.05; *** p-value <0.001; [+] risk ratios not conducted due to small sample size in SOC arm or no SOC data

1068 RE-ENGAGING PERSONS WITH HIV OUT OF CARE: RADICAL CHANGE IS NEEDED

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Background: Despite improvements in the care continuum approximately 35% of persons with diagnosed HIV (PWH) in the US were not virally suppressed in 2020. Interventions to improve re-engagement with care are needed. We report interim data for Instacare: a prospective randomized trial evaluating the behavioral intervention "60-minutes-for-health" combined with rapid restart of antiretroviral therapy (ART) on re-engagement with care.

Methods: PWH in San Diego, California who were not on ART for the previous 2 weeks and either out of care or poorly engaged with care (PWH-OOC) were randomized to "60-minutes-for-health" or control at study entry. All participants were offered rapid ART within 7 days of contact. Case management with linkage to care, adherence counseling and financial counseling were provided over the first 4 weeks. Study follow up was performed at 4, 24 and 48 weeks. The primary outcomes were viral suppression (VL ≤50 copies/ml) and engagement with care (2 HIV care visits ≥90 days apart) at 24 weeks.

Results: Between November 2020 and August 2022, 51 participants were enrolled with demographics and baseline data shown in **Table 1**. The most common reported reasons for previously stopping ART were housing instability (29.8%), insurance barriers (27.7%), mental health barriers (25.5%) and substance use barriers (25.5%). 28 persons (54.9%) reported being too sad or depressed to seek HIV care, 25 (49.0%) had previous mental illness diagnosis and 44 (86.3%) had a history of substance use. Among 31 participants on study for at least 24 weeks, only 15 (48%) participants attended week 24 follow up with just 11 participants (35.5%) achieving viral suppression. Among the 15 participants with follow up 5 (62.5%) in the intervention arm and 6 (66.7%) from the control arm were virally suppressed. Among 33 participants with ≥36 weeks on study or who had attended their week 24 visit, 6/16 (37.5%) in the intervention group and 10/17 (58.8%) in the control group were engaged with HIV care.

Conclusion: This randomized trial of a behavioral intervention to improve re-engagement in care among PWH-OOC did not show a significant difference in HIV primary care attendance or viral suppression at 24 weeks. The loss-to-follow up was substantial (>50%) and highlights the challenges of performing studies in this hard-to-reach population. It is probable that very significant additional resource allocation will be required to improve engagement in care and viral suppression for this treatment experienced population.

Table 1: Baseline demographics of participants in Instacare: a prospective randomized study of the behavioral intervention "60-minutes-for-health" and rapid antiretroviral therapy.

Variable	Controls	Intervention 60-Minutes-for-health	Total
Gender, N (%)			
Male	22 (84.6)	24 (96.0)	46 (90.2)
Female	3 (11.5)	0 (0.0)	3 (5.9)
Trans-female	1 (3.8)	1 (4.0)	2 (3.9)
Years of age, mean (sd)	43.5 (12.6)	46.0 (9.7)	44.8 (11.2)
Race, N (%)			
White/Caucasian	14 (56.0)	16 (64.0)	30 (60.0)
Native American	2 (8.0)	2 (8.0)	4 (8.0)
Black or African American	9 (36.0)	3 (12.0)	12 (24.0
Multi-racial	0 (0.0)	4 (16.0)	4 (8.0)
Ethnicity, N (%)			
Hispanic	6 (23.1)	10 (40.0)	16 (31.4)
Non-Hispanic	19 (73.1)	15 (60.0)	34 (66.7)
Monthly household income, N (%)			
<$500	18 (69.2)	9 (36.0)	27 (52.9)
$500 - $999	1 (3.8)	4 (16.0)	5 (9.8)
$1000 - $1999	5 (19.2)	4 (16.0)	9 (17.6)
>$2000	2 (7.7)	8 (32.0)	10 (19.6)
Mean years since HIV diagnosis (sd)	15.2 (10.3)	14.6(10.3)	14.9 (10.2)
Mean previous years on ART, years (Range)	6.5 (1 – 30)	8 (1 – 25)	6.5 (1 – 30)
Recreational drug use past 1 month (excl. cannabis), N (%)	16 (61.5)	10 (40.0)	26 (51.0)
Unstable housing, N (%)	13 (50.0)	10 (40.0)	23 (45.1)

1069 THE IMPACT OF FINANCIAL INCENTIVES AND A DECISION-SUPPORT APP ON THE HIV CARE CASCADE

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Background: In South Africa, the HIV care cascade remains suboptimal among men. In a 2x2 factorial cluster randomized controlled trial, "Home-Based Intervention to Test and Start" (HITS), we previously demonstrated the effectiveness of small conditional financial incentives (CFI) on home-based HIV testing uptake and the moderate effect of CFI or a gender-sensitised HIV-specific decision-support app (EPIC-HIV) on early linkage to care (< 6 weeks). Leveraging 20 years of on-going HIV surveillance program in the trial area, we aim to assess the impact of HITS interventions on the HIV care cascade.

Methods: In 2018, in uMkhanyakude district of KwaZulu-Natal, 45 communities were randomly assigned to one of four arms: (i) CFI for home-based HIV testing and linkage to care within 6 weeks (R50 [$3] food voucher each); (ii) EPIC-HIV which is based on self-determination theory; (iii) both CFI and EPIC-HIV; and (iv) standard of care. EPIC-HIV was individually offered to men via a tablet at the point of HIV test offer or 1 month after home-based HIV testing if individuals who tested positive had not linked to care. Linking HITS trial data to national ART programme data and HIV surveillance program data, we estimated HIV status awareness, ART status 3 month after HITS and viral load suppression one year later. Analysis included all known HIV positive individuals in the study area including those who did not participated in the HITS trial

Results: On the 33,776 residents in the surveillance area, 2,753 men and 7,236 women were documented as HIV positive. No significant difference was found for HIV awareness, linkage to ART and viral suppression between arms at baseline. Compared to control arms, individuals aware of HIV-positive status were more in CFI arms among men (86.1% vs 82.6%, RR 1.04 [1.00-1.09], p=0.05) and women (92.2% vs 90.4%, RR 1.02 [1.00-1.04], p=0.05) but not in the EPIC-HIV arms (table 1). Three months after the intervention, no differences were found for linkage to ART between arms. On the 3,150 and 1,829 viral load measurements available in 2018 and 2019 respectively, viral load suppression increased but not significantly among both men (60.2% vs 57.4%, p=0.45) and women (67.4% vs 66.4%, p=0.64) with similar increase between arms.

Conclusion: Small CFIs were associated with a reduction in the proportion of HIV-infected people unaware of their result in the surveillance area. However, neither CFIs nor EPIC-HIV were sufficient to increase linkage to ART and viral suppression at a community level.

Table 1. Factorial analysis of risk factors for HIV status awareness, linkage to ART and viral suppression following HITS visit among HIV positive men and women, 2018-2019 (n=9,989).

	Men (n=2,753)			Women (n=7,236)		
	n/N (%)	Risk Ratios (95% CI)	p-value	n/N (%)	Risk Ratios (95% CI)	p-value
HIV status awareness						
CFI arms	779/905 (86.1)	1.04 [1.00-1.09]	0.050	2223/2410 (92.2)	1.02 [1.00-1.04]	0.051
No CFI arms	1527/1848 (82.6)	*ref*		4363/4826 (90.4)	*ref*	
EPIC-HIV arms	788/943 (83.6)	1.00 [0.95-1.04]	0.871	2261/2378 (90.8)	1.00 [0.97-1.02]	0.759
No EPIC-HIV arms	1518/1810 (83.9)	*ref*		4325/4730 (91.1)	*ref*	
ART status (3 months after HITS visit)[a]						
CFI arms	459/892 (51.5)	0.96 [0.87-1.06]	0.421	1425/2378 (59.9)	0.99 [0.92-1.06]	0.727
No CFI arms	975/1823 (53.5)	*ref*		2869/4730 (60.7)	*ref*	
EPIC-HIV arms	515/930 (55.4)	1.07 [0.99-1.17]	0.093	1485/2434 (61.0)	1.02 [0.95-1.09]	0.675
No EPIC-HIV arms	920/1785 (51.5)	*ref*		2809/4674 (60.1)	*ref*	
Virally suppressed (1 year after HITS visit)[b]						
CFI arms	43/77 (55.8)	0.91 [0.76-1.09]	0.295	230/352 (65.3)	0.97 [0.78-1.22]	0.824
No CFI arms	206/332 (62.0)	*ref*		720/1068 (67.4)	*ref*	
EPIC-HIV arms	65/99 (65.7)	1.10 [0.87-1.39]	0.413	281/388 (72.4)	1.12 [0.97-1.29]	0.136
No EPIC-HIV arms	184/310 (59.4)	*ref*		669/1032 (64.8)	*ref*	

ART: antiretroviral treatment, CFI: Conditional financial incentives, EPIC: Empowering People through Informed Choices for HIV

Note: risk ratios are computed using modified Poisson regression with adjustment for clustering of standard errors at the community level. P-values were calculated using Wald tests.

[a] 38 men and 128 women were excluded from the ART status because they were documented as dead or transferred out

[b] One year after the HITS visit, viral load measurement was available for 409 men and 1,420 women. Viral load results are corrected with a post-stratification weight based on age and sex.

1070 THE HIV CARE CONTINUUM AMONG TRANSGENDER WOMEN IN 2010-2020 IN THE NETHERLANDS

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ATHENA observational HIV cohort

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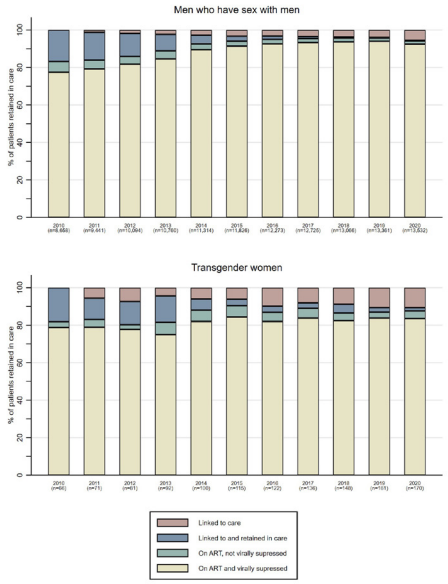
Background: Transgender women are at increased risk for acquiring HIV and earlier studies observed low retention in HIV care, as well as lower rates of antiretroviral therapy (ART) uptake, adherence and viral suppression. We compared HIV care retention between transgender women and men who have sex with men (MSM) in the Netherlands. Additionally, we compared the proportion of new HIV diagnoses those in care per year and proportion of late presenters.

Methods: Using data from the ATHENA cohort and a repeated cross-sectional design, we assessed the different stages of the HIV care continuum (linkage to care, retention in care, ART use, and viral suppression) among transgender women and MSM between 2010 and 2020. We described new HIV diagnoses among all individuals living with HIV within a calendar year. The proportion of individuals with a late diagnosis was calculated by dividing the number of late presenters (defined as a CD4 count of < 350 cells/µl or an AIDS-defining event) by the number of newly diagnosed individuals in a given year.

Results: Between January 2010 and December 2020, 15,371 individuals attended at least one clinic visit; 188 (1%) transgender women and 15,183 (99%) MSM. Over time, the majority of transgender women and MSM were retained in care, received ART and were virally suppressed (Figure), albeit with greater gaps for transgender women than MSM. Of 170 transgender women and 13,532 MSM linked to care in 2020, fewer transgender women than MSM were retained in care (89% vs 95%, p=0.004), used ART (88% vs. 94%, p< 0.001) and were virally suppressed (84% vs. 92%, p< 0.001). The proportion of transgender women newly diagnosed with HIV ranged from 6% (4/67) in 2010 to 6% (9/156) in 2020; for MSM, this varied from 8% (699/8,756) in 2010 to 2% (215/12,892) in 2020. The proportion of transgender women who were late presenters varied between 25% and 75% over time, while for MSM it varied between 37% and 46%.

Conclusion: Over a 10 year time period, the vast majority of transgender women and MSM diagnosed with HIV in the Netherlands were linked to and retained in care, received ART and were virally suppressed. the HIV care continuum for transgender women continues to lag behind across its stages and late presentation remains more common. Identifying barriers to HIV care and designing targeted interventions, jointly with the transgender community, will be crucial to improve HIV care retention and outcomes.

Linkage to and retention in care, cART use and viral suppression among transgender women and men who have sex with men between 2010 and 2020, the Netherlands



1071 PROJECTED IMPACT OF IMPROVING HIV CARE ON LIFE EXPECTANCY AMONG BLACK AND WHITE MSM

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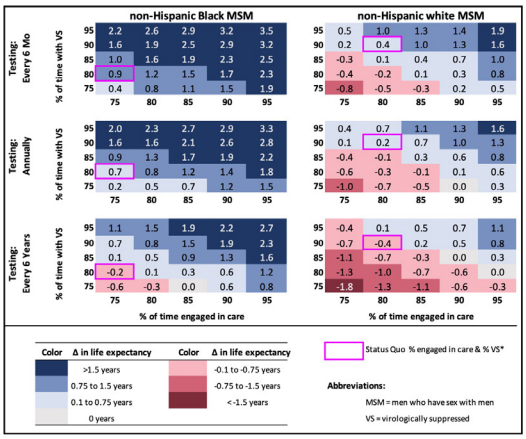
Background: Inequities across the HIV care continuum persist between non-Hispanic Black and white men who have sex with men (MSM) in the US, due partly to structural barriers, systemic racism, and stigma. We examined the impact of diagnostic testing, engagement in care, and virologic suppression (VS) rates on life expectancy (LE) among non-Hispanic Black MSM (BMSM) and white MSM (WMSM) with HIV.

Methods: Using the validated CEPAC microsimulation HIV model, we projected LE among BMSM and WMSM who acquire HIV under simulated *Status Quo* HIV care conditions. *Status Quo* HIV care was modeled using race-stratified 2019 data from the Centers for Disease Control and Prevention and estimates of: 1) average age at HIV infection (BMSM: 26.8y, WMSM: 35.0y), 2) average HIV testing frequency (BMSM: every 4.9y, WMSM: every 4.1y), 3) percent of time engaged in care for the 5y after diagnosis (BMSM: 75.2%, WMSM: 80.6%), and 4) percent of time with VS while in care after ART initiation (BMSM: 82.0%, WMSM: 91.2%). To account for non-HIV-related mortality, we adjusted national race-stratified life tables for increased tobacco-related mortality, given the high prevalence of tobacco use among MSM with HIV. We conducted sensitivity analysis by varying HIV testing frequencies (6m; annually; 6y), engagement in care (75%-95%), and VS (75%-95%).

Results: Among MSM who acquire HIV, average age at diagnosis was 30.3y for BMSM and 38.3y for WMSM. We projected LE to be 67.2y (BMSM) and 73.5y (WMSM) with *Status Quo* care. In sensitivity analysis (Figure 1), BMSM would gain 0.7 or 0.9 life years (LY) if testing frequency improved to annually or every 6 months, respectively (assuming *Status Quo* engagement in care and VS); WMSM were projected to gain 0.2 or 0.4LY, respectively. If testing frequency decreased to every 6 years, LE would decrease by 0.2LY among BMSM and 0.4LY among WMSM. When increasing both engagement in care and VS levels to 95% ("95-95"), BMSM would gain 3.3LY (annual testing) or 3.5LY (6m testing), whereas WMSM would gain 1.6LY (annual testing) or 1.9LY (6m testing) compared to LE under *Status Quo* care.

