

# Topics in Antiviral Medicine™

A publication of the IAS–USA

## Selected Highlights of the 2022 Conference on Retroviruses and Opportunistic Infections (Part 2)

CROI 2022: Neurologic Complications of HIV-1, SARS-CoV-2, and Other Pathogens **CME** 475

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

*Neuroimaging Findings • Aging, Comorbid Diseases, Biomarkers, and Neurologic Complications • Brain Tissue Investigations in Animals and Humans • The Role of Lymphoid Cells in the CNS During HIV Infection • Effects of Antiretroviral and Other Drugs on the CNS • Neurologic Complications of COVID-19 • Other CNS Infections in People With HIV*

CROI 2022: Advances in Antiviral Therapy for HIV, COVID-19, and Viral Hepatitis **CME** 490

*Shauna H. Gunaratne, MD, MPH; Hong-Van Tieu, MD, MS;  
Timothy J. Wilkin, MD, MPH; Barbara S. Taylor, MD, MS*

*Advances in Treatment of COVID-19 • Advances in Treatment of HIV • The HIV Care Cascade and Disparities in Treatment Outcomes • Impact of the COVID-19 Pandemic on HIV Care • HIV Resistance • Advances in Treatment of Hepatitis C • Advances in Treatment of Hepatitis B • Selected Issues in Maternal and Pediatric Health*

CROI 2022: Metabolic and Other Complications of HIV Infection or COVID-19 **CME** 522

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CROI 2022: Tuberculosis and Infectious Complications in Persons With HIV **CME** 528

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

*Tuberculosis • Opportunistic Infections • Kaposi Sarcoma Herpesvirus and Human Papilloma Virus*

## Invited Review

Preventing and Diagnosing HIV-Related Comorbidities in Adolescents **CME** 537

*Hasiya Eihuri Yusuf, MD, MPH; David Griffith, MD;  
Allison Lorna Agwu, MD, ScM*

*Epidemiology of HIV in Adolescents • HIV Comorbidities in Youth • Diabetes • Hypertension and Cardiovascular Risk • Weight Gain • Sexually Transmitted Infections • Mental Health and Substance Use • Way Forward*

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### Correspondence

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

Editor, *Topics in Antiviral Medicine™*

Email: [journal@iasusa.org](mailto:journal@iasusa.org)

Mail: IAS–USA  
 131 Steuart St, Ste 500  
 San Francisco, CA 94105

Phone: (415) 544-9400

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## Learning Objectives

On completion of this activity, which contains 5 articles, the learner will be better able to:

- Describe the important new data presented at the 2022 Conference on Retroviruses and Opportunistic Infections and the potential clinical implications for patients in the areas of epidemiologic trends, prevention research, and basic science research in the HIV and SARS-CoV-2 pandemics
- Describe the potential treatment options for depression and bipolar depression disorders and understand how they impact those with HIV
- Describe the current epidemiology of tuberculosis, shorter regimens for its treatment, and recent advancements in treatment for patients with drug-resistant tuberculosis

## 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.

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*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. (Updated on February 14, 2022)*

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*Invited Review***CROI 2022: Neurologic Complications of HIV-1, SARS-CoV-2, and Other Pathogens****Albert M. Anderson, MD, MHS<sup>1</sup>; Scott L. Letendre, MD<sup>2</sup>; Beau M. Ances, MD, PhD<sup>3</sup>**<sup>1</sup>Emory University, Atlanta, Georgia<sup>2</sup>University of California San Diego<sup>3</sup>Washington University at St. Louis, St. Louis, Missouri

*The 2022 Conference on Retroviruses and Opportunistic Infections featured new and important findings about the neurologic complications of HIV-1, COVID-19, and other infections. Long-term analyses identified that cognitive decline over time, phenotypic aging, and stroke are associated with various comorbidities in people with HIV. Neuroimaging studies showed greater neuroinflammation, white matter damage, demyelination, and overall brain aging in people with chronic HIV infection. Childhood trauma and exposure to environmental pollutants contribute to these neuroimaging findings. Studies of blood and cerebrospinal fluid biomarkers showed that systemic inflammation, neurodegeneration, endothelial activation, oxidative stress, and iron dysregulation are associated with worse cognition in people with HIV. Some animal studies focused on myeloid cells of the central nervous system, but other animal and human studies showed that lymphoid cells also contribute to HIV neuropathogenesis. The deleterious central nervous system effects of polypharmacy and anticholinergic drugs in people with HIV were demonstrated. In contrast, a large randomized controlled trial showed that integrase strand transfer inhibitor therapy was not associated with neurotoxicity. Studies of cryptococcal meningitis demonstrated*

*the cost-effectiveness of single high-dose liposomal amphotericin and the prognostic value of the cryptococcal antigen lateral flow assay. People hospitalized with COVID-19 had more anxiety over time after discharge. The SARS-CoV-2 nucleocapsid antigen is present in cerebrospinal fluid in the absence of viral RNA. Systemic inflammation, astrocyte activation, and tryptophan metabolism pathways are associated with post-COVID-19 neurologic syndromes. Whether these processes are independent or intertwined during HIV-1 and COVID-19 infections requires further study.*

**Keywords:** HIV, CROI 2022, COVID-19, SARS-CoV-2, neurologic complications, cognition, brain, CSF, neuroimaging

**Introduction**

Central nervous system (CNS) effects of HIV-1 were an important theme at the 2022 Conference on Retroviruses and Opportunistic Infections. Presentations focused on HIV pathogenesis and CNS reservoirs, as well as on persistent neurologic dysfunction (as assessed by neuropsychologic testing, imaging, or cerebrospinal fluid [CSF] evaluations) in people with HIV who have virologic suppression. New data were presented on accelerated aging and the effects of aging-related comorbidities on brain function—themes that have become increasingly important as people with HIV live longer as a result of effective antiretroviral therapy (ART). New data also provided encouraging news for treating

**Author Correspondence**

Send correspondence to Albert Anderson, MD, Emory University, 341 Ponce de Leon Avenue, Atlanta, GA, 30308, or email [aande2@emory.edu](mailto:aande2@emory.edu).

cognitive impairment and advancing the HIV cure agenda. This review focuses on major thematic areas that could inform new research initiatives and stimulate novel approaches for the clinical management of people with HIV.

### Neuroimaging Findings

Persistent neuroinflammation may affect the CNS in early and chronic HIV infection and may have a variety of causes. Alagaratnam and colleagues evaluated if neuroinflammation, as measured by positron emission tomography imaging with the translocator protein radioligand [<sup>11</sup>C]PBR28, would be lower in people with HIV who initiated ART during acute HIV infection than in those who initiated it later (Abstract 127). Within a small group of virologically suppressed people with HIV, those with chronic HIV infection had greater [<sup>11</sup>C]PBR28 binding (ie, greater neuroinflammation) than people without HIV. In contrast, [<sup>11</sup>C]PBR28 binding in people who initiated ART during acute HIV infection was similar to that in people without HIV, suggesting early ART initiation may mitigate neuroinflammatory responses. Bolzenius and colleagues showed an analysis of people with acute HIV infection in which brain volume changes were examined in a large Thai cohort (Abstract 419). Participants were categorized by stage of acute HIV infection (Fiebig stage). People in late Fiebig stages (III-IV) had significantly larger volumes in subcortical areas (including caudate, putamen, pallidum, and amygdala) than people without HIV, a finding attributed to possible infiltration of immune cells in response to HIV. Although this neuroinflammation may resolve with continued ART, it could also lead to brain structural changes. For this reason, longitudinal studies are needed that include soluble and cellular biomarkers and neuroimaging. Ham and colleagues studied the effects of childhood trauma (experiencing or witnessing physical or sexual abuse) on cognition, daily functioning, and brain morphology in adults with HIV who were receiving ART and were virologically well controlled (<200 HIV RNA copies/mL) (Abstract 418). They found that people with HIV who had no history of childhood trauma had

larger brain volumes and better cognitive performance than those with such history. However, people with HIV who had childhood trauma and larger subcortical brain volumes had worse learning performance and greater functional impairments. Because the larger brain volumes observed in this cross-sectional analysis may reflect neuroinflammation, further study using longitudinal analyses that combine imaging with soluble and cellular biomarkers could aid understanding. Although con-

***A biomarker of oxidative stress was associated with a larger ratio of abnormal white matter to total white matter***

tinued suppression of HIV RNA with ART has salutary effects, the influence of events before HIV infection and ART initiation on brain volumes and cognitive performance are becoming increasingly clear.

One structural neuroimaging finding that has been consistently associated with cognitive performance is abnormal white matter. To further evaluate this association, Riggs and colleagues analyzed data from the CHARTER (CNS HIV Antiretroviral Therapy Effects Research) project (Abstract 408). The ratio of abnormal white matter to total white matter was measured via magnetic resonance imaging (MRI) in 55 people with HIV. Also, 15 soluble biomarkers were measured in blood and, in 1 subgroup, in CSF. Multivariable analyses identified that higher blood concentration of protein carbonyls, a biomarker of oxidative stress, was associated with a larger ratio of abnormal white matter to total white matter; also associated were older age and Black race. Changes in oxidative stress may result from several distinct processes, with protein carbonyl concentration reflecting an aggregate measure of physiologic stressors.

Neuroimaging studies also yielded evidence of neurodegeneration and axonal loss. Patel and colleagues used myelin water imaging, a novel neuro-

imaging method, to investigate water within myelin bilayers (Abstract 417). They compared the myelin water fraction (MWF), a metric of myelin content, for virally suppressed adults with perinatal HIV with MWF for people without HIV. Global and frontal-lobe MWF was lower in people with HIV than in people without HIV. Lower global MWF was associated with worse executive function in people with HIV. These results indicate that decreased axonal myelination may occur early in perinatal HIV infection and may be associated with worse cognitive performance. However, longitudinal studies are needed that include larger numbers of people with HIV and matched controls to verify these results. Meade and colleagues examined the relationship between serum neurofilament light chain (NfL), a marker of axonal injury and neuronal loss, and white matter integrity, as measured by diffusion tensor imaging, within a cohort of chronically infected people with HIV who were virologically well controlled (Abstract 413). Higher serum NfL levels were associated with greater peripheral inflammation (ie, sCD14) and with reductions within structural connections in subcortical brain regions.

Additional risk factors may also affect brain structure and function on neuroimaging. Peterson and colleagues used machine-learning algorithms to evaluate changes in white matter within the brain with aging. In addition to HIV, older age and vascular disease are associated with changes to cerebral white matter that are detectable on diffusion-weighted MRI. These changes can be quantified using the brain age gap, the difference between true age and neuroimaging-predicted "brain age." In a large cohort of people with and without HIV, white matter aging (ie, progressive accumulation of microstructural damage) was evaluated with respect to age. Compared with people without HIV, people with HIV who had a detectable viral load had an additional 1.5 years of brain age gap per decade, suggesting premature aging. Greater white matter changes were also associated with worse cerebrovascular disease, as measured by Framingham risk score. Aging with detectable plasma HIV RNA and the presence of cardiovascular risk factors are associated with white matter

pathology and may contribute to the development of cognitive impairment in people with HIV.

Environmental pollutants are increasingly recognized for their effects on lung, cardiovascular, and brain function. Wisch and colleagues evaluated a

*Exposure to PM2.5 in the week before assessment was associated with worse learning performance*

community-dwelling cohort of older people with HIV to assess the effects of common air pollutants, including fine particulate matter (PM2.5) and ozone, on cognitive performance and brain structure (Abstract 416). A 10- $\mu\text{g}/\text{mL}$  increase in average exposure to PM2.5 in the week before assessment was associated with worse learning performance. Among people without HIV, greater ozone exposure was associated with smaller temporal lobe volume, but in people with HIV the opposite was true. These findings are consistent with previous literature that suggests a deleterious effect of PM2.5 on cognition.

### **Aging, Comorbid Diseases, Biomarkers, and Neurologic Complications**

Corbett and colleagues examined the prevalence of a new stroke event in people with HIV in South Africa (Abstract 424). A total of 884 strokes were identified, and among people with HIV (68% of whom were taking ART), hypertension and dyslipidemia were less prevalent than among people without HIV. In contrast, concurrent infections (including tuberculosis, syphilis, and cryptococcal infections) were more prevalent in people with HIV than in people without HIV.

People with HIV often have an excess of comorbidities, which may substantially affect mortality and quality of life. Ellis and colleagues attempted to predict long-term cognitive decline based on a simple assessment of comorbid conditions in people with HIV (Abstract 427). A simple comorbidity index (SCI), composed of presence or absence of hypertension,

chronic obstructive pulmonary disease, and depression, was compared with other well-established measures including the Charlson Comorbidity Index,

***Participants with a higher SCI at baseline had significantly worse neurocognitive decline over 12 years of follow-up***

the VACS (Veterans Aging Cohort Study) index, and the Framingham cardiovascular index. Participants with a higher SCI at baseline had significantly worse neurocognitive decline over 12 years of follow-up. Individuals with 2 or more comorbidities at baseline had worse neurocognitive decline than individuals without comorbidities. Compared with other indices such as the VACS and Framingham indices, only the SCI was associated with cognitive decline. The importance of these comorbidities is rooted in their effects on daily functioning and quality of life. Prior studies have assessed overall quality of life, but fewer have assessed the influence of cognitive impairment in people with HIV on health-related quality of life. To address this issue, Alford and colleagues assessed health-related quality of life and its relationship to cognition in people with HIV, finding that cognitive impairment predicted worse health-related quality of life (Abstract 422).

Aung and colleagues longitudinally studied 457 people with HIV yearly over 3 years. At baseline, 31% were cognitively impaired (Abstract 425). The cognitive performance of a minority of participants either (1) declined after 1 (6%) or 2 (7%) years of follow-up, or (2) improved after 1 (4%) or 2 (3%) years. Worse cognitive performance over time was associated with severe depression, worse ART acceptance, and lack of companionship. The investigators concluded overall that the rate of cognitive decline was low owing to good virologic control, which is supported by more integrated healthcare services. Han and colleagues compared phenotypic aging between people with and without HIV using a novel combination of biomarkers (Abstract 615).

Phenotypic age was calculated using chronologic age and a combination of 9 blood-based biomarkers, including complete blood cell counts and inflammatory, metabolic, liver, and kidney-related parameters. To evaluate if phenotypic age was accelerated in people with HIV compared with people without

***Lower CD4+/CD8+ cell ratio and higher VACS index were associated with older phenotypic age***

HIV, the difference between chronologic and phenotypic age was calculated for both groups. Lower CD4+/CD8+ cell ratio and higher VACS index were associated with older phenotypic age in people with HIV. Within the entire cohort, male sex, current smoking, diabetes mellitus, frailty, and higher interleukin (IL)-6 level were associated with an elevated phenotypic aging value.

Measurement of proteins and nucleic acids in extracellular vesicles isolated from body fluids may provide more precise evidence of cellular injury and abnormal intercellular communication. Guha and colleagues compared plasma and CSF concentrations of free and extracellular vesicle (EV)-associated biomarkers from 98 people with HIV with virologic suppression with concentrations of the same biomarkers from 86 people without HIV who were matched for age, sex, and race (Abstract 407). People with HIV were stratified by cognition (52% were impaired) and presence of vascular disease (23.5% had vascular disease). People with HIV had higher levels of plasma NfL and CSF amyloid beta ( $\beta$ )1-42 (A $\beta$ 42). CSF EV-associated A $\beta$ 42 level was lower ( $P=.0002$ ) and CSF EV-associated tau/A $\beta$ 42 ratio was higher ( $P=.001$ ) in people with HIV and cognitive impairment than in people with HIV without cognitive impairment. Lower CSF EV-associated A $\beta$ 42 ( $P<.0001$ ), higher CSF EV-associated tau/A $\beta$ 42 ratio ( $P=.0003$ ), and higher plasma NfL level ( $P=.098$ ) were associated with worse cognitive performance in multivariable models that incorporated the whole group. Cognitive impairment in

people with HIV was also associated with higher levels of plasma intercellular adhesion molecule (ICAM)-1 ( $P=.02$ ), vascular cell adhesion molecule (VCAM)-1 ( $P=.004$ ), and C-reactive protein ( $P=.02$ ). People with HIV had higher levels of EV ICAM-1 and VCAM-1 than people without HIV ( $P<.0001$ ), but these higher levels were not associated with cognitive impairment.

Using data and biospecimens from 376 participants of AIDS Clinical Trials Group (ACTG) clinical trials, Kalayjian and colleagues evaluated relationships between cognitive performance and biomarkers in plasma, including citrate, soluble (s)

***Lower FTL level was associated with worse cognitive performance over time***

tumor necrosis factor receptor (TNFR) I and II, IL-6, sCD14, sCD163, intestinal fatty acid binding protein (IFAB), and vascular endothelial growth factor (Abstract 412). In multivariable models, higher concentrations of sTNFR I, sTNFR II, and sCD163 were associated with both prevalent and incident cognitive impairment. Meanwhile, higher IFAB concentration was associated with lack of prevalent cognitive impairment. In models for prevalent cognitive impairment, significant interactions were present between (1) vascular endothelial growth factor levels and sex and (2) citrate level and age. In mixed-effects models evaluating cognitive change over time, higher sTNFR I, sTNFR II, and citrate levels were associated with greater cognitive decline over time. Although prior research has identified links between inflammation biomarkers like sTNFR I and cognition, the findings with IFAB and citrate are relatively novel and may provide new insights into pathogenesis.

From the same ACTG cohort, Kaur and colleagues evaluated biomarkers of iron homeostasis (plasma ferritin heavy chain [FTH]1; urine T-cell immunoglobulin and mucin domain 1 [TIM-1], an FTH1 receptor; and plasma ferritin light chain [FTL])

(Abstract 406). Cross-sectional multivariable analysis of the entire cohort identified that lower FTL and higher TIM-1 levels were associated with cognitive impairment, and longitudinal analyses identified that a lower FTL level was associated with worse cognitive performance over time. Sex-specific cross-sectional analyses identified that a lower FTH level was associated with cognitive impairment in women, an association that held over time. In men, higher TIM-1 level was associated with worse cognitive performance. These data add to accumulating evidence that disordered iron metabolism contributes to cognitive performance in people with HIV and support a clinical trial of an iron-focused intervention.

In addition to its role in heme synthesis and oxygenation, iron is crucial to the function of many cell types and may further influence neurologic health by its association with inflammation and oxidative stress. Combined with the finding noted earlier linking protein oxidation and abnormal white matter volume, biomarker evidence is growing of the impact of oxidative stress on the CNS in treated people with HIV (Abstract 408). Mitochondria are central to cellular oxidant–antioxidant balance, and Volpe and colleagues reported on comparisons of mitochondrial haplogroups with cognitive performance in 691 women with HIV from the MACS/WIHS (Multicenter AIDS Cohort Study and the Women’s Interagency HIV Study) Combined Cohort Study (Abstract 415). They found that mitochondrial haplogroup L2a was associated with better motor and speed-of-information-processing performance in Black women with HIV, and mitochondrial haplogroup B was associated with better motor performance in Hispanic women with HIV. Most mitochondrial research to date in people with HIV has been in men, so these findings provide important information on sex-related differences in genetic vulnerability to neurologic complications.

Biomarker investigations are affected by the sensitivity, accuracy, and reproducibility of biomarker assays, many of which are antibody based. The quality of these antibodies can vary over time, which can lead to inconsistent results. Newer methods, such as the single-molecule assay method,

may better address these historical limitations. This method was used to develop an assay for NfL in blood, higher concentrations of which have been linked to cognitive impairment in people with HIV. To build on these findings, Trunfio and colleagues used the single-molecule assay method and other methods to measure NfL and Alzheimer's disease-related biomarkers in blood and CSF in 44 people with HIV; they found strong correlations between NfL concentrations in CSF and blood but not for other analytes (Abstract 411). When they compared biomarker levels with cognitive performance, they found that biomarker concentrations in blood correlated more strongly with cognitive performance than concentrations in CSF. Although the current research does not explain the underlying mechanisms of this surprising finding, it holds promise that diagnostic biomarkers for cognitive impairment may be measurable in blood, which would avoid the need to perform lumbar puncture.

Correlation between biomarker concentrations in CSF and blood was the focus of a poster from Kamkwalala and colleagues, who presented findings from the CHARTER cohort (Abstract 409). Comparing data from 2 assessments separated by 12 years, they found that biomarkers in CSF correlated more strongly with each other over time than did biomarkers in blood, particularly for sTNFR II ( $P=7 \times 10^{-29}$ ), A $\beta$ 42 ( $P=8 \times 10^{-33}$ ), and total ( $P=4 \times 10^{-26}$ ) and phosphorylated ( $P=2 \times 10^{-54}$ ) tau. This pattern suggests that the influence of the mechanisms reflected by these biomarkers may be relatively fixed over time in people with HIV, which is a novel finding.

With the expansion of multiplex biomarker assay methods, accounting for type I error is increasingly important. The likelihood of type I error can increase with each additional biomarker. Additionally, many inflammatory biomarkers correlate with each other, which can also add to the likelihood of type I error or produce misleading results. One approach to managing this common error is through use of dimension-reduction methods. Tavasoli and colleagues used one such method, factor analysis, to evaluate the same biomarkers from the CHARTER cohort, again at 2 timepoints 12 years apart (Abstract 410). They found that higher levels of a

factor combining sTNFR II and neopterin in CSF correlated with higher NfL levels in CSF, but only among people with HIV who were virally suppressed with ART at both timepoints (correlation coefficient [ $r$ ], 0.36;  $P=8 \times 10^{-6}$ ). This finding links neuroinflammation with neuronal injury over a long period of observation.

### Brain Tissue Investigations in Animals and Humans

Although CSF and blood analyses can yield valuable insights into HIV pathogenesis in the brain, directly examining brain tissue should provide even more relevant data. To address this goal, White and colleagues simultaneously evaluated brain and

***BLZ945 also decreased SIV DNA in 9 of the 11 analyzed brain regions***

cardiac pathology in CD8+ T-cell-depleted simian immunodeficiency virus (SIV)-infected macaques with AIDS (Abstract 403). Animals were grouped as having (1) cardiovascular disease (CVD) and encephalitis (SIVE) (CVD+SIVE), (2) CVD only or SIVE only, (3) SIV without encephalitis, or (4) none of the conditions. Animals with CVD+SIVE had more CD163+, CD206+, CD68+, and MAC387+ cardiac macrophages than the other groups. Animals with CVD+SIVE also had greater cardiac collagen deposition and higher sCD163 level than those with either CVD or SIVE only. Animals with CVD+SIVE had repeatedly higher CD14+CD16+ monocyte levels in blood at 3 timepoints after infection. A higher CD14+CD16+ monocyte level in the blood correlated with greater cardiac collagen deposition in the entire cohort. These findings link disease-related changes in the heart and the brain, confirming and extending clinical data that have found that cardiovascular disease increases the risk for cognitive impairment in people with HIV.

Given evidence that perivascular macrophages (PVMs) of the brain serve as HIV reservoirs and

that colony-stimulating factor 1 receptor (CSF1R) in PVMs is upregulated in SIV-infected rhesus macaques with encephalitis, Zablocki-Thomas and colleagues evaluated blockade of this receptor in the macaque model (Abstract 347). After CD8+ depletion, they compared untreated animals with animals treated with BLZ945, a selective brain-penetrating CSF1R kinase inhibitor, at high or low dose. They found that PVM count significantly correlated with SIV DNA in the CNS and that high-dose BLZ945 reduced PVMs. BLZ945 also decreased SIV DNA in 9 of the 11 analyzed brain regions. The findings support that inhibiting CSF1R kinase may hold promise in reducing HIV DNA level in the brain.

Mathews and colleagues evaluated glial HIV reservoirs in a triple-humanized mouse model (Abstract 390). In this model, microglia distribute throughout the brain, but astrocytes are limited to the corpus callosum, fornix, and near lateral ventricle. Human oligodendrocytes and neurons are also present in the brain. According to their canonical markers, 15 different clusters of cells were demonstrated. Of the 7 clusters showing myeloid markers, 6 showed the presence of HIV. Individual HIV genes were also found in most groups of myeloid cells. Transcriptomics revealed that 2 clusters had differential gene expression, with upregulation of interferon signaling and increased cytokines or chemokines but downregulation of most other signaling pathways. This humanized mouse model showed evidence of productive HIV infection in microglia but not astrocytes.

In a postmortem study using frontal cortex samples from the Manhattan HIV Brain Bank, Plaza-Jennings and colleagues characterized microglia using 10x chromium single-nucleus RNA-seq (snRNA-seq), integration site analysis, and high-throughput chromatin conformation capture (Abstract 391). Brain tissue from people with HIV who died with HIV encephalitis (HIVE) was compared with brain tissue from people without HIV. snRNA-seq revealed 188 upregulated genes (many related to the immune response) and 276 downregulated genes (many related to the antiviral immune response) in HIVE. HIV integration sites were found in highly expressed microglia genes and were over-represented among differentially expressed genes in

HIVE microglia. Considering these and other findings, the investigators concluded that HIVE leads to widespread 3D-genome restructuring in microglia, including at immune loci, and that these same regions are targeted for viral integration.

In another postmortem study from the same group, Min and colleagues reported on HIV transcript findings using high-throughput snRNA-seq on frontal cortex from 3 groups: (1) people without HIV (n=2), (2) people with HIV and without HIVE (n=3), and (3) people with HIV and HIVE (n=3) (Abstract 402). Among the major brain cell types, HIV transcripts were elevated in a subset of microglia in people with HIV and HIVE but not in people with HIV and without HIVE. Dual RNA-FISH assays with probes complementary to the Iba1 microglial marker and HIV RNA confirmed that microglia express high levels of HIV. In people with HIV and HIVE, HIV transcripts were the top 0.3% most highly expressed transcripts in the microglial transcriptome. In addition, transcription of proinflammatory signaling genes was more elevated in people with HIV than in people without HIV, including purinergic receptors (P2X1, P2X7), NLRP3 inflammasome signaling components (NLRP3, Casp1, ASC), and proinflammatory cytokines (IL-1 $\beta$ , IL-18).

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### The Role of Lymphoid Cells in the CNS During HIV Infection

The preceding findings reinforce well-known associations between myeloid cells and neurologic complications in HIV disease, but increasing evidence supports a role for lymphoid cells as well. For example, Fox and colleagues studied 3 macaques 12 days postinfection with SIVmac251 (Abstract 393). SIV RNA was expressed by 3.67% of blood CD4+ T cells, less than 0.01% of blood monocytes, and 0.15% of brain myeloid and lymphoid cells. The infected blood CD4+ T cells were present in 2 populations distinguishable by the reciprocal expression of RNA for (1) the cytotoxic molecule granzyme B (GZMB) and (2) the transcription factor TCF1 (TCF7). Only the GZMB+TCF7- population of SIV-infected CD4+ T cells (which resemble cytotoxic T cells) were found in the brain, in addition to infected cells

characteristic of microglia (AIF+P2RY12+CD3D-). Flow cytometry confirmed the presence of GZMB+ CD4+ T cells in the brain, and immunohistochemistry/in situ hybridization identified CD4+ T cells

***DNA and cell-associated HIV RNA were detectable in up to 87.5% of participants, with the number of HIV-1 transcripts much higher in CSF-derived cells than in blood-derived cells***

expressing SIV RNA in the brain. This study suggests that HIV in the brain may derive from subsets of T cells, which runs contrary to existing belief that myeloid cells such as brain macrophages and microglia are primarily responsible for HIV replication in the brain. However, 12 days postinfection may be too early to identify all infected cells that may occur in the brain during chronic HIV.

Another report supported the importance of lymphoid cells in the CNS. Zaunders and colleagues characterized cells isolated from CSF and blood of people with HIV taking suppressive ART by using 18-color flow cytometry and the Double-R  $\pi$ Code MicroDiscs assay (Abstract 126). Comparing these findings with information from brain magnetic resonance spectroscopy, they found that CSF cells were 91% memory T cells, and only a minority were monocytes or macrophages. DNA and cell-associated HIV RNA were detectable in 81% and 87.5% of participants, respectively. The number of HIV-1 transcripts was much higher in CSF-derived cells than in blood-derived cells (9226 vs 185 copies/10<sup>6</sup> CD4+ T cells, respectively). Participants who had more HIV-1 transcripts detected in CSF also had evidence of greater brain injury on magnetic resonance spectroscopy, particularly in frontal white matter and posterior cingulate cortex. Kincer and colleagues further supported the importance of lymphoid cells in production of HIV RNA in the CNS by focusing on symptomatic CSF viral escape, a condition typically characterized by having detectable

HIV RNA in CSF and undetectable HIV RNA in blood (Abstract 130). The researchers used single-genome amplification and Illumina MiSeq deep sequencing with Primer ID to assess genetic diversity in partial *env* sequences (V1-V3) and drug resistance mutations. They found that most CSF-escape viral populations had either 1 (47%) or 2 major lineages (33%). A minority of populations were a highly diverse, recombinant population (16%). Relevant to the focus of this section on the contribution of lymphoid cells to HIV RNA in CSF, they also identified that all escape viruses were T-cell-tropic. This finding is similar to previous work that CSF HIV is mostly T-cell-tropic.

