Volume **29** Issue **2** April/May **2021**

Topics in Antiviral Medicine™

A publication of the IAS–USA

Selected Highlights of the 2021 *virtual* Conference on Retroviruses and Opportunistic Infections (Part I) CME

Topics in Antiviral Medicine™

Topics in Antiviral Medicine™

Topics in Antiviral Medicine™ (formerly *Topics in HIV Medicine*) is published by the International Antiviral Society–USA (IAS–USA). This journal is intended to be a resource for practitioners and scientists who are actively involved in medical care and research in HIV and other viral infections.

About This Issue

This issue of *Topics in Antiviral Medicine (TAM)*™ features part I of highlights of the 2021 *virtual* Conference on Retroviruses and Opportunistic Infections (*v*CROI). The best and most consequential original research defined the science at *v*CROI 2021, which included research in HIV, hepatitis viruses, SARS-CoV-2, and other viral infections and their related conditions. Highlights from *v*CROI 2021 on antiviral drugs and therapy, basic science, and liver complications will be featured in the next issue of *TAM*.

Editorial Policy

The views and opinions expressed in this journal are those of the contributors and do not necessarily reflect the views or recommendations of the IAS–USA. *Topics in Antiviral Medicine*™ is supported through grants from several commercial companies that are committed to supporting continuing medical education on HIV, hepatitis C virus, and other viral infections. In the interest of an objective, balanced, and scientifically rigorous publication, the IAS–USA seeks funding that is pooled from companies with competing products; these companies have no input or control over the journal content or the selection of contributors.

This journal may contain information about the investigational uses of drugs or products that are not approved by the US Food and Drug Administration. Please consult full prescribing information before using any medication or product mentioned in *Topics in Antiviral Medicine*™.

Subscription Information

Topics in Antiviral Medicine™ is published 4 to 6 times a year. To obtain a subscription or notify the IAS–USA of a change in your email address, please create or update your user profile at www.iasusa.org.

Correspondence

Topics in Antiviral Medicine welcomes editorial correspondence. Address correspondence to:

Editor, *Topics in Antiviral Medicine*

Email: journal@iasusa.org
Mail: IAS–USA
131 Steuart St, Ste 500
San Francisco, CA 94105

Phone: (415) 544-9400

Website: www.iasusa.org

On the Web

Current and previous issues of *Topics in Antiviral Medicine*™ (as well as *Topics in HIV Medicine*) are available online at www.iasusa.org.

ISSN 2161-5853 (Online)

Grant Support

This activity is part of the IAS–USA national educational effort that is funded, in part, by charitable contributions from ineligible companies. Per IAS–USA policy, any effort that uses grants from ineligible companies must receive grants from several companies with competing products. Funds are pooled and distributed to activities at the sole discretion of the IAS–USA. Grantors have no input into any activity, including its content, development, or selection of topics or speakers. Generous support for this activity has been received from the following contributors.

PLATINUM SUPPORTERS
Gilead Sciences, Inc.
Merck & Co., Inc.
ViiV Healthcare

SILVER SUPPORTERS
Janssen Therapeutics

BRONZE SUPPORTERS
Theratechnologies Inc.

IAS–USA
International Antiviral Society–USA

Volume 29 Issue 2 April/May 2021

Topics in Antiviral Medicine™

A publication of the IAS–USA

Selected Highlights of the 2021 *virtual* Conference on Retroviruses and Opportunistic Infections (Part I) CME

Announcements

POST TEST Visit www.iasusa.org/activites/topics-in-antiviral-medicine or use the QR code in this issue to access the online posttest.

Topics in Antiviral Medicine™

CME Information

The IAS–USA is accredited by the Accreditation Council for Continuing Medical Education to provide continuing medical education (CME) for physicians.

The IAS–USA designates this enduring material for a maximum of 6.5 *AMA PRA Category 1 Credits*™. Physicians should claim only the credit commensurate with the extent of their participation in the activity.

This CME activity is offered from June 4, 2021, to June 4, 2022. Physicians (MDs, DOs, and international equivalents) may receive CME credit for completing this activity. Others will receive a certificate of participation. Visit www.iasusa.org for information on the posttest and evaluation for this activity.

- CME credits available: 6.5 *AMA PRA Category 1 Credits*™
- Release date: June 4, 2021
- Expiration date: June 4, 2022

Learning Objectives

On completion of this activity, the learner will be able to:

- Describe the important new data presented at the 2021 Conference on Retroviruses and Opportunistic Infections and the potential clinical implications for patients in the areas of epidemiologic trends and prevention research in the HIV and SARS-CoV-2 pandemics
- Describe the important new data presented at the 2021 Conference on Retroviruses and Opportunistic Infections and the potential clinical implications for patients in the area of tuberculosis coinfection, cryptococcosis, and talaromycosis
- Describe the important new data presented at the 2021 Conference on Retroviruses and Opportunistic Infections and the potential clinical implications for patients in the area of metabolic, neurologic, and other complications of HIV infection or COVID-19

Intended Audience

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

This activity is also relevant for other practitioners, including nurse practitioners, nurses, physician assistants, pharmacists, and others.

Disclosures of Financial Relationships with Commercial Interests

It is the policy of the IAS–USA to ensure balance, independence, objectivity, and scientific rigor in all its educational activities.

All faculty members (planners, speakers, presenters, etc) participating in IAS–USA-sponsored activities are required to disclose to the program audience any financial relationships with commercial interests within the past 12 months that could be perceived to influence, or give the appearance of potentially influencing, the written or oral presentation. The Accreditation Council for Continuing Medical Education (ACCME) defines a financial interest as an interest in any amount and defines a commercial interest as "any entity producing, marketing, re-selling, or distributing health care goods or services consumed by, or used on, patients. The ACCME does not consider providers of clinical service directly to patients to be commercial interests—unless the provider of clinical service is owned, or controlled by, an ACCME-defined commercial interest." The information is intended to make the IAS–USA audience aware of speaker and contributor interests and commitments with commercial interests, enabling the audience members to form their own judgments about such associations.

The IAS–USA will identify and resolve ahead of time any possible conflicts of interest that may influence CME activities with regard to exposition or conclusion. Financial relationship information about authors is included here and at the end of each article.

Planner/Reviewers

Planner/reviewer 1 has been a consultant to Antiva Biosciences, Gilead Sciences, Inc, and Viriome, Inc. Planner/reviewers 2 and 3 have no relevant financial affiliations to disclose.

Contributors

Dr Buchbinder has no relevant financial affiliations with ineligible companies to disclose at this time. Dr Liu has received investigator-initiated research grants from Viiv Healthcare and Gilead Sciences and has participated in research trials that received provision of medicines from Gilead Sciences, Inc. Dr Sarkar has no relevant financial affiliations to disclose. Dr Brown has served as a consultant for Gilead Sciences, Inc, Merck & Co, Inc, Theratechnologies, and ViiV Healthcare. Dr Ances has no relevant financial affiliations to disclose. Dr Anderson has no relevant financial affiliations to disclose. Dr Letendre has had travel paid for by ViiV Healthcare. Dr Kerkhoff has no relevant financial affiliations to disclose. Dr Havlir has no relevant financial affiliations to disclose.

Independent educational grants for the 2021 *Improving the Management of HIV Disease*® CME program:

PLATINUM SUPPORTERS
Gilead Sciences, Inc
Merck and Co, Inc
ViiV Healthcare

SILVER SUPPORTER
Janssen Therapeutics

BRONZE SUPPORTER
Theratechnologies Inc.

Drug and Product Disclaimer

This activity may contain information about the investigational uses of drugs or products that are not approved by the US Food and Drug Administration. Please consult full prescribing information before using any medication or product mentioned in this activity.

The views and opinions expressed herein are those of the contributors and do not necessarily represent the opinions or recommendations of IAS–USA.

Invited Review

CROI 2021: Epidemiologic Trends in the HIV and SARS-CoV-2 Pandemics and HIV Prevention Research

Susan Buchbinder, MD; Albert Liu, MD, MPH

At the 2021 virtual *Conference on Retroviruses and Opportunistic Infections , several speakers described the disparities in both HIV and SARS-CoV-2 infections and outcomes in racial and ethnic minorities. A household survey suggested that there may have been more than 39 million SARS-CoV-2 infections in the United States by October 30, 2020, with an estimated infection fatality ratio of 0.64%; this compares with an estimated 7.3 million confirmed cases at that time. Several presentations found severe disruptions in HIV testing, prevention, and treatment services during COVID-19-related lockdowns; models suggest that severe interruption of antiretroviral therapy services could lead to a 1.5- to 3-fold increase in mortality. HIV testing remains the gateway to both treatment and prevention, and innovative strategies to improve testing uptake were presented. Preexposure prophylaxis (PrEP) agents may delay detection of HIV infection using standard testing algorithms. Data were presented on promising investigational PrEP agents, including cabotegravir, islatravir, and the dapivirine vaginal ring. Progress is being made in point-of-care assays to measure PrEP adherence with tenofovir-based regimens. HIV incidence remains low in populations of PrEP users, with higher rates among persons who never refilled their prescription. More work remains to be done to increase PrEP uptake among populations most heavily impacted by HIV.*

Keywords: HIV, CROI 2021, SARS-CoV-2, pandemic, PrEP, HIV prevention, COVID, testing, STI

HIV Epidemiology

Hildreth gave an excellent plenary on racial and ethnic disparities in both HIV and COVID-19 (Abstract 15). He traced US governmental lack of involvement in both epidemics in their early phases, leading to worsening situations. He also pointed out that inequities are best understood in terms of their social determinants of health, and named 5 components: 1) education access and quality; 2) health care quality; 3) neighborhood and built environment; 4) social and community context; and 5) economic stability. He gave examples of how inequities in these areas lead to disparities in COVID-19 outcomes, including issues such as poor access to health information, poorly managed chronic diseases, multi-generational households, and mass incarceration. He also pointed out that from 1908 to 2008, the United States never had more than 2.5% of its physicians being black. In fact, currently only 5% of physicians are black and only 5.8% are Latinx, not at all representative of their proportions in the general population. He ended by discussing the importance of health equity (rather than equality), in which each individual and community has their needs met, requiring different interventions for different groups. He called for a coordinated response across disciplines to do the hard work required to address health equity in the United States.

Iqbal and colleagues pointed out that in 2018, 66% of all new HIV diagnoses in the United States were among men who have sex with men (MSM), and most of those were among black and Latino MSM (Abstract 106). The US Centers for Disease Control and Prevention (CDC) funded 7 jurisdictions to conduct THRIVE (Targeted Highly Effective Interventions to Reverse the Epidemic), a collaborative effort between local health departments, community-based organizations (CBOs), health care practitioners, and behavioral and social service providers to improve HIV prevention and care services for black and Latino MSM. Included in the services provided were increased HIV testing, provision of preexposure prophylaxis (PrEP) through CBOs and clinics, practitioner capacity building to provide PrEP, and social and community education campaigns. The 7 THRIVE-funded jurisdictions saw significant reductions in new HIV diagnoses compared with 12 jurisdictions that qualified for THRIVE funding but were not funded: -4.2 vs 0%, respectively, estimated annual percentage change (EAPC) for black populations, and -2.7 vs +1.7, respectively, EAPC for Latinx populations. The authors acknowledged that these were ecological associations only (cannot attribute causality) and that substantially more progress could be made. Nonetheless, these data suggest that supporting collaboration between health departments, CBOs, and clinical and social service providers to drive down infections in these heavily impacted populations may be successful.

Sembajwe and colleagues reported on rates of new HIV diagnoses among American Indians/Alaskan Natives (AI/AN), both nationally, and in persons utilizing services through the Indian

Dr. Buchbinder is Director of Bridge HIV in the San Francisco Department of Public Health and Clinical Professor of Medicine and Epidemiology at the University of California San Francisco. Dr Liu is Clinical Research Director at Bridge HIV in the San Francisco Department of Public Health and Associate Clinical Professor of Medicine at the University of California San Francisco. Send correspondence to Albert Liu, MD, MPH, Bridge HIV, Population Health Division, San Francisco Department of Public Health, 25 Van Ness Avenue, Ste 100, San Francisco, CA 94102 or email albert.liu@sfdph.org.

Health Service (IHS) (Abstract 108). She noted that from 2012 to 2016, there was a 34% increase in new diagnoses among AI/AN overall, and that the rate increased 58% among AI/AN MSM over that time period. In the period of this study (2014-2018), the rates remained stable overall, both nationally and in the IHS, with increases among AI/AN aged 13 to 34 years and aged 35 to 44 years. Among new diagnoses, 63% of them were among MSM, 11% in people who inject drugs (PWID), 12% in MSM/PWID, and 14% in heterosexuals. Overall, death rates declined by 31.4% over that time. The stable rate overall, as well as the increased rates in the 2 age tiers, indicate that we are not making substantial progress in the population of AI/AN, and that more effort is needed to address the disparate rates of diagnoses in these populations.

Golden and colleagues evaluated different methods for determining the proportion of new diagnoses that are designated as "late" – being newly diagnosed with HIV within 12 months of an AIDS diagnosis or a CD4+ count below 200 cells/μL (Abstract 644). He pointed out that in 2018, the rate of late diagnosis was 20.8% nationally. Using data from King County, Washington, from 2010 to 2020, he found that using a standard definition, 25.9% of diagnoses would be designated as late. However, if one were to remove all cases with acute HIV infection or with a negative HIV test within 2 years, that proportion considered "late" would decrease to 20%. If one were further to remove all persons with a self-reported previous HIV diagnosis and persons within 1 year of immigration to the United States, that would further drive down the estimated proportion of late diagnoses to 16.8%. Using the most stringent definition of late diagnosis would have reduced the overall proportion of new diagnoses in King County by 35.1% overall, with even higher proportional reductions among MSM (37.8%) and African-born persons (48.3%).

Based on the natural history of HIV infection and the expected CD4+ count after infection, even if the median time to diagnosis were 9 months, one might expect that a minimum of 8% of new diagnoses would be counted as late. The authors suggest that it is unlikely that we will be able to get late diagnoses to be reduced below 8% to 10%, and that integrated HIV surveillance data into estimates of late diagnoses may improve their accuracy.

Prata Menezes and colleagues presented data on 7380 HIV-negative PWID in India and the association between injection network characteristics and use of HIV prevention services (Abstract 719). They found that the median injection network size was 3 partners, but 17% reported more than 10 injection partners. Overall, only 15% of participants received an HIV test in the previous 6 months, 20% of participants engaged in medication for opioid use disorder in the prior month, and 27% of participants used syringe access services in the prior month; only 3% of participants engaged in all 3 prevention modalities. Injection network size was not associated with receiving HIV testing. However, compared with persons with 0 or 1 injection partner, those with more than 10 partners were less likely to use medication for opioid use disorder (adjusted odds ratio [aOR], 0.55; $P<.01$) but more likely to access syringe services (aOR, 1.54; $P<.01$). Sharing injection equipment with a known HIV-positive partner was associated with having a recent HIV test (aOR, 2.54; $P=.04$). The authors concluded that engagement in prevention services may be associated with perception of need, such as HIV testing among persons injecting with a known positive partner. However, persons with larger injection networks were more likely to use community-based services (ie, syringe access) than facility-based services (ie, HIV testing, medication for opioid use disorder), leading the authors to hypothesize that some of these services should be offered in community settings.

Pines and colleagues presented data on transmission patterns between populations in the Tijuana/San Diego Border Region using phylogenetics (Abstract 652). They found that 50% of transmission events were from people who inject drugs transmitting to MSM, 30% from transgender women who inject drugs to transgender women who do not inject drugs, and 20% from MSM to transgender women. Transactional sex accounted for 32% of transmissions. These results suggest that interventions targeting transactional sex and injection drug use could have a substantial impact on the local epidemic.

Modeling HIV Outcomes

Fojo and colleagues developed a web-based tool to help local policy makers determine the most impactful combination of testing, PrEP, and treatment services within a given jurisdiction (Abstract 668). The user can select a jurisdiction in the United States, and look at the impact of scale up of these interventions in select populations (by age, race/ethnicity, sex, and risk group).[1]

Schnure and colleagues applied the Johns Hopkins model to 4 US cities: Los Angeles, New York, Atlanta, and Baltimore (Abstract 775). Although there were differences in the specifics of what the cities needed, the overall findings were that scaling up PrEP use among MSM led to substantial reductions in new infections, expanding to include older men had a modest marginal benefit. Working toward viral suppression for persons with HIV of all ages also had a substantial impact on the number of new infections. Although they recommended focusing on treatment for all but PrEP only for younger men, combining both approaches still did not reach the Ending the HIV Epidemic (EHE) target of 90% reduction in new HIV infections by 2030. This suggests that broadly applying both PrEP and viral suppression will be required to achieve these targets.

Booton and colleagues evaluated 14 separate transmission dynamic models to evaluate the contribution of key populations to HIV epidemics in Southern and Eastern Africa (Abstract 669). For female sex workers, their clients, and MSM, the models suggested that they transmit more infections than they acquire over a 10-year period, reflecting ongoing secondary transmissions. Young women, on the other hand, appeared to acquire more infections than

they transmit over a 10-year period. The authors concluded that more than one measure is required to adequately describe the impact of key populations in different geographic locations.

Clement and colleagues created a model to predict the risk of HIV acquisition using electronic health records at Duke University (Abstract 773). They evaluated risk within the entire cohort of 368 incident infections among 1.6 million total patients, as well as among the subset of 93 incident infections in women. Globally, the most predictive variables were race, age, and zip code. For the total cohort, the most predictive variables were hepatitis A virus (HAV) infection, receipt of intramuscular ceftriaxone, and receipt of intramuscular or intravenous penicillin, pointing out that acquiring other sexually acquired infections is a marker for HIV risk. For the women-only cohort, the most predictive variables were HAV infection, buprenorphine treatment, and a history of domestic or sexual abuse. They next plan to use this model to tailor PrEP counseling for persons at high risk for HIV acquisition in a clinical setting.

SARS-CoV-2 Epidemiology

Sullivan and colleagues assessed the cumulative incidence of SARS-CoV-2 infection and epidemic metrics in the United States (Abstract 636). They used an address-based probability sampling schema and mailed 39,500 test kits to US households; approximately 15% of eligible households responded. Using data from nasal swabs and dried blood spots, and adjusting for waning antibody levels, they estimated that the cumulative incidence of SARS-CoV-2 on October 30, 2020, was 12.0%, suggesting that the true number of SARS-CoV-2 infections in the US was more than 39 million, with a 95% credible interval of 34 million to 44 million persons; at that time, only 7.3 million confirmed cases were reported in the United States. The estimated infection fatality ratio was 0.64% (95% credible interval, 0.58%-0.75%). Prevalence ratios (PRs) were significantly higher in Latinx (PR, 3.11) and black (PR, 2.15) than white individuals, higher in persons aged 18 to 34 years (PR, 2.7) and 35 to 44 years (PR, 2.96) than those older than 65 years, and higher in persons living in a metropolitan area (PR, 2.52) than persons in nonurban areas. The authors emphasize the role of household surveys in generating unbiased estimates, and the importance of adjusting for waning antibody levels to generate credible epidemic metrics.

The true number of SARS-CoV-2 infections in the United States on October 30, 2020, may be more than 39 million, rather than the reported 7.3 million

Nash and colleagues reported on risk factors for incident seroconversion from May 2020 to January 2021 in the CHASING (Communities, Households, and SARS-CoV-2 Epidemiology) COVID-19 cohort study (Abstract 637). They recruited 6745 adults from all 50 US states, Washington, DC, Puerto Rico, and Guam. Of 3280 persons who were seronegative at the first time point and had an additional specimen at the second time point (from November 2020 to January 2021), 145 seroconverted, indicating a SARS-CoV-2 seroincidence of 9.3/100 person-years. Demographic factors associated with seroconversion included being male (relative risk [RR], 1.3), Hispanic (RR, 2.1), non-Hispanic black (RR, 1.8), living in a rural area (RR, 1.5), and living in the Midwest (RR, 1.6), South (RR, 1.7), or West (RR, 1.3) compared with the Northeast. Essential workers were also at increased risk (RR, 1.7). A number of household and behavioral factors were associated with seroconversion including living in a more crowded household, having a household member with COVID-19, indoor dining, visiting places of worship, indoor grocery shopping, visiting non-household members, working indoors, attending a salon or gym, gathering in groups of 10 or more either indoors or outdoors, and recent air travel. These risk factors for more recent seroconversion emphasize the importance of non-pharmacologic behavioral interventions in controlling the spread of the virus, and the continued increased risk among people of color and essential workers.

Tordoff and colleagues analyzed the phylogenetics of SARS-CoV-2 introductions into Washington State (WA) (Abstract 138). She reminded us that the first US case was identified in Washington State on January 21, 2020, with the second case on February 28, 2020, which was likely due to a separate introduction. After sampling approximately 6% of confirmed cases in WA (1.8% of all estimated infections), they found at least 287 distinct introductions of SARS-CoV-2 into WA, and 204 exported lineages out of WA through mid-September 2020. Almost 90% of all introductions were with the spike 614G variant, and 42% of the exported variants were of the A clade. Overall, 73% of introductions occurred before May 1, 2020, with the first wave of introductions peaking on March 29, 2020, 6 days before the WA "Stay-Home Stay-Healthy" order. Two waves of exported lineages peaked on January 29, 2020, and March 30, 2020. These patterns suggest that lockdowns can be immediately effective in reducing interstate transmission. They estimated that 61% of introductions into WA were from elsewhere in the United States; with only 28% of introductions in western WA coming from eastern WA, but 65% of introductions in eastern WA coming from western WA. They attributed this to the transportation routes (roadways, airports) providing greater access from out of state to western WA. They estimated that the size of downstream clades from a single introduction ranged from 1 to 2193, with 72% resulting in a single WA sequence, indicating that many introductions do not

Patterns of SARS-CoV-2 transmission suggest that lockdowns can be immediately effective in reducing interstate transmission

result in substantial local transmission. However, 6% resulted in 6 to 20 sequences and 6% in more than 20 sequences, suggesting long chains of local transmission.

Smith and colleagues presented data on the dynamics of SARS-CoV-2 transmission at the California/Mexico border (Abstract 632). They identified 622 unique introduction events into the region, including 381 clusters of size 3 or greater from 2 or more locations. Their phylogenetic analysis demonstrated bidirectional migration events across the border, and they called for transnational intervention approaches.

Capoferri and colleagues reported on increasing viral diversity of SARS-CoV-2 sequences over time in the United States in 2020 (Abstract 639). They analyzed sequences from 36,299 SARS-CoV-2 genomes accessed before December 15, 2020, when vaccinations began in the United States, and found a 3-fold increase in diversity, with substantial viral divergence over time. They identified at least 47 new amino acid changes, including 3 in the spike protein, that map to known antibody epitopes. They also found mutations in the spike region that were common to the United Kingdom, South African, and Brazilian variants as early as the winter/spring of 2020. The authors underscored the importance of increasing genomic sequencing to track evolution of the virus.

Riou and colleagues presented data exploring the "inverse care law" in Switzerland, a statement that the availability of good medical care varies inversely with the needs of the population served (Abstract 139). They evaluated the association of SARS-CoV-2 testing, test positivity, hospitalizations, intensive care unit (ICU) admissions, and death by socio-economic position (SEP) index, an index by neighborhood that takes into account income, education, profession, and crowding. Among the 1.27 million small neighborhoods in Switzerland, investigators conducted nearly 3 million tests, almost 500,000 of which were positive, with approximately 20,000 hospitalizations, 2000 ICU admissions, and 7600 deaths. They found that increasing SEP index (higher socioeconomic status) was associated with increased SARS-CoV-2 testing but reduced test positivity, hospitalizations, and ICU admissions, with a trend toward reduced mortality, after adjusting all models for age, sex, period, and canton. They concluded that this was an example of the inverse care law, despite universal access to healthcare in Switzerland.

Scully and colleagues reported on sex differences in SARS-CoV-2 outcomes among a cohort of patients presenting for testing and care in the Johns Hopkins Healthcare System (Abstract 140). Test positivity was 8% in women and 9% in men, but differed according to age, with higher positivity rates in men aged 18 to 74 years and higher in women 75 years or older. There were no differences in asymptomatic disease by sex. Among 2626 patients admitted with SARS-CoV-2 infection, Charlson comorbidity scores were similar, although there were differences in the specific comorbidities, with women having more obesity at all ages. Men had higher inflammatory markers, such as ferritin, interleukin (IL)-6, and C-reactive protein. Men aged 18 to 49 years were 2.58-times more likely to have severe disease or die than women. In exploring potential mediators of this difference, adjusting for initial inflammatory laboratory markers dropped the aOR to 1.39, suggesting that the elevated inflammatory markers were a mediator of elevated risk, and should be explored as a possible mechanism of sex differences in outcomes.

Hermann and colleagues evaluated risk factors for hospitalization among 897 patients with polymerase chain reaction (PCR)-positive SARS-CoV-2 infection in Southern Germany (Abstract 633). Overall, 85% of all cases were mild, not requiring hospitalization. Risk factors for hospitalization included age (OR, 1.05/year) and a history of previous lung conditions (OR, 3.09). Female sex was protective (OR, 0.51).

Varshney and colleagues presented data on the association between household overcrowding (defined as having 1 or more persons per room in the household) and the risk of COVID-19 death in the 85 cities in Los Angeles County, the region with the largest number of COVID-19 cases nationally (Abstract 631). They found that the number of overcrowded households had the largest effect on the risk of COVID-19 death (P=.001), followed by the number of cases of COVID-19 (P=.014) and the number of individuals aged 60 years and older (P<.001). This speaks to the structural factors underlying disparities in the distribution of COVID-19 deaths.

Interaction of HIV and SARS-CoV-2

Islam and colleagues evaluated racial/ethnic disparities in COVID-19 diagnoses among people with HIV in the United States (Abstract 141). Using data from the National COVID Cohort Collaborative, a dataset of medical records from 41 sites with more than 3 million patients from January 2020 to January 2021, they found that, among people with HIV, those diagnosed with COVID-19 were more likely to be non-Hispanic black (aOR, 1.59; 95% confidence interval [CI], 1.37-1.86), Hispanic (aOR, 2.17; 95% CI, 1.68-2.83), or non-Hispanic Asian (aOR, 2.18; 95% CI, 1.30-3.63) than white. This study confirms that the racial and ethnic disparities of SARS-CoV-2 infection seen in the general population are also true of the population with HIV.

Research confirms that the racial and ethnic disparities of SARS-CoV-2 infection seen in the general population are also true of the population of people with HIV

Del Amo presented data addressing whether people with HIV are more likely to be tested for SARS-CoV-2, more likely to test positive, and if they test positive, more likely to have more severe outcomes (Abstract 31). The literature is mixed in addressing these questions, but she summarized, that people with HIV are more likely to be

tested for SARS-CoV-2 if their access to health care is the same as persons without HIV, as demonstrated in the VACS (Veterans Aging Cohort Study) database. She also found that in most unadjusted analyses, people with HIV appeared to be more likely to acquire SARS-CoV-2, but in most studies, after adjusting for sociodemographic factors such as age, sex, race/ethnicity, and location, there no longer appeared to be an increased risk. She also found that people with HIV were more likely to have more severe outcomes from SARS-CoV-2 infection in unadjusted analyses, but stated that more data are needed to identify if there is any increased risk after adjusting for comorbidities and other sociodemographic factors. Finally, she asked whether all people with HIV are at equal risk for severe outcomes; this question is not fully answered, with some question about whether or not persons with low CD4+ cell counts might be at higher risk. She cited 3 studies suggesting that persons on tenofovir disoproxil fumarate (TDF)/emtricitabine (FTC)-based regimens were at decreased risk of SARS-CoV-2 infection and poor outcomes; there are 2 randomized controlled trials underway to assess the influence of TDF/FTC on prevention and on treatment of SARS-CoV-2.

Park and colleagues evaluated SARS-CoV-2 testing and positivity rates among people with HIV and people without HIV in 6 clinical cohorts in North America (Abstract 626). They found higher testing rates among people with HIV, but similar SARS-CoV-2 positivity among people with and without HIV. Salters and colleagues presented data on SARS-CoV-2 testing positivity among people on antiretroviral therapy (ART) and people on PrEP among drug treatment program patients in British Columbia (Abstract 628). They also found no difference in test positivity between these two populations, that mirrored the overall test positivity in British Columbia.