Conclusion: Projected LE for Black MSM with HIV is substantially lower than white MSM with HIV, but inequities decline with improved HIV testing, engagement in HIV care, and VS for Black MSM. Our findings highlight the need for an equity-driven approach to HIV care interventions around testing and engagement in care.

Figure 1: Model-projected differences in life expectancy (LE, years) from Status Quo care with variation in diagnostic testing frequency, % engagement in care, and % virologic suppression (VS) among non-Hispanic Black MSM (left) and white MSM (right) with HIV. Dark blue represents greater increase in LE; darker red represents greater decrease in LE. *Status Quo levels: engagement in care (BMSM: 75.2%, WMSM: 80.6%); VS (BMSM: 82.0%, WMSM: 91.2%). Status Quo testing frequency is not shown in the figure (BMSM: every 4.9y; WMSM: every 4.1y).



1071.5 RETENTION IN CARE AMONG PERUVIAN MSM AND TGW IN A REAL-WORLD HIV PrEP PROGRAM

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Background: Tenofovir-based daily oral HIV pre-exposure prophylaxis (HIV PrEP) is a highly efficacious HIV prevention modality, but sustained use over time is needed for continued protection among individuals at high risk for HIV exposure. Suboptimal adherence and retention in care threaten to diminish the impact of HIV PrEP on reducing HIV burden. PrEP PERU is an ongoing, multi-site, prospective cohort study evaluating HIV PrEP implementation among adult men who have sex with men (MSM) and transgender women (TGW) accessing care at non-government health centers in Peru. We sought to evaluate HIV PrEP adherence and retention in care among PrEP PERU participants prior to the onset of COVID-19 service disruptions.

Methods: We analyzed baseline and follow-up data from the PrEP PERU study through 3/15/2020, the first day of Peru's COVID-19 lockdown. MSM and TGW ≥18 years of age with at least one HIV risk factor were eligible for enrollment. After the first follow-up visit at 4 weeks, TDF/FTC refills and clinic visits occur quarterly, at the discretion of the prescribing clinician. The medication is provided free of charge, but participants pay for laboratory testing plus a small service fee for clinic visits. Data is collected at baseline and quarterly follow-up visits on sexual risk behaviors and HIV PrEP use. We used bivariate analysis to evaluate the association between baseline factors and 6-month HIV PrEP retention in care. As a proxy for adherence, pharmacy dispensation records were used to calculate the proportion of days covered (PDC) by TDF/FTC.

Results: Overall, 351 participants started TDF/FTC at four study sites in Lima from 1/23/2017 to 3/15/2020. Of this analysis population, 94% were cisgender men, 10% identified as bisexual, and median age was 31 (interquartile range [IQR], 27 – 38). Among those with at least 6 months of observation time (n=302), 91% attended ≥1 follow-up visit and 77% attended ≥2 follow-up visits during the 6 months after enrollment. The proportion with favorable adherence (PDC ≥0.8) was 85%. There were 6 confirmed HIV seroconversions in the analysis period (1.2 per 100 person-years).

Conclusions: In this analysis of HIV PrEP outcomes among MSM and TGW prior to COVID-19 pandemic disruptions in Peru, over 3/4 of the population remained in care and had favorable measures of adherence during the first 6 months after starting HIV PrEP. This level of HIV PrEP engagement compares favorably to reports from similar settings of HIV PrEP implementation in Latin America.

Baseline characteristic	Total (N=351)	Attended ≥1 F/U Visit*	Attended ≥2 F/U Visits*	Adherence (PDC ≥0.8)*‡
Gender Identity	*n (%)*	*RR (95% CI)*	*RR (95% CI)*	*RR (95% CI)*
Cisgender man	330 (94%)	1.53 (0.75 – 3.13)	1.29 (0.63 – 2.65)	1.08 (0.69 – 1.68)
Transgender woman	5 (1.4%)	reference	reference	reference
Not reported	16 (4.6%)			
Sexual Orientation				
Bisexual	36 (10%)	1.07 (0.99 – 1.15)	***1.16 (1.00 – 1.34)***	0.90 (0.75 – 1.08)
Homosexual or "Other"	290 (83%)	reference	reference	reference
Not reported	25 (7.1%)	-	-	-
Age				
≥30 years	198 (56%)	1.07 (0.9 – 1.16)	***1.24 (1.08 – 1.43)***	0.99 (0.90 – 1.09)
<30 years	136 (39%)	reference	reference	reference
Not reported	17 (4.8%)	-	-	-
Monthly Income				
>2000 Soles	182 (52%)	1.02 (0.95 – 1.10)	1.14 (0.99 – 1.30)	1.06 (0.96 – 1.17)
≤2000 Soles	146 (42%)	reference	reference	reference
Not reported	23 (6.6%)	-	-	-
Health Insurance				
Any insurance	239 (68%)	1.00 (0.92 – 1.09)	1.11 (0.94 – 1.30)	1.04 (0.93 – 1.16)
No insurance	88 (25%)	reference	reference	reference
Not reported	24 (6.8%)	-	-	-
STI in last 3 months?				
Yes	54 (15%)	0.91 (0.80 – 1.04)	0.88 (0.71 – 1.08)	1.01 (0.89 – 1.14)
No	288 (82%)	reference	reference	reference
Not reported	9 (2.6%)	-	-	-
HIV+ sex partner in last 30 days?				
Yes	125 (36%)	1.01 (0.94 – 1.08)	0.99 (0.87 – 1.13)	***1.10 (1.01 – 1.20)***
No	212 (60%)	reference	reference	reference
Not reported	14 (4.0%)	-	-	-
CAS in last 30 days?				
Yes	200 (57%)	1.01 (0.94 – 1.09)	0.97 (0.86 – 1.10)	1.05 (0.96 – 1.16)
No	142 (40%)	reference	reference	reference
Not Reported	9 (2.6%)	-	-	-
Alcohol use w/ sex in last 30 days?				
Yes	253 (72%)	0.99 (0.91 – 1.08)	0.91 (0.79 – 1.04)	0.98 (0.88 – 1.09)
No	70 (20%)	reference	reference	reference
Not Reported	28 (8.0%)	-	-	-

*RR estimates calculated for n=302 participants with at least 6 months observation time prior to March 15, 2020. ‡Adherence defined as Proportion of Days Covered (PDC) by PrEP medication ≥0.8. RR: relative risk; PrEP: pre-exposure prophylaxis; CI: confidence interval; MSM: men who have sex with men; STI: sexually transmitted infection; CAS: condomless anal sex.

1072 PrEP KNOWLEDGE, EVER USE, AND DISCONTINUATION AMONG LAKE VICTORIA FISHERFOLK IN UGANDA

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Background: There is limited population-level data on the PrEP care continuum in eastern Africa. We assessed PrEP knowledge, ever-use, and discontinuation at the population-level following PrEP rollout in a Lake Victoria fishing community in Uganda with 40% HIV prevalence.

Methods: We used cross-sectional data collected between June 2018 and November 2020 from a Lake Victoria fishing community under surveillance in the Rakai Community Cohort Study (RCCS) to measure levels of self-reported PrEP knowledge, ever use, and discontinuation following PrEP rollout in key populations in 2017. Our analysis included HIV-negative persons who reported having ever received an HIV test result, with discontinuation measured among those reporting ever-use only. We also examined associations between demographic, behavioral, and health utilization factors with each outcome using modified Poisson regression adjusted for age with all analyses stratified by gender. Associations were reported as adjusted prevalence ratios (adjPR) with 95% confidence intervals (95%CI).

Results: There were 1,401 HIV-negative participants, of whom 1,363 (97%) reported ever receiving an HIV test result. Median age was 29 years (IQR: 23-36), and 42% (n=577/1363) were women. While PrEP knowledge was high (85.5%), PrEP ever-use was low (14.5%), with no significant differences in levels of knowledge or ever-use by gender. Among those likely PrEP eligible as assessed from RCCS demographics and self-reported risk behaviors (n=514), PrEP ever-use was 22.4%. Having ever used PrEP was strongly associated with perceived HIV risk: those reporting higher perceived risk were more likely to report PrEP ever-use compared to those who reporting not being at risk (p< 0.001). Women reporting transactional sex also were more likely to report PrEP use vs. women who did not (adjPR: 1.81; 95% CI: 1.21-2.71), as were those reporting a recent HIV test in the last year vs. those who did not (men: adjPR=2.98; 95%CI:1.58-5.62: women: adjPR=4.03; 95%CI:1.80-9.01). Among 116 men and 81 women who reported ever using PrEP, 48.3% and 46.9% discontinued PrEP, respectively.

Conclusion: In this community with high HIV prevalence, there were low levels of self-reported PrEP use and high rates of discontinuation despite high levels of PrEP awareness. Efforts that enhance awareness of HIV risk and increase access

to PrEP through HIV testing may help increase PrEP use among HIV-negative persons in African settings with high HIV burden.

1073 STRUCTURAL INFLUENCES ON PrEP CASCADE AMONG YOUNG WOMEN IN POST-ABORTAL CARE IN KENYA

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Background: Women accessing care at post abortion care (PAC) clinics have had recent and potentially ongoing condomless sex, placing them at risk for subsequent unintended pregnancy, HIV, and other STIs depending on their geographic settings. Few studies have assessed PAC settings for delivery of HIV prevention services, including pre-exposure prophylaxis (PrEP), and for influential structural factors.
Methods: Using medical records data abstracted from adolescent girls and young women (AGYW) aged 15 to 30, we describe PrEP offers, uptake, and refills within an implementation science project that launched PrEP delivery in 9 private and 6 public PAC clinics in Kenya. Poisson regression models were used to estimate the effect of clinic- and provider-level factors, determined by technical assistants, on PrEP outcomes.
Results: From March to August 2022, 1945 AGYW in PAC settings were offered PrEP, of which 403 (20.7%) initiated PrEP and 30 (7.4%) of those received at least one refill. Among PAC clinics, PrEP offers were more common among clinics that that had fully incorporated PrEP into routine clinical tasks (vs. separate, prevalence ratio (PR): 1.17 95% CI: 1.03, 1.33) and less common in clinics that were private (vs. public, (PR): 0.84, 95% CI: 0.77, 0.92), had low client volume (PR: 0.5, 95% CI: 0.45, 0.54), had sufficient staffing (PR: 0.14, 95% CI: 0.11, 0.18) or space (PR: 0.84, 95% CI: 0.77, 0.92), and lacked a champion PrEP provider (PR: 0.86, 95% CI: 0.78, 0.94). The frequency of PrEP uptake was higher among clinics with sufficient space (PR: 1.53, 95% CI: 1.26, 1.87) and lower among clinics that were private (vs. public, PR: 0. 4, 95% CI: 0.33, 0.49), had a low client volume (PR: 0.33, 95% CI: 0.27, 0.41), had sufficient staffing (PR: 0.14, 95% CI: 0.08, 0.25), and lacked a champion PrEP provider (PR: 0.74, 95% CI: 0.6, 0.9). PrEP refills were less frequent among clinics that had at the same point of care for refills (vs. different, PR: 0.05, 95% CI: 0.02, 0.12), were private (vs. public, PR: 0.05, 95% CI: 0.01, 0.22), and had a low client volume (PR: 0.15, 95% CI: 0.06, 0.39).
Conclusion: PrEP outcomes for AGYW accessing services integrated into PAC are influenced by larger structural factors in the healthcare ecosystem, including clinic structure, staffing, and the presence of PrEP champions. Young women accessing PrEP services may benefit from the sufficient space and privacy in PrEP program clinics and access to PrEP champions.

1074 HIGH LEVEL OF HIV PREVENTION-EFFECTIVE CONTINUATION IN A LARGE PrEP PROGRAM IN KENYA

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Efficiency Study Team
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Background: HIV pre-exposure prophylaxis (PrEP) delivery is rapidly scaling up globally, but variable discontinuation rates in early real-world data has made it difficult to define programmatic success. Whether discontinuation reflects non-use at times of risk or appropriate non-use during periods of low or no risk (i.e., prevention-effective use) is unknown for most PrEP programs.
Methods: Between 2020 and 2022, we administered a standardized phone survey to clients who initiated and later discontinued PrEP at 4 public clinics in Central Kenya that participated in the Partners Scale-Up Project, a stepped-wedge cluster-randomized pragmatic trial of PrEP delivery integrated in public HIV clinics as part of Kenya's national PrEP roll-out. The survey assessed duration of PrEP use, perceived HIV risk at initiation and present, satisfaction with current HIV prevention choice, primary reason for PrEP stop, experience at last clinic visit, and impact of clinic factors (i.e., wait time, visit frequency, staff attitude).
Results: Of 300 interviewed, 63% were female, 33% ≤30 years, 80% in serodifferent partnership at initiation. About 85% had high self-perceived risk of acquiring HIV at PrEP initiation and 57% used PrEP for ≥3 months. Two-thirds reported it was their own decision to start PrEP and a third a shared client-provider decision. Overall, 73% reported their HIV risk status changed (feeling no longer at risk, U=U with virally suppressed partner, or separation from partner) and that was the primary reason for PrEP stop. Pill burden (9%) and side effects (11%) were relatively uncommon primary reasons for PrEP stop. Notably, >98% were satisfied with experience at the last clinic visit; < 1% attributed stopping to clinic factors. Overall, no method at all (24%), not feeling at risk (39%), practicing U=U (19%), no sexual partner (26%), condom (14%) were common HIV prevention choices practiced at time of the interview. Importantly, the majority (94%) were satisfied with their current HIV prevention method choice.
Conclusion: Nearly three-quarters of PrEP discontinuations in large national public PrEP program in Kenya were appropriate PrEP non-use aligned with low HIV risk states or other prevention strategies, and almost all clients were satified with their current HIV prevention choice. Our findings illustrate that using client-level PrEP continuation rates without contextual dynamic individual risk and use of other HIV prevention options is not an appropriate measure of real-world PrEP program success.

