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Topics in Antiviral Medicine™

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Selected Highlights of the 2024 Conference on Retroviruses and Opportunistic Infections (Part 2)

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Topics in Antiviral Medicine™

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On completion of this activity, which contains 3 articles, the learner will be better able to describe and utilize the important new data presented at the 2024 Conference on Retroviruses and Opportunistic Infections and the potential clinical implications for patients in the areas of:

- Neuropsychiatric complications in people with HIV, including cardiovascular disease, cancer, obesity, and frailty
- SARS-CoV-2, including long COVID and its clinical manifestations
- Management of long-acting injectable antiretroviral therapy for patients with HIV, including adherence challenges
- Hepatitis B, C, and D epidemiology and treatment

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

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

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Invited Review

CROI 2024: Neuropsychiatric Complications in People With HIV

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Abstract: *The 2024 Conference on Retroviruses and Opportunistic Infections featured new and impactful findings about neuropsychiatric complications in people with HIV and other infections. Reports included new evidence from low- and middle-income countries, HIV persistence in the central nervous system, aging-related complications (including cerebrovascular disease), additional data relevant to pathogenesis, and therapeutics. Also included were new evidence of active HIV RNA transcription in cells from cerebrospinal fluid and the brain during virally suppressive antiretroviral therapy as well as links between neuropsychiatric complications or brain imaging findings in people with HIV and a) carotid artery inflammation and cerebrovascular disease, b) Alzheimer's disease genetic risk, c) social determinants of health, including exposure to pollution, and d) epigenetic aging. New therapeutic findings were presented on the cerebrospinal fluid inhibitory quotient, the effects of polypharmacy, and clinical trials of tesamorelin and telmisartan. This review summarizes these and other new findings and highlights new research directions for the neuro-HIV field.*

Keywords: HIV, CROI, neuropsychiatric complications, cognition, brain, depression, cerebrospinal fluid, neuroimaging, comorbidities

Introduction

The effects of HIV on the central nervous system (CNS) were the focus of several presentations at the Conference on Retroviruses and Opportunistic Infections (CROI) again in 2024. This summary is organized into 5 categories that reflect the breadth of the data that were presented: reports from low- and middle-income countries, HIV persistence in the CNS, aging-related complications (including cerebrovascular disease), additional data relevant to pathogenesis, and therapeutics. These data provided novel insights into how HIV affects the brain and will continue to inform new research and treatment strategies to improve the health and welfare of people with HIV (PWH) and other infections that affect the CNS. This year's review is dedicated to Albert (Bert) Anderson, MD, who made many valuable contributions to the neuro-HIV field and coauthored this article in past years. Bert passed away in the past year and will live on in the memory of his family and all the friends, patients, and colleagues whose lives he touched.

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Reports From Low- and Middle-Income Countries

Most people with HIV live in low- and middle-income countries, but most reports about the neuropsychiatric complications of HIV have historically been published by researchers in high-income countries. Several reports at CROI 2024 helped narrow that gap. Nakasujja and colleagues (Abstract 569) compared the verbal learning (a list-learning task) and memory (recall after 20 minutes) performance of 350 virally suppressed PWH with few comorbidities from the Rakai Community Cohort Study in Uganda with the performance of 250 sociodemographically similar people without HIV from the same region. No statistically significant differences were identified in performance on these brief assessments between the groups. The South African CONNECT (Cognition, Neuropsychiatric Symptoms, and Neuroinflammation Switching to Dolutegravir in Cape Town) study, presented by Nightingale and

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colleagues (Abstract 553), administered a more comprehensive assessment that included tests in 7 cognitive domains to 145 PWH who switched from efavirenz- to dolutegravir-containing antiretroviral therapy (ART) and compared their performance with 95 sociodemographically similar people without HIV. PWH were more likely to have impaired cognitive performance at baseline when they were taking efavirenz (30.1% vs 11.7%; $P<.001$), but not a year later when they were taking dolutegravir (8.3% vs 7.5%; $P>.99$). Combined, these findings provide reassurance that cognitive impairment may not be as common as in past reports when the HIV-associated neurocognitive disorder (HAND) approach was used.

In contrast, Wilson and colleagues (Abstract 571) presented a study that administered a brief assessment of 5 tests to 2737 people living in Nigeria, Kenya, Uganda, and Tanzania (the AFRICOS [African Cohort Study] cohort) and found that neuropsychologic test z-scores were lower in PWH than in people without HIV whether they had achieved viral suppression (n=1393) or not (n=871). A panel of 4 inflammation-associated protein biomarkers (CXCL10, CCL2, soluble CD163, and soluble CD25) in blood indicated that greater inflammation was associated with worse cognitive performance in PWH even in those with viral suppression. None of the biomarkers were associated with worse cognitive performance in people without HIV. Consistent with prior reports, a test of motor performance, grooved pegboard, had the strongest associations, implicating subcortical processes in HIV-driven brain injury. Reports from Uganda and Lebanon also found that mental health issues appeared to be common among PWH. In a Lebanese study presented by Rizk and colleagues (Abstract 570), 61.5% of 39 participants had depression and 46.2% had anxiety, and each of these was associated with experiencing HIV stigma. In a second study from Uganda, Rubin and colleagues (Abstract 573) presented results on 277 PWH who underwent a mental health assessment. The data were analyzed using a pipeline of dimension reduction, hierarchical density-based spatial clustering, and gradient-boosted multivariate regression, and this identified 4 clusters, 1 with minimal symptoms (n=39), 1 with prominent posttraumatic stress disorder symptoms (n=76), 1 with prominent anxiety symptoms (n=32), and 1 with mixed anxiety and depression symptoms (n=130). Early life adversity, particularly sexual abuse, emerged as a risk determinant for unfavorable mental health, highlighting the importance of addressing the psychosocial challenges faced by PWH globally.

HIV Persistence in the CNS

Several impactful presentations on HIV persistence in the CNS during ART were presented in an oral session. Kincer and colleagues (Abstract 112) presented cross-sectional findings from 78 PWH who had taken ART for at least 1 year and did not have neurologic symptoms. They compared HIV RNA level in cerebrospinal fluid (CSF) measured by standard (40 copies/mL) and single-copy (limit of detection of 0.25 copies/mL) assays with a panel of 12 inflammation-associated protein biomarkers as well as performance on 11 neuropsychologic tests. Higher HIV RNA level in the CSF was significantly associated with higher CSF matrix metalloproteinase-9, higher plasma tissue inhibitor of matrix metalloproteinase-1, higher CSF total protein, higher CD4+ T-cell count, and worse global and processing speed performance. These findings confirm prior findings that low levels of HIV RNA during ART appear to stimulate an immune response that can injure the brain.

Low levels of HIV RNA during ART appear to stimulate an immune response that can injure the brain

Farhadian and colleagues (Abstract 114) applied single-cell immune profiling and T-cell receptor repertoire analyses to CSF and blood cells from 8 virally suppressed PWH. The group examined 129,544 CSF cells and 262,818 blood cells: transcriptionally active HIV RNA-producing cells were present in 72.7%

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of CSF and 54.5% of blood samples. Most (83.6%) HIV RNA-producing cells were CD4+ central memory cells and a higher frequency of infected cells was observed in CSF than in blood. Thirty-six T-cell clones contained infected cells with 22% of clones containing infected cells shared between CSF and blood and 28% with evidence of clonal expansion, which suggests that maintenance and expansion of infected T-cell clones contribute to the CNS reservoir even during ART.

Findings support that the brain is a transcriptionally active HIV reservoir even during viral suppression with ART

Churchill and colleagues (Abstract 113) extended findings of a transcriptionally active reservoir in the CNS by using digital droplet polymerase chain reaction HIV transcriptional profiling in postmortem brain tissue specimens from the frontal cortex of 12 virally suppressed donors. Transcription initiation (HIV TAR), early elongation (long LTR), multiple splicing (Tat/Rev), completion of HIV transcription (PolyA), and HIV p24 protein were detected in some or all specimens. Total and intact HIV proviruses were quantified by the intact proviral DNA assay and correlated with HIV transcripts. Together, the findings support that the brain is a transcriptionally active HIV reservoir even during viral suppression with ART. Tang and colleagues (Abstract 494) pre sented data highlighting the extended survival of infected human brain myeloid cells during ART. The group used RNAscope to show that levels ranged from 0.67 to 16.67 RNA dots/1000 nuclei in the brains of 4 virally suppressed PWH following a rapid autopsy. Brain myeloid cells were resistant to cytopathic effects after viral infection, and cell viability remained comparable between infected cells and mock-infected cells. Together, these findings indicate that infected resident cells in the brain can have extended survival and produce HIV transcripts, which present challenges for HIV cure efforts.