The contribution of lymphoid cells to neurologic complications in HIV disease was further supported by 2 reports from SEARCH (Southeast Asia Research Collaboration in HIV) cohorts in Thailand. Mitchell and colleagues polyclonally expanded CD8+ T cells from blood and CSF of 15 people with HIV with acute infection and 6 people with HIV with chronic infection before and after ART initiation (Abstract 392). They then sequenced the T-cell receptor beta chain and measured functional HIV-specific responses. Within-sample clonality was measured with the Simpson clonality index and between-sample clonality with the Morisita index. Simpson clonality index was significantly higher in CSF-derived cells than in blood-derived cells before ART and after 24 and 96 weeks of ART, particularly among participants with acute HIV infection. Participants with acute HIV infection had higher Simpson clonality from CSF cells than participants with chronic HIV infection before ART but not at 24 or 96 weeks. The Morisita index was significantly higher (indicating less turnover) for cells derived from blood than for cells from CSF at weeks 24 and 96. Lastly, higher CSF Simpson clonality before ART correlated with increased frequencies of Env-, Nef-, and Rev/Tat-specific CD8+ T cells in the CSF at 24 weeks. The second SEARCH-cohort report, from Corley and colleagues, performed single-cell analyses of cells from CSF, lymph node, gut, and T-follicular cells from an ART-naive person with chronic HIV infection (Abstract 394). The team mapped out the cellular makeup of each tissue type, showing

for example that all detectable HIV transcripts in the CSF compartment were from CD4+ memory T cells, similar to findings reported in Abstract 126. Clonotype tracking of sorted C-X-C chemokine receptor type 5 (CXCR5)+ T-follicular helper cells revealed exclusive shared clonotypes with lymph

***After ART interruption, only 1 of 6 animals rebounded in CSF compared with all 6 animals that responded in blood***

node only. On the basis of the capture across compartments of 71 single transcriptionally active HIV+ cells with a paired T-cell receptor, all T-cell clones were determined to be unique in cells containing HIV transcripts from CSF, gut, lymph node, and CXCR5+ T-follicular helper cells. Although this work focused on the logistical feasibility of international single-cell multiomics, the findings provide additional support for the influence of lymphoid cells in the CNS.

Although debate has tended to focus on whether lymphoid or myeloid cells are more important in the CNS of people with HIV, both types likely influence pathogenesis, along with others such as astrocytes and oligodendrocytes. The report from Veenhuis and colleagues may shed light on the interplay between lymphoid and myeloid cells in the CNS (Abstract 129). In ART-treated SIVmac251-infected macaques, CD4+ T cells were depleted with CD4R1, an anti-CD4 antibody, and the macrophage-latent reservoir was assessed by an intact proviral DNA assay and a macrophage quantitative viral outgrowth assay. After ART interruption, only 1 of 6 animals rebounded in CSF compared with all 6 animals that responded in blood, further supporting the importance of lymphoid cells in HIV replication in the CNS. The investigators did, however, observe an increase in the reactivatable reservoir in the brain in the CD4+ T-cell-depleted animals, which reinforces that lymphoid and myeloid cells likely each have roles in maintenance of the brain reservoir.

## **Effects of Antiretroviral and Other Drugs on the CNS**

### **ART Drugs and the CNS**

Several questions remain about ART pharmacology in the CNS. These include questions about the extent of ART drug distribution into the brain and CSF, the influence of ART on control of HIV in the CNS, and the toxic effects of ART drugs in the CNS. In recent years, data have emerged to support that ART drugs may reach higher concentrations in the brain

***Brain tissue concentrations were lower than CSF concentrations for tenofovir, lamivudine, and dolutegravir and higher than CSF concentrations for efavirenz***

than in CSF. Higher concentrations should result in better control of HIV replication but could also increase the risk of toxicity. In a postmortem study from Uganda, Nicol and colleagues measured ART drug concentrations in blood and CSF from 65 deceased individuals with HIV, as well as in brain tissue in a subgroup (Abstract 450). They found that brain tissue concentrations were lower than CSF concentrations for tenofovir, lamivudine, and dolutegravir and higher than CSF concentrations for efavirenz. Concentrations across the 12 evaluated brain regions were heterogenous, but interindividual variability was greater than intraindividual variability. CSF concentrations did not correlate with mean brain concentrations of tenofovir or dolutegravir but strongly correlated for lamivudine ( $r=0.90$ ;  $P<.001$ ).

The observation that efavirenz concentrations may be higher in the brain than in CSF may explain its well-documented neurotoxicity. The 8-hydroxy(OH) metabolite of efavirenz has previously been implicated in its neurotoxicity. Ranzani and colleagues investigated this concept further by measuring efavirenz and 8-OH-efavirenz in blood along with

cognitive performance, mood, and sleep (Abstract 398). They confirmed that 8-OH-efavirenz concentrations in blood were associated with CNS adverse events including increased depressive symptoms and worse sleep as well as overall CNS symptom score. They posit that measuring 8-OH-efavirenz concentrations in blood in the clinic may identify people with HIV who are at risk for CNS complications. Interindividual variation in 8-OH-efavirenz concentrations is due in part to variation in genes involved in drug metabolism and elimination, like the gene that encodes cytochrome P450 2B6. Variation in this gene may be responsible for a severe but uncommon CNS complication of efavirenz: late-onset efavirenz neurotoxicity syndrome, which is associated with isoniazid coadministration. Investigators from South Africa characterized genetic variation in cytochrome P450 2B6 and in the N-acetyltransferase 2 gene that encodes a protein involved in the metabolism and elimination of isoniazid (Abstract 395). They identified that all participants who had late-onset efavirenz neurotoxicity syndrome were slow metabolizers of cytochrome P450 2B6 and slow acetylators of N-acetyltransferase 2; these participants also had efavirenz concentrations in blood that were more than 12 times higher than the upper limit of therapeutic range. Caution is advised when coadministering efavirenz and isoniazid, and ideally drug concentrations are measured or genotyping is performed when the drugs are used together.

Three other groups also reported on the effects of ART on the CNS. In addition to the CNS effects of efavirenz, a CNS safety signal has been reported for integrase strand transfer inhibitors (InSTIs), like dolutegravir. Analyzing data from ACTG clinical trials, O'Halloran and colleagues reported on people with HIV who (1) switched their ART to an InSTI-containing regimen; (2) underwent at least 2 cognitive assessments before the switch and 1 afterward; and (3) maintained viral suppression throughout observation (Abstract 400). The dataset was substantial, with 5824 assessments in 395 people with HIV over a mean duration of observation of 9 years pre- and 3 years post-switch. Overall cognitive performance (based on a 4-test composite) improved over time and the slopes were similar before and after the

InSTI switch, supporting the conclusion that InSTI-containing regimens did not adversely affect overall cognition. Within the composite, the Hopkins Verbal Learning Test–Revised had a small but statistically significant decrease after the switch ( $P=.03$ ). This may or may not have been significant after adjustment for numerous comparisons.

Given the declining use of efavirenz, a known neurotoxic drug, and growing data supporting that InSTIs are not neurotoxic, has the prevalence of cognitive impairment declined in people with HIV? Data

***The prevalence of cognitive impairment substantially declined from 37.6% between 2009 and 2011 to 15.6% between 2018 and 2020***

from Mastroianni and colleagues support a decline in prevalence (Abstract 132). Analyzing data from 1365 people with HIV who had 2383 assessments performed over 4 periods (2009–2011, 2012–2014, 2015–2017, 2018–2020) at a single center, they found that the prevalence of cognitive impairment substantially declined from 37.6% between 2009 and 2011 to 15.6% between 2018 and 2020. It was not clear if this may have been due to earlier treatment in the later time periods, but InSTI therapy was associated with lower risk of impairment in multivariable models. Although such analyses are prone to survivor bias (and other biases), they provide further support that current therapies are less neurotoxic than in the past. Another report supports the conclusion, however, that the findings may be at least partially due to the reversibility of ART neurotoxicity after a switch in therapy. Taramasso and colleagues identified 60 ART treatment-limiting CNS adverse events in 4751 people with HIV who were monitored over time (Abstract 399). Follow-up data were available for 52 of the 60 participants with CNS adverse events and identified that the effects resolved after discontinuation in nearly all (92.3%) and did not differ by use of an InSTI or another drug class.

Because CNS complications in people with HIV could result from persistent low levels of HIV RNA in the CNS and the resulting immune response, ART intensification could be beneficial for people with HIV who have CNS complications like cognitive impairment. To investigate this possibility, Letendre and colleagues performed a clinical trial

***Improvement in cognitive performance in the active treatment arms did not differ from that in the dual-placebo arm and thus did not support the conclusion that ART intensification benefits people with HIV who have cognitive impairment***

in the ACTG, in which 191 people with HIV who had cognitive impairment and were taking suppressive ART were randomly assigned to intensify their existing ART regimen with a combination of (1) dolutegravir and maraviroc, (2) dolutegravir and placebo, or (3) dual placebo (Abstract 133). The study arms were well balanced, and consistent with practice effect, cognitive performance improved in all 3 arms. The improvement in cognitive performance in the active treatment arms did not differ from that in the dual-placebo arm and thus did not support the conclusion that ART intensification benefits people with HIV who have cognitive impairment. Of note, the overall cognitive performance of the active treatment arms also did not decline, adding further evidence against the neurotoxicity of INSTIs.

### **Concurrently Prescribed Drugs and the CNS**

Along with findings on the diminished neurotoxicity of newer ART drugs, data were reported at the 2022 Conference on Retroviruses and Opportunistic Infections about the neuropsychiatric effects of the non-ART drugs prescribed to people with HIV.

Doctor and colleagues presented cross-sectional data on the effects of anticholinergic drugs on falls and frailty in the multicenter POPPY (Pharmacokinetic and Clinical Observations in People Over Fifty)

***People with HIV who used 2 or more anticholinergic drugs were much more likely to have had recurrent falls***

study (Abstract 35). Participants were categorized based on self-report of recurrent falls (at least 2 in 28 days) and Fried frailty criteria. Approximately one-quarter of participants (27%) used at least 1 anticholinergic drug, the most common being codeine, citalopram, loperamide, and amitriptyline. Multivariate modeling showed a trend between anticholinergic use and frequent falls as well as frailty. People with HIV who used 2 or more anticholinergic drugs were much more likely to have had recurrent falls (hazard ratio [HR], 3.6; confidence interval [CI], 1.4-9.4). This study supports avoiding the use of multiple anticholinergics in older people with HIV if possible.

Dastgheyb and colleagues investigated the influence of non-ART prescribed drugs by analyzing data from 920 virally suppressed people with HIV in various neurologic HIV cohorts assessed between 2015 and 2019 (Abstract 423). The participants reported use of a median of 6 prescribed drugs from more than 200 drug classes, which were analyzed using principal-components analysis to reduce the component number to 16. Another dimension-reduction method, self-organizing maps, was applied to cognitive performance and identified 10 cognitive profiles, which were compared with prescribed drug use and other data. Several prescribed drug components were associated with cognitive profiles, including one that combined several types of drugs that have CNS effects or are used to treat CNS conditions. These findings provide further evidence of the potential adverse effects of non-antiretroviral prescribed drugs on cognitive health.

## Neurologic Complications of COVID-19

The neurologic complications of COVID-19 are of continued interest. The syndrome of post-acute sequelae of COVID-19 (PASC) frequently includes

***SARS-CoV-2 N-Ag was detected in 31 of 35 CSF specimens***

neurologic symptoms. Eden and colleagues presented a cross-sectional study evaluating SARS-CoV-2 nucleocapsid antigen (N-Ag) levels in CSF and plasma (Abstract 131). They enrolled 44 hospitalized individuals with moderate to severe COVID-19 and 10 healthy COVID-19–negative controls; they also included specimens from 41 pre-pandemic control individuals. A total of 23 of the 44 had CNS symptoms (almost all with encephalopathy). None of the participants had SARS-CoV-2 RNA detectable in CSF. However, SARS-CoV-2 N-Ag was detected in 31 of 35 CSF specimens, and CSF concentrations highly correlated with N-Ag concentrations in plasma ( $r=0.84$ ;  $P<.001$ ). CSF N-Ag concentrations correlated with CSF neopterin ( $r=0.38$ ;  $P=.01$ ) and CSF interferon gamma ( $\text{IFN-}\gamma$ ) ( $r=0.42$ ;  $P=.01$ ). Regardless of CNS symptoms, participants with COVID-19 had higher CSF concentrations of  $\beta$ 2-microglobulin, neopterin, IL-6, IL-10, and tumor necrosis factor ( $\text{TNF}\alpha$ ); however, these concentrations were not significantly different when comparing COVID-19 participants with or without CNS symptoms. Those with CNS symptoms had higher concentrations of CSF  $\text{IFN-}\gamma$ , but not CSF IL-1 $\beta$ , IL-2, or NfL. Although the high detectability of N-Ag from CSF is notable, it may not necessarily indicate viral neuroinvasion given the high correlation with blood level and lack of viral RNA in CSF, although this finding could also indicate a nonproductive infection of glial cells, such as occurs when astrocytes are infected by HIV-1. A non-mutually exclusive explanation is that N-Ag could have properties that allow efficient crossing of the blood–CSF barrier. However, CSF

N-Ag concentrations were only about one-tenth of blood concentrations.

Peluso and colleagues analyzed 121 participants at 2 time points (median 52 days and median 123 days) after COVID-19 diagnosis (Abstract 631). Blood was collected for biomarker analysis at both time points, and participants were interviewed at the second visit for somatic symptoms, including CNS-related symptoms. At the first visit, participants with CNS symptoms had higher concentrations of glial fibrillary acidic protein (GFAP) ( $P=.02$ ) and chemokine ligand 2 (CCL2) ( $P=.03$ ). At both visits, those with CNS symptoms had higher concentrations of IL-6 ( $P=.006$  and  $P=.01$ , respectively) and  $\text{TNF}\alpha$  ( $P=.003$  and  $P=.02$ , respectively). CNS symptoms were not associated with NfL, IL-10,  $\text{IFN}$ -inducible protein-10 (IP-10), or SARS-CoV-2 antibody concentration. In contrast, participants with CNS symptoms had significantly lower  $\text{IFN-}\gamma$  levels at the second visit. These

***Antibodies against at least 1 SARS-CoV-2 antigen were detected in 7 of 10 CSF specimens***

findings suggest that CNS symptoms after COVID-19 may be associated with certain aspects of systemic inflammation that persist after the infection.

McAlpine and colleagues presented data from 34 individuals who had neurologic symptoms after acute COVID-19 diagnosis and 21 controls (Abstract 635). They measured levels of neopterin, NfL, total tau, GFAP, YKL-40, and soluble TREM2, and the presence of anti-SARS-CoV-2 spike, receptor-binding domain, and nucleocapsid antibodies in blood and CSF. The most common post-COVID-19 symptoms were cognitive impairment, depression/anxiety, fatigue, and headache. From blood, post-COVID-19 participants had significantly higher D-dimer (median, 0.44 vs 0.26 mg/L;  $P=.039$ ) and GFAP (median, 84.4 vs 42.4 pg/mL;  $P=.006$ ). Antibodies against at least 1 SARS-CoV-2 antigen were detected in 7 of 10 CSF specimens and in all 8 blood specimens in the post-COVID-19 group. This study adds to

evidence that astrocyte activation, as evidenced by higher GFAP, may play a role in PASC.

Vergori and colleagues presented neuropsychologic testing data on 302 individuals after COVID-19 diagnosis (Abstract 632). Assessments were performed at 3, 6, and 12 months after COVID-19 diagnosis and included 10 neuropsychologic tests. Also included were questionnaires on depression, anxiety, and sleep. Nearly 60% of participants had

***Higher quinolinic acid level was associated with worse cognitive performance in people who had COVID-19***

been hospitalized, and hospitalized participants were more likely to be older, male, and have a high body mass index and at least 1 comorbidity. Lactate dehydrogenase and IL-6 levels were significantly higher in hospitalized participants than in those who were not hospitalized but there was no difference between the 2 groups in C-reactive protein level, lymphocyte count, or ferritin level. Hospitalized participants were more likely than non-hospitalized participants to be cognitively impaired at the 3-month visit (41.4% vs 11.1%, respectively;  $P=.004$ ) but not at 6- or 12-month visits. Hospitalized participants had more anxiety symptoms at the 3- ( $P=.034$ ) and 12-month visits ( $P<.001$ ) (55.6% and 31.4, respectively) but less sleep disturbance at 3 months ( $P=.028$ ). Depressive symptoms did not differ at any of the 3 timepoints. Anxiety appears to be common after hospitalization for COVID-19.

The kynurenine pathway of tryptophan metabolism appears to be dysregulated during COVID-19 and may have a role in neuroCOVID outcomes. Cysique and colleagues evaluated 128 individuals at 2, 4, and 12 months after COVID-19 diagnosis (Abstract 634). Assessments evaluated cognition, olfaction, and mood. Blood testing included tryptophan, kynurenine, and several metabolites including quinolinic acid. Cognitive and olfaction impairment did not improve over the 3 visits, including when practice effects were accounted for. At the 2-month

mark, disease severity was associated with anosmia ( $P=.05$ ) but not cognition, and cognitive deficits were more common in those with anosmia ( $P=.05$ ). Also, at 2 months, anxiety and depressive symptoms were associated with higher quinolinic acid concentration ( $P<.005$ ). After an initial increase, quinolinic acid declined steeply by 12 months. In multivariate mixed-effects models, higher quinolinic acid level was associated with worse cognitive performance in people who had COVID-19. This study supports further investigation of the relationship between the kynurenine pathway and neuroCOVID syndromes.

To evaluate the effects of the COVID-19 pandemic on mental health in people with HIV, Bares and colleagues evaluated depression, anxiety, sleep, and alcohol intake in 95 individuals (50 people with HIV and 45 people without HIV) before the COVID-19 pandemic and again in early 2021 (Abstract 633). Mean depression severity and alcohol use increased significantly in both groups ( $P<.001$  in people with HIV and  $P=.003$  in people without HIV), and alcohol use was higher in men than in women ( $P=.002$ ). The percentage of people (both with and without HIV) who moved into a more severe category of depression after the onset of the pandemic was identical (18%). Adverse mental health outcomes

***Hypoxia-inducible factor 1-alpha (HIF1- $\alpha$ ), a marker of tissue hypoxia, was upregulated in several brain regions of SARS-CoV-2-infected animals***

therefore appear to have increased as a result of the COVID-19 pandemic, but people with HIV may not fare worse than people without HIV.

In a nonhuman primate model of COVID-19, Fischer and colleagues infected 4 rhesus macaques and 4 African green monkeys with 2019-nCoV/USA-WA1/2020 and compared them with 2 controls of each primate species (Abstract 404). Microgliosis and neuronal cell death were present only in infected animals and were associated with the presence of

virus in the brain. Similar to COVID-19 human studies, there was evidence of microhemorrhages in several brain regions. These findings were present regardless of acute respiratory distress syndrome status. Hypoxia-inducible factor 1- $\alpha$  (HIF1- $\alpha$ ), a marker of tissue hypoxia, was upregulated in several brain regions of SARS-CoV-2–infected animals, except for cerebellum. However, SARS-CoV-2 was found only rarely in the brain and, when present, appeared to colocalize with the endothelial cell marker von Willebrand factor. This study shows that similar to humans, neuropathology in association with SARS-CoV-2 in the nonhuman primate model does not require direct viral neuroinvasion.

### Other CNS Infections in People With HIV

In a cost-effectiveness study, Muthoga and colleagues examined data from the AMBITION-CM (Ambisome Therapy Induction Optimisation – Cryptococcal Meningitis) study, which showed the noninferiority of single high-dose liposomal amphotericin B in combination with 14 days of oral flucytosine plus fluconazole compared with World Health Organization (WHO) standard-of-care treatment (which includes 1 week of amphotericin deoxycholate plus flucytosine) for cryptococcal meningitis (Abstract 664). Costing tools were developed for each of the 5 countries involved (Botswana, Malawi, South Africa, Uganda, and Zimbabwe). The Malawi context was chosen for the primary analysis. Mean costs, cost-differences, and an incremental cost-effectiveness ratios were calculated. Additional sensitivity analyses were performed based on the potential for the liposomal amphotericin B regimen to reduce the length of hospital admission under real-world implementation conditions. For Malawi, the mean incremental cost-effectiveness ratio was US \$128 (95% CI, \$53–\$257) per life-year saved with liposomal amphotericin B. Using a real-world laboratory monitoring schedule, the mean incremental cost-effectiveness ratio cost per life-year saved fell to US \$80 (95% CI, \$15–\$275) with liposomal amphotericin B. For the other countries, incremental cost-effectiveness ratio cost per life-year saved ranged from US \$92 to \$152 for in-trial and US

\$71 to \$121 for real world schedules. In the countries with higher costs for inpatient hospitalization (Botswana and South Africa), the liposomal amphotericin B regimen was cost-saving compared with the control treatment if patients could be discharged 1 or 2 days earlier. Extrapolating to high-income countries, cost savings with liposomal

***People with HIV with cryptococcal or tuberculous meningitis and detectable CMV DNA detected in blood had 59% increased hazard of death at 18 weeks***

amphotericin B for cryptococcal meningitis may be even higher. Notably, the WHO issued a press release in April 2022 that endorsed the single-dose liposomal amphotericin protocol.

In an AMBITION-CM substudy, Leeme and colleagues examined the prognostic value of using a semiquantitative lateral flow assay to detect cryptococcal antigen from blood and CSF (Abstract 665). Using the Botswana and Malawi sites, the team evaluated mortality in participants with high or low blood cryptococcal antigen titer, which is dichotomized by the assay. Among 187 individuals whose titers were analyzed, 56% had high titers and 44% had low titers. People with high titers had significantly higher CSF fungal burden by colony forming units (CFU) per milliliter. Over 10 weeks of follow-up, those with high titers had an 88% increase in mortality hazard than those with low titer ( $P=.04$ ). This difference remained significant after adjustment for age, sex, and treatment group. Use of this lateral flow assay could potentially risk-stratify people with cryptococcal meningitis.

In a substudy of the ASTRO-CM (Adjunctive Sertraline for the Treatment of HIV-Associated Cryptococcal Meningitis) and RifT (High Dose Oral and Intravenous Rifampicin for Improved Survival From Adult Tuberculous Meningitis) studies, Skipper and colleagues evaluated the association between cytomegalovirus viremia and mortality (Abstract 667).

A total of 340 individuals with HIV and meningitis were evaluated, 90% of whom were from ASTRO-CM, and 36% of whom had detectable cytomegalovirus (CMV) from blood. Those with CMV viremia had lower hemoglobin concentration and were less likely to have CSF pleocytosis. Mortality at 18 weeks was 50% for participants with CMV viremia and 34% for participants without CMV viremia. In separate Cox proportional hazards modeling that accounted for low CD4+ T-cell count and Glasgow coma scale, people with cryptococcal or tuberculous meningitis and detectable CMV DNA in blood had 59% increased hazard of death at 18 weeks than people without CMV present. The findings may reflect more immune dysfunction in people with CMV viremia; the possible benefit of anti-CMV therapy is still untested but should be considered for future studies.

In a 3-country study in people with HIV living in sub-Saharan Africa, Kanyama and colleagues assessed the effects of implementation of a standardized management algorithm of CNS infections (Abstract 663). This algorithm included bedside rapid diagnostic tests and WHO-recommended treatments. In the preimplementation phase, only 10.1% of participants had microbiologically confirmed CNS infection; in the implementation phase, this level markedly improved with 75% (269/356) having a probable or confirmed CNS infection, and 77.3% (174/225) being microbiologically confirmed. In the implementation phase, the most common infection was cryptococcal meningitis (55%), driven by participants from Malawi and Tanzania. CNS toxoplasmosis was the most common infection in Cameroon. Median CD4+ T-cell count was lowest for cryptococcal meningitis (37/ $\mu$ L), followed by CNS toxoplasmosis (87/ $\mu$ L), tuberculous meningitis (104/ $\mu$ L), and bacterial meningitis (148/ $\mu$ L). Ten-week mortality was up to 45% for all infections except CNS toxoplasmosis, for which 10-week mortality was 21%. This study showed that standardized

algorithms for CNS infections can drastically improve diagnostic certainty and guide management, which should improve survival. 

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*Invited Review***CROI 2022: Advances in Antiviral Therapy for HIV, COVID-19, and Viral Hepatitis****Shauna H. Gunaratne, MD, MPH<sup>1</sup>; Hong-Van Tieu, MD, MS<sup>1,2</sup>; Timothy J. Wilkin, MD, MPH<sup>3</sup>; Barbara S. Taylor, MD, MS<sup>4</sup>**<sup>1</sup>Columbia University Irving Medical Center, New York, New York<sup>2</sup>New York Blood Center, New York, New York<sup>3</sup>Weill Cornell Medicine, New York, New York<sup>4</sup>University of Texas Health Science Center at San Antonio

*The 2022 Conference on Retroviruses and Opportunistic Infections provided a rich source of new data and comprehensive reviews on antiviral therapy. For COVID-19, intramuscular sotrovimab was noninferior to intravenous sotrovimab, serostatus did not predict the efficacy of sotrovimab, and molnupiravir appeared safe and modestly effective in decreasing hospitalization rates. Trials from low- and middle-income countries provided data to support transitioning those on first-line therapy with or without virologic suppression and those virologically suppressed on second-line therapy to dolutegravir-based regimens. Additional data supported the use of lenacapavir as a long-acting antiretroviral drug. Data across the United States demonstrate the negative impact of the COVID-19 pandemic on the HIV care continuum, although enhanced outreach efforts and decentralization of antiretroviral therapy delivery were associated with improvements in care engagement outcomes. Researchers described potential mechanisms for the emergence of integrase strand transfer inhibitor resistance. Studies on proviral genotyping highlighted the limitations of its use in predicting clinically significant resistance. Several studies looked at the epidemiology and treatment of*

*hepatitis C and B and the status of current hepatitis C virus elimination efforts. Data presented on HIV, COVID-19, and maternal and pediatric health included 2-year virologic outcome data of very early antiretroviral therapy in potentially reducing the latent HIV reservoir in infants with HIV. Data presented on COVID-19 and HIV therapeutics in children included SARS-CoV-2–neutralizing monoclonal antibodies in children younger than 12 years of age, remdesivir in hospitalized infants and children, and long-acting therapies for HIV treatment in children.*

**Keywords:** HIV, COVID-19, SARS-CoV-2, sotrovimab, lenacapavir, hepatitis B, hepatitis, hepatitis C, healthcare delivery

**Advances in Treatment of COVID-19****Antivirals and Monoclonal Antibodies for Treatment of Nonhospitalized Patients With COVID-19**

Kumarasamy and colleagues presented results from a phase III trial of molnupiravir for treatment of mild SARS-CoV-2 in India (Abstract 101). Their multicenter, open-label, randomized controlled trial enrolled more than 1200 adults with mild SARS-CoV-2 infection within 5 days of symptom onset and confirmed SARS-CoV-2 positive results by reverse transcriptase polymerase chain reaction (RT-PCR). Patients were randomly assigned to receive oral molnupiravir 800 mg twice daily or standard of care.

**Author Correspondence**

Send correspondence to Dr Shauna Gunaratne, 180 Fort Washington Ave, 6th Floor, New York, NY, 10032, or email [shg2130@cumc.columbia.edu](mailto:shg2130@cumc.columbia.edu).

The primary endpoint of hospitalization by day 14 was reached in 1.5% of patients (9 patients) in the treatment arm compared with 4.3% (26 patients) in the standard of care arm, which was statistically significant ( $P=.0053$ ). They also observed a faster time to clinical improvement, increased rates of SARS-CoV-2 negativity, and reduced viral loads (inferred from cycle thresholds) in the treatment arm compared with the standard of care arm. They did not observe an increased rate of serious adverse events in the investigational arm. These results were similar to observations from a randomized controlled trial conducted in the United States, where modest improvements in rates of hospitalization or death were seen.<sup>1</sup>

Strizki presented data on errors in SARS-CoV-2 RNA with the use of molnupiravir from the MOVE-OUT (Efficacy and Safety of Molnupiravir in Non-Hospitalized Adult Participants With COVID-19) trial (Abstract 471). Molnupiravir's mechanism of action

***The study authors did not find any mutations associated with molnupiravir resistance or any treatment-emergent mutations in the spike protein that had not previously been observed without the presence of molnupiravir***

is to insert mutations into the viral RNA, thereby inhibiting viral replication. The authors observed a statistically significant increase in the mean number of mutations in the molnupiravir 800 mg group compared with the placebo group ( $P<.0001$ ). The majority of mutations observed were transition errors. After molnupiravir treatment, the authors observed a few mutations but no change in susceptibility to molnupiravir. They observed 11 spike protein mutations in 6 of the study participants who received molnupiravir, and reported that all mutations were seen in previously circulating virus. The

authors concluded that no mutations associated with molnupiravir resistance or any treatment-emergent mutations in the spike protein were found that had not been previously observed without the presence of molnupiravir.