1075 DEPRESSION ASSOCIATED WITH PrEP HOLIDAYS AMONG KEY POPULATIONS IN NAMIBIA

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Background: Mental health challenges negatively impact HIV outcomes, including engagement in prevention services. Key populations may be more vulnerable to these impacts, particularly in the context of oral PrEP, which requires frequent dosing decisions and ongoing engagement with the health system. Mental health among oral PrEP users in Africa has not been well described.
Methods: We enrolled new and continuing PrEP users from 13 facilities in Namibia in a cross-sectional study characterizing PrEP use decisions and determinants among adolescent girls and young women (AGYW) and key populations. We measured mild, moderate and acute depression using the Patient Health Questionnaire (PHQ9). A referral pathway was established to link clients with acute depression or suicidal ideation to mental health services. We also measured self-reported alcohol and drug use, HIV risk perception, condom use, "PrEP holidays," missed pills, and side effects. We described relationships between the variables with chi-square tests and used log binomial regression to estimate mental health impacts on PrEP holidays. The study was approved by the JHU and Namibia MOHSS IRBs.
Results: The study (n=500) included 39 MSM, 28 male sex workers, 254 AGYW, and 214 FSW. Mean age was 25.5 (SD = 6.6). Overall, 222 (44%) vs. 278 (66%) were new vs. continuing PrEP users. Among 499 providing responses to the PHQ9, 11% and 5% had scores suggesting moderate and acute depression, respectively; 29% reported suicidal ideation. FSW were more likely to report acute depression (p< 0.001). In unadjusted analyses, taking a "PrEP holiday" was associated with depression (p=0.03), alcohol use disorder (p< 0.01), and drug use (p< 0.01). Depression was further associated with missing pills on weekends (p=0.02), reporting side effects (p=0.04), HIV risk perception (p< 0.001), and drug use among FSW (p< 0.001) and MSM (p=0.02). In adjusted analyses, depression predicted PrEP holidays among MSM (B= 3.4; SE: 1.7).
Conclusion: Clients accessing oral PrEP represent marginalized populations who may be at greater risk for mental health issues. PrEP can be an entry point for screening and referral to mental health services. Programs should integrate mental health with HIV services, to address high rates of depression and support continuation in HIV services.

1076 CONDUCTING RESEARCH IN A SETTING OF SEVERE POLITICAL INSTABILITY: THE GHESKIO MODEL

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Background: GHESKIO, a Haitian NGO that has been conducting HIV-related clinical trials for decades, is located in epicenter of the massive civil unrest and gang violence that has devastated Haiti for the past 3 years. Armed gangs are in control of much of Port-au-Prince with road-blocks, kidnappings, protests, and violence against civilians. Many Haitian medical staff have fled the country, there are widespread hospital closures.

Methods: GHESKIO has implemented a comprehensive strategy to facilitate participant enrollment and follow-up in the context of these major challenges. Key interventions include: (1) Creation of a welcoming clinic environment, with supportive relationships between staff and participants; (2) Phone calls every 2 days for the first month, then every 2 weeks for the study duration; (3) Immediate contact for missed visits; (4) Option for clinic visits or ART pick-up and viral load testing at GHESKIO community sites (or in rare cases home medication delivery) when it is too dangerous to travel to the main GHESKIO facility; (5) Hot meal at every study visit, plus a package of staple foods for home; and (6) Transportation subsidy and phone card at each visit (combined cost of $2.00/visit). As an example of the impact these services have on research, we report retention and viral suppression rates for an ongoing trial of participants with viral suppression on second-line ART; participants were randomized to continue a boosted protease inhibitor regimen or switch to bictegravir/tenofovir alafenamide/emtricitabine. We report the outcomes for participants with 48 weeks of potential follow-up time for both groups combined.

Results: From October 30, 2020, to September 6, 2021, 208 participants were enrolled in the study. 115(56%) were female, with a median age of 50(IQR: 42, 57); all had HIV-1 RNA < 200 copies/mL at screening. Of these, 198 (95.2%) had HIV-1 RNA < 200 copies/mL during the 48-week visit window; 1 (< 1%) had HIV-1 RNA >200 copies/mL during the 48-week visit window; 1 (< 1%) was lost to follow-up with HIV-1 RNA >200 copies/mL; and 8 (3.8%) had HIV-1 RNA < 200 copies/mL at last visit but no viral load during the 48-week visit window (2 died, 3 left the country, and 3 were in care but unable to attend clinic for viral load).

Conclusion: Outstanding research outcomes are possible in settings of severe political and civil unrest, with a comprehensive approach to social and nutritional support for study participants.

1077 A MODEL OF SUCCESSFUL ART INITIATION IN THE CONTEXT OF MASSIVE CIVIL UNREST IN HAITI

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Background: Haiti is experiencing massive civil unrest and violence, with armed gangs in control of over 50% of the country. This has major consequences for HIV care, as kidnappings are common, and roads are frequently blockaded due to protests or gang-related activity; many Haitian health care providers have left the country.

Methods: The GHESKIO Centers, in Port-au-Prince, Haiti, is located at the epicenter of gang activity. They have developed a model of care for initiating tenofovir-lamivudine-dolutegravir (TLD) in the midst of major civil unrest which includes: (1) Staff have created a welcoming environment, based on dignity and respect for everyone; (2) Patients are called in advance of each visit, and on day of a missed visit; patients who cannot be reached by phone are visited at home; (3) Patients who can't come to the GHESKIO clinic are offered ART at community ART refill sites; ART is provided at home for patients who can't leave danger zones of gang activity; (4) Visits are scheduled every 1 to 3 months for the first year of ART, but a minimum of 4 months of ART is dispensed at each visit; visits are conducted by phone as needed; (5) Patients receive nutritional supplementation at ART initiation, and a hot meal at every visit; (6) Counseling is based on the principles of motivational interviewing. We conducted a prospective cohort study to evaluate 12-month outcomes in patients receiving this model of care during a period of major civil unrest in Haiti.

Results: Between December 2020 and June 2022, 193 patients initiated ART. Of these, 47% were female, the median age was 40 (IQR: 33, 47), 66% were living on < $US 1.00/day, and 48% had no education or primary school only. 190/193 (98.4%) had an HIV-1 RNA test conducted within 6 months after enrollment, and 179 (94.2%) had HIV-1 RNA < 200 copies/mL; 174 had viral suppression at initial testing, and 5 had viral suppression after counseling and repeat testing. 106 patients had at least 12 months of potential follow-up time. Of these, 3 (1.6%) died (2 were killed in gang violence and 1 died of metastatic cervical cancer), 13 (6.7%) were lost to follow-up, and 13 (6.7%) remain in care without 12-month viral load testing. Of the 77 (72.6%) who received 12-month HIV-1 RNA testing, 71 (92.2%) had < 200 copies/mL.

Conclusion: In the midst of massive civil unrest and gang violence in Haiti, ART outcomes were outstanding with the provision of TLD with social and nutritional support.

1078 EMERGENCY RESPONSE TO RESTORE HIV TREATMENT SERVICES IN AMHARA REGION, ETHIOPIA, 2022

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Background: The June 2021 armed conflict in northern Ethiopia caused massive population displacement, destruction of health facilities (HFs), and disruption of health services, including anti-retroviral treatment (ART) in Amhara region. In June 2021,146092 people were on ART. By December 2021, at the end of the conflict, this fell to 120967. An emergency response task force was established, and the Regional Health Bureau (RHB), and Ministry of Health (MOH) began to immediately re-establish ART services.

Methods: Initial assessments identified priority activities for rapid ART restoration, including immediate replenishment of ART drugs, and reestablishment of laboratory and information systems. Recoverable electronic medical records (EMR) were reviewed to determine ART status and identify patients with treatment interruptions. Service restoration and data recovery was done to HFs. Training, psychosocial support, and mentoring was provided to health workers.

Results: Of the 189 ART HFs in conflict affected zones, 105 were damaged or looted. Forty-nine (53%) and 71 (76%) of the 93 assessed HFs were unable to provide ART and laboratory services respectively. ART status for 41980 clients could not be verified. In response, data recovery support was provided to 64 reprioritized HFs in January 2022. Programs provided training, replenished computers, furniture, microscopes, cervical cancer treatment machines, and services were restarted. The ART status for 36436 persons (87% of the backlog) experiencing treatment interruption was verified from EMR data and they were restarted on ART. As of April 2022, all the189 HFs except six were able to re-start service and 95% of the regional ART cohort was on ART. By June 2022, the recovery efforts contributed to regaining and growth of the regional ART cohort to 147817, surpassing the pre-conflict cohort size.

Conclusion: While armed conflict threatened ART, well-coordinated emergency response efforts rapidly reinstituted key HIV commodities, re-engaged health workers, and verified the active ART status of 95% of persons at risk for interruption. The rapid recovery of ART services was possible through the MOH coordination platform, RHB leadership, a trained health workforce, a bring back to care campaign, multi month dispensing of ART and the health information systems built through 18 years of collaboration with PEPFAR/CDC support. The emergency response tools and procedures provide a model for other areas impacted by armed conflict.

Key words: Emergency Response, ART

1079 8-YEAR CARE TRAJECTORIES IN AN URBAN COHORT OF PWH RECEIVING CARE: WASHINGTON, DC

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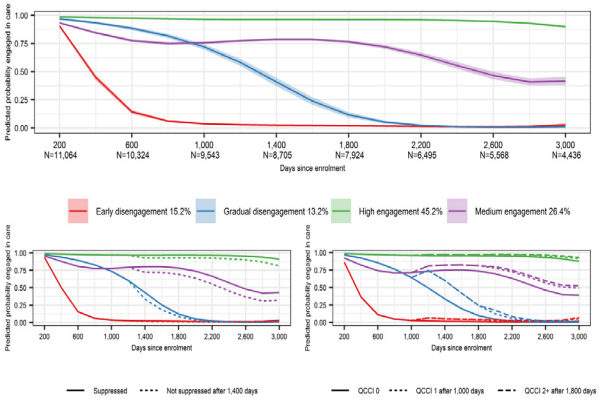
Background: As many as 50% of PWH are not engaged in care and others cycle in and out of care. We sought to identify and characterize different groups of longitudinal care trajectories among a cohort of PWH who have been linked to HIV care in Washington, DC.

Methods: We used data from participants in the DC Cohort, a longitudinal multi-site cohort of PWH receiving care at 14 clinics in DC, who were ≥18 years and enrolled from 1/1/2011 to 6/30/2021. To identify longitudinal care trajectory groups we used grouped-trajectory modelling. Participants were considered "engaged" if they had ≥1 HIV visit, CD4 or VL during a specified 200-day interval. Time-stable risk factors were added to the group membership probabilities to identify predictors of class membership using multinomial logistic regression. Time-varying risk factors of viral suppression [VS (HIV RNA< 200 copies/ml)] and the modified Quan-Charlson comorbidity index (QCCI), a predictor of mortality, were added to the model of the trajectory shapes.

Results: 11,064 participants were included in the analysis (baseline: median age 47.3 years, 72% male, 63% non-Hispanic Black, 48% ≥10 years since HIV diagnosis, 75% VS). Four latent trajectory groups were identified: those with high engagement (45%), medium engagement (26%), gradual disengagement (13%), and early disengagement (15%). Compared to those with high engagement, those with early disengagement were significantly more likely at enrollment to have a CD4< 500 cells/μL, not be VS, homeless, privately insured, younger, diagnosed within 4 years, and ARV naïve (all p< 0.05). Those with gradual disengagement were significantly more likely to not be VS, younger, male, and diagnosed within 4 years compared to those with high engagement (all p< 0.05). Those with medium engagement were significantly more likely to have CD4< 500 cells/μL, not be VS, privately insured, and younger compared to those with high engagement (all p< 0.05). When including time-varying covariates of VS and co-morbidity, not being VS significantly lowered the probability of engagement whereas the probability of engagement significantly increased with increasing numbers of co-morbidities using the QCCI (Figure).

Conclusion: Identifying characteristics of those disengaged in care using longitudinal approaches can help guide intervention development to improve HIV care engagement. To further promote optimal long-term care engagement, differentiated care models may be needed at various stages of a PWH's HIV care trajectory.

Figure: Estimated trajectory groups for the main model (A), time-varying viral suppression (B), and modified Quan Charlson Co-morbidity Index (QCCI) (C).



1080 PREDICTORS OF RETENTION IN THE WOMEN'S INTERAGENCY HIV STUDY: 2011-2019

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Background: Women of color and women of low socioeconomic status (SES) are underrepresented in HIV research, but their participation is crucial to improving HIV outcomes. We assessed baseline factors associated with visit attendance and dropout in women with HIV (WWH) and women without HIV in the Women's Interagency HIV Study (WIHS).

Methods: Women enrolled in WIHS from 2011-2015 were followed for up to 10 consecutive semiannual visits through 2019. Dropout was defined as no further attended visits with no passive follow-up and measured from the first missed visit. We assessed the association of baseline factors with full (100%), partial (71-99%) and low (≤70%) visit attendance rates by chi-square and then performed multivariable ordinal logistic regression adjusting for HIV status and factors with p< 0.10 in the bivariate analysis. A separate model in WWH included HIV-related factors. We then identified factors associated with early (visits 2-3), intermediate (visits 4-6) and late (visits 7-10) dropout compared with no dropout by chi-square.

Results: 1214 (886 WWH, median age 44 years, 81% Black, 69% from study sites in the U.S. South, 59% income< $12,000/year) participants were included. 76% had full visit attendance, 14% had partial visit attendance, and 10% had low visit attendance. In the adjusted model, greater visit attendance was associated with age >50, Black race, living in one's own residence, study site in the U.S. South, and history of hypertension (Table). Among WWH, greater visit attendance was associated with age >50, Black race, taking antiretroviral therapy (ART), and study site in the U.S. South. The retention rate was 81%. Early, intermediate, and late dropout occurred in 65(5%), 78(7%), and 82(8%) participants, respectively. Compared with no dropout, early dropout was associated with more depressive symptoms (CES-D score >16), lower health perception, smoking, HIV RNA >200 copies/ml, not on ART, and CD4 count< 200 cells/mm3. Intermediate dropout was associated with non-Black race, no history of diabetes, and being born outside the U.S. Late dropout was associated with employment, smoking, HIV RNA >200 copies/ml, not on ART, ever experiencing physical violence, and not getting regular HIV care.

Conclusion: Retention in WIHS of predominantly Black, low SES women with and without HIV was excellent. Different baseline factors were associated with different study dropout times suggesting that different retention strategies may be required over time in a longitudinal HIV cohort study.

