Highlights of the 2019 Conference on Retroviruses and Opportunistic Infections

CROI 2019: Advances in Basic Science Understanding of HIV
Mario Stevenson, PhD
Virology • Reservoirs and Cure

CROI 2019: Advances in HIV Prevention and Plans to End The Epidemic
Susan P. Buchbinder, MD; Albert Y. Liu, MD
Ending the Epidemic • U=U • HIV Testing • Drug Use • Sexually Transmitted Infections • Microbiome • Preexposure Prophylaxis: What’s New?

CROI 2019: Neurologic Complications of HIV Disease
Beau M. Ances, MD, PhD, MSc; Scott L. Letendre, MD
HIV-Associated Neurocognitive Disorders • Comorbidities and HAND • Neurodegenerative Diseases and HAND • CNS Effects of InSTIs • Neuroimaging in NeuroHIV • Effects of HIV on Neuropathogenesis • Effects of Host Mechanisms on Neuropathogenesis

CROI 2019: Complications and Coinfections in HIV Infection
Judith S. Currier, MD; Diane V. Havlir, MD
Tuberculosis: Women and Children • Fungal Infections • Sexually Transmitted Infections • Noncommunicable Diseases • Malignancies Among People Living with HIV

CROI 2019: Highlights of Viral Hepatitis
Anne F. Luetkemeyer, MD; David L. Wyles, MD
Hepatitis C Virus Care Cascade • Impact of Opioid Use on HCV and Fibrosis • Acute HCV and Epidemiology in High-Risk Populations • Complications of HCV • Hepatitis B • Intrahepatic Evaluation of HCV and HBV • Hepatitis A • Liver Inflammation, Nonalcoholic Fatty Liver Disease, and Nonalcoholic Steatohepatitis

CROI 2019: Advances in Antiretroviral Therapy
Barbara S. Taylor, MD, MS; Hong-Van Tieu, MD, MS; Joyce Jones, MD, MS; Timothy J. Wilkin, MD, MPH
Clinical Trials and New Antiretroviral Agents • The HIV Care Cascade and Getting to 90-90-90 • Novel Data on Epidemiology and Implications Antiretroviral Resistance • Selected Issues in Maternal and Pediatric Health
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- Basic science understanding of HIV
- Preexposure prophylaxis and other HIV prevention efforts
- Neurologic complications of HIV infection
- Coinfections and other complications of HIV infection
- Viral hepatitis
- Antiretroviral therapy for HIV prevention and management

Intended Audience
This enduring material is designed for physicians who are actively involved in the medical care of people with HIV and hepatitis infections.

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Invited Review

CROI 2019: Advances in Basic Science Understanding of HIV

Mario Stevenson, PhD

The annual Conference on Retroviruses and Opportunistic Infections remains the preeminent venue for the sharing and dissemination of research advances in the field of HIV and AIDS research. The 26th conference in Seattle featured highlights including news of additional individuals who experienced long-term virologic remission following a bone marrow transplant. The factors driving reservoir persistence gathered a lot of interest, as well as data presented on new factors involved in regulating HIV-1 latency. The effectiveness of the conference in disseminating new findings is further enhanced through themed discussions that focus the attention of participants on abstracts with a common theme. In addition, the Program Committee workshops provide an outstanding venue, directed to new investigators, fellows, and students, to receive updates on different aspects of HIV and AIDS research. These sessions add to the information-sharing environment provided by the conference.

Keywords: CROI, 2019, HIV, virology, reservoirs, cure

Virology

The basic virology presentations at the 2019 Conference on Retroviruses and Opportunistic Infections (CROI) each year continue to challenge our notions that we know everything there is to know about HIV-1. During the replication of HIV-1, the integrated provirus usurps cellular factors that interact with the long terminal repeat (LTR) to promote transcription of viral RNA that are then used as templates for production of viral proteins. A full understanding of the transcriptional regulation of the virus is key to the design of strategies to eliminate viral reservoirs through, for example, “shock and kill” or “block and lock” (terms coined for strategies that reactivate viral latency or that lock the virus in a latent state, respectively).

More than 30 years of research has shed considerable insight into the cellular factors that regulate HIV-1 transcription. Goff (Abstract 110) presented findings on a cellular complex that blocks HIV-1 transcription. More than 40 years ago, researchers observed that the transcription of many retroviral genomes such as murine leukemia virus (MLV), was inhibited in developmentally primitive cells such as embryonic and hematopoietic stem cells. The phenomenon was also noted by gene therapy researchers showing that vectors introduced into human hematopoietic stem cells were silenced. Silencing has also been shown to occur with unintegrated viral genomes. The extent of transcriptional silencing is profound, essentially affecting 100% of the genomes and possibly occurring in all cell types, not just undifferentiated cells. Tripartite motif-containing 28 (TRIM28) is the major factor involved in silencing of retroviral DNA in developmentally primitive cells. TRIM28 is a ubiquitin E3 ligase and serves as a scaffold to link transcriptional silencing proteins to a DNA target.

Unintegrated NDA is also potently silenced. This is evident when a cell is infected with a viral variant that has an inactivating mutation or deletion in the viral integrase. The degree of silencing is particularly striking with unintegrated viral DNA and is also cell-type independent. The silencing can almost completely be reversed with the addition of histone deacetylase inhibitors such as trichostatin, demonstrating that the silencing involves histones. Histones are loaded onto viral DNA rapidly upon entering the nucleus and the loaded histones or nucleosomes are retained after integration of the viral genome. These histones rapidly acquire acetylation modifications that drive silencing of the viral genome including H3K9 trimethylation. A whole-genome CRISPR (clustered regularly interspersed short palindromic repeats) knockout screen was then used to silence 20,000 genes in HeLa cells that were subsequently infected with an integrase minus MLV. Cells in which factors involved in silencing of viral DNA would then allow expression from the unintegrated DNA (as evidenced by expression of a green fluorescent protein [GFP] transgene in the viral vector). The screen revealed 3 proteins, periphilin, transgene activation suppressor (TASOR), and M-phase phosphoprotein 8 (MPP8) that comprise the human silencing hub (HUSH) complex.

The recent demonstrations that simian immunodeficiency virus (SIV) Vpr and Vpx proteins have evolved to inactivate the HUSH complex suggests that they hinder viral replication. Silencing of components of the HUSH complex resulted in gene expression from unintegrated MLV DNA. The authors further demonstrated that the DNA binding protein NP220 is required for silencing of unintegrated DNA by tethering the HUSH complex to unintegrated DNA. These proteins disappear from integrated DNA and the process through which that occurs, is as yet, not understood. In conclusion, HUSH and NP220 are the major proteins directing...
silencing of unintegrated DNA. Whether these protein mediate HIV-1 silencing in the memory CD4+ T cells has yet to be determined.

This research sheds light on a long standing question in the field, namely, why unintegrated retroviral DNA serves as a very poor transcriptional template. This information could help in the design of next-generation retroviral vectors that do not integrate. This would alleviate the hazards associated with integration such as insertional activation of cellular genes. Future studies will may also help define whether agents that inactivate the HUSH complex could be employed for reactivation of HIV-1 latency.

Abstract 168 provided a twist on the conventional wisdom surrounding mechanisms of HIV-1 drug resistance. Virologic failure in individuals on regimens containing the integrase strand transfer inhibitor dolutegravir can occur without mutations in integrase. The authors attempted to define what governs dolutegravir resistance in this instance. Dolutegravir-resistant virus was derived in vitro and resistant viruses were found to have mutations in the gp41 region of the viral envelope (Env) gene. Two Env mutants, Env-A556T and Env-A559V, were studied in order to define how they underscore dolutegravir resistance. Each mutant was found to increase the efficiency of cell-to-cell transmission relative to a wild-type virus. In the presence of 1.5 nM dolutegravir, cell-to-cell fusion of wild-type virus was blocked. However, the 2 Env mutant viruses remained competent for cell-to-cell fusion in the presence of dolutegravir. This was reflected by accelerated replication kinetics of the Env mutants relative to wild-type virus.

When cells were infected with a GFP reporter virus, the geometric mean fluorescence of cells infected with the Env mutants was far higher than that of cells infected with wild-type virus, suggesting that there may be more infection events per cell following infection by the Env mutants. The authors propose a model in which concentrations of dolutegravir that efficiently inhibit cell-free transmission are insufficient to block cell-to-cell transmission because of the numerous integration events occurring in those cells. Therefore, Env mutations that increase the efficiency of cell-to-cell infection, may further promote insensitivity to dolutegravir inhibition. This study provides insight into the mechanism by which mutations outside the target can confer resistance in vitro. It remains to be determined whether envelope mutations are involved in drug resistance in individuals on dolutegravir-containing regimens.

Viral Reservoirs and Cure

Timothy Brown, formerly known as the Berlin Patient, is the only individual known to have been cured of his HIV infection. In 2006, Mr Brown received 2 bone marrow transplants to treat his leukemia. His physician, Gero Hütter, used bone marrow from an individual with a chemokine receptor 5 (CCR5)-Δ32 mutation. This mutation renders the CCR5 receptor incapable of acting as a cell receptor for HIV-1 infection. In addition, Mr Brown underwent intensive chemotherapy and whole-body irradiation to kill the resident leukemic cells. He is now considered to be cured of his HIV infection. The most sensitive approaches have failed to reveal any remnants of the virus and in addition, Mr Brown no longer has antibodies to the virus. Although this cure galvanized researchers who are trying to develop a safe and scalable strategy to cure HIV-1 infection, it is a single case. Not surprisingly, presentations on potential additional cures generated considerable conference and media interest at the conference.

In Abstract 29, Gupta described HIV-1 remission in an individual who underwent an allogeneic CCR5-Δ32 stem cell transplant. Gupta described an individual who was diagnosed with HIV-1 infection in 2003. In 2013, the man (whose identity remains undisclosed) was diagnosed with Stage IVb Hodgkin’s lymphoma. The numerous lines of chemotherapy failed as did an autologous stem cell transplant. At that point he was a candidate for an allogeneic hematopoietic stem cell transplant, and fortunately, a human leukocyte antigen match with a CCR5-Δ32 mutation was found.

Antiretroviral therapy (ART) was maintained throughout the transplant procedure. One-hundred percent chimerism was achieved by day 30 post-transplant. At 16 months after the transplant, the clinical care team received approval to interrupt ART. As of February 2019, the patient has been off ART for 18 months with no viral rebound. During this time, cellular viral DNA levels have been below the limit of detection and several viral outgrowth assays using 25 million CD4+ T cells were negative.

Perhaps most telling is the demonstration that this patient exhibited diminished antibody responses to HIV-1. In addition, although there were T-cell responses to HIV-1 gag pretransplant, those responses are no longer evident. There are important parallels as well as differences between this subject (now referred to as the London patient) and Mr Brown. Although both individuals had transplants with CCR5-Δ32 stem cells and exhibited mild graft versus host disease and 100% chimerism, the London patient received a single transplant with reduced intensity conditioning and no whole-body irradiation (as opposed to 2, high intensity conditioning stem cell transplants and whole-body irradiation in Mr Brown). It remains to be conclusively shown whether the London patient is another cure. Although to date, there has been 18 months of virologic remission, cases involving infants who despite being treated very early, rebounded after extended virologic remission, show the need for caution in calling this a cure yet.

The issue surrounding reductions in HIV-specific antibodies declining following the stem cell transplant in the London patient was further expanded upon in Abstract 386. Salgado, talking on behalf of the ICISTEM (International Collaboration to Guide and Investigate the Potential for HIV Cure by Stem Cell Transplantation) consortium of which the London patient was a participant, reported results from 15 individuals who underwent allogeneic hematopoietic stem cell transplant under ART. Longitudinal plasma samples were examined
using qualitative and low sensitivity HIV-1 antibody assays. Anti p24 (gag) and p31 (integrase) antibodies disappeared within several months in 9 of 13 patients whereas anti-envelope antibodies persisted in most individuals. However, antibody levels in 2 individuals declined to below detectable levels. As these subjects remain on ART, the authors propose to use HIV-specific antibody levels as a tool to prioritize individuals who could be considered for a treatment interruption. These studies, although pointing to important markers that could be used to inform on the status of a cure trial, need to be taken in context. The use of stem cell transplant for hematologic malignancies in individuals with HIV-1–infection offers an opportunity to identify correlates of a cure. However, it is important that researchers transmit these findings to the lay community in a way that does not convey false hope for individuals living with HIV-1.

Studies investigating the mechanism of persistence of the viral reservoir under effective ART, as well as approaches to measure the reservoir, continue to dominate the basic science sessions. Understanding how HIV-1 is able to persist under effective ART is key to the design of strategies that eliminate the reservoirs. Most of the attention has focused on the role of memory CD4+ T cells and their ability to sustain lifelong viral persistence. The persistence of HIV-1 is dependent on its ability to integrate into the genome of the host cell. The integrated provirus can then enter a latent state for extended intervals where it is invisible to immunologic clearance mechanisms of the host.

In the past few years, several groups demonstrated that, during the process of cell division, the latent provirus can be duplicated by mitosis to result in 2 daughter cells harboring identical proviruses with identical integration sites. This can apparently occur without cytopathic effects of the virus on the host cell undergoing mitosis. The integrated provirus contains transcriptional regulatory elements in the LTR and as such, can influence the activity of neighboring cellular genes. If that cellular gene is involved in cell cycle regulation, the provirus can promote dysregulated expression of the cellular gene, which would result in an increased rate of host cell division. For that reason, expanded proviruses can represent a substantial proportion of the proviral population in memory CD4+ T cells. Duplicated proviruses are also competent for virus production and viruses in plasma can originate from the duplicated provirus pool. Since viruses originating from expanded proviruses are derived from a chronic source, they would be expected to be unaffected by ART.

Abstract 22 presented data that might explain persistent, low-level viremia during effective ART. Peripheral blood mononuclear cells (PBMCs) were obtained at to time points from 9 individuals on effective ART who exhibited residual plasma viremia of greater than 20 HIV RNA copies/mL for more than 6 months. Proviruses were characterized by single-genome sequencing and integration site analysis. In 6 of 9 subjects, viral sequences in plasma matched proviral sequences in PBMCs. Plasma viral RNA and proviral sequences were identical to viral sequences in viral outgrowth assays in 4 subjects. Intact proviruses comprised 4% to 15% of all proviruses in PBMCs. This study demonstrates that expanded proviruses can generate measurable levels of plasma viremia in the face of suppressive ART. It remains to be determined as to the relative contribution of the expanded proviral pool to viral rebound if treatment is interrupted.

The relationship between intact proviruses in PBMCs and plasma rebound viruses was discussed in Abstract 340. The results were derived from a clinical trial involving 15 patients that examined the impact of 3 administrations of a broadly neutralizing antibody (bNAb) combination (8NC117 and 10-1074) during an analytic treatment interruption. In that study, it was shown that antibody administration significantly delayed (by approximately 6 months) time to viral rebound upon treatment interruption. The authors sought to understand the relationship between the viruses in the latent reservoir that existed before bNAb administration and rebounding viruses after analytical treatment interruption. PBMCs were obtained 2 weeks before antibody administration, viral outgrowth assay was performed to assess the latent proviruses, and near full length polymerase chain reaction (PCR) was performed to identify the intact latent proviruses. Single genome envelope PCR was performed on the rebounding plasma viruses. There was an approximately 40% overlap between envelopes from intact proviral sequences and envelopes from inducible proviruses. However, there was no overlap between latent proviruses and envelopes in rebounding plasma. Instead, approximately 50% of the viruses in the rebounding viruses were recombinants of sequences present in the latent proviruses. Since recombination requires 2 viral genomes in an individual infected cell, this is surprising. The frequency of memory CD4 T-cells harboring a provirus is in the order of several hundred per million. The majority of those are defective and as such, the chances of a functional recombinant emerging is very small. It is also unclear whether the recombinants were present prior to antibody administration and treatment interruption.

Regardless of the mechanism behind the frequent presence of recombinants in the rebounding plasma in this study, an equally important issue is the poor correlation between rebounding viral sequences and proviral sequences in PBMCs. If rebounding plasma reflects the nature of the viral reservoirs that persist under ART, it is possible that the PBMC provides a very limited or perhaps distorted window into that reservoir. Additional studies are required to determine the relationship between proviruses in PBMCs and the viral reservoir that fuels viral rebound upon treatment interruption.

The role of central nervous system (CNS) reservoirs in viral persistence is poorly understood. Although neuro-pathogenic manifestations of HIV-1 infection appear to persist in a substantial proportion of individuals on effective ART, it is unclear whether viral activity is responsible. The composition of the viremia that rebounds following treatment interruption can provide insight into the nature of the reservoir
The density of CD4 on the macrophage is 25 times lower than that on a T-cell. To use such CD4 levels, the envelopes of macrophage-tropic viruses have a high CD4 affinity. This higher CD4 affinity confers the ability to efficiently fuse with macrophages. The laboratory of Clapham has demonstrated the presence of macrophage-tropic envelopes in post-mortem CNS tissue of individuals with and without neuropathology such as pleiocytosis. Similarly, Swanstrom presented evidence that more than half of individuals with HIV-associated dementia, who started therapy at low CD4+ cell counts and who exhibited phylogenetic compartmentalization between blood and CNS, had macrophage-tropic viruses in the CSF. Some individuals on ART exhibit CSF escape, which is characterized by episodes of transient or more prolonged CSF viremia. Viral envelopes obtained from individuals with transient CSF viremia were T-tropic. However, envelopes obtained from individuals with prolonged CSF viremia under ART were macrophage-tropic. This provides a clearer picture of the nature of CSF escape in individuals on effective ART.

Transient CSF viremia reflects a genetically homogeneous and drug-sensitive virus. In contrast, the persistence of HIV in the CSF reflects can occur in either the presence or absence of CNS symptoms. These viruses are genetically heterogeneous and contain drug-resistant mutations suggesting that they can replicate during ART suppression in the circulation. However, during treatment interruption, viral rebound in blood occurs earlier than in CSF, and as a result, viral rebound in CSF is obscured by blood viruses in trafficking T-cells. Therefore, there may be a CNS reservoir that is hidden from detection due to predominance more rapidly emerging blood viruses. As such, the presence of a CNS reservoir comprising macrophages remains unanswered. The “last gift” cohort of Smith comprises terminally ill, individuals with HIV-1 infection who have consented to donate their body for AIDS research postmortem (Abstract 327). The material provided by these exceptional individuals could provide answers to long-standing scientific puzzles around the nature of the reservoirs that persist under ART.

Abstract 392 assessed the composition of rebounding virus in blood and seminal plasma following treatment interruption in individuals enrolled in a therapeutic vaccine trial. Viral rebound in semen was significantly delayed and of lower magnitude than that in blood. Gag, pol, and envelope sequences in paired blood and semen for 5 individuals rebounding virus was determined using an Illumina miSeq platform. Viral diversity was higher in semen for all subjects. In addition, unique viral populations were found in semen that were not present in blood. Whether these results reflect distinct reservoirs in these separate anatomic compartments is unclear. However, the study illustrates the challenges involved in characterizing the viral reservoirs that persist during of ART.

Analytic treatment interruption may inform not only on the nature of the viral reservoir fueling viral rebound, but also on the size of the reservoir. However, use of treatment interruption to gauge viral reservoirs has caused concern since treatment interruption may reset the viral reservoirs. For example, individuals with a small reservoir may reseed the reservoir during a treatment interruption. Abstract 389 examined subjects in the ISALA (Analytical Treatment Interruption in HIV Positive Patients) trial, which was a multicenter, nonrandomized prospective study to determine posttreatment control in individuals with a smaller reservoir size. Inclusion criteria included low levels of cell-associated RNA and unspliced viral RNA in PBMCs. Fourteen individuals underwent a treatment interruption. All participants had rebound within 8 weeks of treatment interruption. Virologic control was achieved within 12 weeks of reinitating ART. In conclusion, no parameters were found to be predictive of the dynamics of viral rebound. However, treatment interruption was found to have a relatively minor impact on the size of the reservoir after treatment was reinitiated. This study indicates that, based on measures of cell-associated viral DNA and RNA, reservoir size...
returns to pretreatment interruption levels upon reinitiation of treatment and alleviates concerns surrounding use of treatment interruptions to gauge the viral reservoirs.

Although the HIV research field is attempting to define strategies to eliminate viral reservoirs, there remains the challenge of how best to measure the reservoir so that the efficacy of those cure strategies can be followed. As outlined above, PBMC sampling may offer a limited window into the viral reservoirs. It has been known for more than a decade that the blood accounts for perhaps less than 2% of the infected cells in an individual. However, tissue access in living subjects is a challenge especially when large cell numbers are required. Therefore, researchers have looked to in situ approaches to visualizing and quantifying the reservoir. These discussed progress in developing tissue imaging approaches for examining viral reservoirs (Abstract 4). The greatest progress has been made in development of RNA and DNA Scope in situ hybridization tools to image the viral reservoir. These methods are now being used to define the total virus burden, including active (viral RNA positive) and total (viral DNA positive) reservoirs, before and during ART. These approaches also allow visualization and quantitation of virion-associated genomic viral RNA. Application of these methods to the non-human primate model has provided detailed insight into the size, distribution, and dynamics of the viral reservoir on and off ART. One important observation from those studies was that ART had a relatively modest impact on the frequency of viral RNA-positive cells. When these methods were applied to individuals with HIV-infection on long-term ART, there was a 2 log decline in viral DNA-positive cells in the lymph nodes but surprisingly, almost no reduction in the frequency of viral DNA-positive cells in the rectum even after 2 years of ART. Furthermore, there was no difference in the overall frequency of DNA-positive cells between the lymph node and rectum after 2 years of ART. This effectively meant that even after 2 years of suppressive ART, there were between 2 x 10^7 and 10^8 infected cells in these compartments. Estes described a new tool, multiplexed ion beam imaging, developed by Nolan, which can define the spatial arrangement of numerous targets in a tissue section that can be reproduced in a manner similar to confocal images. This approach provides a platform to examine the nature of the infected cell in the context of the environment in which it resides. This powerful approach can identify signals that may reside on infected cells, and perhaps, on latently infected cells.

All cited abstracts appear in the CROI 2019 Abstracts eBook, available online at www.CROIconference.org

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Presenter: Michael S. Saag, MD; David H. Spach, MD

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Presenter: Raphael J. Landovitz, MD

Update on HIV Cure Strategies—Tuesday, July 16, 2019
Presenter: Katharine J. Bar, MD

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Presenter: Victor G. Valcour, MD, PhD

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Date of Last Review: February 11, 2019
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Invited Review
CROI 2019: Advances in HIV Prevention and Plans to End The Epidemic

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At the 2019 Conference on Retroviruses and Opportunistic Infections (CROI), a plan for ending the HIV epidemic in the United States was presented. More rapid HIV diagnosis and treatment is a key component needed nationwide. In international settings, substantial scale up of HIV testing and treatment has led to substantial declines in HIV incidence. U=U (undetectable equals untransmissible) is a powerful concept that can reduce stigma and encourage engagement in testing and care, but raises a number of clinical questions. HIV testing remains a gateway to HIV prevention and treatment, and innovative testing strategies, including HIV self-testing, show promise. Opioid overdose deaths are on the rise, highlighting the need for comprehensive prevention efforts. Molecular data are being used to identify rapidly growing clusters of infections for intervention. Rates of sexually transmitted infections have increased substantially in recent years. A new preexposure prophylaxis (PrEP) combination, tenofovir alafenamide/emtricitabine (FTC), was demonstrated to be non inferior to tenofovir disoproxil fumarate/FTC, with improved bone and renal safety. PrEP uptake is increasing globally, but use is lower in several populations, including African Americans, cis- and transgender women, and youth. Same-day PrEP initiations are a promising approach to increasing access, but PrEP discontinuations remain a challenge.

Keywords: CROI, 2019, HIV, epidemiology, prevention, U=U, testing, STIs, microbiome, PrEP, adherence, resistance, persistence, end the epidemic, PWID, MSM

Ending the Epidemic

Fauci gave a special presentation at the Opening Session of the 2019 Conference on Retroviruses and Opportunistic Infections (CROI) on the plan for ending the HIV epidemic in the United States. He pointed out that 1.1 million Americans are living with HIV, 14% of whom are unaware of their HIV infection. Approximately 40,000 new infections occur each year, without a substantial decline in recent years. He reviewed the science behind treatment as prevention, demonstrating that people who are durably virally suppressed cannot transmit HIV to their sexual partners. However, only 60% of people living with HIV in the United States are virally suppressed. A daily pill of preexposure prophylaxis (PrEP) is more than 95% effective in preventing HIV acquisition, but only 269,000 people are estimated to be on PrEP, of more than a million who could benefit from this prevention modality. He pointed out that new infections are heavily concentrated in certain demographic populations such as African Americans, men who have sex with men (MSM), and people who inject drugs (PWID). The epidemic is also concentrated in geographic areas; more than 50% of the new infections are concentrated in only 48 counties, along with Washington, DC, and Puerto Rico, and 7 southern states have substantial epidemics in rural areas. The combination of widespread treatment and prevention, if effectively implemented, could theoretically end the HIV epidemic in the United States. Fauci laid out the national plan to end the epidemic, the first time that a number of Health and Human Services Agencies are working together with a focus on increasing treatment and prevention in highly concentrated target populations. The 4 components of the plan are to 1) focus initially on high incidence geographic areas; 2) emphasize early diagnosis, immediate treatment, and engagement in care, with a plan to increase viral suppression from 60% to 90% nationally; 3) expand uptake of PrEP to at least 50% of those who need it; and 4) respond rapidly to emerging clusters of infection. With this plan, the goal is to reduce new HIV infections by 75% in 5 years and by 90% in 10 years.

The combination of widespread treatment and prevention, if effectively implemented, could theoretically end the HIV epidemic in the United States

Several presentations demonstrated the ongoing need for more rapid HIV diagnosis and treatment in the United States. Balaji and colleagues reported on trends in the probability of being diagnosed within the first year after HIV acquisition (Abstract 848). They based their estimates of early diagnosis on modeling, using CD4+ cell counts, and modelled HIV incidence. Based on this
methodology, they found that early diagnosis increased for persons aged 13 to 24 years but decreased for persons aged 25 to 34 years. The rates were stable in all other groups, suggesting limitations in current testing programs in finding people early in infection.

Crepaz and colleagues reported on the period of time that persons living with HIV might be potentially infectious in the United States, based on data from 27 jurisdictions with complete CD4+ cell count and viral load testing from 2012 to 2016 (Abstract 153). They modeled the duration of infection prior to diagnosis based on CD4+ cell count at presentation, a strategy that may introduce error into estimates. They then evaluated the time from diagnosis to viral suppression based on viral load testing. Overall, median time from infection to diagnosis decreased from 43 months to 39 months over that time, although 25% were estimated to have been infected for 98 months at diagnosis. Time from diagnosis to viral suppression dropped from 8 months to 5 months, with 25% estimated to take 12 months to reach viral suppression. Time from infection to diagnosis was slower in male heterosexuals (median, 63 months) and Latinos (median, 45 months). These data suggest that although progress is being made in achieving viral suppression more quickly after diagnosis, much work remains to be done, particularly with more rapid diagnosis after infection, where the incremental gains have been substantially smaller.

Several presentations demonstrated the potential impact of increasing HIV testing and treatment on HIV incidence rates in international settings. Hayes and colleagues presented data on the HIV Prevention Trials Network (HPTN) 071 PopART study (Population Effects of Antiretroviral Therapy to Reduce HIV Transmission) (Abstract 92LB). The investigators randomly assigned 21 communities in Zambia and South Africa to one of 3 arms. Arm A received the full PopART package, consisting of universal home-based counseling and testing, voluntary male medical circumcision referral, referral for prevention of mother-to-child transmission for pregnant women, screening for sexually transmitted infections (STIs) and tuberculosis, and provision of condoms. Persons in Arm A received antiretroviral therapy (ART) regardless of CD4+ cell count. Arm B received the same package, except that treatment was initiated according to country-specific guidelines. These national guidelines changed over the course of the trial, so that ART initiation was immediate for more than 50% of the entire study period. Arm C received the standard of care at current local provision.

An entire session was devoted to the concept of U=U (undetectable equals untransmittable), that persons fully virally suppressed on antiretroviral therapy cannot transmit HIV to their sexual partners

levels. HIV incidence decreased by 30% comparing Arm B with Arm C (adjusted rate ratio, 0.50; 95% confidence interval [CI], 0.55-0.88; P = .006). Unexpectedly, no significant decline was seen comparing Arm A with Arm C, and further analyses are underway to try to understand the lack of effect in this study arm. Nonetheless, the trial demonstrates that with substantial scale-up of testing and treatment, HIV incidence can be notably reduced. The data also suggest that additional prevention modalities, such as PrEP, may be needed to have a larger impact at a population level on HIV incidence.

MacKellar and colleagues reported on a study of scale up of HIV testing, linkage, and ART service delivery in Mozambique from 2014 to 2017 (Abstract 98). They attempted to target the 90-90-90 levels of testing, ART uptake, and viral suppression. HIV testing increased from 67% to 88%, ART uptake increased from 60% to 79%, and viral suppression increased from 41% to 66%. Despite not reaching the target levels, the investigators reported a change in estimated incidence of 1.9% per year to 0.9% per year using recency-based testing. If accurate, this demonstrated a 54% reduction in HIV incidence (incidence rate ratio, 0.46; 95% CI, 0.22-0.94). This would suggest that population-level increases in viral suppression can lead to reductions in HIV incidence.

U=U

An entire session was devoted to the concept of U=U (undetectable equals untransmittable), that persons fully virally suppressed on ART cannot transmit HIV to their sexual partners (Symposium S-6). Vernazza reviewed the history of available data in support of U=U (Abstract 116). In 2008, a group of Swiss investigators made the statement that persons on ART with suppressed viral load and without STIs were unable to transmit HIV to their partners, based on seeing no cases of documented transmission in this situation. The motivation for making this statement was both to help people living with HIV to have healthy sexual lives, and to avoid the legal actions being taken against persons living with HIV because of concerns of exposure to their sexual partners. He estimates that at that time, the upper bound of the 95% confidence interval for the risk of HIV transmission would have been approximately 0.2/100 person-years. Vernazza discussed the difficulty of proving a negative result, quoting the philosopher Copi who stated that one can assume reporting of rare events, and thus the absence of detection can serve as positive proof of non-occurrence. Vernazza then reviewed the additional data from HPTN 052, PARTNERS (Partners of People on ART—A New Evaluation of the Risks) -1 and -2, and the Opposites Attract studies that would now indicate that the upper limit of a 95% CI would be 0.07/100 person-years. This provides compelling evidence that transmission does not occur when a person is fully virally suppressed on ART.

Nwokolo discussed clinical conundrums related to counseling patients about U=U (Abstract 117). She raised the question of whether post-exposure
prophylaxis (PEP) should be recommended for a person with numerous partners, all of whom either state they are on PrEP or have an undetectable viral load. She suggested that without verification of viral suppression, one should presume that viral load may not be suppressed, citing data from last year’s CROI that in one study 47% of MSM who reported an undetectable viral load had some virus detected on dried blood spots. The presence of STIs does not appear to affect U=U. In evaluating whether someone should be offered PEP for an occupational needle-stick exposure from a patient with an undetectable viral load, she pointed out that guidelines differ between the United States, which recommends offering PEP versus the United Kingdom and Switzerland, which recommend against PEP. Breastfeeding has been shown to transmit HIV, despite viral suppression in the blood. This may be for several reasons, including: 1) transmission through cell-associated virus, not measured by viral load; 2) the quantity of breastmilk exposure (more than 150 liters over 6-12 months); 3) immune activation in breast milk, where HIV replication occurs 10-times more than in blood; 4) immune vulnerability of the infant gut; or 5) difficulty with ART adherence during the post-partum period. Nwokolo pointed out that little evidence exists about the risk of transmission through needle sharing if detectable, with PEP not recommended in the United Kingdom and Australia, but it is recommended in the United States guidelines. She pointed out that additional challenges may exist in interpreting U=U in developing world settings, where viral load testing may be less frequent or a higher threshold is used than in resource-rich countries. She ended by emphasizing that combination prevention, including PrEP, may be needed to see truly substantial declines in incidence across populations.

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The U=U campaign from 97 countries. Foote suggested that the U=U campaign has 4 main effects, including that it: 1) transforms social, sexual, and reproductive lives; 2) dismantles stigma; 3) encourages that persons get tested and remain on treatment and in care; and 4) provides a strong public health argument for the necessity of access to care. However, she recognized that not everyone is able to achieve viral suppression and that “V does not equal V” or that having detectable virus does not equate with a person’s value or worth. Foote also provided coaching on language around U=U, urging not to “recommend condoms, just in case” or to say “you’re only as good as your last viral load”. Rather, she urged recommending that condoms can prevent other STI transmission but are not clinically necessary to prevent HIV transmission in the setting of undetectable viral load, and that persons who are taking their medication and getting tested regularly need not worry about HIV transmission.

Grulich addressed the population level impact of treatment as prevention, also known as “UTT” or universal testing and treatment throughout generalized epidemics in sub-Saharan Africa, and concentrated MSM epidemics in developed countries (Abstract 119). He pointed to the 5 large UTT trials conducted to date, highlighting the differences in baseline HIV prevalence, knowledge of serostatus, and treatment uptake at baseline across the trials. All of the trials have been impacted by World Health Organization guidelines for immediate testing regardless of CD4+ cell count that occurred after the trials launched, with some trials showing no difference between treatment arms in HIV incidence, and others showing modest (20%-30%) decreases in incidence in the intervention arms. He suggested that these modest effects may indicate that additional combination prevention strategies are needed to further drive down infection rates. He then reviewed new diagnoses in MSM in Australia, England, and the United States, demonstrating in various jurisdictions that increased testing and treatment coincided with substantial declines in new diagnoses. He pointed out that these declines are difficult to attribute solely to testing and treatment scale-up, as PrEP was also rolled out during that time frame. Grulich ended by emphasizing that combination prevention, including PrEP, may be needed to see truly substantial declines in incidence across populations.

Several posters addressed implementation in clinical settings. Gillani and colleagues evaluated patients with HIV from a clinic in Southern Alberta, Canada (Abstract 1058). They calculated the total days of follow-up for which patients were suppressed (<200 copies/mL), unsuppressed (≥200 copies/mL), or transmittable (≥1500 copies/mL, a level previously associated with transmission). Overall, 92% of days were spent suppressed, and 8.2% were unsuppressed, including 6.6% of the time as transmittable. However, patients disengaging from care who accounted for 5.5% of all patients accounted for 34% of the days spent unsuppressed and 37% of transmittable days of follow-up. Both abstracts suggest that most patients were able to maintain viral suppression, as long as they were retained in care.