Aging-Related Complications

The effects of premature aging on the brain are increasingly important and were the subject of several abstracts. This area of investigation encompasses a broad range of research, including cognitive decline as PWH age into their 60s and beyond; aging-related complications including cerebrovascular disease and frailty; and indicators of biologic aging including epigenetics and brain imaging.

Cerebrovascular disease was the focus of many abstracts at this year's conference. Berry and colleagues (Abstract 567) measured circulating endothelial cell-derived microvesicles, which have been linked to cerebrovascular disease risk, in 8 untreated PWH and 8 people without HIV. Levels of circulating endothelial cell-derived microvesicles were higher in PWH, and cells treated with endothelial cell-derived microvesicles from PWH had lower nitric oxide production than those from people without HIV. Although sparse, the data supported the conclusion that HIV is associated with a phenotype of pathologic circulating endothelial cell-derived microvesicles, which could increase the risk of ischemic stroke. One important consideration in this study is that the participants were not taking ART.

Shifting to large, clinical cohorts, Chow and colleagues (Abstract 565) presented data from the WIHS (Women's Interagency HIV Study) and the MACS (Multicenter AIDS Cohort Study) on atherosclerotic cardiovascular disease in 1773 PWH and 1264 people without HIV. They found that traditional cerebrovascular disease risk factors predicted subsequent cognitive performance in all participants irrespective of HIV infection, but this was not true in subgroup analyses of women. Greater cerebrovascular risk only predicted worse subsequent cognitive performance in women with HIV but not women without HIV. A separate report from the same cohort (Abstract 566) extended this finding; cumulative exposure to several cerebrovascular disease risk factors (eg, body mass index, lipid profile, methamphetamine use) had stronger associations with cognition in women, including women with HIV, than men. This effect was modest, and they

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concluded that the clinical significance is unclear but the combined findings reinforce the importance of screening for and treating cerebrovascular disease risk factors in women with HIV. Consistent with the links between vascular risk factors and cognition, Brouillette and colleagues (Abstract 597) presented another cohort of 865 adults with a mean age of 53 years who underwent longitudinal cognitive assessments for a mean duration of 7.3 years. Cognition declined in a quarter of participants, and this was associated with higher number of cardiovascular disease risk factors but not HIV disease factors.

Moving beyond clinical risk factors to brain imaging, a magnetic resonance imaging (MRI) study by Bolden and colleagues (Abstract 587) quantified white matter hyperintensity volume using high-resolution T1-weighted images in 97 PWH and 37 sociodemographically similar people without HIV. White matter hyperintensity volume is a structural indicator that is historically associated with vascular disease and cognitive performance. This volume was greater in those with cerebrovascular disease risk factors, older age, and Black race. In contrast, investigators found only a trend association with HIV status (P=.07), but in the subgroup of PWH, longer HIV disease duration and lower CD4:CD8 ratio were associated with larger white matter hyperintensity volume. A study by Cassidy and colleagues (Abstract 564) measured white matter hyperintensities using T2 MRI in 71 participants with acute HIV in Thailand. White matter hyperintensities increased in 75% of participants over a 2-year period following diagnosis and initiation of ART. White matter hyperintensity volume was associated with higher blood pressure, tobacco smoking, and larger body mass index, but not HIV disease indicators such as CD4+ T-cell count. In contrast with reports in people with chronic HIV infection, white matter hyperintensity volume was not associated with cognitive performance. In this same cohort, Bolzenius and colleagues (Abstract 590) found evidence of larger brain volumes in the later stages of acute HIV infection. Prior studies of large brain volumes in PWH have suggested that this may be due to the migration of immune cells to the brain and inflammation.

Vascular inflammation has been demonstrated in the heart and aorta of PWH on virally suppressive ART. Few studies have examined carotid arterial inflammation in people with HIV. During the oral session, Wilson and colleagues (Abstract 111) presented data on 47 virally suppressed PWH (98% men; mean age, 60 years) with moderate to high risk for cerebrovascular disease who underwent 18F-fluorodeoxyglucose positron emission tomography to examine arterial inflammation. Greater carotid, but not aortic, inflammation was associated with worse cognitive performance. Adjusting for current tobacco smoking (which was associated with poorer cognition) attenuated the correlation. Since no people without HIV had imaging performed, investigators were unable to conclude whether the findings differed in PWH. Like the previously mentioned study from Uganda, Rubin and colleagues (Abstract 573) also collected data on social determinants of health (posttraumatic stress, early childhood stress). Not only were these associated with global cognitive performance, but the correlation between carotid inflammation and cognition became nonsignificant after adjusting for early childhood stress. This highlights the complex interplay between social determinants of health, cerebrovascular disease risk, and cognitive performance.

Greater carotid, but not aortic, inflammation was associated with worse cognitive performance

As noted by El Helou and colleagues in Abstract 570, depression is common among PWH. It has also been linked to stroke risk. An oral presentation by Ma and colleagues (Abstract 110) adjudicated 173 incident strokes in 13,817 people with HIV (mean age, 45 years) with at least 1 assessment for self-reported depressive symptoms. Depressive symptom severity was associated with higher stroke risk (adjusted hazard ratio, 1.16), with greater impact in those younger than 50 years. New-onset depressive

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symptoms were associated with the highest stroke risk. A causative link is plausible, perhaps via common mechanisms of inflammation, depression, and cerebrovascular disease. Medications used to treat depression can also have metabolic adverse reactions. Alternatively, lifestyle (eg, physical inactivity) and comorbid factors (eg, stimulant use) in PWH who are depressed could increase risk. Of note, adjustment for sociodemographic factors reduced the strength of the association but did not eliminate it.

Depressive symptom severity was associated with higher stroke risk

Transitioning to studies that reported on the effects of aging separate from cerebrovascular disease, Kennedy and colleagues (Abstract 599) compared the cognitive aging trajectories of 391 PWH with those of 269 people without HIV for up to 15 years. Although PWH performed worse than those without HIV at baseline, global cognitive change over time did not differ between virally suppressed PWH (76% of the cohort) and people without HIV. In contrast, those with detectable HIV RNA (>50 copies/mL) performed more poorly and had faster rates of decline, underlining the importance of maintaining virologic control as PWH age.

Discussion of the effects of aging on cognition must also consider Alzheimer's disease-type pathology. Curtis and colleagues (Abstract 589) found that an Alzheimer's disease polygenic risk score was associated with worse cognitive performance in 115 PWH with a mean age of 58 years. Polygenic risk scores were associated with smaller total gray matter volume and lower caudate cerebral blood flow. HIV disease factors were not associated with polygenic risk scores. The investigators concluded that worse cognitive performance in older PWH may be related to age-related factors that are prevalent in people without HIV. Wilson and colleagues (Abstract 591) performed a retrospective analysis of 74 cognitively impaired PWH (mean age, 67 years) who underwent amyloid positron emission tomography. Unexpectedly, they found lower rates of amyloid positivity in PWH than in 65 cognitively unimpaired people without HIV of a similar age (8.5% vs 21.5%; P=.024). Although this finding remains unexplained, the investigators commented that it may be due to selection bias. The eligibility criteria required the pattern of cognitive impairment to be typical for HIV but not for Alzheimer's disease. Indeed, 2 PWH who were excluded went on to develop Alzheimer's disease. Investigators also found no differences in cognitive decline between PWH with amyloid positron emission tomography positivity and those without it.

Alzheimer's disease polygenic risk score was associated with worse cognitive performance in PWH

Data on an Alzheimer's disease mouse model were also presented by Bhattarei and colleagues (Abstract 575), with humanized T cells and microglia allowing for HIV infection in the CNS, as well as the Swedish mutation associated with familial Alzheimer's disease. Mice infected with HIV had higher levels of soluble and insoluble amyloid-β (1-42) in the brain than in those not exposed to HIV. In several areas where HIV colocalized with amyloid-β (1-42) plaques, transcriptional changes in neurons, microglia, and astrocytes were increased compared with brain areas with amyloid-β (1-42) plaques alone. Investigators interpreted this to indicate that HIV could enhance amyloid pathology, at least when untreated.