Table. Bivariate and multivariable association of participant characteristics at study enrollment with WIHS visit attendance

Characteristics at Enrollment	Full Visit Attendance N=924 N (%) or median (Q1, Q3)	Partial Visit Attendance N=173 N (%) or median (Q1, Q3)	Low Visit Attendance N=119 N (%) or median (Q1, Q3)	p-value	Adjusted Odds ratio (95% confidence interval)	p-value
Living with HIV (vs without HIV)	685 (74.1)	118 (68.2)	83 (69.8)	0.20		0.13
Age Category, years (vs 20-29)				**0.01**		**0.03**
30-39	234 (25.3)	58 (33.5)	42 (35.3)		0.88 (0.52-1.49)	
40-49	346 (37.4)	60 (34.7)	41 (34.5)		0.69 (0.35-1.02)	
≥50	**285 (30.8)**	**39 (22.5)**	**25 (21.0)**		**0.55 (0.31-0.97)**	
Race/Ethnicity (vs White, non-Hispanic)				**0.0002**		**0.0009**
Black, Non-Hispanic	**770 (83.3)**	**132 (76.3)**	**79 (66.4)**		**0.50 (0.32-0.77)**	
Hispanic or Other	89 (9.6)	23 (13.3)	21 (17.7)		0.83 (0.49-1.44)	
Study Site Region (vs North)[b]				**0.008**		**0.006**
West	84 (9.1)	26 (14.5)	16 (13.5)		0.94 (0.58-1.51)	
South	**666 (72.1)**	**102 (59.0)**	77 **(64.7)**		**0.61 (0.43-0.85)**	
Born in the US or US territory	814 (89.0)	147 (85.0)	89 (86.4)	0.28		
Employed at Enrollment	281 (30.5)	45 (26.0)	38 (31.9)	0.44		
Resides in Own Residence	**651 (70.5)**	**107 (61.8)**	**66 (55.5)**	**0.0008**	**0.61 (0.46-0.82)**	**0.0009**
History of Incarceration	470 (50.9)	81 (46.8)	71 (59.7)	0.09	0.95 (0.70-1.28)	0.73
Depressive Symptoms (CES-D)[a]				0.72		
Score <16	520 (56.5)	96 (56.1)	61 (52.6)			
Score >16	400 (43.5)	75 (43.9)	55 (47.4)			
Health Rating (vs low (<30))[b]				0.74		
Medium (30-70)	371 (46.7)	66 (48.9)	52 (51.0)			
High (>70)	396 (49.9)	63 (46.7)	45 (44.1)			
History of Diabetes	110 (11.9)	10 (5.8)	11 (9.2)	0.0496	0.76 (0.46-1.26)	0.28
History of Hypertension	**518 (56.1)**	**68 (39.3)**	**48 (40.3)**	**<0.0001**	**0.69 (0.52-0.93)**	**0.01**
Smoking at Enrollment	432 (46.8)	83 (48.0)	69 (58.0)	0.07	0.82 (0.61-1.10)	0.18
HIV RNA Viral Load <200 copies/mL[a]	482 (73.1)	78 (68.4)	39 (49.4)	<0.0001	0.91(0.57-1.46)	0.71
ART Use[a]	**558 (81.5)**	**87 (73.7)**	**51 (61.4)**	**<0.0001**	**0.55 (0.34-0.89)**	**0.02**
Receive Regular HIV Care[a]	479 (90.6)	62 (90.9)	30 (93.8)	0.11		
CD4 Count ≥200 cells/mm[3][a]	611 (90.9)	105 (89.7)	74 (89.2)	0.82		

[a] WIHS, Women's Interagency HIV Study; Q1, Quartile 1; Q3, Quartile 3; NH, Non-Hispanic; CES-D, Center for Epidemiologic Studies Depression Scale. Higher CES-D score indicates more depressive symptoms; ART, antiretroviral therapy.
[b] Health Rating extracted from the Medical Outcomes Study (MOS) Quality of Life Instrument. North sites: Bronx, NY, Brooklyn NY, Chicago, IL, and Washington, D.C., West sites. Los Angeles, CA, and San Francisco, CA, South sites. Chapel Hill, NC, Atlanta, GA, Birmingham, AL/Jackson, MS, and Miami, FL
[c] Among WWH only

1081 RETENTION IN OPIOID AGONIST THERAPY AMONG PEOPLE LIVING WITH HIV IN BRITISH COLUMBIA

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*Presented at CROI by a nonauthor colleague

Background: The illicit drug toxicity crisis in British Columbia (BC) has reduced the survival gains among people living with HIV (PLWH) achieved by combination antiretroviral therapy. Supporting PLWH with concurrent opioid use disorder (OUD) to engage and remain on opioid agonist therapy (OAT) is necessary to optimize HIV care. We examined correlates of retention on OAT among a cohort of PLWH who received at least one OAT dispensation in BC.

Methods: We analyzed data from the Seek and Treat for Optimal Prevention of HIV/AIDS database between April 1996 and March 2017. Those with known gender, age of ≥19 years old, and ≥12 months of follow-up were included. We identified OAT dispensation as the receipt of methadone or buprenorphine/ Naloxone (introduced to BC in 2008) through the PharmaNet database. Treatment episodes with no interruptions in the prescribed doses lasting ≥ 3 days for methadone, or ≥ 6 days for buprenorphine were constructed. A period of continuous retention in treatment was evaluated as no interruption in the prescribed doses for at least 12 months. We examined temporal trends in retention over the calendar years. A generalized estimating equation (GEE) model was built to assess correlates of 12-month retention in OAT. Of note, in the present setting, methadone was the recommended treatment in BC until July 2017.

Results: A total of 13,433 PLWH were included in the analysis of whom 2,151 (16.01) had at least one OAT dispensation (methadone: 2,075; buprenorphine: 76). Median (Q1, Q3) age was 37 years (31, 43) and 60.1% (n=1,293) were male. PLWH initiated on buprenorphine versus (vs.) methadone were more likely to be older 42.5 (34, 52) vs. 37 (31, 43), and had a significantly higher comorbidities n (%): depression 40 (52.6) vs. 821 (39.5); chronic pain 39 (51.3) vs. 440 (21.2), hepatitis C 47(61.8) vs. 802 (38.6); chronic obstructive pulmonary diseases 6 (7.80) vs. 65 (3.1); cancer 22 (28.0) vs. 254 (12.2). There was a decline in retention at the rate of 1.34 per year (p< 0.0001). Table 1 presents correlates of retention among PLWH.

Conclusion: Our findings indicated that OAT retention among PLWH has declined over time. Higher odds of retention were associated with a ten-year increase in age, previous retention history, achieving therapeutic dose (≥ 60mg methadone; ≥12mg buprenorphine), and methadone treatment. To meet and sustain the UN 95-95-95 by 2025 Targets among PLWH with comorbid OUD, optimal management of OUD and implementation of OAT aimed at maximized retention is necessary.

Table 1. Correlates of retention in OAT among PLWH between April 1996-March 2017

Table 1. Correlates of retention in OAT among PLWH between April 1996-March 2017

	Unadjusted Model OR (95% CI)	Adjusted Model OR (95% CI)
Gender[^]		
Men [ref]	1.00	1.00
Women	0.88 (0.79, 0.99)	0.90 (0.79, 1.02)
Age (years)[^] (10 years increase), median (Q1, Q3)	1.43 (1.33, 1.54)	**1.35 (1.25, 1.46)**
HCV Co-infection (lifetime)[^]		
No [ref]	1.00	0.90 (0.79, 1.02)
Yes	0.77 (0.68, 0.86)	
Ever Retained before entering cohort[^]		
No	1.00	1.00
Yes	1.43 (1.18, 1.73)	1.38 (1.14, 1.67)
No OAT Before Entering	0.80 (0.69, 0.92)	0.89 (0.77, 1.03)
Total days on previous OAT (365.25 days increase) *	0.93 (0.92, 0.95)	**0.98 (0.97, 1.00)**
OAT Type **		
Methadone [ref]	1.00	1.00
Bup/Naloxone	0.39 (0.33, 0.47)	**0.35 (0.27, 0.44)**
Depression *		
No [ref]	1.00	Not used for selection
Yes	0.94 (0.82, 1.08)	
Mood & Anxiety Disorder *		
No [ref]	1.00	Not used for selection
Yes	0.95 (0.84, 1.07)	
Psychosis *		
No [ref]	1.00	Not selected by the model
Yes	0.74 (0.61, 0.90)	
Chronic Pain *		
No [ref]	1.00	Not Selected by the Model
Yes	0.78 (0.68, 0.86)	
HIV Viral Load suppression *		
Not Suppressed [ref]	1.00	1.00
Suppressed <200 copies/mL	0.80 (0.72, 0.89)	1.13 (1.00, 1.27)
Unknown	0.99 (0.91, 1.08)	1.02 (0.92, 1.13)
Prescriber Type *		
GP/Community Medicine [ref]	1.00	1.00
Specialist	0.92 (0.76, 1.11)	0.97 (0.79, 1.20)
Unknown	0.69 (0.60, 0.78)	0.83 (0.72, 0.96)
Achieved the Therapeutic Dose ***		
No [ref]	1.00	1.00
Yes	3.40 (3.13, 3.70)	3.54 (3.23, 3.88)

The logistic GEE model is modeling the probability that retained = 1.;
This model is built upon all episodes; Covariate selection for the adjusted explanatory models was based on Type III P-values;
Potential covariates that did not indicate a significant effect in the univariate model were not considered in the adjusted model;

[^] Time-fixed variables measured at OAT initiation
* Time-varying variable measured at the beginning of each new OAT episode
** Time-varying variable measured as of the end of each OAT episode
*** Therapeutic dose was defined as ≥60 mg for methadone, and ≥12 mg for buprenorphine

1082 A RANDOMIZED CONTROL TRIAL OF AN HIV CARE INTERVENTION BUNDLE FOR PEOPLE WITH HIV

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Background: Prompt initiation of antiretroviral therapy (ART) is now considered the standard of HIV care. Factors associated with delayed or inconsistent HIV care HIV care include: poverty, lack of transportation, lack of healthcare coverage and fear of HIV stigma. Strengths-based case management, intensive outreach, and patient navigation are well-supported interventions to improve care that have largely been tested/implemented in isolation. We developed an HIV care intervention bundle that combines these strategies using pre-/post-visit telehealth calls to provide psychosocial and educational support, health system navigation, and enhanced healthcare communication.

Methods: We conducted a longitudinal randomized control study to compare participant time to viral suppression and care-related measures (eg visit adherence). Participants were randomized to receive the intervention (n=20) or receive the standard of care (n=20). Intervention participants received up to seven additional telehealth sessions with a Registered Nurse. Intervention participants were screened for psychosocial needs, addiction services, clinical symptoms, and referred for assistance when necessary. One-on-one education and psychosocial support were provided to the intervention group. Virologic and care-related data were abstracted through prospective record review. Participation lasted one year with measures evaluated at baseline, six-months, and 12-months.

Results: Our sample included 40 adult men (70%) and women (30%) with detectable viral loads (>1000 copies), aged 18-65 (μ=36.30±10.82 years) who were African American (50%), White (47.5%), or multi-racial (2.5%). There were no significant differences in the distribution of gender, age, race, or baseline viral load or antiretroviral uptake between the intervention and control groups. Intervention participants reached viral suppression significantly more quickly than control participants (see table, p=0.04), were more likely to complete scheduled visits (p=.005), were less likely to be lost to follow-up in the first year (p=.04), and to be undetectable at the 12-month time point (p=.01)

Conclusion: Our results demonstrate the potential of a telehealth intervention bundle to help patients reach viral suppression sooner, promote early identification of distress and difficulties, and help strengthen clinical relationships with the healthcare team. A healthcare bundle which focuses on supporting the needs of PWH may improve overall health and reduce the spread of HIV.

Primary and Secondary Outcomes

Primary and Secondary Study Outcomes

	Intervention-P2H (n=20)		Standard of Care-SOC (n=20)		
Outcome	**Median**	**Range**	**Median**	**Range**	***p****
Time to Undetectable (Days)	67	29-365	158	40-507	*.04**
Missed Visits	2	0-8	3	0-10	.40
Completed Visits	5	2-9	3	0-10	*.005**
Outcome	**n**	**%**	**n**	**%**	***p****
Lost to Follow Up					
Yes	1	5%	7	35%	*.04***
No	19	95%	13	65%	
Reached Undetectable by 12-month Timepoint					
Yes	16	80%	7	35%	*.01***
No	4	20%	13	65%	

*Significance level reflects Wilcoxin rank-sum test comparison of distributions in each group

**Significance level reflects Fisher's Exact Test due to Expected Cell Counts <5

1083 LONG-TERM OUTCOMES OF RAPID ANTIRETROVIRAL THERAPY IN AN INTEGRATED HEALTH SYSTEM

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Background: In 2017, the World Health Organization recommended rapid ART based on studies showing improved virologic suppression and care retention. Prior studies on rapid ART examined short term outcomes (1-2 years follow-up) with small cohort sizes. Here, we compare both short- and longer-term clinical outcomes of patients newly diagnosed with HIV who received rapid or standard ART strategies.

Methods: This is an observational cohort study of adults ≥18 years old newly diagnosed with HIV between January 2015 - December 2020 who initiated ART within one year of diagnosis at Kaiser Permanente Northern California (KPNC). Rapid and standard ART were defined as initiation ≤7 days versus >7 days after HIV diagnosis, respectively. Using electronic health records, data

were collected on HIV viral load (VL), clinical encounters, and ART refills. Short term outcomes included time to virological suppression (< 200 copies/ml) and retention in care at one year after diagnosis. Retention in care was defined as ≥1 VL measurement and 2 HIV primary care office visits at least 3 months apart within 1 year of diagnosis. Long-term outcomes included viremia copy-years (VCY), defined as the area under patients' longitudinal VL curve, and proportion of days covered (PDC) with dispensed ART until lost to follow up or 31 December 2021. Differences between groups were assessed using Chi-Square and Kruskall Wallis tests for categorical and continuous data, respectively.

Results: Median days to viral suppression was shorter in the rapid ART group (48 vs 77, p< 0.001). At one year from diagnosis, no significant difference in virologic suppression was found between groups, and the standard ART group had higher retention in care (81.5% vs 76.3%, p< 0.05). Over the study duration, however, patients in the rapid ART group had improved median PDC (100% vs 90%, p<0.001) and lower median VCY (3.6 vs 3.8 $\log_{10}$ copy x year/mL, p< 0.01).

Conclusion: While one-year follow-up showed similar levels of viral suppression and improved retention in care with standard ART, over a longer period of follow-up, individuals with rapid ART had higher PDC and lower VCY. These findings suggest that rapid ART may improve long-term clinical outcomes compared to standard ART. Lower retention in care in the rapid ART group highlights opportunities for better engagement in care soon after rapid ART initiation.

Outcomes of KPNC adults newly diagnosed with HIV between 2015-2020

Outcomes of KPNC adults newly diagnosed with HIV between 2015-2020

Characteristics	Overall (N=1,411)	Standard ART (N=929)	Rapid ART (N=482)	P-Value[1]
Median days to VL <200 copies (IQR)	69.0 (45.0-110.0)	77.0 (54.0-119.0)	48.0 (34.0-89.0)	**<0.001**
VL <200 copies within one year of HIV diagnosis	1,293 (91.6)	860 (92.6)	433 (89.8)	0.08
Retained in care for one year after HIV diagnosis	1,125 (79.7)	757 (81.5)	368 (76.3)	**<0.05**
Median proportion of days covered with ART (IQR)	1.0 (0.8-1.0)	0.9 (0.8-1.0)	1.0 (0.9-1.0)	**<0.001**
Median viremia copy-years [log10 copy x year/mL] (IQR)	3.8 (3.1-4.4)	3.8 (3.2-4.4)	3.6 (2.8-4.4)	**<0.01**

IQR, Interquartile range, i.e. 25th to 75th percentile

Results are presented as No. (%) unless otherwise noted.

[1] P value for the Chi Squared Test of Association for categorical variables and Kruskal Wallis Test for continuous variables.