HIV Testing

Testing is the gateway to HIV prevention as well as treatment, and thus an
important component of any efforts to end the epidemic. A number of presentations focused on the use of self-testing to increase uptake of testing and identify undiagnosed persons. Dovel and colleagues presented data on a randomized controlled trial of HIV self-testing among partners of clients on ART in Malawi (Abstract 93). They randomly assigned 135 participants to standard of care (participant given a referral slip to give to partner for testing), and 349 to standard of care plus receipt of HIV self-test kits. Although the HIV testing uptake was significantly higher in those given a self-test kit (73% vs 27%, respectively; adjusted odds ratio [aOR], 10.4), only 22% of self-testers who were positive initiated ART within 6 months. In addition, 65% of self-testers reported needing help in conducting the test, and 8% were unable to interpret the test results. This suggests that additional support is needed in this environment to ensure that persons testing HIV positive on self-testing are linked to care and treatment. Pintye and colleagues presented data on distribution of self-test kits for couple-based testing of the unknown serostatus male partners of HIV uninfected women seeking routine antenatal care at 10 facilities in Kenya (Abstract 926). They found that 63% of 758 women were willing to take a self-test kit for their male partner, 76% of those offered the self-test kit to their partner, and 93% of men offered the self-test kit used it with their female partner. Of 296 men performing the self-test kit, they identified 4 HIV positive individuals, with an additional 4 who were unable to read their results; the remaining tests were negative. Overall, 4 persons reported experiencing harm from distribution of self-test kits in that their partner was upset; they denied physical or verbal harm from the encounter. However, 8% of women not accepting an HIV self-test kit and 14% of women who took a kit but did not distribute it to their partner cited fear of intimate partner violence as the reason for not distributing the test kits. For women without this concern, this approach appeared to be a safe and effective means of testing a minority of male partners (36% of total).

Medley assessed the interest, HIV positive test yield, and cost of 3 strategies of obtaining HIV testing among male partners of women attending antenatal clinics: 1) facility-based testing through invitation letters; 2) Home-based testing by a trained counselor; and 3) HIV self-testing, with the ability to take up to 3 oral fluid based tests for themselves and their partners (Abstract 928). Men using home test kits were also given incentives of approximately US $2 for receiving posttest counseling and for returning home test kits via text or physically to the facility. Of 1166 women enrolled, 223 male partners were tested at the facility (9% HIV positive rate), 28 men had home-based testing (7% HIV positive rate), and 668 men received an HIV self-test kit (6% HIV positive). Costs per confirmed HIV positive were estimated to be $355 for facility-based testing, $1038 for home-based testing, and $2350 for self-testing. Self-testing was most popular, but only 60% received post-test counseling despite incentives, and this modality was the most expensive. Nonetheless, it seems that a variety of testing strategies will be required to maximize uptake of HIV testing by male partners of pregnant women. Cele and colleagues also calculated the cost of facility-based versus HIV self-testing in 30 communities in Zambia (Abstract 1080). Participants randomized to receive HIV self-testing underwent a second randomization to either a self-referral card alone or combined with a patient escort to a local healthcare facility. The yield of newly diagnosed positive tests per person was 1% for HIV self-testing and 3.2% for facility-based testing. Among those testing newly HIV positive in the self-testing group, 54% of those given a self-referral card initiated ART within 3 months compared with 92% of those with an escort. The cost per newly positive diagnosis was $583 for self-testing and $80 for facility-based testing. However, when calculated as the cost per ART initiation, the cost was substantially lower for the self-testing arm offered an escort than the self-testing with referral cost only ($668 vs $1698, respectively) because of the substantially higher linkage rate for the former group. The authors concluded that community-based HIV self-testing may identify youth who would not otherwise have tested for HIV, but that it should be provided with an offer of escort to ART services for those testing newly positive.

HIV self-testing was also evaluated among MSM in several settings. Dunn and colleagues presented baseline data from a randomized controlled trial of HIV self-testing in England that enrolled 10,112 MSM through the internet (Abstract 937). Among men at higher risk of HIV (having 2 or more condomless anal sex partners in the prior 3 months), 12% had never had an HIV test and 47% had tested more than 6 months previously, indicating the strong need for testing in this population. Okoboi and colleagues reported that they distributed 10 HIV self-test kits each through 15 MSM peers in Uganda (Abstract 934). The yield of his testing (10 confirmed positive results) was higher than for usual testing in the local program (4/147, P=.02). Of self-testers, 77% had never tested or had not tested in the prior 12 months. This suggests that distribution of self-test kits through MSM peer networks may be a promising strategy for increasing knowledge of serostatus in this population with high HIV prevalence. HIV self-testing was also assessed for MSM in Brazil, Mexico, and Peru (Abstract 936). Of 18,916 survey respondents, 20% had never tested for HIV; major reasons for never testing include fear of a positive test result (28%), perceived low risk of infection (22%), and the shame of getting tested (21%). Willingness to test was highest in Brazil (44%), followed by Mexico (36%) and Peru (32%). Nearly

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90% thought that post-test counseling with a health professional is essential, and more than 80% stated that they think people would have difficulty dealing with a positive test result. Willingness to use a self-test was associated with higher income, education, and willingness to use PrEP in all 3 countries.

Roxby and colleagues conducted a randomized controlled trial of home-based couple education among 391 couples in which the woman was pregnant in Kisumu, Kenya (Abstract 927). Women were randomly assigned to receive home-based couple education with rapid syphilis testing and counseling about prevention strategies, or to receive an invitation letter to give to their male partners to receive HIV testing. Overall, 7% of men tested in the intervention arm and 2% of those tested in the control arm were newly diagnosed with HIV. In addition, men randomly assigned to the intervention arm were significantly more likely in unadjusted analysis to report seeking any STI services (relative risk [RR], 1.6). There was no effect on men seeking voluntary medical male circumcision nor to linkage to HIV care and treatment services. This suggests that a more intensive intervention is needed to improve uptake of prevention modalities for men testing HIV negative and linkage to treatment for men testing HIV positive. Kim and colleagues presented data from a cluster randomized trial of HIV testing for men and women in KwaZulu-Natal, South Africa (Abstract 54LB). They randomly assigned 45 communities in a factorial design to receive home-based couple education with rapid syphilis testing and counseling about prevention strategies, or to receive an invitation letter to give to their male partners to receive HIV testing. Overall, 7% of men tested in the intervention arm and 2% of those tested in the control arm were newly diagnosed with HIV. In addition, men randomly assigned to the intervention arm were significantly more likely to test than those in the control arm. They concluded that a more intensive intervention is needed to improve uptake of prevention modalities for men testing HIV negative and linkage to treatment for men testing HIV positive.

Drug Use

Bosh and colleagues reported on the increased rate of unintentional opioid overdose deaths in people with HIV infection from 2011 to 2015 (Abstract 147). Although total deaths decreased by 13% among people with HIV during this time, unintentional opioid overdose deaths increased by 43%, accounting for 2% of all deaths in 2015. PWID had the highest rates and increased by the greatest amount (80%) over this time. MSM who injected drugs had the second highest rate. Although rates increased in all age groups, rates were highest among 50 to 59 year olds, followed by 40 to 49 year olds. Rates were somewhat higher in women than men but increased in both groups. Rates were highest in the Northeast and lowest in the South, although the rates increased most in the South. The West was the only region in which rates decreased. These data show the intensity and worsening of rates of unintentional opioid overdoses and demonstrate that more comprehensive prevention efforts are needed overall, as well as within groups with the highest rates or fastest growth.

Additional data on overdoses were presented in several posters. Genberg and colleagues reported on fatal and non-fatal overdoses among persons enrolled in the ALIVE cohort in Baltimore, MD (Abstract 883). They reported an overdose death rate of 7.06 per 1000 person-years. People living with HIV were significantly more likely than HIV negative persons to die of overdose deaths (adjusted hazard ratio [aHR], 1.7); older people and women were significantly less likely to die of overdose (aHR, 0.96 and 0.49, respectively). Non-fatal overdoses were very common in this cohort, with an incidence of 24 per 100 person-years. Factors associated with non-fatal overdoses included more recent years (2017 and 2018 compared with 2013, aHR, 3.9 and 4.4, respectively), any opiate use (aHR, 7.0), and any injection drug use (aHR, 6.2). Dorsey and colleagues reported on accidental overdose deaths in Washington, DC, from 2013 to 2017 (Abstract 881). They reported that accidental overdose deaths increased 218% over that time, accounting for 6.8% of all deaths among people living with HIV over that time period. Compared with other causes of death, persons dying of accidental overdoses were significantly more likely to have injected drugs (aOR, 2.9), to have had Stage 1 disease (aOR, 4.6) and to have had a CD4+ count above 200 cells/μL (aOR, 3.6). They pointed out that these are preventable deaths with naloxone and medically assisted therapy, and that providers should pay particular attention to this risk among their patients with a history of injection drug use.

Althoff and colleagues reported on suicide rates among adults living with HIV in the United States from 2000 to 2015, using data from the North American AIDS Cohort Collaboration on Research and Design (NA-ACCORD) cohort (Abstract 895). Among men, rates were highest among white PWID (adjusted incidence rate ratio [aIRR], 9.98) followed by white non-PWID (aIRR, 5.92), black PWID (aIRR, 2.21) compared with black non-PWID. Suicide was relatively rare among women. Carriero and colleagues reported on multi-level predictors of suicidality among substance users living with HIV in 11 US cities, based on data from the National Institute on Drug Abuse Clinical Trials Network (Abstract 921). Of 801 participants, 18% reported suicidal thoughts, 7% considered methods for suicide, and 2% had thought of plans for suicide at baseline into the cohort. Suicidality decreased significantly over 12 months of follow-up. Suicidality was associated with a lower rate of viral suppression.
In 2017, metropolitan counties accounted for 91% of all HIV diagnoses among people who inject drugs

harmful effects of opioids including changes to drug formulations, drug monitoring programs, and US Centers for Disease Control and Prevention (CDC) guidance on reducing opioid prescribing. However, an unintended consequence has been an increase in use of heroin and increased injection frequency among some users, leading to increased harmful consequences including HIV outbreaks, unintended overdose deaths, and increased rates of hepatitis C, soft tissue infections, and endocarditis. The spread of opioid use disorder has occurred in urban, suburban, and rural settings, making it difficult to predict where outbreaks will occur. Bluthenthal recommended several steps toward addressing the opioid crisis including making medically assisted therapy and syringe access programs more available, increasing PrEP availability for PWID, reducing stigma, and piloting and implementing safer injection sites.

Pakianathan reported on chemsex or the use of substances during sex, generally to enhance pleasure (Abstract 64). He noted that the drugs may be used to increase libido, enhance pleasure, increase self-confidence, reduce inhibitions, promote sexual adventure, or advance intimacy. However, the drugs may also be associated with poorer outcomes, including an increased risk of STIs (aOR, 3.5), increased newly diagnosed HIV (aOR, 5.1) and increased hepatitis C (aOR, 9.2). He pointed to the many potential mechanisms for increased risk, including an association with riskier sexual practices, more prolonged sex, higher community viral load among partners, increased trauma or inflammation at mucosal surfaces, and an increased likelihood of injection drug use. He reported that 70% of patients in his chemsex clinic reported negative consequences, including problems with work, finances, criminal justice, accidental overdoses, and hospitalizations. He concluded that more research is required in understanding the factors that may increase risk for negative outcomes.

Simbayi discussed the relationship between alcohol and poor HIV-related outcomes (Abstract 65). Maps of hazardous alcohol consumption, defined as drinking to become intoxicated, show highest levels in Eastern Europe and parts of sub-Saharan Africa, areas with high HIV prevalence. In several meta-analyses, alcohol consumption was associated with an increased risk of HIV acquisition, with an odds ratio of 1.7. Problem drinkers were more likely to become HIV infected than non-problem drinkers (odds ratio [OR], 2.0 vs 1.6, respectively; \( P = .04 \)). Simbayi pointed out that whereas the negative consequences for men often come from their own drinking, women may be put at increased risk because of their male partner’s drinking, which is associated with partner violence. Among people living with HIV, alcohol use is associated with lower CD4+ cell counts, faster HIV disease progression, and poorer adherence to ART. He called for more research on interventions to address the intersection of alcohol and HIV, including the development and evaluation of interventions to reduce harmful effects of alcohol.

Lyss and colleagues reported on the new HIV diagnoses among PWID across the United States from 2010 to 2017 (Abstract 886). They point out that the longstanding decline in new diagnoses in PWID has stalled over this period of time, particularly since 2014. In 2017, metropolitan counties accounted for 91% of all HIV diagnoses among PWID. However, comparing 2017 with 2014, the greatest absolute increase in HIV diagnoses in PWID have been in large, fringe metro counties (population >1 million), and the greatest relative increase has occurred in areas with 29% or lower of all HIV diagnoses.
in micropolitan communities (centered on urban areas with population 10,000-49,999). They recommend prompt detection and investigation of clusters occurring in newly diagnosed PWID, and recommend that health departments have HIV outbreak response plans and proactively evaluate such potential outbreaks. Dasgupta and colleagues presented data on injection and sexual behaviors among PWID enrolled in the Medical Monitoring Project (Abstract 887). Among 233 HIV positive participants, 11% reported sharing syringes and 53% reported disposing of syringes improperly. Of the 57% who reported needing drug or alcohol treatment, only 65% had received it. HIV-positive PWID were more likely than HIV-positive non-PWID to report not having sustained viral suppression (48% vs 35%, respectively; \( P = .008 \)), having condomless sex (63% vs 31%, respectively; \( P < .001 \)), having exchanged sex (17% vs 2%, respectively; \( P < .001 \)), and being at risk of HIV sexual transmission (22% vs 7%, respectively; \( P < .001 \)). This reinforces the need for access to clean injection equipment and methods for safely disposing of used equipment, increased access to drug and alcohol treatment programs, better engagement in HIV care, and other strategies to reduce the behavioral risk of HIV transmission.

Samet and colleagues reported on academic detailing for improving physician practices in opioid prescribing (Abstract 889). They conducted a cluster randomized trial of 2 safety-net clinics in which 41 practitioners were randomly assigned to a collaborative care intervention versus standard practice. The intervention consisted of providing a nurse care manager with an electronic registry to manage patients, providing education and academic detailing, and providing access to addiction specialists. At 12 months, patients at the intervention clinic were significantly more likely to have 2 or more urine drug tests (70% vs 18% in standard care, respectively; \( P < .0001 \)) and to have an opioid treatment agreement (76% vs 12%, respectively; \( P < .0001 \)). There was a trend toward a lower likelihood of early refills (21% vs 30%, respectively; \( P = .11 \)), with no difference in viral suppression rates (88% vs 84%, respectively; \( P = .69 \)). Practitioners in the intervention arm were somewhat more likely to routinely use a prescription monitoring program (75% vs 45%, respectively; \( P = .05 \)). This suggests that this type of intervention may improve adherence to CDC guidelines for prescribing of chronic opioids.

**Female Sex Workers**

Mwanamsangu and colleagues presented data on HIV seroconversion among female sex workers (FSWs) in Tanzania (Abstract 832). They measured an HIV incidence rate of 8.6/100 person-years among the 17,977 FSWs who presented for repeat testing. Risk factors independently associated with seroconversion included age 35 years or greater (aHR, 2.4), having a syndromic STI (aHR, 1.8), not using a condom in the last 3 sex acts (aHR, 1.3), and using alcohol at last sex act (aHR, 1.4). The authors state that these data suggest the importance of offering biomedical and behavioral prevention services to this population with exceedingly high rates of HIV seroconversion. Kerrigan and colleagues reported on a 2-community randomized trial of a community empowerment model of combination HIV prevention for FSWs (Abstract 952). Although HIV incidence was high in both the intervention and control arms (5% vs 10.4%, respectively), participants in the intervention community were significantly less likely to become infected at 18 months of follow-up (OR, 0.38; \( P = .047 \)) and demonstrated a greater decrease in inconsistent condom use (\( P = .042 \)). This suggests that community empowerment may be useful for FSWs in reducing the risk of HIV acquisition, although additional interventions are also needed as the infection rate remained high in the intervention condition.

**Social and Sexual Networks**

Oster presented a plenary talk on the use of molecular data to identify rapidly growing clusters of people living with HIV for intervention (Abstract 68). She described using data from resistance testing to compare sequences, identify closely related viruses, and then identify clusters. Nationally, approximately 40% of people diagnosed with HIV have sequences reported, and sequences are available for more than 340,000 people living with HIV. On average, 4 transmissions occur from every 100 people living with HIV. However, looking at the top 13 clusters identified by cluster analysis, transmission rates were 53/100 persons, and for the first 60 clusters, transmissions occurred in 44/100, demonstrating the ability of such analyses to identify populations who may benefit from interventions. Such interventions include treatment for those diagnosed with HIV and prevention (including PrEP) for the uninfected contacts of the cluster. To date, more than 145 priority clusters have been identified, and data were shared with local health departments for monitoring and intervention. She gave several examples where identifying rapidly growing clusters led to increased efforts for testing, linkage to care, and prevention.

Golden and colleagues presented data on an HIV outbreak among homeless, heterosexual PWID in a 3-square mile area of North Seattle, Washington (Abstract 891). Based on an astute disease intervention specialist who noted 3 epidemiologically linked cases, a total of 15 cases in the cluster were identified as part of a larger uptick in cases among heterosexual PWID. Although the cluster was identified approximately 9 months after it appeared to have begun, several steps were taken to prevent further spread, including a rapid needs assessment of local PWID needs, increased HIV testing in jails, outreach to local emergency rooms and clinics, expanded mobile syringe exchange, and a community-based mobile clinic providing services, including PrEP, for women who exchange sex. The authors pointed out that molecular epidemiology was not quick enough nor sensitive enough to pick up this cluster, and made recommendations for improvements in these algorithms for the future.

Long and colleagues examined sexual networks using respondent driven sampling among MSM and transgender...
women in Lima, Peru (Abstract 841). They found there was little overlap between sexual networks between these populations. Only 7% of partners of transgender women reported a cisgender male partner in the last 3 months. However, 60% reported condomless anal sex in the past 3 months and 54% of partners reported not knowing their HIV status. This suggests that

In recent years, there have been dramatic increases in bacterial sexually transmitted infections, with a very high burden seen globally

partners of transgender women may need separate outreach of prevention interventions.

John and colleagues reported on using molecular surveillance as a means to expand an outbreak investigation in Massachusetts (Abstract 857). In mid-2016, the Massachusetts Department of Public Health identified an increase in HIV diagnoses among PWID in northeastern Massachusetts. Initially, 36 of 129 cases (23%) were molecularly linked. By December 2018, the addition of molecular data expanded the number of persons linked to the investigation by 44%. Numerous molecular clusters among those being investigated suggests several introductions of HIV into the community of PWID. In addition, a substantial proportion of named partners were HIV positive, indicating the importance of partner services to link persons to care.

Torian and colleagues reported on attempting to use real-time molecular surveillance to inform data-to-care efforts in New York City (Abstract 860). Clusters were inferred based on genetic distance, and cluster members out of care for more than 1 year or with viral loads above 1500 copies/mL were prioritized for assistance with partner services and reengagement in optimal care. They identified 225 clusters containing 2778 members; 91% were among MSM. Of these, 784 were closely linked (first degree partners) and the focus of their investigation efforts. Overall, 147 (5%) were out of care and 108 (4%) were viremic. The team was able to return to care 15% of those out of care, and were able to have a practitioner conference or facilitate optimal care for 77% of those who were viremic but in care. The authors concluded that this helped them prioritize patients for outreach.

McLaughlin and colleagues calculated an HIV lineage-level diversification rate, a measure of between host transmission rates suggesting increased risk of transmission (Abstract 862). They found that among people living with HIV in British Columbia, Canada, the diversification rate (and hence, risk of transmission) was higher for men, younger age, PWID, history of hepatitis C, high viral load, and living in the Northern health authority. Factors associated with lower diversification included being black and ever having had AIDS. The authors suggest that this could help prioritize groups for treatment and prevention services.

Sexually Transmitted Infections

Marrazzo presented a plenary talk on STIs in the era of effective HIV treatment and prevention (Abstract 12). In recent years, there have been dramatic increases in bacterial STIs, with a very high burden seen globally. In the United States, there were 1.6 million cases of chlamydia in 2017 (5% increase from 2015), nearly 500,000 cases of gonorrhea (19% increase), and almost 50,000 cases of syphilis (18% increase).

Syphilis cases have continued increase in the post-ART era, with 88% of cases occurring in men, of whom 80% were MSM; 46% of these MSM were HIV positive. In women, there was a 156% increase in primary and secondary syphilis compared with 2013, with 918 congenital syphilis cases occurring in 2017. In California, more than half of these cases occurred without prenatal care and often in the setting of methamphetamine and heroin use. Rates of gonorrhea in MSM have increased steeply since 2011, with a considerable number of infections occurring at extragenital (eg, rectal or pharyngeal) sites. There has been an international spread of gonococcal resistance to ceftriaxone, our last reliable drug for gonorrhea. Many of these cases had contacts in South East Asia, where antibiotics are available over-the-counter. Globally, 24% and 81% of countries had evidence of gonococcal resistance to ceftriaxone and azithromycin respectively, and 7 and 30 countries had a more than 5% rate of gonococcal resistance to these drugs. Two topoisomerase inhibitors, zoliflodacin and gepotidacin, are novel antimicrobials under study for gonorrhea treatment. She also pointed to an interesting study in New Zealand showing a 53% decrease in gonorrhea among individuals who received an outer membrane vesicle (OMV) meningococcal vaccine as part of outbreak control. This raises the possibility that the new group B meningococcal vaccine, which also contains the OMV antigen, may also protect against gonorrhea. She also reviewed results of a substudy within the IPERGAY (Action to Prevent Risk Exposure By and For Gay Men) PrEP trial in which participants randomly assigned to doxycycline postexposure prophylaxis administered 24 to 72 hours after sex was associated with a 70% decrease in time to chlamydia and syphilis infection, but had no impact on gonorrhea infection. She noted the advantages of this strategy, including the effectiveness in early studies, relatively safety of the drug, being easy to administer, having few other options for prevention, and considerable interest in MSM. Disadvantages include the limited data on this intervention, unclear duration of treatment, adverse effects, antibiotic resistance, and effects on the microbiome. Marrazzo raised the provocative question on whether STIs need to be controlled to reach Getting to Zero goals for the HIV epidemic. She pointed to data in San Francisco showing declining HIV infections concurrent with decreased condom use and increasing STIs. However, although STIs in MSM are often asymptomatic and seen as inconvenient, STIs in women are highly stigmatizing and
can lead to pelvic inflammatory disease, infertility, and adverse pregnancy outcomes. She also pointed out that although most STIs are asymptomatic, they confer an increased risk of HIV acquisition, with 10% of HIV infections among MSM attributable to gonorrhea or chlamydia infections based on a modeling study. She also highlighted the global shortage of penicillin that can

These findings support sexually transmitted infection testing every 3 months for men who have sex with men (MSM) on PrEP and at least annually for sexually active MSM, and testing at all anatomic sites of potential exposure

further limit treatment efforts. She concluded with several recommendations, including the need to deploy rapid, accurate diagnostic tests for STIs in high incidence settings, rather than relying on syndromic management; scaling up STI screening in asymptomatic people in HIV care and prevention; expanding partner management strategies; addressing supply chain challenges; and investing in vaccine and therapeutic development.

Several presentations reported increasing STI rates in different populations. Mayer and colleagues assessed trends in bacterial STIs among more than 19,000 men in Boston (Abstract 851). Between 2005 and 2015, gonorrhea and chlamydia diagnoses increased more than 12- and almost 8-fold, respectively. During this period, there was a 2- to 3-fold increase in screening and a 5- to 8-fold increase in diagnosis rates for gonorrhea, and similar trends were seen for chlamydia, suggesting that the increase in STI rates is not only the result of increased screening. Test positivity rates were highest in HIV-positive and PrEP-using patients, highlighting the need for regular STI screening in these populations.

Li and colleagues evaluated gonorrhea incidence and testing rates among 4727 HIV-positive individuals in the HIV Outpatient Study (Abstract 853). Between 2007 and 2017, both gonorrhea incidence and testing rates increased among MSM and non-MSM. Incident gonorrhea cases were disproportionately represented in younger patients, MSM, and patients with a prior STI. Only half of HIV-positive MSM had gonorrhea testing in the prior 12 months, suggesting missed opportunities for STI diagnosis and treatment. Furthermore, urethral testing only would miss a substantial number of extragenital STIs, highlighting the need for more gonorrhea testing across anatomic sites. Jansen and colleagues presented data on HIV, PrEP, and STI prevalence among MSM in Germany (Abstract 850). Among 2303 MSM recruited in STI clinics, 30% tested positive for an STI. STIs were predominantly rectal, and only 32% reported STI related symptoms; urogenital screening would only have detected 28% of STIs. The prevalence of Mycoplasma genitalium was high at 17%. HIV positive MSM and those using PrEP were independent risk factors for having an STI diagnosis. The high prevalence of extragenital STIs was also reported by Chapin-Bardales and colleagues (Abstract 968). Among 1922 MSM, 15% of PrEP users and 12% of non-PrEP users had a pharyngeal or rectal infection. MSM on PrEP were more likely to have rectal chlamydia (prevalence ratio, 1.6). These findings support STI testing every 3 months for MSM on PrEP and at least annually for sexually active MSM, and testing at all anatomic sites of potential exposure. Delany-Morewedge and colleagues evaluated the prevalence and incidence of STIs among African women in the HPTN 082 study (Abstract 965). Among 451 participants enrolled, 38% were diagnosed with an STI at baseline. STI incidence during 12 months of follow-up was high, with 1 out of 3 acquiring chlamydia and one out of 10 acquiring gonorrhea. Davey and colleagues evaluated the prevalence and determinants of STIs in 242 pregnant women in South Africa (Abstract 1003). Overall STI prevalence was 33%, with higher prevalence in HIV-positive compared with HIV-negative women (39% vs 28%, respectively; \( P = .04 \)). Among 80 women diagnosed with an STI, only 8% were treated syndromically in antenatal care. Factors associated with having an STI included being unmarried or not cohabiting with the father, being HIV-infected, and having recent STI symptoms. These findings highlight the need for novel approaches to STI diagnosis and management in pregnancy.

Akselrod and colleagues measured the HIV transmission risk associated with incident STIs among people living with HIV in Washington, DC (Abstract 849). Among 8021 participants followed for a median 3.4 years, 10% had at least 1 STI, of which 40% had 2 or more episodes. Among those with any STI, 17% had a viral load above 200 copies/mL and 13% had a viral load above 1500 copies/mL (sometimes used as a threshold for infectiousness) within 1 month of STI diagnosis. Individuals aged 18 to 24 years, cisgender women, blacks, and people reporting heterosexual HIV acquisition had the highest proportion of viral load above 1500 copies/mL in the setting of an STI. Among those with incident STIs, 52% of participants spent time with viral load above 200 copies/mL and 41% with viral load above 1500 copies/mL. The investigators suggested that health care practitioners should communicate about the risk of transmission in patients who are not virally suppressed, and highlight the importance of rapid testing and treatment of partners.

Bilinska and colleagues presented on the use of an online tool to assist with partner notification of STIs in the United Kingdom (Abstract 1005). This study tested SXT, an online tool that supports easy, anonymous partner notification via text message or email. Overall, 6414 cases initiated partner notification between December 2017 and July 2018. The number of verified tested partners per diagnosis via SXT was higher than national partner notification rates. Electronic partner notification also reduced workload, with 23% to 34% of partner notifications either verified in clinic or self-verified.
online by partners. In multivariable analyses, being MSM, black, and having a diagnosis of Trichomonas was associated with being less likely to have a partner tested using the tool, highlighting areas for future improvement.

Microbiome

Vaginal bacterial community species have been associated with increased risk of HIV acquisition in sub-Saharan African women. Marrazzo and colleagues evaluated the impact of a contraceptive vaginal ring containing estrogen/progesterone on the vaginal microbiome among women in Kenya (Abstract 998). In this study, 122 women treated for bacterial vaginosis (BV) were randomized to continuous versus cyclic use of the contraceptive vaginal ring. Continuous ring use with menstrual suppression was associated with decreased quantities of vaginal bacteria previously associated with increased risk of acquiring HIV, while maintaining Lactobacillus crispatus, a species associated with decreased HIV risk. Similar effects were observed in a small subset of 22 HIV-infected women. These findings suggest that contraceptive ring use could be a feasible intervention to promote Lactobacillus crispatus abundance as a strategy to reduce HIV risk in women and has implications for the delivery of multipurpose prevention technologies containing both contraceptive and antiretroviral agents.

Two studies evaluated whether BV modifies the effect of hormonal contraception on HIV acquisition. Sabo and colleagues tested this hypothesis in a prospective cohort of 1,985 FSWs in Kenya (Abstract 999). In this cohort, depot medroxyprogesterone acetate (DMPA) and oral contraceptive pills both conferred an increased risk of HIV seroconversion, however BV did not modify this association. Use of a contraceptive implant was not associated with HIV acquisition in the presence or absence of BV in this cohort.

Noël-Romas assessed whether the microbiome modifies HIV risk associated with hormonal contraceptives among 685 women in the CAPRISA (Centre for the AIDS Programme of Research in South Africa)-004 trial (Abstract 254). Using a metaproteomics-based approach to quantify the vaginal microbiome in 685 women, they found that DMPA use in women with Lactobacillus dominant vaginal communities was associated with a more than 3-fold increased rate of HIV acquisition relative to women using other hormonal contraceptives. In contrast, this relationship was not seen in women with non-Lactobacillus dominant communities. These results highlight the importance of considering the vaginal microbiome when evaluating the safety of hormonal contraceptives.

Aziz and colleagues assessed whether penile bacterial species are associated with increased HIV risk in heterosexual men (Abstract 239). In a case control study of 267 uncircumcised men participating in a male circumcision trial, they identified 21 penile bacterial species associated with increased risk of HIV acquisition. These included many of the same anaerobic bacteria shown to be reduced by male circumcision, an intervention that substantially reduces HIV risk in men; many of these species have also been implicated in HIV risk in women (such as Prevotella bivia). Each 10-fold increase of these penile bacterial species abundance was associated with a 22% to 57% increase in the odds of HIV seroconversion.

Preexposure Prophylaxis: What’s New?

Investigational PrEP Agents

Compared with tenofovir disoproxil fumarate (TDF), tenofovir alafenamide (TAF) achieves more rapid and higher intracellular tenofovir diprophosphate (TFV-DP) levels in peripheral blood mononuclear cells (PBMCs), has lower plasma tenofovir levels, and has demonstrated improved renal and bone safety when used for HIV treatment. Hare and colleagues presented the primary results from the phase III DISCOVER study evaluating the efficacy and safety of TAF/emtricitabine (FTC) compared with TDF/FTC for PrEP among cisgender MSM and transgender women at risk for HIV acquisition (Abstract 104LB). Participants were randomly assigned 1:1 to blinded daily TAF/FTC versus TDF/FTC and followed up for up to 96 weeks in this non-inferiority trial. Overall, 5,387 adults were enrolled across 94 sites in 11 countries in North America and Europe, with 60% in the United States. The median age of participants was 34 years, 9% were black, and 24% were Latinx/Hispanic; the trial enrolled 74 (1.4%) transgender women. The study observed 22 HIV infections during 87,561 person-years of follow-up, with 7 infections in the TAF/FTC arm (incidence rate 0.16/100 person-years) and 15 infections in the TDF/FTC arm (0.34/100 person-years), for an incidence rate ratio of 0.47 (95% CI, 0.19-1.15) favoring TAF/FTC, which was not significantly different and fell below the pre-specified non-inferiority margin of 1.62. Participants who seroconverted were younger and more likely to be diagnosed with a rectal STI or syphilis; no transgender women became infected during the study. Among the 22 new HIV infections, 5 were suspected to be infected at baseline (1 in TAF/FTC arm, 4 in TDF/FTC arm). Furthermore, 5 participants in the TAF/FTC and 10 in the TDF/FTC arms had low levels of TFV-DP in dried blood spots, leaving 1 infection occurring with medium to high TFV-DP dried blood spot levels in each study arm. In a sensitivity analysis that excluded suspected baseline infections, noninferiority was maintained (incidence rate ratio, 0.55; 95% CI, 0.20-1.48). Evidence of FTC resistance was observed in 4 seroconverters in the TDF/FTC arm, all of whom had suspected infection at baseline. Both study drugs were well tolerated.

TAF/FTC was noninferior to TDF/FTC in preventing HIV infection among men who have sex with men and transgender women, with better bone and renal safety outcomes.
with adverse events balanced between arms, and only 3 leading to drug discontinuation. Overall, 57% participants were diagnosed with an STI and 21% with rectal gonorrhea during the study, with STI incidence rates of 145 and 159 per 100 person-years in the TAF/FTC and TDF/FTC arms respectively. Bone mineral density was measured in a subset of 383 participants at week 48 and showed a 0.5% and 0.18% increase at the spine and hip in the TAF/FTC arm, compared with a 1.12% and 0.99% decline, respectively, in the TDF/FTC arm.

**Rapidly dissolving inserts are being developed for on-demand topical PrEP and are user-friendly, have a favorable safety profile with low systemic drug exposure, and can be formulated in drug combinations**

(P<.001). There were small but statistically significant differences in median changes in estimated glomerular filtration rate (eGFR) between the arms (1.8 mL/min increase in TDF/FTC arm vs 2.3 mL/min decline in TDF/FTC arm; P<.001), and statistically significant differences in proximal tubular protein to creatinine ratios favoring TAF/FTC. Participants in the TAF/FTC arm had a mean increase in weight of 1.1 kg at 48 weeks compared with no weight gain in the TDF/FTC arm. As this study did not include a placebo comparison arm, the researchers used CDC-reported HIV surveillance data to calculate a counterfactual background HIV infection rate for US MSM not on PrEP of 4.02 per 100 person-years, compared with observed HIV incidence rates of 0.08 per 100 person-years for TAF/FTC and 0.45 per 100 person-years for TDF/FTC at the US DISCOVER sites. However, it was noted that this background rate was not adjusted for race. The investigators concluded that TAF/FTC was noninferior to TDF/FTC in preventing HIV infection among MSM and transgender women, with better bone and renal safety outcomes than TDF/FTC. It is important to note that no cisgender women were included in this study.

A previous study showed that oral TAF/FTC was highly effective in preventing vaginal simian HIV (SHIV) infection in female pigtail macaques. As TAF has potential as a long-acting single agent delivered from an implant, Massud and colleagues evaluated the efficacy of single-agent TAF for protection against vaginal SHIV infection in pigtail macaques (Abstract 102). A clinically equivalent dose of TAF (1.5 mg/kg) was administered orally 24 hours before and 2 hours after weekly vaginal SHIV challenge. Overall, 3 out of 7 animals treated with TAF became infected, with a delay in infection among TAF-treated animals compared with controls, for an efficacy of 73%. Similar TFV-DP levels and TFV-DP/deoxyadenosine triphosphate (dATP) ratios in PMBCs were observed among protected and infected animals receiving TAF. She concluded that a clinically equivalent dose of TAF conferred moderate vaginal protection despite high TFV-DP levels. These findings point to an important contribution of FTC in the protection seen with TAF/FTC and highlight the importance of defining the TFV-DP levels in PMBCs associated with complete vaginal protection from single agent TAF.

Rapidly dissolving inserts are being developed for on-demand topical PrEP and are user-friendly, discreet, easy to carry, and can be self-administered without an applicator), have a favorable safety profile with low systemic drug exposure, and can be formulated in drug combinations. Dobard and colleagues evaluated an on-demand TAF/elvitegravir (EVG) insert in a female pigtail macaque model (Abstract 101). Although both drugs had very low systemic drug exposure in plasma following vaginal dosing, vaginal tissue TFV-DP reached target levels 4 to 24 hours post-dosing, and high EVG tissue levels were observed 2 and 4 hours after dosing. TAF/EVG inserts administered vaginally 4 hours before weekly vaginal challenge protected 5 of 6 animals over 13 weeks, with 1 breakthrough infection occurring after the ninth challenge, for an overall efficacy of 92%. These results support the upcoming clinical evaluation of the TAF/EVG insert administered vaginally or rectally in phase I human trials.