Lee and colleagues analyzed the impact of HIV infection on COVID-19 outcomes among hospitalized patients in 6 large hospital trusts in England (Abstract 142). They point to the limitations of other analyses, particularly those without matched controls. In this analysis, 6612 patients were admitted to these hospitals during the time of study, with 68 being HIV positive with 181 matched controls. Patients were matched on hospital site, sex, SARS-CoV-2 test date, age, and index of multiple deprivation, a national index that measures socioeconomic deprivation. The primary outcome variable was time from COVID-19 diagnosis to either a 2 point or greater improvement from baseline clinical status, or hospital discharge, whichever came first. On unadjusted analyses, people with HIV had a hospital stay of 10 days, versus 7.5 days for patients without HIV. However, in a multivariable analysis, HIV status was not an independent predictor of SARS-CoV-2 clinical improvement or hospital discharge; clinical frailty score (aOR, 0.79; 95% CI, 0.65-0.95), malignancy (aOR, 0.37; 95% CI, 0.17–0.82), and body mass index less than 25 (aOR, 0.46; 95% CI, 0.21-0.99) were significantly associated with longer time to clinical improvement or hospital discharge.

HIV status was not an independent predictor of SARS-CoV-2 clinical improvement or hospital discharge

Blanco and colleagues also conducted a case control study of death among people with and without HIV who were hospitalized in Spain from February to September 2020 (Abstract 641). They matched 204 controls in a 1:1 fashion to cases based on center, age, sex, and calendar week of admission. People with HIV were significantly more likely to have chronic liver disease (aOR, 8.7) and cardiac disease (aOR, 2.09) and significantly less likely to be obese (aOR, 0.30) than their HIV-negative controls. In a multivariable analysis controlling for chronic liver disease, cardiac disease, and obesity, they found that people with HIV were marginally more likely to die than their HIV-negative controls (aOR, 5.27; 95% CI, 1.00-27.72). In separate multivariable models, factors associated with mortality for people with HIV included age (aOR, 13.72) and chronic obstructive pulmonary disease (aOR, 4.06). Among controls, the only variable significantly associated with mortality was neoplasm (aOR, 8.81). In this analysis, current and nadir CD4+ cell count and CD4+/CD8+ cell ratio, detectable HIV RNA, and specific antiretroviral drugs were not associated with mortality.

Spinelli and colleagues assessed the SARS-CoV-2 seropositivity and binding and neutralizing antibody titers between people with HIV and a matched HIV-negative cohort (matched on age and date of specimen collection) at San Francisco General Hospital (Abstract 627). Using remnant specimens from 955 people with HIV and 1062 without HIV, they found only 3.7% of those with HIV to be seropositive, compared with 7.4% among HIV-negative patients (aOR, 0.48; 95% CI, 0.34-0.71). Latinx patients were significantly more likely than white patients to be SARS-CoV-2 positive (aOR, 7.7; 95% CI, 3.5-17). Severe disease was more common among those with HIV than among HIV-negative patients with SARS-CoV-2 (10% vs 2%; P=.04). IgG titers were 45% lower among people with HIV (95% CI, 22%-61%) than those without HIV, and neutralizing antibody titers were 63% lower (95% CI, 2%-78%). These lower titers raise questions about whether people with HIV have less robust protection against reinfection, and suggest studies need to evaluate the immune response to vaccination among people with HIV.

Kambugu explored the potential impact of the SARS-CoV-2 pandemic on the HIV pandemic globally (Abstract 32). He pointed out that progress was being made in the UNAIDS 90-90-90 goals and the number of new HIV infections globally before the SARS-CoV-2 pandemic, and outlined 3 mechanisms by which COVID-19 may interrupt HIV control measures: 1) COVID-19 mitigation and containment measures (eg, decreased access to health facilities); 2) differential allocation of resources toward COVID-19 responses (eg, diversion of healthcare workers from HIV

to COVID-19 care services); and 3) direct COVID-19 effects (eg, SARS-CoV-2 infection of healthcare workers). He presented models from a consortium of modelers that found that interruption of ART services would have the greatest impact on outcomes, including a 1.5- to 3-fold increase in mortality, should services be severely interrupted. He went on to show global data suggesting substantial declines in HIV testing rates, partner notification services, and PrEP, but lesser impact on ART access. He ended by outlining some mitigation strategies that could be implemented to reduce the risk of decreased services.

Drammeh and colleagues presented data on HIV testing and linkage to care in 11 countries in sub-Saharan Africa (Abstract 143). Practitioner-initiated testing and counseling decreased in 7 countries (64%), and the number of persons testing positive decreased in 10 countries (91%) comparing January to June 2020 with January to June 2019, suggesting that both were impacted by restrictions imposed in health care facilities to limit the spread of SARS-CoV-2. This resulted in an overall decline in the number of persons tested and testing positive of 20% and 23%, respectively. However, in 5 countries, index partner testing and HIV case finding increased by 13% and 17%, respectively, suggesting that this may be a strategy that can be used, even in the midst of a pandemic. Overall, the number of people linked to care decreased in 7 countries, suggesting that more efforts are needed not only to find people with HIV, but to ensure rapid linkage to care.

Menza and colleagues presented data on public health testing of HIV and bacterial sexually transmitted infections (STIs) in Oregon, comparing the period before stay-at-home orders (June-September 2019 and January-February 2020) with during stay-at-home (March-May 2020) and after stay-at-home (June-September 2020), controlling for month (Abstract 144). They found that 4th generation antigen/antibody testing declined by 50% during and by 38% after stay-at-home orders in the state were lifted. Gonorrhea and chlamydia testing decreased by 58% during and 44% after stay-at-home orders. Syphilis testing declined by 58% during and 38% after stay-at-home orders. HIV diagnoses declined by 36% during and increased by 12% after stay-at-home orders, but these differences were not statistically significant. Chlamydia diagnoses were significantly lower during (34%) and after (15%) the stay-at-home period, and gonorrhea diagnoses were only significantly reduced during the stay-at-home period (23%). Primary and secondary syphilis diagnoses increased significantly after stay-at-home orders were lifted (45%), emphasizing the importance of ongoing testing despite the SARS-CoV-2 pandemic. The authors implemented an at-home testing program that delivered HIV and STI testing services through mail-in kits to more than 900 individuals, 38% of whom had never had an HIV test previously.

Primary and secondary syphilis diagnoses increased significantly after stay-at-home orders were lifted, emphasizing the importance of ongoing testing despite the SARS-CoV-2 pandemic

Scott and colleagues compared HIV and viral load testing volume and PrEP visits in San Francisco throughout 2020 (Abstract 730) with volume in 2019, matched by month. They found that HIV testing at 4 laboratories declined to a nadir of 54% of 2019 levels in April 2020, with a partial rebound to 8% to 15% below 2019 levels later in the year. HIV testing volume at a large community-based testing site nadired at 87% lower volume in April 2020 than in April 2019, with a partial rebound to 40% to 45% lower rates later in the year. HIV positivity rate remained stable, raising the possibility of lower HIV case finding. Among those testing positive, linkage to care within 1 month of diagnosis occurred for 93% of patients compared with 97% in 2019. HIV viral load testing from 12 laboratories nadired at 57% below 2019 levels, rebounding to 15% to 20% fewer tests than 2019 later in the year. PrEP visits at a large community site declined by 90% at the nadir in April 2020, with a rebound to 20% to 30% lower than 2019 levels later in the year. These data indicate that the SARS-CoV-2 pandemic had a profound impact on HIV prevention and care services in San Francisco, with partial but not full rebound to pre-SARS-CoV-2 levels. The authors suggest several mitigation strategies, including defining HIV prevention and care services as essential (even during lockdowns), expanding telemedicine services, and safer sex messaging during the pandemic.

Delaney and colleagues reported data from a commercial laboratory in the National Syndrome Surveillance Program run by the CDC (Abstract 739). Like the previous studies, they saw dramatic declines in HIV and viral load testing from March 13 to September 30, 2020, compared with a similar period in 2019: nearly 670,000 fewer HIV screening tests, nearly 5000 fewer HIV diagnoses, and more than 67,000 fewer viral load tests were performed, just from this single laboratory. Although the numbers of tests have rebounded, they were still below 2019 levels by the end of September 2020. The authors suggest that home testing, home sample collection, and telemedicine can help to address this shortfall.

Huang and colleagues drew from a national prescription database (IQVIA [formerly Quintiles and IMS Health, Inc] Real World Data) to evaluate trends in PrEP prescriptions from March 15 to September 30, 2020, compared with an earlier period of time (Abstract 731). Overall, there was a 21% decrease in the number of PrEP prescriptions and a 28% reduction in the number of new PrEP users over that time. Among the 10 states with the highest number of PrEP prescriptions prior to the COVID-19 pandemic, there was marked variability in these changes. For example, the number of new PrEP users declined by 18.2% in Texas but by 47.2% in Illinois. They also reported more decreases

in PrEP prescriptions for 16 to 29 year-olds than for other age groups, and more decreases for cash payers or users of the Medication Assistance Programs than persons with public health insurance. The authors cautioned that it is unclear if the decline was due to decreased access to PrEP or to decreased risk behavior (or both), but urge ongoing follow up to ensure adequate access to PrEP services.

Mitchell and colleagues modeled the impact of changes in sexual practices and HIV prevention and care service delivery from COVID-19 on numbers of new HIV infections and HIV-related deaths among MSM in the United States (Abstract 735). Their inputs to their model (number of sex partners, condom use, HIV testing, viral suppression, PrEP initiations and adherence, HIV testing on PrEP, and ART initiation) came from a published national survey and Boston clinic data. They found that, of different service disruptions, a 10% decrease in viral suppression would have the greatest impact both on the number of new HIV infections and deaths. A 25% decrease in partnerships would offset the negative impact of combined service disruptions on the number of new HIV infections, but would have no impact on the number of deaths. The authors conclude that maintaining access to ART and adherence support are the most important factors to minimize excess mortality, and they called for scale up and evaluation of telemedicine and other delivery models.

Rapid HIV Testing and Self-Testing

Sundararajan and colleagues presented data from a cluster-randomized trial of traditional healers delivering HIV testing in Uganda (Abstract 180). The authors noted that 80% of people in sub-Saharan Africa use traditional healers, and a recent cross-sectional survey found that only 34% of traditional healers had received an HIV test in the prior 12 months. They selected 17 traditional healers and randomly assigned them to the intervention or the control arm of the study. The intervention and control healers were trained to provide HIV education to their patients; intervention-arm healers were also trained to administer a rapid point-of-care oral fluid HIV antibody test, and linkage to care for those testing HIV positive. The primary outcome of the trial was HIV testing within 90 days of seeing the traditional healer; secondary outcomes were the number of new HIV diagnoses, and linkage to care of those individuals. Of the 250 participants seen in each arm of the study, 100% of those seeing the intervention healers received HIV testing, compared with 22.8% of the control arm (risk reduction, 77.2%; 95% CI, 72.8%-81.6%). Ten people in the intervention arm tested HIV positive (4%) compared with none in the control arm (P=.002). Of those found to be HIV positive, 70% were successfully linked to care. The authors concluded that training traditional healers to deliver rapid HIV antibody tests is a highly effective strategy to increase testing among sexually active adults in rural Uganda.

Training traditional healers to deliver rapid HIV antibody tests is a highly effective strategy to increase testing among sexually active adults in rural Uganda

Dovel and colleagues presented data on a cluster-randomized trial of HIV self-testing to optimize facility testing in Malawi (Abstract 181). Three clinics were each randomly assigned to provide HIV testing through practitioner-initiated testing, passive self-testing (group education, leaving it up to the patient to take the test and seek out medical help if needed), or active self-testing (group education, patients taken to an adjacent space for private self-testing). In total, 3182 participants joined the study. HIV testing rates remained relatively stable for the practitioner-initiated testing clinics (testing rates increased from 9% to 11%, an 18% increase), and for passive self-testing (6% vs 8%, a 33% improvement). Uptake of testing was higher in the clinics assigned to active self-testing (5% to 16%, a 220% increase). However, the authors acknowledged that even in the active arm, testing uptake was low, suggesting more information is needed about why this did not work, and new strategies should be tested to improve on these small numbers.

Jiang and colleagues pointed out that male partner testing remains low, and that self-testing may help increase testing (Abstract 674). They offered 798 pregnant women either clinic or home self-testing for retesting; women choosing HIV clinic testing could refer their partners, and women selecting self-testing could offer their partner either home- or clinic-based testing. By 14 weeks postpartum, 38% of women selecting clinic-based testing and 60% of women selecting home self-testing reported that their partner had been tested, and 87% of the partners had a negative test. Of women who selected home self-testing and whose partners tested, 64% of partners opted for home-based testing and 33% chose clinic-based testing. This suggests that secondary distribution of HIV self-testing to male partners of women receiving perinatal services can successfully increase partner testing coverage.

Peruski and colleagues evaluated whether HIV rapid testing algorithms improve care outcomes compared with standard HIV testing algorithms (Abstract 676). They evaluated national data reported to the US National HIV Surveillance System through December 2019, for all persons aged 13 years or older with HIV diagnosed during 2018 in the United States. Linkage to care was defined as having at least one CD4+ cell count or viral load test recorded. Of 33,500 persons diagnosed with HIV who resided in a jurisdiction with complete laboratory testing reported, 1508 (4.5%) were diagnosed using a rapid testing algorithm. Median time to linkage to care was significantly shorter among persons undergoing the rapid testing algorithm (16 vs 23 days, respectively, in EHE jurisdictions and 19

vs 22 days, respectively, in all other jurisdictions). Median time to viral suppression was also more rapid (2.9 vs 4.0 months, respectively, in EHE jurisdictions and 3.4 vs 3.9 months, respectively, in all other jurisdictions). However, use of rapid testing algorithms has decreased over time, particularly in EHE jurisdictions.

Bien-Gund and colleagues reported on HIV self-testing and risk behaviors among MSM in 23 US cities (Abstract 677). Data were drawn from the CDC National Behavioral Health Surveillance survey in 2017, a venue-based sampling of cisgender MSM. Of 6563 MSM who reported that they were HIV negative or of unknown serostatus and who had an HIV test in the previous 12 months, only 7.7% reported self-testing in the past year. Self-testers were younger, had higher levels of education, and had higher incomes. They were also more likely to report both increased test frequency and more recent testing, without reporting more condomless anal sex, STIs, or new HIV diagnoses than men who did not self-test. The authors posit that HIV self-testing could be very important in the COVID-19 era, when HIV testing rates have declined.

Vaccari and colleagues reported on a highly successful HIV testing program in an emergency department (ED) in London (Abstract 684). They had organizational commitment to opt-out testing, and included prominent signage to inform patients of the opt-out option as well as to routinely test all venipuncture samples, unless a person had opted out in the past 6 months or if this was a repeat HIV test. Patients not receiving testing were sent a text to let them know they could request a home test kit. They report that 97% of 25,366 eligible patients were tested for HIV; of these, 244 had non-negative test results. Of these, 66% were known to be HIV positive and in care, 4% were known positive and reengaged in care, 17% had false positive results, 6% were confirmed as a new HIV diagnosis, 5% were pending follow up, and 2% were lost to follow up. Of the 15 newly diagnosed persons, 13 are now engaged in care and receiving ART, and the other 2 have declined care. Overall, 57% of newly diagnosed persons and 56% of those who had previously defaulted their care had CD4+ counts less than 200 cells/μL.

Linley and colleagues used data from the National HIV Surveillance System to evaluate levels of previous HIV testing among newly HIV diagnosed black persons in the United States from 2013 to 2018 (Abstract 687). They found that of 11,742 black persons newly diagnosed with HIV in 2013, only 66% had had any prior HIV testing; this proportion declined significantly in 2018, with 61% of 10,881 black persons newly diagnosed who had had a previous HIV test. These declines in testing were true among those aged 13 to 44 years, with an average decline of 3% per year over that period of time across all age strata. This decline was seen in MSM, women who injected drugs, and heterosexual men. However, rates were relatively stable in the other groups, indicating that we are not making progress in any subgroups. These data suggest we are missing opportunities to detect infection earlier in black persons, and need substantial attention paid to this deficit.

The 4th pillar of the EHE effort is to respond rapidly to detect and respond to growing HIV clusters and prevent new infections. Curran and colleagues evaluated the baseline timeliness of HIV case and sequence reporting to health departments to determine the feasibility of intervening in these situations (Abstract 688). They considered timely case reporting to occur within 30 days of diagnosis, and timely sequence reporting to be within 45 days of diagnosis. Of 37,428 diagnoses in 2018 in persons 13 years of age or older, 59% had case reports entered within 30 days after diagnosis (median time, 24 days). Timely case reports were less frequent in large metropolitan areas, the Northeast and West, and in EHE jurisdictions. Among 19,289 diagnoses with viral sequences, 71% had specimens collected within 30 days after diagnosis, but only 6% had sequences entered within 45 days after diagnosis, with a median time to reporting of sequences being 74 days (interquartile range [IQR], 31.5-117.5 days). Across facilities, geographic areas, and jurisdictions, fewer than 10% of sequences were entered within 45 days of diagnosis. Targets for the new EHE initiative include 75% of the case reports entered within 30 days after diagnosis, and HIV sequence reporting occurring within 45 days after diagnosis. Much work remains to be done to be able to use sequence data to investigate clusters of transmission.

Sexually Transmitted Infections

Mugo and colleagues reported on rates of herpes simplex virus (HSV)-2 acquisition among HIV-negative women enrolled in the ECHO (Evidence for Contraceptive Options in HIV Outcomes) trial, a randomized controlled trial of 3 contraceptive methods and their association with HIV acquisition (Abstract 152). Several previous studies had found an association between use of intramuscular depot medroxyprogesterone acetate (DMPA-IM) with HSV-2 acquisition, which is of concern as HSV-2 acquisition increases the risk of HIV acquisition by 3-fold in women. However, other studies had not found such an association, and the previous datasets were often small and had potential confounding by sexual activity, as the control condition was often non-contraceptive users. The ECHO study enrolled 3898 women who were HSV-2 seronegative, with definitive HSV-2 serologic results at the baseline and final study visits. Women were randomly assigned to receive DMPA-IM, levonorgestrel implant (LNG), or the copper intrauterine device (IUD). Women were 16 to 35 years of age, recruited from 4 African countries, and followed up for 15 to 18 months. Overall HSV-2 incidence was 12.4/100 person years, without substantial differences between study arms (10.9/100 years in DMPA-IM arm, 12.7 in the LNG implant arm, and 13.7 in the copper IUD arm). HSV-2 seroconversion was associated with HIV seroconversion (incidence rate ratio [IRR], 4.1; 95% CI, 3.2-5.1), *Chlamydia trachomatis* infection (IRR, 1.3; 95% CI, 1.1-1.5), *Neisseria gonorrhea* infection (IRR, 1.6; 95% CI, 1.2-2.2), and having multiple partners (IRR, 1.3; 95% CI,

1.04-1.6). Living with one's partner was associated with reduced risk (IRR, 0.6; 95% CI, 0.5-0.7). The authors suggested that these data support use of long-acting contraceptive methods for young women in sub-Saharan Africa without risk of increased HSV-2 acquisition.

Silhol and colleagues created a mathematical model to determine the impact of HSV-2 infections on new HIV infections globally (Abstract 708). They reported that 37% (95% CI, 33%-43%) of HIV infections from 2009 to 2018 could be attributed to HSV-2 coinfection if HSV-2 only increases HIV acquisition, but 51% of all infections (95% CI, 43-58) if HSV-2 also increases HIV transmission. The contribution of HSV-2 to HIV infection was higher in Africa, and higher in female sex workers, their clients, and older adults, where HSV-2 prevalence is higher; the contribution of HSV-2 to HIV infections was lower in Europe. The authors posit that future HSV-2 control measures, including a HSV-2 vaccine, could have a substantial impact on incident HIV infections, particularly in sub-Saharan Africa.

No participant on doxycycline prophylaxis developed syphilis or chlamydia

Grennan and colleagues reported on results of a pilot randomized controlled trial of doxycycline for preexposure prophylaxis against chlamydia and syphilis in MSM and transgender women in British Columbia (Abstract 709). Fifty HIV-negative participants (49 MSM, 1 transgender woman) were given daily oral PrEP with TDF/FTC, and then randomly assigned to receive daily doxycycline 100 mg starting at baseline (immediate arm) or starting at 24 weeks (deferred arm); follow up was through 48 weeks. No participant on doxycycline prophylaxis developed syphilis or chlamydia, with an odds ratio for development of any STI of 0.18 (95% CI, 0.05-0.68). Ten participants in the deferred arm developed chlamydia in the first 24 weeks, and 1 developed syphilis in this time frame. On the other hand, there were 8 cases of gonorrhea in the first 24 weeks in the deferred arm and 4 cases in the immediate arm; an additional case in the immediate arm occurred after 24 weeks. Tetracycline resistance in *Staphylococcus aureus* was found in 1 of 3 persons in the immediate arm at 24 weeks, and 3 of 6 at 48 weeks; 1 of 3 in the deferred arm after 24 weeks. Self-reported adherence (taking >95% of doses) was 89.5% in the immediate arm and 72.7% in the delayed arm. The authors reported that this was a promising intervention that will be followed up on with a 500-person randomized controlled trial.

Wang and colleagues presented data on a study of 400 adolescent girls and young women (AGYW), aged 16 to 21 years in Kenya (Abstract 721). Of 292 who were sexually active during the follow-up period, 163 developed an STI, on average, 39 months from sexual debut. Seventy had a subsequent STI. In total, 81% of STIs were chlamydia, 11% gonorrhea, 7% *Trichomonas vaginalis* infections, 14% HSV-2, and 13% had multiple STIs. Risk factors for developing an STI included bacterial vaginosis (BV) (RR, 1.49; 95% CI, 1.09-2.03), having a new sex partner (RR, 2.02; 95% CI, 1.26-3.26), and failure to disclose sexual activity (RR, 2.72; 95% CI, 1,93-3.83). These data suggest that AGYW are at high risk of acquisition of STIs shortly after sexual debut, and speak to the need for increased screening (rather than relying on syndromic management) to detect and treat STIs, particularly chlamydia infection.

Roxby and colleagues presented data from the same cohort of 400 AGYW in Kenya, 80.5% of whom reported no prior sexual activity at enrollment, to evaluate risk factors for development of BV. Participants were followed up to 60 months and had a median of 11 BV tests over that time. Prior to sexual activity, only 2.8% of visits resulted in a positive test for BV, and after sexual activity, 13.7% of visits resulted in a positive test for BV. A BV diagnosis was increased after first sexual intercourse (OR, 3.5; 95% CI, 2.3-5.3) and among women reporting more than 1 sex act in the prior 3 months (OR, 1.8; 95% CI, 1.36-2.39). On longitudinal analysis, several sociodemographic and behavioral factors were associated with increased risk (recent sexual activity: OR, 1.4; $P=.03$; urban residence: OR 1.4; $P=.01$; no income: OR, 1.7; $P<.01$). BV was also associated with both chlamydia (OR, 1.78; $P<.001$) and HSV-2 infection (OR, 1.8; $P<.001$). Protective factors included self-reported virginity (OR, 0.4, $P<.01$) and longer time from menarche to first sexual activity (OR, 0.5, $P=.03$). The authors noted that such low rates of BV were uncommon among older women in Kenya, and that products are needed to promote optimal vaginal health.

Liroff and colleagues reported on delayed treatment for syphilis (more than 14 days between diagnosis and treatment) among persons living in Washington, DC, the jurisdiction with the highest rates of syphilis in the United States (Abstract 724). They found 2723 new diagnoses of syphilis from January 2015 to December 2019, 45% of which were in people with HIV, and more than 90% of whom were male. Almost all (99.8%) had adequate treatment for syphilis. Overall, for 5.6% of people with HIV, this HIV test led to a new diagnosis of HIV, and 20.8% of all people with HIV with syphilis diagnoses had an HIV viral load greater than 10,000 copies/mL, suggesting increased transmissibility of HIV. Delayed treatment was associated with viral load below 10,000 copies/mL (aOR, 1.82; 95% CI, 1.03-3.23); black race (aOR, 1.82; 95% CI, 1.01-3.29); race not reported or refused (aOR, 2.11; 95% CI, 1.09-4.10); and early latent syphilis (aOR, 3.2; 95% CI, 1.96-5.24). Compared with receiving care in Federally Qualified Health Centers or community health clinics, patients seen in private practice settings were significantly less likely to be treated late (aOR, 0.08; 95% CI, 0.01-0.69). The authors pointed out that intervening simultaneously for HIV and syphilis in persons coinfected could reduce the transmission of both infections.

Preexposure Prophylaxis

Novel PrEP Agents and Formulations

Landovitz and colleagues presented an updated analysis of laboratory data on

HIV infections in the HPTN (HIV Prevention Trials Network) 083 study, a phase IIb/III randomized trial comparing long-acting injectable cabotegravir (CAB-LA) administered every 8 weeks with daily oral TDF/FTC in cisgender men and transgender women who have sex with men (Abstract 153). This study found that CAB-LA and TDF/FTC were each highly effective for HIV prevention. Overall there were 12 incident infections and 4 participants infected at baseline in the CAB-LA arm, and 39 incident and 3 baseline infections in the TDF/FTC arm. HIV incidence was

CAB-LA can delay detection of HIV infection using standard HIV testing algorithms

0.37 per 100 person years in the CAB-LA arm versus 1.22/100 person years in the TDF/FTC arm, with a hazard ratio of 0.32 (95% CI, 0.16-0.58) demonstrating superiority of CAB-LA over oral TDF/FTC. Retrospective back testing of samples using multiple sensitive assays was performed to determine the time of first infection. Among the 4 baseline-infected participants who received CAB-LA prior to detection of infection, 1 was found to have treatment-emergent integrase strand transfer inhibitor (InSTI) resistance with Q148K and E148K mutations. Another participant with baseline infection detected 10 weeks after enrollment who had received 2 injections of CAB-LA had "escape" viremia during the pharmacologic tail phase (HIV viral load of 76,010 copies/mL about 35 weeks after enrollment) but no emergence of resistance. Five infections occurred after a prolonged hiatus after CAB-LA administration, 3 of which likely occurred during the pharmacologic tail phase; none of these cases had InSTI resistance.

Among 3 participants who acquired HIV during the CAB-LA oral lead-in period, 2 had cabotegravir plasma levels indicative of cabotegravir exposure, and both developed InSTI resistance with the Q148R and accessory mutations. Four participants became infected in the setting of on-time CAB-LA injections and cabotegravir levels consistent with 8 times the protein-adjusted 90% inhibitory concentration ($PAIC_{90}$) at most visits, levels found to be protective in prior nonhuman primate models. Retrospective testing with more sensitive assays detected HIV infection 6 to 17 weeks prior to the detection of HIV infection by site testing. In 2 participants in which genotypic testing could be performed, InSTI resistance with the R263K mutation emerged in one, and with Q148R and G140A mutations in another. Aside from 2 participants who were lost to follow up, all participants were subsequently started on ART and achieved full viral suppression. In the TDF/FTC arm, 37 of 39 of the incident infections occurred in the setting of low adherence based on plasma or dried blood spot testing.

Overall, these findings suggest that CAB-LA can delay detection of infection using standard HIV testing algorithms, and InSTI resistance was seen when viremic "escape" occurs at higher cabotegravir concentrations, but was not seen in the 3 tail-phase infections or 1 tail-phase "escape" case. Taking into consideration these results, the oral lead-in period will be made optional in the upcoming OLE (Open Label Extension) of HPTN 083, which may help avoid early infections associated with possible adherence challenges or delayed time-to-onset of protection. Additionally, the utility of HIV viral load testing at all visits as a primary screen for HIV infection will be assessed in the HPTN 083 OLE. Landovitz highlighted that prompt diagnosis and ART initiation in the setting of CAB-LA are needed to avoid resistance emergence.