Kohli presented results from the COMET-TAIL (COVID-19 Monoclonal Antibody Efficacy Trial – Treatment of Acute COVID-19 with Intramuscular Monoclonal Antibody) trial, a phase III randomized, controlled, noninferiority study examining intramuscular (IM) versus intravenous (IV) sotrovimab (Abstract 102). The investigators enrolled patients who were at least 12 years of age with COVID-19 with symptoms within 7 days of onset and who were at high risk of progression, including those who were at least 55 years of age or had comorbidities such as diabetes, chronic kidney disease, chronic lung disease, chronic liver disease, and immunosuppression. The investigators initially had 3 arms comparing IV sotrovimab 500 mg, IM sotrovimab 500 mg, and IM sotrovimab 250 mg, but the IM sotrovimab 250 mg arm was discontinued due to an increased rate of hospitalization compared with the other 2 arms. The primary endpoint was all-cause hospitalization by day 29. Of note, enrollment had been completed by August 2021, so they primarily studied the effect of sotrovimab on the Delta variant before the rise of the Omicron variant. The adjusted risk difference was 1.07% (95% confidence interval [CI],  $-1.25\%$ - $3.39\%$ ) between IM sotrovimab 500 mg and IV sotrovimab 500 mg. The IM formulation was noninferior to the IV formulation based on the prespecified margin of 3.5%. The investigators observed a low rate of adverse events and injection site reactions in the IM group.

Shapiro presented results from the COMET-ICE (COVID-19 Monoclonal Antibody Efficacy Trial – Intent to Care Early) trial, which examined the effect of positive baseline SARS-CoV-2 anti-nucleocapsid (N) antibody on response to sotrovimab (Abstract 103). N immunoglobulin G (IgG) antibody was obtained on the first day of the study, before any infusion was administered. The patient population studied was unvaccinated adults at least 55 years of age or unvaccinated adults at least 18 years of age with a comorbid condition, and with COVID-19

within 5 days of symptom onset. Patients with a history of prior COVID-19 were not enrolled. Of note, patients were enrolled through March 2021, before the emergence of the Delta or Omicron variants. The primary outcome was all-cause hospitalization rates by day 29. The investigators observed decreases in hospitalization rates in seropositive and seronegative groups that were consistent with the overall study population. They noted lower baseline SARS-CoV-2 viral loads and a trend toward lower rates of hospitalization in seropositive patients, but firm conclusions were limited due to the small number of patients observed. The study authors noted that sotrovimab appeared to reduce progression to severe COVID-19 and hospitalization despite serostatus. Serostatus testing did not appear to be useful in the outpatient setting in predicting which patients may respond better to sotrovimab, unlike in the RECOVERY (Randomised Evaluation of COVID-19 Therapy) trial, which showed that negative serostatus was correlated with decreased mortality when casirivimab (CAS) and imdevimab (IMD) were evaluated in hospitalized patients.<sup>2</sup>

O'Brien and colleagues presented results from a phase III randomized, double-blind, placebo-controlled trial examining the use of CAS/IMD as pre-exposure prophylaxis in household contacts of patients with COVID-19, with infusions administered within 96 hours of the index case's positive RT-PCR result (Abstract 104). The primary outcome was the proportion of patients who developed SARS-CoV-2 infection confirmed by RT-PCR (irrespective of presence of symptoms). Of note, this study completed enrollment in October before the emergence of the Omicron variant, and it enrolled primarily during the era of the Delta variant. The investigators observed an 81.2% risk reduction of symptomatic SARS-CoV-2 infections with the use of CAS/IMD (odds ratio [OR], 0.17; 95% CI, 0.09-0.31;  $P < .0001$ ) and a 68.2% risk reduction of symptomatic or asymptomatic SARS-CoV-2 infection (OR, 0.27; 95% CI, 0.20-0.37;  $P < .0001$ ). The investigators observed a protective effect up to 5 months after administration, with waning efficacy 6 to 8 months after administration. When limiting the observation period to 5 months (when the CAS/

IMD was found to be fully protective), there was a 100% risk reduction of symptomatic SARS-CoV-2 infections and an 89.5% risk reduction of all SARS-CoV-2 infections.

Jilg and colleagues conducted a phase II trial looking at efficacy outcomes for camostat, a serine protease inhibitor that inhibits SARS-CoV-2 in vitro (Abstract 105). When looking at outcomes of hospitalization or death, they did not see any significant difference in the event rate between the camostat arm (5.6%) and the placebo arm (4.7%) ( $P = .76$ ). They also did not observe any significant difference in time to virologic clearance and time to symptom

***The study authors concluded that camostat did not show any efficacy for treatment of SARS-CoV-2***

improvement. The authors concluded that camostat did not show any efficacy for treatment of SARS-CoV-2. Jilg and colleagues presented data from a second placebo-controlled trial of camostat for the treatment of outpatients with COVID-19 and a high risk of progression (Abstract 459). They randomly assigned 295 participants (57% female, 60% Hispanic, 7% Black). Progression to hospitalization or death was low in the camostat and placebo groups (5.3% and 6.1%, respectively). There were non-definitive trends toward faster clearance of SARS-CoV-2 infection by PCR. Based on these results, it appears that camostat should not be pursued further for treatment of COVID-19.

Taiwo and colleagues presented data on SAB-185, a bovine-derived, fully human polyclonal immunoglobulin, studied in nonhospitalized patients with mild to moderate symptomatic COVID-19 infection (Abstract 454). Two hundred thirteen participants were randomly assigned to the SAB-185 arm or the placebo arm (median age, 38 years; 54% women; 50% Hispanic; 7% Black). The investigators found no difference in the proportion of participants with SARS-CoV-2 RNA suppression over 2 weeks, and no difference in time to resolution of symptoms.

Webb and colleagues reported on the safety of remdesivir in a placebo-controlled trial of 562 non-hospitalized patients with COVID-19 at high risk

*Remdesivir appears safe and well tolerated in nonhospitalized patients with COVID-19*

of progression (Abstract 456). The primary efficacy results showing an 87% reduction in COVID-19–related hospitalization or death with remdesivir have been published.<sup>3</sup> Remdesivir was dosed as 200 mg intravenously on day 1, and 100 mg on days 2 and 3. Remdesivir recipients experienced a slightly higher rate of drug-related nausea (6.5% vs 3.5%), and a grade 3 or greater decrease in creatinine clearance (5.6% vs 1.9%). The creatinine levels generally remained in the normal range, and the changes in clearance resolved in follow-up. Other adverse events were generally similar between groups. The authors concluded that remdesivir was safe and well tolerated in outpatients at high risk for progression.

Nomah and colleagues investigated the potential benefit of tenofovir disoproxil fumarate (TDF)/emtricitabine (FTC) for modifying COVID-19 infection and disease among people with HIV (Abstract 469). They performed a propensity score-matched analysis within an ongoing cohort study. They compared patients receiving TDF/FTC, tenofovir alafenamide (TAF)/FTC, and abacavir/lamivudine (ABC/3TC). There was a suggestion that patients receiving TDF/FTC

*Data did not support a role for tenofovir in preventing or modifying SARS-CoV-2 infection*

may be less likely to have a SARS-CoV-2 diagnosis, but patients receiving TAF/FTC had similar rates of SARS-CoV-2 to patients receiving ABC/3TC. The authors concluded that the differences observed with TDF/FTC were likely due to more favorable baseline

prognostic factors, and that these data did not support a role for tenofovir to modify SARS-CoV-2 infection or disease.

### **Treatment of Hospitalized Patients With COVID-19**

Investigators from the PAN-COVID (Global Pregnancy and Neonatal Outcomes in COVID-19) study group presented a randomized, factorial study comparing TDF/FTC with no TDF/FTC, and baricitinib plus dexamethasone versus dexamethasone alone (Abstracts 460 and 463). They randomly assigned 355 adults with COVID-19 (97% hospitalized; 72% with 1 or more comorbidity; 65% male; median age, 67 years). There was no significant difference between TDF/FTC versus no TDF/FTC with regard to mortality (2.2% vs 4%, respectively) or disease progression (22.5% vs 20.3%, respectively). The authors concluded that TDF/FTC did not improve outcomes. Of the 355 participants, 287 (81%) were randomly assigned to baricitinib plus dexamethasone or dexamethasone alone. Baricitinib is a Janus kinase 1 inhibitor that inhibits intracellular signaling pathways of several cytokines known to be increased in COVID-19. Baricitinib accelerated recovery time for COVID-19, especially for those participants on noninvasive ventilation, in a clinical trial enrolling 1033 participants.<sup>4</sup> In this trial, several clinical parameters favored baricitinib, but none reached statistical significance.

Two analyses investigated the role of monoclonal antibodies targeting the interleukin (IL)-6 receptor in patients with severe COVID-19. Mussini and colleagues reported on a cohort of 992 patients who did or did not receive tocilizumab for progressive disease (Abstract 465). There was no difference in mortality in the unadjusted analysis. Several analyses adjusted for various disease severity markers and demographic data suggested a survival benefit with tocilizumab. Any potential benefit from tocilizumab was limited to those with a C-reactive protein (CRP) level greater than 7.5 mg/dL, and there was a suggestion of harm in patients with lower CRP concentrations. Mastrorosa and colleagues presented data on a randomized, open-label trial of sarilumab for treatment of severe COVID-19 (Abstract 466). One

hundred seventy-six participants were randomly assigned 2:1 to sarilumab plus standard of care or standard of care alone. The primary endpoint was time to a 2-point improvement on the 7-point COVID-19 ordinal scale. The investigators did not find an overall benefit to sarilumab. There was a suggestion of potential benefit in the group with CRP concentrations less than 7 mg/dL. The reason for these somewhat disparate findings is not clear.

### Treatment Outcomes for COVID-19

Price and colleagues from the National COVID Cohort Collaborative (N3C) pooled data from 3,766,433 people with COVID-19 from 69 centers across the United States to determine which therapy or combination of therapies for COVID-19 are associated with hospital discharge at week 4 (Abstract 637). The analysis used elastic net penalized multinomial logistic regression to determine probabilities of treatment effects for different ordinal scale outcomes for COVID-19, but did not find any standard combination of treatments that predicted discharge by week 4. Steroids with or without monoclonal antibodies, antibiotics, or antivirals, depending on the Charlson comorbidity index and timeframe, were most effective for those hospitalized on ventilators, extracorporeal membrane oxygenation, or vasopressors. Combinations without steroids but including antivirals, monoclonal antibodies, or anticoagulants appeared most effective for those hospitalized with or without oxygen supplementation. The investigators did note an impact of the Delta variant compared with previous variants on the effectiveness of various regimens. For example, anticoagulants only appeared in some of the most effective treatment combinations in the post-Delta variant era. These data suggest there are many possible effective therapeutic options for COVID-19 treatment, and disease severity and variants will continue to influence response to treatments.

Data from the N3C were used to explore the effect of HIV diagnosis on COVID-19 hospitalizations and mortality, and the impact of age on these outcomes (Abstract 901). Of 2,422,864 adults with COVID-19 in the cohort, 15,188 (0.62%) were people with HIV. Investigators created an exact

matched cohort matching people with HIV to those without HIV on age, sex, race, and ethnicity and found people with HIV had higher odds of hospitalization (OR, 1.50; 95% CI, 1.42-1.58) and death (OR, 1.48; 95% CI, 1.29-1.69) than those without HIV. A propensity score matching analysis demonstrated that people with HIV had a higher risk of hospitalization until the age difference reached 13 years, and a higher risk of death until the age difference reached 6 years. When people with HIV were

*Lenacapavir as a part of combination regimen led to sustained virologic suppression in patients living with HIV*

stratified by CD4+ cell count, age thresholds for those with CD4+ counts under 200 cells/ $\mu$ L were reduced to 6 years for hospitalization but extended to 11 years for death. These findings suggest that the acceleration of aging known to be present for people with HIV may lead to the elevated risk of hospitalization and death from COVID-19, and that immunodeficiency, based on CD4+ cell count, likely also impacts those outcomes.

## Advances in Treatment of HIV

### Investigational Agents

**Lenacapavir.** Gupta and colleagues presented data from the CALIBRATE (Study to Evaluate the Safety and Efficacy of Lenacapavir in Combination With Other Antiretroviral Agents in People Living With HIV) trial on various lenacapavir (LEN)-based regimens in treatment-naïve people with HIV (Abstract 138). The study enrolled 182 people with CD4+ count above 200 cells/ $\mu$ L and plasma HIV RNA level above 200 copies/mL who had never received antiretroviral therapy (ART) (median age, 29 years; 7% female; 52% Black; 45% Hispanic). Participants were enrolled into 1 of 4 groups. Groups 1 and 2 received LEN orally for 2 weeks followed by

subcutaneous injections given every 6 months with daily TAF/FTC through week 28. At week 28, group 1 continued daily TAF without FTC and subcutaneous LEN. Group 2 continued subcutaneous LEN and changed TAF/FTC to bicitegravir (BIC) daily. Group 3 received LEN orally and daily TAF/FTC through week 54, and group 4 received BIC/FTC/TAF through week 54. The week 28 results were previously presented, wherein 94% in the LEN groups achieved a plasma HIV RNA level below 50 copies/mL. For those suppressed at week 28, all groups exhibited high rates of viral suppression at week 54, ranging from 90% to 94%. Resistance to LEN emerged in 2 participants: 1 at week 10 and a second at week 54. Both participants had evidence of nonadherence to TAF/FTC. Three participants discontinued LEN due to injection site reactions. These preliminary data support the continued evaluation of LEN for treatment of HIV, including its use in novel 2-drug regimens.

Ogbuagu and colleagues presented additional data on LEN for the treatment of multidrug-resistant (MDR) HIV from the CAPELLA (Study to Evaluate the Safety and Efficacy of Lenacapavir in Combination With an Optimized Background Regimen [OBR] in Heavily Treatment Experienced Participants Living With HIV-1 Infection With Multidrug Resistance) trial (Abstract 491). This study enrolled participants with ongoing viremia who had resistance to 2 or more drugs in 3 or more major drug classes. The results combined a cohort randomly assigned to LEN or placebo for 14 days and a nonrandomized cohort. The authors presented week 52 data; the week 26 data had been previously presented. The analysis included 72 participants (25% female; 38% Black; 21% Hispanic; median age, 52 years). The median plasma HIV RNA level was 4.5 log<sub>10</sub> copies/mL, and 64% had a CD4+ count less than 200 cells/μL. Overall, 81% had a plasma HIV RNA level below 50 copies/mL at week 52 (88% below 200 copies/mL). LEN appeared well tolerated, with only 1 person withdrawing due to injection site reactions. These data support the use of LEN for patients with MDR HIV infection.

**Broadly neutralizing antibodies.** Juelg and colleagues presented the antiviral activity of 3 broadly

neutralizing antibodies (bNAbs): PGDM1400, PGT-121, and VRC07-523LS (Abstract 139). Four participants received the triple combination. The investigators observed a mean decline of 1.76 log<sub>10</sub> copies/mL through 7 days. One participant was lost to follow-up while having a declining plasma viral load through 25 days. The other participants exhibited viral rebound between 13 and 70 days postinfusion. Two of the 3 participants had reduced susceptibility to 1 or more antibodies at baseline. All participants showed reduced susceptibility at failure of 1 or more bNAbs compared with baseline.

Caskey and colleagues presented data on the antiviral activity of a combination of 2 bNAbs, 10-1074LS and 3BNC117-LS, in people with HIV (Abstract 140). Participants were required to be off ART or never treated. They enrolled 6 participants with a median CD4+ count of 523 cells/μL and a median plasma HIV RNA level of 48,700 copies/mL. All participants received single infusions of the 2 bNAbs. Four participants showed a transient decline in plasma HIV RNA of approximately 1.9 log<sub>10</sub> copies/mL. The other 2 participants showed sustained viral suppression for 16 and 24 weeks, respectively. Phenotypic testing of HIV DNA revealed that the 4 participants with transient declines in viremia had predicted resistance to 1 or both antibodies, although the 2 achieving suppression had predicted sensitivity to both antibodies. Of note, these participants also had lower viral loads at baseline.

Casazza and colleagues presented data on an adenoviral vector transferring a gene encoding VRC07, a bNAb targeting HIV (Abstract 498). They enrolled 8 participants with HIV on suppressive ART who received 1 of 3 doses of the adenoviral vector. The vector appeared safe in this small study. It led to detectable VRC07 concentrations, which were sustained through 3 years of follow-up. Higher concentrations were observed at the higher doses. A few participants developed antidrug antibodies to VRC07 that reduced concentrations. The antibodies generated from the gene transfer exhibited expected functionality in ex vivo experiments. Although therapeutic concentrations of VRC07 were not achieved in this study, it does provide

proof-of-concept of a gene transfer approach to induce production of bNAbS.

**Long-acting cabotegravir and rilpivirine.** Overton and colleagues presented additional data from the ATLAS-2M (Long-acting Cabotegravir and Rilpivirine Dosed Every 2 Months in Adults With HIV-1 Infection) trial that compared outcomes with every-4-week and every-8-week dosing of long-acting cabotegravir and rilpivirine (CAB-LA/RPV) (Abstract 479). Participants in this trial were enrolled from the oral ART arm and CAB-LA/RPV arm of the ATLAS trial, as well as de novo participants who were suppressed on oral ART. Overall, 85.9% and 87.4% at week 152 in the every-4-week and every-8-week arm, respectively, had plasma HIV RNA level below 50 copies/mL. The reasons for nonsuppression in the 2 groups appeared somewhat different, with more participants leaving the study with a plasma HIV RNA viral load of more than 50 copies/mL in the every-8-week group. However, participants in the every-4-week group were more likely to choose to leave the study; the treatment satisfaction was substantially greater among participants in the every-8-week group. A total of 13 participants had resistance emerge through week 152; 11 were in the every-8-week group, and 2 were in the every-4-week group. These data support the long-term efficacy of and participant satisfaction with the every-8-week regimen.

**Clinical trials of second-line therapy in low- and middle-income countries.** Mulenga and colleagues presented results from the VISEND (Dolutegravir With Recycled nRTIs Is Noninferior to PI-based ART) study, which enrolled Zambian people with HIV currently receiving TDF, 3TC, and efavirenz (EFV) or nevirapine (NVP) (Abstract 135). Overall, 1201 participants were enrolled (61% female; median age, 40 years). Participants were divided into group A or group B based on plasma HIV RNA (<1000 copies/mL and  $\geq$ 1000 copies/mL, respectively). In group A, 418 participants were randomly assigned to TDF/3TC/dolutegravir (DTG) or TAF/FTC/DTG. At week 48, 80% and 74%, respectively, were below 50 copies/mL using the intention-to-treat (ITT) analysis. TAF/FTC/DTG did not achieve noninferiority to

TDF/3TC/DTG in this study using an HIV RNA cut-off of less than 50 copies/mL but did achieve non-inferiority using a 1000 copies/mL cutoff. Group B randomly assigned 773 participants to TDF/3TC/DTG, TAF/FTC/DTG, or the standard of care regimen (zidovudine, lamivudine, and atazanavir/ritonavir or lopinavir/ritonavir). At week 48, 72%, 80%, 70%, and 56% of participants had plasma HIV RNA less than 50 copies/mL in the TDF/3TC/DTG, TAF/FTC/DTG, atazanavir, and lopinavir arms, respectively. TAF/FTC/DTG appeared superior to TDF/3TC/DTG in this study using the less than 50 copies/mL cut-off. TAF/FTC/DTG and TDF/3TC/DTG each appeared superior to the combined protease inhibitor (PI) arms. The authors concluded that the data support the use of DTG with TAF/FTC or TDF/3TC for patients switching off a first-line nonnucleoside reverse transcriptase inhibitor (NNRTI)-based regimen.

Engamba and colleagues reported the outcomes of enhanced adherence counseling (3 adherence counseling sessions over 3 months) for participants who experienced virologic failure in the VISEND trial (Abstract 490). They found that 66% of participants achieved subsequent viral suppression (78% and 71% for the TAF/FTC/DTG and TDF/3TC/DTG arms, respectively; 62% and 53% for the atazanavir and lopinavir arms, respectively).

Paton and colleagues presented follow-up data from the NADIA (Nucleosides and Darunavir/Dolutegravir in Africa) trial (Abstract 137). This trial randomly assigned patients in whom a NNRTI, TDF, and 3TC or FTC was failing in a factorial design to receive TDF/3TC or zidovudine/3TC, and to receive DTG or darunavir/ritonavir. The week 48 results have been published.<sup>5</sup> The trial enrolled 464 participants (61% female). At week 96, 89.8% of the DTG group and 86.9% of the darunavir group had plasma HIV RNA viral loads of fewer than 400 copies/mL. This result was consistent in a variety of subgroup analyses. In particular, the viral suppression rates were similar among those with 0 or 1 active NNRTIs in their assigned regimen. DTG-based regimens led to sustained virologic suppression as second-line therapy even with significant NNRTI resistance. The viral suppression rates appeared lower among those with 2 active NNRTIs, likely because this group is

enriched for those with nonadherence. Those receiving TDF had superior virologic outcomes to those receiving zidovudine. In the subgroup analyses, TDF maintained similar rates of efficacy when having varying amounts of NNRTI resistance at baseline including the K65R mutation. No resistance to darunavir was detected in study follow-up. Nine

***DTG-based regimens led to sustained virologic suppression as second-line therapy even with significant NNRTI resistance***

participants developed DTG resistance: 6 received zidovudine (5 with high-level DTG resistance), and 3 received TDF (none with high-level resistance). The authors concluded that DTG and TDF/3TC give durable suppression as second-line therapy even if there are no predicted active NNRTIs. They also noted that DTG resistance was a concern that may be reduced by using TDF/3TC instead of zidovudine/3TC.

Ombaja and colleagues reported on a randomized controlled trial enrolling virally suppressed individuals suppressed on a second-line PI-based regimen (Abstract 136). Participants (n=791) were randomly assigned to switch to TDF/3TC/DTG or to maintain their current PI-based regimen. Of note, there were no available resistance data for participants. Participants included 66% women with a median age of 46 years. The primary endpoint was proportion with plasma HIV RNA greater than 50 copies/mL according to the US Food and Drug Administration (FDA) snapshot regimen. This occurred in 5.0% and 5.1% of the TDF/3TC/DTG and PI arms, respectively, meeting the protocol definition of noninferiority. There were no obvious differences in adverse events between the 2 groups. The authors concluded that switching virally suppressed patients on second-line therapy to TDF/3TC/DTG was safe and efficacious even in the absence of prior resistance data. This provides further support to current World Health Organization (WHO) recommendations.

**Additional cohort data on first-line therapy in low- and middle-income countries.** McCluskey and colleagues presented on outcomes on Ugandan patients with HIV on first-line regimens who transitioned to TDF/3TC/DTG (Abstract 487). Among 500 people, 95% had plasma HIV RNA suppressed with less than 50 copies/mL at the time of transition. At 1 year, 92% were virally suppressed and in care, 5% had plasma HIV RNA of 50 copies/mL or greater (median, 252 copies/mL), 2% were lost to follow-up, and 1% died. In addition, 3% of participants discontinued TDF/3TC/DTG prior to week 48.

Kityo and colleagues presented data from ACTG (AIDS Clinical Trial Group) A5381, the HAKIM (Observational Cohort to Assess Therapeutic Efficacy and Emergence of HIV Drug Resistance Following Initiation of Tenofovir-Lamivudine-Dolutegravir for First- or Second-Line ART or With Rifampin-Containing TB Treatment) study (Abstract 488). This study will describe the efficacy and development of resistance occurring in the setting of TDF/3TC/DTG rollout globally. In this analysis, they reported on the 6-month outcomes of people with HIV initiating TDF/3TC/DTG as a first regimen (n=179), and patients with virologic suppression on a first-line regimen switching to TDF/3TC/DTG (n=421). For those initiating TDF/3TC/DTG, 42% were female, and the median age was 35 years. Follow-up for both arms was impacted by COVID-19. Among those with an HIV RNA result, 85% of those starting TDF/3TC/DTG as an initial regimen were suppressed to below 50 copies/mL. For those switching to TDF/3TC/DTG while suppressed on a first-line regimen, 80% were female and the median age was 40 years. Among those with available viral load data, 96% had plasma HIV RNA level below 50 copies/mL. One participant developed a new integrase mutation T97A/T. The authors concluded that these preliminary data are supportive of the ongoing TDF/3TC/DTG rollout.

## Clinical Pharmacology

**Alternative modes of ART administration.** Some patients have difficulty or are unable to swallow pills. Massih investigated the pharmacokinetics

of ingesting fixed-dose elvitegravir/cobicistat/FTC/TAF dissolved in 120 mL of tap water in 12 volunteers without HIV infection (Abstract 447). They found that although the pharmacokinetic profiles did not meet the definition of equivalence, the observed differences were unlikely to be clinically meaningful. There were no complaints about the taste of the solution. The authors concluded that this may be a reasonable option for this subset of patients with substantial swallowing difficulties.

DeJesus and colleagues investigated administering ibalizumab via a slow IV push in people with and without HIV (Abstract 429). Ibalizumab is a long-acting attachment inhibitor administered by IV infusion indicated for MDR HIV. They found that this route of administration was bioequivalent to the standard infusion, and it may be a simpler option for administering the drug.

**Urine tenofovir to predict viremia.** Hermans and colleagues investigated the use of the point-of-care (POC) urine tenofovir assay to predict viremia among participants in a randomized, controlled trial of first-line ART regimens (Abstract 451). They found that a negative tenofovir result had a sensitivity of 69%, and 100% specificity for concomitant viremia. They also noted that participants with ongoing viremia and tenofovir detected were more likely to have drug resistance. The authors asserted that this assay may be useful by providing rapid insight into adherence.

**Islatravir and LEN interactions.** Zhang and colleagues evaluated possible pharmacokinetic interactions between islatravir and LEN, a novel investigational combination for long-acting ART, in 55 participants without HIV infection (Abstract 433). They found that drug concentrations for the 2 drugs met the predefined equivalency definition compared with administering the drugs separately. The authors concluded that there were no significant drug-drug interactions.

**ART in severe renal disease.** Weber and colleagues investigated the pharmacokinetics of a single oral dose of LEN in patients with severe re-

nal dysfunction compared with those with normal renal function (Abstract 434). They found that LEN exposure was greater in those with severe renal impairment, including a 162% increase in the maximal concentration and an 84% increase in the area under the curve over 50 days. The authors did not believe that dose adjustment was necessary given available safety and pharmacokinetic data.

Molto and colleagues reported on the removal of doravirine by hemodialysis in 8 patients with HIV with end-stage renal disease (Abstract 435). They found an extraction coefficient of 35%; the concentration of doravirine in blood leaving the hemodialysis machine was 35% lower than blood entering the machine. Overall, dialysis reduced doravirine concentrations by 20%, but concentrations remained far above the target concentrations.

**Drug-drug interactions involving contraceptives.** Mngqibisa and colleagues presented data on the use of the emergency contraceptive levonorgestrel in women without HIV on rifampin-based tuberculosis therapy (Abstract 77). Rifampin is a potent inducer of cytochrome P450 and is expected to lower levonorgestrel concentrations. They enrolled 34 women who received levonorgestrel 3 mg, twice the normal dose. They compared the pharmacokinetics with a control group of women with HIV receiving DTG-based therapy, not on rifampin, who were enrolled in a different arm of the same trial. They found that the maximal concentration was 27% higher in the double-dose group, and the half-life was reduced by 57% leading to lower concentrations at 48 hours postdose. The authors noted that the efficacy of this contraceptive strategy is thought to be related to the maximal concentration and recommended this strategy to overcome the drug-drug interaction.

Chappelle and colleagues investigated a strategy to overcome a known drug-drug interaction whereby EFV lowers etonogestrel concentrations (Abstract 884). They randomly assigned 72 Ugandan women with HIV receiving EFV-based ART to receive a single etonogestrel implant or 2 implants. All women also received a copper intrauterine device for known effective contraception. The double

implant group achieved etonogestrel concentrations that were more than twice that of the single dose group, but still lower than historic controls. The double implant strategy reduced the odds of ovulation by 97% compared with the single implant group (2 vs 47 ovulation events, respectively). The authors recommended this strategy when using etonogestrel implants in women receiving EFV-based ART.