The investigational broadly neutralizing antibodies (bNABs) 10-1074, a V3 glycan bNAb, and 3BNC117, a CD4 binding site bNAb, have protected against rectal and vaginal SHIV challenges in prior macaque studies. Garber and colleagues evaluated the protective efficacy of these bNABs against penile or intravenous SHIV challenges (Abstract 100). Macaques were administered a single subcutaneous injection of 10-1074 alone or in combination with 3BNC117 followed by weekly penile or intravenous (IV) challenges until they were systemically infected. Animals administered 10-1074 became infected after a median of 15.5 penile challenges, compared with the control condition in which they were infected after a median of 2.5 penile challenges. One animal that became infected early had evidence of an anti-drug antibody response. In the IV challenge model, macaques receiving 10-1074 and 3BNC117 became infected after a median of 5 challenges, compared with a median of 1 challenge in the control animals.

**Several studies tested novel strategies to increase uptake of PrEP in men who have sex with men, a population highly vulnerable to HIV infection**

There were no differences in peak viremia in animals receiving the bNABs versus control for either penile or IV SHIV challenges. Both bNABs reached peak levels at 1 week, but 10-1074 reached higher levels and achieved greater persistence in vivo. As levels of 3BNC117 were undetectable at the time of SHIV breakthrough, the authors suggested that protection in these animals was being provided predominantly...
by 10-1074. They also reported that plasma levels associated with breakthrough infection were similar for all mucosal routes of HIV acquisition (penile, vaginal and rectal), but was higher for IV challenges, which may reflect the higher challenge virus dose. These findings support the continued development of 10-1074 as a long-acting prevention method for men, women, and PWID.

**PrEP Uptake and the PrEP Continuum**

Several studies tested novel strategies to increase uptake of PrEP in black MSM, a population highly vulnerable to HIV infection. Teixeira da Sliva and colleagues evaluated an intervention to link black MSM to PrEP as part of partner notification and network testing services (Abstract 954). In this pilot study, 143 participants were randomly assigned to a 65-minute face-to-face session with an interventionist to develop an individualized linkage roadmap followed by mini-booster sessions by phone or care as usual. Although overall linkage to PrEP care was low, participants in the intervention arm were 2.55-times more likely to be linked to PrEP care than those in the control arm (23% vs 10%), and were more likely to initiate PrEP (19% vs 10%) respectively. Participants linked to PrEP care were more likely to be older and less likely to be gay-identified. Staffing turnover and barriers to contacting participants were implementation challenges in this study.

Siegler and colleagues piloted a PrEP telemedicine system for young black MSM aged 18 to 30 years in the rural Georgia and Mississippi areas (Abstract 955). The home-based PrEP intervention (ePrEP) was designed to overcome geographic- and stigma-related barriers to accessing PrEP and included home specimen self-collection kits for HIV and STI testing and creatinine level monitoring (urine, rectal or pharyngeal swabs, and finger prick blood), a telemedicine visit with a clinician for PrEP prescribing, and PrEP navigation support and linkage to care. Among 50 young black MSM recruited through social media advertisements, 25 completed a telemedicine visit and were prescribed PrEP, and 21 picked up a prescription. Only 9 were linked to care after prescription pick-up, with several refusing linkage to care, suggesting possible dissatisfaction with PrEP referral options available locally. The majority of the participants found all intervention components acceptable, with most (93%) willing to use ePrEP in place of a standard clinic visit, and two-thirds reported they were more likely to remain on PrEP if ePrEP were available.

Marcus and colleagues reported on the use of electronic health record (EHR) data to identity potential PrEP candidates in a large health care system (Abstract 105). They developed an HIV risk prediction model using EHR data in a cohort of Kaiser Permanente Northern California members seen between 2007 and 2014. There were 44 predictors retained in the final model, including demographics, social history, laboratory tests and results, medication use, and diagnoses; this model had a high concordance statistic (C-statistic) (0.86) indicating high discrimination between HIV cases and non-cases. The full model performed well when validated prospectively using 2015 to 2017 data (C-statistic, 0.84), and outperformed simpler models including only MSM status and STI positivity (C-statistic, 0.57-0.66), particularly among black individuals. The full model identified nearly half (46%) of new HIV cases among men, by flagging only 2% of the general population, however the model did not identify any HIV cases among women. The investigators concluded that routinely collected EHR data can be used to identify patients at high risk for HIV acquisition. Additional work is needed to optimize this tool for identifying women at risk for HIV.

Finlayson and colleagues assessed temporal changes in PrEP awareness and use among MSM in the United States (Abstract 972). In an analysis of National HIV Behavioral Surveillance data from 2014 to 2017, PrEP awareness in MSM increased from 60% to 90% overall and across all racial/ethnic groups. However PrEP awareness remained lower among black and Hispanic MSM compared with white MSM in 2017, although this was no longer significant after controlling for income, health insurance, and census region. PrEP use increased overall from 6% to 35% during this period, also with increases across all racial/ethnic groups, however fewer black MSM reported PrEP use when compared with white MSM in 2017 (30% vs 42%, respectively). Several presentations focused on PrEP attitudes and use in the Chicago metropolitan area. Mustanski and colleagues evaluated the association between PrEP stigma and PrEP uptake and adherence in 105 young MSM and transgender women enrolled in the RADAR cohort study (Abstract 988). They found that participants with higher positive attitudes toward PrEP were more likely to report current PrEP use (OR, 5.05), and participants who reported higher PrEP stigma were less likely to report current PrEP use (OR, 0.50). Additionally, participants who reported missing at least 1 dose in the past week had higher stigma scores. These results suggest that interventions to reduce stigma and improve positive attitudes toward PrEP could increase PrEP uptake and adherence. In the same cohort, Phillips and colleagues evaluated the impact of a citywide advertising campaign, PrEP4Love, on PrEP uptake. Overall, 76% of participants had seen an advertisement for PrEP in Chicago (Abstract 974). Those who had seen the PrEP4Love advertisements were 2.8 times as likely to have a conversation with a medical practitioner about PrEP, twice as likely to have initiated a conversation about PrEP, and 1.9-times as likely to have taken PrEP in the past 6 months. Those who had seen the advertisements were also more likely to perceive that their friends and gay or bisexual men nationwide were taking PrEP, which could help reduce perceived stigma. As those who had seen the advertisements were
more likely to initiate discussions with clinicians about PrEP, it is recommended that those rolling out PrEP campaigns should host trainings with medical practitioners on PrEP to prepare them for these conversations.

Two presentations focused on PrEP attitudes and uptake in cisgender women in the United States. Hirschhorn presented on PrEP knowledge, attitudes, and experience among 370 black cisgender women in Chicago (Abstract 978). Overall, 38% met criteria for PrEP, and only 30% had heard of PrEP. Despite low levels of PrEP knowledge, 29% considered starting PrEP in the next 6 months, with Latina women, those with a recent STI or more worried about HIV, and those with increased belief in PrEP’s effectiveness more likely to have considered initiating PrEP. In qualitative data, women thought that open communication and trust with their practitioner were key during the PrEP decision-making process. Although women reported seeing PrEP advertisements, they thought they could be better tailored for women and their community. Blumenthal and colleagues presented on HIV risk and characteristics of women seeking PrEP in a demonstration project (Abstract 979). The 136 women enrolled were aggregated into 3 HIV risk groups: being in a serodiscordant relationship (47%), having partners of unknown HIV risk behavior (38%), and engaging in sex work (15%). Sex workers reported higher numbers of partners, and were more likely to report problem drinking and intimate partner violence in the past year. Women in a serodiscordant relationship were less likely to report taking PrEP to protect themselves from HIV (self-focused) compared with sex workers and women with unknown partner risk (33% vs 95% and 85%, respectively; \( P < .001 \)). Although most (80%) women reporting a main partner were aware of their partner’s HIV status, black women were less likely to know their partner’s HIV status, than white or Latina women (28% vs 58% and 56%, respectively; \( P = .03 \)). Given the differences in HIV risk profiles and motivations, the investigators suggest that interventions to increase uptake of PrEP among women may need to be tailored by HIV risk group.

Liu and colleagues evaluated the PrEP continuum in the San Francisco Bay Area using a mobile phone survey (Abstract 973). Among 893 HIV-uninfected MSM and transgender women enrolled between June 2018 and February 2019, PrEP awareness was high (≥95%) in both MSM and transgender women, with 48% of MSM and 41% of transgender women having ever initiated PrEP. Current PrEP use was lower among transgender women than among MSM (20% vs 39%, respectively), as was reported high adherence (17% vs 37%, respectively). The most common reasons for PrEP discontinuation included not feeling at risk for HIV (42%), insurance or access issues (27%), adverse effects or concerns about these effects (20%), and adherence concerns (5%). PrEP initiation was lower in Latinx participants, and younger participants and transgender women had lower PrEP persistence. Participants reported that novel PrEP dosing strategies and formulations, particularly on-demand PrEP, could increase PrEP initiation or reinitiation among those who had previously discontinued PrEP. Of note, on-demand PrEP is not recommended in cisgender women or transgender women on hormone treatment.

Toy and colleagues assessed uptake of PrEP in a publicly funded population-based program in British Columbia, Canada (Abstract 956). During the first year of their program in 2018, there were 3351 PrEP applicants, 98% of whom met eligibility criteria. Almost all were men (98%) and resided in the Greater Vancouver area (84%), with only 2.3% in a rural location. There were 554 enrolling PrEP prescribers in their program, of whom 52% had no previous HIV care or treatment experience. PrEP discontinuations or lapses in PrEP prescription were noted in only 9% of clients, and there have only been 2 cases of HIV seroconversion to date, both occurring in individuals who had discontinued PrEP.

Koppe and colleagues evaluated non-prescription PrEP use in Germany (Abstract 957). Among 2005 PrEP users recruited, 79% completed an anonymous online survey. Overall, 20% of participants used non-prescription sources; these individuals had used PrEP longer than PrEP users with prescription drug use, were more likely to use PrEP intermittently or on-demand, and were at higher risk for not completing medical test prior to initiating PrEP or during PrEP use. The investigators highlighted the need for patients to access PrEP through healthcare systems to support the safe use of PrEP.

Lubwama and colleagues reported on the scale-up of PrEP for key populations in Uganda (Abstract 959). From July 2017 to June 2018, 3846 individuals initiated PrEP through their national program: 67% were sex workers, 9% MSM, 0.4% transgender persons, and 24% other key and priority populations. As uptake was initially low in urban sites, they changed service delivery models to include community-based MSM-friendly drop-in centers, which resulted in a 36% increase in MSM uptake. Retention at 3 and 6 months was low for sex workers and fisherfolk, and somewhat higher for serodiscordant couples. These results indicate that retention strategies should be strengthened, particularly for sex workers and fisherfolk who may be highly mobile.

To inform PrEP delivery to FSWS, Lancaster and colleagues evaluated preferences for PrEP delivery among 150 FSWS in Malawi using a discrete choice experiment (Abstract 958). They found that dispensing location was the most important factor for PrEP delivery, with women preferring family planning clinics or non-governmental organization supported drop-in centers. Provision of additional services was the second important factor, with cervical cancer screening and contraceptive provision being the most preferred services. Clinic wait time was the least important factor, and pregnancy testing and partner risk reduction counseling were less preferred services.

Omari and colleagues evaluated the PrEP cascade among Nigerian MSM (Abstract 977). Among 614 participants recruited through respondent driven sampling and approached for PrEP initiation, 93% showed interest in taking PrEP
Among 7250 PrEP users in a commercial research database and 349 PrEP users in a Medicaid database, Medicaid-insured PrEP users had shorter persistence than commercially insured PrEP users

successfully contacted and scheduled for a PrEP appointment. Higher social support was associated with being successfully contacted, scheduled for an appointment, and initiating PrEP. The investigators suggest use of online support groups and community pharmacies to increase social network support could improve PrEP uptake among Nigerian MSM. Oluoch and colleagues evaluated PrEP uptake among adolescent girls and young women (AGYW) in a prospective cohort study in Kenya (Abstract 964). Among 400 AGYW aged 16 to 20 years, 42% were assessed as eligible for PrEP, of whom 15% had a laboratory confirmed STI. Of the 168 AGYW eligible for and offered PrEP, only 9 (5%) accepted a PrEP prescription, 4 of whom had a confirmed STI; this was despite over three-quarters of those eligible for PrEP reporting condomless sex at their last sexual encounter. As PrEP uptake remained low in a setting of experienced PrEP counselors and a girl-friendly environment with easy access to PrEP, the investigators highlight the need to gain a better understanding of AGYW perspectives and factors that would support their uptake of PrEP for HIV prevention.

Poteat and colleagues presented data on PrEP awareness and willingness among transgender women in South Africa (Abstract 981). Among 214 participants enrolled in the T-MAPP (Transgender Women Mobilizing and Preparing for High-Impact Prevention) study, 51% had heard of PrEP. Among those aware of PrEP, 83% knew where to get PrEP, and 40% knew other transgender women taking PrEP. Among HIV-uninfected participants, 15% had ever taken PrEP, and 11% were currently on PrEP; 52% of PrEP-naive participants were willing to take PrEP. Of concern, 21% of PrEP users reported that a healthcare practitioner had told them to stop hormone therapy and 16% had their hormone dose changed by their practitioner because they were taking PrEP. These results highlight the need to increase PrEP awareness in transgender communities. The researchers emphasize the importance of including transgender women in designing strategies to increase PrEP use in these communities.

**PrEP Persistence, Adherence, and Discontinuations**

Huang and colleagues reported on PrEP persistence in 2 cohorts of PrEP users with either commercial or Medicaid insurance from 2011 and 2016 (Abstract 106). Non-persistence was defined as having a gap in prescription fills for more than 30 days. Among 7250 PrEP users in a commercial research database and 349 PrEP users in a Medicaid database, Medicaid-insured PrEP users had shorter persistence than commercially insured PrEP users (median, 7.6 vs 14.5 months, respectively), with 54% versus 56% of PrEP users persisting at 12 months, respectively. In multivariable models, younger age, female sex, and living in a rural area were associated with non-persistence among commercially insured PrEP users; younger age, female sex, and black race were associated with non-persistence among Medicaid-insured PrEP users. The investigators conclude that tailored interventions are needed to improve PrEP persistence in different populations, particularly among those with the highest rates of new HIV diagnoses.

Several presentations evaluated patterns and reasons for PrEP discontinuations in different populations. Serota and colleagues assessed PrEP persistence and discontinuations in an observational cohort of 298 young black MSM in Atlanta (Abstract 963). Among 125 participants who initiated PrEP, 37% remained fully persistent, 63% discontinued PrEP for 2 or more weeks at least once during the study, and 31% had stopped PrEP and never restarted. Frequent stopping and restarting PrEP were common in the cohort; overall person-time on PrEP after initiation was 69%. The median time to first discontinuation was 219 days, and the median time to final discontinuation was 690 days. Younger age, marijuana use, having an STI in the past 12 months, and having fewer than 3 anal sex partners in the past 6 months were associated with PrEP discontinuation. As HIV incidence remained high in this cohort at 6% despite access to PrEP, these results highlight the need for interventions tailored to youth and those who use substances to support PrEP persistence. The investigators suggest future research to evaluate the utility of on-demand PrEP in young MSM who may discontinue PrEP due to lower levels of risk activity. Newcomb and colleagues evaluated predictors of PrEP discontinuation among young MSM and transgender women in Chicago (Abstract 989). Older participants were more likely to discontinue PrEP, and bisexual individuals were less likely to discontinue PrEP. Young MSM and transgender women with increasing condomless anal sex were less likely to discontinue PrEP, as were those with health insurance, and those entering into a relationship were more likely to stop PrEP.

Koppe evaluated reasons for stopping PrEP among PrEP users in Germany (Abstract 990). The most common reasons for stopping PrEP included uses related to taking the medication (45%), a change in partner situation (32%), access issues (28%), and other prevention strategies being sufficient (25%). PrEP discontinuation was associated with younger age, having used PrEP intermittently, being unhappy with their current sex life, and always or often using condoms. However, more than a third of former PrEP users reported inconsistent condom use, highlighting the need for HIV prevention strategies tailored to this population.
Wahome and colleagues evaluated factors associated with refusing or stopping PrEP among MSM in Kenya (Abstract 991). Among 143 MSM who initiated PrEP, 22% stopped PrEP. Lower education and paying for sex were associated with refusing or stopping PrEP. Qualitative data indicated that misconceptions about PrEP and low perception of HIV risk contributed to refusing PrEP, and pill burden, stigma, storage challenges, and adverse effects contributed to stopping PrEP. These results highlight the need for community engagement and education to correct misconceptions, increase awareness, and reduce PrEP-related stigma among Kenyan MSM.

Kagaayi and colleagues presented data on acceptability and retention of clients on PrEP in Uganda (Abstract 997). Among 2980 individuals screened for PrEP, 94% were eligible, and 93% enrolled on PrEP. Overall, 51% were sex workers, 22% fisherfolk, and 13% truck drivers. Retention dropped rapidly, with median retention of 45 days. Among women, loss to follow-up was higher among AGYW and fisherfolk, than among serodiscordant couples. Among men, fisherfolk and truck drivers had lower retention. Similarly, Olsen and colleagues evaluated short-term retention on PrEP in the Democratic Republic of Congo (Abstract 996). Among 356 individuals who initiated PrEP, 77% were FSWs, 20% MSM, and 2% PWID. Overall retention was 64% at month 1 but increased to 82% at month 3 and 86% at month 6 as a result of increased outreach efforts. Irungu and colleagues evaluated PrEP use among African men and women continuing PrEP in public health clinics in the Partners Scale-up Project (Abstract 992). Among 4205 PrEP initiators, 85% had an HIV-positive partner. Overall, 65% continued PrEP use at 3 months. PrEP continuation was associated with age 30 years and older, having an HIV-positive partner, and female sex. Among 71 dried blood samples tested, 96% had detectable TFV-DP, with a median TFV-DP concentration of 515 fmol/punch. These data support the continued programmatic implementation of PrEP in public health settings in Africa, particularly when additional support can be provided for long-term retention.

Several studies focused on PrEP adherence and persistence among young women in Africa. Mugwanya and colleagues evaluated PrEP persistence in African adolescents and young women in maternal child health and family planning clinics in Kenya (Abstract 993). Among 2304 women who initiated PrEP, continuation rates were 21% and 10% at 3 and 6 months, respectively. PrEP continuation rates were higher among women with HIV-positive male partners (52% continuing at 3 months) and in women 35 years and older (37% continuing at 3 months). The most common reasons for discontinuing PrEP included low self-perceived HIV risk, adverse effects, pill burden, and that partner is HIV negative. Celum and colleagues demonstrated high PrEP adherence among AGYW in Cape Town (Abstract 994). Participants were provided adherence counseling including drug level feedback and half were randomly assigned to receive financial incentives for achieving high drug levels in dried blood spots. Among 200 young women (median age, 19 years) who initiated PrEP, half had high adherence based on TFV-DP levels in dried blood spots at 3 months, and 80% had medium or better adherence at 2 and 3 months. High PrEP adherence was associated with having an HIV-positive or unknown status partner, not having sex in the prior 30 days, and disclosing plans to give PrEP to someone else.

Celum and colleagues also evaluated PrEP adherence among young African women in the HPTN 082 study (Abstract 995). Among 427 women (median age, 21 years) who started PrEP, 84% had detectable TFV-DP levels at month 3, 25% had levels at or above 700 fmol/punch (associated with 100% PrEP effectiveness in MSM), and 23% had levels between 350 and 699 fmol/punch. At month 3, 70% of women reported they attended at least 1 adherence club offered through the study. Predictors of high adherence at month 3 were attending an adherence club, not reporting symptoms of depression, and number of sexual partners. These disparate results across studies highlight the need for additional research to better understand the support young women need to achieve adherence and persistence on PrEP.

Several posters described the use of urine testing for tenofovir to measure PrEP adherence. Gandhi presented on the validation of a novel urine tenofovir immunoassay for real-time PrEP and ART adherence testing (Abstract 464). When tested on 637 urine samples from patients taking 2, 4, or 7 doses per week using directly observed dosing, the sensitivity and specificity of the urine immunoassay was 99% and 94%, respectively. A cutoff of 1500 ng/mL accurately classified 98% of patients who took a dose within 24 hours as adherent, and was chosen as the cut-off for a point-of-care urine test using a lateral flow immunoassay. This test will be low cost (<$2/assay) with a result available in approximately 5 minutes. She pointed to limitations of the test, including it being a short-term measure and providing a yes or no response. However, a more expensive urine test with a reader will have gradations of adherence. Spinelli and colleagues evaluated the use of this urine assay in the iPrEx Open Label Extension (Abstract 947). Among 125 participants in the urine substudy, the median urine tenofovir level was 15,000 ng/mL in those who remained HIV-negative, 5550 ng/mL among 11 participants who eventually seroconverted, and below 1000 ng/mL in all 9 participants at the time of seroconversion. Low (<1000 ng/mL) versus high (>25,000 ng/mL) urine tenofovir levels were associated with 14-fold higher odds of future seroconversion. The investigators point to the potential utility of point-of-care urine testing to trigger real-time adherence...
feedback and interventions in the setting of low adherence.

Drug Resistance and PrEP Failures

Misra and colleagues evaluated the impact of PrEP on drug resistance and acute HIV infection in New York City (Abstract 107). New York State guidelines recommend nucleic acid amplification testing (NAAT) for persons with symptoms of acute HIV infection or a negative antibody test who report condomless sex in the past 4 weeks. Among 3685 recently diagnosed persons assigned for partner services between 2015 and 2017, 2% had reported prediagnosis PrEP use, with a median duration of PrEP use prior to HIV diagnosis of 106 days.

Among individuals with genotypes available (75% of PrEP users and 62% of never users), M184I/V/I/MV was more prevalent among prior PrEP users versus never-users (29% vs 2%, respectively). No K65R mutations were observed among prior PrEP users. Pre-diagnosis PrEP users were more likely to be diagnosed with acute HIV infection than never users (33% vs 9%, respectively), possibly due to them receiving regular healthcare. Although a quarter of PrEP users had a negative NAAT prediagnosis, only 5% had a negative NAAT in the 0 to 2 day window before PrEP start, a possible indication of PrEP screening. The investigators suggest that rigorous screening, including NAAT, can reduce PrEP initiation during undetected HIV infection, and highlight the importance of routine genotype testing at HIV diagnosis for persons with a recent history of PrEP use. In a symposium presentation, Molina provided an overview of different types of PrEP failures (Abstract 160).

He highlighted that PrEP failures can occur at any point along the PrEP continuum of care, including the user, system, health care practitioner, assay, and drug level. He showed that most PrEP users in 2019 are located in North America, with 275,000 PrEP users in the United States, and called for increased awareness and access to PrEP globally. Challenges with HIV diagnostic testing include ruling out acute HIV infection during PrEP initiation, diagnosing HIV infection during PrEP follow-up, and managing false-positive HIV tests. He reviewed the sequential appearance of viral markers and antibodies during acute HIV infection, with the eclipse period being about 11 days, p24 antigen appearing 6 days later, and the first antibody test appearing in an additional 5 days. In the IPERGAY trial, there were 13 HIV infections in which the Western Blot assay was initially negative; only the fourth-generation antigen/antibody Architect test was able to identify most (11) of these infections, with the remaining 2 with HIV RNA levels under 500 copies/mL. Similarly, there was an 18% non-reactivity rate for the fourth-generation assay in an acute infection study in Thailand. As most individuals are asymptomatic during acute HIV infection, he highlighted International Antiviral Society–USA (IAS-USA) guidelines recommending fourth HIV antigen/antibody testing to determine PrEP eligibility, and to send an HIV RNA assay if acute HIV infection is suspected, even without symptoms. He reviewed data from the Partners PrEP study that showed a delay in detection of HIV infection in the PrEP arm, associated with lower plasma HIV RNA levels, but no differences in the Architect signal to cut-off at any stage. In the case of ambiguous HIV test results during PrEP, he reviewed guidelines that recommend repeating serologic tests, RNA tests, and possibly DNA tests, and using tests from another manufacturer, to confirm the presence or absence of infection. Another consideration is whether to continue or stop PrEP: if PrEP adherence has been high and the likelihood of infection low, an option is to continue PrEP to maintain protection, although this may increase the risk of resistance if the individual is infected. Another option is to stop PrEP and reassess HIV status, which may facilitate diagnosis but may put the individual at risk for acquiring HIV during the period off PrEP; a third option is to initiate ART, which may be the recommended option if the individual was not adherent to PrEP, raising the likelihood of infection. However, it is important to confirm HIV diagnosis in this scenario.

He pointed to a toll-free PrEPline (1-855-448-7737) in the United States for expert guidance on managing ambiguous HIV test results. Another concern raised is the acquisition of virus resistant to TDF/FTC in the setting of high PrEP adherence; however, to date there have been only a few cases reported in the literature. He reviewed data from animal studies showing 100% protective efficacy of TDF/FTC in macaques challenged rectally with SHIV containing the M184V mutation, which may be due to hyper-susceptibility to TDF in the setting of the M184 mutation. In contrast, reduced TDF/FTC efficacy was observed with the presence of the K65R mutation. Rates of transmitted HIV-1 resistance to TDF/FTC have remained low (<1%) across a number of studies, although in the discussion it was mentioned that rates of K65R mutation may be higher when using more sensitive assays. A case of PrEP failure with TDF/FTC-sensitive virus has been reported in Amsterdam; potential explanations of this breakthrough infection include high virus inoculum, concomitant STI infection with inflammation, possible exposure during a brief period of nonadherence, or variable pharmacokinetics of TDF/FTC in the blood or rectal mucosa. Molina reviewed data from PrEP clinical trials showing that emergence of drug resistance occurred most commonly at enrollment when PrEP was started in the setting of acute HIV infection, with 41% having resistant virus, in almost all cases with the M184V mutation. In contrast, rates of resistance were below 3% among individuals who seroconverted after enrollment. He highlighted the importance of ruling out acute HIV infection before starting...
PrEP, and testing for HIV RNA level in baseline samples, if available, in cases of infection being detected at the first follow-up visit. In terms of treatment of HIV infection occurring when on PrEP, he recommended starting ART immediately with a regimen with high barrier to resistance, including a TDF/ FTC or TAF/FTC backbone plus boosted darunavir or dolutegravir/bictegravir. Regimens can then be simplified after HIV genotype is available. It is important to reinforce adherence to ART in these scenarios.

**Safety of PrEP**

In a themed discussion, 2 presentations focused on renal safety and monitoring among TDF/FTC PrEP users (Themed Discussion TD-14). Liegeon and colleagues assessed the renal safety of on-demand TDF/FTC PrEP in the National Agency for AIDS Research (ANRS)-IPERGAY randomized trial and open-label extension (Abstract 960). A median of 15 and 18 pills per month were used during the blinded and open-label phases of the study respectively. Among 389 participants enrolled in the blinded phase, the mean slope of eGFR decline per year was not statistically significantly different between the TDF/FTC and placebo groups (-1.53 mL/min vs -0.88 mL/min, respectively; \( P = .27 \)). Furthermore, the slope of eGFR reduction was not greater in participants with baseline eGFR below 90 mL/min, age above 40 years, or with hypertension. A dose-response relationship was seen between higher TDF/FTC exposure as measured by number of pills taken and tenofovir plasma concentrations and lower eGFR at the following visit. The investigators suggest that the overall reduction and intermittent exposure to TDF/FTC may explain the good renal safety observed with on-demand PrEP.

Pintye and colleagues evaluated the implementation of point-of-care creatinine testing within a large-scale PrEP program in Kenya (Abstract 961). From June 2017 to December 2018, 4149 HIV-uninfected women seeking routine antenatal, postnatal, and family planning services were screened for PrEP per national guidelines, which recommend, but do not require, creatinine testing prior to PrEP initiation. In this PrEP implementation program, the feasibility of assessing creatinine level using validated, handheld point-of-care machines was demonstrated. Overall, low creatinine clearance rate was rare, with only 8 (0.2%) having a creatinine clearance rate below 50 mL/min, and 122 (3%) having a creatinine clearance rate below 60 mL/min. These findings support the recommendation of not mandating creatinine testing at TDF/FTC PrEP initiation.

Spinelli and colleagues assessed declines in bone mineral density associated with long-term TDF/FTC exposure in the iPrEx Open-Label Extension study (Abstract 946). Among 254 MSM and transgender women in a dual-energy X-ray absorptiometry (DXA) substudy, there was dose-dependent decline in spine bone mineral density by increasing average weekly adherence as measured by TFV-DP levels in dried blood spots, with a 1.2% and 0.5% mean decline in spine and hip bone mineral density, respectively, in highly adherent PrEP users. Additional decline did not occur after 24 weeks of DXA assessment. The investigators suggest that dose-limiting strategies such as intermittent PrEP, should be evaluated for their impact on toxic effects.

Mikati and colleagues assessed the safety of same-day PrEP starts within sexual health clinics in New York City (Abstract 962). Following a negative rapid HIV test, PrEP candidates were provided a 30-day supply of TDF/FTC prior to return of other laboratory results if no medical contraindications are present, including acute HIV symptoms, history of kidney disease, or hepatitis B infection. Among 1437 PrEP initiation candidates evaluated, 97% started PrEP the same day, of whom 99% had no medical contraindications to PrEP. The prevalence of having any PrEP contraindication was higher among delayed versus immediate PrEP patients (14% vs 0.7%, respectively; \( P < .001 \)). Among 1587 immediate PrEP patients, 10 had medical contraindications, including 2 with positive HIV NAAT, 2 with GFR below 60 mL/min, and 6 with reactive hepatitis B surface antigen (HbsAg), considered a relative contraindication. Among the 50 (3.5%) individuals who delayed PrEP, 7 had a medical contraindication, including 1 with a positive HIV NAAT, 4 with GFR below 60 mL/min, and 2 with reactive HbsAg. Patients older than 40 years were 6-times more likely to have a medical contraindication than younger patients, although these were uncommon in both age groups (3% vs 0.5%, respectively; \( P = .01 \)). Among the 43 delayed PrEP patients who did not have medical contraindications, only 35% initiated PrEP within 60 days. Delayed PrEP patients were more likely to be women, older than 40 years, and have medical contraindication to PrEP initiation; none of the 58 women evaluated for PrEP had actual medical contraindications to PrEP initiation. The investigators concluded that immediate PrEP initiation is a safe and promising model to increase PrEP initiations among patients within walk-in settings such as sexual health clinics.

**Cost-effectiveness**

Wang and colleagues evaluated the cost-effectiveness of PrEP among black and white adolescent MSM aged 16 to 18 years in the United States (Abstract 1085). The incremental cost effectiveness ratio was $33,064 per quality-adjusted life year (QALY) gained for black MSM, and $427,788 for white MSM. Using a below $100,000/QALY gained as a benchmark for cost-effectiveness, these results suggest that PrEP is cost effective in black but not white adolescent MSM in high prevalence US settings.

Roberts and colleagues evaluated the incremental costs of PrEP delivery in antenatal, post-natal, and family planning clinics in Kenya (Abstract 1082).
Overall, the cost per client-month of PrEP dispensed was $26.52, which is similar to costs reported for delivery to other key populations. Total annual costs could be reduced by postponing creatinine testing and prioritizing PrEP to those at high risk for HIV acquisition. Van Vliet and colleagues evaluated the cost-effectiveness of targeting long-acting injectable PrEP to injectable contraceptive users in South Africa (Abstract 1077). The impact of long-acting PrEP on number of infections averted depends on its effectiveness. Long-acting PrEP will only be cost-effective at a price of $40 or less, assuming ART coverage of 85% in 2030; PrEP will not be cost-effective at an ART coverage of 95%. If low prices are not possible, they recommend targeting long-acting PrEP for women at highest risk of HIV infection.

All cited abstracts appear in the CROI 2019 Abstracts eBook, available online at www.CROIconference.org

Financial affiliations in the past 12 months: Dr Buchbinder and Dr Liu have participated in research trials that received provision of medicines from Gilead Sciences, Inc.

Additional References Cited in Text
Invited Review

CROI 2019: Neurologic Complications of HIV Disease

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Investigators reported many new neuroHIV research findings at the 2019 Conference on Retroviruses and Opportunistic Infections (CROI). These findings included confirmation that HIV-associated neurocognitive disorder (HAND) remains common with an increasingly recognized role for comorbidities (eg, obesity) and neurodegenerative conditions (eg, Alzheimer’s disease), especially as persons living with HIV (PLWH) advance into their seventh decade of life and beyond. HAND is increasingly recognized as a heterogeneous disorder that differs between individuals (eg, by sex) in the trajectory of specific neurocognitive abilities (eg, executive functioning). A more recent focus at this year’s conference was toxicity of combination antiretroviral therapy: neurocognitive performance and neuroimaging data from several studies were presented but did not consistently support that integrase strand transfer inhibitors are associated with worse neurologic outcomes. Neuroimaging studies found that white matter changes reflect a combination of the effects of HIV and comorbidities (including cerebrovascular small vessel disease) and best correlate with blood markers of inflammation. The pathogenesis of HIV in the central nervous system (CNS) was the focus of a plenary lecture and numerous presentations on HIV compartmentalization in the CNS and cerebrospinal fluid viral escape. Novel findings were also presented on associations between HIV-associated neurologic complications and glycomics, neuron-derived exosomes, and DNA methylation in monocytes. This summary will review findings from CROI and identify new research and clinical opportunities.

Keywords: CROI, 2019, HIV, neurology, HAND, comorbidities, central nervous system, neurodegenerative disorders, InSTI, neuroimaging, neuropathogenesis, host mechanisms

Introduction

The effect of HIV in the central nervous system (CNS) was an important theme of several oral and poster presentations at the 2019 Conference on Retroviruses and Opportunistic Infections (CROI). Neurologic presentations continued to focus on HIV pathogenesis and reservoirs in the CNS, persistent neurologic dysfunction (as assessed by neurocognitive testing, neuroimaging, and cerebrospinal fluid [CSF] evaluations) in virologically well-controlled persons living with HIV infection (PLWH). The role of comorbidities and their effects on brain function have become increasingly relevant as PLWH treated with antiretroviral therapy (ART) continue to age into their seventh decade and beyond. This summary is not meant to be an exhaustive review of all material presented at CROI 2019. Instead, this review concentrates on major thematic areas that may inform new avenues of research and stimulate further discussions regarding clinical management of PLWH.

A “therapeutic window” may exist in which ART initiation might prevent the development of HAND

HIV-Associated Neurocognitive Disorders

HIV-associated neurocognitive disorder (HAND) remains common and continues to persist despite ART. Within a large cohort of ART-naïve PLWH who resided in Uganda, the presence of HAND at initial evaluation was associated with 68% increased odds of death at 2 years and a 98% increased odds of death within 5 years (Abstract 425). These results indicate that HAND diagnosis carries substantial morbidity and mortality risks. In the WIHS (Women’s Interagency HIV Study), greater immune activation before the initiation of ART was associated with higher rates of neurocognitive impairment on subsequent follow-up (Abstract 407). In a cohort of individuals with acute and early HIV infection from Peru, Robertson and colleagues showed that early initiation of ART improved cognition (Abstract 445). PLWH who were recently infected (<3 months) or those individuals who initiated ART within 6 months of seroconversion, cognitive impairment improved regardless of when therapy was initiated. These results suggest that a “therapeutic window” may exist in which ART initiation might prevent the development of HAND. Overall, these results suggest that early HIV diagnosis, early initiation of therapy (especially within the first 6 months of seroconversion), and reduction of the inflammatory cascade after infection may stabilize cognitive function.