Patel and colleagues presented on the pharmacokinetic (PK) threshold and dose selection for monthly oral islatravir for PrEP (Abstract 87). Islatravir is an investigational novel reverse transcriptase translocation inhibitor with high potency, robust activity against drug resistant variants, and a long half-life. Based on efficacious concentrations observed in prior HIV treatment studies, rhesus macaque PrEP and postexposure prophylaxis challenge studies, and data from the literature regarding efficacious concentrations of TDF-disphosphate (DP), an islatravir-triphosphate (ISL-TP) PK threshold of 0.05 pmol/10^6 peripheral blood mononuclear cells (PBMCs) was established for HIV prevention, which is approximately 5-times higher than the in vitro wildtype IC_{50}. In PK model simulations and based on interim data from an ongoing phase IIa islatravir trial, the monthly dose of 60 mg oral islatravir selected for phase III trials resulted in ISL-TP concentrations exceeding this PK threshold within hours, and ISL-TP concentrations were maintained above the PK threshold from the first dose of administration in all participants, even among those with a delayed or missed monthly dose. Interim PK analysis from the phase IIa trial suggested rapid, sustained, and adequate distribution of ISL-TP in target tissues.

Matthews and colleagues presented data on islatravir-eluting implants for yearly HIV PrEP (Abstract 88). This phase I study evaluated the safety, tolerability, and PK of a next-generation radiopaque islatravir implant in healthy HIV-negative men and women. Twelve participants each were randomly assigned to 12 weeks of a 48-mg, 52-mg, or 56-mg implant inserted using the Nexplanon applicator, with an additional 8 weeks of follow up after implant removal. ISL-TP concentrations were above the PK threshold of 0.05 pmol/10^6 PBMCs for the 52- and 56-mg implants. The half-life after removal of the implant was similar to the half-life of orally dosed islatravir (198 hours for the 56-mg implant). Using a population PK model, the 56-mg implant was projected to lead to concentrations above the PK threshold for 52 weeks. The implants were generally well tolerated. All adverse events were mild or moderate in severity, with 61% of participants reporting at least 1 implant adverse event (eg, erythema, tenderness, pruritus, induration). There was no clear relationship between dose and adverse event frequency or severity; no effects on laboratory studies, electrocardiogram results, or vital signs; and no discontinuations due to an adverse event. These findings support the

continued development of the islatravir implant as a potential once-yearly PrEP option.

Li and colleagues described the development of a long-acting coformulated biodegradable implant for HIV prevention and contraception (Abstract 728). Implants tested included one of 2 well-characterized progestins, LNG and etonogestrel (ENG), and 2 antiretroviral drugs (ARVs), TAF and islatravir filled in polycaprolactone extruded tubes. They demonstrated sustained zero-order release of ARVs and hormones up to 1 year with a high level of purity. Although similar ARV-release rates were seen with islatravir as a coformulation and as a single formulation, TAF release was altered by the presence of hormones in the coformulation.

Liu and colleagues presented data on the safety, PK, and acceptability of 2 3-month dapivirine vaginal rings in 49 HIV-uninfected women and those assigned female sex at birth (Abstract 147). Extended duration vaginal rings could reduce user burden and cost, streamline follow-up visits, and encourage adherence. Participants in this phase I trial were randomly assigned in a 1:1:1 fashion to receive the 25-mg dapivirine ring replaced monthly, or the 100-mg or 200-mg vaginal ring worn continuously for 13 weeks. All 3 rings were well tolerated with no statistically significant differences in reported adverse events across arms. Geometric mean dapivirine concentrations for the extended duration rings were 1.3- to 1.9-times higher in plasma and 1.5- to 2.9-times higher in cervicovaginal fluid than for the monthly 25-mg ring, and cervical tissue concentrations were 2.3- to 3.9-times higher in the 200-mg ring arm. Overall, 82% reported being fully adherent to ring use, and most participants reported they liked the ring and would use the ring in the future if effective. These findings support further evaluation of 3-month dapivirine vaginal rings for HIV prevention.

Massud and colleagues reported on the PK and efficacy of weekly oral TAF in protecting macaques from vaginal SHIV infection (Abstract 714). Twelve pigtailed macaques were treated once weekly with oral TAF at either 13.7 mg/kg or 27.4 mg/kg dosing (equivalent to 225 mg and 450 mg, respectively, in humans) and exposed vaginally to $SHIV_{162p3}$ twice a week for 6 weeks. Five out of 6 macaques treated with 27.4 mg/kg or 13.7 mg/kg were protected over the 12 challenges, compared with 9 of 10 untreated controls that became infected, resulting in an efficacy of 92% for both doses. Tenofovir diphosphate (TFV-DP) levels in PBMCs were high and sustained (>1300 fmols/10^6 cells); TFV-DP levels were lower in the animal that had a breakthrough infection in the 27.4 mg/kg arm (405 fmols/10^6 cells) but high in the breakthrough infection in the 13.7 mg/kg arm (3,457 fmols/10^6 cells). Tenofovir exposures in plasma were low and mostly below the limit of detection. These findings suggest that weekly oral TAF may be a feasible option for long-acting vaginal PrEP protection and support further testing in humans.

Makarova and colleagues presented on the PK of TAF/elvitegravir (EVG) rectal inserts in 6 pigtailed macaques and the impact of rectal wash on drug distribution (Abstract 715). Rectal application of a single TAF/EVG insert resulted in high tissue EVG and TFV-DP levels at 4 hours that were within the range associated with vaginal protection and remained detectable after 3 days. There was a linear decline in levels of EVG and TFV-DP from 4 cm to 25 cm from the anal sphincter. Rectal cleansing resulted in fewer samples having levels below the limit of detection and increased colon concentrations of EVG and TFV-DP by 40 to 200 fold.

Bauermeister and colleagues presented on the acceptability and preference for 3 placebo rectal products used with receptive anal sex (Abstract 716). This study enrolled 217 young HIV-negative MSM (79%), transgender women (19%) and transgender men (1%) from 7 sites in the United States, Peru, Malawi, South Africa, and Thailand into a randomized cross-over trial in which participants used a placebo rectal insert, enema, and suppository each for a 4-week period, then completed a conjoint experiment exploring preferences for 7 product features. In conjoint analyses, efficacy was the strongest determinant of stated choice overall (30.4%), followed by product delivery vehicle (18.0%), and adverse effects (17.2%). The preferred bundle of attributes included an enema used approximately 30 minutes before sex, which has 95% efficacy, provides protection for 3 to 5 days, can be dosed once a week, has no adverse effects, and is available over the counter without a prescription. Participants' product preference at the final visit varied by context. For example, the enema was preferred in situations in which the product would make one feel clean after use and make sex more pleasurable, the suppository was most preferred as a good alternative to lubrication, and an insert was most preferred when the product needed to be stored discreetly. These findings highlight the importance of creating behaviorally congruent biomedical options that fit the needs of intended end users.

Measuring Adherence to PrEP

Several presentations reported on advances in pharmacologic assays for measuring adherence to PrEP and ART regimens. Sevenler and colleagues described the validation of a newly developed rapid lateral flow assay for urine tenofovir (Abstract 352). In this assay, the test line intensity becomes brighter with decreasing concentrations of tenofovir and is read by an optical reader or 2 independent people using a visual grading scorecard. In testing 586 urine samples from 28 participants with quantified tenofovir concentrations, the correlation between tenofovir concentration and optical reader intensity measurement was high (Spearman's R, -0.91). The sensitivity and specificity for classifying samples using a 1500-ng/mL cutoff (no dosing in the last 24 hours) were 87% and 92%, respectively, for the visual readout and 85% and 96%, respectively, for the optical reader. When using a cut-off of 150-ng/mL (no dosing in last >4 days), sensitivity and specificity were 84% and 89%, respectively, for visual readout and 87% and 95%, respectively, for the optical reader. As each method provides results in 5

minutes with no sample processing required, the authors suggest that rapid testing for urine tenofovir could be a scalable method to assess recent tenofovir ingestion.

Niu and colleagues presented data on the use of the same urine lateral flow assay to assess tenofovir dose recency in the TARGET (Tenofovir Adherence to Rapidly Guide and Evaluate PrEP and HIV Therapy) study (Abstract 353). In testing 268 urine samples from 28 adults taking daily TDF/FTC in a 6-week directly-observed therapy (DOT) study, average visual scores and optical reader readings were highly correlated with time since last dosing (Spearman's R [r_s] correlation coefficients of 0.80 and 0.83, respectively, [both $P < .01$]). A visual score above 1.5 or optical reading above 1500 correctly identified all samples if the last dose was ingested more than 24 hours ago, and no samples with a visual score above 2.5 or optical reading above 3000 were from participants who dosed in the last 48 hours.

As plasma tenofovir levels are nearly 10-fold lower with TAF than TDF, Johnson and colleagues compared urine tenofovir levels in individuals taking TAF versus TDF (Abstract 355). Using data from TAF in dried blood spot (DBS) samples, a DOT study of 36 participants taking different dosing regimens of TAF, and the TARGET study with DOT TDF, urine tenofovir concentrations were 74% lower with DOT TAF than with TDF ($P < .001$). Given these results, the researchers concluded that a separate, lower tenofovir cut-off level will be needed for any point-of-care assay designed to assess adherence to TAF versus TDF. Using data from TAF in dried blood spot samples, Spinelli and colleagues determined the optimal cut-off for a urine-based point-of-care test for adherence to TAF (Abstract 354). Although 1500 ng/mL was the optimal cut-off for TDF dosing, a urine tenofovir cut-off of 300 ng/mL optimized specificity for daily TAF dosing, with a specificity for nonadherence at 24 hours of 98%, and sensitivity for nonadherence at 120 hours of 98%.

Rosen and colleagues evaluated the use of hair mass spectrometry imaging to identify different patterns of PrEP dosing (Abstract 356). Using infrared matrix-assisted laser desorption electrospray ionization (IR-MALDESI) mass spectrometry imaging (MSI) to assess daily adherence to FTC-based regimens in 8 young MSM over a 2 month period, 4 patterns of longitudinal daily PrEP adherence were identified: consistent high adherence, high adherence with occasional missed doses, improved adherence after study initiation, and intermittent adherence. FTC-TP level was able to detect short-term adherence changes, and a cumulative measure of FTC-TP level in hair over the last 60 days was highly correlated with TFV-DP levels in DBS samples (r_s, 0.79). Rosen and colleagues also used IR-MALDESI MSI to assess daily adherence to maraviroc in the HPTN 069/ACTG (AIDS Clinical Trial Group) 5305 study. Maraviroc, a basic lipophilic compound, is highly bound to melanin in hair strands leading to variation in drug accumulation based on hair color. Accuracy of adherence classification was increased by normalization of maraviroc hair strand concentrations by a melanin biomarker. Among 32 hair samples from 19 individuals analyzed in HPTN 069/ACTG 5035, IR-MALDSI MSI was able to distinguish between individuals who were adherent (8/19) versus nonadherent to daily maraviroc throughout the prior month.

HIV Diagnosis and Resistance on PrEP

Colby and colleagues reported on the impact of PrEP use on the diagnosis of acute HIV infection in Thailand (Abstract 179). Among 3117 individuals who started PrEP in the Thai Red Cross Anonymous Clinic, 8 had acute HIV infection at PrEP initiation (approximately 1/400). Five of these acute infection cases were identified by a positive pooled Aptima Qualitative HIV RNA Test, and 3 were identified by positive serology at 1 to 3 months after PrEP initiation, with quantitative HIV RNA detected on retrospective testing of pre-PrEP stored samples. Among 6 of these individuals who enrolled in an acute infection cohort, PrEP use prior to HIV diagnosis ranged from 2 to 91 days; all participants were switched immediately to ART upon diagnosis. Pre-PrEP viral load ranged from 32 copies/mL to 223,361 copies/mL. A 4th generation HIV test was nonreactive in all 6 cases at week 0 (prior to ART initiation), reactive in 1 individual at week 24, and in a second individual at week 48. The 3rd generation test was reactive in 3 of the 6 individuals at week 0 and in 5 of the 6 individuals at week 24. The 2nd generation test was reactive in 1 of the 6 individuals at week 0 and 3 of the 6 cases at week 24. Western blot testing was either indeterminate or negative at all timepoints, and Geenius testing performed at week 48 was nonreactive in all participants. In 1 individual with low viral load (maximum 276 copies/mL) pre-ART, serologies for all tests remained nonreactive through week 48. In this study, the 4th generation antigen/antibody test was the least sensitive at detecting acute infection, and the 3rd generation antibody test was most sensitive. These results suggest that standard serologic testing and algorithms may not confirm HIV infection when PrEP or ART are started early in acute infection, and alternate testing strategies, including nucleic acid amplification testing, may be needed for accurate diagnosis of acute infection.

Chohan and colleagues assessed HIV drug resistance among PrEP seroconverters in Kenya (Abstract 427). More than 2000 service providers were trained and 340 blood collection kits distributed as part of a national study to assess the frequency of drug resistance among PrEP seroconverters. Among more than 26,000 PrEP users in Kenya's national PrEP rollout program, 67 PrEP seroconverters were identified, and 30 blood samples were successfully genotyped. Of these, 10 (33%) had major HIV drug resistance mutations detected: none (0%) had resistance to tenofovir (no K65R or K70E mutations), 5 (17%) had emtricitabine resistance (with M184V), and 9 (30%) had 1 or more major nonnucleoside reverse transcription inhibitor (NNRTI) mutations, including K103N, Y181C, and G190A. These findings highlight the importance of HIV drug resistance monitoring in PrEP seroconverters,

and monitoring the incidence of NNRTI resistance with the upcoming rollout of the dapivirine vaginal ring.

Cox and colleagues reported on drug resistance in the DISCOVER PrEP trial (Abstract 428). Resistance testing was performed using standard Next Generation Sequencing (detecting ≥2% of the viral population) and ultrasensitive resistance testing using unique molecular identifiers for application of viral variants (detecting ≥1% of the viral population). Of 5335 participants randomly assigned to either TDF/FTC or TAF/FTC in the study, 27 acquired HIV through week 144 (11 in the TAF/FTC arm, 16 in the TDF/FTC arm). Five had suspected baseline infection and 19 had low levels of TFV-DP in dried blood spot samples suggesting suboptimal adherence. Four seroconverters in the TDF/FTC arm had the M184V/I mutation detected on standard and on ultrasensitive testing, which was thought to be transmitted resistance at baseline, and 1 seroconverter in the TAF/FTC arm had the M184V mutation detected only by unique molecular identifier testing. An additional 8 participants had resistance to other drug classes and were thought to be transmitted drug resistance mutations. All participants with virus that resistant to study drugs were successfully treated with ART and virologically suppressed.

PrEP and Gender-Affirming Hormones

Yager and colleagues evaluated whether the PK of estradiol and testosterone were altered with daily PrEP use in transgender adolescents (Abstract 366). In a DOT study of 24 transgender men (50% receiving testosterone intramuscularly and 50% subcutaneously) and 25 transgender women (52% receiving oral estrogen and 48% intramuscular estrogen) aged 15 to 24 years, there were no statistically significant differences in concentration area under the curve (AUC) or maximum concentration (C_{max}) levels in estradiol or free or total testosterone before or after DOT dosing with TDF/FTC. Furthermore, estradiol and testosterone levels in the study pop-ulation were at or above the target range recommended by current Endocrine Society guidelines (100-200 pg/mL for estradiol and ~300-1000 ng/dL for testosterone).[2] These findings provide reassurance for transgender men and women that taking PrEP does not impact concentrations of gender-affirming hormones. From the same study, Yager and colleagues presented data on intracellular TFV-DP and FTC-TP levels in PBMCs in transgender adolescents taking gender-affirming hormones and TDF/FTC PrEP (Abstract 367). After 2 to 3 weeks of DOT TDF/FTC dosing, transgender men had significantly higher PBMC concentrations of TFV-DP (56.0 vs. 75.1 fmol/10^6 PBMCs, respectively; geometric mean ratio [GMR], 1.34; P=.049) and FTC-TP (4.29 and 6.19 pmol/10^6 PBMCs, respectively; GMR, 1.44; P=.003) than transgender women. Differences in TFV-DP concentrations were partially driven by higher baseline renal function in transgender women. Despite these differences, the geometric mean PBMC concentrations were within the ranges of median concentrations observed in prior studies (36.3-71.2 fmol/10^6 cells for TFV-DP and 2.2-5.34 pmol/10^6 cells for FTC-TP). In a post-hoc analysis, PBMC concentrations were lower among transgender women using intramuscular than those using oral estradiol for both TFV-DP (GMR, 0.58; 95% CI, 0.38-0.88; P=.01) and FTC-TP (GMR, 0.58; 95% CI, 0.43-0.79; P=.001), a finding that warrants further study.

PrEP Use in Pregnancy

Davey and colleagues reported on the impact of common adverse effects on PrEP persistence in pregnant South African women (Abstract 149). Of 846 women enrolled into an observational cohort study, 90% reported recent condomless sex, and 31% were unsure of their partner's HIV serostatus. Baseline STI prevalence was high (34%), with 65% of infections being asymptomatic that would have been missed under syndromic management. Following counseling, 90% of women initiated PrEP at their first antenatal visit. Having a same-day STI diagnosis was a facilitator of adherence, and being married and reporting high internalized PrEP stigma were barriers to PrEP initiation. PrEP persistence (returning for repeat PrEP prescription) was 59% for post-partum and 74% for pregnant women at month 1, and 41% and 53%, respectively, at month 6. PrEP persistence was lower in postpartum women who did not return to the same facility for antenatal care (aOR, 0.31). Self-reported adherence was 74% to 82% at month 1 and 77% to 79% at month 3, and 61% of those who reported taking PrEP in the last 30 days had detectable levels of TFV-DP in dried blood spot sampling. Overall, 31% of women reported adverse effects at the 1 month follow-up point, including dizziness (25%), nausea/vomiting (22%), and headache (8%). Women in the first or second trimester of pregnancy had 2.6-times the odds of reporting adverse effects than postpartum women. Reporting adverse effects at the month 1 visit was associated with 0.5 the odds of PrEP persistence and adherence at month 3; being at 20 or more weeks of gestation and having a lower educational level were also associated with poorer PrEP persistence and adherence. As the reporting of PrEP adverse effects can overlap with pregnancy symptoms, these findings highlight the opportunity for improved clinical management of nausea/vomiting during pregnancy and counseling to normalize early, transient adverse effects that may improve maternal PrEP use.

PrEP adverse effects during pregnancy were associated with lower PrEP adherence and persistence

Kinuthia and colleagues presented results of a cluster randomized trial evaluating risk-based versus universal PrEP delivery during pregnancy in Kenya (Abstract 707). In the PrIMA (PrEP Implementation for Mothers in Antenatal Care) study, 20 maternal/child health clinics were randomly assigned to either universal offer of PrEP (universal) or targeted PrEP offer guided by an HIV risk assessment score and partner HIV self-test (targeted). Among

4447 pregnant women enrolled (2250 to the universal arm, and 2157 to the targeted arm), PrEP acceptance was 19.6% in the universal arm and 17.6% in the targeted arm. Appropriate PrEP use (PrEP use in women at high risk and no PrEP use in women at low risk) was similar in the universal (68.4%) and targeted (59.1%) arms (aRR, 1.1; 95% CI, 0.8-1.5). Median duration of PrEP use was 8.6 months in the universal arm and 8.9 months in the targeted arm. HIV incidence was similar in the universal (0.4/100 person years) and targeted (0.3/100 person years) arms (aRR, 0.7; 95% CI, 0.2-2.1). The researchers highlighted several benefits of universal PrEP offer, including less stigma and being female controlled and readily scalable.

Pintye and colleagues reported on tenofovir hair levels among pregnant and postpartum PrEP users in the PrIMA study (Abstract 710). Among 164 hair samples (32% collected during pregnancy and 68% postpartum) from 109 women, median hair tenofovir concentration was 0.005 ng/mg (IQR, 0.002-0.030) across pregnancy visits and 0.005 ng/mg (IQR, 0.002-0.028) across postpartum visits. Overall, 29% of samples had tenofovir levels of 0.023 ng/mg or higher indicating 4 or more PrEP doses per week, with no differences during pregnancy versus postpartum (28% vs. 31%, respectively; P= .68). Having a partner with HIV was associated with higher tenofovir hair levels during pregnancy (0.024 ng/mg) and postpartum (0.036 ng/mg). These findings suggest that hair tenofovir levels provide a cumulative measure of PrEP exposure and may not need adjustment for PK differences in the perinatal period.

Adolescents, Youth, and PrEP

Symposium 10 entitled "Adolescents, Youth, and PrEP" addressed different aspects of the challenges and potential solutions to applying PrEP in young populations. Kinuthia presented on PrEP use during pregnancy and breastfeeding (Abstract 66). He pointed to the increased risk of HIV acquisition during the peripartum period, citing that approximately 30% of infant infections are thought to be due to acute infection in the mother during pregnancy or the breastfeeding period. He reviewed data on infant safety during PrEP use during pregnancy and postpartum. PK data suggest that high levels of adherence are important for pregnant women, due to increased renal clearance of tenofovir as well as hemodilution. Kinuthia also discussed strategies to integrate PrEP services into maternal/child health clinics to improve PrEP uptake and persistence of PrEP. Mellins presented on adolescent brain development, and the many factors that may influence adolescent health (Abstract 68). She pointed out that in 2019, 25% of new infections globally occurred in adolescents, aged 10 to 24 years. PrEP was only approved for adolescents (under 18 years of age) in the US in 2018, and although uptake is increasing in some settings, adherence has been poor in numerous studies globally. Mellins likened the adolescent brain to a car with a well-developed accelerator but only partially developed brakes, a function of the limbic system development outpacing that of the prefrontal cortex. However, she made the case that the increased brain plasticity can be harnessed to come up with creative solutions that address the bio-pyscho-socio-neurocognitive factors that serve as barriers to healthy practices, and put forth some concrete steps that should take place at the practitioner and clinic levels to address adolescent needs.

Hosek reviewed a number of different interventions that have been developed to support PrEP adherence and persistence for young women in sub-Saharan Africa, and young MSM (Abstract 67). Very light touch interventions and drug level feedback did not appear adequate to support PrEP use over time. Disclosure of PrEP use to friends, family, and partners and use of adherence clubs were strongly associated with PrEP adherence. Rousseau spoke about how we might market PrEP to youth (Abstract 69). Just like fast food, youth want PrEP that is quick, easy to access, inexpensive, with lots of choices, incorporates socializing, and takes into account busy lifestyles. Her talk included a number of insights into what young people may want to make PrEP more appealing, with examples of ways to reach out to youth.

PrEP Uptake, Adherence, and Implementation

Molina and colleagues presented updated data on daily and on-demand PrEP use in the ANRS (French National Agency for Research on AIDS and Viral Hepatitis) Prevenir Study (Abstract 148). In this open-label prospective cohort study of 3067 participants (98% MSM) in the Paris area, participants could opt for either daily or on-demand PrEP at baseline and could switch their PrEP regimen during the follow-up period. At baseline, 49% of participants chose on-demand PrEP, and 10% to 15% switched regimens during follow up. On-demand PrEP users had fewer condomless sex acts and fewer sex partners at baseline. Overall, 96% of daily PrEP users reported using PrEP at their last sexual intercourse, compared with 82% of on-demand PrEP users, with condom use reported in 17% to 20% of episodes. As expected, TFV-DP levels were higher among participants using daily PrEP than among those using on-demand PrEP (1264 and 691 fmol/L, respectively; P<.0001), and the proportion with undetectable FTC-TP, an indicator of recent PrEP use, was higher in the on-demand than the daily PrEP users (55% and 10%, respectively; P<.001). The self-reported median number of pills taken in the past week was 7 among daily PrEP users and 2 in on-demand users (P<.0001). Overall HIV incidence in the study was 0.11/100 person years with a mean follow-up time of 22.1 months. Three HIV infections occurred among daily PrEP users, and 3 among on-demand PrEP

HIV incidence was low (0.11/100 person years) among PrEP users on daily or on-demand PrEP regimens

users, resulting in a similar HIV incidence of 0.12/100 person years in both groups (IRR, 0.99; 95% CI, 0.13-7.38). All HIV infections occurred in the setting of stopping PrEP in the weeks to months before infection. Only one of these 6 participants had drug resistance (with an M184V mutation) at baseline, occurring in an on-demand PrEP user. Based on the HIV incidence of 6.6/100 person years observed in the placebo arm of the IPERGAY (Antiretroviral Pre-Exposure Prophylaxis for HIV Infection in Men Who Have Sex With Men) study, it is estimated that 361 HIV infections were averted by PrEP use in this cohort. The number of sexual encounters and condomless sex acts increased after PrEP initiation, particularly among PrEP-naive participants, although the overall number of sexual partners decreased in both PrEP-naive and -experienced participants. The incidence of STIs was high (66.5-75.5/100 person years) in this cohort, although STI rates declined during COVID-19 lockdown (32.4/100 person years). Hepatitis C incidence was high (0.69/100 person years) with 39 new diagnoses during the study. The rate of PrEP-related adverse events was low overall but higher in the on-demand group (7.52 and 5.82/100 person years, respectively), mostly due to an increase of gastrointestinal events, but only 3 participants (2 on daily and 1 on demand PrEP) discontinued PrEP due to gastrointestinal adverse events. Incidence of low creatinine clearance rate (<50 mL/min) was low (0.5/100 person years) and did not differ by PrEP arm, with no permanent discontinuations due to declining renal function. Overall, these findings further support the use of on-demand PrEP as an effective prevention strategy among MSM.

Tassi and colleagues presented data on the first 3 years of PrEP implementation in France (Abstract 698). Using data from the French national health database between 2016 and 2018, they identified 9893 PrEP users (99% men), with 95% of PrEP prescriptions from a hospital prescriber. The median number of PrEP dispensations per patient was 9 (IQR, 4-14), and 8% never refilled their PrEP prescription. HIV testing was completed in 64% of PrEP users at 1 month in 81% at quarterly testing, which remained stable over time. PrEP users were more likely to complete HIV testing if their last prescription was written by a hospital prescriber (OR, 2.04; $P<.001$) but were less likely to test if they never refilled their PrEP prescription (OR, 0.06-0.15; $P<.001$). There were 29 HIV diagnoses identified during the follow-up period, resulting in an HIV diagnosis rate of 0.19 cases per 100 person years (99% CI, 0.12-0.30). Among 18 infections that occurred more than 3 months after PrEP initiation, the median duration between last PrEP dispensation and HIV diagnosis was 180 days (IQR, 124-490). In this subgroup, PrEP users who never refilled their prescription were more likely to become HIV infected (RR, 4.7; 99% CI, 1.2-18.2).

Hoover and colleagues reported on trends in TDF/FTC and TAF/FTC prescriptions for PrEP in the United States

After approval of TAF/FTC for PrEP in the United States, 36% of new PrEP users were prescribed TAF/FTC, and 29% of TDF/FTC users switched to TAF/FTC

(Abstract 696). Based on data from the IQVIA prescription database, 36.3% of new PrEP users were prescribed TAF/FTC after its approval for PrEP on October 3, 2019, and 28.5% of 228,299 TDF/FTC users switched to TAF/FTC. PrEP users who switched from TDF/FTC to TAF/FTC were more likely to be older (aRR, 1.13 per 10-year increase), male (aRR, 3.15), Hispanic/Latino (aRR, 1.11), or living in the Midwest (aRR, 1.17), South (aRR, 1.56), or West (aRR, 1.08) compared with the Northeast, and were less likely to be cash payers (aRR, 0.71) or beneficiaries of other third party payers (aRR, 0.57) than those who had public insurance. These findings highlight the importance of monitoring the use of new patented and generic PrEP drugs as they become available to better understand implications for US healthcare expenditures.

Henny and colleagues reported on trends in PrEP users and prescribers in 48 EHE phase I urban jurisdictions by federal funding status (Abstract 703). From 2014 to 2019, based on data from the IQVIA national prescription database and the Healthcare Resources and Services Administration (HRSA) Uniform Data Systems, the number of PrEP users increased more rapidly in Federally Qualified Health Centers (FQHCs) (81-3625 respectively; estimated annual percent change [EAPC], 101.5) than in non-FQHCs (1575-23, 854; EAPC, 56.2). Similarly, the number of PrEP prescribers increased more quickly in FQHCs (22-229; EAPC, 49.1) than in non-FQHCs (564-3406; EAPC, 37.8).