**ART and the HIV reservoir/viral kinetics.** Daar and colleagues presented data from ACTG A5354, looking at viral load in patients with acute and early HIV infection (Abstract 492). They grouped patients into categories based on their Fiebig stage. Group 1 consisted of 49 patients in Fiebig stage I and II, group 2 consisted of 30 patients with Fiebig stage III/IV, and group 3 consisted of 60 patients with Fiebig stage V. These patients started ART during the early HIV period, 98% with integrase strand transfer inhibitor (INSTI)-based regimens. Group 1 participants had higher rates of undetectable HIV viral load at week 24 than groups 2 and 3 ( $P=.005$ ). By week 72, all groups reached undetectable viral load at similar rates. The study authors postulated that the shorter time to undetectable viral load in group 1 participants (those in Fiebig stages I and II, with only viral load or p24 antigen positivity but antibody negativity) may indicate benefit in starting ART right away, perhaps decreasing the viral reservoir.

Imaz and colleagues conducted a small, open-label, randomized, pilot clinical trial looking at viral kinetics of HIV in blood plasma, semen, and rectal fluid after initiation of ART (Abstract 495). They randomly assigned ART-naïve cisgender men with an HIV viral load below 500,000 copies/mL to either a DTG plus 3TC arm or a TAF/FTC/BIC arm. Median HIV RNA was 4.56  $\log_{10}$  copies/mL in blood, 2.38 in serum, and 3.2 in rectal fluid. The authors did not observe any differences between treatment groups in viral load decline in any of the 3 body fluids. They did note that semen and rectal fluid viral load dropped to undetectable more quickly than in blood in both treatment arms; by day 28, more than 80% of individuals in both arms had achieved viral load below 20 copies/mL in semen and rectal fluid.

Jing and colleagues presented data on low-level viremia (LLV) and association with virologic failure (defined as a viral load of 1000 copies/mL or greater) in a Chinese cohort of more than 75,000

*Data from participating in PEPFAR showed that linkage to care increased from 60% in 2016 to 90% in June 2020*

patients (Abstract 497). ART regimens were not discussed in the abstract. They found LLV to be quite common overall, in about 23.2% patients. LLV from 200 copies/mL to 399 copies/mL was associated with virologic failure (adjusted hazard ratio [aHR], 1.39; 95% CI, 1.27-1.53), and LLV from 400 copies/mL to 999 copies/mL was more strongly associated with virologic failure (aHR, 2.02; 95% CI, 1.87-2.18). LLV below 200 copies/mL was not associated with virologic failure (aHR, 0.90; 95% CI, 0.84-0.97). Conclusions are limited by not knowing ART regimens, but it suggests LLV above 200 copies/mL is predictive of virologic failure, whereas LLV below 200 copies/mL is more reassuring as it is not associated with virologic failure.

## The HIV Care Cascade and Disparities in Treatment Outcomes

### New Population and Cohort-Based Data on the HIV Care Continuum

New population data across countries receiving support from PEPFAR (US President's Emergency Plan for AIDS Relief), the United States, and Spain all highlight continued challenges in the HIV care continuum, and investigators in Atlanta explored the impact of churn, or patients moving in and out of care, on outcomes. Data from quarterly reports from 41 countries participating in the PEPFAR program were aggregated to examine trends in linkage to HIV treatment over the past 5 years (Abstract 89). PEPFAR has supported the initiation of

same-day ART since 2015, and this analysis used a proxy for linkage to treatment—the number of people reported to be newly linked to treatment divided by the number of positive HIV tests in each quarter—to determine changes in linkage over time. In a dataset that included 99.3% of PEPFAR’s HIV testing and treatment results, the investigators found that this proxy linkage percentage for people with HIV increased from 60% in March 2016 to 90% in June 2021. The increase was attributed to improved counseling during HIV testing events, implementation of same-day ART initiation, and expansion of capacity to provide linkage to treatment after testing. The analysis was limited by its use of aggregate data that could not determine length of time between diagnosis and the initiation of ART on an individual basis. In this context, data on linkage to care could represent those diagnosed many months ago, if not years ago, who are now presenting for care. Despite this reservation, the increase in proxy linkage over time highlights the importance of enhanced efforts to support linkage to care and the start of same-day ART.

Johnson Lyons and colleagues from the US Centers for Disease Control and Prevention (CDC) used data from the US National HIV Surveillance System (NHSS) in 2019 to assess the key goals of the Ending the HIV Epidemic in the United States (EHE) plan: linkage to care, defined as at least 1 CD4+ cell count or viral load test within 1 month of HIV diagnosis, and viral suppression to below 200 copies/mL within 6 months of diagnosis (Abstract 768). Across 45 jurisdictions, 77.8% of individuals newly diagnosed were linked to care, and 63.1% achieved viral suppression in 6 months. Unfortunately, only 5 jurisdictions met or exceeded the EHE target of 95% linked to care, and only 1 jurisdiction met the 95% target for viral suppression. The range of outcomes was also wide for both metrics, varying from below 50% for some areas to over 90% for others. There appeared to be more variation in outcomes for jurisdictions with fewer than 500 HIV diagnoses in 2019. These data demonstrate the continued challenges across the care continuum throughout the United States and highlight geographic disparities in outcomes.

The same NHSS dataset and care cascade outcomes were used by Mawokomatanda and colleagues at the CDC to focus on foreign-born persons in the United States, who account for 13% of the US population but 16% of new HIV diagnoses (Abstract 769). The authors found that linkage to care at 1 month was higher for people diagnosed with HIV who were foreign born (87.4%) than US born (81.3%). Similarly, viral suppression

***Non-US-born people with HIV were more likely to receive late-stage diagnoses, but they experienced higher prevalence of linkage to care at 1 month and viral suppression than US-born people with HIV***

at 6 months after diagnosis was seen in 77.1% of foreign-born people with HIV and in 68.1% of US-born people with HIV. Statistically lower outcome metrics were noted in European-born persons for linkage to care and viral suppression, and in those older than 55 years of age, men who inject drugs, and those listed as living in an “unknown or other” population area for viral suppression. The investigators also examined the outcome of late diagnoses, defined as stage 3 at time of diagnosis, and found that 26% of foreign-born patients received a late-stage diagnosis, compared with 19% of US-born persons. The analysis underscores the challenges in access to HIV testing experienced by this population leading to delays in diagnosis, but is encouraging in demonstrating improved care cascade outcomes for foreign-born individuals with HIV. An analysis of the same dataset focusing on Hispanic or Latino persons with HIV found the same improved care cascade outcomes but higher frequency of late-stage diagnosis for foreign-born Hispanic or Latino persons than for US-born Hispanic or Latino persons. There were some variations by country of origin, with Mexican- and Central American-born persons having

comparable care cascade outcomes to US-born persons (Abstract 899).

Alejos and colleagues also examined care cascade outcomes data within CoRIS (Cohort of the Spanish AIDS Research Network), which included 14,513 people with HIV receiving care between 2004 and 2020 at numerous hospital-based care centers across Spain (Abstract 890). Encouraging trends indicate improvements in timely diagnosis and linkage. Time from diagnosis to the initiation of ART decreased from more than 19 months in 2004 to less than 1 month in 2020 ( $P$  for trend  $<.001$ ). Median CD4+ count at the initiation of ART increased from less than 250 cells/ $\mu\text{L}$  in 2004 to more than 350 cells/ $\mu\text{L}$  since 2012 ( $P$  for trend  $<.001$ ). Two key care cascade metrics increased over the same observation period: linkage to care within 1 month of HIV diagnosis and viral suppression to below 200 copies/mL within 3 months of diagnosis. Linkage at 1 month increased from 41% to 83%, and viral suppression at 3 months increased from 4% to 41% (both  $P<.001$ ). Viral suppression at 3 months was more likely for women, non-Spanish-born Europeans, Latin Americans, and those older than 50 years of age, and less likely for people using injection drugs, and those with CD4+ counts above 200 cells/ $\mu\text{L}$ . These encouraging improvements in care cascade outcomes across Spain demonstrate the impact of policy changes, such as the removal of CD4+ cell count–based initiation restrictions and the use of InSTI-based regimens, but it is unclear whether CoRIS is representative of the general population with HIV in Spain.

Gopalsamy and colleagues explored the impact of “churn,” or the cycle of intermittent engagement in care experienced by some people with HIV, on care cascade and clinical outcomes (Abstract 772). Among 1303 people with HIV in newly establishing care in the Grady Infectious Disease Program in Atlanta between 2012 and 2017, 15.3% experienced churn, defined as a 1-year or more gap between either clinic visits or lab testing. Those returning to care were likely to have viral load measurements over 1500 copies/mL, but churn was not associated with increased odds of AIDS-defining illness, death, or loss to follow-up.

Thus, in this clinic experience, the primary consequence of churn was the decreased prevalence of viral suppression and implied increased HIV transmission risk for the community.

### **Policy Changes and Programmatic Structures’ Impact on the HIV Care Continuum**

Decentralized ART distribution models, including community pharmacy-based refills, clinics with quick access or walk-in services, and community-based refill groups including peers or family members, can lower barriers to ART access for many people with HIV and may impact HIV care continuum outcomes. Onovo and colleagues compared the proportion of

*Community pharmacy-based ART refills may support retention in care over time and may help to increase access to ART in the context of COVID-19 or other barriers to clinic-based care*

patients retained in care, defined as being alive and remaining on ART for at least 12 months after ART start, among 6 different decentralized ART distribution models serving 85,245 people with HIV in 2 Nigerian states (Abstract 936). Only 16% of patients experienced treatment interruption between October 2001 and December 2020, and overall retention probability was 62% at 36 months for the cohort. The median retention time in the community pharmacy-based ART refills program was 73 months, statistically significantly longer than median time in any of the other drug distribution models, which ranged from 14 to 49 months and included community-based refill clubs and expedited clinic and laboratory testing services. The observational nature of this study posed several challenges. Most notably, different implementation timeframes for the various distribution models likely impacted the analysis. Models that began enrolling patients later may have been more likely to show benefit because

of other factors impacting retention, such as the use of NNRTI-based regimens. The COVID-19 pandemic led to 5 of the 6 models expanding services to unstable patients during the last year of observation. Despite these limitations, the data presented demonstrate that community pharmacy-based ART refills may support retention in care over time in this real-world cohort.

Fennell and colleagues evaluated the impact of the expansion of access to free ART to noncitizen residents of Botswana in 2019 (Abstract 92). The investigators used data from an 18-site network to assess engagement in antenatal care, ART coverage, and adverse birth outcomes for pregnant citizens and noncitizens, comparing the time period before and after access to free ART was available for noncitizens. Of the 205,909 people delivering between August 2014 and September 2021, the proportion of noncitizens with unknown HIV status decreased from 6.3% to 1.3% after expansion of access to free ART. The proportion of noncitizens attending antenatal care increased from 79.3% to 87.3%, and among those with HIV, receipt of ART increased from 65.5% to 89.3%. Disparities in adverse birth outcomes between citizens and noncitizens decreased after free ART was provided for noncitizens. These data demonstrate that expanding access to ART to noncitizens can have substantial impacts on engagement in antenatal care and outcomes in addition to increasing HIV testing and treatment in this population.

Two abstracts examined the impact of AIDS Drug Assistance Program (ADAP) policies on HIV care continuum outcomes in the people with HIV served by the program. McManus and colleagues used HIV prevalence data from the CDC and aggregate ADAP State data to evaluate trends from 2008 to 2018 in ADAP utilization for key populations (Abstract 910). The percentage of people with HIV served by ADAP increased substantially, from 13.9% to 23.0% over the observation period, with similar trends across geographic regions. However, concerning disparities by race and ethnicity were observed. ADAP utilization for White people with HIV increased by 23% over the observation period, a statistically significant change from baseline, compared with increases seen for Black people with HIV of 11% and Hispanic

people with HIV of 9%, neither of which were statistically significant from baseline. There was also a substantial increase in ADAP utilization for people with HIV of 13 to 24 years of age. These disparities in ADAP utilization bear further investigation as they are likely related to underlying disparities in access to care. Individual-level analyses, rather than State aggregated data, may be able to shed further light on differences by age and race/ethnicity.

Investigators from the NA-ACCORD (North American AIDS Cohort Collaboration of Research and Design) examined the impact of ADAP formularies on the care cascade outcomes of ART treatment and viral suppression (Abstract 771). They compared data on 14,415 people with HIV between 2014 and 2017 in states with open formularies that included all FDA-approved medications with those with otherwise restricted formularies. The proportion of people with HIV achieving timely ART initiation, defined as receipt of ART within 6 months of cohort enrollment, was 87% among people with HIV in open formulary states and 79% for states with restricted formularies, a statistically significant difference with adjustment for demographic, insurance, income, and geographic variation. The opposite was seen for achieving viral suppression, defined as a viral load of HIV RNA below 200 copies/mL within 1 year of ART initiation: 86% of people with HIV in open formulary states and 90% of those with HIV in restricted formulary states achieved viral suppression, but this difference did not reach statistical significance. These data suggest that the initiation of ART may be timelier in states with an open formulary, although the impact on viral suppression, the final step of the care cascade, is unclear. The analysis was limited by the heterogeneity of the definition of restricted formulary and inability to account for other ADAP program characteristics, such as eligibility thresholds, that served as structural barriers to care in this context.

### **Medical and Structural Interventions to Improve the HIV Care Continuum**

Mpoudi-Etame and colleagues presented long-term outcomes from the fourth year of follow-up within the NAMSAL (New Antiretroviral and Monitoring

Strategies in HIV-Infected Adults in Low-Income Countries) trial,<sup>6</sup> which randomly assigned more than 600 people with HIV initiating ART in Cameroon to first-line treatment with a DTG-based regimen or an EFV 400 mg–based regimen (Abstract 493). Viral suppression, defined as HIV plasma RNA level below 50 copies/mL at week 192, differed

***A transition to DTG-based regimens in low- and middle-income countries may lead to improvements in viral suppression but was also associated with weight gain, particularly for women***

between the EFV arm (61.7%) and the DTG arm (69%) in the ITT analysis, but did not reach statistical significance ( $P=.057$ ). A per protocol analysis showed 65.7% viral suppression in the EFV arm and 74.8% in the DTG arm, a difference that did reach statistical significance ( $P=.035$ ). The investigators also tracked body weight gain over the 4 years of follow-up and noted more weight gain in the DTG arm and more substantial weight gain among women. These data suggest that the transition to DTG-based regimens in low- and middle-income countries (LMICs) may lead to improvements in viral suppression. However, considering co-occurring metabolic and cardiovascular risk for people with HIV, the prevalence of weight gain associated with DTG-based regimens is of concern.

Investigators from CoRECT (Cooperative Re-Engagement Controlled Trial) presented results of their multisite prospective randomized control trial conducted in Massachusetts, Connecticut, and the city of Philadelphia (Abstract 94). They compared standard of care with a data to care approach that used HIV surveillance data to identify and reengage people recently out of care. Researchers defined newly out of care as those who received HIV care within the last 12 months but then either: a) did not have a CD4 or HIV plasma RNA level test for over

6 months and/or b) missed appointments or had no clinic visit for 6 months. Primary outcomes were reengagement at 90 days, retention in care at 12 months, viral suppression at 12 months, and durable viral suppression at 18 months. The intervention arm achieved 54.9% reengagement compared with 42.1% in the standard of care arm ( $P<.0001$ ), and improvements in retention were 51.2% in the intervention arm and 46.5% in the standard of care arm ( $P=.04$ ). However, they did not find statistical differences in durable viral suppression, including in several sensitivity analyses. It is concerning that this intervention, which increased engagement in care and retention, did not lead to improvements in viral suppression over time.

Randomized control trials testing interventions to address structural barriers to care that impact the HIV care continuum are challenging to conduct, and the 2022 Conference on Retroviruses and Opportunistic Infections provided several examples of studies that tackled this issue with innovative study design. Solomon and colleagues assessed the efficacy of nonmonetary incentives in improving HIV treatment outcomes, including viral suppression, among men who have sex with men (MSM) and people who inject drugs (PWID) in India (Abstract 93). A pair-matched cluster design created 8 pairs from 16 participating integrated care centers that provide nondiscriminatory services for the 2 key populations, but do not provide ART. Pairs were matched on target population, estimated population size, HIV prevalence, viral suppression metrics, and the percentage of viremic persons in the community. The investigators established cohorts of 150 participants with HIV at each site and randomly assigned 8 clusters to standard of care and 8 to the intervention. The intervention offered nonmonetary incentives of between US \$1.30 and \$7.00 for attendance at visits for follow-up pre-ART initiation, ART initiation, motivational interviewing, and timely ART refills. The planned primary outcome was viral suppression to below 150 copies/mL at 24 months, but the initiation of the COVID-19 national lockdown in March 2020 led to a revision of the primary outcome to plasma HIV RNA level below 150 copies/mL at 12 months. Most participants in the intervention

arm earned at least 1 incentive, but the primary outcome of percentage achieving viral suppression, as measured by an adjusted prevalence ratio of 1.22 (95% CI, 0.63–2.34) in the intervention arm compared with the control arm, did not differ significantly. Statistically significant differences were also not noted when the outcomes were stratified

***A multisectoral agricultural intervention was not associated with increased viral suppression when compared with standard of care, but was linked to marked differences in food insecurity and other health-associated outcomes***

by key population (MSM or PWID), nor in a sensitivity analysis including only ART-naïve participants. The lack of impact of the intervention, particularly in the context of low prevalence of viral suppression overall, which was 65% in the intervention cohort and 46% in the control cohort at 12 months, highlights the need for more effective strategies to support viral suppression, particularly for key populations.

In another cluster randomized trial, Cohen and colleagues addressed food insecurity in Kenya by randomly assigning 8 pairs of health facilities to a climate adaptive intervention that included human-powered water pumps, bank loans for farming commodities, and training in sustainable agriculture, financial literacy, and agribusiness (Abstract 891). Their primary outcome, absolute change from baseline at 24 months in viral suppression to less than 200 copies/mL among the 720 individual participants, improved in both arms from 82% to 86% at baseline to 95% at 24 months, but did not differ statistically between groups. However, compared with the control arm, the intervention arm participants had substantial improvements in food security, social support, and stigma scores at 12 months, which were sustained at 24 months. The investigators noted that widespread test-and-treat policies were

launched during the study period. Despite the intervention's lack of effect on the primary outcome, the marked differences in food insecurity and other health-associated outcomes speak to its broad impact on participants.

Wohlfeiler and colleagues conducted a cluster randomized controlled trial of a web portal and mobile app that parsed health record data to provide actionable alerts for clinicians in 20 healthcare centers caring for almost 16,000 people with HIV in the southern United States (Abstract 908). The intervention provided care engagement alerts to clinicians for the following criteria: no visits for 4 months with none scheduled in the next 2 months; single visit in the prior 12 months with missed visit and none scheduled in the next 2 months; 2 sequential missed visits and none scheduled in the next 7 days; and an HIV viral load above 1000 copies/mL over 3 months ago without a more recent viral load under 20 copies/mL and no visit scheduled in the next 7 days. The investigators noted that changes were made during the study period in these parameters because scheduling within 7 days was deemed impractical, and that a viral load threshold of below 50 copies/mL was more consistent with standard of care. Although differences were seen in the number of return visits after alerts between the intervention and control arms, none of the tests for statistical significance presented differed between arms. The investigators also noted challenges in incorporating the study intervention into existing retention in care efforts, competing demands on staff time, and the impact of the COVID-19 pandemic and extreme weather events on clinic operations.

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## **Impact of the COVID-19 Pandemic on HIV Care**

### **Interventions and Disruptions in the HIV Care Continuum During the COVID-19 Pandemic**

Assessment of the impact of the COVID-19 pandemic on the HIV care continuum has begun, and COVID-19–related disruptions in the HIV care continuum were examined by Castel and colleagues in a 15-site network of HIV treatment clinics in

Washington, DC, a metropolitan area severely impacted by both the HIV and COVID-19 epidemics (Abstract 940). Care continuum metrics of care engagement—defined as at least 1 clinic visit, plasma HIV RNA measurement or CD4+ cell count measurement on ART based on prescription refill data, and viral suppression to HIV RNA levels below 200 copies/mL—were compared for 8288 people with HIV in 2 timeframes: prepandemic (January 1, 2019–February 28, 2020) and peripandemic (March 1, 2020–September 1, 2021). Significant declines were seen in all 3 metrics: care engagement decreased from 71.1% to 62.7%, on ART decreased slightly from 92.7% to 91.0%, and viral suppression decreased from 69.6% to 61.7% (all *P* values for difference <.001). A subsample of people with HIV (*n*=801) participated in a survey of the self-reported impact of COVID-19, and 20% of participants reported challenges in making appointments for HIV care. This analysis demonstrates setbacks in HIV care continuum progress during the first year and a half of the COVID-19 pandemic in a large urban cohort and highlights the need for increased care engagement efforts.

Chaudhuri and colleagues also compared HIV care outcomes between a pre-COVID-19 period, March 2019 to February 2020, and during the COVID-19 pandemic, March 2020 to February 2021, for 9740 people with HIV receiving care in a New York City–based clinic network (Abstract 946). They noted that although the prevalence of viral suppression, defined as a plasma HIV RNA level below 200 copies/mL on last check, remained stable from 87.9% pre-COVID-19 to 90.7% during COVID-19, 18% of the cohort did not have HIV plasma RNA levels measured during the first 12 months of the COVID-19 pandemic, and 15% did not have laboratory testing or clinic visits. In adjusted analysis, predictors of the combined outcome of viral nonsuppression or absence of HIV plasma RNA measurement included male sex, transgender individuals, those under 50 years of age, heterosexual men, and PWID. Investigators also noted that, although clinic visits and lab checks decreased during COVID-19, ART prescription rates remained consistent. These data highlight how adjustment for viral

load measurement is important in these analyses, and the need for further care engagement efforts during the pandemic, particularly for marginalized populations.

Masters and colleagues examined the impact of telehealth on HIV care quality indicators before and during the COVID-19 pandemic in 2 Chicago clinics, 1 academic-based and 1 community-based (Abstract 937). Indicators were assessed during 4 overlapping 15-month periods between January 2019 and September 2021, and 64,447 people with HIV were included in the analysis. Despite the rapid adoption of telehealth visits, the proportion of patients with a clinician encounter in the last 8 months decreased from 89% in the first timeframe to 68% in the final, and all 3 time periods that occurred during the pandemic were statistically significantly lower than the first prepandemic measurement. Significant decreases were also seen in other indicators, including testing for plasma HIV RNA, blood pressure, A1c measurement, and mammograms and STI screening. Although changes were not noted over time in viral suppression to less than 50 HIV RNA copies/mL, nor in diabetes or blood pressure control, it is possible that these indicators were falsely elevated during the pandemic because of lack of measurements, for which no adjustments could be made in the analysis. The data demonstrate worsening across several HIV care metrics, despite transition to telehealth.

Cross-sectional self-reported care engagement data from 773 people with HIV enrolled in the C3PNO (Collaborating Consortium of Cohorts Producing NIDA Opportunities) study were used by Lesko and colleagues to examine predictors of missing HIV care visits or ART doses (Abstract 945). Thirteen percent of respondents reported missing a medical visit in the past month, and 19% had missed at least 1 ART dose in the past week. Investigators assessed reasons for missed ART doses, and 21% of respondents reported they were unable to refill ART or were concerned about entering a pharmacy because of the risk of COVID-19. After adjustments for demographic, structural, and clinical predictors, smoking was associated with missing

visits, and male sex, low reported resiliency, cocaine use, cannabis use, and disruptions to substance use treatment were all associated with missed ART doses. These data suggest that an increased focus on care engagement for those with substance use disorder could support the HIV care continuum during the pandemic, but do not reveal whether these predictors are exacerbated by COVID-19.

Spinelli and colleagues reported on the impact of the COVID-19 pandemic on HIV care cascade outcomes at a safety net clinic in San Francisco, California (Abstract 888). They noted an initial drop

***A multicomponent strategy for care engagement, including housing support and expedited visits, reduced barriers to achievement of virologic suppression for PWH during the COVID-19 pandemic***

in viral suppression, defined as a plasma HIV RNA level below 200 copies/mL, from a mean of 84% pre-COVID-19 to 81% in April 2020. The clinic implemented various simultaneous engagement in care strategies at the end of March 2020, including phone outreach, resumption of in-person visits, expansion of the permanent housing program, a shelter-in-place hotel room program, and an expansion of POP-UP (Positive Health Onsite Program for Unstably Housed Populations), an existing program for people with unstable housing and virologic nonsuppression with dedicated staff, walk-in clinic visits, and incentives. Telehealth services increased during shelter-in-place and remained at 10% of visits in April 2021. The investigators found that outreach workers contacted 91% of all people with HIV served by the clinic, and that 7.3% of people with HIV were in care at other sites, reducing the true loss to follow-up rate to 2.8 per 100 person-years, which was comparable to the rate prior to COVID-19. Investigators also found that the proportion achieving viral suppression increased 1.05-fold

per month (95% CI, 1.01-1.08) from April 2020 to April 2021; it reached 90%. Based on the data presented, it is unclear if this analysis was adjusted for number of plasma HIV RNA measurements, which could falsely elevate estimates of viral suppression. Despite this limitation, the clinic's experience suggests that the multicomponent strategies implemented reduced barriers to achievement of virologic suppression for people with HIV and continued to have an impact in the second year of the COVID-19 pandemic.

## HIV Resistance

### Epidemiology of HIV Resistance

Garcia presented resistance prevalence data on newly diagnosed ART-naive patients in southern Europe from 2018 through 2021 (Abstract 516). They studied more than 2700 patients; median viral load was 108,006 copies/mL, 56.3% had subtype B, and prior pre-exposure prophylaxis (PrEP) use was not mentioned. The overall prevalence of nucleoside analogue reverse transcriptase inhibitor (nRTI)-resistance mutations was 3.73%; 0.85% had M184V, 0.18% had M184I, 0.04% had K65R, and 2.66% had presence of other thymidine analogue mutations. The overall prevalence of InSTI-resistance mutations was very low at 0.23%; they found 1 for each of the following mutations: T66I, T66A, E138T, E138K, E92Q, and R263K. The prevalence of clinically relevant resistance, which they defined as a score of 3 or more by Stanford interpretation, was 2.42% for InSTIs and 1.76% for nRTIs. The investigators found that 0.89% had resistance to either TDF or TAF, and 1.15% had resistance to either 3TC or FTC. There were higher rates of resistance to first-generation InSTIs raltegravir and elvitegravir (about 2.3%), but only 0.18% to BIC and 0.18% to DTG. Based on these prevalence numbers, there were low rates of higher-generation InSTI resistance, and it is unlikely these mutations would be of consequence to newly diagnosed patients placed on more modern regimens.

Novitsky and colleagues presented on the epidemiology of transmitted drug resistance in newly

diagnosed patients with HIV from 2004 to 2020 in Rhode Island (Abstract 517). They looked at data from more than 1100 patients and found that transmitted drug resistance to any drug increased from 8% in 2004 to 26% in 2020 (Mann-Kendall statistic, 0.47; 95% CI, 0.16-0.68). Of all drug classes, NNRTI-associated resistance mutations increased most dramatically, from 5% in 2004 to 18% in 2020, most commonly K103N. Drug mutations associated with nRTIs increased from 2% in 2004 to about 8% in 2020, with 0.5% with M184V/I, and no instances of K65R transmitted drug resistance

*Hu and colleagues' findings suggest a mechanism for more clinical failure with L74I-containing virus; although the presence of this mutation itself does not confer resistance to cabotegravir, when combined with other integrase mutations, it allows for improved replication capacity, enhancing cabotegravir resistance conferred by other integrase mutations*

(TDR). PI-associated mutations remained low, from below 2% in the mid-2000s to an estimated 2% to 3% in 2019 to 2020. The investigators did not find major InSTI mutations, although this information was limited to 49 samples. TDR to 2 or more classes was uncommon. Overall, the study found increasing TDR rates over the study period from 2004 to 2020, mostly driven by an increase in NNRTI-associated resistance mutations, with no substantial evidence of drug resistance mutations (DRMs) to components of first-line regimens.

### **Resistance Patterns of Existing Agents (Including Long-Acting Agents)**

Hu and colleagues examined the effect of the L74I mutation in integrase on viral replication (Abstract

506). L74I in A6 subtype virus was associated with higher rates of virologic failure in trials of CAB-LA and RPV. The investigators found that presence of L74I in subtype A6 virus did not affect susceptibility to CAB. However, virus with L74I outcompeted wild-type L74 virus in growth competition assays, indicating greater viral fitness of L74I-containing virus. When L74I was combined with other mutations causing resistance to InSTIs, specifically either G118R, G140R, Q148R, or R263K, this virus had significantly higher replication capacity than wild-type L74 virus with integrase resistance mutations. There was no difference in replication capacity when L74I was combined with Q148H or Q148K. L74I when combined with N155H lowered replication capacity compared with wild-type L74 virus with N155H. Those viruses containing G140R and Q148R were unable to replicate to assess capacity adequately. The results slightly differed in the presence or absence of CAB. When L74I was combined with other InSTI-associated mutations, either G118R, G140R, G148H, G148R, or R263K in the absence of CAB, this virus had significantly higher replication capacity than wild-type L74 combined with InSTI-associated mutations. In the presence of 2 nM of CAB, only L74I combined with either G118R or G140R had increased replication capacity. The L74I combinations with G148H, G148R, or R263K no longer had statistically significantly increased replication capacity in the presence of 2 nM of CAB. In the presence of 4 nM of CAB, these findings were similar, except L74I and R263K virus had higher replication capacity than wild-type L74 and R263K. These findings suggest a mechanism for more clinical failure with L74I-containing virus; although the presence of this mutation itself does not confer resistance to CAB, when combined with other integrase mutations, it allows for improved replication capacity enhancing CAB resistance conferred by other integrase mutations. The effect is not equal for all integrase mutations in the presence of CAB.