Identification of individuals at increased risk for development of HAND is important as precision medicine through tailored therapies (eg, anti-inflammatory or higher CNS penetration ART) may be beneficial for select PLWH. The diagnosis of HAND in chronically...
infected PLWH can fluctuate over time. De Francesco and colleagues (Abstract 420) evaluated changes in cognition over 2 years in virologically well-controlled PLWH (n=173) compared with HIV-seronegative individuals (n=77). At baseline evaluation, 20% of the PLWH and 3% of the HIV-seronegative individuals had cognitive impairment using a multivariate normative comparison (MNC) score. At 2-year follow-up, 13% of PLWH and 6% of the HIV-uninfected individuals had cognitive impairment based on the MNC. Although none of the cognitively impaired HIV-uninfected participants changed over the 2 years of follow-up, 46% of the PLWH improved (changed from cognitively impaired to not cognitively impaired). For those individuals who were cognitively normal at baseline, 2% of the PLWH and 4% of the HIV-uninfected participants developed cognitive impairment. Among PLWH, 10% had a reliable decline in cognition, 79% remained stable, and 11% had improved cognition. Among HIV-uninfected individuals, 7% had a reliable decline in cognition, 92% remained stable, and 1% improved. These results suggest that most PLWH who are virologically well controlled remain cognitively stable over 2 years. In contrast to other neurodegenerative disorders, in which there are progressive declines, approximately half of all PLWH who have cognitive impairment at a given time point may improve over time. HAND is characterized by fluctuations in cognition over time rather than a gradual progressive decline seen in other neurodegenerative diseases.

PLWH who have HAND may be considerably heterogeneous regarding the domains that contribute to neurocognitive impairment. Fitzgerald and colleagues identified distinct clusters of age-related changes in declarative memory in PLWH and HIV-uninfected individuals (n=1752) followed up in the WIHS (Abstract 408). Using a Bayesian Dirichlet process mixture model, 4 subgroups were identified: normal slow decline, normal accelerated decline, impaired accelerated decline, and impaired but stable cognition. Approximately 55% of the women had accelerated cognitive decline (both normal and impaired at baseline) that was attributable to several risk factors including reduced neurocognitive reserve (less education, more unemployment, and depressive symptoms). Metabolic factors (obesity, diabetes, and substance use). In a cohort of PLWH and HIV-uninfected persons followed up at the US National Institute of Health and the US Department of Defense (n=597), risk factors for worse cognitive impairment included currently smoking, history of alcohol abuse, and unemployment (Abstract 414). Overall, these results suggest that cognitive impairment seen in PLWH may reflect changes in the brain due to HIV early in the disease and additional risk factors later in the disease process.

Comorbidities and HAND

Several comorbidities appear to increase the risk of cognitive impairment in virologically well-controlled PLWH. Within cohorts of PLWH at the University of California San Diego, anemia was associated with worse overall neurocognitive performance cross-sectionally and longitudinally (Abstract 426). Changes in cognition were observed in several domains including speed of information processing, motor functioning, and working memory. The authors postulate that chronic inflammation affects iron metabolism that leads to anemia. Within the HAILO (HIV Infection, Aging, and Immune Function Long-term Observational) study, gait speed and cognition were assessed in PLWH (n=929). Increased levels of hemoglobin A1C, cognitive impairment, and African American race were associated with declines in gait speed (Abstract 703). Within this HAILO group, Perez and colleagues longitudinally investigated the relationship between obesity, frailty, and cognition over time (Abstract 129). Similar to De Francesco and colleagues (Abstract 420), 78% of PLWH had no cognitive deficits and continued to have normal cognition over a 3-year interval, and 10% had cognitive impairment at both time points, 6% had an improvement in cognition at the second time point, and 6% developed impairment over the 3-year interval. Obesity and older age, but not frailty, were the greatest risk factors for developing cognitive impairment over 3 years. Finally, Chow and colleagues investigated the association between presence of cardiovascular disease (CVD) as assessed by the Atherosclerotic Cerebrovascular Disease [ASCVD] and Framingham Heart Study CVD Risk Score (FRS) and risk of developing neurocognitive impairment in the HAILO cohort (Abstract 128). In unadjusted and adjusted models, higher baseline ASCVD risk score or FRS was associated with worsening in cognition over 4 years. Although the negative impact of cerebral small vessel disease (CSVD) on cognition was seen for both men and women, effects were significantly greater in women. Overall, these results point to focusing on modifiable risk factors including anemia, diabetes, and metabolic factors as intervenable targets for potentially stabilizing neurocognitive function in PLWH, especially women. Preventive interventions geared toward these comorbidities in PLWH may be important for patient care.

Neurodegenerative Diseases and HAND

A symposium presentation by Valcour focused on the potential increasing prevalence of aging-related neurodegenerative diseases in PLWH (Abstract 159). Questions remain if clinicians can successfully distinguish Alzheimer’s disease (AD) from HAND and if an accelerated phenotype exists within older (>60 years old) PLWH. Inflammation persists in virologically suppressed PLWH with impairment, in the periphery (eg, plasma measures) and centrally (eg, positron emission
tomography [PET] measures). However, the contribution of inflammation due to HIV is contentious, as a recent PET imaging study did not observe elevated neuroinflammation in virologically suppressed PLWH compared with matched HIV-uninfected persons (Abstract 460). Controversy also remains regarding whether HIV and aging accentuate or accelerate changes in brain integrity. Some studies have demonstrated a greater rate of brain atrophy in PLWH than in HIV-uninfected persons and others have demonstrated that HIV and aging independently cause changes.

**Several studies at CROI 2019 reported the CNS effects of initiating or switching to InSTI-containing antiretroviral therapy**

Differences may reflect the presence of CSVD or the sample cohorts studied. Several markers could potentially distinguish AD from HAND. PET imaging of amyloid and tau, pathologic hallmarks of AD, were not abnormal in small cohorts of PLWH compared with HIV-uninfected individuals.\(^1\)\(^2\) Although these studies were performed in younger PLWH, cognitively impaired individuals were included. Furthermore, if PLWH do have accelerated aging, PLWH who are 50 years of age or older should be at increased risk for developing AD. However, the few studies that have been performed in this age range have not shown an increase in the prevalence of AD. The presence of AD in older PLWH may reflect aging and genetic risk factors and may not be specifically due to HIV. CSF amyloid and tau also serve as useful biomarkers for distinguishing AD from HAND. Conflicting results have been observed with some studies demonstrating mild alterations in CSF amyloid but not CSF tau in PLWH. Trunfio and colleagues evaluated PLWH (n = 181) who were 45 years of age or older and virologically suppressed and only 1 individual (<1%) had CSF values characteristic of AD (Abstract 415). Further longitudinal studies of neuroimaging and CSF biomarkers in older cohorts of PLWH are needed.

**CNS Effects of Integrase Strand Transfer Inhibitors**

Integrase strand transfer inhibitors (InSTIs) are potent components of initial ART regimens and their use is growing worldwide. With the report of more frequent neuropsychiatric adverse events (NP-AEs) in a clinical population,\(^3\) questions have arisen about the CNS safety of InSTIs.

Several studies at CROI 2019 reported the CNS effects of initiating or switching to InSTI-containing ART. Mora-Peris and colleagues, for example, evaluated 8 PLWH who remained on a raltegravir-containing regimen and 12 PLWH who switched to a dolutegravir-containing regimen (Abstract 443). Neurocognitive performance, neuroimaging, and CSF measures were assessed at baseline and after 120 days. Although the group sizes were small, no statistically significant differences were observed between the groups in any of the assessments, supporting the conclusion that switching to dolutegravir-containing ART is safe for the CNS. This conclusion was also supported by data from the Thai SEARCH (South East Asia Research Collaboration in HIV) study (Abstract 440). Participants (n=254) diagnosed with acute HIV infection had taken at least 24 weeks of ART (median, 144 weeks) and were subsequently switched to a dolutegravir-containing regimen. They were evaluated before and after the switch using multimodal assessments (neurocognitive testing, the Patient Health Questionnaire-9 [PHQ-9], major depression screening, and an assessment of distress). After switching, participants reported more somatic symptoms on the PHQ-9 and more symptoms of depression, although they only trended toward having more symptoms on the cognitive/affective subscale of the PHQ-9 and were not more likely to have evidence of moderate-to-severe depression. Importantly, no participants discontinued dolutegravir for NP-AEs and no statistically significant changes in cognitive performance or distress were observed after switching. Two other studies reported on participants who were initiating or currently taking InSTIs without an observed therapy switch. A study from Barcelona assessed participants who initiated InSTI-containing ART during early HIV infection (n=12) similar to the SEARCH study, but in contrast, compared them with those who initiated InSTI-containing ART during chronic HIV infection (n = 15) and to persons without HIV (Abstract 439). In addition to a 12-test neurocognitive test battery, participants were assessed with structural neuroimaging and an assessment of daily functioning. Cognitive performance improved in all 3 groups over time and did not differ among the groups. Functional assessments identified that the early HIV infection group had evidence of greater stress levels 4 weeks after initiating ART (but was similar to other groups at 48 weeks) and that the chronic HIV infection group trended toward having worse depressive symptoms at 48 weeks. Neuroimaging identified that the chronic HIV infection group also had evidence of a reduction in medial orbitofrontal gray matter volume at weeks 4 and 48 that did not appear to be present in the other groups. Since both HIV infection groups were taking InSI-containing ART, however, this is more likely to be due to later initiation of ART than to InSTI-specific declines.

In a cross-sectional analysis, O’Halloran and colleagues compared neurocognitive performance and neuroimaging measures in participants who were taking InSTI-containing (n=99) or non-InSTI-containing (n=103) ART (Abstract 442). The specific InSTI drugs used by participants were raltegravir (40.4%), dolutegravir (30.3%), and elvitegravir (29.3%). InSTI users had worse global neurocognitive performance (specifically in the combined learning/memory domain) than non-InSTI users and this did not appear to differ by InSTI drug (ie, the effect size for dolutegravir was similar to raltegravir and elvitegravir). Neuroimaging identified that InSTIs were associated
with decreases in volumes throughout the brain. This evidence of InSTI neurotoxicity is generally consistent with the prior report from deBoer et al,¹ but stands in contrast to other reports at CROI, and could be confounded by the cross-sectional design of the study.

Concerns about the CNS safety of InSTI drugs were also supported by in vitro and animal experiments (Abstract 435). Oligodendrocytes are not easily infected by HIV, but interest in these understudied myelin-producing glial cells is growing since white matter abnormalities are common in PLWH,⁴,⁵ even in those taking suppressive ART, and have been linked to worse cognitive performance.⁶ In carefully planned experiments, Jordan-Sciutto and colleagues administered elvitegravir or raltegravir to primary rat oligodendrocytes and monocyte-derived macrophages (MDMs, either uninfected or infected with HIV) (Abstract 435). They observed that HIV-infected MDMs inhibited oligodendrocyte differentiation but, somewhat unexpectedly, that elvitegravir (but not raltegravir) did as well. In animal experiments, investigators induced demyelination in mice with cuprizone and found that elvitegravir inhibited remyelination. Experiments that are more mechanistic in design are being performed but these findings suggest a possible biologic basis for InSTI-associated neurotoxicity.

Other scientists reported on investigations regarding the potential neurotoxicity of other antiretroviral drugs and comitant drugs at CROI 2019. For example, instead of focusing on switching to an InSTI-containing regimen, one study focused on the switch to tenofovir alafenamide (TAF)/emtricitabine (FTC) from either tenofovir disoproxil fumarate (TDF)/FTC or abacavir/lamivudine (Abstract 436). Twenty PLWH were evaluated with cognitive testing and CSF assessments at 3 and 12 months after switching. No statistically significant changes were seen in cognitive performance or CSF biomarkers (neopterin, neurofilament light [NFL], β2-microglobulin, IgG index) in this small study, supporting the CNS safety of switching to TAF/FTC. In a much larger analysis, Li and colleagues aimed to determine if cognitive performance of men enrolled in the MACS (Multicenter AIDS Cohort Study) improved after discontinuing efavirenz (Abstract 441). This analysis of nearly 2000 PLWH failed to show differences in the cognitive trajectory over time between men who either discontinued or continued efavirenz, supporting the long-term CNS safety of efavirenz. The longitudinal design and large sample size of this analysis were strengths, but an important limitation was that only 44 (2.2%) men remained on efavirenz throughout the period of observation.

DeFranceso and colleagues also focused on the CNS safety of nucleoside/nucleotide reverse transcriptase inhibitors (nRTIs) by comparing concentrations in blood of 4 nRTIs (abacavir, TDF, FTC, and lamivudine) with cognitive performance in more than 600 participants of the POPPY (Pharmacokinetic and Clinical Observations in People Over Fifty) study (Abstract 419). Population pharmacokinetic modeling estimated maximum and trough drug concentrations as well as the area-under-the-time-concentration curves. Higher concentrations of TDF and FTC were associated with worse cognitive performance in unadjusted analyses but these associations weakened above statistical significance after adjustment for potential confounding factors such as age, sex, efavirenz use, and recreational drug use. In contrast, higher abacavir concentration was associated with worse cognitive performance and this association remained statistically significant even after adjustment. Although antiretroviral drugs may have neurotoxicity, they are not alone: other drug classes such as anticholinergics can also adversely affect the CNS. Published studies have reported that PLWH typically take more concomitant prescribed drugs than the general population, including drug classes with known neurocognitive adverse events (eg, Rubin et al).⁷ Consistent with this, Ma and colleagues reported in cross-sectional analyses that polypharmacy, or using 5 or more concomitant drugs, was associated with worse cognitive performance (Abstract 437), particularly in learning, memory, and verbal fluency. Anxiolytics, antipsychotics, opioids, and antimicrobials were the classes of concomitant drugs that were most commonly associated with worse cognitive performance. Statistically adjusting for the underlying conditions for which these drugs were prescribed did not substantially weaken the associations, but careful longitudinal analyses are required to clearly delineate whether the observed adverse impact on the CNS is due to the underlying condition, the drug, or both.

**Structural neuroimaging measures may detect changes not seen with cognitive performance testing**

**Neuroimaging in NeuroHIV**

Neuroimaging is currently not included in the evaluation for HAND, but several studies demonstrated the potential relevance of this technique in PLWH. As previously noted, CSVD may lead to vascular cognitive impairment. A combination of both CSVD and HIV may lead to the substantial cognitive changes that are observed despite ART. However, it can be difficult to differentiate the contributions of HIV from CSVD. Within the MACS, Wu and colleagues longitudinally evaluated HIV uninfected controls (n=46) and PLWH (n=76) (Abstract 456). Annualized rates of change in white matter hyperintensities (WMH), a proxy of CSVD, were similar between HIV-uninfected controls and PLWH. PLWH who had diabetes or hypertension had a greater annual increase in WMH volume. Sanford
and colleagues also longitudinally evaluated changes in WMH (using CSVD) in virologically suppressed PLWH (n = 119) compared with HIV-uninfected persons (n = 55) (Abstract 453). They also examined if an interaction occurred between CSVD and HIV for neuroimaging and cognitive measures.

**5 of 21 (23.8%) people with HIV infection with CSF viral escape who had previously responded to ART optimization had a recurrent episode of escape**

WMH burden was similar for PLWH and HIV-uninfected individuals. Older age and the presence of hypertension were associated with a greater risk of an increased WMH burden. These results suggest that both HIV and CSVD may independently contribute to brain atrophy. Modifiable risk factors (eg, hypertension and diabetes) should be aggressively treated in PLWH. Structural neuroimaging measurements (including magnetic resonance spectroscopy and diffusion tensor imaging) were also obtained from several cohorts of virologically suppressed PLWH. Using principal components analysis of neuroimaging data, Cysique and colleagues defined a composite neurochemical marker (CNM) or “signature of HIV disease,” which strongly correlated with CSF NFL concentrations but not neurocognitive impairment (Abstract 454). Ruiz-Saez and colleagues demonstrated that perinatally infected adults living with HIV have substantial reductions in frontal brain volumes compared with matched HIV-uninfected individuals (Abstract 458). Overall, these results suggest that structural neuroimaging measures may detect changes not seen with cognitive performance testing. Observed changes may reflect neurodegeneration and inflammation that occurred soon after seroconversion and before the initiation of ART. Longitudinal neuroimaging studies of acutely infected PLWH who were administered ART are needed.

**Effects of HIV on Neuropathogenesis**

Many published studies have identified HIV characteristics that may influence its neurovirulence, including HIV subtype, envelope sequence, macrophage tropism, and CD4 and chemokine receptor type 5 (CCR5) affinity. These and other issues related to how HIV interacts and adapts to the brain were summarized in a plenary lecture by Swanstrom (Abstract 121). His presentation highlighted the importance of distinguishing HIV that uses R5 to enter T cells from HIV that uses CCR5 for entry specifically into macrophages (R5-macrophage tropic), which express approximately 25-times less CD4 than T-cells. He also reviewed important data supporting that approximately 25% of PLWH have evidence of compartmentalized HIV in CSF even at the time of early infection. The presence of compartmentalized HIV in the CNS may be associated with viral escape from ART in the CNS (Abstract 449) and has implications for eradication of HIV from the CNS.

Several abstracts presented new data on CSF viral escape. A CSF Viral Escape Consortium was organized by the National Institute of Mental Health and proposed an approach to classify different forms of CSF viral escape. Kincer and colleagues identified 14 PLWH who had one form, symptomatic CSF viral escape, and they commonly had T-cell tropic and drug-resistant HIV in CSF (Abstract 446). Similar to the seminal report from Canestri et al in 2010, nearly all participants responded to optimization of their ART regimen. Dravid and colleagues, who previously published evidence linking CSF viral escape to use of protease inhibitors, reported follow-up data on CSF viral escape (n = 41) after one of 2 interventions, ART optimization or intensification (Abstract 451). Intensification may be a more clinically implementable strategy since it does not require genotypic resistance testing of HIV from CSF, which is not feasible in many clinical settings. Approximately 80% of participants had suppressed CSF HIV RNA (≤20 copies/mL) with either approach. Concerns about the durability of the initial response of CSF viral escape to ART optimization were raised by Ferretti and colleagues, who identified that 5 of 21 (23.8%) PLWH with CSF viral escape who had previously responded to ART optimization had a recurrent episode of escape (Abstract 447). Recurrence only occurred, however, if the optimized regimen was simplified (n = 4) or was not taken (n = 1). Although CSF viral escape remains uncommon and these data are sparse, patients and clinicians should be educated to continue the optimized regimen and efforts should be made to support adherence. In addition to use of protease inhibitors, the risk of CSF viral escape has been linked to low nadir or current CD4+ cell count in chronic HIV infection. To date, no one has reported on the incidence of CSF viral escape in early HIV infection, a shortcoming that was addressed by Handoko and colleagues by analyzing data from the Thai SEARCH 010 Study (Abstract 450). Among PLWH who initiated ART during early HIV infection (Fiebig I-V) (n = 89), only 1 (1.1%) met criteria for CSF viral escape at 24 weeks.

**Deep sequencing was used to identify that 64% of people with HIV infection (n=50) had evidence of HIV compartmentalization in the cerebrospinal fluid**

Of 46 PLWH evaluated after 96 weeks of ART, none had CSF viral escape. These data add to prior evidence that initiating ART early in disease protects the CNS. Smith and colleagues identified that participants who had CSF viral escape were approximately twice as likely to have the HIV-encoded protein, Tat, detected in CSF (Abstract 417). The putative neurotoxicity of extracellular Tat remains controversial but this analysis found that participants who had a Tat concentration that exceeded 1000 pg/mL were nearly 4-fold more likely to have cognitive impairment than those who had lower concentrations.
The presence of Tat in CSF was also associated with lower CSF amyloid-β 1-42 concentrations, suggesting that it may be associated with AD-type neuropathology. In addition to these informative presentations, other scientists presented new findings relevant to how HIV interacts with the CNS. In Uganda, where non-B HIV subtypes (predominantly subtypes A and D) may affect the CNS differently than subtype B that is common in North America, Joseph and colleagues used deep sequencing to identify that 64% of PLWH (n=50) had evidence of HIV compartmentalization in the CSF (Abstract 449). The frequency of compartmentalization did not differ by HIV subtype. Few details were provided about the cognitive assessment, but the investigators noted that CSF compartmentalization was associated with worse verbal fluency in untreated PLWH, although this difference was no longer significant after ART initiation. de Oliveira and colleagues sequenced HIV envelope DNA by high-throughput single genome amplification from brain tissue collected at autopsy from 12 donors enrolled in the North American National NeuroAIDS Tissue Consortium, identifying that a third of the participants had evidence of compartmentalization compared with HIV DNA from lymph node or spleen (Abstract 452).

Measuring CSF HIV RNA down to the single-copy level may have value, but single-copy assays are not clinically available. The Cobas-TaqMan HIV-1 Assay v2.0 is commonly used in the clinic and has a lower limit of quantification (LLQ) of 20 copies/mL. If HIV RNA is suppressed below the LLQ, the report for this assay will indicate whether the HIV RNA concentration is at or below 20 copies/mL or below the limit of detection, which may be lower than 10 copies/mL. Motta and colleagues previously identified that having HIV RNA in CSF below the limit of detection is associated with lower CSF neopterin concentrations than having HIV RNA suppressed below 20 copies/mL. At CROI, Farhadian and colleagues extended these findings to link lower HIV RNA in CSF to lower blood-brain permeability and better executive functioning. Although these findings generally support that better suppression of HIV RNA, even at very low levels, may lead to better outcomes, the findings of this study may be conflated by group differences in baseline HIV RNA concentrations and nadir CD4+ T-cell counts. (Abstract 126).

Effects of Host Mechanisms on Neuropathogenesis

Even though HIV can adapt to the CNS environment, which may increase its neurovirulence, the host environment also plays a critical role, particularly among a population that is more likely than the general population to be adversely affected by comorbid conditions, such as obesity, cardiovascular disease, and drug toxicity, as discussed above. Observations from cohort studies and clinical trials are crucially important elements of translational research, but the development of clinically useful biomarkers and beneficial interventions ultimately hinges on a clear, mechanistic understanding of pathogenesis. New findings were reported at CROI 2019 that advance our understanding of the mechanisms by which the host environment increases the risk of CNS disease in PLWH.

Four presentations focused on the immune system, a key contributor to HIV pathogenesis in the CNS. One novel report focused on CD30, a CD4+ T-cell surface protein that is enriched in infected cells. Concentrations of soluble CD30 in the CSF may indicate the extent of ongoing migration of transcriptionally active T-cells during suppressive ART, although CD50 may also be solubilized from the surface of an as-yet unidentified cell type within the CNS. Peluso and colleagues measured soluble CD30 in CSF from 130 PLWH and identified that concentrations in CSF, but not blood, remained elevated during suppressive ART. Higher CSF concentrations of soluble CD30 correlated with higher concentrations of NFL, an axonal protein that has been strongly linked to risk for HAND (Abstract 125). Of note, the CD30/CD50 ligand axis has been implicated in experimental autoimmune encephalitis, a disease model of autoimmune encephalitis that has some features similar to HIV encephalitis. Another report from the SEARCH 010 study team built on published research about DNA methylation signatures in monocytes in HAND (particularly those associated with the nervous system and the immune response to HIV) to identify that similar signatures are present in early HIV infection (median, 17.5 days after infection) (Abstract 409). Nearly a year after initiating ART, most DNA methylation changes were minimally restored except for interferon-related genes (eg, IFI27, IRF7, and MX1), suggesting that DNA methylation of these genes in blood-derived monocytes identifies HAND risk very soon after infection and might be a future, clinically accessible biomarker.

Nearly all research in the neuroHIV field is challenged by the heterogeneity of the HAND phenotype: numerous conditions contribute to HAND risk and these differ from individual to individual. Chief among these differences may be sex: women and men appear to differ substantially in the conditions that predispose to impaired cognition and mental health disorders. Rubin and colleagues extended their work in this area by using novel methods (Dynamic matrix factorization; Cluster Identification using Frobenius residual; Ingenuity Pathway Analysis) to analyze data from a 42-plex biomarker array measured at several time points in participants in the WIHS (Abstract 407). They found that biomarker profiles, including biomarkers classified as being associated with the antiviral immune response, oxidative stress, and vascular dysfunction within 2 years of initiating ART distinguished women living with...
HIV from women not living with HIV as well as predicted cognitive trajectory over 12 years. Among women living with HIV, biomarkers classified as “Myeloid, T Cell, and Endothelial Cell Communication” or “Microglial Chemokine-Mediated T Cell Recruitment to Brain” seemed to be broadly deleterious (as estimated by their association with performance in cognitive domains) and those classified as “Immune Activation and Vascular Dysfunction” or “Leukocyte Recruitment to Brain” appeared to be more beneficial overall. This distinction between neuropathogenic and neuroprotective mechanisms highlights an important issue in the field. To date, neuroHIV research has focused more on deleterious mechanisms associated with the neurologic complications of HIV than on mechanisms associated with resilience.

In this regard, Giron and colleagues presented very novel glycomics data, an area that has not yet been addressed in the neuroHIV field (Abstract 124). HIV causes a persistent state of hyposialylation that interferes with binding of sialic acid to sialic acid binding protein and that does not appear to reverse with ART. Sialic acid binding proteins are expressed on monocytes, macrophages, and other cells and the binding of sialic acid to them may contribute to the persistent inflammation that occurs in PLWH. In this initial cross-sectional analysis (n = 108), HIV was associated with persistent alterations in plasma and IgG glycomes, including decreases in anti-inflammatory highly sialylated glycans, compared with controls. The investigators found that 7 glycan structures (e.g., A2G3S3, LacNac Glycans) differed between participants who had cognitive impairment and those who did not. In general, maintenance of higher levels of sialylation in blood plasma was protective: higher levels of sialylated oligosaccharides correlated with better cognitive performance. Data on the CSF glycome were also presented and were similar to the findings from blood. Although high-dimensional, discovery-driven methods such as glycomics have limitations, the reported results are promising and strongly support the value of additional research.

In addition to the glycomic exosome work, Pulliam and colleagues presented impactful data on neuron-derived exosomes (NDEs) in blood (Abstract 411). A non-exosomal neuronal biomarker, NFL, has been measured in blood and may have clinical utility, but its measurement in blood currently requires a specialized instrument (Quanterix Simoa) and its concentrations in blood can be very low during suppressive ART. In this analysis, the investigators identified sex-based differences in NDEs. In women, cognitive impairment was not associated with NFL concentrations but was associated with concentrations of 7 NDE proteins (eg, microtubule associated protein tau and neuronal cell adhesion molecule), with a consistent pattern being that the proteins were higher in women who had asymptomatic neurocognitive impairment (ANI) and lower in women with symptomatic mild neurocognitive disorder (MND). In men, the expected association between higher NFL concentrations and cognitive impairment was present, but impairment was also associated with 12 NDE proteins (eg, mesencephalic astrocyte-derived neuropotrophic factor and “a disintegrin and metalloproteinase” [ADAM] metalloprotease 23) that differed from those of women and were higher in both ANI and MND than in unimpaired PLWH. Although exosome methods remain a specialized method, the prospect of identifying biomarkers of CNS neuronal injury using blood is promising and requires additional research.

All cited abstracts appear in the CROI 2019 Abstracts eBook, available online at www.CROIconference.org

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Invited Review

CROI 2019: Complications and Coinfections in HIV Infection

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The 2019 Conference on Retroviruses and Opportunistic Infections provided a considerable amount of new information on the progress in implementation of strategies to reduce morbidity and mortality from complications and coinfections that occur in people with HIV infection, and on the clinical management of these important problems. This review will address new insights into the prevention and treatment of tuberculosis, fungal infections, sexually transmitted infections, malignancies, and a range of metabolic complications and noncommunicable diseases.

**Keywords:** CROI, 2019, HIV, complications, coinfection, tuberculosis, multidrug-resistant, STIs, fungal infection, metabolic, malignancies

**Tuberculosis: Women and Children**

The call to ramp up isoniazid preventive therapy (IPT) for HIV-infected pregnant women to reduce the risk of tuberculosis (TB)-related complications during and after pregnancy was called into question after a recent study suggested worse maternal and infant outcomes when IPT was given to pregnant women during versus after delivery. Salazar-Austin reported on a cohort of 155 pregnant women with HIV infection in South Africa observed between 2011 and 2014 who did (46%) or did not take IPT. Adverse pregnancy outcome, maternal or fetal death, or TB was present in 16% and 28% (P = .08) of women exposed and not exposed to IPT, respectively (Abstract 77). There was only 1 case of TB, which occurred in a woman not receiving IPT. The authors suggested that these data are somewhat reassuring on the safety of IPT administered during pregnancy; however, features of this study (small and non-randomized; use of older antiretroviral therapy (ART) regimens in mothers and infants, inclusion of women beyond periconception only, differential follow-up), limit its ability to inform the ongoing policy discussion that weighs the protective benefit of IPT versus potential safety issues.

Contraception efficacy during pregnancy for women with HIV is complicated by drug interactions with concomitant use of rifampin and efavirenz often used during TB treatment. In a pharmacokinetic study of HIV-infected women receiving efavirenz, rifampin, and depot medroxyprogesterone acetate (DMPA), 5 of 42 (11.9%) women had subtherapeutic medroxyprogesterone acetate (MPA) levels compared with 1 of 16 (6.3%) historical controls (HIV-infected, ART-naive) after 12 weeks (Abstract 78). Drug exposure to MPA was lower and clearance of MPA was faster in the women receiving rifampin and efavirenz than in historical controls. Although MPA levels were lower in patients receiving a dolutegravir (DTG)-containing ART regimen can be given for TB was 92% and 61% in the intervention and control arms, respectively (P = .07). This study provides some insights on improving TB screening among children, but the main message is that current approaches are failing to reach and protect well over half of these children, which calls for more research in this area.

**TB and ART Drug Interactions**

An important question in the TB prevention field is whether the proven short-course (12 week), isoniazid (INH), and rifapentine weekly regimen can be given in patients receiving a dolutegravir (DTG)-containing ART regimen. There are 2 major concerns with this combination. The first is that rifapentine’s enzyme induction properties will lower DTG levels to subtherapeutic levels, jeopardizing viral suppression. The second concern is safety. A pharmacokinetic study in HIV-uninfected persons evaluating this combination was halted due to unexpected and serious systemic toxicity. Investigators revisited this question in...
a phase I/II study with the rationale that hypersensitivity reactions with TB drugs such as rifamycins may be less in an HIV-infected versus uninfected person (Abstract 80). In interim results of the first 60 subjects, DTG bioavailability was 29% lower in the presence of INH and rifapentine. Trough levels in the presence of INH and rifapentine were lower, but exceeded, the DTG 90% inhibitory concentrations (IC50) in all cases but one, and all participants maintained viral suppression during the period of observation. The serious toxicities seen in the HIV-uninfected study exposed to this combination were not observed among these HIV-infected study subjects. To date, only 1 patient had a possible hypersensitivity grade II reaction and was able to resume dosing. These data are reassuring, but represent only a small group of individuals that differ from the original study by both ethnicity and HIV status. Continued vigilance will be required with the planned expansion of this regimen globally.

For TB treatment, lopinavir/ritonavir (LPV/r) is the recommended protease inhibitor (PI) with rifampin-containing regimens, but the data are sparse for darunavir/ritonavir (DRV/r), a recommended PI regimen from the standpoint of HIV treatment. Maartens and colleagues reported findings from a pharmacokinetic study that provided a clear, but disappointing answer for the use of DRV/r with rifampin (Abstract 81). Both of the 2 dose-adjusted regimens of DRV/r (1600 mg/200 mg daily and 800 mg/100 mg given every 12 hours) to HIV-infected persons without TB were associated with unacceptable toxic effects. Six of the first 17 participants developed grade 3 or greater hepatotoxicity, a finding that prompted cessation of the study. In addition, subtherapeutic DRV levels were uniformly present with daily dosing and among some patients on the twice-daily regimen. Thus at present, for patients requiring a PI and rifampin, LPV/r is the safest choice, and DRV/r should not be used.

### DRV/r dose and frequency adjustments among persons receiving rifampin to compensate for drug interactions are associated with serious hepatotoxicity and reduced DRV levels, these combinations should not be used in clinical practice

Combination of promising investigational agents such as bedaquiline and delamanid for treatment of multi-drug-resistant (MDR) TB require rigorous assessment of potential life-threatening toxic effects, such as serious QT interval prolongation, which occurred with both drugs, prior to large-scale use. In a much anticipated phase II study that randomly assigned adults with MDR TB to bedaquiline, delamanid, or both, the mean millisecond increase (95% confidence interval [CI]) in QT interval was 11.9 (7.4, 16.5); 8.6 (4.0, 13.2) and 20.7 (16.1, 25.4) in the 3 arms, respectively (Abstract 84). The increases in QT interval were all less than grade 3, and no cardiac events were observed. Thus, QT prolongation with the combination of bedaquiline and delamanid in this trial setting was moderate and not more than additive with this 2-drug combination. It is important to note that if use of this combination goes forward, that the safety established in this trial was in the setting where persons with baseline electrocardiogram abnormalities, receiving moxifloxacin or clofazimine (drugs causing QT prolongation and used in MDR TB treatment) were excluded. In addition, careful monitoring and replacement of electrolytes (eg, magnesium, potassium) was conducted.

High-dose isoniazid (INH) is included in short-course MDR TB treatment regimens, but the optimal dosing and contribution to microbiologic efficacy is not known. Dooley and colleagues conducted a study to inform this question in a phase II randomized evaluation of INH doses of 5, 10, or 15 mg/kg for the first 7 days of treatment (n=43) in HIV-infected persons with MDR TB and inhibit alpha (inhA)-mediated (low-level) INH resistance (Abstract 82). Microbiologic efficacy was compared with a parallel evaluation of standard-dose INH in persons with non-MDR TB (n=16). The reduction in TB burden measured in solid or liquid culture systems was comparable between the 2 high-dose INH regimens and that seen with standard dose INH for drug-sensitive TB. In this short-term, selected population with inhA mutation and unknown acetylator status, high-dose INH appeared efficacious. More information and data are needed to understand the role of this regimen in contemporary and evolving INH mono-resistant and MDR TB regimens.

### Bedaquiline and delamanid each increase QT interval, but even in combination the magnitude remains moderate suggesting future MDR TB regimens may include this combination with close monitoring

The risk of cryptococcal disease among persons with HIV infection presenting with low CD4+ cell counts is well established, and the basis for current recommendations to screen and treat those with asymptomatic and symptomatic disease. There is another population, which has received little attention (those on ART with virologic failure), that may be also be at high risk of cryptococcal disease. Mpoza and colleagues tested 1186 persons who had samples of viral loads sent to assess and confirm virologic failure in 2017 and 2018 (Abstract 708). Cryptococcosis was present in 35 of 1186 (3.0%). The median prior ART duration was 42 months. Nearly all (32/35) cases were among those with HIV RNA levels above 5000 copies/mL, and median HIV RNA levels in the pre-
levels were higher among those with (53,700 copies/mL) than without (11,650 copies/mL) cryptococcal antigenemia. Among the subset of 21 persons with cryptococcosis in whom follow-up data were available, meningitis-free survival was 62% at 6 months. This analysis is interesting and important in light of the evolving treatment landscape in sub-Saharan Africa where HIV RNA testing is ramping up, and CD4+ cell count testing is being scaled back, including among individuals with virologic failure. With the rollout of ART, there will be a growing population of persons with virologic failure that this study suggests could benefit from cryptococcal antigen screening and treatment to reduce morbidity and mortality.