Pathela and colleagues reported on the use of remnant sera testing to assess PrEP uptake in New York City sexual health clinics (Abstract 699). Among 744 patients with a newly diagnosed STI, 33% had serum samples with detectable tenofovir/FTC levels using liquid chromatography/mass spectrometry (LC-MS). Prevalence of PrEP use was highest in MSM with syphilis (44%) and lowest in women with gonococcus or syphilis (2%). PrEP use was also lower among black (20%) and Hispanic (28%) clients than among white clients (45%). Agreement between LC-MS and self-reported PrEP use was high (91%). In a multivariable model, PrEP use was associated with age 24 to 44 years (compared with age 15-24 years), having 6 or more sex partners in the past 3 months, having any partners with HIV in the past 6 months, and inconsistent or no condom use.

Dean and colleagues reported on the use of pharmacy reversals as a novel population-based metric of gaps in the PrEP care continuum (Abstract 700). They defined a PrEP reversal as an adjudicated and approved PrEP prescription that is not picked up by the patient and the claim is withdrawn from the pharmacy. Using a national claims database including up to 85% of all PrEP prescriptions in the United States, they identified 59,219 patients who were prescribed TDF/FTC as PrEP.

Among the 11,388 (19.2%) patients who did not pick up their prescription and had a reversal, 2344 (20.6%) had a delayed PrEP initiation (filled their prescription within 90 days), 962 (8.4%) had a very delayed initiation (filled a prescription within 90-365 days), and 8082 (71%) abandoned their prescription (did not fill a prescription within 365 days). Subsequent HIV diagnosis was more common among patients who abandoned their PrEP prescription (5.7%) than those who had picked up their initial prescription (2.2%) or had a delayed PrEP initiation (2.4%). The researchers suggest that intervening at pharmacy point-of-sale may be an opportunity to support PrEP engagement, and the first 90 days are crucial for retention.

Having a social network contact who started PrEP was associated with PrEP uptake in Kenya and Uganda

Koss and colleagues reported on the role of social networks in predicting PrEP uptake in the SEARCH (Sustainable East Africa Research in Community Health) study in rural Kenya and Uganda (Abstract 151). Among 8898 persons at elevated HIV risk with at least 1 network contact within PrEP intervention communities, 29% initiated PrEP. Individuals with a serodifferent partner or in a polygamous marriage were more likely to initiate PrEP, whereas those under age 25 years; in a fishing, bar, or transportation occupation; or who were mobile were less likely to initiate PrEP. For both men and women, having a network contact who started PrEP was associated with starting PrEP (aRR, 1.57; 95% CI, 1.44-1.70). In contrast, having a network contact with HIV was not associated with PrEP uptake, after adjusting for serodifferent partner and other predictors. These findings suggest that interventions that leverage existing peer networks and strengthen social connections to other PrEP users may help foster PrEP uptake.

Wagner and colleagues reported on predictors of PrEP uptake in a sexual health clinic offering immediate PrEP initiation (Abstract 705). Individuals eligible and interested in PrEP were immediately referred to a pharmacist for a 30-day supply of TDF/FTC and a case manager for PrEP care navigation. Among 2149 individuals tested, 1348 were eligible for PrEP. Of these, 517 (38%) were interested in PrEP and referred to the pharmacist, 333 (24%) started PrEP, 278 (21%) were linked to PrEP, and 78 (6%) were retained in PrEP care at 3 months. The mean number of days from HIV testing to PrEP dispensation was 4.1, and the mean number of days from dispensation to PrEP start was 1.1. Black individuals were less likely to start PrEP (aOR, 0.50) and be linked to PrEP care (aOR, 0.32), and those with private insurance were more likely to be linked to PrEP care (aOR, 1.85) and be retained in PrEP care (aOR, 3.94). Those with a greater number of sex partners in the past 3 months were more interested in PrEP (aOR, 1.06/partner increase) and were more likely to be retained in PrEP care (aOR, 1.13), and those with gonorrhea at screening were more interested in PrEP (aOR, 2.44), be more likely to initiate PrEP (aOR, 5.00) and be linked to PrEP care (aOR, 2.31).

Townes and colleagues reported on linkage to a PrEP prescriber and PrEP prescription among black women in the THRIVE Demonstration Project (Abstract 701). Among 7137 black cisgender women who were HIV negative enrolled across 7 THRIVE sites in the United States, 38% were eligible for PrEP and 35% were referred to a PrEP prescriber. However, only 3% were successfully linked with a PrEP prescriber and only 2% were prescribed PrEP. Approximately two-thirds of women were screened for STIs, with a 3.2% positivity rate for syphilis, 4.6% positivity rate for gonorrhea, and 4.8% positivity rate for chlamydia. These findings highlight the need for programmatic activities focused on meeting the HIV prevention needs of black women.

Watson and colleagues reported on rates of PrEP counseling among black youth after diagnosis with an STI in 2 primary care/government-subsidized clinics in Philadelphia (Abstract 723). Among 416 PrEP-eligible youth (63% assigned female sex at birth, 13% sexual/gender minority), 35 received PrEP counseling within 6 months of STI diagnosis, of which more than 80% were sexual/gender minority patients assigned male sex at birth. Receipt of PrEP counseling was associated with being assigned male sex at birth (aOR, 40.2; 95% CI, 3.32-487) and having a rectal STI (aOR, 61.7; 95% CI, 6.63-574), but was not associated with receipt of primary care services (aOR, 0.3; 95% CI, 0.05-1.84). Only 14 patients started PrEP, 12 of whom were sexual/gender minority patients assigned male sex at birth who received primary care services. Among 54 sexual/gender minority patients assigned male sex at birth, 5 (11%) seroconverted during this period. These findings support the need for PrEP inclusive sexual health services for black youth, including cisgender heterosexual women.

Rao and colleagues presented data on PrEP use and referral to PrEP care among black partners of people with HIV in the HIV partner services program in the United States (Abstract 702). Among 710 HIV-negative black partners of people with HIV identified through partner services across 20 health departments, only 52 (7.3%) reported taking PrEP at the time of contact. PrEP use did not vary by age, sex, or geographic region. Among 608 HIV-negative black partners not on PrEP, 251 (41.3%) were offered referrals to a PrEP prescriber. Black partners living in the South were less likely (14%; adjusted prevalence ratio [aPR], 0.25) and those in the Midwest more likely (70.4%; aPR, 1.23) than those in the Northeast (55.4%) to have been referred to PrEP prescribers. The researchers call for partner services programs

Cisgender women reporting physical or sexual violence had lower adherence to PrEP

to identify and remove barriers to improve PrEP services among black women at risk for HIV.

Freeman and colleagues presented data on the use of PrEP among MSM who experienced sexual violence in 23 US cities (Abstract 712). Among 7121 HIV-negative MSM participating in the 2017 National HIV Behavioral Surveillance, 5% reported sexual violence in the past 12 months. MSM who reported sexual violence were more likely than those not reporting sexual violence to have a clinical indication for PrEP (83% and 77%, respectively; P=.08) and use PrEP in the past year (35% and 26%, respectively; P=.01). Although percentages of PrEP use among black and Latino MSM were similar among those reporting versus not reporting sexual violence, white MSM who experienced sexual violence were more likely to use PrEP (44% and 32%, respectively; P=.028). MSM reporting sexual violence were more likely to use PrEP regardless of age, insurance status, or experience of same-sex discrimination in healthcare settings. These findings suggest that screening for sexual violence in clinical settings may provide an opportunity to identify PrEP needs and assess safety of MSM.

Anderson and colleagues reported on the impact of violence on PrEP adherence among cisgender women in the United States (Abstract 711). Among 136 women (38% black and 19% Latina) enrolled in the AEGiS (Adherence Enhancement Guided by Individualized Texting and Drug Levels) open-label PrEP study, 22% reported violence in the past year, including 16% reporting physical violence and 15% reporting sexual violence; 30% reported lifetime sexual violence. At week 4, 43% of participants were highly adherent, defined as having tenofovir diphosphate levels in DBS consistent with 4 or more doses/week. The odds of high adherence were lower among women reporting past year physical violence (aOR, 0.24; P=.03), past year sexual abuse (aOR, 0.25, P=.04), past year physical or sexual violence (aOR, 0.20; P<.01), and lifetime sexual abuse (aOR, 0.27; P<.01). These findings suggest that PrEP programs should emphasize trauma screening and care as a strategy to improve PrEP adherence.

Blumenthal and colleagues reported on PrEP adherence and retention among 136 cisgender women in the AEGiS open-label PrEP demonstration study (Abstract 713). At week 48, 61% of women were retained, and 31% had TFV-DP concentrations in DBS sampling consistent with 4 or more doses/week. In univariate analysis, black women (OR, 0.31), those attending sites in Los Angeles versus San Diego (OR, 0.37), and those having partners of unknown HIV risk (OR, 0.29) were less likely to have consistent TFV-DP levels with 4 or more doses/week across visits. In multivariable models, only black race and having partners of unknown HIV risk remained significantly associated with suboptimal adherence. For retention, severe drug abuse on the Drug Abuse Screening Test-10 was associated with lower likelihood of retention (OR, 0.23), and interest in becoming pregnant in the next 6 months was associated with greater likelihood of retention (OR, 3.07). In multivariable models, only pregnancy interest remained significantly associated with study retention.

Sullivan and colleagues presented results of a randomized trial of a Mobile App to improve HIV prevention and care outcomes among MSM (Abstract 706). The M-Cubed App was built on social cognitive theory and incorporated prevention messages on condoms, PrEP, STI, and HIV care; core services including establishing an HIV testing plan and service locators for PrEP, HIV testing and HIV care; and ordering of condoms and HIV/STI test kits. Among 1220 MSM enrolled in Atlanta, Detroit, and New York City, 427 were assessed as higher-risk HIV-negative, 410 lower-risk HIV-negative, and 383 with HIV. Higher-risk HIV-negative MSM randomized to receive the App had increased HIV testing at the immediate post-intervention assessment (PR, 2.02) and increased PrEP use 3 months post intervention (aOR, 2.41), however no significant effects were seen for lower-risk HIV-negative MSM and those with HIV.

Symposium 8 entitled "What Does PrEP Deliver", Palanee-Phillips discussed key considerations and lessons learned in implementing PrEP in young women (Abstract 53). Of the more than 300,000 people globally who have initiated PrEP, she highlighted that only a minority are women. PrEP demonstration projects have shown that women can initially adhere to PrEP. Early drop off is seen in approximately half of women, although restarting PrEP is also common. She recommended measuring prevention effective adherence, or adherence to PrEP during periods of risk. Flexibility in refill timing is important, as young women may not use PrEP daily and may only come for refills when they are out of pills. She emphasized the importance of awareness and demand creation; recognizing high rates of STIs, depression, and a history of intimate partner violence; and including messaging on the importance of adherence while at high risk for HIV exposure. As stigma is a barrier to sustained use, framing PrEP in a positive, empowering way that avoids linking it to relationship risk, may encourage PrEP uptake.

Millett spoke about challenges and opportunities in implementing PrEP in key populations (Abstract 54). He reminded us that currently, key populations make up more than half of all new infections globally, including 80% of new infections outside of sub-Saharan Africa, and 25% in sub-Saharan Africa. In a series of studies evaluating the PrEP cascade, he showed that knowledge of PrEP was low in many key populations, including MSM in low and middle income countries, and female sex workers and transgender persons globally. Despite high proportions of these key populations expressing willingness to take PrEP, uptake is low, and persistence, even after just a few months, is almost nonexistent. Some of the barriers to PrEP uptake and persistence include criminalization of sex work or homosexuality, stigma, cost, and access to care. He also presented data that, in countries in which sex work or homosexuality is criminalized, HIV prevalence is markedly higher, suggesting that this

restricts use of effective prevention strategies.

Kamya discussed innovative models and lessons learned in delivering PrEP in East Africa (Abstract 55). In 2019, there were 177,000 new HIV infections in the East Africa. As of December 2020, there were an estimated 83,000 PrEP users in Kenya, 68,000 in Uganda, 23,000 in Tanzania, and 5500 in Rwanda. He provided examples of several different PrEP delivery models, including facility-based models providing PrEP to serodifferent couples in HIV clinics, integrating PrEP service delivery into maternal/child health and family planning clinics where women are already receiving reproductive health services, and diversifying service delivery settings into community settings through community clinics and safe spaces, drop-in centers, mobile testing units, and in fishing communities. Although PrEP continuation rates were modest across a number of programs,

Diversifying PrEP delivery sites and simplifying service delivery can facilitate scale-up of PrEP

Kamya emphasized that we should not expect that the PrEP cascade look like the ART cascade because of varying patterns of risk, and continuation may be higher among persons with ongoing risk. Several programs have shown evidence of lower HIV incidence in PrEP programs than in historical controls or models, including the SEARCH study, in which PrEP initiators had a 74% lower HIV incidence than matched controls. For the next phase of PrEP scale-up, he highlighted the need to further diversify and simplify service delivery, including reducing laboratory monitoring and providing longer refills, streamlining facility-based care, expanding to additional community sites such as pharmacies and home delivery services, and training and supporting prescribers, including via virtual networks.

Pillay discussed important considerations in incorporating injectable PrEP and newer formulations in lower- and middle-income countries (LMICs) (Abstract 56). He pointed out that LMICs are not homogenous, but vary by a number of factors including demography, economy, leadership and decision making, regulatory environment, and role of development and implementing partners. Uptake of PrEP has been low in a number of LMICs, with only 1325 PrEP initiations in India as of December 2020. He discussed several strategies to enhance delivery and uptake of long-acting PrEP agents in LMICs, including use of social media to introduce new products, leveraging online delivery platforms, and use of community-based services such as pharmacies and community health workers. He reviewed a framework for planning for the introduction of new technologies, including regulatory and policy considerations, implementation and financial planning, preparing for service delivery, and developing communication and social mobilization to create demand. He discussed the need for strategies to manage ambiguous HIV test results in the setting of long-acting PrEP, including mechanisms to facilitate discussion between clinicians and virologists. Key informant interviews with PrEP users highlighted the importance of choice in PrEP options. He recommended that long-acting PrEP be offered in a mainstream approach and should not be stigmatized as was done with oral PrEP, which was focused in marginalized communities.

Modeling the Impact of PrEP and Cost

Neilan and colleagues presented on the cost effectiveness of long-acting PrEP among MSM and transgender women in the United States (Abstract 150). Using a microsimulation model to simulate a PrEP-using population with characteristics similar to US HPTN 083 trial participants, they examined the cost and impact of 4 PrEP strategies: no PrEP, generic TDF/FTC, branded TAF/FTC, and CAB-LA. Model parameters included an annual cost of $8300 for generic TDF/FTC, $16,600 for branded TAF/FTC, and $25,800 for CAB-LA (based on the price for injectable cabotegravir/rilpivirine for ART) plus program costs of $400 for TDF/FTC and TAF/FTC and $700 for CAB-LA to admininster injections. Over a 10-year period, the model estimated that the no PrEP strategy would result in 178,000 HIV transmissions at a cost of US $33 billion, generic TDF/FTC and branded TAF/FTC 122,000 transmissions ($45 and $60 billion, respectively), and CAB-LA 107,000 transmissions ($76 billion). CAB-LA yielded the highest total quality-adjusted life expectancy (QALY). Despite assuming a more favorable safety profile with TAF/FTC, the incremental QALY of branded TAF/

To be cost effective, CAB-LA should be priced competitively with generic TDF/FTC

FTC over TDF/FTC was only 2000 per QALY. The incremental cost effectiveness ratio (ICER) for CAB-LA compared with generic TDF/FTC was $1,069,000 per QALY, much higher than commonly accepted cost-effectiveness thresholds ($100,000/QALY). The ICER for branded TAF/FTC indicated that this regimen had a higher cost and delivered fewer benefits than generic TDF/FTC and CAB-LA combined. CAB-LA was found to be cost effective if the price was reduced to $11,600 (maximum price premium over generic TDF/FTC, $3300) and cost-savings if CAB-LA cost was reduced to $10,200 (price difference, $1,900 with generic FTC/TDF). The researchers conclude that CAB-LA would not be cost-effective if CAB-LA for HIV prevention is priced the same as combination cabotegravir/rilpivirine used for treatment, and instead should be priced competitively with generic TDF/FTC.

Jacobson and colleagues modeled the effects of additional HIV prevention and treatment spending on the likelihood of achieving EHE goals in the United States (Abstract 704). Using an estimate of current public and private HIV prevention spending of $2.8 billion, they projected the impact of an additional $0.5 billion/year spending in 2020 and 2021, an additional $1.5

billion per year in 2022 and 2024, and an additional $2.5 billion per year in 2025 and 2029. They also considered 3 scenarios of spending optimization (allocating spending to the most effective intervention until no one else can be reached, then shifting spending to the next most effective intervention): no optimization, optimization started in 2025, and optimization started in 2022. Over a 10-year period, new HIV infections decreased by 186,737 to 239,881 infections with additional spending. Annual new HIV infections in 2029 dropped to 7814 with no optimization, 3194 with optimization starting in 2025, and 2368 with optimization starting in 2022. These findings suggest that increased funding with early spending optimization is required to reach target EHE goals (<3000 cases by 2029), although this may be difficult due to barriers in reallocating funds among public and private funds.

Luz and colleagues modeled the impact of PrEP uptake on HIV transmission among MSM in urban centers in Brazil (Abstract 771). Using the Cost-Effectiveness of Preventing AIDS Complications (CEPAC) model, they estimated that increasing PrEP uptake to 60% over a 2-year period could decrease HIV incidence by 32% to 36% in 5 years and 39% to 45% in 10 years in Rio de Janeiro, Salvador, and Manaus. In sensitivity analyses, mean age of the cohort, PrEP dropout rates, and PrEP adherence significantly impacted the number of HIV infections averted.

Bórquez and colleagues modeled the impact and cost-effectiveness of PrEP among MSM and transgender women in Peru (Abstract 772). Using a dynamic HIV transmission model and data on PrEP uptake, retention, and adherence from the ImPrEP demonstration project, they estimated that 26% of new HIV infections could be averted by scaling up PrEP coverage to 20% of the MSM and transgender women populations between 2022 and 2030. The impact would be highest among transgender women and male sex workers. The cost of one year of PrEP was estimated at $680, and cost per disability-adjusted life year (DALY) averted was $3953, which would be considered cost-effective under most thresholds.

All cited abstracts appear in the *v*CROI 2021 Abstract eBook, available online at www.CROIconference.org

Financial affiliations in the past 24 months: Dr Buchbinder has no relevant financial affiliations with ineligible companies to disclose at this time. (Updated 01/21/21) Dr Liu has received investigator-initiated research grants from Viiv Healthcare and Gilead Sciences and has participated in research trials that received provision of medicines from Gilead Sciences, Inc. (Updated 4/22/2020)

Additional References Cited in Text

1. Fojo A, Schnure M, Kasaie P, Dowdy D, Shah M. The Johns Hopkins epidemiologic and economic model: A mathematical model in service of ending the HIV epidemic in the US. Available at: URL: https://jheem.shinyapps.io/EndingHIV/. Accessed March 30, 2021.
2. Hembree W, Cohen-Kettenis P, Gooren L et al. Endocrine treatment of gender-dysphoric/gender-incongruent persons: An endocrine society*clinical practice guideline. *The Journal of Clinical Endocrinology & Metabolism* 2017;102(11):3869-3903.

Top Antivir Med. 2021;29(2):309-327.

Invited Review

CROI 2021: Metabolic and Other Complications of HIV Infection or COVID-19

Sudipa Sarkar, MD; Todd T. Brown, MD, PhD

Comorbid conditions have a major impact on the health, quality of life, and survival in people with HIV, particularly as they age. The 2021 Conference on Retroviruses and Opportunistic Infections featured excellent science related to specific comorbidities as well as multimorbidity. A number of presentations related to comorbidities in women with HIV reflected a new wave of research aimed at understanding how the epidemiology and pathogenesis of comorbidities may differ by sex. Weight gain related to antiretroviral therapy was also a major theme of the comorbidity abstracts presented at the meeting. Several presentations demonstrated the importance of comorbid conditions in COVID-19 outcomes in people with HIV and described persistent symptoms after acute SARS-CoV-2 infection has resolved, a nascent topic that will expand over time. This review focuses on research presented at the conference in these areas, highlighting those with the most clinical impact.

Keywords: HIV, CROI 2021, comorbidity, COVID-19, weight, cardiovascular disease

Multimorbidity

Comorbid conditions are common in people with HIV. When these comorbid conditions cooccur, it is termed multimorbidity, which is a major threat to lifespan and healthspan in people with HIV. Paudel (Abstract 525) used administrative claims data from Optum Research Database in the United States to determine whether the prevalence of specific comorbidities and multimorbidity in a single calendar year (2018) differed in 20,256 people with HIV and 40,512 people without HIV, matched by age, sex, race, region, and insurance type. The mean age was 52 years, 80% were male, 46% were white, and 59% lived in the US South. Multimorbidity, defined as the presence of 3 or more comorbidities based on International Classification of Diseases (ICD)-9/10 diagnosis codes from medical claims, was more common in people with HIV than in people without HIV (37.2% vs 31.7%, respectively; $P<.01$). Along with this higher prevalence of multimorbidity, polypharmacy (≥5 non-antiretroviral therapy [ART] medications) was more prevalent among people with HIV than among people without HIV (76% vs 61%, respectively; $P<.001$). Given the type of data used, some key variables, such as body mass index (BMI), were not accounted for in the analysis. Nevertheless, these findings provide strong evidence regarding the magnitude of multimorbidity and polypharmacy in people with HIV, a crucial indicator how people with HIV may age.

As the population living with HIV ages over the next 10 years, the prevalence of multimorbidity will increase. Investigators from the PEARL (Pilot Randomized Clinical Trial of Early Coronary Angiography Versus No Early Coronary Angiography for Post-Cardiac Arrest Patients Without ECG ST Segment Elevation) study used Centers for Disease Control and Prevention (CDC) surveillance data and longitudinal data from the NA-ACCORD (North American AIDS Cohort Collaboration On Research and Design) to estimate the number of people in the United States who will be receiving ART from a period from 2017 to 2030 and the prevalence of several key comorbidities, including diabetes mellitus, hyperlipidemia, hypertension, myocardial infarction, chronic kidney disease, end stage liver disease, depression, and anxiety (Abstract 102). The models also took into account projected changes in BMI, smoking, and chronic hepatitis C and examined specific risk groups.

Overall, the median age of ART users in the United States is expected to increase from 50 years in 2020 to 53 years in 2030 with more than 25% being 65 years old and older

Overall, the median age of ART users in the United States is expected to increase from 50 years in 2020 to 53 years in 2030 with more than 25% being 65 years old and older. The prevalence of multimorbidity (defined as 2 or more of the conditions) is expected to increase in the population between 60 and 70 years and those older than 70 years. Among those older than 70 years, the prevalence of multimorbidity is expected to be 69% in 2030, up from 58% in 2020. In other age groups, the prevalence of multimorbidity increased from 2009 to 2020, but is expected to remain relatively stable until 2030. The comorbidities that are expected to rise the most in prevalence between 2020 and 2030 are anxiety (increase of 11.3%), chronic kidney

Dr Sarkar is Assistant Professor of Medicine at Johns Hopkins University in Baltimore, Maryland. Dr Brown is Professor of Medicine at Johns Hopkins University in Baltimore, Maryland. Send correspondence to Todd T. Brown MD, PhD, Professor of Medicine and Epidemiology, Division of Endocrinology, Diabetes, and Metabolism, Johns Hopkins University, 1830 East Monument Street, Suite 333, Baltimore, MD 21287 or email tbrown27@jhmi.edu.

disease (9.4%), and diabetes mellitus (8.6%). The greatest increases in multimorbidity prevalence were in men who have sex with men, particularly among African American and Latinx populations. These data have important implications for the health care needs of aging people with HIV over the next 10 years.

Sex Differences in Comorbidities

An emerging theme in HIV comorbidities at CROI 2021 was the potential difference in the prevalence and underlying pathogenesis of comorbid conditions by sex. Collins and colleagues used data from the MACS/WIHS (Multicenter AIDS Cohort Study/Women's Interagency HIV Study) Combined Cohort Study (MWCCS) to determine whether the increase in comorbidities with aging that is observed in people with HIV differs in women than in men (Abstract 526). Using data from 2009 to 2019 and summarizing data at the most recent available visit, investigators determined whether the burden of comorbidities (a count of 10 different common comorbidities) differed by sex, and whether older age and HIV serostatus modified these relationships. Overall, the mean number of comorbidities was higher in women than in men (3.4 vs 3.2, respectively; $P = .015$). Notably, the comorbidity burden increased markedly by age group in men and in women and was higher in those with HIV. These differences persisted after adjustment for race, BMI, smoking, drinking, crack/cocaine use, and socioeconomic status. The major finding of this analysis is that the 3-way interaction term between age, HIV status, and sex was statistically significant, meaning that the HIV-related differences in the increasing comorbidity burden with age was greater in women than in men. These data raise the question of whether or not screening and treatment practices for comorbid conditions in people with HIV should occur at an earlier age in women than men.

Increased systemic inflammation may drive the pathogenesis of multimorbidity in people with HIV and sex-based differences in inflammation and immune activation may be an important underlying mechanism to explain the increased comorbidity burden in women with HIV compared with men with HIV. Schnittman and colleagues (Abstract 98) conducted a case cohort study within CNICS (Centers for AIDS Research Network of Integrated Clinical Systems) examining 11 different inflammatory biomarkers measured 1 year after ART-mediated viral suppression in persons who were subsequently diagnosed with an incident type 1 or 2 myocardial infarction, ischemic stroke, or venous thromboembolism and at the same time point in a randomly selected group that did not develop the one of the outcomes. After adjustment for age, nadir CD4+ cell count, smoking, injection drug use, atherosclerotic cardiovascular disease (ASCVD) risk score, and hepatitis C history, women had higher concentrations of multiple biomarkers than men, including C-reactive protein (CRP), lipopolysaccharide-binding protein (LBP), soluble cluster of differentiation 14 (sCD14), soluble urokinase-type plasminogen activator receptor (suPAR), intercellular adhesion molecule (ICAM)-1, and cytomegalovirus immunoglobulin (CMV IgG) ($P < .03$ for all). In general, many of the biomarkers were associated with the outcomes. However, there were some inflammatory markers that were associated with cardiovascular disease (CVD) events more strongly among women than in men with HIV (ie, kynurenine to tryptophan [KT] ratio and sCD14). In contrast, the biomarkers sCD14 and soluble tumor necrosis factor receptor 2 (sTNFR2) were associated more strongly with venous thromboembolism in men than women. These data suggest increased immune activation in women with HIV compared with men. In addition, sex can modify the relationship between increased systemic inflammation and clinical events.

Cardiovascular Disease

CVD is a major cause of mortality in people with HIV. Silverberg and colleagues assessed traditional CVD risk factors in a cohort of patients, including people with HIV (n=8,285 [5% of the cohort]) and people without HIV (n=170,517 [95% of the cohort]), within a single integrated health care system (Abstract 97). Patients with a history of CVD were excluded from the study. The authors calculated a disease management index (DMI) to reflect how well traditional CVD risk factors, including hypertension, dyslipidemia, and diabetes, were managed. A DMI of 100% indicated optimal management of a condition over a period of time. They found that the prevalence values of these risk factors did not differ significantly by HIV serostatus and that the DMI for these risk factors were similar between people with HIV and peo ple without HIV, except for lower hemoglobin A1c values (DMI 73% and 65%, respectively) and worse triglyceride levels (DMI 78% and 86%, respectively) in people with HIV. The risk of incident CVD was higher overall in people with HIV (adjusted hazard ratio [aHR], 1.18; 95% confidence interval [CI], 1.07-1.30) than in people without HIV and higher in people with HIV with well-managed hypertension than in those without HIV with well-managed hypertension, although the risk was not significantly higher in people with HIV with well-managed dyslipidemia or people with HIV with well-managed diabetes than in people without HIV. That the DMIs for CVD risk factors were similar between people with and without HIV in this specific integrated health care system but the risk of incident CVD was nonetheless increased in people with HIV with well-managed hypertension points to the need for more studies on optimizing CVD risk management in people with HIV.