Dekker and colleagues examined mutations in the 3'-polypurine tract (3'PPT) that may confer DTG resistance and explored the mechanism of action (different from integrase mutations) (Abstract 507). They cultured 3'PPT variants in the presence of DTG

and noted that certain 3′PPT mutations that conferred DTG resistance reduced viral fitness but actually improved replication activity. The 3′PPT mutations are able to work around integrase inhibition by triggering replication that is independent of the process of integration and therefore still able to replicate in the presence of DTG-inhibiting integration. Prior studies had shown that 3′PPT mutated virus may need an external trigger (eg, HTLV-1 Tax protein<sup>7</sup>), and it is not quite known what the clinical implications are for these in vitro findings. Similarly, van Kampen and colleagues examined the 3′PPT region in patients with HIV in Brazil in whom ART with DTG was failing and found 3′PPT mutations in 6 of 45 of these patients (Abstract 512). Further research is ongoing to determine the effect of these mutations on fitness, replication, and InSTI susceptibility.

Boyce and colleagues examined samples of pregnant women from IMPAACT 2010 (Evaluating the Efficacy and Safety of Dolutegravir-Containing Versus Efavirenz-Containing Antiretroviral Therapy Regimens in HIV-1-Infected Pregnant Women and Their Infants) who had confirmed virologic failure on ART and looked for DRMs (Abstract 509). The rates of virologic failure and presence of drug resistance were lower (meeting statistical significance, with  $P < .05$ ) in the DTG arms than in the EFV arms. In the DTG plus TDF/FTC group, 1.9% of participants had drug resistance at virologic failure compared with 6.2% in the EFV/TDF/FTC arm ( $P = .023$ ). Furthermore, 0.9% of participants in the DTG plus TAF/FTC group had resistance ( $P = .0032$  compared with EFV arm). The investigators were able to genotype 35 samples of 42 virologic failures and found 54% (19 of 35) of these samples had drug resistance. Seventy-nine percent of samples with drug resistance (15 of 19) had resistance at the time of entering the study, and 47% (9 of 19) also had new mutations at the time of virologic failure. In the women who had drug resistance at the time of virologic failure, 54% in the EFV arm had new EFV-associated mutations (K103N, V106M, and P225H, along with some additional nRTI mutations). One of 6 women (17%) who had drug resistance at time of virologic failure had major InSTI-associated mutations, including N155H, L74I, S147G, and S230R. The authors

concluded that those in the EFV-based arm were more likely to have virologic failure and develop new DRMs at the time of virologic failure than those in the DTG arms.

DTG plus darunavir/cobicistat (DRV/c) is often used by patients with MDR-HIV infection. This regimen was studied in an open-label multicenter randomized trial by Ramón Santos and colleagues to assess efficacy (Abstract 510). They enrolled adults with HIV on a 3-drug ART regimen who had been virally suppressed with HIV RNA level below 50 copies/mL for at least 6 months prior to random assignment. Participants had to have resistance against 2 drug classes but not the presence of resistance to an InSTI

***Dual therapy with DTG plus DRV/c was an effective option for patients with MDR-HIV without InSTI and DRV mutations***

or DRV. Results were presented from 45 patients enrolled in the investigational arm to switch to DTG plus DRV/c, and 44 patients enrolled in the control group to continue their current regimen. The primary outcome of HIV RNA level below 50 copies/mL at week 48 was similar between both groups, with a rate of 95.6% in the investigational group versus 90.9% in the control group (log rank  $P = .392$ ). No virologic failures were observed in the investigational group, compared with 2 in the control group, but this difference was not statistically significant ( $P = .147$ ). Ultimately, the authors concluded that dual therapy with DTG plus DRV/c was an effective option for patients with MDR-HIV without InSTI and DRV mutations.

Allesandri-Gradt presented in vitro susceptibility of HIV-1 non-M groups (O, N, and P) to ibalizumab (Abstract 501). They found 100% of the O and N groups tested were susceptible to ibalizumab, and group P was naturally resistant. Their work suggests that further testing on large panels of virus is needed but hints that ibalizumab could be used as treatment for HIV-1 groups O and N.

## Resistance Patterns of Novel Agents

Margot and colleagues presented data on LEN susceptibility and treatment response in treatment-experienced patients with MDR-HIV from the CAPELLA study (Abstract 508). LEN is a capsid inhibitor that interferes in various stages of the viral life cycle, including nuclear transport of the capsid, viral assembly and release, and capsid assembly. They evaluated whether LEN susceptibility was affected by the presence of entry inhibitor mutations to maraviroc, ibalizumab, enfuvirtide, and fostemsavir. In the 62 patients studied with information about entry inhibitor mutations, resistance to entry inhibitors was widespread, with 67.2% of isolates resistant to maraviroc, 31.5% to fostemsavir, 29.3% to ibalizumab, and 8.6% to enfuvirtide. In these isolates, there was no change in LEN susceptibility despite the level of resistance. Changes in the envelope or tropism did not affect LEN susceptibility. Treatment outcomes at week 26 did not differ in those patients on LEN with entry inhibitor mutations compared with those without mutations. The authors concluded that there was no association between resistance to entry inhibitors and susceptibility or clinical response to LEN, and this supports the use of LEN in treatment-experienced patients.

Montaner and colleagues examined the bNAb combination of 3BNC117 and 10-1074 (Abstract 503). They screened 61 patients with HIV who were virally suppressed with HIV RNA level below 20 copies/mL and who had a CD4+ count of at least 450 cells/ $\mu$ L. Twenty-four percent of patients had reduced susceptibility to 3BNC117, and 31% had reduced susceptibility to 10-1074. Fifty-six percent of the patients screened had virus that was susceptible to both bNAbs. The investigators did not find a correlation between susceptibility to either bNAb ( $r=.10$ ). This indicates that there is presence of reduced susceptibility in circulating virus, and caution is needed when using a combination of 2 bNAbs as treatment.

Zacharopoulou and colleagues presented data on 173 patients with primary HIV infection in the United Kingdom who had been on ART for at least 1 year with an undetectable viral load (Abstract

505). Of these patients, 38.7% had resistance to either or both bNAbs. Resistance to 10-1074 was more common; it was present in 66% of the samples with resistance mutations. Interestingly, there was evidence for transmitted resistance and in-host evolution. The authors concluded that screening before administration of bNAbs was key to ensuring that patients' virus would be susceptible, as nearly 40% of this cohort had some baseline resistance

*Hoffman and colleagues' findings highlight the variability of proviral genotyping with its limitations in interpretation and usefulness in clinical decision making*

to the bNAbs. Pahus and colleagues looked at concordance between a monoclonal antibody assay and 2 genotypic prediction algorithms for sensitivity of 2 bNAbs, 10-1074 and 3BNC117 (Abstract 504). The 3 methods were concordant in predicting susceptibility to 3BNC117 52% of the time, and susceptibility to 10-1074 79% of the time.

Smith and colleagues presented data on susceptibility of HIV-2 to GSK2838232, a maturation inhibitor that is being studied in phase II trials for treatment for HIV-1 (Abstract 500). They found HIV-2 was intrinsically resistant to this agent, and it retained little activity against HIV-2, suggesting that GSK283 could not be used for treatment of HIV-2 infection.

## Clinical Implications of Resistance Testing

Hoffman and colleagues examined the temporal variability of proviral genotype sequencing in patients with MDR-HIV who had been virally suppressed on an ART regimen (Abstract 513). They examined proviral genotyping from samples from 2017 and 2020 in patients who had evidence of mutations associated with resistance to at least 3 classes of ART. These patients had sustained viral suppression with no treatment interruptions or viremia; the

median time of viral suppression was 9.0 years. Using a cutoff of above 15%, proviral genotyping was able to find 63% of baseline resistance mutations, as well as 7% of previously undetected resistance mutations. Interestingly, less than 40% of the mutations were found at both timepoints. Using cutoffs of above 1% yielded more favorable numbers, with proviral genotyping finding 76% of baseline mutations and 19% of previously undetected resistance mutations. With the above 1% cutoffs, less than 50% of the mutations were found at both timepoints. Twenty-three percent of patients had higher rates of detected resistance-associated mutations (RAMs) in 2020 than in 2017, whereas 50% of patients had lower rates of detected RAMs in 2020 than in 2017, and 27% of patients had similar rates at the 2 timepoints. Detection rates were not associated with level of proviral DNA, time of virologic suppression, or ART regimen. Rates were numerically increased in those patients with CD4+ count nadir below 50 cells/ $\mu$ L and CD4+ count below 750 cells/ $\mu$ L in 2020, but the differences did not reach statistical significance. This highlights the variability of proviral genotyping, with its limitations in interpretation and usefulness in clinical decision making.

Gaitan and colleagues examined whether proviral genotyping from samples before initiation of ART would detect resistance mutations that could impact clinical outcomes (Abstract 514). Of note, both tests were congruent for major resistance mutations except for 2 K103N mutations that are found only in proviral DNA. Eleven InSTI-associated resistance mutations (using a cutoff of >2%) were found in HIV proviral genotyping. However, mutations found in proviral DNA with a cutoff of greater than 2% were not associated with virologic failure with a follow-up period of about 25 months. Ultimately, the proviral genotype mutations observed did not predict virologic failure, and RNA genotyping was congruent with proviral DNA genotyping for major resistance mutations. However, the study authors recommended caution in using NNRTI-based regimens for initial therapy, as major resistance mutations (eg, K103N) were not found on RNA genotyping but found on proviral DNA genotyping, which may lead to eventual resistance.

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## Advances in Treatment of Hepatitis C

### Epidemiology of Hepatitis C Virus

Hudson and colleagues presented data on HIV and hepatitis C virus (HCV) infection incidence rates in PWID from Kanawha County, West Virginia, which includes the state capital of Charleston (Abstract 536). They observed a very high rate of HCV seropositivity at 94% in PWID diagnosed with HIV. HCV diagnosis was found before HIV diagnosis in 82% of patients, with a median interval of 46 months, or almost 4 years (interquartile range [IQR], 29-71). They concluded that HCV infection is a high-risk predictor of subsequent HIV infection, and HIV testing and PrEP services should be scaled up in these populations. Ma and colleagues conducted a cross-sectional study looking at HCV infection rates in transgender women with HIV in the Centers for AIDS Research (CFAR) Network of Integrated Clinical Systems (CNICS) cohort from 2014 through March 2021 (Abstract 537). They observed higher rates of HCV infection in transgender women than cisgender men (adjusted odds ratio [aOR], 1.70;  $P < .01$ ), and transgender women were more likely to be HCV viremic (aOR, 1.54;  $P = .03$ ). When controlling for injection drug use, transgender women still had higher rates of HCV infection than cisgender men (aOR, 1.61;  $P = .01$ ). This study demonstrates that transgender women remain at high risk for HCV acquisition even in absence of injection drug use and should receive frequent screening. Hung presented data about HCV elimination in people with HIV in Taiwan from 2013 to 2021, where patients with HIV were screened for HCV and then received treatment (Abstract 538). They observed a 78% decrease in prevalence of HCV viremia from 2013 to 2021, and an 84.6% decrease in the incidence rate of viremia from a peak of 131.6 per 1000 person-years of follow-up in 2011 to 20.3 per 1000 person-years of follow-up in 2021. They observed a 67.9% decrease in the incidence rate of HCV seroconversion from 2013 to 2021. This is in contrast to HCV rates in MSM in Germany presented by Ingiliz and colleagues, where the researchers examined the effect of COVID-19 on HCV elimination efforts (Abstract

539). They found no change in HCV infection incidence through 2019 despite the use of direct-acting antivirals (DAAs), but they saw a decrease in 2020 and 2021, which they postulated was secondary to behavioral changes due to the COVID-19 pandemic.

Sun and colleagues examined the impact of an alternative HCV screening method using the HCV core antigen (HCVcAg) (Abstract 541). Advantages

*HCVcAg could remain a viable screening tool in low-resource settings that are unable to use HCV viral loads as screening, and could increase detection when used with HCV antibody testing*

of HCVcAg screening include a lower cost of testing than HCV RNA screening and earlier detection of infections than HCV antibody testing. HCVcAg can be detected 1.5 months before HCV antibody is detected in the serum and HCVcAg can be detected 1 to 2 days after HCV RNA is found in serum. The investigators tested blood samples from 1639 participants including persons at high-risk and at low-risk. Of the blood samples tested, 3.8% were positive for HCV RNA, and 87.1% of these samples tested positive for HCVcAg (sensitivity). Also, 12.9% of the patients with a positive HCV RNA had a negative HCVcAg assay with a median HCV RNA of 3.2 log<sub>10</sub> IU/mL. In the negative HCV RNA blood samples, 99.4% also tested negative for the HCVcAg (specificity). Given the prevalence of 3.8%, they calculated a positive predictive value of 85.7% and a negative predictive value of 99.5%. The authors concluded that HCVcAg has high specificity but decreased sensitivity, especially in those with a low HCV viral load. However, this could remain a viable screening tool in low-resource settings that are unable to use HCV viral loads as screening, and could increase detection when used with HCV antibody testing.

## Treatment of HCV

Menétrey presented final data from Storm-C-1 (Strategic Transformation of the Market of HCV Treatments), an open-label, single-arm, phase II/III clinical trial in Malaysia and Thailand on the use of ravidasvir,<sup>8</sup> which is a pan-genotypic nonstructural protein 5A inhibitor developed through the Drugs for Neglected Diseases initiative (DNDi) for use in LMICs (Abstract 528). This trial enrolled 603 patients with hepatitis C who were between the ages of 18 and 69 years, either without cirrhosis or with Child-Turcotte-Pugh class A cirrhosis, and gave them ravidasvir plus sofosbuvir (SOF) for 12 weeks (or 24 weeks to those with cirrhosis) and measured sustained virologic response (SVR) 12 weeks after treatment ended (SVR12). Forty-nine percent of patients had genotype 3 infection, and 40% had either genotype 1a or 1b infection. Thirty-nine percent of patients had compensated cirrhosis, and 32% had coinfection with HIV. The overall rate of

*Ravidasvir and SOF were safe and effective in achieving SVR12 even in complex populations (eg, patients with cirrhosis, HIV-coinfection)*

SVR12 was 96.8% and remained above 96% in patients with cirrhosis, HIV coinfection, and prior treatment with interferon alfa. There appeared to be slightly lower rates of SVR12 in the genotype 6 group, with SVR12 achieved in 88.5% of the population, but there were only 61 patients total. There was 1 serious adverse event (acute kidney injury) possibly attributed to SOF. The study authors concluded that the combination of ravidasvir and SOF was safe and effective in achieving SVR12 even in complex populations (ie, patients with cirrhosis, HIV coinfection).

Martín-Carbonero and colleagues examined the effectiveness of a pangenotypic combination of SOF

plus velpatasvir plus voxilaprevir (SOF+VEL+VOX) in patients with HIV and HCV coinfection in whom previous HCV treatment with other DAAs failed (Abstract 529). They studied 56 patients in Spain with a median age of 51.9 years and an 18% rate of cirrhosis. Seventy-three percent of patients had an undetectable HIV viral load at time of enrollment (<50 copies/mL). Sixty-eight percent of patients had genotype 1 HCV, 13% had genotype 3, and 16% had genotype 4. The group was mostly treatment experienced with exposure to 1 prior regimen in 77% of patients, 2 prior regimens in 16% of patients, and 3 or more in 8% of patients. Most patients had been treated with a combination of SOF and ledipasvir (50% of participants). Nine percent of patients had been previously treated with glecaprevir/pibrentasvir, and 9% had been previously treated with SOF and daclatasvir. The investigators observed an 80% rate of SVR12 in their ITT group, and a 96% rate of SVR12 in their per protocol group. They observed a 90% rate of SVR12 in patients with cirrhosis in the ITT and per protocol groups. They did not observe a significant change in rates of SVR12 among different genotypes. The study authors concluded a regimen of SOF+VEL+VOX was effective in achieving SVR12 in patients with HIV and HCV coinfection in whom previous DAA regimens had failed, regardless of genotype or presence of cirrhosis.

Sowah and colleagues examined the association of adherence with SVR12 in the ACTG A5360 MINMON (Minimal Monitoring) trial, the results of which were recently published showing that minimal monitoring of HCV treatment with a 12-week course of SOF plus VEL was safe and effective in achieving SVR12 (Abstract 530).<sup>9</sup> Patients enrolled were HCV treatment naive; those with decompensated cirrhosis were excluded. Ninety-five percent of patients overall achieved SVR12 with 12 weeks of SOF plus VEL. Adherence at week 4 was highly associated with SVR, with 96% of patients reporting taking all their doses at week 4 achieving SVR12 ( $P<.01$ ). In contrast, SVR was achieved in 77% of those who reported not taking all their doses at week 4. Adherence at week 24 and overall adherence were not associated with SVR12. Age under 30 years was highly associated with not taking all

doses by week 4 (OR, 7 in a multivariate model). The study authors concluded that for HCV programs using the minimal monitoring approach, identifying those patients with suboptimal adherence at 4 weeks would be important, as this was predictive of achieving SVR12. More resources can be utilized to help this population, as well as younger patients, with adherence to increase the rate of SVR.

### **HCV Outcomes**

Berenguer and colleagues presented data looking at the composite outcome of decompensation, hepatocellular carcinoma, or death in patients with HIV and HCV coinfection with advanced fibrosis (F3) or cirrhosis (F4) treated with DAA agents (Abstract 531). They examined 1300 patients (median age, 52 years); almost all patients (98%) were on ART, and 94% of patients had undetectable HIV viral load. The investigators observed increased rates of clinical progression in patients who had decompensated cirrhosis at baseline (HR, 2.25;  $P=.029$ ) and male sex (HR, 1.99;  $P=.011$ ). There was also an association with age (HR, 1.06;  $P=.001$ ) and liver stiffness per 4-kPa increase (HR, 1.03;  $P<.001$ ), but these effects were less pronounced than the prior variables mentioned. Higher serum albumin level and change in liver stiffness per 10% decrease at 1 year after therapy were associated with decreased risk of clinical progression (HR, 0.59;  $P<.001$ ; and HR, 0.84;  $P<.001$ , respectively). These metrics can be used to develop scores to predict groups at high risk of progression to decompensation, hepatocellular carcinoma, or death in HIV and HCV coinfecting patients who have been treated.

Requena and colleagues compared mortality rates in patients with HIV and HCV coinfection whose HCV infection was treated with DAAs and patients with HIV mono-infection (Abstract 532). There were low rates of cirrhosis (8.7%) in the HIV and HCV coinfection group, and the investigators used Poisson models controlling for age, AIDS status, and CD4+ count nadir, along with other variables. There were higher rates of death up to 36 months in the coinfecting group, with an incidence rate ratio (IRR) of 1.59 (95% CI, 0.97-2.62) compared with mono-infecting patients. This effect was most pronounced

from 18 to 36 months, when the risk of death for monoinfected individuals with HIV was significantly lower than risk of death for coinfecting patients compared with the period of time from 0 to 18 months after SVR. Serero and colleagues found that noninvasive testing, such as Baveno VI and expanded Baveno VI criteria, was predictive of large esophageal varices needing treatment in patients with hepatitis B virus (HBV)-, HCV-, or HIV-related chronic liver disease compared with the gold standard of esophagogastroduodenoscopy (Abstract 533). These noninvasive tests can be used to decrease the rate of invasive procedures, especially in resource-limited settings. Mocroft and colleagues looked at rates of mortality and end-stage liver disease in patients with triple-infection with HBV (HBV surface antigen [HBsAg]+), HCV (RNA+), and HIV, compared with groups with 2 coinfections, and with HIV mono-infection (Abstract 534). Triple-infected patients had higher mortality rates than those with HIV/HBV coinfection (IRR, 0.66; 95% CI, 0.46-0.94), HIV/HCV coinfection (IRR, 0.75; 95% CI, 0.56-1.00), and HIV mono-infection (IRR, 0.49; 95% CI, 0.36-0.66), but similar mortality rates to patients with HIV/HBV infection with positive HCV antibody and negative HCV RNA (IRR, 1.05; 95% CI, 0.7-1.58). Triple-infected patients tended to have higher rates of end-stage liver disease, but this was not significantly elevated above the HIV and HCV coinfecting group (HR, 0.71; 95% CI, 0.47-1.06).

### **Outcome Delivery of HCV and the Care Cascade**

Ortega and colleagues developed models to examine the effect of COVID-19 on HCV elimination in the United States (Abstract 72). They used a general population model stratified by age and risk factor (ie, PWID) and validated it using 2019 estimates of new HCV infections. They modeled the HCV infection incidence and mortality from 2015 through 2030 with 3 scenarios: 1 model with no change to elimination strategies, 1 model with a 1-year reduction in strategies, and 1 model with a 2-year reduction in strategies. The target of 80% reduction in incidence of HCV infection was not reached in

any model, even the model without any treatment interruptions. The relative reduction in HCV infection incidence was 5.5% in the 2-year disruption model (95% CI, 5.1-5.8) and 29.7% in the uninterrupted model. They modeled that there would be

*The study authors concluded that scale-up of current HCV reduction efforts are needed to meet these elimination targets*

990 new additional HCV infections with 1 year of disruption (95% CI, 417-1330) and 1933 new additional infections in the 2-year disruption model (95% CI, 800-2599). The target of 65% reduction in HCV infection mortality was also not reached in any model, with a relative reduction of 30.6% in the 1-year disruption model (95% CI, 21.7-38.4) and a 20.6% reduction in mortality in the 2-year disruption model (95% CI, 14.4-29.5). The authors concluded that scale-up of current HCV infection reduction efforts is needed to meet these targets.

Van Santen and colleagues used pooled cohort data of more than 45,000 people with HIV from 5 countries from 2010 to 2019 to examine whether they were on track to meet the WHO target of reducing HCV infection incidence by 30% in 2020 and 80% in 2030, as well as if there is a “treatment as prevention” effect on incidence of HCV infection (Abstract 73). They observed a 49% reduction in incidence from 2015 (time of introduction of DAAs; 0.91/100 person-years; 95% CI, 0.8-1.03) to 2019 (0.46/100 person-years; 95% CI, 0.35-0.60). Mean incidence before the introduction of DAAs was 1.27 per 100 person-years. They observed a decrease in HCV incidence of about 0.009 per 100 person-years every 6 months after the introduction of DAAs (95% CI, -0.02--0.005). The authors concluded that most cohorts were on track to meet WHO targets and that treatment as prevention did reduce incidence of HCV infection when there was broad access to DAAs.

## Mother-to-Child Transmission of HCV

Chappell and colleagues compared the incidence of HCV infection with risk-based screening versus universal HCV screening (which is now recommended in major guidelines) among pregnant individuals (Abstract 27). They examined more than 24,000 individuals; the majority were White (about 72%-74%) and nearly half were on public insurance with Medicaid or Medicare. Overall, HCV antibody IgG testing rates increased dramatically in the universal population (81%) compared with the risk-based screening group (23%). The prevalence of IgG positivity was 1.9% in the universal population group and 1.2% in the risk-based screening group ( $P<.01$ ). The rate of HCV RNA testing also increased in the universal group, with 95% of HCV IgG-positive groups with RNA tested, compared with the risk-based group, with 22% of IgG positive-groups with RNA tested ( $P<.01$ ). This led to higher rates of HCV RNA positivity (indicating active HCV infection) in the universal screening group at a rate of 0.68% than in the risk-based screening group at a rate of 0.091% ( $P<.01$ ). They found 5 infants with HCV infection in the universal screening group and 1 infant in the risk-based screening group. The authors concluded that universal screening resulted in increased detection of active HCV infection, supporting the ongoing use of this strategy.

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## Advances in Treatment of Hepatitis B

### Epidemiology of Hepatitis B Virus

Phinius and colleagues examined rates of HBV infection in people with HIV in Botswana and found a 7.9% positivity rate with screening when using HBsAg (Abstract 543). They found that 7.2% of patients with positive HBsAg were also HBV core immunoglobulin M (HBcIgM) positive, indicating recent infection, and 13.9% of patients with HBV had HBV e antigen (HBeAg) positivity. Male sex was more associated with HBV infection (OR, 1.85; 95% CI, 1.37-2.50). They found statistically significant variation in rates of positivity among regions of Botswana.

### HBV Infection Treatment

Das and colleagues presented the antiviral effect on a tenofovir long-acting prodrug formulation named NM1TFV in 2 mouse models with HBV infection (Abstract 545). After a single IM injection of NM1TFV, HBV DNA remained undetectable in the blood of infected mice up to 12 weeks, which may provide new possibilities for long-acting HBV treatment.

### HBV Vaccination

Huang and colleagues examined the effect of double-dose HBV revaccination (40 µg) versus standard vaccination (20 µg) in MSM who were vaccinated against HBV as infants in Taiwan (Abstract 544). In a randomized controlled trial, they looked at men born after July 1986, when neonatal HBV vaccination was rolled out in Taiwan, with negative HBsAg, negative HBV core antibody (HBcAb), and HBV surface antigen (HBsAb) titer under 10 mIU/mL. Seventy-five percent of the patients enrolled were people with HIV, and those not on ART were excluded. Seventy percent of participants had CD4+ counts of more than 500 cells/µL, and 95% had HIV viral loads of less than 50 copies/mL. At 28 weeks, the investigators found higher seropositivity in the double-dose group (96%) than in the standard group (88%) ( $P=.018$ ). The high-titer response rate (defined as a titer of HBsAb  $\geq 100$  mIU/mL) was higher in the double-dose group than in the standard group at week 24 (86% vs 74%, respectively;  $P=.013$ ) and at week 48 (77% vs 61%, respectively;  $P=.003$ ). They also observed similar response rates to HBV vaccination in persons with HIV and CD4+ counts of more than 500 cells/µL and in MSM who were HIV negative.

Jain and colleagues presented data on HBV vaccination in people with HIV (Abstract 546). In addition to studying rates of HBV vaccination, they also used Cox proportional hazards models to determine associations with HBsAb positivity after vaccination and various factors. CD4+ counts of more than 200 cells/µL were associated with a higher rate of HBsAb positivity (aOR, 1.81; 95% CI, 1.17-2.79;  $P=.008$ ). Hispanic White men had lower rates of HBsAb positivity (aOR, 0.55; 95% CI, 0.30-1.00;  $P=.050$ ). Jain

and colleagues also looked at cohort data to examine predictors of HBV infection in people with HIV (Abstract 548). HCV infection was correlated with higher rates of HBV infection (aOR, 3.08; 95% CI, 1.72-5.51;  $P=0.002$ ), as well as nonhepatocellular carcinoma malignancies (aOR, 1.96; 95% CI, 1.13-3.42;  $P=0.02$ ). The largest risk factor for HBV acquisition was nonimmune HBsAb titer. Interestingly, the investigators did not observe a protective effect of HBV-active ART on HBV acquisition, but it is not clear whether patients were adherent at the time of acquisition. Prior studies have shown that ART can function as effective HBV prophylaxis.<sup>10-13</sup> An interesting area of future study would be trying to understand why HBV-active medications were not associated with decreased rates of HBV infection in people with HIV in this cohort.

### Mother-to-Child Transmission of HBV

Segeral and colleagues conducted a single-arm prospective trial in Cambodia to prevent mother-to-child transmission of HBV in women who were HBsAg-positive without relying on the use of HBV immunoglobulin (HBIG) for the infant due to difficulty

HBsAg and HBV DNA viral load at 6 months. They enrolled nearly 1200 pregnant women who were HBsAg-positive in the study, with a median age of 29 years and at a median of 23 weeks of gestation. Of these women, 338 were eligible for TDF. The median HBV DNA level was 7.9 log<sub>10</sub> IU/mL in the TDF-eligible group and 2.5 log<sub>10</sub> IU/mL in the TDF-ineligible group. The overall rate of infants with HBV was 1.26%; in the 85% of infants who did not receive HBIG, the rate was 1.48% (95% CI, 0.40-3.74). The rate of HBV-positive infants was 0% in women who received TDF for more than 4 weeks before delivery (95% CI, 0-1.41) and 8.33% for those women who were TDF-eligible but received treatment for fewer than 4 weeks before delivery (95% CI, 1.75-22.5). The rate of HBV in infants born to women ineligible for TDF was similar in those who did not receive HBIG (1.06%; 95% CI, 0.39-2.30) and all infants born to women ineligible for TDF (0.98%; 95% CI, 0.4-2.02). The study authors concluded that TDF given to women who are eligible for TDF for more than 4 weeks prior to delivery was effective at preventing transmission of HBV to the infant in the absence of HBIG use.