In Southeast Asia, *Talormyces marneffei* (Tm) infection has a high mortality, and is the major common serious fungal opportunistic infection. A new Tm antigen (TmAg) test Mp1p has higher sensitivity than blood culture for the diagnosis of clinical disease, but the assay has not been evaluated as a screening tool for asymptomatic disease in persons with advanced HIV disease. Thu and colleagues in Vietnam evaluated 1082 patients with CD4+ count below 100 cell/µL followed up between 2015 and 2017 (Abstract 710). TmAg was detected in 45 (4.2%). Risk for TmAg was 3.5-fold higher in those with CD4+ count below 50 cell/µL, and 3.4-fold higher in those living in highland regions. The probability of death was 12.7% in the cohort, and was higher (30.0%) in the TmAg-positive patients than the TmAg-negative patients (11.9%); log rank, P = .002. This study would suggest that preemptive therapy for Tm should be evaluated in this high-risk, low CD4+ cell count population in Southeast Asia.

### Sexually Transmitted Infections

Ranchandani evaluated the relationship between syphilis and hearing loss in a convenience sample of 362 individuals with syphilis who had cerebrospinal fluid (CSF) evaluated, regardless of syphilis disease stage (Abstract 1013). The odds of high-frequency hearing loss were greater in the presence of CSF pleocytosis, *Treponema pallidum* detection by polymerase chain reaction (PCR) in the blood, and older age. The odds of low or medium frequency hearing loss were greater in those with *T. pallidum* in CSF, history of injection drug use, and older age. Syphilis stage, ART use, HIV RNA level, and CD4+ cell count were not associated with any form of hearing loss. The authors noted the high incidence of hearing loss in this population, and postulate pathophysiology for high frequency and low frequency hearing loss may differ based on different levels of CSF inflammation. In a second report on syphilis, Robertson and colleagues performed formal cognitive function evaluations on 186 individuals with syphilis (Abstract 1014). The study population was young (median age, 35 years) and largely male (98%); 82% had primary syphilis, and 19% and 21% reported using stimulants or cannabis, respectively. Cognitive impairment was mild (39%), moderate (10%), or severe (10%) in the study population. Rapid plasma reagin titer of 1:32 or above in these 3 groups was 72%, 79%, and 100%, respectively (P = .02). Moderate or severe cognitive impairment was more frequent among those with asymptomatic early latent or late latent (34%) than those with primary or secondary disease (21%; P = .05). HIV status was not associated with cognitive impairment. The authors’ interpretation of these results was that bacterial burden may contribute to cognitive impairment with syphilis and is most commonly detected in latent disease.

The standard treatment for lymphogranuloma venereum (LGV) is doxycycline 100 mg twice daily for 21 days. The authors evaluated the efficacy of the standard doxycycline regimen versus 1 gram azithromycinonce weekly for 3 weeks (Abstract 1011). All subjects received a single dose of ceftriaxone. There were 136 men (95% were HIV infected) with confirmed LGV proctitis in the study. Clinical (12 week) and microbiologic cure (4 week) were high in both arms: 99% and 97% for the azithromycin group and 95% and 100% for the doxycycline group. Diagnosis and treatment of LGV remains challenging due to lack of rapid diagnostic tests, and treatment of persons with sexually transmitted infections are complicated by presence of numerous pathogens. Larger randomized studies will be needed to determine benefits and risks of azithromycin compared with doxycycline in populations with sexually transmitted infections and suspected LGV.

### Noncommunicable Diseases

#### Cardiovascular Disease

Two studies focused on sudden cardiac death (SCD) this year, a topic that has received little attention in the past. Friberg and colleagues from the Veterans Aging Cohort Study meticulously reviewed medical records and death certificates to assess the occurrence of SCD in people living with HIV (PLWH) compared with a well matched control population. They found that PLWH had a 14% higher risk of SCD and that uncontrolled HIV infection appeared to increase this risk (Abstract 32). Tseng and colleagues in San Francisco conducted an impressive population-based prospective study evaluating all incident out-of-hospital death cardiac arrests in San Francisco with full autopsies, histology, toxicology, and record reviews between 2011 and 2016. These complete evaluations allowed them to identify which deaths were actual sudden arrhythmic deaths (Abstract 33). The adjusted rates of both presumed SCDs...
and autopsy-defined sudden arrhythmic death syndrome (SAD) were 82% and 83% higher, respectively, in the HIV-infected and the uninfected populations. Importantly, occult drug overdose accounted for 34% of SCD in PLWH and 14% in the general population. Histologic studies identified higher rates of cardiac fibrosis in PLWH, which may underlie the excess risk for SAD. Collectively these studies highlight the need for better screening modalities for substance use and for cardiac fibrosis in PLWH.

Myocardial Infarction

Studies presented this year continued to focus on identifying and quantifying risk factors for myocardial infarction (MI) in PLWH. Using a large commercial database, O’Halloran and colleagues compared the rates of major cardiovascular endpoints (MI, ischemic stroke, coronary artery bypass grafting, or percutaneous coronary interventions) among adults who initiated ART with integrase strand transfer inhibitors ( INSTIs ), PIs, or nonnucleoside reverse transcriptase inhibitors (NNRTIs) (Abstract 680). The population was relatively young (mean age, 40 years) and was predominantly men with a median follow-up of 561 days. Treatment with an INSTI-based regimen was associated with a 43% reduction in major adverse cardiovascular events; most notable MI (acute MI occurred in 11 [0.21%] in the INSTI group and in 55 [0.36%] among those who received non-INSTI treatment.) Although the event rate is small and follow-up is short, these data supplement data on virologic outcomes that underlie the choice of INSTIs as preferred agents for initial therapy.

Previous studies have suggested that HIV increases the risk of atherosclerosis in women to a greater extent than in men. Hanna and colleagues previously reported higher rates of HIV-related cardiovascular mortality in women than in men across New York City, but concerns lingered about confounding. In a new analysis they focused on women from the Bronx where socioeconomic status was less variable, and found that the sex difference was attenuated (Abstract 663). Whether the higher rates of cardiovascular mortality in women were due to access to preventive care or other biologic mechanisms remains to be defined.

Several studies examined the relationship between specific biomarkers and measures of atherosclerosis. Higher levels of interleukin-10, an anti-inflammatory cytokine, were associated with less coronary plaque (specifically non-calcified plaque) as measured by computerized tomography (CT) angiography in PLWH, after control for other risk factors and biomarkers including MCP-1 and CD163 (Abstract 631). The mechanism that underlies this association remains poorly defined.

Chronic Obstructive Pulmonary Disease

Chronic obstructive pulmonary disease (COPD) is thought to be increased in PLWH and may be underdiagnosed. Crothers and colleagues used data from more than 25,000 PLWH followed upon the Center for AIDS Research (CFAR) Network of Integrated Clinical Systems (CNICS) cohort to link the presence of COPD (which was diagnosed in 423 participants based on treatment information) with an increased risk of MI, most notably Type 2 MI (thought to be caused by supply-demand mismatch). The association persisted after control for traditional risk factors for MI. These findings highlight the importance of early recognition and treatment for COPD in PLWH (Abstract 31).

Obesity

At this year’s conference there was a substantial focus on obesity. HIV infection occurs in populations with high background rates of obesity globally (Abstract 677). Therefore a key question is whether ART drugs increase the risk of excessive weight gain. Although it is clear that INSTIs have a favorable profile with respect to lipids, there is a lingering concern about weight gain with this class of drugs. It has been challenging to sort out the contributions of the “return to health” phenomenon to increases in weight in those initiating ART from a direct effect of specific ART agents. Limited data are available from the randomized registrational trials of INSTIs beyond what has been reported from AIDS Clinical Trials Group (ACTG) 5257 (comparing raltegravir with atazanavir/r and darunavir/r). In this study, women, blacks, and people with lower CD4+ cell count and higher HIV RNA level appeared at greater risk. Several observational trials examined these issues (Abstracts 669, 670, 671, 672, 673, 674, 675).

McComsey and colleagues, in a study sponsored by Gilead Sciences, examined electronic medical records of 3468 adults to identify factors associated with changes in weight among virally suppressed PLWH who received different initial ART regimens (Abstract 671). A number of factors were associated with weight gain of more than 3% in this analysis, specifically being overweight or normal body mass index at baseline, female sex, and a history of psychiatric disorders. Although use of INSTIs was more prevalent in the group that gained more than 3% weight, this difference did not persist after controlling for the other risk factors, highlighting the complex interaction between many factors and changes in weight over time.

In one of the largest studies reported to date on the topic of weight changes and ART, NA-ACCORD (North American AIDS Cohort Collaboration on Research and Design) investigators also examined the issue of weight gain and ART among 21,886 adults (87% men) with a median age of 42 years and follow-up out to 5 years for each drug class, and with individual INSTI drug exposures at 1 and 2 years (Abstract 670). The analyses controlled for several important measures including baseline CD4+ count, HIV RNA level, sex, race, and baseline weight, but no information on diet or activity were reported. Weight gain was greatest in the INSTI group (n = 4,112) with gains 5.8 kg at 5 years, respectively, compared with 4.1 kg for NNRTI and 5.0 kg for NNRTI and PI users. The difference was statistically significant when comparing INSTI users with NNRTI users but not with PI users. After 2 years of follow-up, raltegravir and DTG users gained more weight than those on NNRTIs, whereas elvitegravir use was associated with less weight gain than with PIs.

Examining the impact of a switch to an INSTI regimen in virologically
suppressed PLWH removes the complexity of examining weight gain among those initiating ART. Lake and colleagues examined changes in weight and waist circumference in virologically suppressed adults in an ACTG cohort who switched to an InSTI-containing regimen by comparing the trajectories (change of weight per year) 2 years before and after the switch. They found that the rate of change in weight was greater for women, blacks, and those older than 60 years. Baseline rates of weight change were on average less than 1 kg per year; however, after the switch to an InSTI (raltegravir, DTG, or elvitegravir) these high-risk groups gained on average 1.5 kg per year. The relatively small sample size limited comparison by specific ART agents in this study (Abstract 669). Another important factor that may influence the quantity of visceral adipose tissue (VAT) is prior exposure to thymidine analogues and didanosine (Abstract 676). In carefully selected participants in a Danish cohort, investigators reported greater VAT area in PLWH with and without prior thymidine analogue or didanosine exposure that persisted for years after these drugs were discontinued.

Are weight changes with InSTIs associated with other health consequences? Kerchberger and colleagues led a WIHS (Women's Interagency HIV Study) analysis comparing women who added or switched to an InSTI with those who remained on non-InSTI ART (Abstract 672). The group that switched or added an InSTI experienced a 2.14-kg greater increase in weight, a 0.78 kg/m² greater increase in body mass index, and a 1.35% greater increase in percent body fat. Additionally, those who switched or added an InSTI had a few mm HG higher measures of systolic blood pressure and a higher rate of new onset diabetes (4.5% vs 2.2% those not on an InSTI). Although there may be unmeasured confounders between those who changed treatment and those who did not, these results signal possible negative health consequences associated with this modest weight gain that require further study. Consistent with earlier studies that identified lower CD4+ cell count and higher HIV RNA level with greater weight gain, it was not surprising to see that higher levels of immune activation prior to starting ART were associated in more weight gain (Abstract 673). Importantly, women who gained weight on ART had smaller declines in measures of immune activation on ART. The impact of this residual immune activation on longer-term outcomes may portend future complications.

To round out the story of weight changes and InSTI use, Landovitz and colleagues reported results of retrospective analysis of weight changes during a randomized HIV prevention study (conducted in HIV-uninfected men and women) comparing the investigational InSTI cabotegravir (given initially in oral form followed by long-acting injection every 2 to 3 months) (Abstract 34). This analysis found no significant increase in weight after exposure to cabotegravir in any sub-group. These results suggest that there may be an interaction between the effective treatment of HIV infection and the weight gain observed.

As future studies are considered on the topic of weight gain and changes in fat depots, the question arises how best to measure changes in visceral fat. New software now allows for the estimation of visceral fat on dual-energy X-ray absorptiometry (DXA) scans; however, an analysis comparing DXA VAT with CT-measured VAT suggests that although they are correlated, longitudinal DXA measures may come up short when estimating changes in VAT over time in PLWH (Abstract 682). Additionally, measures of fat density by CT may reveal important changes in the quality of fat tissue, whether this varies by ART drug exposure should be evaluated in larger trials (Abstract 681).

Collectively, the large number of studies examining weight changes on InSTIs highlight the urgent need for more evaluation of weight changes with specific InSTIs in diverse populations of PLWH and underscore the importance of data from randomized trials to complement the information from observational data. Additional information on other factors that impact weight such as diet and exercise will be needed to sort out the direct and indirect effects of specific ART agents on weight.

Renal and Bone Disease

Tenofovir disoproxil fumarate (TDF) has been associated with a decline of the estimated glomerular filtration rate (eGFR), but less is known about the recovery after switch to other agents (Abstract 694). Investigators from the Netherlands conducted 2 studies to examine the recovery of eGFR after a switch to either tenofovir alafenamide (TAF) or abacavir. The studies excluded participants with other comorbidities that would contribute to renal dysfunction (ie, diabetes or hypertension). A more than 50% eGFR recovery from the participants’ baseline was observed in fewer than 50% of participants (28/100 [28%] who switched to TAF and 23/85 [27%] switched to abacavir, respectively; P > .1). In another post TDF observational study of PLWH who switched to TAF, eGFR returned to normal levels in less than half of the participants at 1 year; those receiving an unboosted PI had a higher probability of improving (Abstract 693).

A cross-sectional study of older adults in 4 different ART exposure groups including different combinations of TDF and PIs (no TDF/no PI, TDF/PI, no TDF/PI, TDF/no PI) explored the relationship between renal tubular dysfunction and low bone mineral density (BMD) (Abstract 689). Lumbar spine BMD was lower in female participants, those with a lower body mass index, and a higher retinal-binding protein: creatinine ratio, but the association between lower BMD and renal tubular dysfunction was attenuated after adjustment for TDF exposure. DTG, cobicistat, and rilpivirine each inhibit proximal tubular creatinine secretion with very modest declines in eGFR in clinical trials. Elias and col-
leagues examined changes in eGFR in a large observational study conducted in 21 Spanish sites. Participants who were taking 2 or more inhibitors of creatinine secretion had a greater decline in eGFR than those taking 1, suggesting an additive effect of these agents on measures of eGFR (Abstract 692).

HIV Outpatient Study (HOPS) investigators reported that 7% of adults experienced incident bone fracture between 2000 and 2017. Incident bone fracture was associated with a 50% increase in mortality. Not surprisingly, other factors associated with mortality included CD4+ count below 200 cells/µL, non-AIDS cancer, hepatitis C virus (HCV) infection, and chronic liver, renal, and cardiovascular disease. Among those with incident fracture, chronic renal disease and HCV infection remained independently associated with all-cause mortality. Although it is not possible to assess the causative role of fracture in mortality, these results confirm that fracture may be a poor prognostic sign (Abstract 30).

Malignancies Among People Living with HIV

Breast Cancer
Sadigh and colleagues presented a prospective cohort study of women diagnosed with breast cancer in Botswana (Abstract 16). The study enrolled 430 women, including 31% women living with HIV (WLWH). WLWH were younger than the women without HIV, but receptor status, cancer stage at diagnosis, and treatment plans were similar between groups. They found that the 2-year survival was lower for WLWH than those without HIV (57% and 73%, respectively). The vast majority of deaths were due to cancer and none were due to consequences of HIV infection. The reasons for this marked increase in breast cancer mortality are unclear.

Cervical Cancer Prevention
Firnhaber and colleagues presented a double-blind, placebo-controlled, randomized trial of the quadrivalent human papillomavirus (HPV) vaccine in WLWH being treated with loop electrosurgical excision procedure (LEEP) for cervical high grade squamous intraepithelial lesions (HSILs) (Abstract 14). One hundred eighty were randomly assigned to receive vaccine or saline placebo at entry, week 4, and week 24. LEEP was performed on all women at week 4. Cervical colposcopy with biopsies and cervical cytology were performed for endpoint assessment at week 26 and 52. The investigators found no difference in the primary endpoint, cervical HSILs on cytology or cervical biopsy at week 26 or 52, between the vaccine and placebo arms (53% vs 45%, respectively; relative risk, 1.16; 95% CI, 0.87-1.6). This study does not support HPV vaccination to improve HSIL treatment outcomes in WLWH.

McGrath and colleagues evaluated HPV outcomes in a study that randomly assigned WLWH from Kenya who were diagnosed with cervical HSILs to either cervical cryotherapy or LEEP (Abstract 278). They found that women were more likely to clear cervical HPV infections after treatment with LEEP than after cryotherapy (36% vs 24%, respectively). The rates of reinfection with HPV were similar between arms. These results suggest that availability of LEEP should be expanded in cervical cancer screening programs in low- and middle-income countries.

Kuhn and colleagues presented data on the use of the Gene Xpert test for high-risk HPV for cervical cancer screening, a point-of-care diagnostic test (Abstract 279). They enrolled 586 women without HIV and 535 WLWH from South Africa. The WLWH had a higher prevalence of high-risk HPV than those without HIV (49% vs. 16%, respectively) and a higher prevalence of cervical HSILs on histology (17% vs 5.3%, respectively). For WLWH, they found a sensitivity for Xpert of 93% and a specificity of 60%. Limiting the test to 3 channels that test for 8 of 14 high-risk HPV types improved the specificity to 68% with preserving sensitivity at 91%. Furthermore, they investigated higher HPV DNA thresholds for test positivity that reduced sensitivity to 85% and increased specificity to 77%.

United States Preventive Services Task Force clinical criteria for lung cancer screening (age 55-80 and greater than 30-pack per year smoking history) perform poorly in PLWH

Higher specificity is essential if using primary HPV testing for cervical cancer screening.

Lung Cancer
Sellers and colleagues reviewed participants who developed lung cancer in the MACS (Multicenter AIDS Cohort Study) and WIHS, and whether these cancers may have been detected using the United States Preventive Services Task Force recommended lung cancer screening of adults ages 55 to 80 years with a more than 30-pack per year history of tobacco use with low-dose CT scans (Abstract 15). They found that the criteria performed poorly in PLWH: only 16% of cancers in women and 24% of cancers in men would have been potentially diagnosed by these screening criteria. They found that the optimal criteria for WLWH were ages 49 to 75 years and a greater than 16-pack per year history. For men living with HIV, the optimal criteria were ages 43 to 75 years and a greater than 18-pack per year history.

Kaposi Sarcoma
Histopathology services are limited in sub-Saharan Africa, but this is required for diagnosis of Kaposi sarcoma (KS). Semeere and colleagues presented data on the use of quantitative PCR of Kaposi sarcoma herpesvirus (KSHV) of skin biopsies as an alternative to histopathology for the diagnosis of KS in 506 participants undergoing skin biopsies (Abstract 20). Using a US-based pathology consensus panel as the gold standard.
standard, they found that local interpretation had a sensitivity of 95% and a specificity of 70%. Using an optimized cutoff for KSHV detection in skin biopsy samples, they found that this test had 98% sensitivity and a specificity of 90%. The authors noted the potential for this test to be simplified and implemented in low- and middle-income countries resource constrained settings to improve KS diagnosis.

**Conclusion**

The work presented at this year’s CROI reminds us that we still have work to do to reduce the morbidity associated with long-term HIV treatment, including ending the high impact of TB infection on HIV outcomes.

**Additional References Cited in Text**

Invited Review

CROI 2019: Highlights of Viral Hepatitis

Anne F. Luetkemeyer, MD; David L. Wyles, MD

At the 2019 Conference on Retroviruses and Opportunistic Infections (CROI), there was a major focus on hepatitis C virus (HCV) elimination and improving each component of the hepatitis C care cascade. Many interventions showed promising improvements in diagnosis and linkage to care. Settings with robust access to direct-acting antivirals (DAAs) continue to demonstrate the role of HCV treatment as prevention. However, substantial barriers to accessing curative therapy remain. Reinfecition after treatment presents an important barrier to elimination, particularly in some populations of men who have sex with men (MSM). MSM without HIV infection are at an elevated risk for sexual acquisition of HCV, and several studies reported HCV rates that were as high as those seen in MSM living with HIV. There was also a focus on HCV and HBV in pregnant women. Rates of HCV infection in women of childbearing potential have increased, making prenatal diagnosis a priority. In the first study of HCV treatment during pregnancy, sofosbuvir/ledipasvir started at 28 weeks of gestation led to cure in 8 pregnant women. Hepatitis B virus (HBV)-active antiretrovirals are generally effective in suppressing HBV but have low rates of surface antigen loss despite long term treatment. Initial results from novel laboratory assessments of intrahepatic HBV viral infection events were presented, hopefully paving the way for more effective HBV treatment strategies to control and potentially cure HBV.

**Keywords:** CROI, 2019, hepatitis, pregnancy, HBV, HCV, acute, reinfection

**Hepatitis C Virus Care Cascade**

With the increasing availability of direct-acting antivirals (DAAs) and focus on HCV elimination, there is continuing attention to improving engagement along the hepatitis C virus (HCV) care cascade, particularly for the most vulnerable and difficult to access individuals living with HCV infection. Jail remains an important venue for HCV infection diagnosis with 16% of inmates at the Dallas County jail identified as HCV antibody positive on opt-out testing, 75% of whom were HCV viremic. Despite high rates (85%) of uptake of HCV education during incarceration, linkage to HCV treatment after discharge was very low (<4%) (Abstract 581). People who inject drugs (PWID) are another group highly impacted by HCV. However, PWID were less likely to engage in each step of the care cascade than non-PWID counterparts, as demonstrated in the British Columbia Hepatitis Testers Cohort (Abstract 582). Importantly, rates of sustained viral response at 12 weeks (SVR 12) were similarly high in recent PWID (91%) and never PWID (92%), reinforcing that PWID can be successfully treated when able to access therapy. One effective strategy to improve diagnosis and engagement of PWID involved incentivizing PWID with HCV infection to recruit other PWID for HCV testing and linkage to care. A third of PWID were able to recruit at least 1 colleague, and this proved to be a highly impacted group, 87% of whom were HCV antibody positive (Abstract 575). Unfortunately, there was substantial drop off in those linked to HCV care and ultimately being cured. Trauma patients may also merit HCV screening, as 6.8% of trauma surgery patients at a US urban hospital were HCV RNA positive, with 19% of whom being undiagnosed at the time of surgery-based screening (Abstract 579).

Several studies evaluated intervention packages to improve engagement along the care cascade. The strategy of care facilitation, which included motivational interviewing and patient-specific needs assessment, had a modest impact in improving engagement in the steps of the HCV care cascade, with more impact seen in men receiving active facilitation than in controls (Abstract 578). Random assignment to nurse case management improved linkage to care for HIV/HCV coinfected patients (47% vs 25% without case management), but was not sufficient to impact time to treatment initiation. Overall cure rates remained low (<5%) (Abstract 580). Leveraging non-specialists remains an important means to improve HCV uptake. In King County, Washington, a community-based approach using a combination of emergency medical responder interventions, active linkage to care, and practitioner education tripled the number of individuals tested for HCV and increased HCV treatment tenfold over 4 years (Abstract 583). Training 49 primary care practitioners in HCV care led to treatment initiation in more than 700 individuals with HCV infection, demonstrating the important role non-specialists can play in improving HCV treatment access (Abstract 587). A meta-analysis demonstrated that task shifting to non-specialist achieved similarly high cure rates of 92% compared with specialty care, in PWID and in the general population. HCV testing and treatment in non-referral settings (decentralization) led to higher uptake of HCV testing (88% vs 47%, respectively), and linkage to care (80% vs 53%, respectively), than strategies that required referral-based care (Abstract 588).

Even in settings where DAA treatment is readily available through insurance coverage, substantial barriers can...
remain for patients to access HCV treatment. An HIV/HCV coinfected cohort at an Atlanta public health hospital found 53% of HIV/HCV coinfected individuals had not been treated for HCV; the main barriers identified were alcohol and substance use (60% of those not treated) and poor HIV control (Abstract 573). Similarly, poor HIV control and well as Medicare (vs Medicaid) were associated with lack of HCV treatment in a Johns Hopkins HIV/HCV cohort (Abstract 574).

Impact of Opioid Use on HCV and Fibrosis

In vitro, fentanyl was associated with increased HIV and HCV viral replication, which provides yet another potential route by which the opioid epidemic impacts PLWH or individuals with HCV infection, or both (Abstract 618). A Miami cohort found an association of advanced fibrosis (Fibrosis-4 score [FIB-4] > 1.45) with fentanyl use (odds ratio [OR], 1.67; P = .0035) and HIV infection (OR, 2.25; P = .0025); however, it was not clear if these analyses accounted for concomitant viral hepatitis (Abstract 617).

HCV Diagnostics

HCV core antigen testing is generally a faster and less expensive alternative to HCV RNA testing to confirm HCV infection and identify acute HCV infection. When used by a London sexual health clinic, core antigen testing identified 95% of acute HCV infections. Of the 4 missed, 3 had alanine aminotransferase (ALT) levels above 300 IU/L and 1 had an ALT level 33 IU/L, leading to HCV RNA testing. Notably, using HCV antibody and ALT elevation alone would have missed 47% (37/82) of the acute HCV diagnoses (Abstract 586). Of note, HCV core antigen testing in not approved for use in the United States. The Ora-Quick rapid HCV antibody test yielded a markedly low sensitivity of 6% in HIV/HCV coinfected individuals compared with 100% in those without HIV; specificity was 100% in all groups (Abstract 584). Other groups have reported lower sensitivity of the Ora-Quick rapid HCV antibody test, particularly when shorter incubation times were used, but data on performance in HIV-infected populations are limited

A simple laboratory-based assay to infer recent HCV infection would be a welcome addition to HCV epidemiologic studies. Avidity assays take advantage of the fact that antibodies produced early in the course of chronic infections, such as HIV or HCV, tend to bind less tightly to antigens than antibodies that appear later. Characteristics of a modified HCV antibody enzyme-linked immunosorbent assay (ELISA) (Genedia 3.0 HCV ELISA) were evaluated in samples from 875 sero-positive individuals, including 116 with a well-defined seroconversion, being followed up in prospective cohort studies of PWID (Abstract 601). Using an avidity index (optical density ratio of dissociated well/standard assay well) of less than 40% identified samples from participants with a mean duration of infection of 113 days (range, 84-146 days) with a low false recent rate (FRR) of 0.4% (long-term infections classified as recent). Although the modified assay performed equally well for genotype 1 and 3 infections, HIV infection, particularly in individuals with CD4+ cell counts below 200/µL, was associated with a significant increase in the FRR at a 40% avidity index.

Acute HCV and Epidemiology in High-Risk Populations

The European PROBE-C (Natural History and Treatment of Acute Hepatitis C Virus I (HCV) in HIV-positive Individuals) cohort again demonstrated low spontaneous clearance rates (12%) in acute HCV infection in PLWH (Abstract 576). Evaluation for spontaneous clearance was limited by treatment initiation during the first year after acute HCV diagnosis, which occurred at a median of 14 weeks in those taking interferon alfa (n = 277) and a median of 44 week in those taking DAAAs (n = 47). Notably, a 2-log$_{10}$ decline in HCV RNA at 4 weeks after acute HCV diagnosis was significantly associated with spontaneous clearance ($P < .001$) and identified 96% of those who cleared the virus without treatment. This provides useful guidance for practitioners whose patients who do not want to wait up to 12 to 16 weeks to monitor for spontaneous clearance (per current American Association for the Study of Liver Diseases/Infectious Diseases Society of America [AASLD/IDSA] guidance), during which time they may infect others or become lost to follow-up.

The epidemiology of incident HCV infection in HIV-negative men who have sex with men (MSM) is not well-characterized. An analysis from England examined incident HCV infection in MSM by HIV status (Abstract 598). Among 40 recent HCV infections in MSM identified from 5 clinical sites, 16 (40%) of infections were in HIV-uninfected MSM. This group was younger (34 years vs 44 years old for HIV infected), frequently on pre-exposure prophylaxis (81%), and tended to have higher risk sexual behaviors (eg, more partners, group sex, and fisting). In contrast to HIV sexual transmission, there was little awareness of the potential for HCV sexual transmission. Injection drug use was identified as a risk factor in 1 of 3 of both HIV-infected and HIV-uninfected groups. Phylogenetic analysis based on whole genome sequencing identified extensive mixing within clusters of sequences from HIV-infected and HIV-uninfected MSM.

A Thai study suggested a dramatic increase in HCV incidence among HIV
infected MSM after 2014 (0.37/100 person-years pre-2014 vs 2.21/100 person-years in 2014-2018) and was strongly associated with new syphilis infections (Abstract 599). An analysis from the HPTN (HIV Prevention Trials Network) 078 study identified a high prevalence HCV seropositivity regardless of HIV status in MSM (20% HIV infected, 16% HIV uninfected) from Boston, Baltimore, Birmingham, and Atlanta (Abstract 596). The HCV prevalence in HIV-uninfected MSM is substantially higher than prior estimates and may stem from the recruitment approach in HPTN 078, which used respondent-driven sampling to target HIV-infected MSM without viral suppression (possibly also engaging high-risk HIV-uninfected MSM).

Using a phylodynamic approach based on epidemiologic data and 213 non-structural protein 5B gene sequences from PWID detected during chronic infection (classical group) and from MSM with or without HIV infection detected during acute infection (new group), disease transmission characteristics were estimated (basic reproduction ratio $R_0$ and period of infectivity) (Abstract 594). According to the model, transmission occurs more frequently from MSM with a $R_0$ of 2.35 (compared with 1.8 for PWID) although the period of infectivity is longer in the classical scenario (18 vs 3 months in the new group). The origin of the MSM epidemic was estimated to be in 2001.

A large phylogenetic analysis of HCV-infected PWID (n=486) from 4 cities in India demonstrated extensive clustering, with 52% of samples belonging to a cluster and large cluster sizes (mean 7.4; 6 clusters had >10 samples) (Abstract 593). Seven of 19 clusters (genetic distance <4.5% based on 5 UTR core sequences) contained samples from multiple cities. The extensive clustering among PWID across these various cities in India suggest extensive transmission networks in a mobile population, presenting substantial challenges for harm reduction and elimination efforts.

There was an excellent symposium on acute HCV as well as the potential for an HCV preventative vaccine (Symposium S-5), which is available as webcasts at http://www.croiwebcasts.org/?link = nav&linkc = home.

**HCV Treatment and Treatment as Prevention**

Two abstracts focused on performance of elbasvir/grazoprevir (EBR/GZR) in diverse population outside of clinical trials. In a report looking at combined outcomes from the HEPAVIR-DAA (HIV/HCV) and GEHEP (Group for the Study of Viral Hepatitis-MONO cohorts, responses to 12 to 16 weeks (with or without ribavirin) of EBR/GZR were analyzed for 266 persons with SVR12 data available (Abstract 561). Notable aspects of the cohort included a high prevalence of PWID (53%) and HIV coinfection (27%). Consistent with registries, a high SVR12 of 96% was seen and for 2% experienced virologic failure. Similar SVR12 data were seen in PWID (94%, $P=0.43$). As has been described, numerically lower SVR12 was seen in genotype 1a (92%), although there were relatively few cases (n=64) and resistance-associated substitutions (RAS) testing was not uniformly performed. If available, RAS testing is recommended in genotype 1a infection when EBR/GZR treatment is planned, as an extension of EBR/GZR to 16 weeks with the addition of ribavirin if non-structural protein 5A RAS are detected.4

A prospective cohort from Madrid, RUA-VHC (Registry of the Use of Antiviral Agents for the Hepatitis C Virus), focused on comparing response to EBR/GZR in HIV/HCV-coinfected patients (n=134) with those with HCV monoinfection (n=1486) (Abstract 562). Notable differences at baseline between the two groups included a higher prevalence of genotype 1a (37% vs 15%, respectively) and 4 (43% vs 10%, respectively) infection in coinfected participants; the prevalence of high HCV RNA and cirrhosis were similar between the groups. HIV was well controlled with 95% suppressed on antiretroviral therapy (ART) and a median CD4+ cell count of 695/μL. In unadjusted analyses, SVR12 was lower in the coinfected group (90% vs 94%, respectively; $P=0.035$). The difference persisted in a modified intention-to-treat analysis excluding those lost to follow-up (94% vs 97%, respectively; $P=0.029$). Although HIV infection was associated with non-SVR in a univariate analysis; after accounting for HCV genotype and cirrhosis status in a multivariate analysis the impact of HIV coinfection was lost (OR, 1.04, 0.54-2.02). These cohort data support prior results demonstrating similar DAA treatment response rates outside clinical trials and in key populations such as people who inject drugs and people living with HIV.

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Treatment as prevention of transmission is well established for HIV, and recent data from Dutch and Swiss HIV cohorts indicate this to also be an effective approach to decreasing HCV transmission in high-risk populations such as HIV-infected MSM.5,6 An analysis presented by Garvey and colleagues from 3 large HIV clinics in London lends further support to the notion that aggressive HCV treatment can reduce incident HCV infections (Abstract 85). The study period was from June 2013 to July 2018 with data collection at 6 month intervals focusing on new HCV infections; a uniform testing approach was not used at across the sites. Incident HCV infections were split into first-time HCV infection and reinfections using standard definitions. During this time the National Health Service (NHSE) expanded access to DAAs with removal of fibrosis stage restriction in 2016. However, important limitations on access remain within the NHSE, including lack of treatment for acute infection and no DAA retreatments for reinfection.

Despite these limits, a 68% fall in all incident HCV infections (1.7/100 person-years—0.6/100 person-years) and 80% decrease in new HCV infections...
(excluding reinfecions; 1.5/100 person-years—0.3/100 person-years) was seen from the second half of 2015 (peak) to the first half of 2018 (last time period). However, 2 disturbing trends were noted: 1) the proportion with re-infection had been increasing in recent years (43%-47% in last 2 6-month time-periods) and 2) the overall incidence did not decline in the last 3 time periods studied (0.5-0.6/100 person-years) suggesting perhaps an underlying high-risk population without adequate treatment penetration. As has been seen in other cohorts, an increase in other sexually transmitted infections was seen over time period, suggesting decreased risk behaviors were unlikely to have contributed to the fall in new HCV infections. Decreases in time to starting treatment were seen over the study period, from a mean of 41 months in 2013 to 3 months in 2018, but relied heavily on clinical trial access. Reliance on treatment through clinical trials to provide key public health interventions is not sustainable and calls for a change in NHSE policies that restrict treatment for both acute and recurrent HCV infections.

A number of country-wide efforts targeting enhanced diagnosis and immediate, universal treatment of HCV in MSM with HIV infection have demonstrated dramatic short-term decreases in HCV incidence and prevalence. Although encouraging, HCV transmissions from outside the cohort could hamper elimination efforts. A phylogenetic analysis of 174 genotype 1a E1-E2 HCV sequences from HIV-infected MSM in Amsterdam attempted to determine the date of sequence introduction and further whether the introduction occurred from within the cohort or externally (Abstract 597). Ten transmission clusters with more than 5 sequence members were identified. The estimated dates of introduction ranged from 1993 to 2005, placing them in a similar timeframe to the French phylo dynamic data. The authors then analyzed incident infections by year and determined the ratio of new infection originating from a within transmission cluster (internal) versus outside (external). Notably the only year for which external transmissions outnumbered those from within clusters was 2018 (ratio, 1.35). Although this may be largely due to the aggressive treatment of HCV in MSM with HIV infection in Amsterdam (eliminating the pool for internal transmissions) it raises concerns for exogenous HCV reintroduction.