More studies are needed to determine goals of CVD risk management focused on people with HIV

McGettrick and colleagues studied immune cells and inflammatory biomarkers to better characterize how inflammation is related to coronary

artery disease (CAD) in people with HIV (Abstract 100). Using principal components analysis in a study of people with HIV (n = 51) and people without HIV (n = 50) without prevalent CAD and propensity score matched for CVD risk factors, the investigators observed 3 clusters of 28 proteins and 10 T-cell biomarkers. Clusters 2 (characterized by greater T-cell senescence) and 3 (characterized by greater inflammation) had significantly greater proportions of people with HIV and had the strongest associations with subclinical CAD, which were not significantly attenuated after adjusting for HIV serostatus. This study highlighted the potential major roles that these pathways play in the pathogenesis of CVD, suggesting future targets to reduce the risk of CVD in people with HIV.

Weight Gain and Antiretroviral Therapy

In the context of the risk of developing cardiometabolic complications in people with HIV, Palella and colleagues studied the differential effects

InSTIs accounted for the initial 8 months of weight gain after ART switch, and TAF contributed to subsequent weight gain; no significant difference between InSTIs with regard to weight gain was observed

of ART-related weight changes, specifically in participants in the HOPS (HIV Outpatient Study) who switched to an integrase strand transfer inhibitor (InSTI)-based regimen with or without tenofovir alafenamide (TAF) (n = 441) versus to a non-InSTI-based regimen with or without TAF (n = 295) from 2017 to 2018 (Abstract 504). Although InSTIs accounted for the initial 8 months of weight gain after ART switch, TAF contributed to subsequent weight gain. Moreover, no significant difference between InSTIs with regard to contribution to weight gain was observed.

On a similar note, Patel and colleagues studied the effects of the long-acting InSTI cabotegravir (CAB) plus the nonnucleoside reverse transcriptase inhibitor (NNRTI) rilpivirine (RPV), which is administered intramuscularly every 4 or 8 weeks, compared with the effect of oral daily protease inhibitor (PI)-, NNRTI-, or InSTI-based ART, on weight gain using data from the ATLAS, FLAIR, and ATLAS-2M studies (Abstract 505). Over the 48-week follow-up period after the switch, weight in people with HIV in all 3 treatment groups (CAB + RPV every 4 weeks, CAB + RPV every 8 weeks, and oral ART) increased, with median (range) weight changes as follows: 1.2 kg (95% CI, -27.5-40.9) in the every 4-week CAB/RPV group, 1.25 kg/m^2 (95% CI, -16.0-22.2) in the every 8-week CAB/RPV group, and 1.0 kg/m^2 (95% CI, -28.0-39.0) in the oral ART group. The proportions of people with HIV in the 3 treatment groups whose weight increased by 10% or more were also similar among the groups.

Overweight and obese states are increasing in low- and middle-income countries. Bourgi and colleagues addressed this concern in individuals with HIV in their study on the InSTI dolutegravir (DTG) and its effect on weight gain, compared with the effect of NNRTI-based ART, in ART-naive people with HIV in the AMPATH (Academic Model Providing Access to Healthcare) cohort in Kenya (Abstract 509). Of the 17,053 study participants, 3% were in the DTG-based treatment arm, and 97% were in the NNRTI-based ART arm. At baseline, 25% of participants were overweight or obese, 62% were female, and 64% had a CD4+ count of 200 or more cells/mL. At 18 months, females in the DTG arm had a projected weight gain of 6.1 kg, compared with 2.8 kg in females in the NNRTI-based ART arm, 4.1 kg in males in the DTG arm, and 3.6 kg in males in the NNRTI-based ART arm ($P < .001$). A greater than 10% increase in BMI was associated with the following variables: DTG treatment, female sex, older age, and lower baseline CD4+ cell count. These findings, especially as they pertain to females, should be considered in the context of the benefits of DTG use in this patient population.

Osteoporosis and Frailty

Bone mineral density (BMD) decreases with the initiation of ART and does not return back to baseline during follow-up. Short-term bisphosphonate treatment may be an important strategy to attenuate this bone loss. McGinty presented the results of a randomized controlled trial in which ART-naive people with HIV initiating ART with tenofovir disoproxil fumarate (TDF)/emtricitabine (FTC)-containing regimen were randomly assigned to calcium/vitamin D3 supplementation with either oral alendronate 70 mg weekly or placebo for 2 weeks prior to ART initiation and for a total of 14 weeks (Abstract 96). Fifty people with a median age of

A short course of alendronate may be a useful strategy to attenuate BMD loss with ART initiation

35 years were entered, 86% of whom were male. The primary endpoint was at 50 weeks after ART initiation, at which time total hip BMD decreased by 2.7% in the placebo arm, and remained stable in the alendronate group (median change, 0.50%) ($P = .02$). This difference was seen also at the week-14 timepoint (ie, the end of alendronate course). Early differences were seen in the lumbar spine, however, between the arms at week 14 and week 26 (placebo -2.5% vs alendronate +0.05%; $P = .03$), but at week 50, the alendronate group had decreases in BMD, such that the week 50 differences between the arms were no longer statistically significant (placebo -3.7% vs alendronate -1.4%; $P = .10$). These data suggest that a short course of alendronate may be a useful strategy to attenuate BMD loss with ART initiation. Given the lack of differences between the arms at 50

weeks in the lumbar spine, it is possible that a longer course of alendronate would be needed to preserve lumbar spine BMD with ART initiation. It is also unclear the extent to which these findings are generalizable to women or to older persons with osteoporosis, 2 populations that may have the most clinical benefit.

Frailty has been defined as aging-associated decline and dysfunction across numerous physiologic systems leading to increased vulnerability to acute stressors and has been associated with various adverse outcomes. It has been operationalized using the 5 different phenotype criteria: low grip strength, low energy, slowed walking speed, low physical activity, and unintentional weight loss. Individuals with 3 or more of these criteria are considered frail. Although several studies have shown that the prevalence of frailty is higher than expected in people with HIV, the populations studied have been relatively young, generally 50 to 70 years old. The SEPTAVIH (Frailty in People Living with HIV Aged 70 Years or More: Screening Feasibility, Prevalence, Risk Factors and Impact on Pejorative Events) study enrolled ART-treated people with HIV 70 years and older in France and examined the prevalence and correlates of frailty (Abstract 537). Of the 510 participants, 13.5% were frail, 63.2% were prefrail (1 or 2 frailty criteria met), and 23.4% were robust. The factors associated with frailty were older age, increased comorbidity, and lower socioeconomic status, whereas HIV-related factors showed no association with frailty. Although there was no reference group without HIV, the prevalence of frailty was not markedly high for a population this age. Further follow up of this cohort will be essential to understand how the prevalence of frailty changes over time in this older people with HIV population.

Comorbidities in Special Populations

Turkova and colleagues studied treatment failure of DTG and 2 nucleoside reverse transcriptase inhibitors (nRTIs) versus standard of care ART (ritonavir-boosted PI, NNRTI, or non-DTG InSTI ART) as first- or second-line ART in the ODYSSEY (PENTA 20) randomized trial of 707 children with HIV younger than 18 years (Abstract 174). Among the participants, 88% were African, and 49% were female. The DTG arm was found to be superior with regard to treatment failure, and no significant difference in adverse effects was observed between the 2 groups. At 96 weeks, a greater increase in weight (difference [standard error {SE}], 1 kg [.4]) and BMI (difference [SE], 0.3 kg/m^2 [1]) was noted in the DTG-based treatment than in the standard of care arm. These changes occurred early and plateaued over the course of the study. In addition, lower total cholesterol was noted in the DTG arm at 96 weeks (-15 mg/dL; 95% CI, -19 to -11). Given the effect of DTG on weight gain that has been observed in specific groups of adult people with HIV, this study addresses the important point of the effect of DTG on weight in children. How the use of DTG may affect long-term weight in children is a subject for future study.

In addition to the effect of DTG on weight in children, another study presented at the conference investigated the effect of DTG on weight in pregnant women and the association of antepartum weight change with negative pregnancy outcomes, including stillbirth, preterm delivery before 37 weeks gestational age, small for gestational age (SGA) (<10% percentile), and neonatal death. Hoffman and colleagues studied 643 ART-naive pregnant women with HIV randomly assigned to 1 of 3 treatment arms: DTG plus FTC/TAF, DTG plus FTC/TDF, or efavirenz (EFV)/FTC/TDF (Abstract 176). The greatest weight gain (average, 0.378 kg/week) and the lowest number of adverse outcomes was observed in participants in the DTG plus FTC/TAF group. Women in the EFV/FTC/TDF group had the least weight gain (average, 0.291 kg/week). Low weight gain, as defined by less than 0.18 kg/week, was associated with a greater risk of the composite negative pregnancy outcome result of stillbirth, preterm delivery, and SGA. This study shed a needed light on the effect of DTG on weight in the special population of pregnant women and found that although DTG was associated with greater weight gain, greater weight gain was not associated with worse outcomes during pregnancy.

Biomarkers and Comorbidities

Large-scale proteomic studies have the potential to identify proteins that are associated with mortality risk in people with HIV. Using the VACS-BC (Veterans Aging Cohort Study Biomarker Cohort), a longitudinal study of veterans with and without HIV, of whom more than 90% were men and more than two-thirds were African American, Hsue and colleagues investigated the associations of proteins, which were measured using aptamer-based technology, with mortality risk from 2005 to 2019 (Abstract 99). An aptamer-based platform can measure about 5000 proteins with high sensitivity and specificity, using a relatively small sample amount. In this study, some of the proteins that were found to predict mortality in people with HIV, including EGF containing fibulin-like extracellular matrix protein 1 and vitamin K-dependent protein C, are involved in processes such as cell adhesion and coagulation. Adding the biomarkers interleukin (IL)-6, D-dimer, and sCD14 to a model of protein-based predictors did not affect the ability of the proteins to predict mortality in people with HIV. Given that CVD risk calculators for the general population underestimate CVD risk in people with HIV, the use of proteins in risk prediction models for people with HIV has the potential to have an impact on clinical decision-making in the future.

Similarly, McCrary and colleagues used proteomics to determine whether specific proteins were associated with cardiac dysfunction in children and young adults in Kenya who were perinatally infected with HIV. Cardiac dysfunction was defined by the myocardial performance index measured using echocardiogram (Abstract 612). The investigators found that in a study population of 176 participants, of whom 50% had cardiac dysfunction, those with cardiac dysfunction were older, had a greater body surface area (P < .001

for both), and had greater HIV RNA levels (P=.017). Proteins were measured using a proximity extension-antibody assay. Using the different models, the investigators found 4 proteins associated with an abnormal myocardial performance index. These proteins included suppression of tumorigenicity (ST2) and S100A12 (EN-RAGE), both of which are associated with negative cardiac effects. Similar to the findings in the study by Hsue and colleagues, the study by McCrary and colleagues highlights the role of proteomics in identifying patients with HIV at greater risk of morbidity.

Comorbidities and COVID-19

Comorbid conditions are important risk factors for worse COVID-19 outcomes. Sun and colleagues used data from the US National COVID Cohort Collaborative (N3C) to determine whether HIV or solid organ transplant (SOT) were associated with COVID-19 hospitalization and, among people with HIV, which of the comorbid conditions examined (determined by diagnostic codes in the 2 years prior to COVID-19 diagnosis) were associated with an increased risk of hospitalization (Abstract 103). Of 509,092 patients with COVID-19, 2932 were people with HIV, 4633 had a history of SOT, and 111 were people with HIV who had an SOT. Overall, 32% of the population with COVID-19 were hospitalized. Compared with those without HIV or SOT, the odds of hospitalization was 30% higher among people with HIV, 69% higher among those with SOT, and 65% higher among people with HIV with SOT, after adjustment for age, sex, race/ethnicity, site, liver disease, diabetes mellitus, cancer, renal disease, and comorbidity burden. These findings suggest that people with conditions associated with immune suppression like HIV and SOT have a higher risk of more severe COVID-19 outcomes, independent of other comorbidities. Whether comorbidities and HIV or SOT, when seen together, have an additive or multiplicative risk is unclear. Among those with HIV, individuals who were hospitalized with COVID-19 were more likely to have a history of myocardial infarction, congestive heart failure, peripheral vascular disease, pulmonary disease, or renal disease. Interestingly, diabetes mellitus and liver disease were not risk factors for hospitalization.

Frailty may also be a major risk factor for more severe COVID-19 disease among people with HIV. Lee and colleagues conducted a matched cohort analysis in which people with HIV who were hospitalized (n=68) were matched with HIV-negative persons hospitalized with COVID-19 (n=181) by hospital site, test date, age, sex, and socioeconomic status (Abstract 142). The primary outcome measure was clinical improvement over 28 days. People with HIV were less likely to have clinical improvement over 28 days (hazard ratio [HR], 0.57; 95% CI, 0.39-0.85; P=.005 compared with HIV-negative patients), but this effect was attenuated after adjustment for ethnicity, clinical frailty score, BMI, baseline hypoxia, duration of symptoms, hypertension, diabetes, malignancy, cardiac, lung, and renal disease. These findings suggest that concomitant comorbidity is a major driver of poorer outcomes in people with HIV hospitalized with COVID. Among the comorbid conditions examined, clinical frailty score (a even-point score) 1 was inversely associated with the primary outcome measure (HR, 0.79 per 1-point increase; 95% CI, 0.39-0.85), suggesting that frailty at baseline is a major determinant of COVID-19 hospitalization course.

Data were presented suggesting that frailty at baseline is a major determinant of COVID-19 hospitalization course.

Long-Term Complications of COVID-19

It has been more than a year since the first case of COVID-19 was diagnosed in the United States, and long-term complications of COVID-19 affecting numerous organ systems in survivors have become apparent. Shoucri and colleagues conducted a retrospective review using chart abstraction of long-term symptoms of COVID-19 at 3 months (n=488) and 6 months (n=364) in 1190 patients with COVID-19 who were hospitalized in New York City (Abstract 554). At 6 months, the following proportions of patients had evidence of symptoms: 28% with cardiopulmonary symptoms, 26.4% with generalized symptoms, 24.2% with neuropsychiatric symptoms, and 20.6% with gastrointestinal symptoms. Shoucri and colleagues' study demonstrates that a significant number of patients hospitalized with COVID-19 experienced at least 1 symptom months after initial hospitalization.

Along the same line, Darley and colleagues studied persistence of symptoms after COVID-19 infection in the ADAPT (Adjuvant Dynamic Marker-Adjusted Personalized Therapy Trial Optimizing Risk Assessment and Therapy Response Prediction in Early Breast Cancer) study (Abstract 551). Eighty-five patients with mild to moderate COVID-19 infection who received community-based care and 11 patients who were hospitalized with COVID-19 were included. Hospitalized patients were significantly older, with a mean age of 59 years (+/–9.6), compared with 43 years (+/–14) in patients with moderate COVID-19 and 47 years (+/–16) in patients with mild COVID-19, and predominantly male (90.9% in hospitalized patients and 62.2% in those with mild COVID-19 and 47.9% in those with moderate COVID-19). In addition, hospitalized patients were more likely to have diabetes, at 36.4%, than those with mild or moderate COVID-19 (<10% for both groups). At 3 to 4 months of follow up, 18% of patients reported fatigue, and 16% reported shortness of breath; at 8 months of follow-up, 30% of patients reported fatigue, and 17% reported shortness of breath. However, at 8 months of follow up, a majority of patients (80%) said that they had resumed their usual activities of living. This study illustrates that although a sizeable minority of patients experienced adverse symptoms after initial infection with COVID-19, the majority

reported returning to their baseline level of function by 8 months.

All cited abstracts appear in the CROI 2021 Abstract eBook, available online at www.CROIconference.org

Dr Sarkar has no relevant financial affiliations to disclose. (Updated April 8, 2021) Dr Brown has served as a consultant for Gilead Sciences, Inc, Merck & Co, Inc, Theratechnologies, and ViiV Healthcare. (Updated June 11, 2020)

Additional References Cited in Text

1. Rockwood K, Song X, MacKnight C et al. A global clinical measure of fitness and frailty in elderly people. *CMAJ* 173(5), 489-495.

Top Antivir Med. 2021;29(2):328-333.

Invited Review

CROI 2021: Neurologic Complications of HIV-1 Infection or Covid-19

Beau M. Ances, MD, PhD; Albert M. Anderson, MD; Scott L. Letendre, MD

The 2021 Conference on Retroviruses and Opportunistic Infections (CROI) featured a timely review of the neurologic complications of COVID-19 as well as new research findings on mechanisms by which SARS-CoV-2 may affect the brain. CROI included new and important findings about the neurologic complications of HIV-1, human polyomavirus 2 (also known as JC Virus), and cryptococcus. New long-term analyses of cognition in people with HIV-1 identified that cognitive decline over time is associated with multimorbidity, particularly diabetes, chronic lung disease, and vascular disease risk conditions. These conditions are associated with aging, and the question of whether people with HIV are at risk for premature aging was addressed by several reports. New findings from large analyses of resting state networks also provided valuable information on the structural and functional networks that are affected by HIV-1 infection and cognitive impairment. Several reports addressed changes after initiating or switching antiretroviral therapy (ART). Findings that will improve understanding of the biologic mechanisms of brain injury in people with HIV were also presented and included evidence that host (eg, myeloid activation, inflammation, and endothelial activation) and viral (eg, transcriptional activity and compartmentalization) factors adversely affect brain health. Other research focused on adjunctive therapies to treat HIV-1 and its complications in the central nervous system. This summary will review these and other findings in greater detail and identify key gaps and opportunities for researchers and clinicians.

Keywords: HIV, CROI 2021, COVID-19, SARS-CoV-2, neurologic complications, cognition, brain, CSF, neuroimaging, aging, neurotoxicity

Introduction

The effects of HIV-1 and SARS-CoV-2 in the central nervous system (CNS) was an important theme of several presentations at the 2021 *virtual* Conference on Retroviruses and Opportunistic Infections (CROI). Presentations focused on HIV pathogenesis and CNS reservoirs' persistent neurologic dysfunctions (as assessed by neuropsychiatric testing, imaging, or cerebrospinal fluid [CSF] evaluations) in virologically controlled people with HIV. New data were also presented on premature aging and the effects of aging-related comorbidities on brain function, which have become increasingly important as people with HIV age into their seventh decade and beyond. New data also provide encouraging news for reducing the neurotoxicity of antiretroviral therapy (ART), for treating cognitive impairment, and for advancing the HIV cure agenda. This review will focus on major thematic areas that may inform new research and stimulate further discussion of clinical management of HIV infection.

Observational Findings on the Effects of HIV-1 on the Brain

New Data on Cognition and Mood

People with HIV are highly diverse and differ in many characteristics including age, sex, race, ethnicity, drug use, and living location and conditions. A substantial proportion of people with HIV contracted their infection more than 20 years ago and are now aging into their seventh decade and beyond because of the benefits of ART. In the United States, this group has been the particular focus of research cohorts such as the MWCCS (MACS/WIHS Combined Cohort Study) and the CHARTER (CNS Antiretroviral Therapy Effects Research) study. CHARTER investigators reported on cognition and depression in people with HIV after more than a decade of follow up (Abstract 101). The 397 participants had been followed up for a mean of 12.4 years and had a mean age of 56 years. Nearly all took ART (mean duration, 15.3 years) and 91.9% had a plasma HIV RNA level below 200 copies/mL. Nearly a quarter (23.4%) had evidence of cognitive decline, compared with 5% of a normative population of people without HIV. Decline was associated with the presence of several comorbid conditions, including chronic lung disease (P=.021), diabetes (P=.004), major depressive disorder (P=.016), and hypertension (P=.021), as well as longer duration of ART (P=.048), nonuse of antihypertensive

In the CHARTER study, cognitive decline over 12 years was associated with chronic lung disease, diabetes mellitus, major depressive disorder, and hypertension

Dr Ances is the Daniel J. Brennan, MD, Professor of Neurology at Washington University at St. Louis in Missouri. Dr Anderson is Associate Professor at Emory University in Atlanta, Georgia. Dr Letendre is Professor of Medicine at University of California San Diego. Send correspondence to Scott Letendre at University of California, San Diego, Antiviral Research Center, 220 Dickinson St, Suite A, Mailcode 8208, San Diego, CA 92103 or email scottl@hey.com.

drugs ($P = .001$), and lifetime cannabis use disorder ($P = .043$) (model $P < .0001$). Speed of information processing, working memory, motor functioning, and verbal fluency were the cognitive abilities that contributed the most to global decline.

The HNRP (HIV Neurobehavioral Program) at the University of California San Diego reported on cognitive decline in a larger group of participants (n = 1195), but over a shorter period of observation (mean, 7.1 years), finding that a commonly used index of comorbid conditions, the Charlson Comorbidity Index, was associated with more rapid global cognitive decline, particularly in working memory ($P = .007$) and executive functioning ($P = .001$) (Abstract 328). The medical conditions that were most strongly associated with cognitive decline were diabetes, mild liver disease, and congestive heart failure.

A continuing debate in the field concerns the extent to which HIV and its effects on the immune system drive brain injury compared with comorbid conditions like diabetes, as this influences treatment approaches to managing conditions like cognitive impairment and depression. The CHARTER analysis did not find that either HIV RNA level or CD4+ cell count was associated with cognitive decline but the HNRP analysis found that lower CD4+ cell count was statistically significantly associated with cognitive decline in with in-person analyses. Of note, neither analysis included measures relevant to activity of the HIV reservoir among people with HIV who are taking suppressive ART, such as low-level HIV RNA production (eg, using a single copy assay) or cell-associated HIV DNA. Since HIV-1 infection increases the risk for many of these conditions (eg, diabetes, heart disease) compared with the general population, it may indirectly be responsible for cognitive impairment even in the absence of direct effects on the brain.

Another approach was used by Lam and colleagues to determine if people with HIV were at greater risk for incident dementia (Abstract 330). They analyzed data from more than 165,000 electronic health records from the Kaiser Permanente system and compared the incidence of dementia between people with HIV on ART (n = 11,302) and people without HIV (n = 154,620) who were followed up in primary care clinics between 2000 and 2016. Incident all-cause dementia diagnoses were identified using the International Classification of Diseases (ICD) codes that were confirmed via chart review for more than 300 randomly selected patients. A total of 264 people with HIV and 2006 people without HIV developed dementia during follow up. Incidence of dementia was 4.4 (people with HIV) and 2.1 (people without HIV) per 1000 person-years, for an incident rate ratio of 2.0 (95% confidence interval [CI], 1.8-20). The incidence rate ratio was highest in younger people with HIV but declined in older people with HIV, a pattern that has been identified elsewhere.

Chan and colleagues reported results from people who were first assessed in Thailand shortly after contracting HIV in the SEARCH (South East Asia Research Collaboration on HIV) program. This group focused on longer term changes (6 years) with regard to depression instead of cognition (Abstract 340). Prior studies have found that depressive symptoms, like cognitive performance, often improve after initiation of ART, but most have reported on shorter term change in people with chronic HIV infection. The focus of the Thai cohort on people with acute HIV infection is a strength that better allows indexing changes from the time of infection and ART initiation. Participants completed the 9-item Patient Health Questionnaire (PHQ-9) for depression symptoms and the Distress Thermometer (DT) for anxiety/stress at baseline (before ART initiation) and then again 12, 24, and 96 weeks after ART initiation and every 48 weeks thereafter. At baseline, the prevalence of moderate (21%) and moderate to severe (27%) depression symptoms were high. Those individuals who had a higher baseline PHQ-9 score also had a higher plasma HIV RNA level and a greater frequency of acute retroviral syndrome. As expected, both the PHQ-9 and DT scores improved after starting ART and were at subclinical levels after 24 weeks. In those who maintained viral suppression on ART for 6 years, depressive symptoms remained stable or improved.

As people with HIV age, they appear to develop aging-related diseases such as diabetes and hypertension more frequently than people without HIV. This has raised concerns about premature aging of people with HIV, which may be linked to the inflammation that can persist even during suppressive ART. An important question is whether people with HIV will also develop Alzheimer's disease more frequently or at a younger age than people without HIV. Several research groups have identified that cognitive impairment in people with HIV has different phenotypes, and this has been categorized by the National Institute of Mental Health in a Research Domain Criteria (RDoC) framework.[1] Using criteria from the Alzheimer's disease field, Moore and colleagues previously identified that a subgroup of people who were categorized as having HIV-associated neurocognitive disorder (HAND) may actually have amnestic mild cognitive impairment (aMCI), a distinction that has implications for therapeutic management. In another analysis based at the University of California San Diego, Moore and colleagues classified 264 people with HIV as having either aMCI (n = 25), HAND (n = 65), neither (n = 81), or both (n = 95) in order to determine if this influenced their progression over time (Abstract 331). The 4 groups did not differ in duration of HIV disease, ART use, or plasma HIV RNA level, but did in age, CD4+ cell count, and baseline cognitive performance, with the impaired groups performing worse than the group with neither aMCI nor HAND. Over a mean of 4.2 years of follow up, none of the groups had significant decline based on fully adjusted models, which was contrary to hypotheses. The absence of cognitive decline would seem to be reassuring, but since 3 of the 4 groups had cognitive impairment at baseline, this also means that the impairment did not improve, which could mean that the injury is irreversible or that new therapies are needed for people with

HIV who remain cognitively impaired even if they are already taking suppressive ART. This group also analyzed Alzheimer's disease-related biomarkers (amyloid-β 1-42 [Aβ42] and phosphorylated tau *p*-tau] 181) in CSF from

NAA, a marker of neuronal health, was lower at baseline but normalized after 24 months of ART. In contrast, choline, an inflammation marker, continued to be elevated 24 months after ART initiation

31 people with HIV who were older than 50 years and enrolled in the NNTC (National NeuroAIDS Tissue Consortium), finding that a higher p-tau/Aβ42 ratio, which is typical of people with Alzheimer's disease, was associated with worse Learning and Delayed Recall. Together, these (and other) findings support that people with HIV may develop Alzheimer's disease-type pathology, but they do not support the conclusion that people with HIV are at greater risk than the general population.

New Data on Imaging

In addition to the depression findings (Abstract 340), the SEARCH program also reported on the effects on white matter brain metabolism of 2 years of ART that was initiated following acute HIV infection (Abstract 163). A total of 37 people with HIV were assessed by magnetic resonance spectroscopy (MRS) within the left frontal white matter (FWM) prior to ART (baseline) and 24 months after ART initiation. Compared with people without HIV, people with HIV had lower total N-acetylaspartate (NAA) level, a marker of neuronal health, at baseline but values normalized after 24 months of ART. In contrast, choline, an inflammation marker, continued to be elevated 24 months after ART, supporting the conclusion that people with HIV do not only have persistent systemic inflammation during suppressive ART but persistent neuroinflammation as well. In Abstract 318, the potential difference in neuroimaging measures as a function of sex was examined. Kelly and colleagues compared brain volume proportion in virologically-controlled people with HIV (n=286) and people without HIV (n=105) of both sexes to assess how biologic sex may modify the effects of HIV on the brain. Total brain, white matter, and gray matter proportions were plotted as a function of age. In general, brain volume proportions were higher in women than in men irrespective of HIV status. Greater loss of white matter volume over time was seen in men with HIV than in women with HIV. Consistent with this observation, men with HIV also had higher concentrations of the axonal biomarker, neurofilament light, than women with HIV (P=.02). These findings reinforce the importance of designing mechanistic and therapeutic research that focuses on potential sex-based differences.

With the growth of imaging datasets in recent years, high dimension analytical methods, such as machine learning, are increasingly used in neuroHIV

The greatest differences in resting-state network topology identified by deep learning occurred in the dorsal and rostral lateral prefrontal cortex, anterior cingulate, parietal regions, and caudate

research. For example, Luckett and colleagues identified potential relationships between HIV infection, structural and functional organization of the brain, cognition, and aging (Abstract 146). These authors used a machine learning-based approach within a cohort of virologically controlled people with HIV (n=297) on ART and people without HIV (n=1509) to identify resting-state networks that relate to cognitive impairment. The salience (SAL) and parietal memory networks most strongly distinguished people with HIV (either cognitively impaired or unimpaired) from people without HIV. Comparing cognitively impaired people with HIV with those without HIV, additional involvement of the frontal parietal network (FPN) was observed. Limiting the dataset to just people with HIV, the SAL, FPN, basal ganglia, and ventral attention network most strongly distinguished cognitively impaired from unimpaired participants. A deep learning model was also used to generate voxelwise maps of resting-state networks that identified changes in resting-state network topology among the 3 groups. Anatomically, the greatest differences in resting-state network topology identified by deep learning occurred in the dorsal and rostral lateral prefrontal cortex, anterior cingulate, parietal regions, and caudate. These results support that different resting-state networks are affected by HIV and cognitive impairment.