*The study authors concluded that TDF given to women who are eligible for TDF for more than 4 weeks prior to delivery was effective at preventing transmission of HBV to the infant in the absence of HBIG use*

in access to this intervention (Abstract 28). Their 3-pronged approach included use of rapid diagnostic tests for HBsAg, HBeAg, and alanine aminotransferase (ALT) level with use of tenofovir from 24 weeks onwards if HBeAg positive or HBeAg negative with ALT of 40 IU/L or greater, as well as HBV vaccination for all infants within 2 hours of birth. The primary outcome was proportion of infants with positive

## Selected Issues in Maternal and Pediatric Health

### HIV, COVID-19, and Maternal/Pediatric Health Outcomes

Data on the impact of the HIV and COVID-19 pandemics on birth outcomes among women with HIV, particularly in settings with high HIV prevalence, are limited. Maternal deaths and infant adverse birth outcomes among women in Botswana who were routinely screened for COVID-19 at delivery were compared by maternal COVID-19 status, COVID-19 variant (pre-Delta vs Delta), and HIV serostatus during the 2020 to 2021 period when access to COVID-19 vaccinations in the country was limited (Abstract 29). Data were analyzed from the Tsepamo study, which conducted birth outcomes surveillance among women at 13 government hospital sites throughout Botswana. The analysis included

women who had singleton deliveries, known HIV serostatus, and received COVID-19 screening using rapid antigen or PCR testing 14 days before and up to 3 days after delivery. Of 20,410 deliveries during the study period, 11,483 (56%) were screened for COVID-19. Overall, 4.7% of the women who had been screened for COVID-19 tested positive, with

***Infants born to women with HIV who had COVID-19 had the highest risk for most adverse birth outcomes***

women with HIV more likely to test positive at delivery than women without HIV (5.6% vs 4.2%, respectively;  $P < .01$ ). Among women with HIV, ART use was highly prevalent, with 97% of the women receiving ART and more than 75% initiating ART prior to conception. Maternal mortality was higher in women with COVID-19, with maternal deaths occurring in 19 women with COVID-19 (4%) versus 12 women without COVID-19 (0.1%) (age-adjusted risk ratio [aRR], 31.6; 95% CI, 15.4-64.7); the rates did not differ by HIV serostatus. Maternal mortality was higher during the wave of the Delta COVID-19 variant than during pre-Delta waves. Rates of any adverse birth outcomes (defined as preterm delivery, small for gestational age, stillbirth, or neonatal death) were significantly higher among infants born to women with COVID-19 than among women without COVID-19 (34.5% vs 26.6%, respectively; aRR, 1.31; 95% CI, 1.16-1.48). Specifically, rates of preterm delivery (21.4% vs 13.4%; aRR, 1.60; 95% CI, 1.35-1.90) and stillbirth (5.6% vs 2.7%; aRR, 1.97; 95% CI, 1.37-2.84) were higher among infants born to women with COVID-19. Rates of any adverse birth outcomes were highest among infants born to women with HIV who also had COVID-19 (43.1% vs 30.4%; aRR, 1.78; 95% CI, 1.47-2.16). The authors concluded that maternal mortality was higher in women with COVID-19, infants born to women with COVID-19 had more adverse birth outcomes, and infants born

to women with HIV who had COVID-19 had the highest risk for most adverse birth outcomes. The authors also emphasized further research is needed to understand the biologic interactions between COVID-19, HIV, and adverse birth outcomes, as well as to evaluate how care delivery barriers during the COVID-19 pandemic in Botswana impacted these findings.

Other research findings on the impact of COVID-19 on maternal and child health were presented. In Abstract 671, the authors compared adverse pregnancy outcomes in pregnant women with and without SARS-CoV-2 infection in Kenya. Of 998 women who completed pregnancy follow-up, 169 (22%) tested positive by PCR for SARS-CoV-2, of whom 93 (55%) were symptomatic. Fourteen pregnant women with COVID-19 required hospitalization, though none necessitated intensive care unit (ICU) admission. Very low birth weight (<1500 g), very preterm birth (<34 weeks), and preterm birth (<37 weeks) were significantly more common among women with COVID-19 than among those without COVID-19. The study did not find a significant association between COVID-19 in pregnancy and stillbirths, prenatal deaths, hypertensive disorders of pregnancy, preeclampsia, or eclampsia.

In Abstract 672, the clinical outcomes of SARS-CoV-2 infection and pregnancy were evaluated in a retrospective cohort study of 1315 pregnant and nonpregnant women 18 years old or older who were hospitalized at health facilities in 6 sub-Saharan African countries and who were tested for SARS-CoV-2 infection with PCR. Among the women who had SARS-CoV-2 infection, pregnancy was associated with an increased risk of ICU admission and oxygen supplementation. Among pregnant women, those who had SARS-CoV-2 infection had increased risk of ICU admission, oxygen supplementation, and in-hospital maternal mortality compared with those who were not infected with SARS-CoV-2. Pregnant women who had SARS-CoV-2 infection were more likely to deliver by cesarean section than pregnant women who did not have SARS-CoV-2 infection. In this study, preterm birth, low birth weight, and neonatal mortality did not differ significantly by SARS-CoV-2 infection status.

## COVID-19 Treatment in Children

Several abstracts covered therapeutics for COVID-19 in the pediatric population. Abstract 743 presented results from an open-label, phase III, clinical trial addendum (BLAZE-1 [A Study of LY3819253 {LY-CoV555} and LY3832479 {LY-CoV016} in Participants With Mild to Moderate COVID-19 Illness]) that evaluated the safety, pharmacokinetics (PK), and efficacy of SARS-CoV-2 neutralizing monoclonal antibodies bamlanivimab (BAM) and etesevimab (ETE) administered together (BAM+ETE) in 111 children younger than 18 years of age who were at increased risk for severe COVID-19. BAM plus ETE received emergency use authorization by the FDA in December 2021 for treatment of mild-to-moderate COVID-19 in patients younger than 12 years of age. Of note, BAM plus ETE is not recommended for use in areas of the United States where Omicron is the predominant variant due to its lack of efficacy against the variant. In this trial, dosing of BAM plus ETE varied by weight, with those weighing 40 kg or more receiving 700 mg BAM plus 1400 mg ETE (similar to the authorized adult dose) and those weighing less than 40 kg receiving weight-based dosing; all participants received a single-dose infusion. In children receiving weight-based dosing, PK analysis showed that drug exposures as represented by serum area under the curve for BAM and ETE were similar to those seen in adults and children aged 12 to under 18 years weighing at least 40 kg. Treatment with BAM plus ETE in children was found to be safe and well tolerated, with no reports of serious adverse events, hospitalizations, or deaths. Adverse events included 1 report of an infusion site extravasation related to study drug that was moderate in severity, 1 report of a rash that occurred more than 24 hours after infusion, and 1 report of blood creatine phosphokinase elevation on day 1 that was graded as severe and that decreased to within normal range by day 29. There were no new safety concerns of BAM plus ETE in children aged 0 to under 12 years. BAM plus ETE treatment resulted in a decrease in HIV viral load, and the median time to symptom resolution was 5 days.

In Abstract 744, safety, clinical, and virologic outcome data were presented from the ongoing

CARAVAN (Study to Evaluate the Safety, Tolerability, Pharmacokinetics, and Efficacy of Remdesivir [GS-5734] in Participants From Birth to  $\leq 18$  Years of Age With Coronavirus Disease 2019 [COVID-19]) open-label, single-arm study of remdesivir in 53 hospitalized infants and children under 18 years of age with COVID-19. Remdesivir was administered intravenously for up to 10 days, with dosing stratified by weight. The median age of the children was 7 years; at baseline, 76% of the children were on supplemental oxygen, including 23% who received invasive ventilation and 34% who had high-flow oxygen. The median number of doses of remdesivir received by the children was 5. Serious adverse events were reported in 21% of the children, with none that were related to the study drug. Two children who had transaminitis at baseline had elevation in ALT level, which led to study drug discontinuation; there were 2 deaths that occurred during the 30-day study period. Grade 3 or higher laboratory abnormalities, most commonly decreased hemoglobin and decreased estimated glomerular filtration rate, were reported in 42% of the children. No new safety concerns were reported. Overall, 25% (3 of 12) of the children who received invasive ventilation at baseline continued to be on invasive ventilation at the last available study evaluation. A majority (85%) had clinical improvement ( $\geq 2$ -point increase from baseline) at their last evaluation. The recovery rate (score of 6 or 7) was 83% at their last evaluation. The median time to hospital discharge was 8 days. The time to first confirmed negative SARS-CoV-2 PCR result from nasal or oropharyngeal specimens was 5 and 7 days in the 2 cohorts of children with available data.

## HIV, ART, and Pregnancy Outcomes

Stunted growth in infancy has negative implications on cognitive development and adult height. A post hoc analysis of IMPAACT 2010, a randomized open-label clinical trial of 643 pregnant women with HIV in 9 countries, assessed the impact of 3 different maternal ART regimens during pregnancy and breastfeeding on infant growth through 50 weeks postpartum (Abstract 30). Women were randomly assigned to initiate 1 of the following maternal

ART regimens at 14 to 28 weeks gestation: (1) DTG plus TAF/FTC, (2) DTG plus TDF/FTC, or (3) EFV/TDF/FTC. Infant length and weight were measured, and Z-scores for length-for-age (LAZ), weight-for-age (WAZ), and weight-for-length (WHZ) were calculated according to WHO standards. Overall, 78% of the infants were initiated on breastfeeding and continued for a median of 50 weeks; only 4 infants (0.6%) acquired HIV infection. Infants in the EFV/TDF/FTC arm were smaller than in the 2 DTG-containing arms, with LAZ and WAZ scores lower than the DTG arms. Growth was similar in infants exposed to maternal TDF versus TAF with DTG/FTC, with no mean differences between the 2 arms in LAZ or WAZ scores at weeks 26 and 50. There were no differences in mean WHZ scores across the 3 arms. Rates of severe stunting, defined as LAZ score below  $-2$ , were high across the 3 ART arms, with a higher proportion of infants in the EFV/TDF/FTC arm experiencing severe stunting than in the DTG plus TAF/FTC and DTG plus TDF/FTC arms at weeks 26 and 50 (20% vs 15% and 15% at week 26, and 21% vs 13% and 14% at week 50, respectively). The authors postulated that a potential mechanism to explain this finding is the differential weight gain by ART regimen experienced by the women during pregnancy.

### **Early Treatment and HIV Reservoirs in Children**

A major obstacle to ART-free remission and cure for HIV is the latent reservoir for HIV in resting memory CD4<sup>+</sup> T cells and macrophages.<sup>14</sup> Research efforts have been ongoing to develop strategies to restrict and eradicate the latent HIV reservoir, including pediatric-specific approaches to achieve long-term ART-free remission in children with early intensive treatment. Data on 2-year virologic outcomes of very early ART and potential for reduction of the latent HIV reservoir in infants in the IMPAACT P1115 (Very Early Intensive Treatment of HIV-Infected Infants to Achieve HIV Remission: A Phase I/II Proof-of-Concept Study) investigation were presented in Abstract 31. The ongoing prospective proof-of-concept study enrolled a total of 460 infants in 2 cohorts in 11 countries. In cohort 1, 440 infants who were at high risk for HIV infection were started on pre-emptive

NVP-based ART within 48 hours of birth. Of these, 34 infants who were diagnosed with in utero HIV infection were continued on ART in the study. In cohort 2, an additional 20 infants who had acquired in utero HIV infection and who had initiated NVP-based ART by age 48 hours were enrolled by age 10 days. The median age at first ART was 7.3 hours for cohort 1 (n=34) and 32.8 hours for cohort 2 (n=20). ART consisted of dual nRTIs combined with NVP, with lopinavir/ritonavir added as age appropriate; NVP was subsequently discontinued in children after 12 weeks of confirmed virologic suppression. At week 24, 75% (24 of 32) of infants in cohort 1 and 88% (15 of 17) in cohort 2 had virologic suppression (viral load <200 copies/mL). The estimated Kaplan-Meier probability of confirmed virologic suppression at age 2 years was 33% in cohort 1 and 57% in cohort 2. In infants with sustained virologic suppression at 2 years of age, 83% in cohort 1 and 100% in cohort 2 tested negative for HIV antibody; 64% in cohort 1 and 71% in cohort 2 had undetectable CA-DNA, with low HIV reservoir size that potentially allows for ART-cessation and ART-free remission. The overall estimated Kaplan-Meier probability of potential eligibility for ART interruption through age 2 years was 33% (29% in cohort 1 and 30% in cohort 2).

### **Pharmacokinetics, Safety, and Acceptability of New HIV Agents for Children and Youth**

Treatment with bNAbs as an alternative to ART in children with HIV in Botswana was evaluated in the Tatelo (Dual bNAb Treatment in Children) proof-of-concept study (Abstract 32). The children had to be at least 96 weeks of age, receive ART continuously from less than 7 days of life (with the exception of 1 child with intrapartum HIV infection who began ART at 31 days), and have undetectable HIV RNA at less than 40 copies/mL for at least 24 weeks prior to study enrollment. The study involved 3 different steps. In step 1, which lasted 8 to 32 weeks, the children received overlapping treatment with ART (lopinavir/ritonavir-based ART) and dual bNAb IV infusions with VRC01LS and 10-1074, which were administered every 4 weeks. After at least 8 weeks of overlap therapy, ART was stopped and treatment

with dual bNAbs was continued up to 24 weeks in step 2, with HIV viral load checked every 1 to 2 weeks. In step 3, bNAb treatment was stopped, and

***Dual broadly neutralizing antibody therapy with VRC01LS and 10-1074 was found to be safe and well tolerated in children with HIV***

ART was restarted for children who had an HIV viral load above 400 copies/mL or who had completed 24 weeks of bNAb treatment. Of 28 children who started step 1 of the study, 25 (89%) continued to the bNAb-only treatment (step 2); of the 3 children who did not continue, 2 experienced viral rebound on the day bNAb therapy was started and 1 had viral rebound at 4 weeks into step 1 (ART/bNAb overlap phase). Eleven children (44%) maintained an HIV RNA level below 40 copies/mL through 24 weeks of bNAb-only treatment (step 2) and after ART reinitiation (step 3). Fourteen children (56%) had viral rebound to above 400 copies/mL before completing 24 weeks of bNAb-only treatment (step 2), with a median time to failure of 4 weeks; these children were immediately restarted on ART and all achieved suppression to below 40 copies/mL at a median of 4.1 weeks from ART reinitiation. In a further comparison of the characteristics of the 11 children who maintained viral suppression through 24 weeks of bNAb-only treatment with the 13 who did not, the authors found that children who had a longer ART and bNAb overlap period, who enrolled earlier in the study with longer continuous viral suppression on ART, and who had lower mean HIV DNA in peripheral blood mononuclear cells (as a marker for viral reservoir) were more likely to achieve treatment success. Dual bNAb therapy was found to be safe and well tolerated, with no infusion-related reactions and five grade 3 events reported, including 1 neutropenia that was possibly related to study drug.

In Abstract 732, 24-week safety and PK profile of VRC07-523LS, a long-acting bNAb targeting

the CD4 binding site of the HIV envelope protein, in infants exposed to HIV was presented. Formulated infants in cohort 1 received VRC07-523LS 80 mg subcutaneously (SC) as a single dose within 72 hours of birth, and breastfed infants in cohort 2 were administered 80 mg SC within 5 days of birth and 100 mg SC at week 12 if still breastfeeding. VRC07-523LS SC was found to be safe and well tolerated in infants, with local site reactions that were grade 1 and 2 in severity and most resolving within 24 hours; no grade 3 or higher adverse events were related to the study drug. PK data showed that VRC07-523LS had rapid absorption and slow elimination, with a T<sub>1/2</sub> of approximately 34 hours, which allows for dosing every 3 months to achieve target levels above 10 µg/mL.

Abstract 737 provided PK and week 4 safety results from the IMPAACT 2019 phase I/II open-label dose confirmation study for once-daily ABC/DTG/3TC in dispersible tablet form in 14 children weighing 6 kg to less than 14 kg. No grade 3 or higher adverse events related to study drug were reported, and no study drug discontinuations occurred as a result of adverse effects. The PK profile of the dispersible tablet formulation was favorable and met study criteria.

Safety, tolerability, and PK data from the IMPAACT 2017 (MOCHA [More Options for Children and Adolescents]) phase I/II open-label trial of CAB-LA and RPV in adolescents with HIV were presented in Abstract 738. Adolescents aged between 12 to 18 years who were virologically suppressed on stable ART were enrolled into cohort 1C (CAB) (n=8) or cohort 1R (RPV) (n=15) based on background ART. The participants underwent a 4-week lead-in period with oral CAB (30 mg once daily) or RPV (25 mg once daily), followed by CAB-LA (600 mg/3 mL at week 4; 400 mg/2 mL at weeks 8 and 12) or RPV-LA (900 mg/3 mL at week 4; 600 mg/2 mL at weeks 8 and 12) via IM injection in the gluteus muscle. Background ART was continued. PK samples were collected to assess oral and LA dosing. All participants in cohorts 1C and 1R were virologically suppressed (HIV viral load <50 copies/mL) at week 16. Injection site reactions were reported as grade 1 or 2 in severity, with none resulting in study product

discontinuation. There was 1 grade 3 adverse event in each cohort that was considered related to the study drug (insomnia in cohort 1C and hypersensitivity in cohort 1R, which resulted in withdrawal from the study). The PK parameters met prespecified study targets. The authors concluded that CAB-LA or RPV-LA IM administration in combination with background ART in adolescents achieved drug levels that were comparable to those observed in adults receiving monthly IM dose regimens, with no new or unanticipated safety issues found. In Abstract 739, acceptability of and experiences related to CAB-LA and RPV-LA IM injections were evaluated using in-depth interviews with 21 adolescents enrolled in the IMPAACT 2017 MOCHA Study and their parents or caregivers. The participants recounted the relative advantages of LA injections to oral pills, such as not having to remember to take pills, avoiding the stress of monitoring daily adherence to pills, and not having to be concerned about hiding pills from peers. Concerns for using LA agents for long-term ART included apprehensions about maintaining a routine injection schedule with competing interests such as school, extracurricular activities, and work.

### **HIV Viral Load Testing in Children**

In Abstract 33, Patel and colleagues presented results from a randomized controlled clinical trial evaluating the impact of an intervention involving POC HIV viral load testing every 3 months, targeted DRM testing for HIV viral load of 1000 copies/mL or greater, and clinical management support for practitioners versus standard of care following Kenyan national guidelines (HIV RNA testing every 6 months; DRM testing was restricted to second-line ART failure using a centralized approval system) over 12 months in children aged 1 to 14 years receiving first- or second-line ART in Kenya. Of the 704 children who were enrolled, the mean age was 9 years, 76% of the children had baseline viral suppression, and the median duration on ART was 5.8 years. Viral suppression at 12 months (defined as HIV RNA level <1000 copies/mL) was similarly high in both groups, with 90.4% (283 of 313) in the intervention arm and 91.7% (287 of 313) in the standard of care arm (RR, 0.99; 95% CI, 0.94-1.03). Among

children in the intervention arm, 138 episodes of viremia from 81 children were detected; 107 (89%) samples had DRM testing, with 100% of samples having any DRM detected and 85% having any major DRM identified. Among children in the standard of care arm, 72 episodes of viremia from 56 children were found; however, only 2 samples had DRM testing, with both samples (100%) having any DRM detected and having any major DRM isolated. After any episode of nonviral suppression, there was no statistically significant difference in viral resuppression at 12 months between the 2 groups, with 69.5% (91 of 131) of children in the intervention arm versus 63.1% (101 of 160) in the standard of care arm achieving viral resuppression. The median turnaround time for viral load results was shorter in the intervention arm, with median turnaround time of 1 day in the intervention arm versus 15 days in the standard of care arm. The authors concluded that combination interventions that integrate POC viral load, DRM testing (including further research into POC DRM testing), and behavioral support for children and their families would be beneficial in optimizing ART and viral suppression in this population. 

The authors dedicate this article in memory of Dr Scott M. Hammer.

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**All abstracts cited in the text appear in the CROI 2022 Abstract eBook, available online at [www.CROIconference.org](http://www.CROIconference.org)**

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*Invited Review***CROI 2022: Metabolic and Other Complications of HIV Infection or COVID-19****Sudipa Sarkar, MD; Todd T. Brown, MD, PhD**

Johns Hopkins University, Baltimore, Maryland

*Comorbid conditions have a major impact on the health, quality of life, and survival of people with HIV, particularly as this population ages. The 2022 Conference on Retroviruses and Opportunistic Infections (CROI) featured excellent science related to specific comorbidities, such as cardiovascular disease, type 2 diabetes, cancer, and frailty. The role of systemic inflammation in the pathogenesis of cardiovascular disease was an important theme, with strong evidence regarding the impact of microbial translocation. Other studies examined functional impairment, frailty, and potential important contributors, such as concomitant medications and sleep disturbances. The ANCHOR (Anal Cancer/High-grade Squamous Intraepithelial Lesions Outcomes Research) study provided crucial evidence that treatment of high-risk anal lesions reduces the incidence of anal cancer, which has important implications in the prevention of this devastating comorbidity. In addition, numerous 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. This review focuses on the abstracts presented at CROI 2022 in these areas, highlighting those with the most clinical impact.*

**Cardiovascular Disease**

Cardiovascular disease is one of the most common causes of morbidity and mortality among people with HIV, and emerging science in this area was featured prominently at the 2022 Conference on Retroviruses and Opportunistic Infections (CROI). Silverberg and colleagues compared the incidence of myocardial infarction (MI) by HIV serostatus over 2 distinct time periods in 2 large health systems: Massachusetts General Hospital (Partners) and Kaiser Permanente Northern California (KPNC) (Abstract 39). The study included people with HIV who were propensity matched at a ratio of 1 to 4 to people without HIV in the Partners cohort, and matched at a ratio of 1 to 3 to people without HIV in the KPNC cohort. In people without HIV, 1.1% of the group had an MI in the first time period (2005-2009), but the incidence was lower at 0.9% in the second time period (2010-2017). In contrast, this decrease in incidence over time was not observed in people with HIV. Although MI incidence was similar in 2005 to 2009 (1.1%), MI incidence among people with HIV in the second time period was higher than that observed in people without HIV (1.2% vs 0.9%, respectively). After adjustment for demographic factors and Framingham risk score components, the overall risk of MI was 60% higher in people with HIV than people without HIV in the second time period (hazard ratio [HR], 1.6; 95% confidence interval [CI], 1.1-2.4). This report underscores that in recent years people with HIV are more likely to experience MI than people without HIV. The reasons why MI incidence in people with HIV is not decreasing over time, as seen in their counterparts without HIV, require further exploration. Effects of contemporary antiretroviral therapy (ART) and the impact of

**Author Correspondence**

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](mailto:tbrown27@jhmi.edu).

prolonged systemic inflammation could be among the contributing factors.

Systemic inflammation and arterial wall inflammation are thought to be a major driver of cardiovascular disease in people with HIV. Toribio and colleagues used a novel imaging technique to compare macrophage-specific arterial inflammation in people with HIV and people without HIV (Abstract 38). This imaging technique used a macrophage-specific tracer,  $^{99m}\text{Tc}$ -tilmanocept, and single-photon emission computed tomography (SPECT)/computed tomography (CT) imaging. In this study of 30 participants (20 people with HIV on ART and 10 people without HIV) without clinical atherosclerotic cardiovascular disease, the investigators found that people with HIV had greater tracer uptake than people without HIV ( $P=.03$ ) and that a significant interaction ( $P=.0001$ ) existed between HIV serostatus and noncalcified plaque volume in their associations with tracer uptake. This study is one of the first to link macrophage-specific arterial inflammation, systemic monocyte activation, and noncalcified plaque. The findings provide evidence that the pathophysiology of cardiovascular disease may differ by HIV status and raise the possibility that novel imaging could be used in the future to more fully characterize cardiovascular disease risk in this patient population, which is disproportionately affected by cardiovascular disease.

### Bacterial Translocation and Cardiovascular Disease

The sources of systemic inflammation in people with HIV are likely multifactorial. One crucial hypothesized source of systemic inflammation is microbial translocation across the gut. Depletion of CD4+, CD8+, and Th17 cell counts in the gut early in HIV infection is not restored with systemic immune recovery. In this setting, bacterial products may move across from the gut lumen and lead to a systemic immune response and vascular inflammation. Currently, there are no treatments available that target this mechanism.

Diggins and colleagues hypothesized that teduglutide, a glucagon-like peptide (GLP)-2 agonist that

is used for treatment of short gut syndrome and improves the integrity of the intestinal barrier, would decrease immune activation and thus also decrease arterial inflammation (Abstract 134). In this proof-of-concept study, 28 participants were randomly assigned to either teduglutide or placebo for 6 months. The participants underwent fluorodeoxyglucose (FDG)-positron emission tomography (PET)/CT to measure arterial inflammation at baseline and at 6 months. In addition, peripheral blood mononuclear cells and plasma metabolites were measured. Treatment with teduglutide was associated with

***Larger studies on teduglutide in people with HIV may determine how GLP-2 agonist treatment affects immune activation and whether it impacts other sites of vascular inflammation***

significant decreases in arterial inflammation (as measured by target-to-background ratio in the most diseased segments of the carotid arteries), activated monocytes ( $-19.24\% \pm 5.31\%$  vs  $-3.31\% \pm 4.96\%$ ,  $P<.05$ ), and CD8+ T cells ( $-0.33\% \pm 0.39\%$  vs  $0.67\% \pm 0.33\%$ ,  $P<.05$ ). Moreover, teduglutide treatment was associated with an increase, although not statistically significant, in kynurenic acid, which has anti-inflammatory properties. The results of this proof of concept appear promising, and larger studies on teduglutide in people with HIV may determine how GLP-2 agonist treatment affects immune activation and whether it impacts other sites of vascular inflammation.

In the setting of microbial translocation, the specific composition of the gut microbiome and the metabolites these bacteria produce may be important in the inflammatory response and subsequent risk of cardiovascular disease. Wang and colleagues conducted a cross-sectional study among women with or behaviorally vulnerable to HIV in the WIHS (Women's Interagency HIV Study) cohort to examine

the relationships among carotid artery plaque, metabolomic and lipidomic profiles, and gut microbiome diversity and taxonomy (Abstract 37). *Proteus* and *Fusobacterium* in the gut microbiome had a significant, direct association with carotid artery plaque ( $P=.040$  and  $P<.001$ , respectively), and 2 butyrate-producing bacterial genera were associated with a lower likelihood of having carotid artery plaque. The investigators also studied the associations among the lipidome, metabolome, and incident carotid artery plaque in 737 participants in the WIHS and MACS (Multicenter AIDS Cohort Study), which included men with and without HIV. Metabolites were organized into modules based on network analyses. The investigators demonstrated a direct association between *Fusobacterium* and a module that included lysophosphatidylcholines and lysophosphatidylethanolamines, and that an increase of 1 standard deviation in the score of this module was associated with increased incident carotid artery plaque (relative risk [RR], 1.34; 95% CI, [1.09-1.64]). This study highlighted the links between the gut microbiome and subclinical atherosclerotic vascular disease, and the associations of the lipidome and metabolome with each.

### Inflammation, Diabetes, and Fat Fibrosis

The issue of persistent inflammation and its relationship with metabolic comorbidities in people with HIV were a common theme at CROI 2022. Alba and colleagues focused on inflammation, type 2 diabetes, and adipose tissue fibrosis in people with HIV (Abstract 36). In one part of this study, plasma markers of inflammation were measured in 843 participants from the Center for AIDS Research (CFAR) Network of Integrated Clinical Systems who were on ART with viral suppression, and these inflammatory markers were studied in relation to incident diabetes. Greater levels of inflammatory markers, including interleukin (IL)-6 ( $P<.01$ ) and soluble tumor necrosis factor receptor 2 (sTNFR2) ( $P<.001$ ), were associated with incident diabetes. Separately, serum inflammatory markers, insulin resistance, and subcutaneous adipose tissue hydroxyproline, a marker of fibrosis, were measured in participants with and without HIV from the SCOPE (Observational Study

of the Consequences of the Protease Inhibitor Era) cohort. Although a strong correlation between insulin resistance and subcutaneous adipose tissue hydroxyproline was not observed in people with HIV, among participants with a body mass index of less than 30 kg/m<sup>2</sup>, people with HIV had greater levels of subcutaneous adipose tissue hydroxyproline than people without HIV ( $P=.03$ ), indicating greater adipose tissue fibrosis in people with HIV than in people without HIV. Given the unique and incompletely understood risk factors that people with HIV have for developing diabetes and dysfunctional adipose tissue, this study provides insight into possible mechanisms that may contribute to diabetes and adipose tissue dysfunction in this patient population.