A study presented by Thomas and colleagues (Abstract 586) assessed the impact of the *apolipoprotein E (APOE) ε4* allele (the major genetic risk for sporadic Alzheimer's disease) on white matter microstructure on MRI in 76 people (mean age, 56 years), 58 of whom were PWH. *APOE ε4* carriers with and without HIV had significantly reduced fractional anisotropy in various regions of the left arcuate fasciculus compared with people without

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an *APOE ε4* allele. Interactions between *APOE ε4* status and HIV disease were present, and after controlling for age there was a steeper disease duration-related decline in fractional anisotropy in *APOE ε4* carriers in PWH than in people without HIV. Although published data in this area are inconsistent, these investigators concluded based on their findings that PWH who have *APOE ε4* allele could be at greater risk of HIV brain disease as they age.

Some assessments mentioned in this section are unavailable or not routinely ordered in the clinic. The VACS (Veterans Aging Cohort Study) 1.0 index is a score that was developed in part to be easily implemented in outpatient settings. It combines age, CD4+ cell count, HIV RNA level, hemoglobin, FIB-4 index, hepatitis C status, and estimated glomerular filtration rate. It more accurately discriminates mortality risk in virally suppressed PWH than traditional HIV disease markers alone. Yan and colleagues (Abstract 601) compared an updated index, VACS 2.0, which additionally includes body mass index and white blood cell count, with brain imaging findings and cognitive performance in 162 PWH who were age 50 years or older. The VACS 1.0 and 2.0 indexes correlated with smaller brain volumes, but only VACS 2.0 was associated with performance in some cognitive domains and was higher in PWH who were frail. They concluded that clinicians could consider incorporating this index into routine assessments. Riggs and colleagues (Abstract 602) investigated the relationship between the VACS 1.0 index and coinfection with cytomegalovirus (CMV) and Epstein-Barr virus (EBV). Almost all the 485 virally suppressed PWH (mean age, 53 years) were seropositive for CMV (96.5%) and EBV (100%), with DNA detected in peripheral blood mononuclear cells for EBV (95.6%) and HIV (99.2%). In contrast, CMV DNA was detected in peripheral blood mononuclear cells in 47.8%. Higher CMV immunoglobulin G (IgG) titers correlated with higher VACS 1.0 index, HIV DNA level, and EBV DNA level. The authors concluded that an immune response to CMV is an important predictor of adverse clinical outcomes in older PWH. VACS was not associated with CMV DNA suggesting that the immune dysregulation triggered by CMV (indicated by CMV IgG titers) may not be directly related to the burden of CMV DNA in peripheral blood mononuclear cells.

Higher cytomegalovirus immunoglobulin G titers correlated with higher VACS 1.0 index, HIV DNA level, and Epstein-Barr viral DNA

Strano and colleagues (Abstract 598) investigated plasma biomarkers of brain injury in older PWH. Four brain-derived protein biomarkers were measured in plasma from 102 PWH older than 50 years, and 44 people without HIV. None of the brain-derived biomarkers were significantly higher in PWH than people without HIV. In both groups, neurofilament light chain and glial fibrillary acidic protein increased with age. Higher glial fibrillary acidic protein was associated with low nadir CD4+ T-cell count, but not current CD4+ T-cell count, and a longer duration of ART, which the authors interpret as an indication of legacy brain injury with reactive gliosis from previously untreated HIV infection. Higher glial fibrillar acidic protein also had clinical correlates, being associated with reduced handgrip, balance, and digit span.

Additional Data Relevant to Pathogenesis

Several groups assessed epigenetic biomarkers as indicators of CNS complications in HIV. Johnston and colleagues (Abstract 595) used genome-wide DNA methylation profiling and derived epigenetic age estimates of 158 older PWH. Epigenetic age analysis indicated an average epigenetic age advancement of 5.4 years in older PWH. This epigenetic age advancement was associated with a lower Montreal Cognitive Assessment score adjusted for age, sex, and race. Epigenetic age estimates trended toward association with frailty state as well as with survival, with greater estimated age advancement associated with shorter survival over 7 years.

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In a separate presentation, Peterson and colleagues (Abstract 594) presented DNA methylation data from 440 participants (261 women with HIV and 179 women without HIV) in the WIHS. A cell-type-specific epigenetic age estimate, the monocyte epigenetic age, was assessed and significantly associated with nonsomatic depression symptoms reflecting anhedonia. Stanley and colleagues (Abstract 592) described preliminary efforts to establish cell-type-specific single-cell transcriptomic and epigenetic signatures across various brain regions in postmortem tissues from PWH, people with opioid use disorder, and people with both conditions from the SCORCH (Single Cell Opioid Responses in the Context of HIV) consortium. The team generated single-nuclei gene expression and chromatin accessibility data on the 10x Genomics multiome platform (Single Cell Discoveries) from 4 groups, 3 regions per individual, 136 samples, and more than 1 million nuclei. They found that gene expression differed between cell types and brain regions, supporting the complexity of HIV pathogenesis in the rain. Although substantial neuro-HIV research has focused on myeloid cells and more recently lymphoid cells, the investigators conclude based on these preliminary findings that HIV disease and opioid use disorder directly or indirectly affect many other cell types that differ between brain regions and warrant further investigation.

Advances in proteomics assay methods have enhanced disease-associated biomarker detection in biologic fluids. Mukerji and colleagues (Abstract 546) investigated the relationships between baseline plasma neurofilament light, plasma glial fibrillary acidic protein, and longitudinal neuropsychologic performance on a 4-test battery over 6.2 years in 503 participants (median age, 52 years) of the ACTG (AIDS Clinical Trials Group) HIV Infection Aging and Immune Function Long-term Observation Study A5322. Higher baseline plasma neurofilament light and plasma glial fibrillary acidic protein were associated with worse baseline cognitive performance. Higher baseline plasma neurofilament light was associated with subsequent cognitive decline, but baseline glial fibrillary acidic protein was not. This confirms and extends prior published findings on plasma neurofilament light. Coughlin and colleagues (Abstract 109) assessed the contribution of glial activation assessed by positron emission tomography imaging with the translocator protein-ligand, N,N-diethyl-2-(4-[2-fluoroethoxy] phenyl)-5,7-dimethylpyrazolo(1,5-a)pyrimidine-3-acetamide, to cognitive control and declarative memory in 25 virally suppressed PWH. The team found localized microglial activation in the prefrontal cortex, dorsal anterior cingulate cortex, and inferior parietal lobule associated with lower cognitive control. No statistically significant associations were present between microglial activation and declarative memory.

Riggs and colleagues (Abstract 596) investigated proteomic signatures of 206 virally suppressed PWH. They compared proteomic relationships with traditional neurocognitive classifications and 4 biopsychosocial phenotypes identified by unsupervised machine learning. The 4 previously defined biopsychosocial phenotypes were described as healthy, mild cognitive impairment with moderate depressive symptoms, mild to moderate cognitive impairment with severe depressive symptoms and instrumental activities of daily living dependence, and mild to moderate cognitive impairment without depressive symptoms or instrumental activities of daily living dependence. Using the Olink Target-96 inflammation panel Genewiz, CD8 antigen, IL-17C, FGF-21, and FGF-23 were the most frequently associated proteins with neuropsychiatric classifications. Discriminant analysis correctly classified more than 75% of participants in only the phenotypes with mild to moderate cognitive impairment. Several novel associations with proteomics were identified, highlighting the

Several novel associations with proteomics were identified, highlighting the potential value of proteomics and more discovery-driven approaches

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potential value of proteomics and more discovery-driven approaches.

Lozano and colleagues (Abstract 551) performed an immune checkpoint profiling study using multiparametric flow cytometry in a cohort of 50 virally suppressed PWH on stable ART (for ≥12 months) and 50 people without HIV. They found that higher PD-1+ CD4+ T-cell frequencies correlated with better verbal memory (P=.0003) and worse fine motor performance (P=.005). Higher TIGIT+ CD4+ T cells were found to only correlate with worse verbal memory in PWH (P=.01). The group cocultured CD4+ T cells expressing immune checkpoint markers with neuroblastoma cells and found PD-1+ CD4+ T cells increased PD-L1 ligand expression and increased tumor necrosis factor (TNF)-α protein production. PD-L1 blockade reduced the expression of ligand PD-L1, but TNF-α did not decline, highlighting the complex interaction of immune checkpoints on T cells with neuronal cells.