Petersen and colleagues also used machine learning to study brain aging among people with HIV. They examined brain structure (gray and white matter volumes) and function (cerebral cortical blood flow) to characterize deviations from typical aging across the lifespan, finding evidence of accelerated brain aging in people with HIV, that is, machine learning-based overestimation of the actual age of older people with HIV, compared with people without HIV or younger people with HIV. They also showed that cerebral blood flow reductions were specific to older people with HIV who had detectable HIV RNA, and people with HIV with suppressed viral load were similar to people without HIV. Finally, imaging-based estimates of brain aging correlated with cognition, especially motor functioning. These findings suggest that imaging-based brain aging may be a useful noninvasive biomarker of neuropathology and cognitive impairment in people with HIV.

Viral Mechanisms in the Pathogenesis of HIV Disease in the Brain

The observational findings in the preceding section are very valuable, but they do not address the biologic mechanisms of brain injury, which are essential for designing interventions to treat the CNS complications of HIV disease. These mechanisms can be broadly categorized into viral mechanisms and host mechanisms. Before the widespread use of potent ART, published data supported that compartmentalization of HIV in the CNS occurred in a substantial proportion of people with HIV and conferred greater risk of brain injury. With expanding use of ART, clues that HIV itself may continue to affect brain health trajectory are emerging. These clues include data on cell-associated HIV DNA, CSF viral escape, and HIV proteins such as Tat. Joseph and colleagues reported on a new concept, the compartmentalized CSF viral load (CCVL, specifically the product of the percent of CSF-derived sequences in variable regions of the HIV envelope [V1-V3] that are CSF-specific and the quantity of HIV RNA in CSF) (Abstract 341). Among 50 people with HIV assessed in the Rakai Cohort in Uganda, individuals with higher CCVL had worse global cognitive performance (P=.049, particularly speed of information processing), more depressive symptoms (P=.003), and worse self-reported functioning (P=.044) compared with individuals with lower CCVL. This composite measure had larger effect sizes in relation to these outcomes than did each of the individual components used to calculate it. Whether the pre-ART CCVL influences brain health trajectory following ART initiation remains to be proven, but prior research from this group suggests that it may.[2] Using brain tissue from the NNTC, the same group also examined the phylogenetic relationship between envelope sequences from brain, CSF, and blood from 5 people with HIV who had subtype B HIV-1 infection, had HIV-associated dementia, and were not taking ART at the time of death. Three of the participants had brain- and CSF-derived sequences that were compartmentalized from blood-derived sequences. Although the divergence of brain- and blood-derived sequences has been demonstrated many times, the investigators extended their work to show that HIV DNA concentrations were highest in tissue from the basal ganglia, the frontal lobe (white matter), and the occipital lobe. Using the Affinofile assay that allows the density of CD4+ expression to vary, they also found that Env proteins derived from the compartmentalized sequences from CSF and brain had greater affinity for CD4 and thus enter cells with low CD4 density more efficiently, which is typical of the myeloid cells that HIV-1 productively infects in the brain.

Higher compartmentalized CSF viral load was associated with worse global cognitive performance, more depressive symptoms, and worse self-reported functioning

Compartmentalization of HIV-1 in the brain has crucial implications for the HIV cure agenda. To better understand the nature of HIV-1 persistence in the brain, the Manhattan Brain Bank site of the NNTC isolated neuronal and glial nuclei from postmortem frontal cortex collected from 27 decedents (6 people with HIV encephalitis, 15 people with HIV without encephalitis, and 6 people without HIV) and created integration site sequencing libraries 10X chromium single nucleus RNA-sequencing (snRNA-seq). They identified 1279 integration sites, predominantly from the glial cell fraction from those with HIV encephalitis. Glial integration sites were found preferentially in introns, gene dense regions, and active regions of the genome. Glial integration sites showed a stronger preference for integration into short interspersed nuclear element repeats than T-cell integration sites and contained a significantly lower proportion of clonal (5% vs 18%; P < .0001) and recurrent (13% vs 30%;P<.0001) integration sites. Based on snRNA-seq, the investigators were able to identify multiple clusters of cells (eg, excitatory neurons, astrocytes) but HIV expression was only present in those who had HIV encephalitis, primarily in microglia. Differential expression analysis revealed that microglia with active viral transcription had greater expression of core markers of activation (secreted phosphoprotein 1[SPP1], lipoprotein lipase apolipoprotein E [LPL APOE], FMS-related receptor tyrosine kinase 1[FLT1]) and decreased expression of markers of proliferation. These findings are somewhat diminished by many of the findings being present only in those who had HIV encephalitis, a condition that is typically characterized by high levels of HIV expression and that has a greatly reduced incidence in the modern ART era. Even when no HIV transcripts were detected, however, the investigators still found evidence of enhanced microglial activation, suggesting that low-level HIV may still be present even if they did not detect it.

Two groups reported on HIV RNA or DNA quantification in peripheral blood mononuclear cells (PBMCs), CD4+ T cells, or monocytes. The neuroHIV group at St. Vincent's Hospital in Sydney, Australia, extracted cellular DNA and RNA from CSF and blood collected from 20 people with HIV who were taking suppressive ART and used a more sensitive method than has typically been used to quantify HIV-1 transcripts and HIV-1 DNA, specifically the Double-R assay that is based on πCode MicroDiscs platform (Abstract 162). An 18-color flow cytometry showed that cells in the CSF were 91% memory T cells, with roughly equal memory CD4+ and CD8+ T cells. Other CSF cells were 3.1% CD14+CD16+ monocytes, 2.0% natural killer (NK) cells, and 0.4% B cells. HIV-1 RNA transcripts were quantified in CSF in 90% of participants (compared with about 10% in prior reports) and HIV-1 DNA was quantified in CSF in 80% of participants (compared with about 50% of historical controls). Concentrations of both were higher in CD4+ T cells from CSF than in PBMCs, although the significance of this finding is reduced since the comparison of the

CD4+ T-cell subset in CSF with the total mononuclear cell fraction from blood will amplify the differences between the compartments. Participants were also assessed with 1H-magenetic resonance spectroscopy and greater transcriptional activity in CSF cells correlated with lower NAA (ie, worse neuronal integrity) in FWM (P=.04) and posterior cingulate cortex (P=.055).

Greater HIV transcriptional activity in CSF cells correlated with worse neuronal integrity in frontal white matter and posterior cingulate cortex

Using the same overall design as prior SEARCH program analyses (ie, identifying people with acute HIV infection and then following them up over time after ART initiation), investigators isolated monocytes from cryopreserved PBMCs from 30 people with HIV and quantified total monocyte HIV-1 RNA by real-time polymerase chain reaction prior to ART and 96 weeks after ART initiation. Monocyte HIV-1 RNA was detected in 17 (57%) participants at baseline, but only in 3 of 30 (10%) at 96 weeks. The investigators compared these findings with a panel of soluble myeloid activation and proinflammatory biomarkers in blood and performance on a screening battery of 3 neuropsychologic tests and found that participants who had detectable monocyte HIV RNA at baseline had higher neopterin concentrations and worse performance on 2 of the neuropsychologic tests (Color Trails 1, P=.014, and Trailmaking A, P=.05). Taken together, these findings support that HIV itself may continue to affect brain health trajectory, even during suppressive ART, but sufficiently sensitive methods are needed.

Many groups have found evidence of CSF viral escape, which is generally defined as detectable HIV-1 RNA in CSF when it is undetectable in blood or, when HIV-1 RNA in blood is detectable, having HIV-1 RNA at least 0.5 $\log_{10}$ copies/mL higher in CSF than in blood. Its presence can occur with severe neurologic symptoms or with no symptoms at all and some, but not all, studies have found associations with ART (eg, use of HIV protease inhibitors) and HIV-1 (eg, presence of drug resistance mutations) characteristics. Investigators from the Swiss HIV Cohort and the NAMACO (Neurocognitive Assessment in the Metabolic and Aging Cohort) study sought to validate these findings by reporting on CSF collected from 287 people with HIV. CSF viral escape was present in 29 (10.1%), of whom 18 (62%) had suppressed plasma HIV-1 RNA and 11 (38%) had detectable plasma HIV-1 RNA. Characteristics of patients were comparable whether or not they had CSF viral escape, including demographics, cardiovascular and metabolic comorbidities, time since HIV diagnosis (12 vs 16 years, respectively; P = .40), CD4 + T-cell count (553 vs 611 cells/μL; P=.10), CNS Penetration-Effectiveness score (7 vs 8; P=.20), neurocognitive diagnosis, or presence of magnetic resonance imaging (MRI) abnormalities. These findings confirm that CSF viral escape occurs in a minority of people with HIV, but its pathologic significance continues to be unclear, although it may have implications for achieving functional cure in the people who have it.

Host Pathogenesis of HIV Disease in the Brain

The persistent inflammation that occurs in people with HIV increases their risk for numerous aging-related comorbidities, including vascular disease and diabetes. Since inflammation and its downstream consequences have been linked to worse cognition and depression, understanding which of these most strongly influences brain health trajectory is important for directing therapy at the most impactful target. Guha and colleagues studied the potential role of cerebrovascular disease and its contribution to cognitive impairment in people with HIV by focusing on biomarkers that distinguish vascular cognitive impairment from HAND (Abstract 320). They measured soluble biomarkers of vascular injury (ICAM-1, VCAM-1, C-reactive protein), inflammation (interferon [IFN]-α, interleukin [IL]-1β, IL-6, IL-8, IL-15, C-X-C motif chemokine ligand 10 [CXCL10], chemokine ligand 2 [CCL2], vascular endothelial growth factor [VEGF]), and brain injury (total tau, glial fibrillary acidic protein [GFAP], YKL-40) in CSF and blood from 143 people with HIV on ART and 64 people without HIV from the NNTC and the CHARTER Study. Overall, people with HIV had higher levels of intercellular adhesion molecule (ICAM)-1, C-reactive protein, IL-8, IL-15, CXCL10, and VEGF in plasma and higher levels of C-reactive protein, CXCL10, VEGF, and GFAP in CSF than people without HIV. Among people with HIV, those with HAND had higher plasma ICAM-1, vascular cell adhesion protein (VCAM)-1, C-reactive protein, and YKL-40 as well as brain injury biomarkers (CSF total Tau, GFAP, YKL-40) than those without HAND. Furthermore, cerebrovascular disease was more prevalent among people with HIV who had HAND than among those without HAND and was associated with higher VCAM-1 and YKL-40 levels in plasma and higher total Tau and YKL-40 levels in the CSF. Overall, these results support that vascular disease may be more closely related to brain injury in people with HIV on ART than inflammation. The importance of vascular disease was further supported by Cooley and colleagues, who examined the effect of cardiovascular disease risk on white matter integrity, as measured by diffusion tensor imaging in people with HIV (Abstract 319). The Framingham cardiovascular disease risk score was calculated for 166 virologically well-controlled people with HIV and 48 people without HIV. Cognitive performance and fractional anisotropy of major white matter tracts in the brain were compared between low, moderate, and high cardiovascular disease risk for the 2 groups. Results indicated that a moderate or high cardiovascular disease risk was associated with worse cognitive performance (psychomotor speed) and lower fractional anisotropy within several major white matter

tracts including the frontal aslant, frontal occipital, and inferior longitudinal fasciculus for both people with HIV and people without HIV. Since the Framingham cardiovascular disease risk score contains several modifiable components (eg, smoking, blood pressure, and cholesterol), the results suggest that treating these conditions may improve white matter injury in people with HIV.

Molsberry and colleagues also investigated cardiovascular disease risk factors and explored the relationship between statin use and cognitive performance over time in participants from the MACS (Multicenter AIDS Cohort Study) (n = 1407) (Abstract 338). In addition to their lipid lowering effect, statins have anti-inflammatory properties that can improve endothelial function and enhance dynamic cerebral blood flow. These effects could potentially improve cognitive performance. Using multivariable-adjusted linear regression to compare cognitive test performance prior to and after statin initiation, statin use was not associated with improved performance on any neuropsychologic test on the first test completion after statin initiation. Further analysis identified that people with HIV who initiated statins tended to have, on average, a faster rate of cognitive decline. HIV serostatus did not modify this association. These results caution against use of statins to protect or improve cognition.

El-Kamari and colleagues studied the association between cognitive performance and biomarkers of inflammation, insulin resistance, and body fat composition (by dual-energy X-ray absorptiometry [DEXA]) in ART-treated people with HIV (n = 65) and people without HIV (n = 33) (Abstract 329). Cognitive function was evaluated using Cognivue (6 cognitive domains and 2 performance parameters). People with HIV had worse overall cognitive performance and had worse performance in multiple domains (visuospatial, memory, executive function, naming/language, delayed recall, and abstraction). Among people with HIV, worse cognitive performance in multiple domains was associated with higher biomarkers of inflammation in blood (IL-6, soluble tumor necrosis factor receptor (TNFR)-I, soluble TNFR-II, C-reactive protein). Higher body fat composition (total percent fat and visceral adipose tissue) was also associated with worse cognition. These results contrast with those of Abstract 320 and support targeting inflammation but, of note, these investigators did not include vascular biomarkers in their analysis for comparison.

Vecchio and colleagues evaluated sex differences in 16 soluble biomarkers of inflammation and immune activation in CSF in relation to cognitive performance in a cohort of virally suppressed people with HIV (n = 83) in Uganda (Abstract 321). Overall, men performed worse on various cognitive measures including timed gait, motor skills, executive performance, and semantic fluency than women, and men had stronger associations between biomarkers and cognition than did women. Thus, inflammation may more strongly influence cognition in Ugandan men than women with HIV. Further supporting a role for inflammation in men, Anderson and colleagues presented data from the MACS in the United States on GlycA, a composite blood biomarker of glycosylated proteins that reflects acute phase reactants (including alpha1-acid glycoprotein, haptoglobin, and others) in 843 men, 63% of whom had HIV-1 infection (Abstract 324). In multivariable analyses, higher GlycA was associated with impairment when incorporating 5 other biomarkers individually (C-reactive protein, IL-6, CCL2, sCD14, and soluble CD163). The association between GlycA and impairment was driven by people with HIV, particularly those with a higher C-reactive protein level (odds ratio, 1.84; 95% confidence interval, 1.17-2.89). This study provides more evidence that systemic inflammation plays a role in cognition among people with HIV.

Myeloid cells remain critically important in the pathogenesis of HIV-1 in the brain. Several reports extended work in this area, including Veenhuis and colleagues, who used a test-validation approach to assess myeloid cell proportions from 2 independent cohorts of virologically suppressed women with HIV-1 infection in Baltimore (n = 19) and New York City (n = 18) (Abstract 322). A higher proportion of intermediate (CD14+CD16+) monocytes, which express medium levels of CCR2, high levels of CX3CR1, are (C-C chemokine receptor type 5) CCR5 positive, and have proinflammatory effects, was associated with lower global cognitive performance at the time of cognitive testing ($P = .006$) and approximately 1 year before cognitive testing ($P = .02$). A higher proportion of classical monocytes was also associated with better cognition ($P < .05$). In contrast, no associations were found between monocyte subsets and mental health indicators, such as symptoms of depression or anxiety, although lower CD4+ T-cell proportion was associated with higher perceived stress ($P = .03$).

Collazo-Rodriguez and colleagues aimed to determine if exosomes from blood of women with HIV-1 infection induced a shift in uninfected monocytes toward this pathologic intermediate phenotype. They found that exosomes from women with HIV-1 were taken up by both uninfected classical and intermediate monocytes and that they caused a shift in phenotype toward intermediate monocytes and the extent of the shift did not depend on whether women had cognitive impairment or not, although exosomes from women who had cognitive impairment caused a more rapid shift toward the intermediate monocyte phenotype. Because of this well demonstrated importance of myeloid cells in the pathogenesis of HIV-1 in the brain, Hammonds and colleagues evaluated the performance of 4 myeloid cell models, specifically 2 microglial model cell lines (C20, HMC3) and 2 sources of primary cell-derived microglia (monocyte-derived microglia [MMG] and induced pluripotent stem cell-derived microglia [iPSC-MG]) (Abstract 351). Significant differences were observed upon gene expression profiling, with MMG and iPSC-MG clustering closely with primary human microglial cells, and C20 and HMC3 exhibited marked differences. Consistent with these differences,

iPSC-MG and MMG were readily infected with R5-tropic HIV-1, and C20 and HMC3 required pseudotyping for infection. HIV replication dynamics and HIV-1 particle capture, however, differed noticeably between MMG and iPSC-MG. Based on these and other findings, the investigators concluded that the iPSC microglia model provided a more authentic HIV-1 model system than the alternatives. These investigators are developing a 3-dimensional cerebral organoid model using these and other cells.

As noted earlier, people with HIV may experience earlier brain aging than people without HIV-1 and understanding the biologic mechanisms by which

Higher epigenetic age acceleration was associated with worse performance on attention and working memory in people with HIV but not in people without HIV

this occurs is a key gap in the field. In addition to imaging-based methods, brain aging can also be inferred by estimating cellular aging using methods such as DNA methylation or mitochondrial DNA (mtDNA). Shiau and colleagues measured DNA methylation in whole blood using Illumina EPIC Arrays in 69 people with HIV and 38 people without HIV who lived in New York City. The National Institutes of Health (NIH) Toolbox Cognition Battery was used to assess cognitive performance across 5 domains. Overall, chronologic age correlated with DNA methylation-estimated biologic age, but people with HIV had higher mean epigenetic age acceleration (EAA) and extrinsic epigenetic age acceleration (EEAA) than people without HIV. Higher EAA was associated with worse performance on attention and working memory in people with HIV but not in people without HIV.

Solanky and colleagues assessed associations between HIV-1 infection and either the quantity of mtDNA or of the mitochondrial common deletion from a buccal specimen, finding that people with HIV (n=124) had higher levels of both measures than people without HIV-1 (n=25) ($P<.0001$) (Abstract 326). When they compared these mitochondrial measures with a panel of soluble biomarkers in CSF and blood, they found that higher mtDNA level was associated with higher soluble TNFR-II ($P=.042$) and higher amyloid-β 1-42 ($P=.0005$) levels even after adjusting for HIV serostatus and demographic characteristics. The association with amyloid-β 1-42 was present in the subgroup of people with HIV, even after adjusting for duration of HIV and ART, and nadir and current CD4+ T cell count (model, $P<.0001$). A higher level of the mitochondrial common deletion was associated with higher soluble TNFR-II level in blood ($P=.004$) but not for CSF biomarkers.

Volpe and colleagues also worked with mtDNA but used MutPred pathogenicity scores to evaluate the influence of mtDNA variants on cognitive performance (Abstract 325). Among 744 people with HIV, the presence of any deleterious mtDNA variant was associated with motor impairment ($P=.03$), even in multivariable analyses. In ancestry-stratified multivariable analyses, people of European ancestry (n=317) also trended toward having an association with speed of information processing and people of African ancestry (n=357) trended toward having an association with working memory (P values = .06-.08). Overall, these results support that biomarkers that have been linked to premature biologic aging in people with HIV are also associated pathologic events in the CNS.

Interventional Findings on the Effects of HIV-1 on the Brain

Several clinical trials related to the CNS were presented. Yacoub and colleagues reported findings from a randomized, placebo-controlled clinical trial of intranasal insulin in 21 people with HIV who were taking suppressive ART and who had at least mild cognitive impairment. Six participants prematurely discontinued (3 due to nasopharyngeal irritation). Compared with placebo, intranasal insulin was associated with improvements in global cognition ($P=.029$) at 24 weeks, which was

Compared with placebo, intranasal insulin was associated with improvement in global cognition at 24 weeks, which was driven by improvements in verbal memory, visual memory, and attention

driven by improvements in verbal memory, visual memory, and attention. On a personal note, this study was led by Dr Ned Sacktor, whose untimely death in late 2020 cannot overshadow the many important contributions he made to the field.

Considering the importance of myeloid cells in the pathogenesis of HIV-1 disease in the brain, many have considered that CCR5 antagonists, such as maraviroc, might have particular benefit in the brain. Shikuma and colleagues reported findings from a randomized, placebo-controlled trial of adjunctive therapy with maraviroc in people with HIV who had sustained plasma HIV RNA suppression and at least mild cog nitive impairment (Abstract 333). Participants were randomized 2:1 and followed up for 48 weeks, resulting in 39 participants who completed all evaluations. At baseline, those randomly assigned to the maraviroc arm had worse global ($P=.002$) and motor ($P=.001$) performance. Participants in the maraviroc arm had significantly greater improvements in the combined learning/memory domain ($P=.009$) than participants in the placebo arm. No other domains significantly changed between the treatment arms. Of note, the study included people with HIV with very mild impairment who might not meet criteria for HAND (as minimal as neuropsychological testing performance (NPZ),-0.5), and the learning/memory domain change was not

statistically significant after adjusting for type I error.

With ongoing development of new ART drugs and treatment strategies, switch studies continue to provide important, clinically relevant data for people with HIV and their medical practitioners. Perez-Valero and colleagues performed an open-label switch study in which participants either continued a suppressive regimen of dolutegravir/lamivudine/abacavir or switched to darunavir/cobicistat/emtricitabine/tenofovir alafenamide (Abstract 339). Neuropsychiatric symptoms were evaluated with the Hospital Anxiety Scale, Hospital Depression Scale, Pittsburgh Sleep Quality Index, and neuropsychiatric adverse events by the NIH Division of AIDS criteria. At 4 weeks, participants who switched had a reduction in symptoms in 3 of the 4 categories (anxiety, neuropsychiatric adverse events, and sleep) compared with those who did not switch (n = 69 evaluable participants). This was particularly true for participants who had moderate to severe disturbances in sleep quality and sleep latency. Because the switch entailed a change of several drugs, it is unclear which medication(s) may have driven the results.

Calcagno and colleagues also reported a switch study in which people with HIV were randomly assigned to continue a suppressive ART regimen or to change to a regimen that was designed to minimize potential neurotoxicity (darunavir/cobicistat/emtricitabine/maraviroc) (Abstract 335). The study was interrupted for slow accrual after 38 people with HIV had been randomly assigned and had been followed up for 24 weeks. In the switch arm, parietal delta waves on electroencephalography, which can indicate brain injury, decreased ($P = .022$) as did phosphorylated Tau in CSF ($P = .002$) and liver fibrosis as measured by Fibroscan ($P = .038$).

In another switch strategy, Vergori and colleagues reported the results of a single-arm study in which 109 people with HIV on efavirenz/emtricitabine/tenofovir disoproxil fumarate switched to bictegravir/emtricitabine/tenofovir alafenamide (Abstract 334). Change in psychiatric symptoms and 5 domains of cognition were assessed at 48 weeks, at which point symptoms of depression and anxiety were less severe and sleep problems were less common. Global cognitive performance also improved, particularly executive function, attention/working memory, and learning/memory. Since this trial also switched several drugs, improvements cannot be attributed to a single drug. Importantly, the absence of both a comparison arm and the incorporation of practice effects in the analysis of the neuropsychologic test results are limitations of the study.

Another report that has implications for switching ART regimens in the clinic is the report on doravirine concentrations in CSF (Abstract 358). A total of 14 plasma and 15 CSF samples were collected with most participants replacing an integrase strand transfer inhibitor with doravirine. At week 4, 1 participant met a common definition of CSF viral escape with detectable HIV RNA CSF (32 copies/mL) but undetectable in blood plasma. Total doravirine concentrations in CSF were approximately 13% of those in blood. In CSF, doravirine was mostly unbound to drug-binding proteins (76.1%). The total CSF; unbound plasma ratio of doravirine was 0.99, supporting the conclusion that doravirine crosses the blood-brain barrier primarily via passive diffusion.

An additional switch study may have implications for brain health. Serrano-Villar and colleagues reported the effects of switching from a 3-drug to a 2-drug regimen on inflammation biomarkers over time in 148 people with HIV evaluated in the Spanish AIDS Research Network (Abstract 527). In this nonrandomized trial that included many 3- and 2-drug ART regimens, investigators found that participants who remained on a 3-drug regimen experienced a slow decline of numerous biomarkers over time (IL-6, C-reactive protein, soluble CD14, soluble CD163 and D-dimer). In contrast, switching to a 2-drug regimen was associated with increases in IL-6, C-reactive protein, and D-dimer (all P values $\leq .01$) over 3 years, after adjusting for covariates. Although 2-drug regimens have largely been safe for the brain in shorter term analyses, these findings raise concerns about their long-term effects on inflammation and coagulation.

Relevant to the HIV-1 cure agenda, McMahan and colleagues presented an interim analysis of a trial using the programmed cell death protein-1 (PD-1) blocker pembrolizumab (Abstract 345). Six people with HIV with virologic suppression for at least 12 months and CD4+ T-cell count above 350/mL were given a single dose of pembrolizumab. No grade 3 or 4 adverse events occurred but grade 1 or 2 adverse events involving blood, metabolic, and gastrointestinal systems were observed. PD-1+ CD4+ and PD1+ CD8+ T cells in CSF decreased at 3 weeks and appeared to rebound at 24 weeks. Cell-associated HIV DNA in CSF decreased by 46% after 3 weeks and remained persistently decreased by 7.7% after 24 weeks. The findings suggest that single-dose is generally safe in people with HIV and may decrease HIV in the CNS, but this was an interim analysis of a small number of participants within an ongoing study.

A single dose of pembrolizumab reduced cell-associated HIV DNA in CSF by 46% at week three with persistent decrease of 7.7% at week 24

There was also a CNS trial using the nonhuman primate model. Garcia-Mesa and colleagues presented a study in SIV-infected rhesus macaques of dimethyl fumarate, which regulates expression of antioxidant, anti-inflammatory, and cytoprotective genes via its effects on nuclear erythroid 2-related factor 2-antioxidant response element (Nrf2-ARE) pathway (Abstract 347). Five of 9 animals were treated with dimethyl fumarate, followed by examination of 11 brain regions. Several antioxidant enzymes (GPX-1, NQO1, HO-1, and PRDX1) were higher in the brains of the dimethyl fumarate-treated animals

in various brain regions. Dimethyl fumarate was also associated with lower oxidative stress end products (3-nitrotyrosine and 8-hydroxydeoxyguanosine), particularly in the brainstem, as well as lower mitochondrial redox state in both frontal cortex and brainstem. Although SIV RNA concentrations in CSF and blood did not change following dimethyl fumarate, the investigators did not quantify SIV RNA or DNA in brain tissue.

Findings on the Effects of SARS-CoV-2 or Other Infections on the Brain

SARS-CoV-2 Infection

Accumulating evidence shows that infection with SARS-CoV-2 can lead to neurologic complications. In an invited oral presentation, Benedict Michael discussed ongoing work on neuroCOVID in the United Kingdom (Abstract 51). He first contextualized SARS-CoV-2 in relation to other viruses that cause neurologic disease, including herpesviruses, West Nile virus, influenza virus, and Japanese encephalitis virus. He discussed the fact that viruses do not necessarily need to be neuroinvasive to cause neurologic disease, and that some viruses cause harm to the CNS by parainfectious and autoimmune pathways. This led to the initiation of numerous neuroCOVID studies, including a large surveillance system to monitor neuroCOVID cases, which had identified 511 cases to date in the United Kingdom. More than half (54%) involved a cerebrovascular event, which appears to be more common in older patients, and neuropsychiatric syndromes are more common in younger patients. However, cerebrovascular cases were generally younger than non-COVID-19 stroke cases collected from other surveillance systems. Patients with cerebrovascular events presented around the same time as the onset of respiratory symptoms, and patients with other neurologic symptoms more frequently presented about 2 weeks after onset of respiratory symptoms. The most significant predictors of poor outcome overall were older age and frailty. This surveillance system could serve as a model for other countries to monitor neuroCOVID cases.