### Predicting Weight Gain With Integrase Strand Transfer Inhibitors

Guaraldi and colleagues used a machine-learning algorithm to predict a weight gain of 5% or more in people with HIV 9 months after switching to an integrase strand transfer inhibitor (INSTI)-based regimen, with or without tenofovir alafenamide (TAF) (Abstract 597). Weight gain associated with each of these ART approaches is an issue of high clinical relevance, and the mechanisms are incompletely understood. Data from 2817 patients from a single clinic and who were ART experienced were used. Highly ranked variables in the model included weight obtained at the time of prediction, and variables such as current CD4+ cell count and waist circumference were more highly ranked in the model than the type of ART switch. Machine-learning models such as the one presented by Guaraldi and colleagues underscore the importance of developing predictive models to more accurately identify those people with HIV at risk of weight gain and the associated metabolic consequences.

### Functional Impairment Around the Globe in People With HIV

Numerous studies have shown that people with HIV have decreased physical function compared with demographically matched peers. However, most of these studies have examined populations in

resource-rich settings. Erlandson and colleagues used baseline data from the REPRIEVE (Randomized Trial to Prevent Vascular Events in HIV) study (ie, before patients were randomly assigned to pitavastatin or placebo) to determine the prevalence of physical function impairment, the variation across global geographic regions, and its association with cardiovascular risk (Abstract 34). Participants (n=7736) from 5 World Health Organization (WHO)-defined super regions (high income [US, Canada, Spain], Latin America/Caribbean [Puerto Rico, Brazil, Peru, Haiti], South Asia [India], Southeast/East Asia [Thailand], and sub-Saharan Africa [Botswana, South Africa, Zimbabwe, Uganda]) were assessed using the Duke Activity Status Index (DASI). This self-administered instrument records the degree of impairment experienced during a range of daily activities. Overall, 28% of the sample had some functional impairment, whereas 8% had moderate impairment, with the highest prevalence in South

***Impairment in physical function with DASI was associated with higher cardiovascular risk score and higher waist circumference, providing a link between these important comorbid conditions***

Asia (approximately 75%) and the lowest prevalence in Southeast and East Asia (10%). Some of the variation in this measure was hypothesized to be related to cultural differences in the activities probed. In addition, impairment in physical function with DASI was associated with higher cardiovascular risk score and higher waist circumference, providing a link between these important comorbid conditions.

### **Anticholinergic Medications, Falls, Frailty**

Frailty may drive impairments in physical function in people with HIV, and its etiology, as it is in

the general population, is multifactorial. As in the general geriatric population, concomitant medications with anticholinergic properties may increase the risk of falls and frailty. Investigators from the POPPY (Pharmacokinetic and Clinical Observations in People Over Fifty) study, a cohort from the United Kingdom and Ireland of older individuals with and without HIV, examined the prevalence of anticholinergic medication (ACM) use and its association with recurrent falls and frailty (Abstract 35). Among 699 people with HIV and a median age of 57 years, 18% were taking 1 ACM and

***Those who reported taking 2 or more ACMs had 3.6-fold increased odds of recurrent falls compared with those not taking ACMs***

9% were taking 2 ACMs or more. The most commonly used ACMs were codeine, citalopram, loperamide, amitriptyline, and diazepam. Overall, 9% reported recurrent falls and 32% were frail based on the Fried frailty phenotype. After adjustment for demographic and lifestyle factors, those taking ACMs tended to be more likely to have recurrent falls (odds ratio [OR], 1.9 [0.9-4.0];  $P=.08$ ) and frailty (OR, 1.7 [0.9-3.0];  $P=.08$ ). However, when examining whether number of ACMs was associated with these outcomes, those who reported taking 2 or more ACMs had 3.6-fold increased odds of recurrent falls compared with those not taking ACMs (OR, 3.6; 95% CI, 1.4-9.4;  $P=.009$ ). Similar results were seen with the frailty outcomes, but the effect was not statistically significant in fully adjusted models (OR, 2.1; 95% CI, 0.9-5.0;  $P=.09$ ). Although causality cannot be established with this cross-sectional study, these findings support further studies to understand whether discontinuing these medications can lead to improvements in these important aging-related outcomes.

## **ANCHOR Study: Treatment of High-Risk Anal Lesions Decreases Incidence of Anal Cancer**

Anal cancer is common among people with HIV and leads to significant morbidity and mortality. Unlike cervical cancer, another HIV-related malignancy, screening for anal cancer and treatment of high-risk lesions (eg, high-grade squamous intraepithelial lesions [HSILs]) are not routinely recommended. This is due in part to the lack of evidence that identification and treatment of HSILs can reduce the risk of anal cancer. The ANCHOR (Anal Cancer/High-grade Squamous Intraepithelial Lesions Outcomes Research) study screened more than 10,000 people with HIV with high-resolution anoscopy, of whom 52% had biopsy-proven HSILs (Abstract 106). Of these, 2227 were randomly assigned to treatment and 2219 received active monitoring. Treatment consisted of topical or ablative therapy with retreatment, if needed, at 8 weeks and monitoring (and repeat treatment, if indicated) every 6 months. Active monitoring included clinical visits every 6 months and periodic biopsies if indicated. The study was planned to have 5 years of follow-up but was stopped after a median follow-up of 25.8 months and 32 anal cancers were diagnosed. An interim analysis of the 30 cases included revealed a 57% RR reduction in those receiving treatment for HSIL compared with those being actively monitored (9 participants in the treatment arm vs 21 in the active monitoring arm). These findings are essential to developing an evidence-based treatment strategy to prevent anal cancer.

## **Long COVID: Understanding the Syndrome**

Many excellent studies regarding COVID-19 were presented at CROI 2022, including those on long COVID, also known as post-acute sequelae of SARS-CoV-2 infection (PASC). One of the challenges in understanding PASC is the lack of a standardized definition and whether the conditions observed after COVID-19 are specific to those with COVID-19 or would have occurred without SARS-CoV-2 infection. In a large study from Kaiser Permanente

Mid-Atlantic States, Horberg and colleagues examined diagnoses in more than 70,000 people with a positive SARS-CoV-2 test between January 1, 2021, and December 31, 2021, and compared these diagnoses with approximately 70,000 people who tested negative for SARS-CoV-2 during the same period (Abstract 98). The study focused on 2 types of diagnoses: acute and persistent diagnoses, which were defined as occurring between 0 to 30 days after SARS-CoV-2 testing and persisting for 30 to 120 days, and incident/late diagnoses, which were new diagnoses that appeared between 30 and 120 days after testing. The investigators examined 15 different “conditions of focus” that were higher in incidence in those with a positive SARS-CoV-2 test. Overall, 4.1% of those with a positive test had an acute and persistent condition of focus compared with 2.5% of those with a negative test (RR, 1.6; 95% CI, 1.5-1.7), with the conditions most different between the groups being cardiac dysrhythmia, diabetes, electrolyte disorders, malaise, nonspecific chest pain, and lower respiratory disease. For the incident or late diagnosis group, those with a positive test were 12% more likely to have a condition of focus (RR, 1.12; 95% CI, 1.08-1.16), with the largest differences between the groups being for anosmia, cardiac dysrhythmia, diabetes, genitourinary symptoms, malaise, and nonspecific chest pain. These findings demonstrate that there are numerous conditions, both persistent and incident, that are more common in those with a positive SARS-CoV-2 test, and these could form the basis of a case definition for PASC. 

**All abstracts cited in the text appear in the CROI 2022 Abstract eBook, available online at [www.CROIconference.org](http://www.CROIconference.org)**

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*Invited Review***CROI 2022: Tuberculosis and Infectious Complications in Persons With HIV****Andrew D. Kerkhoff, MD, PhD, MSc; Diane V. Havlir, MD**

Zuckerberg San Francisco General Hospital and Trauma Center at the University of California San Francisco

*Early treatment of anal high-grade squamous intraepithelial lesions compared with active monitoring reduced the risk of anal cancer by 57% in persons with HIV in a landmark randomized trial of 4446 participants. In a multi-country randomized trial, an entirely oral combination regimen consisting of bedaquiline, pretomanid, linezolid, and moxifloxacin for 24 weeks outperformed the World Health Organization–recommended 36- to 96-week standard of care regimen for multidrug-resistant tuberculosis (TB), ushering in a new era of shorter multidrug-resistant TB treatment. These and other studies of TB and coinfections in persons with HIV presented at the 2022 Conference on Retroviruses and Opportunistic Infections provided new insights and are summarized herein.*

**Keywords:** HIV, CROI 2022, tuberculosis, coinfection, cryptococcus, human papilloma virus

**Tuberculosis****Drug-Resistant Tuberculosis**

Drug-resistant tuberculosis (DR-TB), including multidrug-resistant (MDR)-TB, is a major public health threat globally. Mortality remains high, treatment

**Author Correspondence**

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, Room 423A, Box 409, San Francisco, CA, 94110, or email [andrew.kerkhoff@ucsf.edu](mailto:andrew.kerkhoff@ucsf.edu).

regimens are 18 to 24 months in duration, and drugs are extremely toxic and may require injection (Symposium 5). Testing of shorter, entirely oral, better-tolerated DR-TB regimens was made possible by the recent introduction of new antimycobacterial agents. Nyang'wa and colleagues presented the preliminary results of TB-PRACTECAL (Pragmatic

***An all-oral regimen of bedaquiline, pretomanid, linezolid, and moxifloxacin (BPALM) for 24 weeks is superior to currently recommended MDR-TB treatment regimens***

Clinical Trial for a More Effective Concise and Less Toxic MDR-TB Treatment Regimen[s]), a randomized, controlled, open-label, phase II/III, noninferiority trial evaluating the comparative efficacy and safety of 3 different 24-week all-oral combination regimens for rifampicin (RIF)-resistant TB (RR-TB) (Abstract 79). Adolescents and adults (>15 years of age) with confirmed RR-TB were enrolled in Uzbekistan, Belarus, and South Africa, and were randomly assigned to 1 of 4 treatment arms: 1) bedaquiline (BDQ) 400 mg daily for 2 weeks transitioned to 200 mg thrice-weekly for 22 weeks, plus pretomanid (Pa) 200 mg daily for 24 weeks, plus linezolid 600 mg daily for 16 weeks decreased to 300 mg for 8 weeks (BPAL); 2) BPAL plus clofazimine (CFZ) 100 mg daily for 24 weeks (BPALC); 3) BPAL plus moxifloxacin 400 mg daily for 24 weeks (BPALM); or 4) the World Health Organization (WHO) standard of care (SoC) regimen for 36 to 96 weeks (control

arm). The primary endpoint was any unfavorable outcome (eg, treatment failure, death, treatment discontinuation, recurrence, loss to follow-up) after 72 weeks, with a noninferiority margin of 12%. Overall, 152 (23% of whom were HIV positive) participants were randomly assigned to BPaL, 126 (22% of whom were HIV positive) to BPaLC, 126 (23% of whom were HIV positive) to BPaLM, and 152 (23% of whom were HIV positive) to the control regimen, before further randomization stopped after the Data Safety Monitoring Board recommended early termination. For the primary endpoint, BPaLM demonstrated superiority to the control arm in modified intention-to-treat analyses (absolute risk difference [ARD], -37.2%; 95% confidence interval [CI],  $[-\infty]$ -[-21.6]), as did BPaLC (ARD, -29.7%; 95% CI,  $[-\infty]$ -[-13.1]), and BPaL (ARD, -25.2%; 95% CI,  $[-\infty]$ -[-7.7]). However, only BPaLM demonstrated noninferiority to the control arm in per protocol analyses (ARD, -8.6%; 95% CI,  $[-\infty]$ -[-4.5]). Grade 3 or greater serious adverse events were common among participants but less frequent in the BPaLM (19.4%), BPaLC (31.9%), and BPaL (21.7%) arms than in the control arm (58.9%). These highly encouraging results showed that although all 24-week, oral, BPaL-based regimens were efficacious and safe for the treatment of RR-TB, BPaLM was superior to the current SoC with respect to efficacy and safety profile.

BDQ, CFZ, and Pa are each increasingly utilized for the treatment of DR-TB. Although each drug is associated with QT interval prolongation, there are limited data on the combined QT effects when these drugs are used in combination. Abdelwahab and colleagues reported the results of modeling the combined effects on QT interval (QTcF) among 105 patients with drug-susceptible TB enrolled in a 14-day early bactericidal activity study of CFZ, alone or in combination with BDQ or Pa (Abstract 655). QT profile was simulated in 3 scenarios: 1) standard dose BDQ and CFZ as part of a MDR-TB regimen; 2) loading dose of CFZ (300 mg) for 2 weeks with standard BDQ dosing; and 3) standard BDQ dosing with Pa as part of BPaL. Patients receiving BDQ and CFZ as a loading dose had the largest QTcF increases, although the effects were less than additive, and those receiving BDQ with Pa had only mild QT

interval increases. Although these data add to the literature of the relative safety of these drugs as part of combination DR-TB regimens, it is important that cardiac monitoring is undertaken, especially during the early treatment period, to mitigate cardiac arrhythmias due to prolonged QT intervals.

## Treatment

Rosuvastatin is a widely available, well-tolerated, and inexpensive cholesterol-lowering medication that has previously shown promise as a potential adjunctive therapy for TB. Cross and colleagues undertook a randomized, controlled, multicountry trial among persons with confirmed RIF-susceptible TB, to determine if rosuvastatin 10 mg daily when given in conjunction with standard anti-TB therapy (intervention) was safe and associated with faster times to sputum culture conversion compared with standard TB therapy alone (control) (Abstract 76). Among 135 participants (4% of whom had HIV coinfection), the primary endpoint, time to liquid culture conversion of sputum within 8 weeks of randomization, did not differ between the intervention and control groups (42 days [95% CI, 35-49] vs 42 days [95% CI, 36-53], respectively; hazard ratio [HR], 1.30 [95% CI, 0.88-1.91];  $P=.188$ ). Grade 3 or 4 adverse events did not differ between groups (5 in the intervention arm vs 4 in the control arm). This study did not show a clear benefit for adding rosuvastatin to standard TB therapy.

Dorman and colleagues previously published the exciting results of the ACTG (AIDS Clinical Trial Group) A5349 TB treatment-shortening study, demonstrating that a 4-month daily regimen of high-dose rifapentine (RPT), moxifloxacin, isoniazid (INH), and pyrazinamide (PZA) (HPZM), but not a 4-month daily regimen of high-dose RPT, INH, PZA, and ethambutol (HPZE), was noninferior to the SoC 6-month TB regimen (2 months RIF/INH/PZA/ethambutol then 4 months of RIF/INH).<sup>1</sup> Chang and colleagues undertook a patient-level pooled analysis of the A5349 study to identify different patient risk groups that might be successfully treated with the HPZE regimen (Abstract 661). Among 2343 patients with drug-susceptible TB, the strongest predictors for poor outcomes and that defined the "high-risk"

group included high disease burden (eg, Xpert *Mycobacterium tuberculosis* [Mtb]/RIF cycle threshold <18, or >50% involvement of chest X-ray) and the presence of HIV or diabetes. In low- and moderate-risk groups (74% of all participants), HPZE was noninferior to both HPZM and SoC regimens. This post-hoc analysis suggests that individuals with TB and lower disease burden and without HIV or diabetes can potentially be successfully cured with the 4-month HPZE regimen as well as with the 4-month HPZM regimen.

There remains an unmet need to identify non-culture-based biomarkers that can reliably predict TB treatment outcomes. Imperial and colleagues analyzed 55 biomarkers from 628 patients with drug-susceptible TB, collected at several time points before, during, and after TB treatment, to determine which ones had the highest predictive value for TB treatment outcomes (Abstract 649). Biomarker signatures that incorporated week 8 serum amyloid A1 (SAA1) and regulated on activation, normal T cell expressed and secreted (RANTES) predicted week 8 sputum culture conversion (area under the curve [AUC], 0.77-0.79) but not TB recurrence after treatment completion (AUC<0.5). Week 0 and 2 serum neopterin levels, and to a lesser extent lipoarabinomannan levels, were the strongest predictors of TB recurrence following treatment completion. These results suggest that differential host and pathogen signatures are likely needed to predict discrete TB clinical outcomes.

## Prevention

Isoniazid preventive therapy (IPT) is an effective tool for the prevention of TB disease among people with HIV, but uptake remains low in many high TB settings. Kakande and colleagues reported the results of a cluster randomized trial in Uganda evaluating the efficacy of a unique approach to increase IPT uptake among people with HIV (Abstract 75). The trial randomly assigned midlevel health managers, who oversee health service delivery at the district level to large populations, to a control arm (39 districts) or a novel strategy (43 districts) consisting of the following: 1) mini-collaboratives facilitated by

Ugandan TB/HIV experts, 2) business leadership/management training for managers, 3) SMS platform access to improve communication, and 4) data feedback via dashboards. Overall, the IPT initiation rate was 0.74 starts per person-year and 0.65 starts per person-year in the intervention and control arms, respectively (incidence rate ratio [IRR], 1.14; 95% CI, 0.88-1.46;  $P=.16$ ). However, after accounting for secular trends, the IPT initiation rate was 0.32 starts per person-year and 0.25 starts per person-year in the intervention and control arms, respectively (IRR, 1.27; 95% CI, 1.00-1.61;  $P=.03$ ). Mixed methods research found greater IPT-specific knowledge among district managers and improved interdistrict collaboration and communication in the intervention clusters. Despite not finding higher IPT rates in the primary endpoint analysis, this study demonstrates that targeted leadership and management training for midlevel health managers represents a promising approach for facilitating the scale-up of recommended evidence-based practices in resource-limited settings.

Four weeks of daily INH and RPT (1HP) is a highly efficacious and patient-centered option for the treatment of latent TB infection (LTBI); however, its safety in persons with HIV taking dolutegravir (DTG)-containing antiretroviral therapy (ART) is unknown. Podany and colleagues presented an interim analysis of the A5372 study (Abstract 78), a multisite pharmacokinetic (PK) study that enrolled virally suppressed adults on a DTG-based regimen to measure DTG trough concentrations during coadministration with 1HP. Twenty-five participants underwent PK sampling, and DTG dosing was increased to 50 mg twice daily during 1HP coadministration. The median DTG trough concentration on day 0 (reflecting daily DTG dosing prior to 1HP) was 1745 ng/mL compared with 4454 ng/mL, 2127 ng/mL, 2594 ng/mL, and 2146 ng/mL at days 3, 14, 21, and 28 of 1HP, respectively. No DTG concentrations were observed below the target trough concentration (>158 ng/mL), and no hypersensitivity or serious adverse events were observed. All participants maintained virologic suppression at day 42. Further data will be needed to inform clinical recommendations, including the potential safety of daily DTG dosing, but

this small interim study preliminarily supports the efficacy and safety of 1HP with twice daily DTG dosing in persons with HIV.

The safety of weekly INH and RPT for 3 months (3HP) for LTBI in persons with HIV receiving a bicistat-boosted darunavir (DRV/c)-containing ART regimen has not been evaluated. Brooks and colleagues reported the results of an open-label, fixed sequence, 2-period crossover study in healthy adults without HIV to evaluate DRV PK parameters when DRV/c is coadministered with 3HP (Abstract 431). Participants received DRV/c 800 mg/150 mg daily for 19 days, and 3HP was coadministered on days

*Single-dose levonorgestrel for emergency contraception should be doubled in women taking rifampicin-containing regimens*

5, 12, and 19. Among 13 participants, DRV trough concentrations (predose plasma concentration [ $C_{0h}$ ] geometric mean ratio [GMR], 0.04:0.19), 24 hours postdose concentration ( $[C_{24h}]$  GMR, 0.04:0.11), and concentration over 24 hours ( $[AUC_{0-24h}]$  GMR, 0.29:0.64) were substantially lower when 3HP was given 48 to 72 hours before and concurrent with DRV/c, respectively. Given significantly lower DRV concentrations, 3HP should not be given as LTBI therapy in patients with HIV on DRV/c-based ART regimens.

Although unhealthy alcohol use is associated TB disease progression and reduced ART adherence, its effects on IPT adherence have not been well documented. Muyindike and colleagues undertook an observational study among persons with HIV in Uganda receiving daily IPT for 9 months to evaluate the association between alcohol use and IPT adherence (Abstract 653). Of 279 participants receiving IPT for 3 or more months, 21.9% and 50.5% were classified as having moderate and unhealthy alcohol use, respectively. Suboptimal IPT adherence at 3 months (31.3%) and 6 months (43.9%) was

common and was independently associated with moderate alcohol use (adjusted odds ratio [aOR], 1.59; 95% CI, 0.94-2.71) and unhealthy alcohol use (aOR, 2.78; 95% CI, 1.62-4.76) compared with abstaining from alcohol. These data suggest that alcohol reduction strategies may be an important facet of larger strategies to improve adherence to TB-preventative therapies among persons with HIV in sub-Saharan Africa.

## Women and Children

To mitigate pregnancy-related health risks for individuals being treated for TB disease, it is crucial that emergency contraception is accessible and safe. Single-dose levonorgestrel (LNG) 1.5 mg, an emergency contraceptive, is metabolized via cytochrome P450 (CYP) 3A4, and the optimal dose when given with RIF, a potent CYP3A4 inducer, is unknown. Mngqibisa and colleagues reported the results of a multicountry, parallel group, PK trial of premenopausal women comparing LNG concentrations in women with TB (but without HIV) who received a 1-time double dose of LNG (3 mg from the standard 1.5 mg dose) (n=34; RIF group) and women with HIV on DTG-based therapy who also received a single dose of LNG 1.5 mg (n=32; control group) (Abstract 77). Overall, the LNG maximal concentration ( $C_{max}$ ) was higher in women in the RIF group (GMR, 1.27; 90% CI, 1.09-1.49), whereas AUC over 8 hours (GMR, 1.16; 90% CI, 1.09-1.49) and 24 hours (GMR, 0.96; 90% CI, 0.79-1.17) was similar between groups. Only 3 participants (2 in the RIF group vs 1 in the control group) had grade 2 or 3 LNG-related adverse events. These results show that a double dose of LNG (3 mg x 1) in women receiving RIF for TB treatment was safe and support current recommendations to increase LNG from 1.5 mg to 3 mg in women receiving RIF for whom LNG is indicated.

Even though CFZ is recommended as part of a combination regimen for the treatment of DR-TB among children, limited safety and PK data are available for CFZ in this population. Ali and colleagues reported the results of an observation study among children with HIV and DR-TB being treated with a

weight-based CFZ-containing regimen to characterize CFZ PK parameters and assess its potential QT interval-prolonging effects (Abstract 656). Among 54 children (65% <5 years old, 9% of whom were HIV positive), the median predose QTcF was 389 ms (2.5th-97.5th percentile, 331-463); there were 6 QTcF prolonged events greater than 450 ms (all mild-to-moderate), and CFZ concentrations were directly associated with QTcF prolongation. The addition of moxifloxacin to CFZ had modest effects (approximately 7%) on QTcF when given with CFZ. CFZ  $C_{max}$  concentrations in children were frequently higher than simulated concentration in adults; the CFZ clearance rate was nearly 2 times higher among children with HIV (oral clearance [CL/F, %], 1.9; 95% CI, 0.3-5.0), but there were only 5 children with HIV included. The authors concluded that their findings did not support allometric scaling (weight-banded dosing) of CFZ among children, and further studies are needed to determine appropriate weight-based dosing ranges.

Diagnosis of pediatric TB remains challenging, in large part because of the limitations of current diagnostic tools and approaches. LaCourse and colleagues evaluated the performance of a novel TB assay: a clustered regularly interspaced short palindromic repeats (CRISPR)-based assay that detects *Mtb*-specific multicopy insertion element (IS6110) in cell-free DNA (CRISPR-TB), for diagnosing pediatric TB and monitoring treatment response (Abstract 645). The CRISPR-TB assay was run on cryopreserved sera collected at weeks 0, 2, 4, 12, and 24, from hospitalized, ART-naive children (<12 years of age) with HIV in Kenya who had been intensively investigated for the presence of TB disease. Among 153 children with HIV (median age, 2 years; 68% with severe immunosuppression), CRISPR-TB had a sensitivity of 100% (95% CI, 75-100) and 84.8% (95% CI, 71.1-93.7) for confirmed and clinical TB, respectively. CRISPR-TB detected that *Mtb* cell-free DNA concentrations declined during therapy and were almost completely cleared after 6 months of anti-TB therapy. CRISPR-TB shows promise for pediatric TB diagnosis and treatment monitoring; however, larger prospective evaluations among diverse populations, including those less ill, are required.

## **TB Epidemiology**

TB notification data and prevalence surveys around the world have demonstrated higher rates of TB among men than among women; however, there are limited data on sex-specific differences for TB in persons with HIV. Chaisson and colleagues conducted a retrospective cohort study of people with HIV in Rio de Janeiro between 2010 and 2016 to evaluate differences in TB incidence rates between men and women (Abstract 657). Of the 54,957 persons with HIV included (65% male; median age, 35 years), TB incidence was higher among men than among women (IRR, 1.24; 95% CI, 1.15-1.34). Sex differences in TB incidence were even more pronounced among those not on ART (IRR, 1.51; 95% CI, 1.33-1.72) and among those with newly diagnosed HIV and CD4+ count less than 350 cells/ $\mu$ L (IRR, 1.68; 95% CI, 1.37-2.04). These data are consistent with prior studies demonstrating a higher TB risk among men and suggest that tailored strategies to improve TB diagnosis and care engagement in men are likely important for TB control efforts.

South Africa has the world's largest HIV-associated TB epidemic. Kujane and colleagues undertook a modeling study to evaluate the impact of scaling up several TB control interventions in South Africa between 1990 and 2019, including ART, directly observed therapy, IPT, increased TB screening, and Xpert *Mtb*/RIF (Abstract 659). During the 30 year analysis period, 8.0 million persons developed TB and 2.1 million died from TB, of whom 67.4% and 76.4%, respectively, were persons with HIV. Between 2009 and 2019, TB incidence declined by 35.3%. It was estimated that 25.2% of reductions in adult TB incidence was attributable to ART, 25.0% to TB screening, 1.7% to IPT, 1.4% to directly observed therapy, and 0.2% to Xpert *Mtb*/RIF. This study demonstrates the public health impact of several interventions on reducing South Africa's TB burden and points to the need to further increase the availability of and access to these important interventions to further decrease TB incidence, especially ART and TB screening.

## Opportunistic Infections

### Cryptococcosis

Central nervous system (CNS) infections, especially cryptococcal meningitis (CM), remain an important cause of death in persons with HIV in low- and middle-income countries. Kanyama and colleagues presented an implementation research project that sought to define the epidemiology of HIV-related CNS infections and reduce associated mortality in Tanzania, Malawi, and Cameroon (Abstract 663). The primary intervention was implementation of a diagnostic and treatment algorithm for HIV-related CNS infections. Scale-up was facilitated by a strategy (DREAMM [Epidemiological Findings and Cryptococcal Meningitis Outcomes]) consisting of empowering local leadership, strengthening health systems, and creating communities of practice. In the preimplementation period, only 10% (n=14/139) of adults with HIV presenting with a suspected CNS infection had a CNS infection microbiologic confirmation. Following implementation of DREAMM, 75% (n=269/356) of such patients had a probable or confirmed CNS infection. CM (55%) and TB meningitis (17%) were the most frequent CNS infections. Overall, all-cause mortality at 2 and 10 weeks was 25% (n=67/264) and 42% (n=110/163), respectively. This study showed that a novel strategy to implement a multifaceted diagnostic intervention was associated with a substantial increase in the microbiologic confirmation of specific HIV-CNS infectious etiologies, of which CM was highly prevalent. Nonetheless, short-term mortality was extremely high, indicating an urgent need to identify and scale-up effective interventions to reduce mortality due to CNS infections among persons with HIV in low-resource settings.