**HCV Reinfecion**

The likelihood of HCV reinfecion following either spontaneous clearance or after SVR12 varies based on the risk factors for initial infection. Among the major risk groups for HCV infection, PWID have traditionally been viewed as a population at high risk for reinfecion. However, several European cohorts have found high HCV reinfection rates in MSM with HIV infection. Few data are available from contemporaneous cohorts in the United States. Fierer and colleagues presented data from the New York Acute Hepatitis C Surveillance Network, spanning 2000 to 2018 that suggested similarly elevated rates of HCV reinfection in MSM with HIV infection (Abstract 86). The cohort consisted of 304 MSM with HIV infection who were predominantly white (82%) with a median age of 45 years. There were 845 person-years of follow-up with a median follow-up duration of 2.2 years. Thirty-eight reinfecions were captured at median of 1.9 years post clearance for an incidence of 4.4 per 100 person-years, which is in the range seen in European cohorts and generally higher than seem in PWID. There was no difference in reinfection rate based on mode of prior clearance, whether spontaneous or treatment induced, although numbers are small and confidence intervals wide. In contrast, an Australian HIV/HCV observational coinfection cohort reported lower reinfection rates after cure at 0.81 per 100 person-years; of note, all 5 reinfecions occurred in MSM (Abstract 577).

**HCV in Pregnancy**

HCV infection in pregnant women has doubled from 2009 to 2014, leading to AASLD/IDSA to recommend universal HCV screening in pregnancy as of September, 2018. The American College of Obstetrics and Gynecology and US Preventive Services Task Force have not yet adopted this recommendation. Chaillon and colleagues demonstrated that universal screening of pregnant women in the United States is cost-effective, including at the US national prevalence of 0.7%, and is even more cost effective in parts of the United States where HCV prevalence in pregnancy is as high as 8% (incremental cost-effectiveness ratio [ICER] of $5,288 at an F2 treatment threshold). Universal screening of pregnant women is anticipated to detect HCV in 33,000 US women (Abstract 589). In a retrospective evaluation of more than 10,000 pregnant women from a large mid-Atlantic healthcare system, overall HCV screening rate was 50%, and 20% of the women with HCV antibody positive test results had no reported HCV risk factor. Notably, 8 of 8 pregnant women treated with ledipasvir/sofosbuvir achieved sustained viral response at 12 weeks. Given the hepatitis B and HIV analogies, there is little doubt DAA treatment will be effective in prevention of mother-to-child transmission of HCV there were racial disparities in screening: women undergoing testing were more likely to be African-American than white (47% vs 33%, respectively) despite a higher percentage of white women testing HCV antibody positive (71% vs 21%, respectively) (Abstract 586). These data highlight the need for more uniform guidance and uptake in HCV screening of pregnant women. Perinatal transmission of HCV occurs in approximately 5% to 6% of births of mothers with HCV viremia, with HIV coinfection increasing this transmission rate. In one of the most anticipated hepatitis presentations at CROI, Chappell and colleagues presented the first data...
of DAA-based treatment of HCV during pregnancy (Abstract 87). Extrapolating from HIV and hepatitis B virus (HBV) infection experience, it is expected that therapy that reduces the maternal viral load to zero would dramatically reduce HCV perinatal transmission.

A phase I study evaluated 12 weeks of ledipasvir/sofosbuvir for genotypes 1, 4, 5, and 6 infection in pregnant women. Key exclusions included HIV coinfection and cirrhosis. Treatment was initiated at 23 to 24 weeks of gestation with follow-up to SVR12. Infants of treated mothers are being followed up to 1 year. Despite extensive efforts by the study team, of more than 170 HCV-infected pregnant women identified, only 29 were screened. Of those screened only 9 enrolled with 10 of 29 being excluded due genotype 2 or 3 infection, for which ledipasvir/sofosbuvir is not effective.

Not surprisingly, treatment was well tolerated (all AEs were grade 1 or 2) and efficacious with 8 of 8 (100%) of women who had completed 12 weeks of follow-up posttreatment achieving SVR12. No infant-related adverse events and no HCV transmission has been documented thus far with 5 of 9 infants having completed 1 year of follow-up. Although this is an exciting initial step, much more data are needed. The fact that 10 of 29 screened women had genotype 2 or 3 HCV infection highlights the need for futures studies with pan-genotypic regimens.

Given the HBV and HIV analogies, there is little doubt DAA treatment will be effective in prevention of mother-to-child transmission (MTCT) of HCV. However, as HCV infection can also be cured after transmission and data with DAAs is now available down to 3 years, the burden of proving safety is higher in HCV.

Complications of HCV

HCV and Diabetes

The benefits of HCV cure on liver-related morbidity and mortality are clear; fewer data are available on potential additional positive effects of cure on extrahepatic organ systems and HIV complications. There is a well-established epidemiologic link between HCV infection and the development of diabetes mellitus. Although few data are available on the possible beneficial effects of HCV cure on diabetes prevention and improved insulin sensitivity, several case reports have suggested a positive effect.

Using the ERCHIVES (Electronically Retrieved Cohort of HCV Infected Veterans), Butt and colleagues assessed incident diabetes mellitus (DM) at more than 12 weeks after completion of HCV treatment compared with an HCV-infected untreated group propensity matched for risk factors associated with diabetes (Abstract 88). After exclusions that included HIV and prevalent diabetes, 26,000 HCV-treated veterans were compared with an equal number of controls. One-third had a body mass index above 30 and 22% had a FIB-4 score above 3.25. Of the treated veterans, 20% received an interferon alfa-containing regimen; in the DAA-treated group the most common regimen was ledipasvir/sofosbuvir with or without ribavirin (50%).

In the primary analysis, HCV group treated with DAAs (but not interferon alfa) had a significantly lower incidence rate of DM than the untreated population (9.89/1000 person-years vs 20.6/ 1000 person-years, respectively, \(P < .0001\)). A significant difference was seen (13.2 vs 19.2/1000 person-years, respectively; \(P < .0001\)) comparing SVR with non-SVR groups among those treated, (13.2 vs 19.2/1000 person-years, respectively; \(P < .0001\)). Factors strongly associated with incident diabetes included black race (hazard ratio (HR), 1.42; \(P < .0001\)), body mass index above 30 (HR, 5.38; \(P < .0001\)) and DAA treatment (HR, 0.48; \(P < .0001\)). Advanced fibrosis determined by a FIB-4 score above 3.25 was also associated with incident diabetes (HR, 1.29; \(P < .0001\)). Although observational in nature, these data strengthen the case for reduced risk of incident diabetes as an extra-hepatic benefit of HCV treatment.

HCV and Cardiovascular Disease

An analysis from the ERCHIVES cohort compared cardiovascular disease (CVD) events (assessed by ICD-9/10 codes) in HCV treated (n=32,575) vs a propensity-matched HCV untreated group of veterans without HIV (Abstract 570). By design the groups were well matched for diabetes, hypertension, and smoking status; statin use was higher in the untreated group, although the absolute difference was less than 1%. FIB-4 score was higher in the treated group at baseline, although the absolute difference was modest (1.95 and 1.70, respectively; \(P < .01\)). CVD disease-free survival was significantly higher in the HCV-treated group out to 36 months with curves splitting about 12 months after therapy. Curiously the benefit was seen regardless of SVR status. Fibrosis stage modulated the risk of CVD events, with more events in those with advanced fibrosis (treated 24.5/1000 person-years vs untreated 44/1000 person-years), though HCV treatment largely abrogated this effect.

Counter to the observations in ERCHIVES, an analysis focused solely on persons with HIV infection stratified by HCV exposure and treatment status found no detrimental impact of HCV coinfection, regardless of HCV treatment status, on the risk of CVD or non-AIDS associated malignancies (Abstract 565). As expected, a strong negative impact of HCV on development of liver-related complications was seen that was ameliorated by successful treatment. High rates of smoking in the cohort (≈50%) and lower rates of HIV control (HIV RNA <500 copies/mL) in HCV-negative (64%) and untreated group (68% versus 90% in treated) may have confounded the results.

Although observations from ERCHIVES and other cohorts have suggested a beneficial impact of DAA therapy on cardiovascular events, mechanistic details are lacking. Proprotein convertase subtilisin-kexin type 9 (PCSK9) functions as a regulator of low-density lipoproteins (LDL) by modulating degradation of LDL-receptors on hepatocytes and inhibitors of PCSK9 form a new class of lipid lowering agents. PCSK9 has also been associated with inflammation and immune activation. Gandhi and colleagues reported the effects of DAA treatment on PCSK9 level
in HIV/HCV-coinfected persons (n=35) and compared levels over time with a well-controlled HIV-monoinfected group (n=37) (Abstract 567). At baseline LDL levels were significantly lower in those with HCV coinfection, though there was no difference in statin use. There was trend toward higher PCSK9 levels in HIV/HCV-coinfected individuals that those with HIV only (307 and 284 ng/mL; P=.06). A significant decrease in PCSK9 levels post-HCV treatment was seen and was modestly correlated with changes in sCD163 and sE-selectin. The significance of these associations is unclear and a causal link cannot be established at this point, particularly given the direct effects of HCV on lipid metabolism including sterol regulatory element binding protein-2, which regulates PCSK9.

In a direct assessment of arterial stiffness, aortic pulse wave velocity (PWV) was measured in controls (n=27), individuals with HIV infection (n=25), with HCV infection (n=35) and with HCV/HIV coinfection (n=39) (Abstract 569). Measurements were taken before and after HCV treatment, with adjustments for age, sex, smoking, hypertension, and body mass index. No difference in PWV was seen before HCV treatment among the groups and no significant change was noted after SVR in groups with HCV. As has been noted previously, select inflammatory markers improve in HCV monoinfected patients after SVR (eg, sCD14) but HIV/HCV coinfected subjects did not show significant improvement. This study was limited by the small sizes of the groups, it is also notable that PWV is not widely accepted as a marker of CVD risk.

**HCV and Renal Disease**

In population-based studies HCV infection adversely impacts renal outcomes, particularly in high-risk groups such as those with diabetes mellitus. In an Italian cohort of 403 HCV-infected persons without HIV infection, including 17% with a pretreatment estimated glomerular filtration rate (eGFR) below 60 mL/min/1.73 m², improvements in renal function were assessed at 12 weeks or later after DAA treatment (Abstract 566). Following treatment dramatic improvements in eGFR were seen in groups with stage 3 (49.8 to 79.7; P<.001) and stage 4 or 5 (23.9 to 73.9; P<.001) chronic kidney disease (CKD). Combined the prevalence of CKD stage 3 to 5 went from 16.9% to 12.2% post-treatment (P<.05). Factors associated with eGFR improvement in multivariate analysis were SVR (HR, 12.2; CI, 1.26-118.11) and presence of decompensated liver disease (HR, 3.43; CI, 1.44-8.18; Child-Turcotte-Pugh score, A/B; C excluded). The specific causes of CKD were not mentioned, but the astounding improvements in eGFR in the most advanced group raise the question of whether a few cases of acute glomerulonephritis, or other severe causes of acute renal injury that are also potentially reversible, were included.

**Hepatitis B**

**Outcomes of HBV Treatment in HIV Coinfection**

The goal of HBV treatment with nucleos(t)ides is HBV DNA suppression and ultimately, loss of HBsAg and immunologic control of infection with gain of HBV surface antibody (HBsAb). In a Texas cohort of HIV/HBV coinfected individuals, 96% of whom were on HBV active ART, only 10% lost HBsAg (median length of follow-up was not reported) (Abstract 624). In a similar analysis from Zambia, 10% of HIV/HBV-coinfected individuals starting tenofovir lost HBsAg over 2 years of follow-up (Abstract 625). These rates are consistent with the 5% to 15% HBsAg loss that has been described in other cohorts of ART-treated HIV/HBV-coinfected individuals. HBsAg loss was associated with lower baseline CD4+ cell count in both cohorts, greater gain in CD4+ cells (Zambian cohort), and AIDS diagnosis (Texas cohort), raising questions about the potential role of immune reconstitution potentially in HBsAg loss. However, HBsAg loss was still low in those with baseline CD4+ cell count below 200 cells/µL at 11% (Zambian cohort).

A German cohort of HIV/HBV-coinfected individuals on tenofovir-containing combination ART reported a similar 18% HBsAg loss over a median of 11 years (interquartile range [IQR], 10-12). HBsAg loss was less likely with low CD4+ cell gain on ART (P=.0043) and in contrast to the Texas cohort, less likely in presence of Centers
for Disease Control and Prevention (CDC)-C diagnosis (P < .001). Persistent HBV viremia despite HIV suppression on tenofovir-based ART has been described, but the etiology is not well understood. An analysis of tenofovir concentrations in dried blood spots demonstrated lower tenofovir concentrations in patients with HBV viremia and HIV suppression. This suggests that lower ART adherence may be responsible for HBV viremia and that there is a differential ART adherence threshold for suppression of HBV and HIV. No HBV drug resistance mutations were reported (Abstract 626).

HBV Reactivation and Revaccination
The US Food and Drug Administration (FDA) raised concerns about risk of HBV reactivation in those with resolved or current HBV infection during HCV treatment with DAAs with a black box warning issued in 2017. A London cohort examined the risk for HBV reactivation during HCV treatment in 271 HIV/HCV-coinfected individuals taking DAAs. In 35% (96/271) HBV core antibody (HbcAb) was positive; of these 6 were HBsAg-positive, 56 had HBsAb above 10 IU/mL, and 26 had only isolated HbcAb-positive; 98% were taking at least 1 HBV-active ART medication. Of the 14 taking lamivudine as the only HBV-active ART, 2 added tenofovir and 6 started entecavir. No HBV reactivation occurred in any of the participants, including the 6 with a positive HBsAg (Abstract 628). Given the small sample size, it is not clear if the addition of tenofovir or entecavir is warranted, particularly in those without surface antigen. Overall, the lack of reactivation during HCV DAA therapy is consistent with results of a meta-analysis of HCV monoinfected individuals demonstrating no clinically significant HBV reactivation in the absence of HBsAg positivity.

Optimal approaches to revaccination for HBV infection after non-response to a first series in HIV-infected persons remain unclear. A randomized trial of standard dose (20 µg) versus double dose (40 µg) Engerix-B given at 0, 1, and 6 months was carried out in HIV-infected persons on ART with preserved CD4+ cell counts (>200/µL) in Taiwan (Abstract 622). No difference was seen in the primary endpoints of anti-HBs response 10 mIU/mL or more 4 weeks after the last dose (88.2% vs 96.9% for standard and high dose, respectively; P = .36). However, geometric mean titers of anti-HBs were significantly higher at all time points in the double-dose group. Conclusions from these results are limited by the small study size. HBV vaccine using a novel TLR9 adjuvant (HEPLISLAV-B) has demonstrated improved antibody responses and are starting to be evaluated in HIV-infected populations.

Mother-to-child transmission of HBV can essentially be eliminated with prompt infant immunoglobulin and vaccination combined with maternal TDF

HBV in Pregnancy
The iTAP (Maternal Antiviral Prophylaxis to Prevent Perinatal Transmission of Hepatitis B Virus in Thailand) study randomly assigned HBV envelope antigen positive pregnant Thai women to receive tenofovir disoproxil fumarate (TDF) or placebo starting at 28 weeks of gestation to evaluate the impact of TDF on MTCT, with added HBV immunoglobulin and HBV vaccination provided to all infants. In an analysis of maternal HBV DNA presented at this year’s CROI, 88% of women randomized to TDF had HBV DNA less than 200,000 IU/mL at delivery, a threshold that has been associated with lower risk of maternal to child HBV transmission (Abstract 629). Although 12% of women had HBV DNA levels above 200,000 IU/mL at delivery, no HBV transmission occurred from any TDF-treated mother to their infant, whereas 3 infections occurred in the placebo arm. The previously published trial was not able to demonstrate a significant benefit of TDF over infant vaccination alone, due to the unexpectedly low rate of MTCT in the vaccination/immunoglobulin-only arm. However, these data are reminder that MTCT of HBV can essentially be eliminated with prompt infant immunoglobulin and vaccination combined with maternal TDF. The impact of maternal TDF on MTCT may vary depending on the specific population risk for transmission.

Another study examined the impact of maternal HBV infection on birth outcomes in an older study (HPTN 046) evaluating nevirapine to prevent MTCT of HIV in sub-Saharan Africa. A total of 88 (4.3%) of mothers with HIV infection were HBsAg positive, 10 of whom had high HBV DNA (>106 IU/mL). More than 80% of mothers were on HIV medications; however, 48% were on ART that did not contain lamivudine, and none were on TDF-based ART. Infants born to mothers with HIV infection who had high HBV DNA levels were more likely to have low birth weight (30%) than those without HBV (10%) or with low HBV DNA (6%) (P = .04), and HBV viremia appeared to have a dose-responsive relationship to low birth weight. High HBV DNA level was also associated with MTCT of HIV in 2 of 10 infants. These data suggest that reduction of maternal HBV DNA level may have benefits beyond maternal health and reduction of infant infection, but this has to be tempered by a small number of mother-infant pairs, particularly in the group with high HBV DNA levels. (Abstract 41LB)

Intrahepatic Evaluation of HCV and HBV
Two studies used the novel technique of single cell laser capture microdissection (sCLCD) to examine viral- and immune-based phenomena at the hepatocyte level in 1) chronic HCV infection early during DAA treatment (Abstract 89) and 2) chronic HBV infection (Abstract 91). In a sub-study of A5329 that evaluated paritaprevir/ritonavir/ombitasvir plus dasabuvir (PrOD) therapy for genotype 1 HCV infection, paired liver biopsy specimens (immediately before and after 1 week of therapy) from 5 HIV-coinfected participants
were evaluated by scLCD for intracellular HCV RNA, interferon-stimulated gene (ISG) expression, and drug levels. Detailed plasma viral kinetics and drug levels were collected concomitantly. All participants had similar HCV (treatment-naive, genotype 1a HCV infection, and without cirrhosis) and HIV (HIV RNA suppressed <40 copies/mL on ART with CD4 cell count >250/µL) parameters; 2 participants were women. As expected, plasma HCV RNA showed a rapid and profound decline (-3 log10 copies/mL) over the first 24 hours followed by a slower decline over the next 6 days (-0.2 log10 copies/mL). Intrahepatic HCV RNA characteristics mirrored, or perhaps more accurately, predicted plasma observations. Before therapy the percentage of HCV-infected hepatocytes was highly correlated with the baseline plasma viral load level (Spearman r, 0.9). Roughly 25% of hepatocytes were infected before treatment (range, 7.4-42.9%) with 8 IU of HCV RNA per cell (IQR, 4-17). Interestingly during therapy the number of infected hepatocytes declined dramatically (1% infected at day 7); however, the amount of HCV RNA per cell did not change (12 IU/cell at day 7; IQR 5-27). A minority of cells at both time points contained more than 100 IU/cell.

Extrapolating intrahepatic HCV RNA expressing cell loss over the course of therapy allowed the investigators to estimate that all infected hepatocytes would be gone or cleared between 5 and 8 weeks of therapy in this small sample. All 4 participants with the second biopsy at day 7 (1 participant’s second biopsy was substantially delayed) attained a SVR, so there was no opportunity to compare early intrahepatic phenomena at the cellular level between cure and viral relapse. Global intrahepatic ISG level fell in tandem with HCV RNA level. Although DAA concentrations were variable, liver concentrations (ng/gl) mirrored peak plasma concentrations (ng/mL) with evidence of intrahepatic concentration particularly for protease inhibitors.

Chronic HBV infection is unique and characterized by the presence of covalently closed circular DNA (cccDNA) in infected cells that, even under suppressive nucleoside-based therapy, serves as a latent reservoir of infection. As novel treatment approaches aimed at HBV cure are advanced, a better characterization of intrahepatic HBV expression is needed. In particular, immune-based therapies aimed at eradicating infected hepatocytes will presumably require active HBV transcription for detection. Liver biopsies from 5 HIV/HBV coinfected persons were studied using scLCD and assays for HBV pregenomic RNA (pgRNA), cccDNA, and total HBV DNA via digital droplet PCR. Three of the 5 biopsies were obtained from persons on TDF-based ART and included 1 person with an undetectable HBV DNA level. In contrast to HCV, in the absence of antiviral therapy, nearly all hepatocytes (>95%) had evidence of HBV infection; in the setting of long-term TDF-based therapy this decreased to around 30%.

In the samples from persons with a HBV DNA level above 100 IU/mL in plasma, HBV transcription, as assessed by HBV pgRNA, was present in nearly all cells analyzed. Conversely, when plasma HBV DNA level was below 100 IU/mL, the ratio of transcriptionally active cells to total cells with cccDNA was below 10 and significantly lower than samples from non-suppressed persons. Prolonged HBV suppression, in this case about 7 years, was associated with substantially less cccDNA per cell; 4% to 5% of all hepatocytes analyzed in these 2 samples still harbored HBV that was transcriptionally silent (no pgRNA but with cccDNA).

**Hepatitis A**

Recent outbreaks of hepatitis A virus (HAV) have been reported in several populations including MSM with HIV infection. Response to a single HAV vaccine dose in a cohort of 73 patients with HIV infection (93% MSM) was suboptimal at 60% 3 months after vaccination (Abstract 620). Vaccine non-response was associated with a low CD4+/CD8+ cell ratio, but not absolute CD4+ cell count, in a multivariate analysis. Loss of protective HAV immunity over time may also contribute and was examined in a HIV clinic cohort (Abstract 621). Twenty patients had clear evidence of loss of HAV immunity; 15 with documented vaccination and 5 with prior positive antibody titers. Although CD4+ cell count was relatively preserved (mean, 376 ±85/µL) only 50% had an undetectable HAV RNA. Although not currently recommended in the United States, consideration of routine booster HAV vaccination may be warranted for certain high-risk populations.

**Liver Inflammation, Nonalcoholic Fatty Liver Disease, and Nonalcoholic Steatohepatitis**

In an observational AIDS Clinical Trials Group (ACTG) study analysis, one third of PLWH without viral hepatitis or heavy alcohol use had elevated aspartate aminotransferase or ALT level on more than one occasion. This transaminitis was associated with traditional risk factors for nonalcoholic fatty liver disease (NASH) (elevated triglyceride level, high blood pressure, female sex) and had a higher hepatitis steatosis index suggesting NALFD, although imaging was not available to confirm fatty liver disease (Abstract 616).

A Copenhagen observational cohort found a lower risk for computerized tomography-diagnosed fatty liver disease (which could include alcohol-associated disease as well as NALFD) in PLWH than in matched controls without HIV (8.5% vs 17.4%, respectively; P<.001). PLWH with fatty liver had typical risk factors (elevated body mass index, diabetes, alcohol use), as well as cumulative exposure time to zidovudine (adjusted OR, 1.23) despite a mean time of 9.4 years since discontinuation (Abstract 615).

All cited abstracts appear in the CROI 2019 Abstracts eBook, available online at www.CROIconference.org

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Additional References Cited in Text


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Invited Review

CROI 2019: Advances in Antiretroviral Therapy

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The 2019 Conference on Retroviruses and Opportunistic Infections included many exciting advances in antiretroviral therapy (ART). Investigators presented a case report of a second patient possibly cured of HIV through an allogeneic hematopoietic stem cell transplant from a CC chemokine receptor 5-Δ 32 donor. Two clinical trials of long-acting injectable cabotegravir and rilpivirine showed promising safety, efficacy, and tolerability as maintenance ART. Test-and-treat and rapid-ART-start strategies show promise in advancing progress toward the HIV care cascade 90-90-90 Joint United Nations Programme on HIV/AIDS/World Health Organization targets. However, late diagnosis and mortality after ART initiation remain high, even in the context of HIV service scale-up, and mortality from unintentional opioid overdose in people living with HIV in the United States is on the rise. In vitro studies were presented that identified and evaluated the effect of resistance-associated mutations on ART susceptibility and elucidated mechanisms of resistance. Epidemiologic data were reported on the prevalence, impact, regional variation, and changes over time of resistance-associated mutations. Decreasing regional and national rates of resistance may be a benefit of increasing use of integrase strand transfer inhibitors (InSTIs). New findings were presented on maternal and fetal health outcomes in women of reproductive potential, drug-drug interactions between hormonal contraception and ART, and further exploration of the association between InSTIs and birth defects.

Keywords: CROI, 2019, HIV, AIDS, antiretroviral, therapy, ART, treatment strategies, investigational drugs, care cascade, resistance, infants, women

Clinical Trials and Investigational Antiretroviral Agents

Possible Cure of HIV-1 Infection

Gupta and colleagues presented on a patient living in London, England, who underwent an allogeneic hematopoietic stem cell transplant (HSCT) from a donor with a homozygous CC chemokine receptor 5 (CCR5)-Δ 32 deletion to treat Hodgkin Lymphoma (Abstract 29). (Aspects of this case are also described in “CROI 2019: Advances in Basic Science Understanding of HIV” by Stevenson in this issue.) The patient was noted to have CCR5 virus before transplant. He discontinued antiretroviral therapy (ART) 17 months after transplantation. All standard and ultrasensitive plasma HIV-1 RNA levels were below the limit of detection for 18 months after cessation of ART. HIV-1 DNA declined below the limit of detection measured by clinical assay. Measured using droplet-digital polymerase chain reaction testing, 1 of 8 replicate showed low-level positivity. Three quantitative viral outgrowth assays were performed and none demonstrated inducible HIV production. Anti–HIV-1 antibodies declined over time, with progressive loss of bands on Western blot, and HIV-1 specific T-cell responses also declined.

An additional case of allogeneic HSCT from a CCR5-Δ 32 donor for acute myelocytic leukemia was presented (Abstract 394). This patient discontinued ART in November 2018, with no viral rebound to date.

Investigational Antiretroviral Drugs

Capsid inhibitor. Sager and colleagues presented pharmacokinetic data on an HIV-1 capsid inhibitor delivered via subcutaneous injection (Abstract 141). GS-6207 inhibits several steps of viral replication, including capsid assembly and disassembly, nuclear transport, and virus production. Single ascending doses of GS-6207 were tested in uninfected volunteers. Pooled safety assessments, which included those for placebo recipients, did not identify any safety concerns. All adverse events were mild or moderate, including mild injection site reactions. Drug concentrations were detected 24 weeks after a single injection and most doses exceeded the 95% effective concentration for 12 weeks or longer. The investigators noted that a study in people living with HIV is ongoing.

Yant and colleagues presented on the in vitro activity of GS-6207 (Abstract 480). This compound retained activity

A patient received a stem cell transplant with a CCR5-Δ 32 deletion and remains virologically suppressed without antiretroviral therapy, becoming the second after the Berlin Patient to achieve this milestone

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against a broad range of HIV-1 resistant to other ART classes including those with Gag polymorphisms conferring resistance to maturation inhibitors. The compound also exhibits activity against HIV-2.

Maturation inhibitor. DeJesus and colleagues presented data from a phase IIa study of a maturation inhibitor, GSK2838232 (Abstract 142). Maturation inhibitors bind Gag and prevent proteolytic cleavage between the p24 and SP1 proteins, inhibiting production of mature virions. GSK2838232 has favorable pharmacokinetic profiles when coadministered with ritonavir. This clinical trial enrolled 33 ART-naive adults living with HIV. In the first part of the trial, GSK2838232 100 mg was administered daily of cobicistat 150 mg for 10 days. After this cohort, sequential dose cohorts were enrolled starting at 200 mg daily descending to 20 mg daily, also for 10 days. The pharmacokinetic profile supported once-daily dosing of cobicistat with a half-life of 16 hours. Investigators observed robust antiviral activity with doses from 50 mg to 200 mg daily, with a maximal plasma HIV-1 decline of 1.3 to 1.7 log_{10} copies/mL, and antiviral activity continuing for 2 to 3 days after the last dose. One participant exhibited phenotypic resistance to GSK2838232 and another had virus that was not sensitive to GSK-2838232 at baseline. No safety concerns were identified. One participant harbored virus with reduced susceptibility to GSK2838232 at baseline and 2 participants had treatment emergent A564A/G gag mutations.

A human immunoglobulin G1 antibody targeting the V3 epitope in Env exhibits potent neutralizing activity against 60% to 70% of global HIV-1 isolates

profile supported once-daily dosing of cobicistat with a half-life of 16 hours. Investigators observed robust antiviral activity with doses from 50 mg to 200 mg daily, with a maximal plasma HIV-1 decline of 1.3 to 1.7 log_{10} copies/mL, and antiviral activity continuing for 2 to 3 days after the last dose. One participant exhibited phenotypic resistance to GSK2838232 and another had virus that was not sensitive to GSK-2838232 at baseline. No safety concerns were identified. One participant harbored virus with reduced susceptibility to GSK2838232 at baseline and 2 participants had treatment emergent A564A/G gag mutations.

Broadly neutralizing monoclonal antibodies. Stephenson and colleagues presented data on PGT121, a human immunoglobulin G1 antibody targeting the V3 epitope in the envelope (Env) (Abstract 145). PGT121 exhibits potent neutralizing activity against 60% to 70% of global HIV-1 isolates. Investigators enrolled 50 adults: 30 were living with HIV (half were viremic and half were virally suppressed), 43 received varying doses of PGT121, and 7 received placebo. PGT121 appeared safe, with only minimal local reactions, including when given subcutaneously. The elimination half-life was 23.5 days among individuals without HIV infection, 19 days for virally suppressed individuals living with HIV, and 13 days for viremic individuals. Among individuals with an HIV RNA level of 3.5 to 5.0 log_{10} copies/mL at baseline, 5 demonstrated a virologic response, with a median decline of 1.7 log_{10} copies/mL through day 7, and 4 participants had no response. All rebound viruses were resistant to PGT121. Two participants with baseline plasma HIV-1 RNA levels of 200 to 700 copies/mL achieved virologic suppression at 7 days and maintained suppression through 140 days and their PGT121 concentrations slowly declined to below the limit of detection; one experienced viral rebound at day 168, without resistance to PGT121, and the second remained virally suppressed. Investigators did not observe enhanced anti–HIV-1 cellular immunity as a result of antibody-antigen complexes, known as the “vaccinal effect,” with broadly neutralizing monoclonal antibodies.

Clinical Trials of Investigational Initial ART and ART Switch

Injectable long-acting (LA) cabotegravir (CAB) and rilpivirine (RPV). Swindells and colleagues presented the results from ATLAS (Antiretroviral Therapy as Long-Acting Suppression), a randomized, open-label trial comparing LA injectable CAB and RPV with standard 3-drug oral ART (Abstract 139). They randomly assigned 616 participants with sustained virologic suppression on a nonnucleoside reverse transcriptase inhibitor (NNRTI), protease inhibitor (PI), or integrase strand transfer inhibitor ( INSTI) with 2 nucleoside reverse transcriptase inhibitors (nRTIs) (33% women, 52% nonwhite, 26% older than 50 years). The control group continued their oral regimen through 48 weeks. The LA injectable group changed their existing ART to oral CAB and rilpivirine for 4 weeks. Those tolerating the drugs and maintaining virologic suppression changed to monthly injections of CAB and RPV. The primary endpoint was a plasma HIV-1 RNA level of 50 copies/mL or higher 48 weeks after randomization. This occurred in 1.6% of the LA group and 1.0% of the control group (difference, 0.6%; 95% confidence interval [CI], -1.2% to 2.5%). This met the prespecified definition of noninferiority. A key secondary objective was achieving a plasma HIV-1 RNA level below 50 copies/mL, according to the US Food and Drug Administration (FDA) snapshot algorithm. This was observed in 92.5% and 95.5%, respectively (difference, -3.0%; 95% CI, -6.7% to 0.7%). This also achieved noninferiority. Three participants in the LA arm discontinued because of injection site reactions. Three participants in the LA arm discontinued for lack of virologic activity: 2 had subtype A1 virus, 1 had AG virus, all developed RPV resistance, and 1 developed CAB resistance.

Orkin and colleagues presented the results from FLAIR (First Long-Acting Injectable Regimen), a randomized, open-label, clinical trial that enrolled ART-naive adults (Abstract 140). There were 629 participants who started dolutegravir (DTG)/abacavir (ABC)/lamivudine (3TC) for 20 weeks. If participants maintained HIV-1 plasma RNA levels below 50 copies/mL at week 16, then they were eligible for randomization at week 20; 569 participants (22% female, 26% nonwhite, 11% older than 50 years)
were randomly assigned to continue DTG/ABC/3TC (control group) or change to LA injectable CAB and RPV. The primary endpoint was a plasma HIV-1 RNA level of 50 copies/mL or higher 48 weeks after randomization. This occurred in 2.1% of the LA group and 2.5% of the control group (difference, -0.4%; 95% CI, -2.8% to 2.1%). This met the prespecified definition of noninferiority. A key secondary objective was achieving a plasma HIV-1 RNA level below 50 copies/mL, according to the US FDA snapshot algorithm. This was observed in 93.6% and 93.3%, respectively (difference, 0.4%; 95% CI, -3.7% to 4.5%), which also achieved noninferiority. Only 2 participants in the LA arm discontinued because of injection site reactions. Four participants in the LA group discontinued because of lack of virologic activity including 3 with protocol-defined virologic failure: all 3 had subtype A1 virus, all developed CAB resistance, and 2 of 3 developed RPV resistance. These studies establish the safety, tolerability, and efficacy of monthly LA injectable CAB and RPV for maintenance therapy of HIV-1 infection. Injection site reactions were common in both trials and were reported more commonly with the initial injections. Participants expressed greater satisfaction with the injectable therapy. Further analyses are needed to determine the relationship between subtype A1 virus and the virologic failure with this regimen.

**DTG/3TC.** Underwood and colleagues presented an analysis of the GEMINI 1 and 2 trials, which enrolled treatment-naive adults living with HIV and randomly assigned them to DTG plus 3TC (2-drug) or a standard (3-drug) regimen (Abstract 490). The proportion of participants with target not detected on the viral load assay was compared with HIV-1 measured below the limit of the detection. The proportions achieving target not detected were similar in the 2-drug and 3-drug groups at week 48 (77% vs 73%; difference, respectively; 3.8%; 95% CI, -0.6% to 8.2%) and all earlier time points. The time to achieving target not detected was also similar in both groups.

**PRO140.** Dhody and colleagues presented data on PRO140 (leronlimab), an investigational monoclonal antibody that blocks binding of HIV to CCR5 (Abstract 486). They enrolled participants with prolonged viral suppression with CCR5-mediated HIV-1, measured by phenotypic testing of proviral DNA. The investigators studied a series of doses given by weekly subcutaneous injection. Participants stopped other ART 1 week after the first injection and were maintained on PRO140 alone thereafter. Investigators observed relatively high rates of virologic failure at doses of 325 mg and 525 mg. They presented interim data on the 700 mg cohort. Among 43 participants, 6 experienced viral rebound by week 12, and no additional viral rebounds were observed through week 24. No participants developed reduced susceptibility to PRO140 or altered coreceptor tropism.

**Archived nRTI resistance and response to an InSti plus 2 nRTIs.** GS-US-380-4050 is an ongoing double-blinded clinical trial that enrolled 585 people living with HIV who were virally suppressed on dolutegravir (DTG) plus tenofovir disoproxil fumarate (TDF)/emtricitabine (FTC) or tenofovir alafenamide (TAF)/FTC and had no history of InSti resistance (Abstract 551). Participants were randomly assigned to bicitretavir (BIC)/TAF/FTC or DTG plus TAF/FTC. Proviral HIV-1 DNA was genotyped to characterize nRTI resistance in addition to historical resistance testing. The blinded week 12 interim results were presented. Virologic suppression was achieved in 99%. Among 30 participants harboring K65R or more than 3 thymidine analogue mutations, 97% (29/30) were virologically suppressed at week 12 compared with 99% of those with any other nRTI resistance and 99% with no nRTI resistance. The data support the use of these regimens in persons with nRTI resistance. However, longer-term follow-up is needed.