Using data and biospecimens from ACTG A5322, Giron and colleagues (Abstract 549) conducted glycomic biomarker profiling in 40 PWH with longitudinal plasma samples over 8 years (10 in each of 4 subgroups defined by sex and cognitive impairment). Cognitive impairment was associated with higher levels of several proinflammatory bisected and agalactosylated IgG glycans. Many of the associations were present in both sexes but some were present only in women. Consistent with their proinflammatory roles, these glycans, specifically G0FB, correlated with higher levels of the inflammatory marker TNF-α. Cognitive impairment was also associated with lower levels of glycans that contain the antiinflammatory sialic acid and fucose. Among inflammation markers, interleuken-10 (IL-10) and sCD14 exhibited positive correlations with cognitive impairment. Although the sample size is small, these exploratory findings suggest aging- and inflammation-associated glycomic dysregulations are linked to the presence of cognitive impairment in PWH on ART in a sex-dependent manner.

Additional findings relevant to the social determinants of health were also presented. Cooley and colleagues (Abstract 581) examined the effects of recent air pollution exposure in the St. Louis, Missouri, region on cognition, immunophenotyping, and plasma biomarkers of inflammation and neurodegeneration in 227 PWH and 107 people without HIV. Pollution monitoring data from the US Environmental Protection Agency were used to calculate the average exposure to pollutants in the week before assessment. The average inhalable particulate matter (PM) exposure over the past calendar year was estimated using satellite data from the US National Aeronautics and Space Administration. Higher recent exposures to PM2.5, PM10, and low-volume lead were associated with worse learning, delayed recall, worse executive functioning, and worse global cognition in PWH and people without HIV. Higher recent ozone and PM2.5 exposure was associated with higher levels of myeloid activation (soluble CD14, soluble CD163) in PWH. Higher recent ozone and PM10 exposures were associated with higher markers of neurodegeneration (neurofilament light, glial fibrillary acidic protein) in PWH and people without HIV. The impact of sociodemographic factors as classifiers of cognitive profiles compared with neuroimaging was also explored in an analysis of 225 PWH (Abstract 583). Sociodemographic features, but not clinical or neurologic features, were the strongest distinguishers of cognitive profiles in PWH. Specifically, lower education and worse premorbid intelligence quotient (estimated by the Wide Range Achievement Test 3) were identified as risk factors for worse cognitive performance.

Higher recent exposures to PM2.5, PM10, and low-volume lead were associated with worse learning, delayed recall, worse executive functioning, and worse global cognition in people with HIV and people without HIV

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Therapeutics

Past published reports have identified that antiretroviral drugs, such as efavirenz and dolutegravir, may have adverse neurologic effects, including effects on sleep, mood, and cognition. Most of these have focused on individual drugs rather than combinations of drugs, as they currently are prescribed. Parra-Rodriguez and colleagues (Abstract 554) addressed this by analyzing data from 1928 assessments in 1072 PWH (mean, 1.8 assessments) residing in the US. The most common regimens in this cohort were: (1) dolutegravir, abacavir, lamivudine (22%); (2) elvitegravir, cobicistat, tenofovir alafenamide, emtricitabine (14%); and (3) efavirenz, tenofovir disoproxil fumarate, emtricitabine (10%). Tenofovir (either formulation) and emtricitabine combined with darunavir (and cobicistat), rilpivirine, or efavirenz were associated with worse cognitive performance over time than other regimens, particularly in memory and executive functioning. One reason this may occur is interindividual differences in pharmacogenetics, which can lead to substantial differences in metabolism and elimination of antiretroviral drugs.

Zhao and colleagues (Abstract 556) investigated the pharmacogenetics of neuropsychiatric adverse events in 128 PWH in South Africa within 14 days of switching from efavirenz, tenofovir, emtricitabine to dolutegravir, tenofovir, lamivudine. Participants were randomly assigned to receive supplemental dolutegravir (50 mg daily; n=65) or placebo (n=63). Seventeen (13.3%) reported insomnia after 2 weeks, but this did not differ between arms. A trend toward higher dolutegravir exposure did occur in those with UGT1A1 rs887829 homozygous TT genotype (P=.058) and the CYP2B6 slow efavirenz metabolizer genotype was associated with lower dolutegravir exposure, but this was only statistically significant in those who received supplemental dolutegravir (P=.006). Although this pharmacogenetic analysis identified associations with dolutegravir concentrations, the clinical relevance is uncertain since neither the genotypes nor the drug concentrations were associated with insomnia.

Another issue related to HIV therapeutics is the distribution of drugs into protected compartments, like the CNS. A limitation of some past published studies, however, is that they again considered only 1 antiretroviral drug at a time. Avedissian and colleagues (Abstract 558) addressed this by modeling antiretroviral drug concentrations for an entire regimen in CSF. The 44 participants took regimens that included tenofovir disoproxil fumarate and emtricitabine and 1 of 6 other drugs (efavirenz, atazanavir [with ritonavir], raltegravir, elvitegravir [with cobicistat], darunavir [with ritonavir], or dolutegravir). They calculated a CSF inhibitory quotient for each drug as a ratio of modeled CSF trough to published 50% or 90% inhibitory concentration values and then calculated the geometric mean of CSF inhibitory quotients of all drugs in each participant's regimen. They found that higher CSF inhibitory quotient for the entire regimen was associated with lower HIV DNA level in CSF (P=.027) and better global cognitive performance (P=.05), but not with a panel of 6 inflammation-associated biomarkers. Although the findings of this small study should be confirmed, they reinforce the potential value of optimizing ART to protect the CNS.

Beyond ART, the search continues for interventions that may prevent or treat the neuropsychiatric disorders that occur in PWH. Ellis and colleagues (Abstract 552) reported the early results of a clinical trial of tesamorelin, a synthetic growth-hormone–releasing hormone, for the treatment of cognitive impairment in PWH who also had abdominal obesity (men, waist circumference ≥95 cm; women, waist circumference ≥94 cm or waist-to-hip ratio ≥0.88). Participants were randomly assigned to start a 24-week course of tesamorelin (1.4 mg by subcutaneous injection daily) immediately (n=43) or after a 24-week delay (n=30). This initial report compared the arms after 24 weeks and, although waist circumference improved more in those who received tesamorelin, cognitive performance did not. Although these preliminary findings do not support the use of tesamorelin for cognitive impairment, additional analyses are underway, including analyses of brain imaging.

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Corley and colleagues from the SEARCH018/RV408 study group (Abstract 593) applied a new ultra-low–input genome-wide DNA methylation profiling assay to CSF cells obtained from 21 men with acute HIV infection who were randomly assigned 2:1 to initiate treatment with ART and with or without the antiinflammatory drug, telmisartan, for 48 weeks. At 48 weeks, those who received telmisartan had 11,433 differentially methylated loci (mean difference in DNA methylation, ≥10%), including the marker of proliferation Ki-67 (*MKI67*), inflammatory gene *IL1B*, immune checkpoint receptor gene *LAG3*, central regulator of stress response gene *CRH*, and interferon-stimulated gene *IFI27*. Twenty-four weeks later, only 5.46% of the differentially methylated loci in CSF cells were still present. Although telmisartan did not appear to alter a small panel of inflammation and neuronal injury biomarkers in CSF, its long-term epigenetic effects may warrant further investigation.

A cell-type–specific epigenetic age estimate, the monocyte epigenetic age, was assessed and significantly associated with nonsomatic depression symptoms

In addition to ART, PWH are often prescribed numerous other medications. As a result, polypharmacy (use of at least 5 prescribed drugs other than antiretroviral drugs) is more common among PWH than people without HIV and is associated with worse neuropsychiatric and other health outcomes. Using data from 870 participants in ACTG A5322, Paul and colleagues (Abstract 555) applied an unsupervised machine learning method, hierarchical density-based spatial clustering, to identify subgroups based on performance on a four-test neuropsychological battery and then compared the results with polypharmacy and hyperpolypharmacy (use of at least 10 prescribed drugs other than ART). Analyses identified 8 cognitive clusters, one of which performed well on all tests (the healthy cluster). Polypharmacy or hyperpolypharmacy was more common in 3 clusters (polypharmacy, 6 and 8; hyperpolypharmacy, 7 and 8) than in the other clusters. Compared with the healthy cluster, the clusters that had more frequent polypharmacy or hyperpolypharmacy (6, 7, 8) included more women and Black or Hispanic people. Consistent with the presence of polypharmacy, people in these clusters were also more likely than the other clusters to have multiple medical diagnoses, including cardiovascular disease, diabetes mellitus, hepatitis C, peripheral neuropathy, and substance use. If validated, these findings could help identify PWH suffering adverse effects from polypharmacy based on just 4 neuropsychological tests.

All cited abstracts appear in the CROI 2024 Abstract eBook, available online at www.CROIconference.org

The IAS–USA will identify and resolve ahead of time any possible conflicts of interest that may influence CME activities with regard to exposition or conclusion. All financial relationships with ineligible companies for the authors and planners/reviewers are below.