1084 MODELLING OF CARE ENGAGEMENT PATTERNS IN A LONGITUDINAL COHORT OF PWH: WASHINGTON, DC

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DC Cohort Executive Committee

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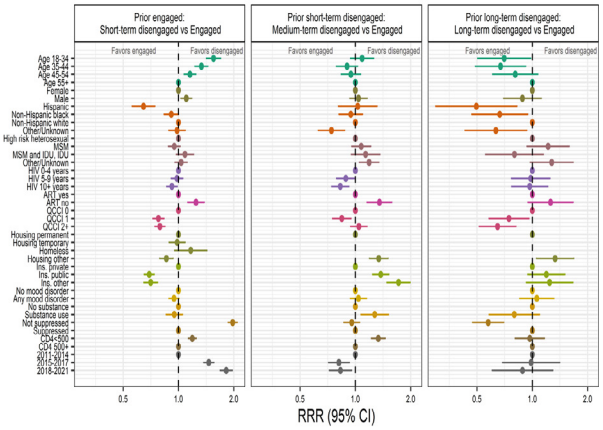
Background: The HIV care continuum emphasizes that PWH should engage in lifelong care and treatment to achieve viral suppression (VS), yet progress along the continuum is non-linear for many PWH. We sought to characterize states of engagement in care and identify potential factors associated with disengagement among a longitudinal cohort of PWH receiving care at 14 HIV clinics in Washington DC enrolled in the DC Cohort.

Methods: DC Cohort participants ≥18 years who enrolled from 1/1/2011 to 6/30/2021 were included. Longitudinal care engagement was determined using discrete multistate modelling using 6 mutually exclusive states (engaged, short, medium-, long-term disengaged, transferred, died) based on care engagement (i.e., having ≥1 HIV visit, CD4 or VL in a 200-day interval). Multinomial logistic regression for repeated measures was used to identify predictors of transitioning between different care engagement states including demographics, HIV indicators, substance use and the modified Quan Charlson Comorbidity Index (QCCI).

Results: Among 11,064 PWH (median age 47 years, 72% male, 63% NH Black, 48% ≥10 years since HIV diagnosis, 75% VS), the probability of remaining engaged was 85%, the probability of disengagement was 14%. After one 200-day period of disengagement (short-term disengagement), the probability of re-engagement was 55%, 21% after two periods (medium-term disengagement), and 4% after ≥3 periods of disengagement (long-term disengagement). During the observation period 14% of PWH transferred their care; 4% died. Factors associated with short-term disengagement compared to those who remained engaged included younger age, race/ethnicity, male, not on ART at baseline, a QCCI score of 0, private insurance, not VS and CD4 < 500 cells/μL (p-values < 0.05). Medium-term disengagement was associated with younger age, not being on ART, lack of permanent/stable housing, any substance use, public insurance, and CD4 < 500 cells/μL (p-values < 0.05). Predictors of long-term disengagement included increasing age, being NH White, not being on ART, lower QCCI score, lack of permanent/stable housing, and being VS (p-values < 0.05)(Figure).

Conclusion: Among a cohort of PWH who linked to care, we found the probability of re-engaging in care decreased with each additional 6-month interval and factors associated with disengagement varied based on the duration out of care. Identifying PWH at risk of early disengagement may minimize the cyclic nature of care and improve long term HIV care continuum outcomes.

RRR (95% CI) for the multinomial regression for the transitions from engaged in care to short-term disengaged vs remaining in care (left panel), from short-term disengaged to medium-term disengaged vs returning to care (center panel), or from long-term disengaged to remaining in long-term disengaged vs returning to care (right panel)



1085 COST DRIVERS OF PROVIDING ADVANCED HIV DISEASE CARE THROUGH HUB/SPOKE MODEL IN MALAWI

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Background: Antimicrobial prophylaxis and treatment for opportunistic diseases immediately before or at the start of antiretroviral therapy (ART) improves the prognosis and decreases the death rates among HIV patients with advanced HIV Disease (AHD). Access to diagnostics and drugs is needed to determine immunosuppression and identify and treat opportunistic diseases. This evaluation estimated the average cost per patient receiving AHD services (PP) and per client retained (PR) at six and 12 months.

Methods: The study population included children, adolescents, and adults enrolled in the AHD program at 32 purposively selected health facilities in Malawi. We performed secondary cost data collection from project financial records, budgets, and invoices. Prices of certain consumables (i.e. drugs) were obtained from the Ministry of Health or the partner responsible for their purchase. Costs were estimated from a health service provider perspective using a micro-costing method, combining top-down and bottom-up approaches to obtain resource use and costs per line item. To estimate the cost PP and PR, we divided the total cost of providing AHD services at six months or 12 months by the number of AHD patients who received AHD services and the number of patients retained, respectively.

Results: We enrolled 254 AHD patients with 219 (86%) retained at six months. The total cost of providing AHD services at 6 months in the selected 32 sites was $38,920, the cost PP was $153 and the cost PR was $178. Consumables and supplies, such as laboratory tests and drugs, were the largest costs (45%), followed by clinic visit costs (24%), travel for supervision and mentorship (19%), site support personnel (6%), training (4%), and meetings (2%). Sensitivity analysis showed that a reduction in the drugs and laboratory costs lead to a reduction in the cost PP and PR.

Conclusion: Conclusion: There is an urgent need to invest in laboratory supplies and drugs to reduce the burden of these on the healthcare system for an optimal AHD program.

Note: 12 months' data will be collected between October and November 2022.

1086 ADVANCED HIV DISEASE CARE PACKAGE IMPLEMENTATION IN LESOTHO AND SOUTH AFRICA

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Background: The advanced HIV disease (AHD) care package reduces mortality in AHD but is barely implemented. We assessed the feasibility of its implementation, including a novel point-of-care CD4-test.

Methods: A mixed-methods study, embedded in the TB TRIAGE+ study (ClinicalTrials.gov: NCT04666311), in patients with TB symptoms presenting at two rural facilities in Lesotho and South Africa. HIV-positive participants received VISITECT CD4 lateral flow assay (CD4 LFA), urine Alere Determine TB-lipoarabinomannan antigen (TB-LAM) LFA, Immy cryptococcal antigen (CrAg) LFA on plasma in case of CD4≤200cells/µL, and treatment referral. We assessed compliance with the testing sequence, observed procedural completeness (Likert-scale) and timing, and assessed acceptability among implementers (questionnaires, group discussions).

Results: In Lesotho and South Africa, respectively, 47.9%(335/700) and 49.3%(341/692) of study participants were HIV-positive. Among those eligible, 99.1%(332/335) and 99.7%(340/341) received CD4 LFA, 100.0%(335/335) and 99.4%(339/341) TB-LAM and 98.7(150/152) and 100.0%(50/50) CrAg (Table 1). Among tested females and males, respectively, 20.2%(70/347) and 40.6(132/325) had CD4≤200cells/µL, TB-LAM was detected in 14.1%(49/348) and 12.3%(40/326), and CrAg in 5.7%(4/70) and 3.1%(4/130). Study procedures were rated complete (n=16 Likert scales). The three tests were performed in 73 [median, IQR:68-85] minutes (n=5 observations). Reasons to not perform a test were patient refusal after HIV diagnosis (1 CD4 LFA and TB-LAM), failure to produce a sample (1 TB-LAM), and expired tests or reagents (3 CD4 LFA, 2 CrAg). Implementers estimated the risk of making mistakes low but found timing of procedural steps, especially for CD4 LFA, initially challenging. Waiting time was reduced by running CD4 LFA and TB-LAM in parallel. Implementers agreed that the package is acceptable for them and patients, easy to perform after a short learning curve, and can be performed anywhere, by any cadre with training. They were in favor of community implementation, where the need was perceived as higher.

Conclusion: We found a high prevalence of AHD, especially in Lesotho, including among people with known HIV. Implementing the AHD care package was feasible at facility level and anticipated to be feasible in the community. Enablers include uninterrupted supplies of tests and good time management. The AHD care package can and should be implemented to reduce AIDS-related mortality in these settings.

Table 1: Test results of advanced HIV disease care package

Results % [95%CI]	CD4 LFA≤200cells/µL	TB-LAM detected	CrAg detected
Lesotho	**45.8% [40-51]**	**16.1% [12-21]**	**2.7% [0.7-6.7]**
Known HIV	41.8% [36-48]	14.3% [11-19]	3.3% [0.9-8.1]
New HIV	80.0% [63-92]	31.4% [17-49]	0.0% [0.0-13]
South Africa	**14.7% [11-19]**	**10.3% [7.3-14]**	**8.0% [2.2-19]**
Known HIV	14.2% [11-19]	10.6% [7.4-14]	8.7% [2.4-21]
New HIV	23.5% [6.8-50]	5.9% [0.1-29]	0.0% [0.0-60]

CDA LFA: CD4 lateral flow assay, CrAg: cryptococcal antigen, TB-LAM: TB-lipoarabinomannan

1087 ARE VENUE-BASED STRATEGIES THE TICKET TO THE LAST MILE IN HIV PREVENTION IN MALAWI?

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CLOVE Study

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Background: In 2016, Blantyre District had the highest adult HIV prevalence in Malawi (17% overall; 22% in women) and the lowest viral suppression rate (60%). In response, the MOH expanded prevention and treatment strategies. We hypothesized that social venues patronized by people with high sexual partnerships rates could identify sub-groups currently missed.

Methods: We conducted cross-sectional bio-behavioral surveys of representative samples of individuals seeking care in government clinics (n=2313) and social venue patrons (n=1802) Jan-Mar 2022. Clinics were randomly selected from government clinics providing HIV testing. Venues were randomly sampled from urban and rural strata with oversampling of rural venues. Sampling weights were based on 2-stage sampling probabilities. We followed national testing protocols for rapid tests, recency testing and viral load measurements. Acute infections were identified by pooling dried blood spots from persons with an HIV- rapid test.

Results: Compared to the clinic population, the venue population was more likely to: be male (68% vs 28%); aged >25 years (61% vs 51%); unmarried (62% vs 40%); drink alcohol daily (43% vs 8%); have more sexual partners in the last year (mean 16 vs 2); report a new sex partner in the past 4 weeks (42% vs 14%); and report transactional sex (52% vs 12%). HIV prevalence (Table 1) was higher among the venue population (19% vs 9%); the proportion HIV+ suppressed was similar (78%). Among women recruited at venues, prevalence increased by age: 0% among age 15-17 to 41% among age 18-21. At venues, factors associated with HIV infection include female sex (39% vs 10%); having a new partner in the past 4 weeks (28% vs 13%) and transactional sex (25% vs 13%). Acute and recent infections were uncommon. Clinic participants who reported visiting venues were less likely to have a suppressed viral load than other PLHIV clinic participants (53% vs 81%). Among both populations, reporting a genital sore in the past 4 weeks was associated with non-suppression (40% vs 20% in clinic; 48% vs 20% in venues).

Conclusion: Lower HIV prevalence and greater viral suppression suggests that Blantyre's HIV epidemic is slowing. Strategies to further reduce transmission should include outreach to venues with higher prevalence of unsuppressed infection and to young women at venues. Testing for acute or recent infection yielded few cases and thus did not provide sufficient value to warrant the cost.

Table 1: Proportion of HIV clinical Outcomes by clinic and venue

Clinical outcome	Clinic	Venue
Total	**2313**	**1802**
HIV Status		
% HIV Negative	91.3 %	80.8 %
% HIV Positive	8.7 %	19.2 %
Among HIV+		
% Suppressed	78.0	78.1
% Not Suppressed	22.0	21.9
Among Not Suppressed		
Total	**50**	**65**
% Acutely infected	0.0	0.7
% Recently Infected	4.6	9.0
% with Chronic Infection	95.4	90.4

Suppression = viral load <1000 copies/mL

1088 COMMUNITY-ENGAGED PrEP DEMONSTRATION PROJECT FOR MSM IN CHINA

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Background: Financial cost, societal stigma, and suboptimal community engagement delayed the scale-up of Pre-Exposure Prophylaxis (PrEP) among key populations in China. To overcome these barriers, we developed a CBO-clinic hybrid model to deliver PrEP.

Methods: The PrEP demonstration project was carried out in two cities (Guangzhou and Wuhan) to provide free PrEP, guided by Community-based participatory research, in which researchers and community stakeholders engage as equal partners. In our model, social workers from community-based organizations (CBO) lead the social media-based recruitment and implementation of the project, such as developing the promotion strategies on the WeChat app or public account, liaising with potential participants, conducting pre-screening, and referring the participants to the clinic for lab testing, while healthcare providers lead the PrEP prescription and monitoring. After enrollment, social workers offered both picking-up or mail delivery of PrEP

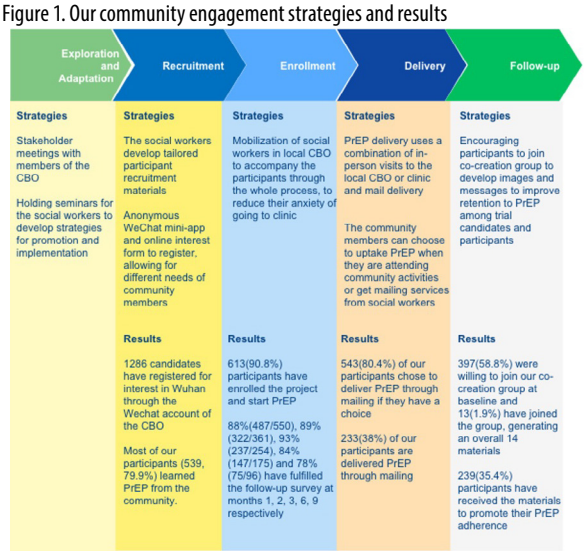
to participants to make the services more convenient. Baseline demographic data and the results of our CBPR strategies were summarized.

Results: From September 2021 to September 2022, PrEP and STI self-testing services were delivered to 675 participants, 391(58%) in Guangzhou and 284(42%) in Wuhan. Overall, 656 (97.2%) of the participants were cisgender men. 653(96.8%) self-identified as MSM (93.5% MSM and 3.3% MSMW). The median age was 28.8. In the 3 months follow-up survey, among those who reported their regimen, 21% (55/260) of participants reported on-demand regimen. The fully-adherent (self-reported taking 6-7 pills per week on daily regimen) rates were 97% (200/205), 96% (120/125), and 97.2% (35/36) at months 3, 6, 9 respectively.

The results of our CBPR strategies suggest that 1286 candidates have registered for interest through CBO's public account, most of our participants (539, 79.9%) learned PrEP from the community, 613(90.8%) participants started PrEP after enrollment, and 233(38%) participants are delivered PrEP by mailing. The detailed strategies and statistics are shown in Figure 1.

Conclusion: Findings from our demonstration project suggest that MSM in China are likely to be incentivized by the community. A hybrid CBO and clinic-based model is an effective way to deliver PrEP, as in-person visit provides professional advice, and mailing promotes the accessibility of PrEP. The mobilization of local CBO that closely works with the community can engage the community by developing people-centered services.

Figure 1. Our community engagement strategies and results



1089 RANDOMIZED TRIAL LEVERAGING ELECTRONIC HEALTH RECORD DATA TO INCREASE HIV PrEP UPTAKE

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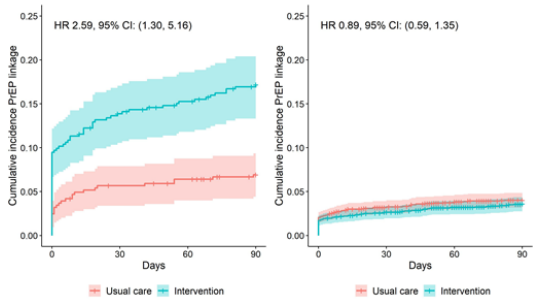
Background: We previously developed and validated a prediction model that used 44 electronic health record (EHR) data elements to identify patients who are at increased risk of HIV diagnosis and not using preexposure prophylaxis (PrEP). Implementing this EHR-based model in primary care has potential to increase linkage to PrEP care among patients likely to benefit from PrEP.