**Andreatta and colleagues** performed a similar analysis of data from 2 studies that enrolled virally suppressed participants and randomly assigned them to BIC/TAF/FTC or a comparator regimen (Abstract 552). Participants with known nRTI resistance were excluded from these trials, but genotyping of proviral HIV-1 DNA found that 22% harbored nRTI resistance mutations, mostly M184V/I and thymidine analogue mutations. Among 70 participants with nRTI resistance detected, 67 (96%) maintained virologic suppression through 96 weeks.

**Raltegravir versus efavirenz during pregnancy.** Mirochnick presented a randomly assigned, open-label clinical trial of raltegravir (RAL) versus efavirenz (EFV) given with zidovudine and lamivudine in pregnant women living with HIV at 20 to 37 weeks of gestation (Abstract 39LB). Of 408 women randomly assigned, 307 were included in the primary per-protocol population with plasma HIV-1 RNA levels above 200 copies/mL and no resistance to study drugs at study entry. Women randomly assigned to RAL were more likely to achieve a plasma HIV-1 RNA level below 200 copies/mL at the time of delivery than those assigned to EFV (94% and 84%, respectively). This difference was only observed in women who were at 28 to 37 weeks of gestation at enrollment. Tolerability was very high in both groups and there was no difference in maternal or infant safety outcomes. There were 6 cases of HIV transmission to infants in the EFV group and 1 in the RAL group (P=.06), all in women who enrolled after 28 weeks of gestation. These data support the use of RAL for preventing HIV transmission during pregnancy, especially when initiating later in pregnancy.

Khoo and colleagues presented data from a randomized, open-label clinical trial of DTG versus EFV given with 2 nRTIs to women living with HIV in their third trimester of pregnancy (Abstract 40). Investigators hypothesized that a faster decline in plasma HIV-1 RNA with DTG would reduce mother-to-child transmission (MTCT) of HIV. There were 249 women included in the intention-to-treat analysis. The primary endpoint of achieving a plasma HIV-1 RNA level below 50 copies/mL at delivery was achieved in 74% in the DTG group and 43% in the EFV group (P<.0001). However, 3 MTCTs occurred, all in the DTG.
group, and all likely occurred in utero. Four stillbirths occurred that were deemed unrelated to medications, all in the DTG arm.

**Novel Investigational ART for Infants, Children, and Adolescents**

**VRC01LS in infants.** McFarland and colleagues presented data on the safety and efficacy of VRC01LS a broadly neutralizing monoclonal antibody targeting the CD4 binding site, in infants born to mothers living with HIV (Abstract 45). VRC01LS refers to amino acid modifications of antibodies, methionine to leucine (L) and asparagine to serine (S), which prolong the half-life of the antibody. Investigators enrolled a cohort of non-breastfed infants who received a single subcutaneous dose of VRC01LS and a breastfed cohort that received 2 subcutaneous doses. All infants were started on ART prophylaxis and received VRC01LS within 5 days after birth. There were no grade 3 or 4 adverse events related to VRC01LS. Grade 1 or 2 local injection site reactions were noted and resolved within 24 hours. The pharmacokinetic parameters were similar to those observed in adults. Investigators concluded that administration of broadly neutralizing monoclonal antibodies is feasible in newborn infants, and future studies will examine the role of broadly neutralizing monoclonal antibodies in treatment of infants and children.

Gaur and colleagues presented data on a single-tablet regimen of BIC/FTC/TAF in children and adolescents living with HIV (Abstract 46). Investigators enrolled 100 virally suppressed individuals on other combination ART regimens (50 adolescents aged 12-17 years and 50 children aged 6-11 years). The pharmacokinetic endpoints were presented previously. No substantial safety concerns were identified. One participant discontinued because of insomnia and anxiety. Among 75 participants who have reached week 48, 74 had plasma HIV-1 RNA levels below 50 copies/mL and no viral resistance emerged. Participants found the study drug to be palatable with an acceptable shape and size. The investigators concluded that this was a promising single-tablet regimen for children and adolescents living with HIV.

**Clinical Trials in ART-Experienced Populations**

**Second-line therapy with DTG plus 2 nRTIs.** Brown and colleagues presented additional analyses from the DAWN-ING (Comparative Efficacy and Safety Study of Dolutegravir and Lopinavir/Ritonavir in Second-line Treatment) study, a randomized clinical trial of DTG plus 2 nRTIs versus ritonavir-boosted lopinavir (LPV/r) plus 2 nRTIs in people whose initial NNRTI-based regimen failed (Abstract 144). The nRTI was selected based on resistance testing, and participants were required to have at least 1 nRTI with clinical activity for enrollment. Investigators analyzed the relationship between virologic efficacy, baseline nRTI resistance mutations, and choice of nRTI. nRTI resistance-associated mutations (RAMs) were present in 90% of participants; M184VI with or without other nRTI RAMs was observed in 82% of participants. Most participants received zidovudine plus 3TC, or TDF plus 3TC or FTC. DTG was superior to LPV/r: 84% versus 70% with virologic suppression at week 48. The virologic efficacy of DTG and 2 nRTIs appeared similar for those with and without M184VI. Among those with M184VI, the virologic efficacy of DTG plus 2 nRTIs appeared similar whether or not 3TC or FTC was used. Similar virologic efficacy was observed in those harboring K65R, and in those with 1 or more thymidine analogue mutations.

**Ibalizumab.** Emu and colleagues presented 96-week data on ibalizumab, a monoclonal antibody that prevents CD4 attachment, currently approved for highly treatment-experienced patients living with HIV (Abstract 485). Of the 40 participants originally enrolled, 27 were still receiving ibalizumab at week 25 when data were last presented. Of these, 22 were still receiving ibalizumab through week 96 (2 patients died, unrelated to ibalizumab; 2 withdrew consent, and 1 physician decided to discontinue). Of the 16 patients with viral suppression (HIV RNA <50 copies/mL at week 25), 14 maintained suppression through week 96, and 1 participant achieved viral suppression. These data support the durability of viral suppression achieved with this compound.

**Although we now have the tools to end the HIV epidemic, time will tell whether the resources and political will allocated to this effort are sufficient to overcome substantial obstacles**

Fauci gave an impassioned description of the new US plan for ending the HIV epidemic announced by President Trump in the 2019 State of the Union speech. Fauci highlighted the tools we have at our disposal to end the epidemic, including preexposure prophylaxis (PrEP) and treatment as prevention (TasP), and described our moral obligation to set ambitious goals. The plan focuses on geographic and demographic “hot spots” in the United States. Forty-eight counties have more than 50% of new HIV diagnoses, and 7 southern states have disproportionate incidences of HIV in rural areas. Black people, people younger than 35 years, and men who have sex with men also bear a disproportionate burden of the US HIV epidemic. Fauci anticipates new resources allocated for PrEP and ART through the Centers for Disease Control and Prevention (CDC) and the Health Resources and Services Administration (HRSA) Ryan White HIV/AIDS Program.
The National Institutes of Health (NIH) will reallocate existing budget to cover implementation science work through existing Centers for AIDS Research (CFAR) locations, although there are some notable geographic discrepancies between priority areas and CFAR locations. Fauci noted that this initiative differs from prior efforts because it is being undertaken by numerous Health and Human Services agencies simultaneously and focuses on specific target populations. Although we now have the tools to end the HIV epidemic, time will tell whether the resources and political will allocated to this effort are sufficient to overcome substantial obstacles, such as access to care, the growing opioid epidemic, HIV-associated stigma, and discrimination.

**Data on the HIV Care Cascade and the Implications of U=U**

Throughout this section we will use the following definitions of HIV care cascade metrics. The “first 90” refers to the percentage of people living with HIV who are aware of their HIV diagnosis, and the target is 90%. The “second 90” refers to the percentage of people living with HIV who know their HIV serostatus and are receiving ART. The second 90 target is 90%, or 81% of total people living with HIV in a community. The “third 90” refers to the percentage of those on ART who have achieved viral suppression, traditionally defined as the most recent HIV RNA measurement being less than 200 copies/mL, although exceptions will be noted. The target for the third 90 is 90%, or 73% of people living with HIV in a community.

Several investigations of treatment as prevention, covered in “CROI 2019: Advances in HIV Prevention and Plans to End the Epidemic” by Buchbinder and Liu in this same issue, demonstrated an impact on the HIV care cascade. The PopART (Population Effects of Antiviral Therapy to Reduce HIV Transmission) trial (Abstract 92LB) examined differences between immediate ART and a package of prevention and linkage interventions by community HIV care practitioners, the same interventions and ART per treatment guidelines, and standard of care (SOC) in 21 urban communities in Zambia and South Africa. In addition to effects on population incidence, investigators noted that overall ART coverage met the care cascade’s first 90 target in both intervention arms. There was also a statistically significant 16% increase in virologic suppression with immediate ART initiation, compared with SOC.

Wirth and colleagues presented care cascade data from the Ya Tsie study (Abstract 95), a community-level cluster randomized trial in Botswana in which a package of HIV prevention and treatment interventions led to a 30% reduction in population HIV incidence in the treatment communities. They conducted a postintervention survey in a subsample of 6 paired communities to determine care cascade outcomes in April 2018, compared with preintervention baseline (October 2013) and found statistically significant improvement in all 3 care cascade metrics between intervention and SOC communities. The first 90 increased from 84% to 93% in the intervention communities, compared with 86% to 88% in the SOC communities. For the second 90, ART coverage increased from 72% to 90% in intervention communities, compared with 76% to 86% in SOC communities. The third 90, viral suppression, increased from 70% to 88% in intervention communities, compared with 75% to 83% in SOC communities. A post hoc analysis also revealed that time to ART initiation was 367 days in SOC and 69 days in intervention communities.

Patel and colleagues presented data from the Rakai Community Cohort Study on the impact of a universal test-and-treat program implemented in 2013 in fishing communities around Lake Victoria in Uganda, a mobile population with a high burden of HIV (Abstract 96). Investigators previously reported dramatic improvements in the care cascade between 2013 and December 2016, surpassing all 90-90-90 targets. In this analysis, 1883 individuals with viral load data at 2 time points were included, to examine changes in virologic suppression over time. Investigators found that prevalence of durable viral suppression (HIV RNA level <400 copies/mL at both paired time points, at least 12 months apart) was 50%. Between December 2011 and December 2016, population-level viral suppression increased from 37% to 77% for women and 21% to 58% for men. Predictors of persistent viremia (HIV RNA level >400 copies/mL at both time points) were an age of 15 to 29 years, having never married, migrating into the cohort at any time during the study period, and having more than 1 sexual partner in the past year.

Data on the “real-world” impact of universal treatment implementation in Brazil suggest less favorable outcomes. Chaisson and colleagues used national surveillance and patient monitoring databases to determine ART uptake between 2014 and 2017 in Brazil, which recommended ART regardless of CD4+ cell count in December 2013, 2 years before its adoption by the World Health Organization (WHO) (Abstract 1022). Of 5750 patients newly diagnosed with HIV between 2014 and 2016, 51% had initiated ART during the observation period. Median time to ART start declined over time, from 46 days to in 2014 to 21 days in 2016. There was a statistically significant association between ART initiation within 3 months and diagnosis in either 2015 or 2016, compared with diagnosis in 2014, for patients in the public sector. However, overall ART initiation rates remained low 3 years after implementation of national test-and-treat guidelines.

Universal test-and-treat strategies appeared to have a profound impact of the HIV care cascade in the context of the PopART, Ya Tsie, and Rakai Community Cohort studies but did not have a similar benefit at the national level in Brazil.
Community Cohort studies but did not have a similar benefit at the national level in Brazil. Offering a unique and important perspective on the last step in the care cascade, Foote presented community perspectives on the Undetectable=Untransmissible (U=U) campaign (Abstract 118). Foote noted that U=U reduces stigma for people living with HIV and urged that existing resources be updated to incorporate U=U messages. She proposed specific language for practitioners for clarity and consistency (eg, using terminology like “prevents HIV” or “can’t transmit” is preferred to “helps prevent HIV” or “is extremely unlikely to transmit”). Foote also urged practitioners to use morally neutral language to avoid unintentionally devaluing individuals with detectable viral loads. Finally, she highlighted areas in which messaging should be clearer, including that U=U is about sexual transmission of HIV and not transmission through breastfeeding or needle sharing and that U=U prevents HIV but not other STIs.

### Rapid Start and Test-and-Treat Strategies to Get to 90-90-90

Puttkammer and colleagues examined the impact of the Haitian national “Test and Start” program, which prioritized rapid initiation of ART after HIV diagnosis and was launched in July 2016 (Abstract 1017). Data from a national electronic medical record system and HIV case-based surveillance system were used to determine time to ART initiation and retention on ART 6 and 12 months after initiation in 148,680 people living with HIV in Haiti. There were clear and sustained reductions in time to ART initiation by year of diagnosis between 2010 and 2018, with 75% initiating ART within 1 year of diagnosis in 2017 and more than 90% of individuals diagnosed in early 2018 initiating ART within the first 2 months. However, in unadjusted and multivariate models, adjusting for sociodemographic and clinical characteristics, there was a surprising association between ART initiation after the day of diagnosis and retention on ART at 6 months (adjusted model) and 12 months (unadjusted model). In the adjusted model, ART initiation between 1 and 4 weeks after diagnosis showed the greatest benefit (adjusted odds ratio [aOR], 1.51; 95% CI, 1.13, 1.51) over same-day ART initiation. Despite other studies documenting the benefits of same-day ART initiation, such as the Thai Red Cross Anonymous Clinic program highlighted in the N’Galy-Mann Lecture given by Phanuphak, these data demonstrate that the impact of same-day start may differ by context.

The SLATE (Simplified Algorithm for Treatment Eligibility) trial evaluated a clinical algorithm to determine eligibility for immediate ART in South Africa and Kenya. The SLATE algorithm assesses individuals presenting for ART initiation for possible challenges to same-day start, including signs or symptoms of illness, substance use, prior ART, other comorbidities, and lack of individual readiness for ART. The trial individually randomly assigned patients presenting for any HIV care, including HIV testing, to either the SLATE algorithm or SOC. South African data were presented last year.1 Rosen and colleagues presented data from the Kenya sites (Abstract 1018), where 98% of individuals enrolled said they would initiate same-day ART if given a choice. However, only 55% of individuals randomly assigned to the SLATE intervention arm were eligible for same-day initiation per the algorithm, and 85% of those determined ineligible were disqualified for symptoms of tuberculosis. There was no difference in retention in care at 8 months between the 2 study arms, but loss to follow-up was high at approximately 40% of all patients. In Kenya, the majority of loss to follow-up occurred after the initiation of ART. The investigators have revised the SLATE algorithm to be less restrictive regarding eligibility for same-day ART and further studies are ongoing.

Hence and colleagues (Abstract 1020) determined the impact of a universal test-and-treat program in 3 correctional facilities in Zambia and South Africa. The program was accepted to most participants, and 86% of the 975 enrolled participants started ART, with a median time to ART start of 1 day after enrollment. As anticipated, follow-up was challenging, and 58% of participants initiating ART were transferred or released from the facility before 6 months of follow-up. Of those remaining in the facilities, 94% were still in care but only 78% had a viral load test result. Viral load suppression (HIV RNA level <1000 copies/mL) was found in 97% of those with tests completed.

Pry and colleagues at the Zambia Center for Infectious Diseases Research implemented a linkage assessment tool to examine the reasons people were declining same-day ART initiation across 3 HIV treatment facilities participating in the national test-and-treat program (Abstract 1024). Of 1274 eligible individuals, 99% declined same-day ART initiation and were asked about 22 potential personal, social, and structural reasons for declining. The most common barrier cited was “clinics are too crowded” (47.8%) followed by “friends and family will condemn me” (36.0%), and “people will see me getting medication” (32.6%). Demographic characteristics associated with declining same-day ART initiation included being older than 25 years, with the highest odds of declining ART in individuals older than 50 years (aOR 15.76; 95% CI, 10.57, 23.49); female; sex; and receiving care in an urban or rural health clinic rather than a hospital setting. Although the study is limited by a lack of data on when and if participants initiated ART, it provides insights into the primary structural and personal barriers to same-day ART initiation. Taken in context with the data on same-day ART from Haiti and the SLATE trial above, these data suggest that the context and structure of rapid start programs is important and there may be a disadvantage to same-day start for some individuals.
New Data on HIV Treatment Outcomes and Mortality

Results from the SEARCH (Sustainable East Africa Research in Community Health) trial in Uganda were presented at the International AIDS Conference in 2018, and Kamya and colleagues presented an oral abstract at CROI 2019 evaluating the impact of the SEARCH intervention on 3-year mortality (Abstract 138). SEARCH was a pair-matched randomized study of 32 rural Ugandan communities in the setting of population-based HIV testing, counseling, and testing, and linkage programs during scale-up of HIV services in rural western Kenya (Abstract 146). Investigators pooled data from a regional health and demographic surveillance system, which used community health worker reports and confirmation of deaths with family or community members for mortality ascertainment, and results from the regional home-based counseling and testing program. All-cause mortality in the community decreased from 10.0 per 1000 in 2011 to 7.4 per 1000 in 2016. There was a statistically significant difference between age- and sex-adjusted mortality for those living with HIV (Abstract 147). They found that being on ART (2.8/1000), those living with HIV not reporting ART use (5.3/1000), and those without HIV (referent). Data on sex and CD4+ cell count differences in mortality are forthcoming, making direct comparison to SEARCH trial data impossible. However, these findings demonstrate that mortality rates among people living with HIV continue to decrease in this region, although they are still substantially higher than in those without HIV, even in the context of HIV service scale-up. The investigators also proposed the possibility of using population mortality as a surrogate indicator for HIV-associated mortality, which would be relevant in areas with high HIV prevalence and reliable mortality estimates.

The opioid epidemic disproportionately impacts people living with HIV and could affect improvements in mortality conferred by ART in the United States

Comparing SOC linkage and treatment to a patient-centered test-and-treat model that included warm hand-offs, rapid ART initiation, flexible clinic hours, and mobile phone triage. This analysis examined 3-year mortality due to illness in those with baseline CD4+ cell counts less than 350 cells/µL, with 22% of the individuals identified as living with HIV. Mortality among those with CD4+ counts less than 350 cells/µL was 28% lower in the intervention communities. However, when stratified by sex, the intervention effect was only statistically significant among men. These data imply that population-based testing combined with linkage to care and rapid ART initiation can reduce mortality even for those late to care, although more data are needed to understand the sex discrepancy. Borgdorff and colleagues also presented data on mortality in the context of population-based HIV counseling, testing, and linkage programs during scale-up of HIV services in rural western Kenya (Abstract 146). Investigators pooled data from a regional health and demographic surveillance system, which used community health

Implications of New Strategies for Laboratory Testing

The impact of CD4+ cell count measurements. As CD4+ cell count criteria for ART initiation are no longer recommended, HIV treatment programs are considering discontinuation of CD4+ cell count monitoring. Sikombe and colleagues explored the possible consequences of no CD4+ cell count monitoring, by examining mortality in people living with HIV in Zambia initiating ART without a pretreatment CD4+ cell count measurement (Abstract 148). They propose that, in their cohort, absence of pretreatment CD4+ cell count measurement is usually caused by reagent being out of stock, equipment failure, or other non-patient-associated factors, creating a natural experiment where absence of CD4+ cell count monitoring is random and its consequences can be examined. Among 33,911 individuals initiating ART, 37.7% did not have a pretreatment CD4+ cell count measured. Two-year mortality in these individuals was 11.5%, compared with 6.6% in those with a documented pretreatment CD4+ cell count measurement. After adjusting for WHO disease

CD4+ cell count monitoring at ART initiation is becoming less common, which poses a clinical challenge for the 25% of individuals presenting with advanced HIV disease

...stage, sex, age, and clinic site, the hazard ratio (HR) for mortality remained elevated (HR, 1.45; 95% CI, 1.06, 1.97) in individuals who did not have pre-treatment CD4+ cell count measurements, compared with those who did. Although these findings imply a potential disadvantage to the elimination of a pretreatment CD4+ cell count measurement, it is difficult to determine whether unmeasured confounders, such as clinician judgement, impacted the results.
Leeme and colleagues also explored the utility of CD4+ cell count monitoring in the era of test-and-treat strategies and viral load monitoring in Botswana (Abstract 149). Using national laboratory system data on 14,425 patients initiating ART between January 2015 and December 2017, 25% had a baseline CD4+ cell count less than 200 cells/µL. Of those with CD4+ cell counts above 200/µL at baseline, only 3.6% experienced a drop to less than 200/µL, 79% of whom remained virally suppressed. The majority (74%) of the individuals with CD4+ cell counts below 200/µL and suppressed viral loads had CD4+ cell counts above 200/µL on repeat testing. The investigators concluded that baseline CD4+ cell count testing remains important, even in a setting where a well-developed HIV care system exists, because it is important to identify those presenting to care with advanced immunosuppression. However, they questioned the utility of ongoing CD4+ cell count monitoring if viral load data are available, particularly once individuals achieve CD4+ cell counts above 200/µL.

Zaniewski and colleagues examined trends in CD4+ cell count and viral load monitoring across 6 countries supported by PEPFAR (the US President’s Emergency Plan For AIDS Relief) in Southern Africa from 2005 to 2018, using data from the JoDea (International epidemiology Databases to Evaluate AIDS) cohort (Abstract 150). Among 542,138 adults initiating ART, there was variation by country in CD4+ cell count monitoring trends, with declines in monitoring in South Africa and Malawi but not in other countries. There was also heterogeneity within the cohort in viral load testing, with South Africa, Malawi, and Zimbabwe all scaling up viral load testing. Overall, a mixed effects model adjusted for age and sex showed that CD4+ cell count measurement at ART initiation decreased over time (OR, 0.92 per year), as did presentation with a CD4+ cell count less than 200/µL (OR, 0.79 per year) and treatment failure (OR, 0.95 per year), all statistically significant differences. However, the adjusted odds of having a viral load measurement after ART initiation increased annually (OR, 1.04). These data when examined alongside data from the other 2 abstracts on CD4+ cell count measurements prior to ART initiation, suggest that monitoring of advanced disease at initiation is becoming less common. This could pose clinical challenges, considering the ongoing presence of advanced disease in a substantial proportion of individuals initiating ART, comprising 20% to 25% in the studies presented here.

New laboratory tests to monitor adherence. Phillips and colleagues presented data on the utility of dried blood spot measurements of tenofovir levels for adherence monitoring (Abstract 462). Among 137 women enrolled, reported adherence was high, with 56% of women reporting 100% adherence. However, dried blood spot tenofovir concentration had a superior area under the curve (AUC) to self-report (AUC, 0.926 vs 0.756) and a comparable AUC to plasma measurements of EFV (AUC, 0.903) and tenofovir (AUC, 0.864). Although some differences in test performance were noted among black participants, these data suggest that ART concentrations measured with dried blood spots are a strong predictor of viral suppression. This technology could be adapted as a point-of-care assay for adherence that is more accurate than self-report and less costly than measuring plasma ART concentrations.

Another novel adherence measure was evaluated by Haaland and colleagues, who used urine FTC and tenofovir concentrations to predict adherence (Abstract 465). In a study of 18 men without HIV, t urine FTC levels correlated with plasma FTC levels, but urine tenofovir levels did not correlate with plasma tenofovir levels. When daily dosing with TDF/FTC was compared with daily dosing of TAF/FTC/elvitegravir/cobicistat, urine tenofovir levels in participants receiving TAF did not correlate with adherence. Based on these data, urine FTC level could be used as a point-of-care test for adherence to ART regimens containing this medication.

Prevalence of virologic failure, low-level viremia, and viral blips after virologic suppression. Lee and colleagues examined the risk of virologic failure, low-level viremia (HIV RNA level of 51-199 copies/mL) and viral “blips” (HIV RNA level of 51-199 copies/mL followed by viral suppression) in 16,944 people living with HIV within the NA-ACCORD (North American AIDS Cohort Collaboration on Research and Design) (Abstract 97). The time between initiation of ART and viral suppression (HIV RNA level <50 copies/mL) was highly predictive of virologic failure. For those in whom it took more than 12 months to achieve virologic suppression, the difference in risk for virologic failure at 6 years was 9.84 (5.08, 19.5) compared with those who achieved virologic suppression in less than 6 months. Black persons and persons who inject drugs were also statistically more likely take more than 12 months to achieve viral suppression.

The investigators did not find any differences in risk for low-level viremia or viral blips across various clinical and demographic predictors. These findings highlight the importance of rapid suppression after ART initiation, which may be clinically important and a marker for other barriers to ART success. However, they are limited by the time frame examined (2006 to 2015), during which InSTIs were less commonly used, since this class of ART is known to achieve viral suppression more rapidly than many other initial ART options.

Novel Data on Epidemiology and Implications of Antiretroviral Drug Resistance

Characterization of Antiretroviral Drug Resistance Mutations

Mutations in the envelope glycoprotein: a potential mechanism for drug resistance outside of target genes. After long-term passage of wild-type virus in the presence of PIs, InSTIs, nRTIs, and NNRTIs, Pham and colleagues (Abstract 540) selected antiretroviral escape mutants with mutations in the Env glycoprotein and Vpu but lacking changes in the target genes. These
antiretroviral resistance mutants were identified in 2 different T-cell lines (one favoring cell-free transmission and another favoring cell-to-cell transmission) and 2 viral subtypes with different coreceptor tropism. The gp41 envelope protein mutants Env-A556T and Env-A539V exhibited multiclass drug resistance and a 4- or 5-fold change to DTG. Several of the Env mutations positions are highly conserved across HIV-1 clades, and 2 of the Env mutations (Y61H and A539V) are found in the Los Alamos National Laboratory clinical database. These findings demonstrate that env can contribute to broad HIV drug resistance in vitro and may be a mechanism by which drug resistance is conferred outside of target genes. Further in vitro and in vivo analyses are ongoing and may help guide the development of more effective treatment.

Van Duyne and colleagues (Abstract 168) conducted a series of in vitro experiments to determine the mechanism by which mutations in gp41 of the Env protein (Env-A556T and Env-A539V, the identification of which are described in Abstract 540) confer DTG resistance. Using a green fluorescent protein reporter virus, viruses that fluoresced with viral gene expression, the replication kinetics of these Env mutants were quantified. The Env mutants demonstrated better cell-to-cell transmission than wild type in the absence and presence of DTG. On days of peak replication, greater geometric mean fluorescence intensity was observed in Env mutant-infected cells than in wild type, implying that not only were the Env mutants better at cell-to-cell transmission but that with each episode of cell-to-cell transmission there were more transmission events per cell. The researchers hypothesized that the enhanced cell-to-cell transmission of Env-A556T and Env-A539V mutants overcomes the DTG inhibition of cell-to-cell infection, thereby conferring DTG resistance. These findings provide insight into how Env mutations in the absence of target gene mutations may confer antiretroviral drug resistance and raises the possibility that Env mutations are a precursor to development of high-level drug resistance; however, the role of these Env mutations in vivo has not been examined.

**Capsid inhibitor RAMs.** Capsid inhibitors are a promising new class of antiretroviral drugs in development that have different mechanisms of action, including capsid assembly and disassembly and virion maturation. Newton and colleagues (Abstract 539) described an in vitro analysis of patient samples submitted for routine drug resistance testing and gag gene site-directed mutants (using previously described capsid assembly inhibitor [CAI] gag substitutions) to 2 maturation inhibitors that target the CA-SP1 cleavage site (bevirimat and PF46396), and 1 CAI inhibitor (PF74). Susceptibility of patient isolates to CA-SP1 cleavage site inhibitors varied more than 100-fold, and CAI inhibitor susceptibility varied less than 4-fold. Sixty-one percent of patient isolates had naturally occurring polymorphisms in the QVT motif in gag (amino acid positions 369–371), and these isolates exhibited less CA-SP1 cleavage site inhibitor susceptibility than those without these polymorphisms. One isolate had a polymorphism (N74N/D) that was previously associated with reduced CAI inhibitor susceptibility.

Site-directed mutants (SDMs) with single L56I, M66I, Q67H, N74D, and A105E substitutions had more than 200-fold reductions in CAI inhibitor susceptibility, and Q67H and N74D had only modest impacts. L56I, M66I, and Q67H conferred modest cross-resistance to CA-SP1 cleavage site inhibitors. SDMs conferring large reductions in PF74 susceptibility did so at an apparent cost to fitness, as these mutants had reduced replication capacity. The characterization of the effects of capsid-related sequence variations and on CAI susceptibility will help guide the development of these promising agents.

The resistance profile of the second-generation investigational HIV maturation inhibitor GSK2838232 was evaluated (Abstract 541). Two recombinant viruses, comprising gag and protease fragments of 2 protease-treated patients in a wild-type laboratory strain, were serially exposed to increasing concentrations of GSK2838232 to derive escape mutants whose gag and protease genes were fully sequenced. In all experiments an A364V substitution was observed. An SDM containing A364V was generated, demonstrating a high level of resistance to GSK2838232, as has been seen with other maturation inhibitors. The frequency of the A364V substitution was found in less than 0.1% of sequences in the Los Alamos National Laboratory HIV database. Investigators concluded that the resistance profile of GSK2838232 is consistent with previous maturation inhibitors and that preexisting resistance is expected to be low.

**Fostemsavir RAMs.** Fostemsavir is a produg of temsavir (TMR), an investigational HIV-1 attachment inhibitor being evaluated for use in highly treatment-experienced patients with limited treatment options. Saladini and colleagues characterized the env genotypic profile and phenotypic susceptibility to TMR among clinical isolates from patients with multidrug-resistant virus enrolled in the Italian PRESTIGIO registry (Abstract 548). Plasma samples from 24 patients were evaluated and in all but 1 sample, infectious pseudotyped viruses were generated. Three of 25 of these samples had TMR RAMs (1 with S375N and 2 with M426L). M426L showed variable reduction to TMR susceptibility. Entry inhibitor use (maraviroc, EFV) and viral tropism had no impact on TMR susceptibility.

**These findings provide insight into how Env mutations in the absence of target gene mutations may confer antiretroviral drug resistance and raises the possibility that Env mutations are a precursor to development of high-level drug resistance**
**InSTI drug resistance mutations (DRMs).** Shahid and colleagues identified integrase gene mutations associated with decreased susceptibility to newer InSTIs (BIC, DTG, CAB), a challenging endeavor given low rates of failure, slow in vitro selection, and the requirement for numerous mutations to confer resistance to these agents (Abstract 143). Investigators selected clinical samples from the British Columbia Centre for Excellence database with a single mutation at 1 of 27 amino acids that differed in prevalence between InSTI-treated and ART-naive individuals. All unique amino acid permutations at these positions were identified, and representative samples were used to make recombinant viruses. Phenotypic analysis of the recombinant viruses showed that mutations at G140, Q148, and R263 were associated with the greatest log-fold change to InSTIs; extensive cross-resistance was noted among DTG, BIC, and CAB, and between RAL and elvitegravir (EVG); accumulation of amino acid substitutions led to increased fold change; additional resistance mutations to baseline double mutants G140S plus Q148H exhibited log-fold-change increases; and 2 variants exhibited a 2-fold change for CAB but were still susceptible to DTG and BIC. Analysis was limited to subtype B virus and clinical correlations of these in vitro data are not yet available; however, this technique is an efficient way to evaluate clinically observed sequence variation and may lead to identification of emerging resistance to these newer agents.

In a study of clinical isolates from 19 patients experiencing virologic failure on an InSTI-based regimen, Sala-dini and colleagues (Abstract 549) identified major InSTI RAMs in all 19 patients (T66A, E92Q, E138K/T, G140A/C/S, Y143C/R, S147G, Q148H/R, N155H, R263K). Nine had previous exposure to RAL only, 4 to EVG only, 5 to RAL and DTG, and 1 to RAL and EVG. With in vitro susceptibility testing, DTG, BIC, and CAB mutants with a Q148R substitution plus 1 or 2 additional InSTI RAMs resulted in substantially decreased susceptibility to all 3 drugs, and comparable activity to all other mutants with major InSTI RAMs was maintained. Isolates with a 148 mutation and 2 or more additional InSTI RAMs had higher than 100-fold changes to DTG, BIC, and CAB. In one patient whose DTG-based regimen failed, the R263K mutation had a 3.5-fold change for DTG and CAB but only a 1.1-fold change for BIC. These findings suggest that the 148 pathway, which is initiated by RAL-associated failure, compromises second-generation InSTIs more than failure of EVG-containing regimens.

Susceptibility to BIC and DTG of clinical isolates obtained from heavily treatment-experienced patients whose InSTI-based regimens failed enrolled in the PRESTIGIO registry was presented (Abstract 550). All 17 patients had historical genotypic tests showing primary PI, nRTI, and NNRTI RAMs, and 14% had previous exposure to DTG twice daily; 27% were on DTG twice daily, and 50% were on RAL twice daily. The primary InSTI RAMs E138A/K, Y143C/H/R, Q148H, and N155 were found in 64% of samples and all exhibited resistance to RAL and EVG with phenotypic testing; 2 showed resistance to BIC and DTG. Fifty percent of isolates had G140S plus Q148H, which conferred intermediate resistance to DTG in all isolates and to BIC in all but 1 isolate. Of isolates, 55%, 50%, 36%, and 36% exhibited sensitivity to BIC, DTG, RAL, and EVG, respectively, with median fold changes of 3.1, 6.1, more than 164.0, and more than 188.0, respectively.

Smith and colleagues (Abstract 553) noted that data on the effectiveness of InSTIs for HIV-2 treatment are limited. To date there are no published case reports or clinical studies describing the use of BIC plus TAF plus FTC to treat these patients with HIV-2. With in vitro studies, HIV-1 and HIV-2 showed comparable sensitivity to BIC in a single cycle of infection (including group O isolates of HIV-1); BIC, DTG, and CAB were equally potent against HIV-1 and HIV-2; the Q148-pathway mutants of HIV-2 showed high resistance to BIC, and N155H mutants showed moderate resistance to BIC; and fold-change values for site-directed HIV-2 mutants were concordant with those reported for clinical isolates of HIV-2 from InSTI-treated patients. The investigators concluded that BIC has a similar potency for HIV-2 and HIV-1. They recommended a clinical trial in West Africa to evaluate BIC plus TAF plus FTC as initial treatment for people living with HIV in West Africa, including those with HIV-2 infection.

Further evaluation to assess the clinical significance of newly detected DRMs and the optimal use of deep sequencing in clinical settings is warranted.

**The 148 pathway, which is initiated by RAL-associated failure, compromises second-generation strand transfer integrase inhibitors more than failure of EVG-containing regimens**
absence of target integrase gene DRMs is warranted including correlation with phenotypic and in vivo analyses.

**Tenofovir RAMs.** Intracellular concentrations of tenofovir with TAF are 4-fold higher than with TDF Cox and colleagues (Abstract 546) hypothesized that the higher intracellular tenofovir levels with TAF could confer decreased resistance with the tenofovir-associated DRM K65R compared with TDF. In vitro studies of clinical isolates with K65R/N mutations in the presence or absence of M184V found that at pharmacologic concentrations of TAF, viral breakthrough was inhibited in 40 of 42 K65R mutants compared with 30 of 42 K65R mutants with pharmacologic levels of TDF. Standard resistance testing does not capture the effects of a 4-fold increase in TAF on intracellular tenofovir, and if further research confirms the clinical significance of these in vitro findings, changes to TAF genotype algorithms and phenotype assays should be indicated.