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Invited Review

CROI 2024: Acute and Post-Acute COVID-19

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Abstract: *Studies of acute and post-acute COVID-19, including their biology, prevention, and treatment, were presented at the 2024 Conference on Retroviruses and Opportunistic Infections. Numerous studies reported on the impact of hybrid immunity (ie, from a combination of prior infection and vaccination) on the natural history, pathogenesis, and outcomes of infection with modern SARS-CoV-2 variants. Several studies demonstrated the continued benefit of SARS-CoV-2 vaccination and the effect of treatment, particularly in the setting of severe disease. New data regarding persistent RNA shedding in immunocompromised populations were presented, demonstrating the potential challenges that this phenomenon poses with regard to viral evolution. In addition, there was a continued focus on post-acute sequelae of SARS-CoV-2 including its clinical manifestations and potential underlying biology. These and other studies are summarized here.*

Keywords: coronavirus disease 2019, COVID-19, severe acute respiratory syndrome coronavirus 2, SARS-CoV-2, post-acute sequelae of SARS-CoV-2, PASC, long COVID, HIV

Introduction

We are now entering the fifth year of the SARS-CoV-2 pandemic. Data presented at the 2024 Conference on Retroviruses and Opportunistic Infections (CROI) demonstrate the remarkable progress that has been made in understanding the epidemiology, natural history, pathophysiology, prevention, and management of COVID-19 since the novel coronavirus emerged in late 2019. This progress has, in part, led to the end of the public health emergency.[1] However, SARS-CoV-2 continues to circulate widely, new variants of concern continue to emerge, and the long-term consequences of infection continue to affect millions of people around the world. This article highlights new research on acute and post-acute SARS-CoV-2 (PASC) infection (long COVID) presented at the 2024 CROI.

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Acute COVID-19

Epidemiology and Natural History of COVID-19

Most of the global population now has acquired immunity to SARS-CoV-2 from vaccination, prior infection, or both. However, important questions remain regarding the epidemiology of infections with new variants, particularly breakthrough infections.

Severity of modern variants. Overall, current SARS-CoV-2 variants seem less likely to cause severe disease and death than the ancestral and Delta variants. Mourad and colleagues (Abstract 868) evaluated data from the placebo arms of 5 studies of mild-to-moderate outpatient COVID-19 in the ACTIV (Accelerating COVID-19 Therapeutic Interventions and Vaccines)-6 platform. Using patient symptom diaries, they observed that the time to recovery decreased over the duration of the trial. They proposed that this could be due to increased pre-existing immunity (infection or vaccine associated), as well as changes in the severity of SARS-CoV-2 variants. These findings have implications for the selection of endpoints in future trials, as it may become more difficult to observe benefits in terms of symptom duration as the pandemic continues, as shown by a recent study of nirmatrelvir/ritonavir.[2]

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With regard to severe infection, Hedberg and colleagues (Abstract 863) presented data demonstrating a reduction of in-hospital mortality from a multinational cohort through the various COVID-19 waves, particularly during the Omicron period. In addition to the changing severity of the virus, this likely also reflects a combination of preexisting immunity, a larger armamentarium of treatments, and greater clinical experience in managing these patients.

Vaccine breakthrough infections and reinfections. Several studies addressed preexisting immunity to SARS-CoV-2 infection from vaccination or prior infection. Butt and colleagues (Abstract 132) reported on a US Department of Veterans Affairs study of the incidence and severity of vaccine breakthrough infection compared with preexisting immunity from previous SARS-CoV-2 infection. They found that compared with reinfections among unvaccinated individuals, the breakthrough infections among individuals with preexisting vaccine-induced immunity were less common and less severe. Tapley and colleagues (Abstract 133) reported on the CoVPN (Coronavirus Prevention Network) 3008 (Ubuntu) trial, a multicenter phase III/IV study of mRNA vaccines in people with HIV (PWH) in sub-Saharan Africa. Compared with those with vaccine-induced immunity only, they found those with hybrid immunity from a combination of prior infection and vaccination had a 42% lower hazard rate for COVID-19 and a 73% lower hazard rate for severe COVID-19. Walmsley and colleagues (Abstract 857) reported on predictors of breakthrough COVID-19 from the STOPCoV (Safety and Effectiveness of Preventative COVID Vaccines) cohort, a decentralized study to compare antibody responses to COVID-19 vaccines between older and younger adults. They found that bivalent boosters matching the circulating SARS-CoV-2 strains had the strongest association of protection against breakthrough infection but were unable to identify a threshold antibody level against which individuals would be protected. Their findings suggest that antibody levels based on measurement of protection against the ancestral strain are not useful for determining the need for boosting, consistent with current clinical practice in most settings. Taken together, these studies suggest that COVID-19 immunity from the combination of vaccination and prior infection provides the most substantial protection against subsequent episodes and that ongoing booster vaccination targeting circulating variants is likely to be of benefit for the foreseeable future.

Compared with reinfections among unvaccinated individuals, the breakthrough SARS-CoV-2 infections among individuals with preexisting vaccine-induced immunity were less common and less severe

Severe COVID-19. Hospitalization for COVID-19 continues to be necessary for individuals with severe infection. Beck-Friis and colleagues (Abstract 866) compared patients with COVID-19 or influenza treated with mechanical ventilation in the intensive care unit (ICU) at a single center. They found that ICU-acquired secondary infections were more common in patients with COVID-19 than those with influenza. *Staphylococcus aureus* was overall most common in both groups, but Gram-negative infections caused most ventilator-associated lower respiratory infections in those with COVID-19. Steroid treatment was associated with a higher risk of these infections in the COVID-19 group. Disparities in the severity of COVID-19 also remain. Koenig and colleagues (Abstract 1076) assessed country-level differences in mortality from COVID-19 across the Western Hemisphere using health ministry data in models adjusted for age differences and underreporting. They found that Andean Latin American countries (eg, Peru) consistently had the highest mortality rates and that,

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overall, the differences between countries could largely be attributed to socioeconomic status (eg, gross domestic product).

Pathogenesis and Immune Responses

Viral fitness and infectivity. Benlarbi and colleagues (Abstract 146) evaluated interactions between SARS-CoV-2 spike from the D614G strain and 13 recent Omicron subvariants and host receptor angiotensin-converting enzyme 2 (ACE2) and found that Omicron subvariants have several properties that are associated with enhanced viral fitness, eg, enhanced cooperativity of spike subunit binding to ACE2. All Omicron spikes exhibited enhanced affinity to ACE2 at low temperatures,[3] and the strength of the spike-ACE2 interaction at body temperature and low temperatures was associated with viral growth rates in the human population, which suggests that improved binding of the virus to host receptors at body temperature and sub-37°C temperatures common in the nose are associated with increased transmission of the virus. Vetick and colleagues (Abstract 141) investigated the mechanism of action of the Middle East Respiratory Syndrome Coronavirus (MERS-CoV) nonstructural protein 1 (Nsp1), which is required for infectivity and reduces gene expression in host cells. The mechanism of action of SARS-CoV-2 Nsp1 was previously known.[4] A high-resolution cryogenic electron microscopy structure of MERS-CoV Nsp1 bound to the 40S ribosomal subunit and structure-guided mutagenesis studies demonstrated that the MERS-CoV Nsp1 carboxy (C)-terminal domain blocks the ribosome mRNA entry channel, similar to the SARS-CoV-2 and SARS-CoV-1 Nsp1 C-terminal domains, even though sequence conservation among these 3 betacoronavirus Nsp1s is not high. This suggests that a small molecule that inhibits Nsp1-ribosome interactions might be a feasible pan-beta-coronavirus therapeutic target.

Prolonged viral shedding. There is a rapidly expanding interest in understanding the frequency, causes, and consequences of prolonged viral shedding, which has been described in a recent community surveillance study.[5] At CROI, most of this work focused on immunocompromised populations. Li and colleagues (Abstract 134) reported on viral shedding and evolution in immunocompromised individuals. They found a hierarchy of immunocompromising conditions that conferred an increased risk of prolonged viral shedding (severe hematologic malignancy/transplant followed by B-cell deficiencies followed by more mild immunodeficiencies). These immunocompromising conditions were associated with a higher amount of SARS-CoV-2 evolution and a greater risk of emerging antiviral resistance. They attributed these findings to differences in the dynamics of antibody and cellular immune responses.