Methods: We conducted a randomized controlled trial of a clinical decision support intervention for PrEP at Kaiser Permanente San Francisco from June-November 2021. Adult primary care providers (PCPs) were randomized to usual care or intervention arms. PCPs who also provide care to people with HIV (PWH) were balanced between trial arms. PCPs in the intervention arm were alerted via EHR-based secure email messages about patients with elevated model-generated risk scores (3-year risk of HIV of ≥0.2%) and upcoming in-person or virtual visits, with prompts to discuss HIV prevention and PrEP. Providers only received alerts for patients aged ≥18 years with no previously documented HIV diagnosis or PrEP prescription. The primary study outcome was the 90-day cumulative incidence of linkage to PrEP care, defined as a PrEP diagnosis code during a clinical encounter (reflecting a PrEP discussion), PrEP referral, or PrEP prescription fill. We report the intervention hazard ratio (HR) and 95% CI from Cox regression models using robust standard errors to account for clustering by provider, with adjustment for and stratification by providers who care for PWH.

Results: 121 PCPs were randomized, including 13 with PWH on their panels, with 5051 eligible appointments (2,471 intervention, 2,580 control). The median age of eligible patients was 39 years (IQR 31-51), with 95.4% men and 42.6% non-Hispanic White, 18.7% non-Hispanic Black, 15.1% Hispanic, and 14.6% Asian. There was a nonsignificant increase in PrEP linkage in the intervention arm (6.0% vs 4.5%, HR 1.31, 95% CI 0.84, 2.1). There was a significant interaction by HIV provider status (see Figure 1), with an intervention HR of 2.59 (95% CI 1.30, 5.16) among providers with PWH on their panels and 0.89 (95% CI 0.59, 1.35) for those without (p-interaction < 0.001).

Conclusion: A low-intensity intervention that leveraged an EHR-based HIV risk prediction model substantially increased linkage to PrEP care after in-person and video visits among PCPs who also care for PWH. More intensive interventions may be needed to increase PrEP linkage among PCPs less familiar with PrEP and HIV care.

Figure 1. Kaplan-Meier-based cumulative incidence curves for PrEP linkage among intervention and control providers, stratified by PCPs with (left) and without (right) PWH on their panels.



1090 COSTS OF PROVIDING PHARMACY-INITIATED PrEP IN KENYA: FINDINGS FROM A PILOT STUDY

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Background: Provision of oral HIV pre-exposure prophylaxis (PrEP) at pharmacies in high HIV prevalence settings can expand access to PrEP and increase convenience to clients; however, implementation costs are uncertain. We conducted activity-based microcosting to analyze costs associated with this novel PrEP delivery model within an ongoing pilot study evaluating pharmacy-based PrEP delivery in Kenya (CT.gov: NCT04558554).

Methods: Trained pharmacy providers at five private pharmacies screened interested clients (≥18 years) for HIV risk and medical safety, conducted HIV testing (using oral self-tests), and dispensed PrEP to those eligible with remote clinician oversight. Costs (2021 USD) were collected from the provider perspective using study budgets, expenditure records, and staff interviews. We interviewed pharmacy owners to obtain financial and economic costs associated with pharmacy overhead, including salaries. We conducted time-and-motion observations of PrEP initiation and refill visits at the pilot pharmacies and examined pharmacy records. We categorized costs into core components of PrEP delivery (HIV risk screening, counseling, HIV testing, prescribing/dispensing) and excluded research costs.

Results: From July to October 2021, we conducted 64 time-and-motion observations of clients initiating (n=15) and continuing (n=49) PrEP at pharmacies. Pharmacy PrEP initiation visits took providers a median of 36 minutes (IQR 27-38), with HIV risk screening accounting for a third of this time (median: 12 minutes, IQR 11-17); continuation visits were ~10 minutes shorter for providers, taking a median of 25 minutes (IQR 21-29). The median financial cost for pharmacy providers to deliver PrEP per client was $7.70 per month (IQR $6.72-$9.41) at initiation and $19.86 per 3 months (IQR $17.21-$21.74) at continuation visits, with PrEP drugs accounting for the greatest proportion of costs. The monthly per client cost of pharmacy PrEP initiation visits was lower

than continuation visits ($6.62, IQR $5.47-$7.29), which account for the majority of clients' visits.

Conclusion: Daily oral PrEP can be delivered at reasonable costs at private pharmacies in Kenya, comparable to PrEP delivery costs at public health facilities. Improving efficiencies in pharmacy PrEP delivery (e.g., provider multitasking) may help decrease pharmacy provider time, resulting in potential cost savings. These estimates can inform policy discussions around PrEP scale-up strategies in Kenya and similar settings.

1091 CLIENT PREFERENCES FOR PrEP REFILLS AT FACILITIES VS PHARMACIES: A PILOT IN KENYA

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Background: In many high HIV prevalence settings, delivery of pre-exposure prophylaxis (PrEP) in public health facilities is challenged by understaffing, long wait times, and stigma. Expanding PrEP delivery to private pharmacies may help mitigate these barriers. To assess whether current PrEP users would choose to refill their PrEP prescription at a private pharmacy if given the option, we pilot-tested such a model in Kenya.

Methods: At two public health facilities in Kiambu County, we recruited adult (> 18 years) clients newly initiating PrEP. Once enrolled, clients were given the option to refill PrEP at a public health facility (for free) or at one of three nearby private pharmacies (for a fee of 300 Kenyan Shillings, or ~$2.50 US Dollars). Pharmacy providers at pilot pharmacies were trained on PrEP delivery, including how to counsel on HIV risk and PrEP adherence, assess medical safety, complete HIV testing, and refill prescriptions. At enrollment, we asked clients their preferred location for refilling PrEP. We then followed clients for up to seven months and assessed whether and where clients chose to refill their PrEP prescription.

Results: From November 2020 to October 2021, we screened 125 clients and enrolled 106. Among enrolled clients, the median age was 31 (IQR 26-38), 59% (n=63) were female, 67% (n=71) were married, and 49% (n=52) were in an HIV serodifferent relationship. At enrollment, clients' preferred refill location was split between public health facilities (55%, n=58) and private pharmacies (45%, n=48). Over 292 total client-months of observation (median: 1 months per client, IQR 1-4), 42% (n=44) of clients refilled PrEP at least once, and only 3 (3%) clients refilled PrEP at a pilot pharmacy. There was no difference in PrEP continuation ($p< 0.05$) based on clients' stated preference for PrEP refill location.

Conclusion: Few clients who initiated PrEP at a public health facility in this pilot opted to refill their PrEP prescription at a private pharmacy, despite over half stating a preference for pharmacy-based refills. This data suggests that once PrEP clients in Kenya have overcome barriers to initiate PrEP at a facility, continuation at this location may be easier than at a new location. Additional research is needed to understand drivers of PrEP refill location choice (e.g., cost, trust in service provider) and test implementation strategies (e.g., vouchers) that might enable clients to select their preferred refill location.

1092 MALE CIRCUMCISION IN BOTSWANA: EFFECT OF QUALITY IMPROVEMENT ON ADVERSE EVENT RATES

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Background: Voluntary medical male circumcision (VMMC) has been shown to reduce heterosexual human immune deficiency virus (HIV) transmission. In 2009, Botswana, a high HIV burden country in southern Africa, rolled out its VMMC program to expand existing HIV preventive strategies. However, an adverse event rate of 6.7% was recorded for the program in 2017. A quality improvement team was introduced to help reduce the adverse event rate. Data on the impact of the team in reducing adverse event rates are limited.

Methods: A quasi-experimental study was conducted using national data extracted from monthly district reporting tools. Interrupted time series analysis was used to compare the trend and magnitude of adverse event rates for the day two, day seven and day forty-two, routine follow-ups in males aged 10 years and older. The comparison was done two years before (April 2015 to March 2017) and two years after (April 2017 to April 2019) the introduction of the quality improvement team. The most common adverse events by age, type, and severity between April 2015 and April 2019 were also reported.

Results: After the introduction of the quality improvement intervention, the day two adverse event rates insignificantly decreased by 0.05% (p=0.099, 95% CI=-0.0012, 0.0001), the day seven adverse event rates significantly reduced by 0.08% (p=0.0175, 95% CI=-0.0014, -0.0001) and the day forty-two adverse event rates insignificantly declined by 0.1% (p=0.148, 95% CI=-0.0226, 0.0035). Between April 2015 and April 2019, 1175 adverse events were reported and majority (68.5%) of these adverse events occurred in the 10-14 years age category. Most of these adverse events were mild (73.8%), and infections were the most common type of adverse event (45.1%).

Conclusion: The trend and magnitude of the day two and day forty-two adverse event rates did not significantly change with the introduction of the quality improvement team, but the day seven adverse event rates changed significantly. Therefore, the quality improvement process had a minimal clinically significant effect on the trend and magnitude of adverse events. Infections were the most common type of adverse event thus highlighting the need for increased infection control measures within the VMMC program, especially for the 10-14 years individuals.

1093 HIV OUTCOMES AFTER EXTENDED 12-MONTH SCRIPTS FOR ART DURING COVID-19 IN SOUTH AFRICA

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Background: There is an urgent need for more efficient models of differentiated anti-retroviral therapy (ART) delivery, with the World Health Organization and PEPFAR calling for evidence to guide whether 12-monthly ART prescriptions and clinic review (12M scripts) should be recommended in global guidelines. We assessed the association between 12M scripts (allowed temporarily during the COVID-19 pandemic) and clinical outcomes in South Africa.

Methods: We performed a retrospective cohort study using routine, de-identified data from 59 public clinics in KwaZulu-Natal. We included PLHIV aged >18 years with a recent suppressed viral load (VL), and who had been referred from their clinic into a community ART delivery programme with a standard 6-month prescription and clinic review (6M script) or a 12M script. In the community ART programme, PLHIV collected ART every two months at external pick-up points, before returning to the clinic after 6 or 12 months for a new script. We used multivariable modified Poisson regression, accounting for clinic clustering, to compare 12-month retention-in-care (not >90 days late for any visit) and viral suppression (< 50 copies/mL) between 6M and 12M script groups.

Results: Among 27,148 PLHIV referred for community ART between Jun-Dec 2020, 42.6% received 6M scripts and 57.4% 12M scripts. The median age was 39 years (interquartile range [IQR] 33-46) and 69.4% were women. Age, gender, prior community ART use and time on ART were similar in the two groups (Table). However, a larger proportion of the 12M script group had a dolutegravir-based regimen (60.0% versus 46.3%). The median (IQR) number of clinic visits in the 12 months of follow-up was 1(1-1) in the 12M group and 2(2-3) in the 6M group. Retention at 12 months was 94.6% (95% confidence interval [CI] 94.2%-94.9%) among those receiving 12M scripts and 91.8% (95% CI 91.3%-92.3%) among those with 6M scripts. 16.8% and 16.7% of clients in the 12M and 6M groups were missing follow-up VL data, respectively. Among those with VLs, 90.4% (95% CI 89.9%-91.0%) in the 12M group and 88.9% (95% CI 88.3%-89.5%) in the 6M group were suppressed. After adjusting for age, gender, ART regimen, time on ART and prior community ART use, retention (adjusted risk ratio [aRR]: 1.03, 95% CI 1.01-1.04) and suppression (aRR: 1.02(1.01-1.03) were higher with 12M scripts.

Conclusion: COVID-19 led to temporary introduction of 12M scripts in South Africa. Wider use could reduce clinic visits without negative impacts on short-term clinical outcomes.

Table: Baseline characteristics of clients referred for community ART delivery between Jun-Dec 2020, split by baseline ART prescription length

		6-month script, N = 11553 (42.6%)	12-month script, N = 15595 (57.4%)
Gender, %(n)	Male	29.4(3395)	31.1(4847)
	Female	70.6(8158)	68.9(10748)
Age in years, median(IQR)		39(33-46)	39(33-46)
Years on ART, median(IQR)		5(3-8)	5(3-7)
ART regimen, %(n)	First line TLD	46.3(5354)	60(9354)
	First line TEE	48.9(5648)	36.4(5683)
	First line other	2.1(242)	1.5(228)
	Second line	2.7(309)	2.1(330)
Previous community ART use, %(n)	No	21.6(2494)	21.5(3346)
	Yes	78.4(9059)	78.5(12249)
Months since first referred to community ART, median(IQR)		22(6-35)	23(6-36)
Days between baseline and previous viral load, median(IQR)		28(0-56)	28(14-55)

TLD = tenofovir disoproxil fumarate, lamivudine, dolutegravir. TEE = tenofovir disoproxil fumarate, emtricitabine, efavirenz.

1094 VIRAL SUPPRESSION TRAJECTORIES DESTABILIZED AFTER COVID-19 AMONG US PEOPLE WITH HIV

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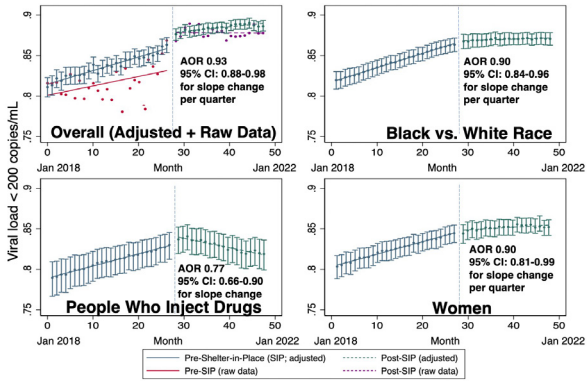
Background: Disruptions in clinical services during the COVID-19 pandemic could compromise past progress towards meeting U.S. Ending the HIV Epidemic (EHE) goals. We examined changes in the proportion with virologic suppression (VS) before and since the onset of COVID-19 in a multi-site U.S. cohort of people with HIV (PWH) using an interrupted time series design.

Methods: We assessed VS (< 200 copies/mL) trajectories 1/1/2018-1/1/2022, comparing trends before and after March 21, 2020 at 8 HIV clinics within the U.S. Center for AIDS Research Network of Integrated Clinical Systems ("CNICS"). Hierarchical mixed-effects logistic regression and interrupted time series analyses examined changes in the trend (i.e., slope) of VS over time, and maximum likelihood estimation was used to account for missing VS data among those lost to follow-up (LTFU) post-COVID-19. Analyses were adjusted for demographics, site, CDC transmission group, CD4 nadir, VS, time on ART.

Results: Data from 17,999 participants were included, providing a total of 120,918 VS assessments. Median age was 53 (interquartile range 42-61); 19% were female sex at birth; the mean time on ART was 9.5 years; 18% were unsuppressed at any point; 17.7% were LTFU. Among the overall population, prior gains in VS slowed during COVID-19 (adjusted odds ratio [AOR] 0.93 per quarter-year; 95% CI: 0.88-0.98; p=0.004; **Figure**). Greater impacts occurred among women (AOR 0.90; 95% CI 0.81-0.99; p=0.05), persons with a history of injection drug use (PWID) (AOR 0.77 95% CI: 0.66-0.90; p=0.001), and Black PWH (AOR 0.90; 95% CI: 0.84-0.96; p=0.001) in whom prior positive VS trends plateaued or began to reverse (**Figure**). VS remained lower among those with unstable housing (AOR 0.44; 95% CI: 0.40-0.50; p< 0.001) but stayed unchanged from the pre-pandemic period.