In an oral presentation, Farhadian and colleagues from Yale and UCSF reported a cross-sectional study of immune responses in CSF collected from 6 hospitalized patients with SARS-CoV-2 infection and 11 healthy controls (Abstract 165). All 6 hospitalized patients had some degree of neurologic symptoms, including encephalopathy, headache, and seizures. None had elevated leukocytes or detectable SARS-CoV-2 RNA in CSF, although some had elevated total protein in CSF. Single-cell mRNA sequencing was performed, showing upregulation of pathways from both CD4+ and CD8+ T cells in CSF (including IL-1 and IL-12 responses) that were not upregulated in blood. Quantification of cytokines confirmed increase in IL-1β and IL-12 p70 in CSF, which again differed from blood (other biomarkers such as CCL2 and IL-8 were elevated in blood). Based on distinct CSF plasma cell clusters that were found in the SARS-CoV-2-infected patients, anti-SARS-CoV-2 antibodies were profiled and monoclonal antibodies were derived, resulting in the identification of 2 antispike antibodies from blood and one from CSF. The monoclonal antibodies were then incubated with mouse brain tissue, resulting in 4 CSF antibodies (including the antispike antibody) that had antineural immunoreactivity. This was followed by incubation of brain sections with whole CSF from SARS-CoV-2-infected patients, which again demonstrated increased antineural immunoreactivity compared with controls. These important findings support that the neurologic consequences of SARS-CoV-2 infection may result from CNS-specific immune responses, including from the humoral immune response. One limitation of the project is that it did not include biospecimens from people with SARS-CoV-2 infection who did not have neurologic complications.

Anti-SARS-CoV-2 antibodies were profiled and monoclonal antibodies were derived, resulting in the identification of 2 antispike antibodies from blood and 1 from CSF. The monoclonal antibodies were then incubated with mouse brain sections, resulting in 4 CSF antibodies that had antineural immunoreactivity

Using an in vitro model, Clough, Mahajan, and colleagues examined the effects of SARS-CoV-2 on the blood-brain barrier (Abstract 346). Human brain microvascular endothelial cells were treated with recombinant SARS-CoV-2 spike protein and heat-inactivated SARS-CoV-2. Compared with controls, cells treated with SARS-CoV-2 had increases in hypoxia inducible factor (HIF)1/2, nitric oxide synthase, the NLRP3 inflammasome, and several cytokines including TNF-α and IL-6. ACE2 (necessary for SARS-CoV-2 cell entry) was upregulated in treated brain microvascular endothelial cells, and blood–brain barrier integrity was decreased by 30% in the SARS-CoV-2 treated samples. Lastly, levels of 4 different tight junction proteins decreased in the SARS-CoV-2 treated samples compared with controls. Based on this study, SARS-CoV-2 appears to have a detrimental effect on the blood–brain barrier, which may be responsible for some of its neurologic sequelae.

Human Polyomavirus 2 Encephalitis

Progressive multifocal leukoencephalopathy (PML), caused by human polyomavirus 2 (also known as JC virus), still occurs in people with HIV, even in some individuals with CD4+ T-cell counts greater than 200/μL. Pinnetti and colleagues (Abstract 336) presented a small open-label study of 5 people with HIV with PML who were taking ART and who were treated with the PD-1 blocker, pembrolizumab. They observed a decrease in PD-1 expression on CD4+ and CD8+ T cells in blood and CSF in all participants, as well as

a decrease in human polyomavirus 2 DNA in CSF and an increase in human polyomavirus 2-specific T cells in blood. However, 2 participants died after a relatively short period and 1 participant experienced immune reconstitution inflammatory syndrome (IRIS). Although the changes in disease indicators is promising, more research is needed on pembrolizumab and other therapies for PML in people with HIV to evaluate safety and efficacy.

Cryptococcosis

Cryptococcal meningitis continues to be a devastating opportunistic infection in people with HIV with low CD4+ cell counts, particularly in sub-Saharan Africa. Drain and colleagues reported a prospective laboratory screening study for cryptococcal antigen in Umlazi Township, South Africa (Abstract 564). This study (n=908) occurred in 3 chronologic phases. Clinician-directed central laboratory cryptococcal antigen testing occurred in the first phase, followed by reflex central laboratory cryptococcal antigen testing based on CD4+ T cell count in the second phase, and then followed by point-of-care CD4+ T cell count and cryptococcal antigen testing by lateral flow in the third phase. Participants in the point-of-care phase were more likely to start ART and less likely to be lost to follow up than those in the clinician-directed phase. There was also a trend toward more frequent diagnosis of cryptococcal meningitis in the point-of-care phase. Thus, point-of-care CD4+ T cell count and cryptococcus testing may be beneficial in settings where low CD4+ T cell counts are common.

Peripheral Neuropathy

Complications of the peripheral nervous system remain common despite ART, although their severity is markedly reduced akin to the pattern observed with cognitive impairment in the modern treatment era. Ellis and colleagues (Abstract 348) evaluated the relationship between peripheral neuropathy pain symptoms and gut microbiota in 373 adults (72% people with HIV, 90% of whom were virologically suppressed). Peripheral neuropathy pain symptoms were more common and more severe in people with HIV ($P<.02$). More severe pain was associated with lower gut microbial diversity (determined by 16S rRNA sequencing) in people with HIV but not in people without HIV. Specifically, change to *Lachnospira* species from either *Ruminococcus* ($P=.007$) or *Streptococcus* ($P=.001$) species was significantly associated with peripheral neuropathy pain symptoms in people with HIV, raising the possibility that manipulation of the microbiome could be an approach to peripheral neuropathy in future studies of people with HIV.

All cited abstracts appear in the CROI 2021 Abstract eBook, available online at www.CROIconference.org

Financial affiliations in the past 12 months: Dr Ances has no relevant financial affiliations to disclose. (Updated April 11, 2019) Dr Anderson has no relevant financial affiliations to disclose. (Updated May 7, 2021) Dr Letendre has had travel paid for by ViiV Healthcare. (Updated March 26, 2019)

Additional References Cited in Text

1. National Institute of Mental Health. Research Domain Criteria. 2021.
2. Bowman NM, Joseph SB, Kincer LP, et al. HIV compartmentalization in the CNS is associated with neurocognitive impairment [CROI Abstract 401]. In Special Issue: Abstracts From the 2016 Conference on Retroviruses and Opportunistic Infections. *Top Antiv Med*. 2016;24(e-1):153.

Top Antivir Med. 2021;29(2):334-343.

Invited Review

CROI 2021: Tuberculosis, Opportunistic Infections, and COVID-19 Among People with HIV

Andrew D. Kerkhoff, MD, PhD, MSc; Diane V. Havlir, MD

Tuberculosis (TB) remains a main driver of morbidity and mortality among people with HIV along with other opportunistic infections. This review summarizes key highlights related to TB, and other opportunistic infections in HIV as well as studies from the virtual *2021 Conference on Retroviruses and Oppoprtunitstic Infections evaluating outcomes among HIV-COVID-19 coinfected patients.*

Keywords: HIV, CROI 2021, tuberculosis, coinfection, cryptococcosis, HPV, KSHV, COVID-19

Tuberculosis

Prevention and Treatment

Shorter tuberculosis (TB) treatment regimens represent a long-awaited advance in the field. Their global impact will be maximized if these regimens are effective and safe in people with HIV. At the *virtual* 2021 Conference on Retroviruses and Opportunistic Infections (CROI), Petit and colleagues reported the important subgroup comparison in people with HIV of the recently completed TB treatment shortening study (TB Trials Consortium Study 31/AIDS Clinical Trial Group [ACTG] A5349) that showed that a 4-month daily regimen of high-dose rifapentine, moxifloxacin, isoniazid (INH) and pyrazinamide (PZA) (rifapentine-moxifloxacin) but not a 4-month daily regimen of high-dose rifapentine, INH, PZA, and ethambutol (EMB)(rifapentine alone), was noninferior to the standard of care (SOC) 6-month TB regimen (2 months rifampicin/INH/PZA/EMB then 4 months of rifampicin/INH).[1] The primary endpoint was TB disease-free survival at 12 months from randomization with a noninferiority margin of 6.6%. Of the total 2516 persons enrolled in the study, 214 (8%) were people with HIV. People with HIV were required to have a CD4+ count above 100 cells/μL and be on an efavirenz-based antiretroviral treatment (ART) regimen. TB disease-free survival occurred in 53 of 58 (91%) in the rifapentine-moxifloxacin arm, 48 of 65 (74%) in the rifapentine-alone arm, and 50 of 59 (85%) in the SOC arm.

The standard 6-month, 4-drug TB treatment can be shortened to a 4-month regimen with high-dose rifapentine, moxifloxacin, isoniazid, and pyrazinamide

The rifapentine-moxifloxacin regimen was noninferior to the SOC regimen (absolute difference [AD] in TB disease-free survival, -6.6%; 95% confidence interval [CI], -18.3-5.0) and the rifapentine-alone regimen was not noninferior to the SOC regimen (AD, +10.9; 95% CI, -3.2-25.0). There was no difference in efficacy for each treatment regimen according to HIV status. Grade III or higher adverse events were less common in the rifapentine-moxifloxacin (14%) and the rifapentine-alone (17%) arms than in the SOC arm (21%); 0 deaths occurred in the rifapentine-moxifloxacin arm compared with 3 in the rifapentine-alone arm and 2 in the SOC arm. This practice-changing study provides strong evidence that a 4-month rifapentine-moxifloxacin regimen is non-inferior to the current standard 6-month regimen and is safe and well-tolerated, independent of HIV status. Notably, this study only enrolled people with HIV on an efavirenz-based ART regimen. As the global scale up of dolutegravir continues, further studies must demonstrate the safety and efficacy of rifapentine once daily with dolutegravir-based regimens before the rifapentine-moxifloxacin regimen can be utilized widely for the treatment of drug-susceptible TB in people with HIV.

The intersection between bictegravir, a highly potent integrase strand transfer inhibitor, and rifapentine, a key agent in the treatment of latent TB infection (LTBI), was explored in 2 studies at CROI this year; both suggest that bictegravir cannot be coadministered with rifapentine. In the first study among people with HIV with LTBI receiving concomitant bictegravir/emtricitabine (FTC)/tenofovir alafenamide (TAF) and daily INH plus rifapentine for 28 days (1HP), Sun and colleagues evaluated the proportion completing LTBI therapy, maintaining therapeutic bictegravir trough concentrations, and virologic suppression (Abstract 132). The study enrolled 50 people with HIV who had been on bictegravir/TAF/FTC for at least 2 weeks, were virologically suppressed (HIV RNA <200 copies/mL), and had evidence of LTBI confirmed by a positive interferon gamma release assay (IGRA). Investigators measured

Dr Kerkhoff is a senior research fellow at Zuckerberg San Francisco General Hospital and Trauma Center and the University of California San Francisco. Dr Havlir is Chief of the Division of HIV, Infectious Diseases, and Global Medicine at the Zuckerberg San Francisco General Hospital and Trauma Center and the University of California San Francisco. Send correspondence to Andrew D. Kerkhoff, MD, PhD, MSc, Division of HIV, Infectious Diseases and Global Medicine, Zuckerberg San Francisco General Hospital and Trauma Center, University of California San Francisco School of Medicine, 1001 Potrero Ave, 409, San Francisco, CA 94110 or email Andrew.Kerkhoff@ucsf.edu.

bictegravir trough concentrations, cytokine levels, and HIV viral load prior to initiation of and at days 14 and 28 of 1HP therapy. Overall, 49 of 50 (98%) participants completed 1HP therapy, with 1 participant discontinuing on day 15 due to fever and generalized rash. At days 14 and 28 of 1HP therapy, 56% and 35% of participants, respectively, had a bictegravir trough concentration above the 95% effective concentration (EC_{95}, 162 ng/mL) and 8% and 2%, respectively, had viral loads of 200 copies/mL or higher; all patients were virologically suppressed 3 months after completion of 1HP.

In the second study, Arora and colleagues undertook a phase I, open-label, 3-period, fixed-sequence, multiple-dose study among healthy HIV-negative volunteers to determine bictegravir/FTC/TAF pharmacokinetic parameters when given with weekly rifapentine (Abstract 369). Participants received bictegravir/FTC/TAF daily on days 1 to 8, underwent a washout period from days 9 to 14, then received bictegravir/FTC/TAF daily on days 15 to 30 with weekly rifapentine given on days 15, 22 (both codosed), and 29 (given 12 hours before bictegravir/FTC/TAF). Bictegravir trough concentrations declined by 40% (codosed) and 57% (12 hours before) following administration with weekly rifapentine, were reduced by up to 83% at 4 days post rifapentine dosing, and did not return to steady-state concentrations between rifapentine doses. These studies collectively show substantially reduced bictegravir concentrations when given with daily or weekly rifapentine; therefore, 1HP and 3HP should not be coadministered with bictegravir/FTC/TAF.

Another critical question in the TB/HIV field is the compatibility of drug interactions between high-dose rifampicin, a potent liver enzyme inducer, with dolutegravir- or efavirenz-based ART regimens. Sekaggya-Wiltshire and colleagues performed a randomized open-label phase IIb trial among people with HIV with newly diagnosed TB in Uganda to determine the safety and effect of high-dose rifampicin on dolutegravir and efavirenz pharmacokinetic parameters (Abstract 90). A total of 120 people with HIV on dolutegravir- or efavirenz-based ART continued their current regimen (dolutegravir adjusted to 50 mg twice daily) and were randomly assigned to receive high-dose

Bictegravir levels are subtherapeutic in patients receiving rifapentine either daily or weekly for TB prevention

rifampicin (35 mg/kg/day) or standard-dose rifampicin (10 mg/kg/day) during the 8-week intensive TB treatment phase. Among those receiving dolutegravir-based ART, mean dolutegravir trough concentrations were 48% lower in those receiving high-dose rifampicin than in those receiving standard-dose rifampicin (geometric mean ratio [GMR], 0.52; 95% CI, 0.23-1.16). However, 16% (n=4) versus 5% (n=1) of participants in the high-dose and standard-dose rifampicin arms, respectively, had trough concentrations below the protein-adjusted 90% inhibitory concentration (IC_{90}) of dolutegravir (≥0.064 mg/L) (P=.36); none had virologic failure after 6 months of TB treatment. Efavirenz mid-dose concentrations were 42% lower among those receiving high-dose rifampicin than in those receiving standard-dose rifampicin (GMR, 0.58; 95% CI, 0.31-1.10), and only 1 participant in each arm had an efavirenz mid-dose concentration below the minimum target threshold (1 mg/L). Grade III or IV adverse events did not differ between the treatment arms. Participants receiving high-dose rifampicin were more likely than those receiving standard-dose rifampicin to achieve 8-week sputum culture conversion (84% vs. 63%, respectively; P=.06). This study shows that high-dose rifampicin appears safe when given with twice-daily dolutegravir and may improve TB treatment efficacy. However, given moderate reductions in dolutegravir serum concentration, at times below the IC_{90}, further studies are needed before high-dose rifampicin coadministered with dolutegravir can be recommended.

Coadministration of dolutegravir with rifampicin substantially reduces plasma dolutegravir levels, and therefore twice-daily dolutegravir is recommended when given with rifampicin. Prior studies had found that dolutegravir levels are increased when given with food. Therefore, Ueaphongsukkit and colleagues conducted an open-label, randomized study among 28 ART-naive, TB-coinfected adults in Thailand to evaluate dolutegravir pharmacokinetic parameters among those receiving dolutegravir 50 mg daily with food (intervention group; n=12) compared with dolutegravir 50 mg twice daily (control group; n=16) (Abstract 370). All participants received SOC treatment for drug-susceptible TB disease (rifampicin 10 mg/kg/day), and dolutegravir was given with 2 nucleoside reverse transcriptase inhibitors (nRTIs). Dolutegravir minimum concentrations (C_{min}) and dolutegravir trough concentrations were 70% (GMR, 0.30; 95% CI, 0.26-0.36]) and 80% (GMR, 0.20; 95% CI, 0.11-0.35) lower, respectively, with daily dolutegravir given with food than with twice-daily dolutegravir. Dolutegravir C_{min} was below the IC_{90} (≥0.064 mg/L) in 17% versus 6% in the daily dolutegravir with food arm and twice-daily dolutegravir arms, respectively (P=.16). After 12 weeks, 75% of participants receiving daily dolutegravir with food were virologically suppressed compared with 82% in the twice-daily dolutegravir arm. These data show that among people with HIV receiving rifampicin, daily dolutegravir with food may result in subtherapeutic dolutegravir levels and increased likelihood of virologic failure, and therefore reinforce current recommendations for twice-daily dolutegravir dosing in this context.

Women and Children

The World Health Organization (WHO) recommends INH for 6 or 9 months as a preventative therapy for TB (IPT) in pregnant people with HIV; however, there is mixed evidence on the safety of INH in pregnancy and limited data on the safety of INH taken during the first trimester. Gupta and colleagues undertook a prespecified secondary analysis

of the BRIEF-TB (Brief Rifapentine-Isoniazid Evaluation for TB Prevention) trial[2] to compare pregnancy outcomes (non-live births, preterm birth, low birth weight, and APGAR scores) among women living with HIV, who became pregnant while they were receiving INH with those who became pregnant after completing IPT (Abstract 178). The present analysis included women 13 years or older, those randomly assigned to the IPT arm (due to a contraceptive requirement in the 1HP arm), and those who became pregnant during the 36 months of study follow up (pregnancy at entry was an exclusion criterion).

INH use in the first trimester of pregnancy is associated with a higher likelihood of non-live births

Overall, 128 of 812 (16%) women in the IPT arm became pregnant and had known pregnancy outcomes, of which 39 (36 definite, 3 possible) were exposed to INH during conception, and 89 became pregnant after completion of IPT. The proportion of women with non-live births was substantially higher in the INH-exposed arm (n=16/39; 41%) than in the INH-unexposed arm (n=19/89; 21%) (relative risk [RR], 1.92; 95% CI, 1.11-3.33). Most non-live births were due to spontaneous abortion (n=25/35; 71%). In an adjusted analysis that excluded induced abortions, composite adverse pregnancy outcomes were higher in the INH-exposed arm (n=13/35; 36%) than in the INH-unexposed arm (n=16/89; 19%) (adjusted RR [aRR], 1.98; 95% CI, 1.08-3.65). Gestational age at birth, birth weight, and APGAR scores did not differ according to INH exposure. These data raise important concerns about the safety of INH during the first trimester of pregnancy in women with HIV and suggest the need for contraception among women of reproductive age to avoid INH exposure during the first trimester.

Multidrug-Resistant TB

The Nix-TB study showed an all-oral regimen for the treatment of highly drug-resistant (DR) TB consisting of bedaquilline 200 mg thrice-weekly, pretomanid 200 mg daily, and linezolid 1200 mg daily for 6 months (BPaL regimen) was highly efficacious through 6 months.[3] An important question centers on this regimen's long-term efficacy and safety, including the effects of linezolid on peripheral neuropathy. Howell and colleagues presented an updated analysis of the efficacy and safety of the BpaL regimen through 2 years of follow up after treatment completion (Abstract 562). Of 109 individuals (65% with extensively drug-resistant tuberculosis (XDR-TB), 35% multi-drug resistant (MDR)-TB, and 51% with HIV), all but 1 individual who survived completed the entire therapy course. Only 2 participants had additional unfavorable outcomes between 6 and 24 months (1 with treatment relapse after 15 months and 1 lost to follow up); therefore, 88% did not have treatment failure or disease relapse through 24 months of follow up. This did not differ by sex or HIV status. Among 103 individuals completing the BPaL regimen, 37 (36%) were able to complete 26 weeks of linezolid at any dose, and only 16 (16%) were able to complete 26 weeks at the 1200 mg daily dose (1200 mg once daily or 600 mg twice daily). Of the 84 participants without peripheral neuropathy at baseline, 57 (68%) developed peripheral neuropathy (23 cases were severe), but this fully resolved by 24 months in 42 of 57 (74%) and lessened in severity among 7 of 57 (13%). These data demonstrate that the BPaL regimen maintains long-term efficacy. Although peripheral neuropathy is common, it improves or resolves entirely in the large majority of individuals.

A 'one-size-fits-all' approach underpins current MDR-TB treatment strategies, but it is unknown whether the optimal treatment duration may differ according to TB disease severity. Garcia-Cremades and colleagues analyzed individual-level patient data from published observational and investigational MDR-TB treatment studies in order to develop a risk stratification algorithm that could predict individuals at higher risk for unfavorable outcomes (treatment failure or death) possibly requiring longer treatment regimens from those at lower risk for poor outcomes who may successfully be cured with shorter treatment regimens (Abstract 561). Of 7750 individuals with known outcomes, 76% (n=5869) were successfully treated, 8% (n=628) had treatment failure, and 16% (n=1253) died. Several variables were associated with unfavorable outcomes, but notably, HIV-positivity was the strongest predictor in 3 separate multivariable models (adjusted odds ratio [aOR], 2.3; 95% CI, 1.7-3.0). Individual risk scores were determined using the multivariable models, and patients were categorized into high-, medium-, and low-risk phenotypes. The proportion of patients with an unfavorable outcome differed substantially according to risk phenotype. Approximately 75% of individuals with MDR-TB classified as at high risk experienced an unfavorable outcome through 36 weeks of follow up. This study suggests that it may be possible to predict treatment success in individuals with MDR-TB and therefore tailor the duration of therapy accordingly. This represents an interesting area for further research.

TB Screening and Detection

In high TB burden settings, systematically testing all individuals presenting to health facilities regardless of symptoms may detect a large burden of TB; however, such a strategy is resource intensive and therefore may not be feasible to implement. Lebina and colleagues undertook a cluster-randomized trial at 60 clinics in South Africa to determine whether a pragmatic strategy of targeted systematic TB testing among individuals at very high risk for TB resulted in a greater number of TB cases detected than the SOC (Abstract 134). At clinics randomizedly assigned to the intervention arm (n=30), systematic TB testing (sputum Xpert Ultra and culture) of individuals belonging to a high-risk group (people with HIV, close contacts of a person with TB in the last year, and those treated for TB in the prior 2 years) was undertaken regardless of symptoms. SOC clinics (n=30) continued use of symptoms-based TB

screening followed by testing for individuals screening positive. Among 30,513 high-risk individuals tested in the intervention arm, the diagnostic yield of microbiologically confirmed TB was high (6.0%) and differed according to risk factor: people with HIV (5.0%), close contact (7.5%), and prior TB (12.2%). The primary specified outcome analysis showed that intervention clinics diagnosed 14% (95% CI, -6%-38%) more TB cases per month, but the difference did not reach statistical significance. In an adjusted difference-in-difference analysis, intervention clinics diagnosed 17% (95% CI, 14%-19%) more TB cases than the prior year, and SOC clinics diagnosed 8% (95% CI, 7%-9%) fewer TB cases than in the preceding year. This study demonstrates that a strategy of systematic, facility-based TB testing of all individuals at very high risk detected many TB cases that may have otherwise been missed and substantially more cases than a symptoms-based screening approach that mirrors current recommendations.

Biomarkers that accurately predict TB disease progression in individuals with LTBI are lacking but could greatly improve prevention and treatment approaches. Kroidl and colleagues evaluated *Mycobacterium tuberculosis* (Mtb)-specific T-cell activation, which has previously shown a strong correlation with active TB disease, among people with HIV with LTBI (remained asymptomatic and Mtb never detected), prevalent active TB disease (Mtb detected at base line visit) and incipient TB (asymptomatic at baseline, Mtb detected during subsequent follow up) (Abstract 557). Patients were drawn from the AFRICOS (African Cohort Study) in which people with HIV from 4 African countries were evaluated annually from 2013 to 2017 for the presence of TB disease using sputum Xpert testing and followed up from between 3 years before and 4 years after TB disease diagnosis. The study included 46 patients matched on age, sex, and ART regimen with longitudinal peripheral blood mononuclear cell (PBMC) samples (11 active TB, 19 incipient TB, and 16 LTBI). Among people with HIV who had active TB disease, CD38 expression on Mtb-specific T cells ($P<.001$), but not bulk CD4+ T cells ($P=.4$), was substantially higher than those with LTBI; CD38 expression on Mtb-specific T cells declined following initiation of TB treatment ($P<.001$). CD38+ Mtb-specific CD4+ T cells were present in 23% and 67% of people with HIV with incipient TB at 12 and 6 months, respectively, prior to TB detection. The majority of individuals with LTBI demonstrated transient Mtb-specific T-cell activation that largely normalized without receipt of IPT. Further, there was persistent Mtb-specific T-cell activation in those with recurrent TB disease following treatment completion. These data support CD38+ Mtb-specific CD4+ T cells as an important surrogate biomarker of TB disease activity in individuals with HIV.

Screening for LTBI, either with tuberculin skin testing (TST) or IGRA, remains a key barrier to improving TB preventative therapy (TPT) coverage among people with HIV in some high TB burden settings. In the pilot period of a larger study aimed at increasing TPT, Chaisson and colleagues evaluated whether integrating IGRA testing with routine blood draws for CD4+ cell counts and viral load monitoring would improve LTBI screening compared with SOC. Among 972 people with HIV, 967 (99%) had an IGRA ordered, 672 (93%) of IGRA orders were paired with CD4+ cell count or viral load monitoring, and 672 (69%) had an IGRA completed, of whom 132 (20%) were positive. These data suggest that routinization of IGRA testing could help overcome barriers to LTBI screening.

The diagnosis of TB in children remains challenging, in large part because existing diagnostic tools are insufficiently sensitive and may require difficult-to-obtain, nonsputum clinical specimens. Exosomes are small extracellular vesicles (EVs) secreted by cells originating from endosomal cell compartments and Mtb-specific EVs (either released from Mtb or Mtb-infected macrophages) that are thought to play in important role in TB pathogenesis. LaCourse and colleagues retrospectively evaluated an internally developed nanoplasmon-enhancing scattering (nPES) assay that detects and quantifies 2 Mtb-specific markers (LprG and LAM) in EVs of cryopreserved plasma from hospitalized children with HIV in Kenya (Abstract 558). All children were intensively tested for TB at entry using Xpert testing and culture of sputa or gastric aspirate samples and Xpert testing of stool samples and were classified as having confirmed, unconfirmed, or unlikely TB. Plasma was collected frequently during the 24 weeks of follow-up. Among 72 hospitalized children with HIV included (81% with severe immunosuppression), the sensitivity of the Mtb-EV nPES assay was 86% (6/7) and 72% (26/36) in those with confirmed and unconfirmed TB, respectively; the specificity was 48% (14/29) in those with unlikely TB. Mtb-EV concentrations were higher in those with confirmed or unconfirmed TB versus those with unlikely TB ($P=.048$) and declined over 24 weeks following TB treatment initiation. This study shows that the nPES assay that detects Mtb-EVs may be a promising non-sputum-based target for improving TB diagnosis and treatment monitoring among children with HIV; however, additional studies are needed, including among less severely ill children with HIV.

Rapid ART Start in Patients with TB Symptoms

Rapid ART start is now the global standard; however, in high TB burden settings, ART initiation is often delayed among people with HIV who have TB symptoms while undertaking TB investigations. This may result in high rates of pre-ART losses to follow up. It is unknown how same-day TB testing and treatment and ART initiation among people with HIV with suspected TB may affect HIV and TB outcomes in resource-limited settings. Dorvil and colleagues randomly assigned 500 newly diagnosed adults with HIV and TB symptoms systematically tested for TB using Xpert Ulta to a same-day TB

test result notification and TB or ART treatment strategy or to Haiti's SOC TB testing and treatment approach (Abstract 184). In the SOC arm, patients initiated TB treatment on day 2 if TB was detected or ART on day 7 if TB was not detected. The proportion of people with HIV with prevalent TB disease (18.0% vs. 16.4%, respectively), started on TB treatment (100% vs. 97.6%, respectively) and initiated on ART (99.6% vs. 97.6%, respectively) did not differ between the same-day and SOC arms. Similarly, the proportion of people with HIV retained in care at 48 weeks (90.8% vs. 93.6%, respectively) and virologically suppressed (72.0% vs. 76.7%, respectively) was similar between the 2 treatment arms. The authors noted that the low 48-week virologic suppression rates might reflect a high prevalence of transmitted efavirenz resistance in this setting (as high as 20%), severe political instability during the study period, and service disruptions caused by the COVID-19 pandemic. This study shows comparable outcomes between same-day or day-7 ART start among people with HIV under evaluation for TB and supports the 2021 updated WHO recommendations for rapid ART in this population.