Ko and colleagues (Abstract 145) evaluated the intrahost evolution of SARS-CoV-2 spike genes in PWH and people without HIV using high-throughput single-genome amplification and long-read sequencing. PWH with CD4+ counts of less than 200 cells/μL had prolonged viral shedding and sequencing demonstrated elevated intrahost diversity early and late after symptom onset with continuous viral evolution during infection shaped by positive selection and adaptive evolution. Their work suggests that rapidly evolving spike genes in PWH with low CD4+ cell counts increase the risk for the emergence of new SARS-CoV-2 variants of concern in this population. It remains unknown whether these methods would detect differences in viral evolution between PWH with low CD4+ cell counts and people with other immunocompromising conditions. In addition to the benefits related to hybrid immunity in PWH, Tapley and colleagues (Abstract 133) also observed 22 individuals with SARS-CoV-2 shedding lasting 50 or more days, in association with unsuppressed HIV level, low CD4+ cell count, and prior tuberculosis infection. This study provides further evidence of the phenomenon of prolonged viral infection, particularly among the immunocompromised.

Elevated body mass index (BMI) is a well-known risk factor for severe acute COVID-19 and is associated with delayed clearance of SARS-CoV-2 RNA

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in the upper respiratory tract after mild infection.[6] Brooks and colleagues (Abstract 342) examined viral dynamics, mucosal immunity, microbiome composition, and neutrophil extracellular trap (NET) production in pigtail macaques fed standard monkey chow vs a high fat and high sugar (HFD) chow and subsequently infected with SARS-CoV-2 Delta variant. During acute infection, HFD animals consistently exhibited lower body mass than control animals, suggesting an effect of acute illness even though the infections were generally mild. In addition, significantly higher levels of viral and subgenomic SARS-CoV-2 RNA were detected in nasal swabs from HFD vs control animals. Strikingly, standard chow macaques cleared viral and subgenomic RNA from stool quickly, while HFD macaques maintained high levels of viral and subgenomic RNA shedding in stool through 30 days post infection. HFD was also associated with greater loss of B cells, more NET production from peripheral blood mononuclear cells (PBMCs), and significant changes in beta diversity of the gut microbiome. This work highlights that diet is an important yet overlooked contributor to virus-host kinetics and viral pathology.

Standard chow macaques cleared viral and subgenomic RNA from stool quickly, while HFD macaques maintained high levels of viral and subgenomic RNA shedding in stool through 30 days post infection

Given the challenges that prolonged shedding poses, Weinstein and colleagues (Abstract 658) conducted a randomized, double-blind, phase II study of nonhospitalized immunocompromised patients with COVID-19 who, within 5 days of symptom onset, were randomly assigned (1:1:1) to nirmatrelvir/ritonavir twice daily for 5, 10, or 15 days. Although the standard-of-care 5-day treatment appeared adequate in nonseverely immunocompromised patients, extension beyond 5 days appears to improve viral clearance in those with more severe immunocompromised (eg, hematologic malignancy), who were less likely to have rapid antigen positivity beyond 10 days if they received the longer duration of treatment (23% vs 4%-6%). No new safety signals were identified with a longer duration of treatment.

Immune responses. During acute SARS-CoV-2 infection, dendritic cells (DCs) are depleted and functionally impaired.[7,8] Bermejo Jambrina and colleagues (Abstract 340) added detail to the DC narrative by demonstrating that, while DCs exposed to the virus do not secrete cytokines or get infected, complement-opsonized SARS-CoV-2–loaded DCs will secrete type I interferons (IFNs) and interleukin (IL)-1β in a manner mediated by the mammalian target of rapamycin and dependent on nucleotide-binding oligomerization (NOD)-like receptor protein 3 (NLRP3) inflammasome activation and intracellular caspase-1 activation. In turn, these cytokines enhance virus-specific T-cell responses and mediate a Th1 response.

Two investigators presented in vitro work on innate immune responses that may limit SARS-CoV-2 replication and could point the way toward new therapeutic pathways. Garcia-Vidal (Abstract 402) examined NOD receptor 1 (NOD1) and NOD receptor 2 (NOD2), which are intracellular pattern recognition receptors whose binding leads to nuclear translocation of nuclear factor kappa-light-chain-enhancer of activated B-cells (NFκB) and the production of inflammatory cytokines. They demonstrated that NOD1 agonists activate an antiviral state in a lung epithelial cell line that inhibits viral replication. Saulle and colleagues (Abstract 401) examined the extracellular function of endoplasmic reticulum amino peptidase (ERAP) 1 and 2. ERAP1 and ERAP2 work within the endoplasmic reticulum to trim peptides before loading onto major histocompatibility complex (MHC) class I and presentation to CD8+ T cells. ERAP1 and ERAP2 can also be secreted from the cell during inflammation,

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where they can enhance myeloid-specific immunity. They demonstrated that intracellular levels of ERAP1 and ERAP2 mRNA and extracellular levels of protein are decreased in people with severe compared with mild COVID-19. They further demonstrated that exposure of neutrophils to recombinant human ERAP1 and ERAP2 enhances their cytotoxic activity and promotes neutrophil migration. Neutrophils preexposed to ERAP2 vs those mock exposed before co-culture with airway epithelial cells and SARS-CoV-2 reduced the amount of productive viral replication in epithelial cells. Together, this work helps clarify how myeloid cell immunity might contribute to the pathogenesis of severe COVID-19.

Sex-specific immune responses to acute COVID-19 are still being actively investigated. Scully and colleagues (Abstract 405) examined sex-specific differences in whole blood transcriptional profiles from people hospitalized with acute COVID-19 and found more differentially expressed genes (DEGs) in males with severe acute COVID-19 compared with mild-moderate acute COVID-19 than DEGs in females with severe vs mild-moderate acute COVID-19. Neutrophil activation and degranulation pathways were enriched in males with severe disease, while the unfolded protein response and endoplasmic reticulum pathways were enriched in females with severe disease; the set of DEGs shared between the sexes was enriched for hypoxia-associated pathways. Increased frequency of neutrophils, using CibersortX estimation of transcriptional profiles, was associated with severe disease in both sexes, further underscoring the importance of myeloid cells in the pathogenesis of COVID-19.

In the fall of 2020, it was reported that neutralizing autoantibodies to type I IFNs were a risk factor for severe acute COVID-19. These autoantibodies abrogate the antiviral activity of the corresponding type I IFN and are present at much higher frequency in people with life-threatening COVID-19 (approximately 10%) than those with asymptomatic or mild disease or healthy controls (less than 1%).[9] Bravo and colleagues (Abstract 147) used IFN reporter cells to measure the neutralization capacity of anti-IFNα2 antibodies in banked serum samples from the United Kingdom (UK) and India. Surprisingly, higher levels of neutralizing anti-IFNα2 antibodies were detected in healthy Indian people than in Indian people with mild or severe acute infection with Omicron subvariants. The authors suspect that anti-IFNα2 antibodies are elicited by COVID-19 vaccination and moderate inflammatory responses to subsequent acute infection with SARS-CoV-2. This interesting finding needs confirmation and may yield a deeper understanding of the role of anti-IFNα2 antibodies in SARS-CoV-2 pathogenesis.

Tissue-based responses. Although it is important to examine peripheral immune responses, there is much to be learned about SARS-CoV-2 pathogenesis by investigating tissue-specific immunity. Martin-Gayo and colleagues (Abstract 339) presented work on bronchoalveolar lavage fluid, peripheral blood, and lung tissue sections from people with severe or fatal COVID-19 that shed light on immune networks in lung tissue. They demonstrated that spike protein induces differentiation of monocytes into highly functional non-classic monocytes in an NFκB- and NLRP3 inflammasome-dependent manner. Additionally, induction of Th1/Th17 cells correlated with increased levels of systemic inflammatory markers including the inflammasome target ferritin.

Other biomarkers. Padilla and colleagues (Abstract 867) evaluated plasma thrombomodulin as a predictor of thrombotic events and mortality for up to 28 patients hospitalized with COVID-19. They found that elevated soluble thrombomodulin levers were associated with thrombotic events and mortality and suggested that measurements of this marker along with other standard clinical biomarkers (eg, D-dimer) could improve the risk assessment for thrombotic events. Overall, this adds to a growing understanding of the role of clotting dysfunction in acute COVID-19.