Conclusion: Previous gains in VS slowed during the COVID-19 pandemic among PWH in a multi-site network of U.S. HIV clinics. Known disparities in VS according to housing status remain unchanged, but VS disparities worsened for PWH who were women, PWID, or Black. Changes in VS trends could be related to socioeconomic impacts of the pandemic, insurance lapses, reduction of in-person clinic services, fear of coming to clinics, or other factors. Renewed investment in HIV public health and clinical services will be vital to achieve the U.S. EHE goals following COVID-19, with additional targeted interventions to support key populations with persistent or worsening disparities needed.

Viral Suppression Trajectories Before and After COVID-19 Shelter in Place



1095 HIV CARE DURING THE SARS-CoV-2 PANDEMIC IN BLACK PEOPLE WITH HIV IN THE UK

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Background: The COVID-19 pandemic disproportionally affected black communities but the impact on HIV care in this group remains poorly understood. We evaluated measures of HIV care during the COVID-19 pandemic in the GEN-AFRICA cohort of black people with HIV living in the United Kingdom.

Methods: We evaluated interruptions to HIV care during the COVID-19 pandemic (01/2020-09/2022) in the GEN-AFRICA cohort at nine UK clinics who provided HIV outcomes for >80% of their participants. We ascertained death, transfers of care, loss to follow up for >12 months, the highest HIV virus load, and interruptions to antiretroviral therapy (ART). We evaluated factors associated with the composite outcome of HIV viraemia (virus load >200 c/mL) and/or an ART interruption using logistic regression analysis; factors associated (P< 0.1) in univariable analysis were included in the multivariable model. We also summarized reasons for ART interruptions where recorded.

Results: On 01/01/2020, 2321 GEN-AFRICA study participants (mean age 51.3 years; 55.8% women; pre-pandemic current/nadir CD4 of 500/204 cells/mm^3 and HIV RNA < 200 c/mL in 92.3%) were under active HIV follow up. Thirty (1.3%) subsequently died, 24 (1.0%) transferred care, and 48 (2.1%) became lost to follow up; 523 (22.7%) reported an episode of COVID-19 and 1771 (87.1%) having been vaccinated against SARS-CoV-2. The composite outcome could be evaluated in 2130 (91.8%); 259 (11.2%) had a documented HIV VL >200 c/mL, 228 (9.8%) an ART interruption, and 325 (14%) had HIV viraemia/ART interruption. In multivariable analysis, older age, a pre-pandemic HIV RNA < 200 c/mL and being vaccinated against SARS-CoV-2 were associated with reduced odds of HIV viraemia/ART interruption (Table) while sex, CD4 (current/nadir), comorbid status and having had COVID-19 were not or no longer associated. Reasons for ART interruption were available for 52 participants; 38% cited domestic logistic reasons, 27% issues related to foreign travel, 19% psychological reasons, 12% lockdown or changes to the daily routine, and 4% personal choice.

Conclusion: During the COVID-19 pandemic, one in seven black individuals with HIV experienced an ART interruption and/or HIV viraemia. Pre-pandemic measures of suboptimal engagement in care, pandemic restrictions, and wider health beliefs as reflected by SARS-CoV-2 vaccination status, contributed to these undesirable HIV outcomes.

Factors associated with HIV viraemia/ART interruption

		Univariable		Multivariable	
		OR	p value	OR	p value
Age	20-29 years	1		1	
	30-39 years	0.51 (0.28-0.95)	0.03	0.49 (0.24-1.01)	0.05
	40-49 years	0.32 (0.18-0.57)	<0.001	0.49 (0.26-0.93)	0.03
	50-59 years	0.34 (0.20-0.59)	<0.001	0.50 (0.27-0.95)	0.03
	≥60 years	0.30 (0.17-0.54)	<0.001	0.51 (0.26-1.00)	0.05
Sex	Female (vs. Male)	0.88 (0.69-1.11)	0.28		
Region of ancestry	West Africa	1		1	
	East Africa	0.69 (0.48-0.99)	0.04	0.74 (0.49-1.10)	0.14
	Southern Africa	0.84 (0.60-1.17)	0.31	0.87 (0.59-1.27)	0.46
	Central Africa	1.40 (0.85-2.30)	0.19	1.35 (0.77-2.38)	0.3
	Caribbean	1.04 (0.72-1.50)	0.83	0.95 (0.63-1.45)	0.82
	Other	1.31 (0.82-2.08)	0.26	1.22 (0.71-2.09)	0.57
Time since HIV diagnosis	Per year	0.98 (0.96-1.00)	0.01	1.00 (0.97-1.02)	0.71
CD4 Nadir (≥350 cells/mm³)	Yes (vs. no)	0.87 (0.65-1.17)	0.36		
CD4 Current (≥350 cells/mm³)	Yes (vs. no)	0.74 (0.57-0.96)	0.02	0.83 (0.62-1.12)	0.22
HIV RNA pre-pandemic (<200 copies/mL)	Yes (vs. no)	0.20 (0.14-0.28)	<0.001	0.23 (0.16-0.34)	<0.001
AIDS	Yes (vs. no)	0.54 (0.17-1.72)	0.30		
Diabetes	Yes (vs. no)	0.96 (0.63-1.46)	0.85		
Hypertension	Yes (vs. no)	0.92 (0.71-4.18)	0.50		
Kidney disease *	Yes (vs. no)	0.82 (0.63-1.05)	0.12		
Cardiovascular disease	Yes (vs. no)	0.94 (0.52-1.72)	0.85		
Obesity **	Yes (vs. no)	0.81 (0.63-1.03)	0.09	0.90 (0.68-1.19)	0.45
COVID-19 vaccination	Yes (vs. no)	0.37 (0.27-0.51)	<0.001	0.39 (0.28-0.55)	<0.001
COVID-19 disease	Yes (vs. no)	1.02 (0.76-1.38)	0.88		

* eGFR <60 mL/min/1.73m²; ** BMI ≥30 kg/m²

1096 DISRUPTIONS IN HEALTH CARE AMONG MWCCS PARTICIPANTS DURING THE COVID-19 PANDEMIC

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Background: The COVID-19 pandemic resulted in disruptions to health care services. Vulnerable populations, including people living with HIV (PLHIV), may have experienced unique challenges when accessing medical care. The objective of this study was to evaluate the impact of social disruptions on health care visits among Multicenter AIDS Cohort Study/Women's Interagency HIV Study Combined Cohort Study (MWCCS) participants.

Methods: A survey collecting data on missed health care visits and social disruptions (i.e., disruptions in employment, childcare, financial support, housing, and health insurance) during the pandemic was administered via telephone to MWCCS participants 1-3 times from March and September 2020. Logistic regression models adjusted for sociodemographics and HIV-status were used to test the association between social disruptions and three medical care interruption outcomes (i.e., missed healthcare appointment, interruption of mental health care, and interruption of substance use care).

Results: Surveys (n=10,076) were conducted among 2238 PLHIV (61% women) and 1427 people living without HIV (PLWoH) (41% women). Overall, 42% of participants reported disruptions in health care with no significant difference by HIV status. Among participants receiving mental health care services and substance use treatment, 52% and 36% reported interruptions of care, respectively. Participants reporting ≥ 2 social disruptions were more likely to report missed health care appointments (adjusted odds ratio [aOR]: 1.81, 95% confidence interval [CI]: 1.54-2.13), and interruptions in mental health care [aOR: 2.42, 95%CI: 1.85-3.17) or substance use treatment (aOR: 1.97, 95%CI: 1.26-3.09), compared to those reporting no disruptions. Participants who were unemployed were more likely to miss health care appointments (aOR:1.46, 95% CI: 1.25-1.71) and report disruptions in mental health care (aOR: 2.02, 95% CI: 1.54-2.66) compared to those who were employed. PLHIV reporting ≥ 2 social disruptions were at increased risk for missed health care appointments (aOR 1.92, 95%CI: 1.56-2.36) and disruptions in mental health care (aOR: 2.54, 95%CI: 1.83-3.53 (Table 1).

Conclusion: Social disruptions as a result of the COVID-19 pandemic have adversely impacted the receipt of health care among PLHIV and PLWoH, including the receipt of treatment for mental health and substance abuse. Providing childcare, financial support, housing, and health insurance may reduce disruptions in care and improve health outcomes.

Adjusted Odds Ratios of Healthcare Disruptions by Number of Social Disruptions Experienced and HIV Status

Table 1. Adjusted Odds Ratios[a] of Healthcare Disruptions by Number of Social Disruptions Experienced and HIV Status

	Missed Healthcare Appointment		Mental Health Care Disruption		Substance Use Treatment Disruption	
Characteristic	PLHIV (2238)	PLWoH (1427)	PLHIV (908)	PLWoH (456)	PLHIV (352)	PLWoH (170)
Social disruptions[b]						
1	**1.51 (1.20-1.90)**	1.08 (0.79-1.47)	**1.60 (1.11-2.30)**	**1.88 (1.11-3.19)**	1.41 (0.76-2.62)	**2.80 (1.09-7.17)**
2+	**1.92 (1.56-2.36)**	**1.65 (1.26-2.17)**	**2.54 (1.83-3.53)**	**2.24 (1.38-3.64)**	1.70 (0.98-2.95)	**2.58 (1.15-5.75)**
Age						
Under 40 vs. 60+	1.03 (0.72-1.47)	0.70 (0.44-1.12)	1.34 (0.77-2.33)	2.06 (0.91-4.69)	1.66 (0.57-4.83)	0.50 (0.07-3.50)
40-49 vs. 60+	1.16 (0.89-1.51)	0.95 (0.65-1.39)	1.21 (0.80-1.81)	1.48 (0.77-2.85)	1.40 (0.67-2.90)	0.89 (0.30-2.66)
50-59 vs. 60+	1.25 (1.01-1.54)	1.15 (0.85-1.56)	1.33 (0.95-1.86)	1.16 (0.69-1.95)	1.35 (0.77-2.38)	1.70 (0.71-4.03)
Race[c]						
Black non-Hispanic	**0.76 (0.59-0.98)**	0.81 (0.57-1.13)	0.87 (0.59-1.30)	0.92 (0.52-1.62)	0.55 (0.28-1.09)	0.95 (0.34-2.67)
Hispanic any race	0.92 (0.68-1.24)	1.03 (0.67-1.60)	0.84 (0.51-1.37)	0.68 (0.32-1.44)	0.40 (0.15-1.05)	0.68 (0.14-3.34)
Other	0.90 (0.63-1.27)	1.07 (0.67-1.72)	1.01 (0.61-1.68)	1.03 (0.50-2.12)	**0.40 (0.16-0.97)**	0.53 (0.14-1.99)

a: Adjusted for age, sex, race, region, employment, income, and combination of cohort (MACS or WIHS) and HIV status
b: Reference category assigned to social disruptions was "0".
c: Reference category assigned to race was "white-non-Hispanic"

1097 UTILITY OF DIGITAL SOLUTIONS IN SUSTAINING ACCESS AND IMPROVING EFFICIENCY OF HIV VL

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Background: Coronavirus Disease 2019 (COVID-19) pandemic disrupted routine program implementation worldwide with significant impact on quality and extent of technical oversight of implementation. Diverse digital reporting solutions and online meetings were some strategies designed to bridge program implementation supervision and reporting gaps worldwide. This paper evaluates usefulness and efficiency of digital solutions deployed by USAIDNigeria to ensure adequate oversight to sustain access and reporting of HIV viral load (VL) services

Methods: To promote accountability and encourage peer-to-peer review and learning among USAID Implementing Partners, daily reporting via digital platforms and virtual weekly peer-review meetings were introduced. This enabled USAID team to monitor IPs' performance at health facilities and during community VL drives against set targets of 100% and 95% patient VL coverage and suppression (VLC/S) respectively. The platforms include National Laboratory Information Management System, remote sample login and Google-based VL Status and Daily Lab Performance dashboards. This study assesses uptake of VL services and clinical outcomes in 16 states of Nigeria between October2019 through March2021 during various levels of COVID-19 lock down. Chi Square test was used to compare the pre-COVID (October2019-March2020), during lockdown (April2020-September2020) and post-COVID lockdown (October2020–March2021) performances at 95 confidence interval and < 0.05 level of significance.

Results: Significant improvements in VL indicators were reported among eight USAID partners across 16 states. Pre-COVID, 591,906 clients on treatment were eligible for VL monitoring, 455,099 were tested and had documented VL results with a 76.9% and 89% VLC/S. During-COVID lockdown, 685,915 became eligible for VL monitoring, 531,371 had documented VL results, with 77.5% and 90% VLC/S. VLC/S increased to 93% each post-COVID lockdown, when 771,149 had documented VL out of 833,463 eligible. There was a significant increase number of clients on treatment who became eligible for VL test and had documented VL results and suppression from pre- during-COVID, and post-COVID lockdown (p=0.001)

Conclusion: Digital solutions deployed by USAID were instrumental to sustaining service delivery with significant growth in access and efficiency to HIV VL services in 16 States in Nigeria despite impact of COVID-19. Program managers should continue to explore cost-efficient innovative approaches for program oversight

HIV Viral Load Performance during Different Period of COVID-19 Response

Phases of COVID Responses	Period of COVID Response	VL Ellgible	VL Test Done	VLC
Pre-COVID Lockdown	Oct 2019 - Mar 2020	591906	455099	77%
COVID Lockdown	Apr - Sep 2020	685915	531371	77%
Post-COVID Lockdown	Oct 2020 - Mar 2021	833463	771149	93%

1098 MITIGATING THE IMPACT OF COVID-19 ON HIV VIRAL LOAD ACCESS AMONG KEY POPULATIONS

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Background: Monitoring of HIV-infected individuals on antiretroviral treatment requires periodic viral load(VL) measurements to ascertain adequate response to treatment. While plasmaVL is widely available in health facilities, it is difficult for use among key populations(KPs) due to their high mobility and sophisticated sample storage and transport requirements, which are not available for community VL sample collection. Use of Dried Blood Spot(DBS) VL measurement has shown promise as an alternative to plasma specimens for KPs. Studies to investigate the performance of DBSVL quantification against the standard plasma VL assay has proven to be within acceptable range. DBSVL was introduced for sample collection among KPs when it became difficult to safely and appropriately collect, store and transport samples during COVID-19 lockdown. This study assessed the usefulness of the use of DBSVL deployed by USAID to ensure access to HIV VL services among KPs in 7 states of Nigeria during COVID-19 lockdown

Methods: To mitigate the impact of COVID-19 lockdown, virtual trainings were conducted for one-stop-shops and community VL champions of USAID partners providing KPs services in seven states of Nigeria on DBS sample collection, storage and transportation and remote test ordering was activated for service providers. Standard operating procedures and job aids were deployed to points of service and laboratory equipment were verified for DBSVL testing. VL sample collection rate(SCR), VL coverage(VLC), VL suppression(VLS), turnaround time (TAT) and cost savings for the program between March2019 and February2021 were compared using the two-sample independent t test pre-COVID (March2019- February2020) and during-COVID lockdown (March2020 –February2021) at 95 confidence interval and < 0.05 level of significance.