Lawrence and colleagues recently presented the results of the AMBITION (Ambisome Therapy Induction Optimisation) trial, which demonstrated that for the induction portion of CM treatment in individuals with HIV, a single high dose of liposomal amphotericin B (L-AmB) (10 mg/kg) given with 14 days of flucytosine 100 mg/kg per day and fluconazole 1200 mg per day (L-AmB regimen) was non-

inferior to and had fewer adverse events than the current WHO-recommended SoC regimen consisting of amphotericin B deoxycholate 1 mg per kg daily for 7 days plus flucytosine 100 mg per kg per day for 7 days followed by fluconazole 1200 mg per day for 7 days.<sup>2</sup> However, because of the high cost of L-AmB compared with amphotericin B deoxycholate (d-AmB), Muthoga and colleagues evaluated the cost-effectiveness of scaling up the L-AmB treatment approach in Malawi and 4 additional high-HIV-incidence countries (Abstract 664). Overall, the authors found that the L-AmB regimen

*Voriconazole is noninferior to amphotericin-based regimens for induction therapy of talaromycosis in persons with HIV*

had a mean cost of US \$1369 (95% CI, 1314-1424) compared with US \$1237 (95% CI, 1181-1293) for the SoC regimen. The L-AmB regimen was associated with a mean incremental cost-effectiveness ratio of US \$128 (95% CI, 53-257) per life-year saved, which was estimated to be even lower under real-world implementation settings (\$80 [95% CI, 15-275] per life-year saved); this was similar across all 5 countries. These results demonstrate that the L-AmB regimen is an effective and cost-effective therapeutic option for CM in patients with HIV in sub-Saharan Africa compared with the current SoC regimen.

### Talaromycosis

Talaromycosis remains an important opportunistic infection among persons with HIV in Southeast Asia, for which L-AmB is recommended for the initial induction phase of therapy. However, because L-AmB is poorly tolerated by many patients and is often unavailable in resource-limited settings, Chen and colleagues evaluated the comparative efficacy and safety of voriconazole versus d-AmB for induction therapy for talaromycosis among adults with HIV in China (Abstract 74). This open-label,

nonrandomized, controlled trial enrolled 359 hospitalized patients with HIV and confirmed talaromycosis; 255 (median CD4+ count, 13 cells/ $\mu$ L) received induction therapy with AmB 0.5 mg per kg to 0.7 mg per kg for 14 days, and 104 (median CD4+ count, 12 cells/ $\mu$ L) received induction therapy with voriconazole 6 mg per kg twice daily for 1 day, then 4 mg per kg twice daily for 3 days, then 200 mg twice daily for 10 days. Mortality at 14 days (adjusted hazard ratio [aHR], 1.90; 95% CI, 0.46-7.78) and 48 weeks (aHR, 1.01; 95% CI, 0.41-2.49) was similar between the voriconazole and d-AmB arms. Patients in the voriconazole induction arm had lower odds of clinical resolution (aOR, 0.54; 95% CI, 0.34-0.87) and fungal clearance at 14 days (aOR, 0.61; 95% CI, 0.38-0.97) than the d-AmB arm. Although participants in the d-AmB arm were more likely to experience severe anemia (hemoglobin <7.4 g/dL) (aOR, 0.51; 95% CI, 0.31-0.83) and severe hypokalemia (potassium level <2.4 mmol/L) (aOR, 0.14; 95% CI, 0.012-1.05), there were no further differences in clinical and laboratory adverse events. This study showed that d-AmB induction therapy results in more rapid clinical and microbiologic improvement of talaromycosis in patients with advanced HIV/AIDS; however, voriconazole induction therapy was associated with similar mortality rates and should be considered when L-AmB is unavailable or cannot be feasibility given.

## Kaposi Sarcoma Herpesvirus and Human Papilloma Virus

### Kaposi Sarcoma Herpesvirus

Little is known about the characteristics, treatment, and outcomes of persons who require admission to the intensive care unit (ICU) with Kaposi sarcoma herpesvirus (KSHV)-associated disorders (KADs, which include Kaposi sarcoma, KSHV inflammatory cytokine syndrome [KICS], primary effusion lymphoma [PEL], and multicentric Castleman disease). Hansen and colleagues presented the results of a retrospective observational study of these patients at a single US center between 2010 and 2021 (Abstract 571). There were 47 patients identified with

KAD who required ICU admission during the defined study period of whom 46 had HIV. Among the patients with HIV, 94% were on ART, the median CD4+ count was 88 cells/ $\mu$ L (interquartile range [IQR], 39-223), and the median HIV RNA level was 23 copies/mL (IQR, 20-95); 38 patients had 2 or more KADs (n=19 had Kaposi sarcoma and KICS)

*Early treatment of anal high-grade squamous intraepithelial lesions greatly reduces the risk of anal cancer in persons with HIV by 57%*

and 21 (45%) received KAD-directed chemotherapy in the ICU. Sixty-day survival was 83%, and the median overall survival duration was 9 months. Patients with PEL or KICS had a substantially higher risk of death (HR, 5.0; 95% CI, 1.5-17.2), and those who received chemotherapy during their admission did not (HR, 1.5; 95% CI, 0.7-3.3). Severe KAD largely occurred among persons with advanced HIV who were suppressed on ART, adding to existing literature showing that KICS and PEL each have a poor prognosis.

### Human Papilloma Virus

One of the most highly anticipated presentations at this year's Conference on Retroviruses and Opportunistic Infections (CROI) was the ANCHOR (Anal Cancer/HSIL Outcomes Research) study, which was presented by Palefsky and colleagues in a special session and followed by a panel discussion (Abstract 106). Persons with HIV, especially men who have sex with men, are at substantially increased risk for the development of anal cancer, a complication of human papilloma virus infection. Anal and cervical cancers are similar diseases, and both are preceded by high-grade squamous intraepithelial lesions (HSILs). Although regular screening for and early treatment of cervical HSIL is widely known to prevent cervical cancer, there is, to date, a lack of evidence to suggest that a similar approach for anal

cancer is effective. To address this important gap in clinical understanding, the ANCHOR study, a randomized, controlled trial, was undertaken to determine the efficacy of HSIL treatment in reducing the incidence of anal cancer compared with active monitoring. Persons with HIV aged 35 years and older were recruited from sites throughout the United States and screened for the presence of HSIL. Those with biopsy-proven HSIL were enrolled and randomly assigned (stratified according to study site, CD4+ cell count nadir, and perianal/anal canal lesion size) to treatment or to active monitoring. Persons in the treatment arm received immediate treatment of HSIL with one of several modalities according to clinician recommendation (eg, electrocautery ablation, infrared coagulation, topical fluorouracil, topical imiquimod), were followed and rescreened for HSIL at least every 6 months (anal cytology, high-resolution anoscopy [HRA]), and retreated if persistent HSIL was identified on biopsy. Persons in the active monitoring arm were also seen every 6 months for anal cytology, swabs, and HRA, and had an annual biopsy to confirm the continued presence of HSIL. The primary study endpoint was time to incident anal cancer. There were 10,723 persons with HIV screened for HSIL before the study was stopped early for efficacy, of which 52% had biopsy-proven HSIL (53% in men, 46% in women, 63% in transgender persons) and 17 had prevalent anal cancer (prevalence, 160/100,000 person-years).

Investigators randomly assigned 4446 people with HIV 1:1 to the treatment arm (n=2227) or to active monitoring (n=2219). Baseline demographics and characteristics (median age, 51 years; 81% male; 51% with CD4+ count <200 cells/ $\mu$ L; approximately 90% with HIV RNA <200 copies/mL) and median follow-up time were similar between arms. The proportion with a large anal/perianal lesion at baseline (13%) was also similar between arms. Ultimately, 30 cases of anal cancer were diagnosed during the follow-up period, 9 in the treatment arm (173/100,000 person-years) versus 21 (402/100,000 persons-years) in the active monitoring arm (57% reduction; 95% CI, 6%-80%;  $P=.029$ ). Adverse events were uncommon; there

were 43 study-related adverse events in the treatment arm, including 7 serious adverse events, and 4 and 1, respectively, in the active monitoring arm. No study-related deaths occurred.

This practice-changing study clearly demonstrates anal HSIL is highly prevalent in men, women, and transgender persons with HIV, and that early treatment of anal HSIL is effective in preventing anal cancer among persons with HIV. It should therefore be considered SoC. The next step will be to optimize implementation strategies in clinical settings. 

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*Invited Review***Preventing and Diagnosing HIV-Related Comorbidities in Adolescents****Hasiya Eihuri Yusuf, MD, MPH; David Griffith, MD; Allison Lorna Agwu, MD, ScM**

Johns Hopkins University School of Medicine

*Adolescents with HIV are growing into adulthood and are at risk for comorbidities. Comorbidities in adolescents often go unrecognized, increasing morbidity and mortality, and contributing to poorer outcomes for youth with HIV. Youth with perinatally and nonperinatally acquired HIV are at risk of developing HIV-associated and non-HIV comorbidities, including cardiovascular diseases, diabetes, mental health disorders, renal diseases, and bone disorders. Youth with HIV are also at risk for altered fat distribution and weight gain associated with certain classes of antiretroviral therapy. Sexually transmitted infections from inconsistent condom use pose a sexual health challenge for youth with HIV. Prompt interventions through comprehensive history taking, physical exams, regular screening, and prevention and treatment of clinically evident comorbid conditions are needed to prevent progression and complications.*

**Keywords:** comorbidities; adolescent; HIV; young adults; youth; prevention

**Background**

Global accessibility and scale-up of effective antiretroviral therapy (ART) have transformed HIV from a potentially progressive, life-threatening disease to a chronic, but manageable, lifelong infection.

**Author Correspondence**

Send correspondence to Allison Agwu, MD, ScM, Johns Hopkins University School of Medicine, 200 North Wolfe Street, Baltimore, MD, 21287, or email [ageorg10@jhmi.edu](mailto:ageorg10@jhmi.edu).

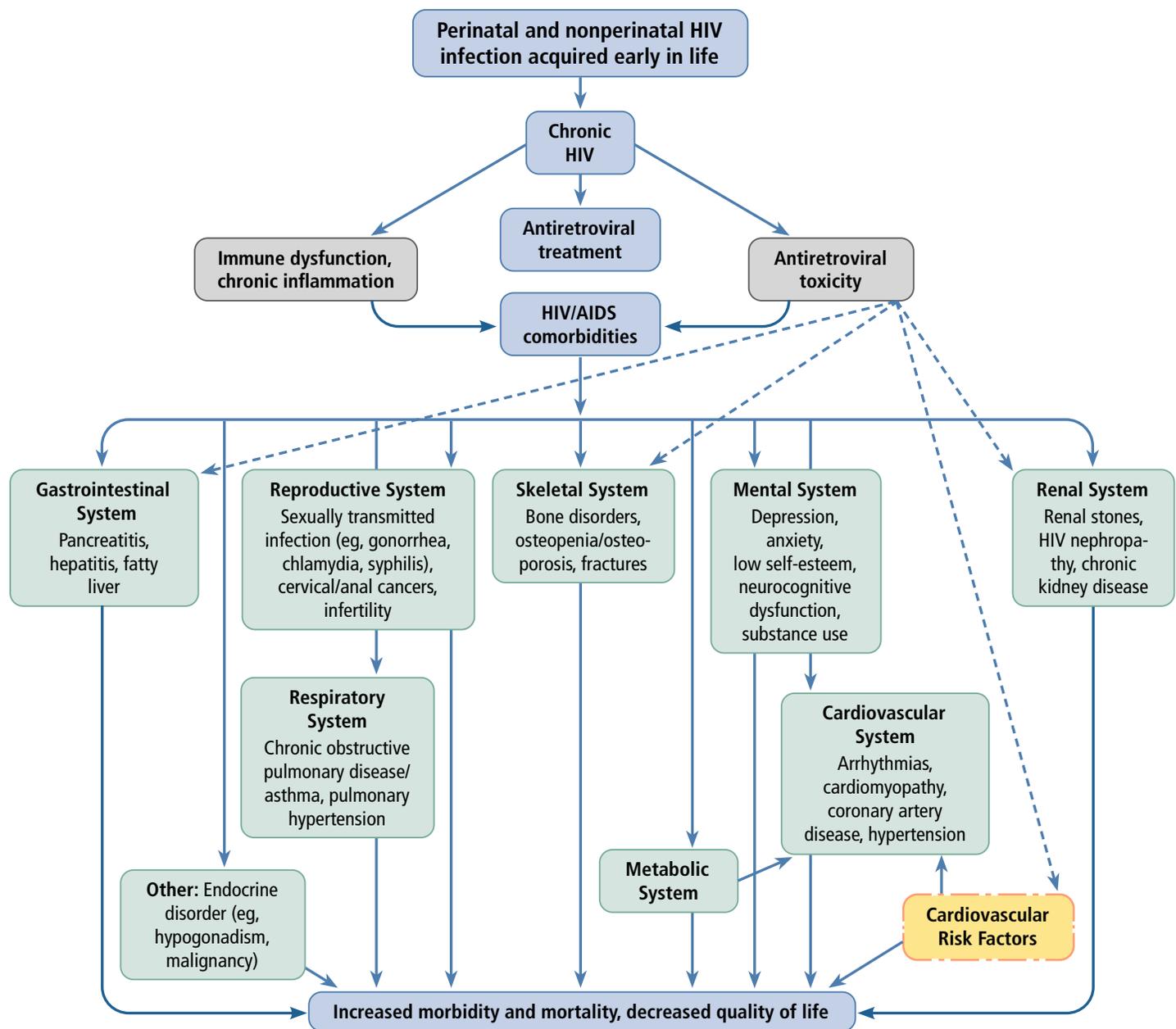
As a result, adolescents with HIV are growing into adulthood. Presently, more than 45,000 adolescents and young adults (AYA) aged 12 to 24 years in the United States are living with perinatally or nonperinatally acquired HIV.<sup>1</sup> Compared with older adults, youth with HIV are less likely to be diagnosed, access care, remain in care, and achieve and maintain

***Comprehensive care for youth with HIV goes beyond achieving viral load suppression. Other aspects of care must be addressed to ensure well-rounded care delivery and to prevent adverse outcomes for youth***

virologic suppression, which is the current end goal of HIV treatment.<sup>2</sup> HIV-associated comorbidities are not limited to older adults and are becoming prevalent in youth with HIV, often going unrecognized due to failure to anticipate and probe for them.<sup>3</sup> Unidentified comorbidities can lead to morbidity or mortality, or worsen the quality of life for youth with HIV. We discuss common comorbidities prevalent among adolescents with HIV, and strategies for their prevention, prompt diagnosis, and treatment.

**Epidemiology of HIV in Adolescents**

The majority of children who acquired HIV in infancy are now 13 years old or older, and up to 40% of them are 25 years old or older.<sup>4</sup> Youth with HIV also include those who acquire HIV as adolescents or



**Figure.** Chronic comorbidities in adolescents and young adults with chronic HIV infection.

young adults, often characterized as nonperinatally acquired HIV. Of the 34,800 new infections diagnosed in 2019, 7648 (21%) occurred in the 13 to 24 year age group.<sup>5,6</sup> Although the HIV epidemic has changed in many ways, the demographics of those affected have remained relatively consistent. Most new infections in AYA are diagnosed in men who have sex with men (MSM), representing 83% of HIV diagnoses in that age group.<sup>5</sup> Racial disparities also characterize the distribution of HIV transmission in

the United States. Nearly 70% of new HIV infections in 2019 occurred among African American and Hispanic or Latinx people, who together make up approximately 30% of the US population.<sup>5</sup> In 2019, 51% of MSM aged 13 to 24 years and diagnosed with HIV were African American, and 32% were Hispanic or Latinx.<sup>1</sup>

The HIV continuum of care (CoC) is a model that examines the level of engagement in care from diagnosis to the attainment of virologic suppression.

Along the continuum, youth with HIV have lower rates of engagement in care, receipt of care, and viral suppression than older adults.<sup>2</sup> Growing awareness of the poor HIV outcomes in youth has motivated clinicians and researchers to focus on optimizing care for this group, with the aim of strengthening treatment adherence and achieving virologic suppression. Although the CoC is a useful framework, comprehensive care for youth with HIV goes beyond achieving viral load suppression. Other aspects of care must be addressed to ensure well-rounded care delivery and to prevent adverse outcomes for youth. Although rigorous efforts in diagnosis and treatment have been instrumental in reducing HIV transmission among AYA,<sup>6</sup> many challenges remain in the management of HIV in AYA that must be addressed.

### HIV Comorbidities in Youth

More than a quarter of American adults older than 65 years of age are reported to have 2 or more comorbid conditions, and these figures are projected

*Like older adults with HIV, youth with HIV are exposed to the immunologic effects of chronic HIV infection*

to rise as the elderly population increases.<sup>7</sup> The prevalence of comorbid conditions is even higher among adults with HIV, who are at greater risk for kidney diseases, cardiovascular events, neurocognitive disorders, and malignancies, and at an earlier age than persons who are HIV negative.<sup>8</sup> Chronic immune activation by HIV is thought to be the major contributor to developing HIV comorbidities.<sup>8</sup>

Like older adults with HIV, youth with HIV are exposed to the immunologic effects of chronic HIV infection and long-term effects of ART. Youth with perinatally and nonperinatally acquired HIV are therefore at risk of HIV-related comorbidities, including cardiovascular diseases, diabetes, liver disease,

mental health disorders, renal diseases, and bone disorders.<sup>4</sup> Despite this evidence, efforts to identify and address comorbid risks in youth with HIV have been limited. For example, in a cohort of South African youth with HIV, 55% had clinically recognizable comorbidities, independent of the route of HIV acquisition.<sup>3</sup> Only a limited number of those with existing chronic comorbidities or risk factors for comorbidities received intervention. There is therefore a need to identify comorbid risks in this group and to implement measures to prevent progression in their early stages.

### Diabetes

Adults with HIV have been found to have higher rates of diabetes than adults who are HIV seronegative.<sup>9</sup> ART has been identified as a risk factor for diabetes in adults with HIV. Early ART regimens, in particular protease inhibitors (PIs), and thymidine analogs are associated with increased risk of diabetes and metabolic complications from alterations in fat distribution.<sup>10</sup> Though many of the early ART regimens are no longer in common use, prior use remains an important metabolic risk factor.<sup>10</sup> The increasing risk of diabetes in the general population has also been seen in AYA. In a large study, new cases of type 1 and type 2 diabetes among youth increased by 45% from 2009 to 2017 to a prevalence of 0.67 per 1000 youths aged 10 to 19 years.<sup>11</sup> A high risk of diabetes has also been reported in youth with HIV. Nearly 15% of adolescents in the PHACS (Pediatric HIV/AIDS Cohort Study) group were found to have evidence of insulin resistance, and observational cohorts have shown an increase in diabetes as youth with HIV age.<sup>12</sup>

Insulin resistance in youth with HIV is multifactorial. As in adults with HIV, insulin resistance in youth with HIV may result from HIV infection itself or the use of ART, especially PIs and nucleoside reverse transcriptase inhibitors (nRTIs) like thymidine analogues (eg, stavudine and zidovudine).<sup>13</sup> Thymidine analogue use has become less common, and the use of PIs as first-line treatment for HIV has been overtaken by the ease and availability of the integrase strand transfer inhibitor (InSTI) drug class. InSTI

use has been associated with weight gain, which may pose additional diabetes risk.<sup>14</sup> In addition to traditional risk factors (eg, obesity, family history) and the effects of ART, chronic HIV infection is believed to play a role in the development of insulin resistance, although its mechanism is not fully clear.<sup>15</sup>

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### **Hypertension and Cardiovascular Risk**

Among adolescents in the general population, 15% to 19% of boys and 7% to 12% of girls have signs of elevated blood pressure (BP).<sup>16</sup> As expected, elevated BP in AYA occurs more frequently in those

*Chronic HIV infection causes changes in the structural integrity of the vasculature, and increases intimal and media thickness in carotid vessels. Among youth with HIV, cardiovascular abnormalities such as ventricular hypertrophy, abnormal cardiac rhythms, and cardiomyopathies have all been reported*

with comorbid conditions, including chronic kidney disease, obstructive sleep apnea, and obesity.<sup>16</sup> Among youth with HIV, wide variations exist in the reported prevalence of elevated BP, with a range of 3% to 20% across several studies.<sup>3,17</sup> Chronic HIV infection causes changes in the structural integrity of the vasculature, and increases intimal and media thickness in carotid vessels.<sup>18</sup> Among youth with HIV, cardiovascular abnormalities such as ventricular hypertrophy, abnormal cardiac rhythms, and cardiomyopathies have all been reported.<sup>4</sup> Youth with HIV have substantially greater coronary arterial wall thickness and markers of cardiovascular disease than youth who are HIV negative.<sup>19</sup> These markers are associated with arterial stiffness, irritation, and other signs of compromised vascular integrity. In

youth with HIV, the elevations in inflammatory markers associated with cardiovascular disease appear to be independent of virologic suppression.<sup>20</sup> Although hard outcomes of cardiovascular diseases in youth with HIV are not very common, these changes are concerning as evidence emerges of long-term cardiovascular comorbidity in this group. In a recent case report, a 23-year-old with long-standing perinatally acquired HIV developed sudden acute chest pain and marked ST elevations on electrocardiogram from 95% left anterior descending artery occlusion, requiring emergent coronary angiography.<sup>21</sup> Such occurrences, though rare, emphasize the need for HIV clinicians to proactively seek out and address cardiovascular risks early, and to intervene to avoid the development of and progression to clinically evident cardiovascular diseases.

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### **Weight Gain**

Currently, 21% of 12- to 19-year-olds in the United States are obese.<sup>22</sup> Data on weight gain in adolescents with HIV are still emerging and appear to be linked to newer drugs in the InSTI class and tenofovir alafenamide (TAF).<sup>23</sup> Guidelines currently recommend InSTI-based regimens as first- and second-line regimens in adolescents, adults, and, more recently, the pediatric age group. InSTI-based regimens are efficacious for achieving virologic suppression and improvement in treatment outcomes; however, they are also associated with substantial weight gain and changes in BMI, both in the adult and youth populations.<sup>14,24</sup> Among the InSTIs, dolutegravir is associated with the greatest weight gain;<sup>14</sup> however, there are emerging data that bictegravir is also associated with weight gain.<sup>25</sup> Other drugs in the class (eg, raltegravir, elvitegravir) cause weight gain, but to a lesser degree and comparable with levels of weight gain with PIs and nonnucleoside reverse transcriptase inhibitors (NNRTIs).<sup>14</sup> TAF is associated with more weight gain when paired with dolutegravir than tenofovir disoproxil.<sup>23</sup>

Several studies on the association between InSTIs and weight gain have been reported, and additional data continue to emerge. The greatest risk of weight gain with InSTIs occurs in women, non-Hispanic

Black individuals, and older adults (>60 years) with HIV.<sup>14</sup> Youth-specific data are comparatively few, and further research is warranted. Nonetheless, available evidence showing a likelihood of weight gain in this group suggests a need for caution and monitoring for weight changes in young patients prescribed InSTIs.

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## Sexually Transmitted Infections

AYA aged 15 to 24 years have the highest rates of sexually transmitted infections (STIs) in the United States, and these rates are increasing. In 2018, more than half of the 26 million diagnosed STIs in the United States occurred among AYA.<sup>26</sup> The rates of gonorrhea, chlamydia, and syphilis increased between 2013 and 2017 among individuals 15 to 24 years of age.<sup>26</sup> STI rates among youth with HIV are similar to the general population, and like those without HIV, youth with HIV also engage in sexual risk behaviors that increase their STI risk.<sup>27,28</sup>

Youth with HIV engaging in sexual activity report high levels of inconsistent condom use.<sup>29</sup> There is a risk for the sequelae of STIs including cancers, ectopic pregnancy, infertility, and chronic pelvic pain. Hence, there is a clear need for STI risk reduction interventions among youth with HIV.

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## Mental Health and Substance Use

Mental health disorders in youth with HIV can negatively impact risk-taking behaviors, treatment adherence, and treatment outcomes.<sup>4</sup> There is a disproportionately high prevalence of mental health disorders in people with HIV, including youth. For example, people with HIV are twice as likely to be depressed than persons who are HIV negative.<sup>30</sup> In one study, the lifetime prevalence of mental health disorders including depression, substance use disorders, and conduct disorder was substantially higher in adolescents who are HIV positive than adolescents of the same age who are HIV negative.<sup>31</sup> Mental and behavioral disorders are also prevalent, with depression, anxiety, and substance use being among the most commonly reported mental health comorbidities in youth with HIV.<sup>3,32</sup>

Despite the risk of mental health disorders, substance use, and their consequences in adolescents with HIV, many clinicians do not frequently conduct mental health assessments of their young patients.<sup>33</sup> Racial disparities in the mental health assessment of youth is also common. African American youth with HIV are less likely to receive mental health

*It is crucial to identify and address these comorbidities through prevention, prompt diagnosis, and early interventions to prevent adverse outcomes and to improve HIV management outcomes for youth with HIV*

services including psychotropic medications than youth of other races.<sup>34</sup> Assessment of youth with HIV for mental health disorders including substance use is essential, as untreated psychiatric disorders in people with HIV increase mortality, contribute to morbidity, and hinder treatment adherence.<sup>31</sup>

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## Way Forward

### Patient History

Tackling current HIV comorbidities for youth with HIV and reducing their occurrence in the future demands a keen sense of observation by everyone involved, especially patients and their clinicians. Prevention of comorbidities begins with interventions that focus on identifying early warning signs and risk behaviors. A good place to begin is with a comprehensive history that takes every aspect of the patient's life into consideration. Adequate history taking ought to include a thorough assessment of comorbid conditions and risks, including tobacco and nicotine products, alcohol and other substances of abuse, and a comprehensive sexual history. History of use of other substances (eg, methamphetamines) with rising rates of use among youth should

also be sought. Sexual history must be obtained in a nonjudgmental and nonstigmatizing manner to perpetuate openness. Clinicians need to ask about sexual activity, not just for STI intervention, but also for counseling on contraception and pregnancy intentions for all populations of young people.

History of other activities that may result in unintentional injury (eg, use of helmets, driving, owning or living in a home with firearms) also needs to be taken. Clinical encounters should include a detailed family history, not merely limited to the first encounter but continually updated as patients and their families evolve. Physical examination must be thorough and geared toward identifying clinical signs that may be of concern (eg, abnormal BMI, elevated BP, central obesity, signs of substance use or abuse). Prompt intervention should be the goal for modifiable risk factors (eg, smoking, diabetes, physical inactivity, elevated BP, high blood cholesterol) of comorbid conditions identified in the course of history taking, examination, and laboratory investigations.

### **Counseling**

The false perception of invincibility that often characterizes adolescence can lead young people to engage in unhealthy habits. Physical activity as a normal lifestyle should be encouraged for all patients without medical contraindications, and linkage to available weight management services can be considered for patients who require them. All adolescents ought to be educated on the health hazards of tobacco products (e-cigarettes, cigarettes, cigarillos, pipes) and given true information on their composition and long-term effects on health. Youth with HIV are able to engage in the use of smoking cessation tools. Lifestyle modifications should be encouraged and counseling incorporated into every component of the visit until the desired change is initiated and ultimately achieved.

### **Screening**

According to HIV primary care guidance, metabolic profiles should be assessed for youth with HIV.<sup>35</sup> Baseline lipid profiles, hemoglobin A1c (HbA1c), and glucose levels need to be monitored given concerns of the metabolic effects of ART. An initial

assessment of metabolic profile sets the tone for future monitoring. HbA1c above 6.5% should raise concern for diabetes and the need for further evaluation and intervention. Regular assessment of weight and BMI and monitoring for weight gain are also essential. Management guidelines also recommend screening for STIs, hepatitis infection, mental health and substance use disorders, and BP, as well as assessing the need for vaccines.<sup>35</sup> Most risk calculators' cardiovascular risk assessment components are not validated for youth. Other methods of assessment should be employed, particularly among youth considered at high risk.

### **Treatment**

Clinicians should initiate prompt treatment for clinically evident comorbid conditions to limit progression and prevent complications. Persistently elevated BP should be treated after exclusion of secondary causes such as renal artery stenosis, chronic kidney disease, and obstructive sleep apnea. Elevation in lipids should be treated with dietary modifications, nutritional counseling, and promotion of physical activity, as well as referral to structured weight loss intervention if indicated. If substantial elevations persist despite these interventions, first-line therapy with statins should be considered, although data is limited in youth with HIV. STI counseling, screening, and treatment, as well as family planning and contraception for interested youth, are crucial. Reproductive intentions should be inquired about with both male and female patients. Youth with HIV with substance use disorders should be offered needed treatments to facilitate recovery. Other mental health disorders can be treated if promptly identified and addressed. It is crucial to intervene early and prevent human papillomavirus (HPV)–associated cancers in youth with HIV with HPV vaccination and screening for abnormalities. Vaccination against hepatitis A and B, as well as other important vaccines protecting against tetanus/diphtheria/pertussis, meningococcus, influenza, pneumococcus, measles/mumps/rubella, and now SARS-CoV-2, can substantially reduce comorbidities.

In conclusion, adolescents with HIV, whether perinatally or nonperinatally acquired, are surviving

into adulthood. Clinicians must be aware of potential comorbidities that may arise in adolescence or early adulthood and set the tone for the patient's health as they move into adulthood. It is crucial to identify and address these comorbidities through prevention, prompt diagnosis, and early interventions to prevent adverse outcomes and to improve HIV management outcomes for youth with HIV. 

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