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Treatment Options

New Data Continue to Emerge on the Benefits Of Treatment for COVID-19

Nucleoside and nucleotide analogues. Remdesivir continues to be an important tool in the armamentarium for COVID-19 treatment, particularly in those with severe disease or for whom protease inhibitor treatment is contraindicated. Di Gennaro and colleagues (Abstract 666) presented real-world evidence on remdesivir use from 2 Italian referral hospitals using a propensity score-matched analysis. They found that remdesivir use was associated with a 37% reduced hazard ratio of mortality and a 75% reduced odds of mechanical ventilation. Mozaffari and colleagues (Abstract 665) reported similar real-world data on dexamethasone with and without remdesivir for the treatment of COVID-19. They conducted a study that utilized 2 methods of addressing confounders in observational research, including propensity score matching and inverse probability of treatment weighting. They confirmed the effectiveness of combination therapy in a study of over 150,000 hospitalized patients with COVID-19 in terms of reducing mortality across all groups requiring supplemental oxygen.

Salvadori and colleagues (Abstract 667) reported on a randomized trial of molnupiravir vs favipiravir in approximately 1000 vaccinated but high-risk Thai individuals infected with Omicron variants. Overall, rates of severe outcomes were very low. Although molnupiravir was not clearly more efficacious in terms of death or hospitalization, pulmonary involvement was less common in the molnupiravir arm.

Protease inhibitors. Leister-Tebbe and colleagues (Abstract 659) assessed the effect of nirmatrelvir/ritonavir on symptom duration among non-hospitalized adults in the EPIC-HR (Evaluation of Protease Inhibition for COVID-19 in High-Risk Patients) phase II/III study of the drug in unvaccinated outpatients with risk factors for progression to severe COVID-19. They found that compared with placebo, antiviral treatment reduced the time to resolution of symptoms across all subgroups (sex, age, severity, etc) by 2 to 3 days.

Mazzotta and colleagues (Abstract 661) performed a pooled analysis of randomized trials comparing drug efficacy for COVID–19 during the Omicron waves. Although the study was limited by the low number of events during the observation period, they showed that nirmatrelvir/ritonavir was superior to tixagevimab/cilagavimab during this era. Additional work presented by Mazzotta and colleagues (Abstract 662) showed that oral antivirals had the highest efficacy for reducing COVID-19-related hospitalization and death, compared with monoclonal antibodies and intravenous antivirals.

Oral antivirals had the highest efficacy for reducing COVID-19–related hospitalization and death, compared with monoclonal antibodies and intravenous antivirals

Considerations regarding resistance. There has been increasing interest in the emergence of resistance against the standard-of-care COVID-19 treatments. Tamura and colleagues (Abstract 135) presented data from the POSITIVES (Post-Vaccination Viral Characteristics) study, a non-hospitalized cohort in which they collected 3-times-weekly nasal swabs during the 2 weeks following diagnosis. They performed deep sequencing on untreated individuals and those treated with nirmatrelvir and remdesivir. Reassuringly, they found that mutations that confer resistance to these agents emerged during treatment at low frequencies and were not associated with viral rebound, suggesting that the risk of widespread emergence of resistant variants due to treatment remains low.

Zhou and colleagues (Abstract 136) investigated the mutation profiles of SARS-CoV-2 in samples

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collected in a study of co-administration of molnupiravir (a mutagenic nucleoside analogue) and nirmatrelvir/ritonavir (a 3-chymotrypsin-like protease inhibitor) to address concerns about the emergence of resistance with combination treatments. They found that co-administration of nirmatrelvir/ritonavir lowered the magnitude of the mutagenic effect of molnupiravir, likely due to the limitation of viral replication. Reassuringly, they did not find evidence to support the concern that combination treatment with these 2 agents would increase the risk of nirmatrelvir resistance emerging.

Monoclonal antibodies. Chew and colleagues (Abstract 669) presented data from the ACTIV-2 trial of amubarvimab/romlusevimab regarding viral and symptom rebound. Overall, they found no differences between the monoclonal antibody and placebo arms of the trial in terms of symptom relapse (5% in each arm) or viral rebound (4% in each arm). In the intensively sampled subpopulation, they found that monoclonal therapy was associated with less virologic rebound, which was potentially related to the long half-life of these agents.

Combination therapy. There is a movement toward the consideration of combination therapies for outpatients with SARS-CoV-2 infection. Khoo and colleagues (Abstract 668) presented data from a phase I study of nirmatrelvir/ritonavir combined with molnupiravir conducted as part of the UK AGILE (A Randomized, Multicentre, Seamless, Adaptive, Phase I Platform Study to Determine the Recommended Phase II Dose and Evaluate the Safety and Efficacy of Combination of Molnupiravir and Paxlovid for the Treatment of COVID-19) platform study. They enrolled individuals with a positive COVID-19 rapid test who had mild-to-moderate symptoms, assigning them 2:1 to combination treatment or standard of care. They reported that the combination was safe and tolerable in adults and concluded that its clinical and virologic benefits should be studied in larger phase II trials.

Other treatments. Grinspoon and colleagues (Abstract 864) presented data from the REPRIEVE (Randomized Trial to Prevent Vascular Events in HIV) trial showing that although statin therapy had no effect on COVID-19 incidence, it did reduce the risk of serious COVID-19 in individuals before vaccination. Vaccination was strongly protective in the study, and the benefit of statin therapy on COVID-19 outcomes was diminished in those who were vaccinated. Overall, this finding suggests that there are mechanisms by which widespread statin use, particularly among PWH, could have collateral benefits given the potential for waning antibody immunity to SARS-CoV-2 and the ongoing COVID-19 pandemic.

Treatment access and uptake. Using electronic health record (EHR) data from 2 states, Levy and colleagues (Abstract 660) estimated that three-quarters of COVID-19 hospitalizations in high-risk patients could have been prevented if all patients had been treated with oral antivirals. These data underscore the large treatment gap with these medications and the potential benefit of improving access to these drugs, especially among those who are older, unvaccinated, or have risk factors for progression. Mozaffari and colleagues (Abstract 663) used a healthcare database to examine disparities in treatment by race and ethnicity among patients hospitalized for COVID-19. They found that Black patients were significantly less likely to be prescribed evidence-based therapeutics for COVID-19. Clearly, additional work is needed to ensure that all those who qualify for treatment and are likely to benefit are able to access antiviral drugs.

Vaccines and Prevention

Tests and Testing Strategies

Novel tests. Nyirenda-Nyang'wa and colleagues (Abstract 1084) presented a loop-mediated isothermal amplification test in Malawi. They found that this alternative nucleic acid amplification test, which does not require specialist laboratories, had approximately 74% sensitivity and 100% specificity compared with polymerase chain reaction (PCR). They concluded that this could be useful

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in diagnostics but noted the availability of other user-friendly tests.

Testing strategies. Songane and colleagues (Abstract 1083) presented data from a randomized clinical trial in Kenya and Cameroon comparing 2 approaches to testing: "screen and test," in which individuals are offered testing if they have COVID-19 symptoms or known exposure, and "test-all," in which testing is offered regardless of screening outcome. They found that the test-all model was likely to be more cost-effective. They suggested that widespread implementation of this model could help identify priority areas for vaccination and implementation of treatment or isolation.

Prophylactics Under Development

Entry inhibition. Bunge and colleagues (Abstract 674) presented a phase I clinical trial of Q-Griffithsin, a broad-spectrum viral entry inhibitor, as a nasal spray for the prevention of SARS-CoV-2 infection. They found that administration was well tolerated and that the agent persisted in anatomic sites without systemic absorption. This agent, if demonstrated to be protective, could have a potential role as an on-demand product for the prevention of COVID-19 for high-risk individuals or in high-risk settings.

New vaccines. Collins and colleagues (Abstract 673) presented data from a first-in-human phase I trial of an adjuvanted SARS-CoV-2 spike ferritin nanoparticle vaccine, which is co-formulated with Army liposomal formulation (ALFQ) containing monophosphoryl lipid A and QS-21. Individuals vaccinated with the active agent mounted antibody responses against numerous sarbecoviruses, suggesting that this is a potential platform upon which future vaccines can be built. Building on this work, Joyce and colleagues (Abstract 387) also reported on efforts to develop novel immunogen designs and understand the breadth of sarbecovirus responses that can be elicited using adjuvanted protein or mRNA platforms. They injected mice with antigens from up to 4 different sarbecovirus strains. They found that adjuvanted protein and mRNA formats provided robust responses against all strains tested. Together, studies like these are beginning to address the anticipated need for next-generation coronavirus vaccines to confer broad protection against SARS-CoV-2 variants and novel coronaviruses that may emerge from zoonotic reservoirs in the future.