Results: There was a significant increase (p< 0.05) in SCR from 73% to 94%, VLC 44% to 85%, and VLS 78% to 95% pre-COVID to during-COVID respectively despite increase in number of clients eligible for VL. However, the median TAT remained unchanged at 29 days. There was a 60% cost savings for the program due to reduction in consumables needed for sample collection and processing and convenience in sampling among KP clients.

Conclusion: Implementation of DBSVL resulted in increases in both VLC and VLS with an improved TAT for KPs clients in seven states of Nigeria. KPs Program implementers should consider introduction of DBSVL sampling among KPs for a better VL access and clinical outcome.

HIV Viral Load Sample Collection, Coverage and Suppression pre- and during-COVID-19

	Pre-COVID March 2019-February 2020	During COVID-19 March 2020-February 2021	p-value
TX_Curr	22568	50784	0.0003191
Samples Collected	11731	36211	0.000536782
Results Documented	7064	32965	0.003389289
Suppressed Results	5528	31373	0.002979203
Viral Load Coverage (%)	44	85	0.009071134
Viral Load Suppression (%)	78	95	0.000633307
Samples Collected Rate (%)	73	94	0.003059948
Median TAT (Days)	29	29	0.205915246

1099 IMPACT OF COVID-19 INDUCED PROGRAM ADAPTATIONS ON HIV SUPPRESSION IN THREE COUNTRIES

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Background: The pandemic response measures have had significant global economic and health impacts with transient reductions in HIV clinic attendance and self-reported anti-retroviral therapy (ART) adherence reported in prior studies. Since viral suppression (VS) is an indication of ART adherence and effective service delivery, we assessed VS in the context of the COVID-19 pandemic in 3 African countries

Methods: Since 2013, the African Cohort Study (AFRICOS) has enrolled individuals 18 years or older with and without HIV, in an approximate 5:1 ratio, at 12 clinics across 5 HIV care programs in Tanzania Uganda, Kenya, and Nigeria. For people living with HIV (PLWH), ART history was extracted from medical records and viral load was assessed at each visit. This abstract assesses VS (< 1000 c/ml) before and during the COVID-19 pandemic (categorized into 4 surges and a consolidated non-surge period; defined in Table 1) among PLWH. Tanzania was excluded due to inadequate pandemic data. Logistic regression with generalized estimating equations, clustered by participant, was used to estimate odds ratios (ORs) and 95% confidence intervals (CI) comparing VS before and during COVID-19. Models are adjusted for age, sex, and program.

Results: Of the 1741 study participants, 368 are from Uganda, 1156 are from Kenya, and 217 are from Nigeria; 730 are males, 1011 are females, and 147 are under the age of 30. PLWH were less likely to be virally suppressed during the first surge period (OR 0.85, CI 0.46-1.56), but VS significantly increased during the second surge period (OR 1.95, CI 1.23-3.04) compared to the pre-COVID period. The third and fourth surge periods also saw a higher VS (table 1). Females are more likely to be virally suppressed than males (OR 1.58, CI 1.09-2.29) and PLWH ages 40-49 have higher VS (OR 2.43, CI 1.32-4.48) compared to PLWH under. PLWH at the AFRICOS sites in Kenya and Nigeria show lower VS than the Ugandan cohort (ORs 0.46, CI 0.26-0.79 and OR 0.32, CI 0.17-0.60 respectively).

Conclusion: The initial drop in VS may be attributed to reduced clinic access due to lockdowns. Many HIV programs supported by the President's Emergency Plan for AIDS Relief (PEPFAR) adapted their strategies to serve PLWH by scaling up community ART dispensing and multi-month dispensing (MMD) of ART for stable clients, which could have led to increased VS during the other surge periods. These findings demonstrate sustained progress made by PEPFAR-supported programs against the HIV epidemic amidst the COVID-19 pandemic

Table 1: Adjusted Odds Ratios of Viral Load Suppression during COVID Pandemic, AFRICOS Sites, March 2020 to June 2022

	Adjusted Odds Ratio	95% Confidence Interval
Time point		
Pre-COVID	Reference	
Surge #1: 1 April to 1 August 2020	0.85	0.46-1.56
Surge #2: 1 October 2020 to 31 January 2021	**1.94**	**1.23-3.04**
Surge #3: 1 June to 31 August 2021	1.28	0.85-1.92
Surge #4: 1 December 2021 to 1 February 2022	1.74	0.98-3.09
Non-surge (remaining periods combined)	1.27	0.94-1.73
Sex		
Male	Reference	
Female	**1.58**	**1.09-2.29**
Age at visit		
15-29	Reference	
30-39	1.91	0.99-3.67
40-49	**2.43**	**1.32-4.48**
50+	**2.72**	**1.47-5.03**
Study site		
Kayunga, Uganda	Reference	
South Rift Valley, Kenya	**0.46**	**0.26-0.79**
Kisumu West, Kenya	0.84	0.42-1.68
Lagos & Abuja, Nigeria	**0.32**	**0.17-0.60**
Pre-COVID data from 1 January 2019 to 31 March 2020		
Modeling the odds of viral suppression (viral load<1000 c/mL)		
Logistic regression with generalized estimating equations, clustered by participant to account for repeated measures, was used to estimate odds ratios (ORs) and 95% confidence intervals (95% CIs		
Bold indicates significance at p<0.05.		

1100 CHANGES IN SERVICE ACCESS AMONG PEOPLE WHO INJECT DRUGS IN PHILADELPHIA, 2018-2022

Tanner B. Nassau, Kathleen A. Brady

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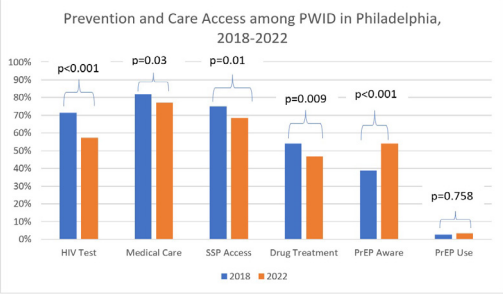
Background: The COVID-19 pandemic disrupted HIV prevention and treatment services, especially for structurally vulnerable individuals like many people who inject drugs (PWID). We sought to compare present levels of access to these services to their levels before the pandemic.

Methods: We used data from 2018 and 2022 collected through the National HIV Behavioral Surveillance (NHBS) survey among PWID in Philadelphia. Using generalized linear regression models, we estimated the associations between our exposure (year) and self-reported HIV testing, medical care, SSP access, PrEP use, and drug treatment in the year prior to interview. We calculated adjusted prevalence ratios (aPR) using multivariable models adjusted for age, race/ethnicity, housing stability, and primary injecting drug.

Results: There were 620 participants in 2018 and 604 in 2022 included in analyses. Compared to the 2018 sample, the 2022 sample was significantly older, non-Hispanic Black, and primarily injected drugs other than heroin. A significantly smaller proportion of participants in 2022 had a recent HIV test (57% vs. 71%), visited a health care provider (77% vs 82%), received sterile needles from an SSP (69% vs 75%), or participated in a drug treatment program (47% vs 54%). Between 2018 and 2022, PrEP awareness increased significantly (39% vs 54%) but PrEP use did not (3% vs 3%). In adjusted models, an 18% decrease in recent HIV testing was observed between 2018 and 2022 (aPR: 0.82; 95% CI: 0.70-0.96). Among those who reported a recent HIV test, there was an 18% increase in testing in clinical settings observed between 2018 and 2022 (aPR: 1.18; 95% CI: 1.10-1.26). Recent medical care, SSP access, PrEP use, and drug treatment were not associated with year in adjusted models.
Conclusion: Access to a full range of social services is necessary for Ending the HIV Epidemic. These findings indicate that HIV prevention services, particularly HIV testing, among PWID have not rebound fully from the pandemic. Considering this and ongoing outbreaks of HIV among PWID, public health practitioners should closely monitor HIV testing frequency among PWID and prioritize expanding access to low-barrier HIV prevention and care services, especially in non-clinical settings.



1101 COST EFFECTIVENESS OF NIRMATRELVIR/RITONAVIR FOR MILD-MODERATE COVID-19 IN SPAIN

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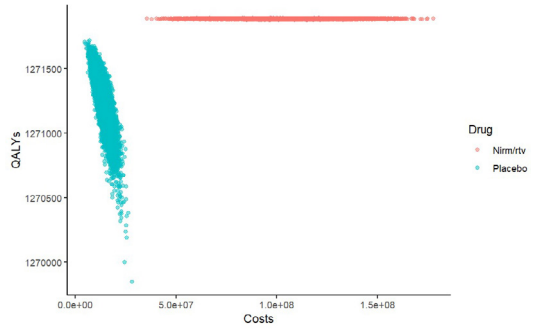
Background: A need exists for safe, affordable, and effective antiviral treatments for less severe COVID-19 outpatients that can prevent infection progression, hospitalization, and death; shorten the time to clinical recovery; and reduce transmission. In our best knowledge, there are not, so far, cost-effectiveness analysis on oral antiviral COVID-19 drugs in Spain. In our study we aim to evaluate cost-effectiveness of oral nirmatrelvir plus ritonavir in COVID-19 mild to moderate outpatients with at least one risk factor for disease progression in Spain.
Methods: A simulation model was constructed in R, to assess the clinical consequences and costs associated with COVID-19 in a hypothetical cohort of non-hospitalized patients older than 65 years with mild-to-moderate COVID and at least one risk factor for progression in Spain. The intervention assessed was nirmatrelvir plus ritonavir 300 mg plus 100mg every 12 hours up to 5 days. The comparator was symptomatic treatment with no antiviral drugs against SARS-CoV-2. The study was contextualized in the Spanish National Health System and the perspective of the service provider was adopted. Quality of life adjusted life years (QALYs) was used as a measure of effectiveness. Drug effectiveness was obtained from a literature review. As a cost measure, the retail price of the drugs was used. As a threshold willing to pay, the Spanish Gross National Product per capita was used. A discount of 3% per year was applied on future health effects. We used a decisional tree model. A univariate sensitivity analysis and probabilistic sensitivity analysis was performed.
Results: We found that nirmatrelvir/ritonavir yielded an extra 620.89 QALYs compared to a baseline scenario without it, at an increase in cost of 89,630,442 € with an Incremental cost-effectiveness ratio of 144,356.4 €/QALY gained. One way sensitivity analysis and probabilistic sensitivity analysis using Monte-Carlo simulations were undertaken and showed that the probability of not being cost-effective was 1 at the current price and willingness to pay threshold. To meet our willingness to pay threshold, nirmatrelvir plus ritonavir 5-days treatment price should be lowered down to 70 €.
Conclusion: According to our analysis nirmatrelvir/ritonavir is not cost-effective in in the Spanish National Health System for outpatients older than 65 years with at least one risk factor for COVID progression. A drug price of 70€ per treatment would meet our willingness to pay threshold.
Cost-Effectiveness plane of the Probabilistic Sensitivity Analysis



1102 OUTCOMES OF A TELEHEALTH VISIT MODEL TO DELIVER TECOVIRIMAT FOR MPOX IN NYC

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Background: A large mpox outbreak in NYC caused significant morbidity beginning in May 2022. Tecovirimat, an anti-Orthopoxvirus medication in the US Strategic National Stockpile available through the Centers for Disease Control and Prevention expanded access investigational new drug protocol, is recommended for patients at risk for or presenting with severe mpox disease. Due to administrative barriers limiting treatment access, our academic medical center at NYU Langone (NYULH) along with our public health system—NYC Health + Hospitals/Bellevue and NYC Department of Health and Mental Hygiene—set up an outpatient telehealth model to deliver tecovirimat to eligible patients. Here we present telehealth outcomes from June 19-August 8 2022.
Methods: Demographic/clinical characteristics and post-treatment outcomes were collected for NYULH and Bellevue patients. We used descriptive statistics and report results by HIV status. Outcomes were followed for 30 days post-treatment.
Results: Of 83 patients treated with tecovirimat, 69 (83.1%) completed an initial telehealth visit. Of this cohort, nearly all (98.6%) were cisgender men. Median (IQR) age was 36 (32-42) with 82.6% men who have sex with men (MSM). Patients were mostly White (43.5%) or Hispanic (10.1%). Table 1 shows outcomes by HIV status. Nearly half (46.4%) had HIV and all were on ART. Out of 20 cases with known viral load within 6 months, 19 were undetectable (< 200copies/mL). Among those without HIV, 77.1% were on PrEP. The most common mpox exposure was sexual contact (71.0%) and 40.6% received empiric STI treatment. The most common tecovirimat indication was mucosal involvement (85.5%), including proctitis, pharyngitis, urethritis or conjunctivitis. Median (IQR) time from symptom onset to testing was 4 days (3-9), and from symptom onset to treatment was 9 days (7-12). Most completed the 14-day treatment (59.4%) and completed at least one visit after treatment initiation (87.0%), while about 33.3% were lost to follow-up. Nearly all (89.9%) reported improvement and median (IQR) time to improvement on treatment was 3 days (2-4). No mpox-related hospitalizations or deaths were observed. Only 4 (5.8%) patients reported fatigue and 3 (4.3%) reported headache on tecovirimat.
Conclusion: In this NYC cohort of mostly MSM receiving tecovirimat, a telehealth model facilitated access to treatment that resulted in positive mpox outcomes. Patients were mostly well-controlled on ART or on PrEP, reflecting a population in care at baseline with high tech literacy.

Table 1. Demographics, clinical characteristics and outcomes by HIV status for patients treated with tecovirimat in NYC via telehealth, June 9 – August 18, 2022

Table 1. Demographics, clinical characteristics and outcomes by HIV status for patients treated with tecovirimat in NYC via telehealth, June 9 – August 18, 2022

Covariate	HIV-Positive (N=32) N (%)	HIV-Negative (N=35) N (%)	Total (N=69)[a] N (%)
Age, median (IQR)	40 (35-44)	34 (30-38)	36 (32-42)
Race/ethnicity[b]			
African-American/Black	4 (12.5)	2 (5.7)	6 (8.7)
White	12 (37.5)	17 (48.6)	30 (43.5)
Hispanic	4 (12.5)	3 (8.6)	7 (10.1)
Most recent CD4, median (IQR)[c] or on PrEP[d]	581 (479-776)[d]	27 (77.1)[e]	
Recovery at 30 days post-treatment			
Yes, without sequelae	14 (43.8)	12 (34.3)	26 (37.7)
Yes, with sequelae	6 (18.8)	11 (31.4)	18 (26.1)
Unknown	12 (37.5)	12 (34.3)	25 (36.2)

[a]2 patients did not have HIV status documented
[b]Patients who identified as both Hispanic and Black or Hispanic and White classified as Hispanic; 3 patients identified as Asian, 2 identified as American Indian/Alaska Native, 13 charts were marked Other race, 2 multiracial and 4 not documented
[c]Last recorded CD4 by chart review within 6 months included 18 known cases out of 32, with 14 not recorded.
[d]The remainder were not on PrEP

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