TB Contact Tracing

Contact tracing and systematic screening for TB among TB patients' household members are recommended but inconsistently implemented in many high-burden settings due to the resources required and its unclear impact on population control. Martinson and colleagues randomly assigned households of index TB patients in South Africa to determine whether intensive household contact TB and HIV screening with supported linkage to care (intensive screening arm) could improve outcomes among household contacts compared with a passive referral strategy (referral arm) (Abstract 133). In the intensive screening arm, all household members were systematically tested for TB (sputum Xpert testing and culture, TST) and HIV, offered home-based IPT initiation (if eligible), and provided immediate linkage support for TB treatment and ART (as necessary). In the referral arm, patients with TB were asked to provide all household members with a referral letter that could be presented at local health facilities for TB and HIV testing. All household contacts were followed up for 15 months to determine the composite endpoint of either incident TB or death. Overall, 1032 households (4129 contacts) and 1030 (4459 contacts) were randomly assigned to the intensive screening and referral arms, respectively. A large burden of previously undiagnosed TB (69/2166; 3.2%) and HIV (104/2972; 3.5%) was detected among household contacts in the intensive screening arm at baseline; however, after 3 months, only 54% of household contacts with TB disease started treatment, 53% of people with HIV and children 5 years or younger initiated IPT, and 80% of newly diagnosed people with HIV started ART. There was no difference in the primary outcome (TB disease-free survival through 15 months) between the study's intensive screening arm (2.9%) and its referral arm, (3.1%) (hazard ratio, 0.90; 95% CI, 0.66-1.24). There was also no difference in the prevalence of undiagnosed/untreated HIV among household members between arms through 15 months (1.3% vs. 1.3%; OR, 1.02; 95% CI, 0.64-1.64). Unexpectedly, the prevalence of TST positivity (≥10 mm) was higher among children in the intensive screening arm than those in the referral arm (4.5% vs. 1.9%; OR, 2.25; 95% CI, 1.07-4.72). This study demonstrated that an intensive testing and treatment strategy among household TB contacts identified many individuals with untreated TB and HIV. It did not substantially improve TB disease-free survival at 15 months compared with a simple contact referral letter strategy. Reasons for the lack of difference in TB disease-free survival between study arms may include limited uptake of TB and HIV treatment in the intensive screening arm, a relatively short follow-up period of 15 months, and widespread access to clinic-based TB and HIV testing and treatment in this setting.

Opportunistic Infections

Cryptococcus

Although the incidence of cryptococcal meningitis has substantially declined since the global expansion of ART coverage, cryptococcal meningitis remains an important cause of death among people with HIV, especially those with advanced HIV (Abstract 565). It is unknown whether using a clinic-based, rapid point-of-care cryptococcal antigen (CrAg) testing strategy among patients with advanced HIV may reduce cryptococcal meningitis and mortality by expediting the initiation of fluconazole prophylaxis. Drain and colleagues undertook a pre-post study in South Africa among individuals presenting for HIV testing to compare outcomes associated with 3 different CrAg testing strategies rolled out over 3 periods: period 1, CrAg testing ordered by a clinician at their discretion (2013-2015); period 2, routine laboratory-based CrAg reflex testing for anyone with a blood sample with a CD4+ count below 100 cells/μL (2015-2017); and period 3, clinic-based point-of-care CrAg testing among persons with a CD4+ count at or below 200 cells/μL (2017-2019) (Abstract 564). Among 908 people with HIV with a CD4+ count at or below 200 cells/μL, clinic-based point-of-care CrAg testing (period 3) increased the proportion screened for CrAg ($P<.001$), had CrAg detected in blood ($P=.020$), started on fluconazole preventative therapy ($P=.010$), and started on ART ($P=.012$), compared with clinician-directed CrAg testing (period 1). The proportion of patients diagnosed with cryptococcal meningitis (4.5% vs. 1.5%; $P=.06$), all-cause hospitalization (9.5 vs. 8.7; $P=.76$), and all-cause mortality (8.1% vs. 9.6%; $P=.65$) was not different between the clinic-based point-of-care testing strategy and the clinician-directed testing strategy, respectively. No outcomes differed between the clinic-based point-of-care testing and laboratory reflex testing strategies. In this quasi-experimental study, a systematic, clinic-based point-of-care CrAg testing strategy for people with advanced HIV did not appear to improve

outcomes meaningfully, but other interventions occurring during the study period may have biased the results.

Human Papillomavirus and Kaposi Sarcoma Herpesvirus

Human Papillomavirus

Cervical cancer is a leading cause of cancer-related mortality in sub-Saharan Africa, especially among women with HIV; however, the prevalence of different high-risk human papillomavirus (HPV) genotypes in sub-Saharan Africa is poorly defined. Uldrick and colleagues prospectively enrolled a cohort of women with and without HIV in Uganda who had abnormalities detected during cervical cancer screening (visual inspection with acetic acid [VIA]) in order to determine the prevalence of and risk factors for high-risk HPV and cervical high-grade squamous intraepithelial lesions (HSILs) (Abstract 474). Among 16,380 women (60% with HIV) screened, 815 (5.0%) had a positive VIA of whom 328 (200 with HIV [median CD4+ cell count, 667/µL], and 128 HIV-negative) had lesions suitably sized for biopsy and were included. High-risk HPV was detected in 67% of women with HIV compared with 45% of HIV-negative women (adjusted prevalence ratio [aPR]: 1.5; 95% CI, 1.2-1.9). Compared with HIV-negative women, those with HIV were also more likely to have multiple high-risk HPVs (aPR, 3.2; 95% CI, 1.2-8.4), and have a high-risk HPV only covered by the nonavalent vaccine (aPR, 1.9; 95% CI, 1.1-3.1) or no vaccine (aPR, 1.7; 95% CI, 1.0-3.0). Among women with HIV, a lower CD4+/CD8+ cell ratio was associated with having any high-risk HPV, multiple high-risk HPVs, and a high-risk HPV only covered by the nonavalent vaccine. Additionally, HSIL was more common in women with HIV than in HIV-negative women (29% vs. 9%, respectively). These data show that high-risk HPV is common among young women in Uganda and more prevalent in women with HIV, and provide support for prioritizing the nonavalent HPV vaccine for adolescents in this setting.

Women with HIV are at increased risk for high-risk HPV associated precancer and cancer of the lower anogenital tract; however, the dynamics of cervical and anal HPV infection and their relationship to anal precancers (HSILs) is poorly understood. Weiss and colleagues enrolled 144 women with HIV in New York City from 2013 to 2019 to determine the prevalence of cervical and anal high-risk HPV infection (HPV 16, 18, and others), the persistence of anal HPV over time, and the association between cervical and anal high-risk HPV infection and anal HSILs (Abstract 473). Overall, 45% had anal high-risk HPV infection only, 28% had both cervical and anal high-risk HPV infection, and 3% had cervical high-risk HPV infection only. Among 41 participants with dual-site high-risk HPV infection, HPV type concordance between the anus and cervix was observed in 56%, and anal high-risk HPV infection persistence was observed in 54% after a median of 534 days. Biopsy-proven anal HSIL was detected in 31%. Anal HSIL was much more likely among those with anal high-risk HPV persistence versus those with clearance (incidence rate ratio [IRR], 6.84; 95% CI, 1.66-28.16), those with anal HPV type 16 or 18 versus not (IRR, 6.22; 95% CI, 3.20-12.09), but not those with cervical HPV type 16 or 18 versus not (IRR = 1.44; 95% CI, 0.57-3.62). These data showed that anal HPV was more common than cervical HPV among women with HIV and that the presence and persistence of anal high-risk HPV but not cervical high-risk HPV predicted anal HSIL. This study suggests that greater consideration should be given to anal cancer screening among women with HIV, independent of cervical HPV status, but further study is required.

Kaposi Sarcoma Herpesvirus

The treatment of Kaposi sarcoma herpesvirus (KSHV) inflammatory cytokine syndrome (KICS) and KSHV-associated and multicentric Castleman disease (MCD) cooccurring with Kaposi sarcoma (KS) may include rituximab with liposomal doxorubicin. However, rituximab can worsen KS in a majority of patients. Therefore, rituximab-sparing treatment options are needed for such patients. Pomalidomide and doxorubicin are 2 systemic treatment options approved for extensive cutaneous KS or visceral KS, but the safety and activity of their combined use in KS alone or with KSHV-associated diseases is not known. To address this question, Ramaswami and colleagues undertook a phase I/II study among 2 groups of patients with KS requiring systemic therapy: those with KS alone (G1) and those with KS plus concurrent MCD or KICS (G2) to assess the safety and tolerability of combination pomalidomide/doxorubicin (Abstract 167). All participants received liposomal doxorubicin 20 mg IV once on day 1 of a 28-day cycle and pomalidomide once daily orally on days 1 to 21 at increasing doses (2 mg, 3 mg, 4 mg) until a plateau in response was observed, disease progressed, or dose-limiting toxic effects occurred. In total, 34 men (94% people with HIV, all on ART [median CD4+ count, 217 cells/µL; median HIV viral load 46 copies/mL]) with severe KS were enrolled of which, 22 (65%) had prior chemotherapy for KS. There were 21 participants in G1 and 13 in G2; those in G2 were more likely to have visceral KS (92% vs. 38%, respectively) and had lower CD4+ counts (92 vs. 286 cells/µL, respectively). No dose-limiting toxic effects were observed in G1, and all were treated with the maximum tolerated pomalidomide dose (4 mg daily). By comparison, 2 participants in G2 had dose-limiting toxic effects at pomalidomide 3 mg daily. After a median of 6 cycles, the response rate (partial or complete) was 81% (17/21) in G1 and 50% (5/10) in G2; among those in G2 with KICS and MCD, 57% (4/7) and 50% (3/6), respectively, showed at least partial response to treatment. The most common adverse event observed was neutropenia in 65% (22/34). This small study demonstrated that the rituximab-sparing pomalidomide/doxorubicin regimen had activity and tolerability among heavily pretreated patients with KS alone or with concurrent KSHV-associated diseases. Larger studies are

needed before this regimen can be recommended in this setting.

HIV and COVID-19

COVID-19 Outcomes Among People with HIV

To date, there is mixed evidence as to whether people with HIV are at increased risk for acquiring COVID-19 or for experiencing more severe COVID-19 compared with HIV-negative individuals. Several studies at this year's CROI added to this literature.

Using patient-level data from 34 US sites in the National COVID Cohort Collaborative (N3C) between January 2020 and February 2021, Sun and colleagues evaluated whether people with HIV and individuals with solid organ transplants with COVID-19 were more likely to be hospitalized or require intubation than those without an immunocompromising condition (Abstract 103). Among 575,445 COVID-19-positive adult patients, there were 2932 people with HIV, 4633 transplant recipients, and 111 people with HIV and a solid organ transplant. Overall, 157,765 (31%) patients required hospitalization (49% of people with HIV, 64% of transplant recipients), and 10,300 (2%) required intubation (6% of people with HIV, 10% of transplant recipients). In unadjusted analyses, people with HIV had a 2.14-times (95% CI, 1.99-2.30) higher odds of hospitalization, and individuals with solid organ transplants had a 4.00-times (95% CI, 3.77-4.25) higher odds of hospitalization. However, multivariable analyses adjusted for comorbidities showed that the odds of hospitalization were strongly attenuated but remained significantly elevated among people with HIV (aOR, 1.32; 95% CI, 1.22-1.43; $P<.01$) and solid organ transplant recipient patients (OR, 1.69; 95% CI, 1.58-1.81). Additional analyses among people with HIV demonstrated that a history of cardiopulmonary or renal disease independently predicted hospitalization. Multivariable analyses also demonstrated that the odds of mechanical ventilation were higher among people with HIV (aOR, 1.86; 95% CI, 1.56-2.22) and solid organ transplant patients (aOR, 1.96; 95% CI, 1.74-2.12) than among individuals without these immunocompromising conditions.

Tang and colleagues undertook a retrospective cohort analysis among 235,609 patients (1.5% people with HIV) at a single center in southern California from March to November 2020 to compare COVID-19–related diagnostic and clinical outcomes between people with and without HIV (Abstract 542). People with HIV were much more likely to be tested for COVID-19 during the study period than HIV-negative individuals (34% vs. 10%, respectively), and among those tested, people with HIV were more likely to be COVID-19 positive (8% vs. 3%, respectively; aOR, 3.41; 95% CI, 2.65-4.39). Among those with confirmed COVID-19, and after adjusting for potential confounders including comorbidities, the likelihood of hospitalization (aOR, 0.61; 95% CI, 0.27-1.38), intensive care unit (ICU) admission (aOR, 1.33; 95% CI, 0.44-3.96), mechanical ventilation (aOR, 2.35; 95% CI, 0.62-8.96), and death (aOR, 3.04; 95% CI, 0.46-19.94) did not differ according to HIV status; however, there was a small number of clinical outcome events as indicated by the wide confidence intervals that may have limited statistical power to detect a true difference if one were present.

Comorbidities are the biggest predictor of poor COVID-19 outcomes in persons living with HIV

Shapiro and colleagues assessed predictors of increased COVID-19 disease severity among all people with HIV with PCR-confirmed COVID-19 disease between March and December 2020 from 7 sites in the Center for AIDS Research (CFAR) Network of Integrated Clinical Systems (CNICS) cohort using Poisson regression models (Abstract 543). Of 15,969 people with HIV in the CNICS cohort, 582 (3.6%) were diagnosed with COVID-19. Female sex (aRR, 1.41; 95% CI, 1.19-1.68), diabetes (aRR, 1.25; 95% CI, 1.04-1.51) and a body mass index of 30 and above (aRR, 1.50; 95% CI, 1.27-1.76) were independent predictors for being diagnosed with COVID-19. Among 582 people with HIV with COVID-19, 104 (17.9%) were hospitalized, 28 (4.8%) required ICU admission and 17 (2.9%) required mechanical ventilation. Independent predictors of hospitalization were age 60 years or older (aRR, 1.78; 95% CI, 1.25-2.54), CD4+ count below 350 cells/μL (aRR, 2.29; 95% CI, 1.63-3.22), hepatitis C (aRR, 1.53; 95% CI, 1.04-2.25), elevated atherosclerotic cardiovascular disease risk score ([per 10% increase] aRR, 1.41; 95% CI, 1.25-1.60), diabetes (aRR, 1.45; 95% CI, 1.02-2.42), use of antihypertensive drugs (aRR, 1.69; 95% CI, 1.17-2.42), and impaired renal function (estimated glomerular filtration rate [eGFR] <60 mL/min/1.73m^2]; aRR, 2.28; 95% CI, 1.61-3.24), although chronic obstructive pulmonary disease had borderline significance (aRR, 1.61; 95% CI, 0.98-2.65). Notably black race and HIV virologic control were not independent predictors of hospitalization among people with HIV.

Yendewa and colleagues undertook a retrospective cohort analysis using the TriNetx database (a large global health research network) to evaluate differences in outcomes according to HIV status among adults with COVID-19 presenting to any of 44 US healthcare facilities from January to December 2020 (Abstract 548). In total, 297,194 adults with confirmed COVID-19 were enrolled, of which 1,638 (0.6%) had HIV (48% had an HIV-1 RNA <20 copies/μL). Compared with HIV-negative COVID-19 patients, people with HIV who had COVID-19 were more likely to be younger, male, African American or Hispanic, have cardiovascular disease, and be obese; people with HIV also tended to have higher procalcitonin and interleukin-6 levels. In a propensity score analysis matched on demographics and medical comorbidities, people with HIV had a higher odds of hospitalization (OR, 1.26; 95% CI, 1.04-1.53; $P=.023$) and ICU admission for mechanical ventilation (OR, 1.32; 95% CI, 1.10-1.58; $P=.003$) than HIV-negative patients. Thirty-day mortality was comparable between people with HIV and without HIV (2.9% and 2.3%, respectively; $P=.123$).

Moran and colleagues determined factors associated with hospitalization among all people with HIV with COVID-19 at 2 hospitals in Atlanta, Georgia, from March to November 2020 (Abstract 547). Overall, 180 people with HIV were enrolled (78% male, 78% black, 14% Latinx), of whom 97% were on ART and 91% had a suppressed HIV viral load. 72% of people with HIV had at least 1 medical comorbidity. The most common comorbidities were hypertension (46%), dyslipidemia (34%), obesity (31%), and diabetes (22%); 22% had 4 or more medical comorbidities. Hospitalization occurred in 33% (n=60) of people with HIV. In a multivariable analysis, only age (aOR, 1.07; 95% CI, 1.04-1.11) and diabetes (aOR, 2.65; 95% CI, 1.03-6.85) were associated with hospitalization. However, in a second analysis adjusted only for age, there was a dose-response relationship observed between the number of comorbidities and the odds of hospitalization, such that people with HIV with 4 or more comorbidities had nearly a 3-times higher odds of hospitalization than people with HIV with none or 1 comorbidity (aOR, 2.85; 95% CI, 1.17-6.91). Notably, CD4+ cell count and HIV viral load were not associated with hospitalization.

To assess the impact of COVID-19 in pregnant women with HIV, De Waard and colleagues conducted an observational cohort study among COVID-19–positive pregnant women attending hospital in Cape Town, South Africa, between May and July 2020 and followed them up through October 2020 to determine pregnancy and birth outcomes (Abstract 171). Overall, 103 of 275 (38%) symptomatic women tested positive for COVID-19, and 100 were included in the analysis; this included 28 (28%) women with HIV who had a median CD4+ count of 441 cells/μL. Demographic characteristics and medical comorbidities did not differ according to HIV status. Half of the women (50%) delivered within 2 weeks of their COVID-19 diagnosis, 40% required supplemental oxygen, 15% required mechanical ventilation, and 8% died. Regarding neonatal outcomes among women with COVID-19 (n=91 live births), 30% were delivered before 37 weeks, and 28% had low birth weight. Notably, no maternal or infant outcomes differed according to HIV status. Maternal deaths among pregnant women with COVID-19 were substantially higher than pregnant women without COVID-19 during the study period (8.8% vs. 0.2%, respectively; $P<.001$).

Collectively, studies from this year's CROI suggest that people with HIV may have an increased risk for severe COVID-19 related outcomes. However, the risk appears to be predominantly driven by comorbid medical conditions, which may be more prevalent among people with HIV than in the general population.

All cited abstracts appear in the *v*CROI 2021 Abstract eBook, available online at www.CROIconference.org

Financial affiliations in the past 12 months: Dr Kerkhoff has no relevant financial affiliations to disclose. Dr Havlir has no relevant financial affiliations to disclose. (Updated April 01, 2021)

Additional References Cited in Text

1. Dorman S, et al. The design and primary efficacy results of study 31:A5349. Symposium SP-10. Poster presented at: 51st Union World Lung Health Conference; 2020;
2. Swindells S, Ramchandani R, Gupta A, et al. One month of rifapentine plus isoniazid to prevent HIV-related tuberculosis. *N Engl J Med*. 2019;380(11):1001-1011.
3. Conradie F, Diacon AH, Ngubane N, et al. Treatment of highly drug-resistant pulmonary tuberculosis. *N Engl J Med*. 2020; 382(10):893-902.

Top Antivir Med. 2021;29(2):344-351.

Guidelines for Authors and Contributors

The IAS–USA publishes *Topics in Antiviral Medicine*™ as a resource for physicians and other health care practitioners who are actively involved in the care of patients with HIV or other viral infections. This open-access journal is now available as an online resource only. It is indexed in Index Medicus/MEDLINE and PubMed.

The following guidelines describe the types of articles and contributions published in the journal, outline its policies, and provide instructions for authors. For further information, contact *Topics in Antiviral Medicine*™ at journal@iasusa.org.

Categories of Articles

Perspectives. Perspective articles are summaries of selected talks given at IAS–USA continuing medical education courses. The lecture content is peer reviewed prior to presentation by at least 2 reviewers. An IAS–USA medical writer prepares a summary manuscript from a transcript of the talk. The manuscript is reviewed and edited by the presenter and the journal's appointed peer reviewer(s).

Reviews. *Topics in Antiviral Medicine*™ welcomes original review articles on current issues related to infection with HIV or other viruses. *Topics in Antiviral Medicine*™ does not publish original research. Manuscripts should be 3000 to 6000 words (excluding references, tables, and figures) and should include numbered references and a brief introductory abstract of approximately 100 to 200 words. Original, adapted, or reprinted figures and tables may be included and should be cited in the text and accompanied by a brief title. Adapted and reprinted work requires proof of permission obtained from the original publishers and authors. Authors interested in submitting unsolicited manuscripts are encouraged to submit an outline or abstract of the proposed manuscript first; please contact the editor for further information.

Editorials. *Topics in Antiviral Medicine*™ invites submission of editorials. Editorials should be approximately 500 to 1500 words (excluding references) and should include numbered references.

Special Contributions. A special contribution article often represents the unique contribution (such as a consensus statement) of an author or group of authors.

Cases From the Field. *Topics in Antiviral Medicine*™ invites submission of case reports accompanied by a scholarly literature review of the topic. Each case report should be 1500 to 3000 words (excluding references, tables, and figures), include numbered references, and seek to teach an important lesson for HIV or viral hepatitis care practitioners.

Stories. Stories for the *Telling Stories* column share the experiences of those involved in the care of people infected with HIV or other viruses. Stories may be approximately 800 to 3500 words; submissions are welcome for consideration.

Commentaries. Discussion on a current issue in the management of viral diseases is welcome as a Commentary. Commentaries should be 500 to 1500 words and include numbered references as appropriate. Commentaries may be invited by the editors; unsolicited submissions are also welcome for consideration.

Letters to the Editor. Letters to the editor are welcome and should be sent to the address listed below. Please limit letters to 300 words.

Special Issues. *Topics in Antiviral Medicine*™ often publishes issues with a special focus, such as summaries of IAS–USA continuing medical education courses and reports from scientific meetings.

Reprints. Reprints of articles by expert panels convened by the IAS–USA are included periodically in *Topics in Antiviral Medicine*™.

Submission of Manuscripts

Manuscripts should be submitted via mail or email to the address below. Each author should complete an Authorship Form, which is available online at https://iasusa.org/activities/topics-in-antiviral-medicine/tam-policies-practices/tam-author-and-contributor-guidelines/ or may be obtained by contacting the editor at the address below. Outlines or abstracts of proposed manuscripts are welcome and may be sent via mail or email.

Editor, *Topics in Antiviral Medicine*™
IAS–USA
131 Steuart St, Ste 500
San Francisco, CA 94105

Email: journal@iasusa.org

Receipt of submitted manuscripts will be acknowledged by editorial staff, and submissions will be reviewed by peer reviewers. Acceptance for publication is based on the quality and relevance of the work.

Copyright

Authorship Requirements

Topics in Antiviral Medicine™ uses the definition of authorship formulated by the International Committee of Medical Journal Editors and published in its *Uniform Requirements for Manuscripts Submitted to Biomedical Journals*.[1] This definition states that authorship "should be based on the following 4 criteria: (1) Substantial contributions to the concept or design of the work; or the acquisition, analysis, or interpretation of data for the work; (2) drafting the work or revising it critically for important intellectual content; (3) final approval of the version to be published; and (4) agreement to be accountable for all aspects of the work ensuring that questions related to the accuracy of integrity of any part of the work are appropriately investigated and resolved… acquisition of funding; general supervision of a research group or general administrative support; and writing assistance" do not constitute authorship. *Topics in Antiviral Medicine*™ will not consider ghost-written articles for publication.

Financial Disclosure

It is the policy of the IAS–USA to ensure balance, independence, objectivity, and scientific rigor in all its educational activities. All authors and contributors to *Topics in Antiviral Medicine*™ are required to disclose any financial relationships with commercial interests within the past 12 months that could be perceived to influence, or give the appearance of potentially influencing, the written or oral presentation. The Accreditation Council for Continuing Medical Education (ACCME) defines a financial interest as an interest in any amount and defines a commercial interest as "any entity producing, marketing, re-selling, or distributing health care goods or services consumed by, or used on, patients. The ACCME does not consider providers of clinical service directly to patients to be commercial interests—unless the provider of clinical service is owned, or controlled by, an ACCME-defined commercial interest." In accordance with IAS–USA policy, the IAS–USA will identify and resolve ahead of time any possible conflicts of interest that may influence CME activities with regard to exposition or conclusion, which includes review by at least 1 reviewer who has no financial relationships with commercial interests.

1. International Committee of Medical Journal Editors. Recommendations for the Conduct, Reporting, Editing, and Publication of Scholarly Work in Medical Journals. Updated December 2015. Available at http://www.icmje.org. Accessed May 24, 2021.

CROI 2014 to 2021 Resources

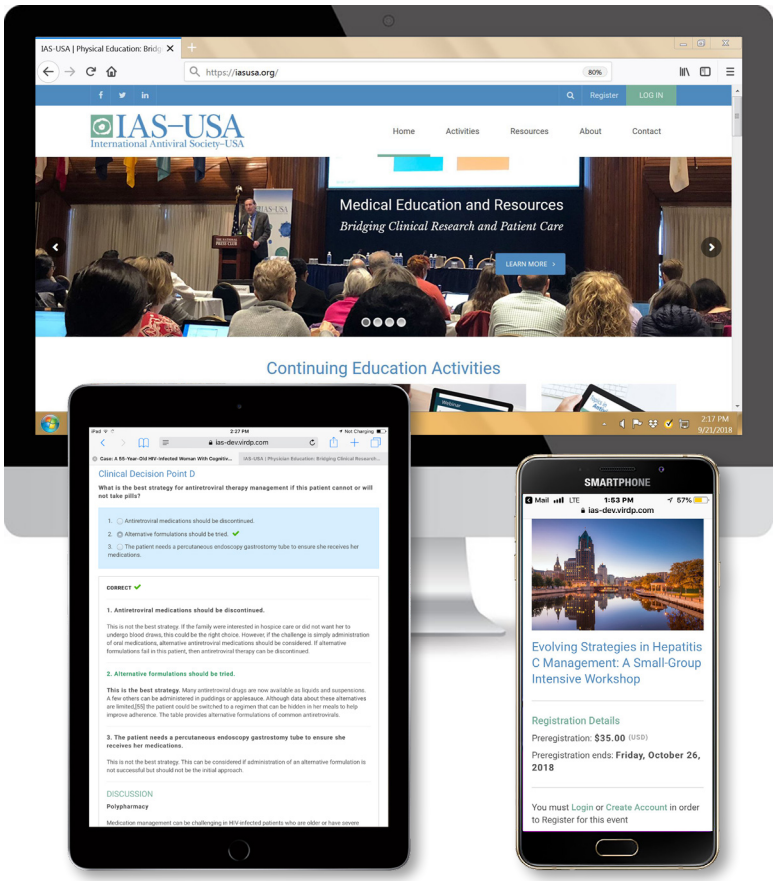
Webcasts and electronic posters from CROI 2014 to 2021 can be found at www.CROIconference.org. The Electronic Materials page includes the following resources and more.

The CROI Program and Conference Information guide includes information about sessions, speakers, and other details about CROI.

In addition to the Special Issue of *Topics in Antiviral Medicine*,™ abstracts from CROI can be viewed in the Abstract eBook and searchable database.

Plenaries, symposia, oral abstract sessions, and themed discussions are available as webcasts. Visit www.CROIwebcasts.org to access webcasts from CROI 2014 to CROI 2021.

Visit the IAS–USA Website



- Mobile-friendly
- On-demand and interactive content:
  - Webcasts and podcasts of previous live courses, including on-demand webinars, virtual spring 2021 courses, and the 2020 Ryan White Clinical Conference
  - Guidelines for clinical HIV treatment and drug resistance mutations
  - Information about upcoming courses and activities

Visit the IAS-USA website at www.iasusa.org and Log In with your email address or Create an Account.