**Technologies to Detect DRMs**

** Archived genotype.** Daeumer and colleagues compared deep sequencing assays with cumulative historical genotypic testing results in a cohort of patients with viral suppression but with known triple-class resistant virus (Abstract 544). Among the 195 patients evaluated, correlation between deep sequencing and historical genotypic testing varied by individual mutation, ART drug class, and assay cutoff. Using deep sequencing and a sensitivity cut-off to detect mutations in 15% of the viral population, 45% of all historical DRMs, 55% of historical nRTI DRMs, 37% of historical NNRTI DRMs, 35% of historical PI DRMs, and 22% of historical InSTI DRMs were detected. With a cutoff of 1%, 60% of all historical DRMs, 68% of historical nRTI DRMs, 49% of historical NNRTI DRMs, 55% of historical PI DRMs, and 41% of historical InSTI DRMs were detected. At a 1% cutoff, the percent of newly detected DRMs was 11% overall and 42% for InSTI DRMs and at a cutoff of 1% to 15%, the proportion of newly detected DRMs was 20% overall and 44% for InSTI DRMs. Patient characteristics, including duration of viral suppression and ART regimen, did not correlate with deep sequencing detection of historical DRMs. This study provides more insight into the applicability of deep sequencing in clinical settings, but further evaluation to assess the clinical significance of newly detected DRMs and the optimal use of this test in clinical settings is warranted.

**Epidemiologic Studies of DRMs**

**National and regional epidemiologic studies.** Moyo and colleagues presented the drug resistance testing results from the 5th South African National HIV Prevalence, Incidence, Behaviour, and Communication Survey, which included collection of dried blood spot samples through which HIV antibody, viral load, ART drug levels, and drug resistance testing were performed (Abstract 152). Of 24,000 individuals surveyed, 2294 tested positive for HIV, 1107 were not virally suppressed, 697 had successful drug resistance testing, and 200 had DRMs; 27% had any DRM, 19% had NNRTI DRMs, 8% had NNRTI and nRTI DRMs, and 0.5% had PI, NNRTI, and nRTI DRMs. Among individuals with ART drug–positive versus ART drug–negative samples, 56% and 23% had any DRM, 14% and 20% NNRTI DRMs only, and 41% and 2% had NNRTI and nRTI DRMs, respectively. Rates of DRMs were highest among individuals who reported taking ART medications but had negative samples (identified as “defaulters” in this study), with any DRM, NNRTI only, and NNRTI and nRTI at 76%, 56%, and 14%, respectively. For individuals reporting never taking ART medications with negative samples (assumed to be ART naive) rates were lowest, at 15% with any DRM, 15% with NNRTI DRMs only, and 0% with NNRTI and nRTI DRMs. The researchers recommend ongoing monitoring of DRMs, stronger adherence support for “defaulters,” strengthening of initial ART regimens in South Africa to include InSTIs, and early switching of patients whose ART regimens are failing to alternative regimens.

The impact of social determinants of health on ART adherence, resistance, and HIV clinical outcomes in the United States was evaluated using publicly available data-bases, measuring the average proportion of days covered of all patients per state in the Symphony Health Solutions claims database, and determining rates of resistance using isolates submitted to Monogram Biosciences for routine clinical testing (Abstract 907). HIV prevalence was highest in the southern and northeast states. Mean proportion of days covered was 73%, with at least 40% of patients demonstrating poor adherence to ART in a majority of states and clustering of poor adherence in the southern states. Across all states, 20% to 54% of isolates tested showed HIV-1 drug resistance. States with higher prevalence of poor ART adherence had higher HIV-1 prevalence and HIV-1 mortality rates. States with higher rates of resistance had higher prevalence of HIV-1 infections. Lower education level, poverty, unemployment, female sex, and nonwhite race were associated with poor ART adherence. Lower education level, unemployment, and non-white race were associated with higher prevalence of poor or suboptimal ART adherence. The regional variation and correlations among social determinants of health, adherence, resistance, and HIV-related outcomes should inform targeting of resources and interventions to promote adherence and prevent resistance.
Clinical isolates from Italy from 2007 to 2017 were evaluated to identify trends in InSTI resistance over time (Abstract 535). Investigators evaluated 3004 isolates from 2598 patients. The prevalence of at least 1 InSTI major resistance mutation decreased from 14% in 2007 to 5% in 2017, and the proportion of isolates with full susceptibility to RAL, EVG, DTG, and BIC all increased during that time (83%-94%, 83%-94%, 94%-98%, and 94%-98%, respectively). Decreases in rates of InSTI resistance and increases in rates of full susceptibility of InSTIs were also seen on isolates from patients on 1 InSTI plus at least 2 ART drugs from other classes and from patients on 1 InSTI and 2 nRTIs. Among InSTI-naive patients, there was no statistically significant change in rates of InSTI resistance; prevalence remained low at 0% from 2007 to 2008 and 0.6% in 2015 to 2017, and susceptibility to all InSTIs remained high (98.0%-99.7%). Among patients on 1 InSTI and another ART drug from a different class (dual therapy), rates of resistance to any InSTI and susceptibility to RAL and EVG remained stable, and rates of susceptibility to DTG and BIC decreased (from 96% to 85%). Overall prevalence of InSTI major resistance mutations was stable aside from Q148R, which decreased from 10.2% (in 2007-2008) to 1.4% (in 2015-2017). The researchers concluded that decreasing rates of InSTI resistance reflect the introduction of more potent InSTI agents (DTG and BIC) along with good clinical practice.

**Pretreatment drug resistance (PDR): public health surveillance.** Avila-Rios presented surveillance data on PDR from the Condesa Clinic, where approximately 70% of all new cases of HIV in Mexico City are diagnosed each year (Abstract 876). Next-generation sequencing was conducted for 2447 individuals initiating ART and diagnosed in the Condesa clinic between September 2016 and June 2018. Prevalence of DRMs to any drug, NNRTI, nRTI, PI, and InSTI were 14.8%, 9.6%, 4.5%, 1.7%, and 0.8%, respectively, with K103N the most frequent DRM identified. Genetic network analysis identified 99 clusters consisting of 2 to 20 individuals, and clustering individuals were more likely to be younger (aOR per year, 0.96), were more likely to be men (aOR, 2.3), and were less likely to reside outside of the central metropolitan area (aOR, 0.11). Among clustering individuals, 18% shared DRMs, with K103N the most commonly shared DRM. Persons sharing DRMs were most likely to be younger (aOR per year, 0.97) and were more frequently observed after 2016 (2017 aOR, 1.7; 2018 aOR, 2.0). A growth of DRM networks was observed over time, with the number of clusters of people sharing DRMs increasing from 5 to 46 to 66 in 2016, 2017, and 2018, respectively. To address the increasing prevalence of PDR and the growth of DRM networks, plans are underway to begin molecular surveillance nearly in real time, routine collection of sociodemographic and behavioral information for all persons being tested for HIV, and alliances with nongovernmental organizations to deliver focused prevention interventions.

**Prevalence of PDR.** McClung and colleagues presented US surveillance data for PDR in people diagnosed with HIV from 2013 to 2016 (Abstract 526). From 36,288 cases in 23 US jurisdictions, 40,083 sequences were analyzed. Of 15,345 patients aged 13 years or older diagnosed with HIV between 2013 and 2017 and reported to the New York State HIV registry (n= 15,345) (Abstract 528). Of 15,345 persons included, 59% had any resistance testing within 3 months of diagnosis, 57% had PR/RT resistance testing, 21% had initial InSTI resistance testing, and 2.5% had only InSTI testing. Resistance to 1 or more InSTI was seen in 0.7% of patients with initial InSTI testing and was the most common. Clinically significant InSTI mutations included T66A/I, E92Q, E138K/A, G140S, Y143C/R, Q148H, and N155H. The Q148H mutation was seen in 4 newly diagnosed individuals. Investigators concluded that clinicians should ensure timely ordering of resistance testing (<3 months after HIV diagnosis per clinical guidelines) and that InSTI genotypic testing should not be ordered without PR/RT genotyping. They also suggested that the observation of Q148H in 4 newly diagnosed patients suggests InSTI resistance is emerging and that InSTI testing should now be ordered in addition to PR/RT genotyping in patients newly diagnosed with HIV infection. The frequency of InSTI PDRMs is low and baseline InSTI resistance testing is not consistent with current IAS-USA guidelines, but the recommendation may change if more resistance emerges with widespread InSTI use.

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previously reported as 1.0% to 4.7%. HIV sequence data were obtained from 3 parent studies (2015-2017) of ART-native cisgender men who have sex with men (n=352) and transgender women (n=144) in Lima, Peru, and consensus gene sequences of part of the HIV pol region were evaluated for DRMs (Abstract 529). Of isolates, 16.8% had any DRM (15% had 1 DRM, and 1.7% had 2 DRMs). The most frequent RAMs conferring high-level NNRTI resistance were K103N/S (7.4% of all isolates) followed by G190A/E (1.1%); 0.8% of isolates had the M184V RAM, and 1.1% had thymidine analogue mutations. Initial ART regimens in Peru are typically EFV plus 2 nRTIs; 15% of isolates showed EFV resistance (9% median-to-high resistance), 1% showed ABC resistance, and 0.9% showed FTC/3TC resistance (all with high resistance). Rates of PDR did not differ based on gender identity. Given these rates and patterns of increasing PDR, the authors recommended urgent adoption of national surveillance for PDR, change in policy to incorporate baseline ART testing, and inclusion of InSTIs in recommended initial ART.

PDR was evaluated for patients who enrolled in the MaxART trial (MaxART: Early Access to ART for All in Swaziland), launched in 2014, through which ART was offered to all people living with HIV in the Hhohho region of Swaziland, regardless of CD4+ cell count and WHO clinical disease stage (Abstract 537). HIV sequences were generated for 2578 available samples; 11% had intermediate- or high-level resistance to EFV/nevirapine (NVP), the initial ART regimen offered to all participants per national guidelines at the time of the study. The prevalence of resistance to any antiretroviral drug was 24%. Dual-class resistance to nRTI and NNRTI was rare at 0.5%. EFV/NVP resistance was associated with female sex (aOR, 1.37) and younger age at initiation of treatment (aOR, 0.961 per 1-year increment). E138A, an HIV-1 subtype C polymorphism associated with RPV resistance, was detected in 13% of sequences and accounted for more than 50% of predicted resistance to NNRTIs. K103N was the next most commonly observed DRM at 7%, and minimal PI and nRTI DRMs were identified (<1%). These high rates of PDR to EFV support Swaziland’s shift to the use of InSTIs in recommended initial ART regimens and public health surveillance of PDR.

The prevalence of PDR and its impact on treatment outcomes was assessed among patients initiating initial ART containing EFV in the ITREMA (Intensified Treatment Monitoring Strategy to Prevent Accumulation of Drug Resistance) trial in rural South Africa. The majority of patients were women (60%) and were started on a regimen of EFV/TDF/FTC (96%); 6% reported prior ART (Abstract 527). Among patients with successful sequencing (n=194), 12% had PDR, 9% of patients without evidence of prior ART had PDR, and 20% of patients with previously undisclosed ART who were found to have EFV exposure had PDR. PDR was associated with poor clinical outcomes, including an HIV RNA level above 1000 copies/mL within 48 weeks, confirmed virologic failure within 48 weeks, and loss to follow-up within 24 weeks of ART initiation.

Prevalence of drug resistance among ART-experienced individuals. The Ministry of Health of Brazil offers genotypic testing to all individuals on an InSTI-based regimen experiencing virologic failure. To characterize InSTI resistance patterns in Brazil, Veras and colleagues evaluated 1467 integrase sequences among ART-experienced patients from 2012 to 2018 in the National System for Genotyping Control (Abstract 533). Rates of InSTI resistance decreased from a peak of 67% resistance to RAL and 5% to DTG in 2013 to 13.7% and 0.8%, respectively, in 2018; there were no DTG-resistant isolates from individuals on DTG for initial ART. There were no demographic, clinical, or regional variations in prevalence of resistance. G140 (7%) and E138 (1%) were the most frequent InSTI RAMs identified, and subtype B (70%) was the most common subtype followed by C (14%), F (9%), and recombinant (7%) subtypes. No national or InSTI RAM transmission clusters were identified.

In the HPTN (HIV Prevention Trials Network) 074 study conducted in Indonesia, Ukraine, and Vietnam, enhanced support for medication-assisted treatment of substance use disorder and ART adherence for people with HIV (with HIV RNA levels ≤1,000 copies/mL) and active injection drug use were associated with decreased mortality and increased viral suppression. HIV-seropositive index participants were asked to recruit HIV-seronegative participants. Zhang and colleagues evaluated baseline HIV drug resistance and ART use among the HIV-seropositive participants (Abstract 534). Among 502 index participants, genotypic test results were obtained for 89% (n=449). Resistance to any ART drug class was detected in 12%, of whom 54% had multiclass resistance, with the most common DRMs identified being K103N and M184V. Of the 449 patients who had geno-type results available, ART drugs were detected in 51 (11%) patients, 73% of whom had 1 NNRTI drug plus 1 or 2 NRTI drugs detected, 20% had an nRTI drug detected alone, and 4% (2 patients) had a boosted PI drug with 1 or 2 nRTI drugs detected. Of participants, 61% had the CRF01_AE HIV subtype, 36% had the A1 subtype, 2% had unique recombinant forms, and 0.7% had the B subtype. Drug resistance was more frequent among individuals with detectable ART drug levels (59% vs 6%), in Indonesia (24%) compared with Ukraine (2.4%) or Vietnam (13%), and among those who reported a history of incarceration (43% vs 11%). These high rates of DRMs and multiclass DRMs highlight the need for enhanced adherence support and use of potent ART drugs with a high genetic barrier to resistance.

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among people with HIV who inject drugs.

In the DAWNING study, an open-label, multinational (58 sites in Latin America, South America, Asia, Eastern Europe, and Africa), multicenter, noninferiority, randomized, phase IIIb trial, patients whose initial ART with an NNRTI plus 2 nRTIs failed who were then randomly assigned to DTG plus 2 nRTIs had superior virologic outcomes to those who were randomly assigned to LPV/r plus 2 nRTIs (84% vs 70% with HIV RNA levels <50 copies/mL at 48 months before switching from an initial to a second-line regimen, but for hospitalized patients a faster switch may be indicated. Among the 305 patients enrolled, more than 70% were on a regimen of EFV/TDF/3TC, the majority were women (54% in Kenya and 69% in DRC), and median time on ART was more than 4 years. Rates of viral and immunologic suppression differed between sites (HIV RNA level ≥1000 copies/mL among 37% in Kenya and 71% in DRC; CD4+ cell count <100/µL among 68% in Kenya and 82% in DRC). Adherence, measured by TDF levels, was suboptimal in 56% of patients in Kenya and 47% in DRC. Among patients with HIV RNA levels of 1000 copies/mL or higher, more than 70% experienced treatment failure (dual-class, intermediate- or high-level-resistance). Of patients with HIV RNA levels of 1000 copies/mL or higher and CD4+ cell counts below 100/µL, 74% in Kenya and 85% in DRC experienced treatment failure. Of sequences, 84%, 86%, 71%, and 40% had intermediate- or high-level resistance to EFV, NVP, 3TC, and TDF, respectively (median regimen-specific genotypic sensitivity score, which assesses the number of active drugs in a regimen based on genotype, was very low at 0.5). Investigators concluded that hospitalized patients on initial ART longer than 6 months with CD4+ cell counts below 350/µL and HIV RNA levels of 1000 copies/mL or higher should be rapidly changed to a second-line regimen, given these high rates of treatment failure.

In a post hoc analysis (Abstract 144), DTG plus 2 nRTIs remained superior to LPV/r plus 2 nRTIs, in the presence of M184VI, even when 3TC or FTC were part of the regimen (85% vs 72%). These results support updated WHO interim guidelines for the inclusion of DTG plus 2 nRTIs as a second-line treatment option for patients whose initial NNRTI- or PI-based regimen failed.

Strategies to identify drug resistance in ART-experienced patients in low- or middle-income countries. Bosward and colleagues (Abstract 151) evaluated rates of DRMs among ART-experienced, hospitalized patients in 2 hospitals in sub-Saharan Africa: one in Kenya and one in the Democratic Republic of Congo (DRC). Per the WHO guidelines treatment failure algorithm, a patient should have 2 consecutive high viral load test results within 3 weeks.10 In a post hoc analysis (Abstract 144), DTG plus 2 nRTIs remained superior to LPV/r plus 2 nRTIs, in the presence of M184VI, even when 3TC or FTC were part of the regimen (85% vs 72%). These results support updated WHO interim guidelines for the inclusion of DTG plus 2 nRTIs as a second-line treatment option for patients whose initial NNRTI- or PI-based regimen failed.

Selected Issues in Maternal and Pediatric Health

The prevalence of maternal HIV/hepatitis B virus (HBV) coinfection and its impact on HIV mother-to-child transmission (MTCT) and maternal and infant clinical outcomes was evaluated by Bhattacharya and colleagues (Abstract 41). Post hoc analysis was performed on maternal-infant pair data and retrospective laboratory testing of maternal samples from HPTN 046, a randomized controlled clinical trial of HIV MTCT in sub-Saharan Africa. Of 2016 women with HIV infection included in the analysis (22% of whom were on ART), 88 (4.3%) were determined to have HBV coinfection (defined as having a positive HB surface antigen). Compared with women with HIV monoinfection, women with HIV/HBV coinfection with high HBV viremia (defined as having an HBV DNA level greater or equal to 106 IU/mL) had lower median CD4+ cell counts at baseline. High maternal HBV viremia was also associated with low birth weight and 6.75 times (95% CI, 1.86–24.50) higher risk of infant HIV infection. The research team did not find any impact of HIV/HBV coinfection on infant mortality or maternal outcomes (ie, maternal premature rupture of membranes and episiotomies) at 18 months. One limitation of this study was the lack of available HIV viral load data. The mechanism by which HBV viremia led to higher risk of HIV MTCT remains unclear.

Ntozini and colleagues conducted a community-based 2x2 factorial cluster randomized trial, known as the SHINE (Sanitation, Hygiene, Infant Nutrition Efficacy) Project, to determine whether 2 nutrition and sanitation interventions
for studies with longer follow-up to assess whether these small differences in early childhood development lead to sustained, meaningful developmental differences in later ages (Abstract 784). Early ART in children in the first year of life is associated with improved clinical and virologic outcomes and with decreased HIV reservoir size, but there are limited data on the impact of early ART in neonates.

Tagarro and colleagues evaluated whether rapid initiation of ART within 7 days (early) versus 7 to 28 days of life (delayed) in HIV-infected neonates had any long-term clinical, virologic, and immunologic effects later in life (Abstract 44). A total of 44 infants with perinatally acquired HIV infection from 4 different cohorts were included in the analysis. The infants were included if they were 28 days of age or younger at the initiation of ART, had no ART interruptions with the first 2 years, and had at least 2 HIV viral load test results during the follow-up period. Infants who were started on triple ART as MTCT and transitioned to ART within 15 days were also included.

Primary clinical endpoints were mortality and progression to AIDS, and primary virologic outcomes included time to viral suppression, time to virologic failure, and proportion of time suppressed. Viral suppression was defined as having at least 2 consecutive HIV RNA levels below 50 copies/mL, and virologic failure was defined as having at least 2 HIV RNA levels of 400 copies/mL or higher. A viral blip was defined as having an HIV RNA level between 50 and 400 copies/mL once followed by viral suppression. Time-to-event analysis using Kaplan Meier curves and flexible spine models was performed. The median follow-up period for the children was 11.5 years. At baseline, there were differences in ART regimens in those treated within 7 days and those treated at 7 to 28 days, and higher viral loads were observed in children who received early treatment.

Time to viral suppression was statistically significantly lower in those treated early, with probability of suppression decreased by 35% for each week the initiation of ART was delayed, after adjustments for ART regimen and baseline viral load at time of initiation. A linear association between age at time of ART initiation and viral suppression was observed. There were no statistically significant differences between early versus delayed ART in other long-term primary endpoints, including progression to AIDS, time to virologic failure, or proportion of time suppressed, as well as in other outcomes (eg, changes to ART regimen or time to immunologic recovery).

**Interactions Between Hormone-Based Contraception and ART in Women With HIV Infection**

Levonorgestrel and nonhormonal copper intrauterine devices (IUDs) are effective, long acting, and reversible contraception approaches that are underutilized by women with HIV infection, especially in LMICs with high HIV prevalence. There are limited safety data for use of IUDs in women with HIV infection. The impact of progestin on HIV viral shedding in the genital tract, used as a proxy marker for HIV transmission risk, remains unclear.

Todd and colleagues presented results from the first randomized, double-blind trial, among 199 South African women with HIV infection aged 18 to 40 years, comparing genital and plasma HIV viral load levels as well as acceptability in women using levonorgestrel IUD (LNG IUD) and those using a nonhormonal copper IUD (C-IUD) (Abstract 50). The analyses were stratified by ART status on entry into the study (those on ART and those not yet initiated on ART). The authors found no statistically significant increase in genital tract HIV viral load shedding and no statistically significant difference in detectable plasma HIV viral loads between the 2 IUD arms, with no differences noted when stratified by ART use. Of the 34 serious adverse events noted, 18% were related to IUD use.

Overall, continued use of IUDs over 24 months was 76%, with expulsions and discontinuations higher in the C-IUD group. Discontinuations of IUDs were mainly due to adverse effects including heavy bleeding, pain, and
dysmenorrhea. The authors concluded that compared with nonhormonal C-IUDs, LNG IUDs do not significantly alter genital tract and plasma HIV viral load levels and that LNG IUDs are a safe and acceptable contraceptive option for women with HIV infection.

Previous research highlighted a concern for drug-drug interactions between EFV and hormone-based contraception, with 1 study showing 45% to 57% lower exposure to LNG in women with HIV infection on EFV-based ART who received standard-dose of LNG subdermal implants, resulting in suboptimal contraception protection and unintended pregnancies.

Scarsi and colleagues explored, in an open-label pharmacokinetic study, whether doubling the dose of LNG (from the standard dose of 150 mg to 300 mg) in subdermal implants would overcome the drug-drug interaction and provide effective contraception in women on EFV-based ART (Abstract 51). The investigators compared the drug plasma concentrations, computed as geometric mean ratios, over numerous visits spanning 48 weeks of 28 Ugandan women receiving EFV-based ART and double-dose LNG implants (along with C-IUDs as backup contraception) and 17 ART-naive historical controls receiving standard-dose LNG implants. Over 48 weeks, in women on EFV-based ART receiving LNG 300 mg implants, LNG concentrations were 33% to 44% lower than in the historical controls receiving standard-dose LNG. A statistically significantly lower proportion of women (46% vs 90%; P < .05) receiving EFV-based ART and LNG 300 mg had a level of LNG of 303 pg/mL or below (identified in prior research as a threshold at which unintended pregnancies occurred), compared with the historical controls receiving standard-dose LNG.

The investigators cautioned about the effectiveness of double-dose LNG implants as contraception in women receiving EFV-based ART, as doubling the dose of LNG still yielded suboptimal LNG levels because of the drug-drug interactions between LNG and EFV. They suggested further research into the pharmacogenetics and variability of LNG levels within individuals.

Haas and colleagues explored the role of pharmacogenetics in explaining the adverse drug-drug interactions between ART and exogenous hormones administered via vaginal rings in the ACTG (AIDS Clinical Trials Group) A5316 study (Abstract 52). ACTG A5316 is a multicenter, multi-country study that enrolled 72 women with HIV infection aged 16 years or older in one of 5 groups: those not yet on ART (designated as the control arm), those receiving EFV-based ART, or those receiving ritonavir-boosted atazanavir (ATV/r)-based ART. On the first day of the study, the women underwent insertion of a vaginal ring releasing etonogestrel (ENG)/ethinyl estradiol (EE) (120/15 mcg daily) over 21 days. Intensive, 8-hour pharmacokinetic sampling was performed for EFV and ATV/r drug levels on days 1 and 21, as was testing for ENG/EE plasma levels on days 7, 14, and 21.

The investigators also genotyped 17 targeted single nucleotide polymorphisms (SNPs), including SNPs that define cytochrome P450 (CYP)2B6 metabolizing genotypes as normal, intermediate, and slow (for EFV), UGT1A1 (for ATV), CYP3A4/5, CYP1A1/2, and other estrogen trait-associated SNPs (for ENG and EE). Compared with the control arm, EFV lowered median ENG concentrations at day 21 by 73%, 77%, and at least 93% in those with CYP2B6 normal, intermediate, and slow metabolizing genotypes, respectively. Similarly, EFV lowered median day 21 EE concentrations by 41% in CYP2B6 normal and intermediate metabolizers, and by 75% in CYP2B6 slow metabolizers. No association was found between the other SNPs and EE/ENG levels in the ATV/r-based ART and control arms.

The investigators concluded that the CYP2B6 slow metabolizer genotype exacerbates the adverse pharmacokinetic interaction of EFV with both ENG and EE, with the purported mechanism being the enhanced induction of CYP that is mediated by exposure to higher levels of EFV. They also suggested that the interaction between EFV and hormones can be lessened, although not completely overcome, by adjusting EFV dosing in individuals based on their CYP2B6 metabolizing genotype.

**Issues in ART and Reproduction**

In the Symposium on ART and Reproduction, the speakers provided updates on ART use in women of reproductive potential and the potential impact of ART drugs on maternal health and pregnancy outcomes, including birth defects. Mofenson underscored that although there are currently 32 ART drugs approved for HIV treatment in adults, there are limited data on the safety of these drugs for clinical use in pregnancy; most have received regulatory approval with only animal data available to assess potential adverse drug effects on the fetus (Abstract 59).

She also discussed the difficulty of accurately determining associations between drug exposures and outcomes with low incidence rates such as birth defects. She stressed that research on fetal effects associated with ART drugs should differentiate between the first trimester of pregnancy and the preconception period, as the exposure to a drug in the latter period would be crucial to assess. She described various caveats to the current data on birth defects associated with ART drugs. These data are often collected after regulatory approval of the drugs, and timing of drug exposure in relation to conception is often difficult to ascertain from cases reported to pharmacovigilance registries. Mofenson emphasized the importance of active, prospective surveillance of birth outcomes as new ART drugs are introduced into the market and the need to weigh considerations for both the mother and the child, balancing the risks of adverse effects to the fetus with the benefits to the mother.
Gandhi reviewed HIV treatment options for women of reproductive potential and pregnant women in high-income countries in (Abstract 60). She summarized current ART guidelines for women of reproductive potential who desire pregnancy, as well as for pregnant women. She discussed the pharmacokinetic issues of ART drugs during pregnancy: changes in absorption, distribution, metabolism, and elimination of drugs, as well as safety, tolerability, and efficacy considerations for different ART regimens. Gandhi also discussed PrEP considerations in women, emphasizing that TDF/FTC is generally safe for use in pregnant women as HIV PrEP, and briefly summarized drug-drug interactions between contraceptives and ART. She concluded that it is ethical and imperative to increase representation of women of reproductive potential and pregnant women in HIV clinical research.

Mukui gave an overview of the public health policy and programmatic considerations for ART implementation in women of reproductive potential in LMICs, with some examples from Kenya (Abstract 61). She highlighted key issues that should be addressed, such as concerns for safety and efficacy of ART drugs in women of reproductive age, expanding access to comprehensive family planning services that include contraception, improving in-country pharmacovigilance and surveillance systems for adverse drug effects affecting maternal and fetal outcomes, and balancing an individualized approach to health care, with specific understanding of a woman’s reproductive and other health desires and choices, with a broader public health approach to program implementation.

Lyerly reiterated the substantial evidence gaps in HIV research resulting from underrepresentation of women in studies, including women who become pregnant while on ART (Abstract 62). She discussed the implications, such as gaps in knowledge about dosing of drugs, safety to the fetus, and maternal and neonatal health outcomes. She highlighted the challenges that may hinder research in women of reproductive potential, including legal and regulatory issues, myths and misunderstandings about what research is permissible within a regulatory environment, a “protectionist” culture with women being perceived as “vulnerable,” insufficient training and experience in conducting research in this population, and misallocated research funding that is more focused on child health outcomes than on the women themselves.

Sex Differences in Safety of ART and in HIV Treatment Outcomes
In a Themed Poster Discussion, studies exploring whether there are differences in ART outcomes, drug exposure, and safety by biologic sex in individuals with HIV infection were presented. Godfrey and colleagues analyzed data from ACTG A5288, an open-label intervention trial in individuals with HIV infection in LMICs whose second-line ART failed (Abstract 518). Women were less likely to have viral suppression at week 48 and more likely to experience failure of third-line ART with a boosted PI (with emergence of resistance) and to experience grade 3 or 4 signs and symptoms than men. The investigators stressed the importance of further research into ART drug exposure and tolerability in women in HIV infection in LMICs.

Differences in immune activation patterns by sex in individuals with HIV infection on ART who are virally suppressed in the observational AFRICOS Study (African Cohort Study) were noted by Son and colleagues (Abstract 517). Significantly higher levels of specific immune activation markers, such as interferon-γ-induced protein 10 and soluble CD25, were observed in women with HIV infection than in men, although these differences by sex were not seen in HIV-negative individuals.

In vaccines and other antiviral treatments, women were similar to those observed in men. A nested case-control study of drug resistance that emerged during breastfeeding among mother-infant pairs enrolled in the PROMISE (Promoting Maternal and Infant Survival Everywhere) trial included 48 transmitting mothers and their HIV-infected infants (in utero or peripartum infections, 37 infections acquired during breastfeeding, and 254 controls who were nontransmitting mothers matched by delivery date and clinical site (Abstract 769). Drug resistance was more prevalent among women who transmitted through breastfeeding (50%) than with in utero or peripartum transmission (4%). In logistic regression, risk of MTCT was associated with higher viral load and no antepartum triple-drug ART regimen, but maternal DRMs were not. DRMs were more likely in infants infected through breastfeeding (54%) than in utero or peripartum (13%). Among infants with longitudinal genotypic data (n = 46), 8 infants with wild-type virus at birth developed DRMs in utero compared with 1 in the breastfeeding cohort. Investigators concluded that drug resistance does not appear to be the driver of MTCT, but with accumulation of DRMs during infancy, exploration of alternate treatment regimens for mothers and infants is warranted.

INSTIs and Birth Defects
The observational TSEPAMO study in Botswana previously reported preliminary results of neural tube birth defects in 4 of 596 (0.67%; 95% CI, 0.26%–1.7%) infants of women receiving DDI-containing ART and 14 of 11,300 (0.12%;
95% CI, 0.07%-0.21%) infants of women receiving non–DTG-containing ART preconception.14,15 Following these results, the WHO, US FDA, and other international regulatory agencies in 2018 issued alerts on a possible increased risk of neural tube defects in infants born to women with HIV infection receiving DTG as part of their ART at the time of conception.16-17 Several posters examining associations between InSTIs, including DTG, and neural tube defects were presented. Barlow-Mosha and colleagues analyzed 69,767 births from a hospital-based birth defect surveillance program from 4 hospitals in Kampala, Uganda, and found that neural tube defects (prevalence, 8.9/10,000 births; 6.8–11.4) were a common congenital malformation affecting births (Abstract 743). No statistically significant difference in the prevalence of neural tube defects was seen by HIV serostatus of the mother. With 9.6% of the infants delivered by women with HIV infection and 80% of women with HIV infection receiving EFV-based ART, 16% NVP-based ART, 0.02% InSTI-based ART, and 3.7% other ART regimens, the investigators did not find an association between ART regimen and increased risk for neural tube defects.

Sibiude and colleagues evaluated data from 808 HIV-infected mother-infant pairs exposed to InSTIs in the multicenter French Perinatal Cohort study, and data from 7318 matched unexposed pairs (Abstract 744). Exposure to InSTIs was categorized in one of 3 groups: 1) ongoing at conception; 2) initiated during pregnancy as initial ART, and 3) initiated during pregnancy as second-line ART. Among 501 infants exposed to InSTIs at conception (218 to RAL, 41 to DTG, and 42 to EVG), a birth defect rate of 5.5% was observed, which was not significantly different from the rates seen in infants with exposure when InSTIs were initiated during therapy as initial ART (2.7%; 5/183) or as second-line ART (2.7%; 9/524). No neural tube defects were found among infants exposed to InSTIs at conception; birth defects were noted in only 2 infants exposed to DTG. Compared with the rate among matched infants who were not exposed to InSTIs, the birth defect rate among infants exposed to InSTIs at conception did not differ significantly (5.7% of exposed vs 2.9% of unexposed).

Cumulative pregnancy outcome data from women with HIV infection receiving RAL through May 2018 were analyzed from 3 sources: a Merck safety database and 2 pregnancy outcome cohorts (National Surveillance of HIV in Pregnancy and Childhood and the French Perinatal Cohort) (Abstract 745). The reports of pregnancy outcome were categorized as prospective if RAL exposure was reported before there was knowledge of the pregnancy outcome, and as retrospective if RAL exposure was reported after pregnancy outcome was known. Among 1991 prospective reports of RAL exposure in pregnancy (55% were during the first trimester, with 66% of these exposures occurring during the periconception period, defined as within 28 days of conception), there were no cases of neural tube defects reported. Among 435 retrospective reports, a total of 4 cases of neural tube defects (1 case of anencephaly, 1 case of encephalocoele, and 2 cases of myelomeningocele) were reported; however, only 1 case of myelomeningocele was reported among live births following exposure to RAL during the periconception period. The investigators concluded that the data do not support an association between neural tube defects and exposure to RAL during the periconception period.

Hill and colleagues analyzed 4 pharmacovigilance databases for reports of neural tube defects associated with 4 InSTIs (DTG, RAL, EVG, BIC), 2 PIs (darunavir, atazanavir) and 2 NNRTIs (NVP, EFV) through August 2018 (Abstract 746). Neural tube defects were reported for all drugs except BIC. Seven cases of neural tube defects were reported for DTG in the WHO VigiAccess database and 6 cases were reported in the US FDA Adverse Event Reporting System database, whereas no cases were reported in the European EudraVigilance and UK Medicines Health Regulatory Authority databases. Investigators cautioned about the limitations of using pharmacovigilance databases to ascertain associations between neural tube defects and specific drug exposures, because of the inability to obtain accurate denominator data. Reporting of adverse drug reactions is not systematic, there is often overlap for reporting of drugs for the same patient because of ART consisting of several drugs leading to duplications, and timing of drug exposure relative to conception in the reports is frequently uncertain.

Serum folate concentrations were measured in 486 women with HIV infection randomly assigned to initiate treatment with DTG- or EFV-containing ART in the ongoing South African ADVANCE trial, to determine whether ART regimen affects folate levels, which could contribute to risk of neural tube defects (Abstract 749). Women on EFV-based ART had declines in mean serum folate concentrations over 24 months, and pregnant women treated with EFV-containing ART had lower mean folate concentrations than women treated with DTG-containing ART. Birth outcomes were also analyzed, with 16 live births, 1 infant death, 1 spontaneous abortion, and 2 congenital abnormalities (naevus flammeus and umbilical hernia); 19 elective abortions have been reported to date.

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Additional References Cited in Text


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