Most SARS-CoV-2 vaccines rely on the stabilization of spike glycoprotein with 2 prolines, and in general, there remains room for improvement in the stability, yield, and immunogenicity of the current generations of vaccines

Most SARS-CoV-2 vaccines rely on the stabilization of spike glycoprotein with 2 prolines, and in general, there remains room for improvement in the stability, yield, and immunogenicity of the current generations of vaccines. Ávila Nieto and colleagues (Abstract 392) evaluated new spike protein stabilization approaches with spike-V987H vaccination in mice and hamsters. They found that this mutation increased the yield of spike protein and suggested this approach could contribute to future vaccine development.

Otte and colleagues (Abstract 107) presented animal model testing of their novel single-cycle infection viruses (SCV) vaccine platform, which was published recently[10] and is comprised of 4 fragments of overlapping DNA encompassing the SARS-CoV-2 genome with deleted envelope (env) gene and, in some SCV variants, deleted orf6 and orf8 genes to downmodulate IFN responses. These are transfected into cells that express the SARS-CoV-2 envelope, so these cells produce SARS-CoV-2 virions with env-deficient genomes incapable of further rounds of replication. Syrian golden hamsters were vaccinated intranasally and then challenged with ancestral SARS-CoV-2. Animals vaccinated with SCV prior to the challenge had

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vastly decreased viral antigens in the lung, reduced virus in nasal washings, decreased IFN and IL-10 responses in the respiratory tract, and did not transmit the virus onwards to other animals, unlike mock-infected animals. When an XBB 1.5 SCV was compared with a recent mRNA vaccine formulation in a challenge model, the SCV-vaccinated animals had decreased virus in the nose. This is a promising platform that needed no adjuvant, but questions about its safety and scalability relative to mRNA vaccines remain.

Monoclonal antibodies for prevention. Cingolani and colleagues (Abstract 670) assessed tixagevimab/cilgavimab as preexposure prophylaxis in patients with hematologic malignancies. They found that although the 1-year incidence of breakthrough infections was less than 25%, the risk increased over time, especially with the emergence of more recent sublineages.

COVID-19 Vaccines

Magnitude and durability of vaccine responses. Several studies addressed questions related to the magnitude and durability of responses to SARS-CoV-2 vaccines. Garrett and colleagues (Abstract 399) presented data from the SHERPA (Sisonke Heterologous mRNA-1273 boost after prime with Ad26.COV2.S) study, a single-arm, open-label, phase III study nested in a South African implementation trial of 500,000 healthcare workers. They evaluated mRNA-1273 boost after an Ad26.COV2.S prime and found that these boosters were well tolerated, immunogenic, and effective against SARS-CoV-2 infection with Omicron variants. There was only 1 severe COVID-19 case among those who had been boosted, compared with 148 cases among the unboosted participants. Serwanga and colleagues (Abstract 394) studied the longitudinal antibody response in a vaccinated cohort in Uganda (Pfizer, AstraZeneca, Moderna). As expected, they observed a decline in the 6 months following vaccination; interestingly, they did not observe an increase in spike antibodies following the booster dose. They argued that this trend contrasts with the expected antibody dynamics observed in other settings and suggested that this serves as an important rationale for developing vaccine strategies that take into account regional differences that may be driven by biologic, social, and environmental factors.

Considerations related to immune responses. Several studies explored the complexities of hybrid immunity and the effects of vaccination on infection-associated immunity. Perez-Caballero and colleagues (Abstract 390) characterized long-term T-cell responses in hybrid immunity by assessing longitudinal PBMCs from 19 SARS-CoV-2 infected and 19 uninfected healthcare workers who underwent 3-dose mRNA vaccination and a subset that had reinfections. They found immunodominant T-cell responses to 13 regions across the SARS-CoV-2 proteome in addition to broader responses in those who had infection preceding vaccination rather than vaccination preceding infection. They suggested that their findings may have implications for future vaccine design. Pusnik and colleagues (Abstract 389) reported on immune responses to SARS-CoV-2 Omicron breakthrough infections. They found that Omicron breakthrough infections did not significantly increase the levels of neutralizing antibodies, B-cell, and T-cell responses specific for mutated regions of the Omicron surface proteins. They concluded that humoral and cellular responses against Omicron infections were predominantly a recall of preexisting vaccine-induced immunity rather than a de novo response toward mutated regions of the spike protein and raised concerns about "original antigenic sin."

Omicron breakthrough infections did not significantly increase the levels of neutralizing antibodies, B-cell, and T-cell responses specific for mutated regions of the Omicron surface proteins

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Finally, Sop and colleagues (Abstract 391) conducted a study to investigate T-cell responses in people with and without HIV who received the bivalent vaccine booster containing ancestral and Omicron BA.5 spike proteins. T-cell IFN-gamma responses to ancestral and BA.5 spike proteins were similar between spike proteins and groups of people with and without HIV. Spike peptide profiling demonstrated that the majority of spike-specific T cells target epitopes not mutated in BA.5. These cross-reactive T cells dominate the spike-specific T-cell response; less than 10% of T cells were monoreactive to BA.5 spike protein. This detailed examination of mRNA booster vaccine T-cell responses will help inform future variant vaccine strategies.

Special Populations of Interest

Acute SARS-CoV-2 Infection and Vaccination in People With HIV

The year 2024 saw an increase in abstracts at CROI specifically focused on SARS-CoV-2 pathogenesis and clinical science in populations of PWH.

Basic and translational science. Fredericks and colleagues (Abstract 341) reported one of the first animal models of HIV-SARS-CoV-2 coinfection. They infected 7 rhesus macaques (RMs) with simian immunodeficiency virus (SIV) with ancestral strain SARS-CoV-2 and found that SARS-CoV-2 infection is associated with mild disease and a transient dip in CD4+ and CD8+ cell counts although not affecting SIV plasma viral load or the CD4+/CD8+ cell ratio. Higher levels of SARS-CoV-2 RNA were found in nasal swab samples of RMs with SIV at 7 to 10 days post infection compared with historic controls without SIV. Additionally, lower neutralizing antibody responses were detected in the plasma of RMs with SIV at 14 days post infection compared with historic controls without SIV. This is concordant with a smaller study of pigtail macaques with and without SIV, in which pigtail macaques with SIV exhibited decreased neutralizing antibody responses and SARS-CoV-2–specific T-cell responses than historic controls without SIV.[11] In this study, SARS-CoV-2 kinetics were indistinguishable at all sites, including the nose. SARS-CoV-2 persisted in upper airways for at least 14 days post infection, whereas other studies found that SIV-negative RMs cleared SARS-CoV-2 from this compartment within 14 days.

Clinical outcomes. Yang and colleagues (Abstract 397) conducted a statewide cohort analysis to assess COVID-19 breakthrough infections among people with and without HIV. They assessed over 2 million individuals, approximately 8000 of whom were PWH. They did not find a higher risk of breakthrough infection among PWH than in those without HIV. Among PWH, they also found that receipt of a booster dose was protective against breakthrough infections before but not during the Omicron period. Burchell and colleagues (Abstract 860) used health administrative databases to address the severity of outcomes following infection with Omicron strains among over 20,000 people with and without HIV in Ontario, Canada. They found that SARS-CoV-2 testing and PCR-confirmed infection were about 50% higher in PWH than in a comparator cohort, although rates of hospitalization and death were more than double. Their findings were broadly consistent with the observation that HIV is an independent risk factor for more severe COVID-19 outcomes on a population level.[12]

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COVID-19 vaccination in PWH. Several studies addressed the biologic effects of vaccination in PWH. Augello and colleagues (Abstract 388) studied immune responses to the wild type/BA.4-5 bivalent

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boosters in PWH. They found that the vaccine increased receptor binding domain (RBD)-binding antibodies and T-cell polyfunctionality against the wild type and BA.4-5 variants. They argued that their findings provide further evidence for the value of boosting PWH against newly emerging strains to protect against severe disease. Tuttle and colleagues (Abstract 385) assessed antigen-specific complement activation in male PWH receiving SARS-CoV-2 mRNA vaccines compared with men without HIV in the MACS (Multicenter AIDS Cohort Study)/WIHS (Women's Interagency HIV Study) Combined Cohort Study. They found that complement activation is a mechanism of protection against SARS-CoV-2 activation, that it can have a greater impact of protection against variants in the absence of neutralizing antibody titers, and that antibodies with greater complement activation potency in men with HIV can compensate for lower antibody titers. Azzoni and colleagues (Abstract 393) conducted a study of PWH undergoing SARS-CoV-2 vaccination. They found that prior COVID-19 was associated with enhanced antibody and T-cell responses, as well as vaccine-induced antibody-dependent complement deposition (ADCD). This finding could also have implications for hybrid immunity.

Liu and colleagues (Abstract 1210) assessed COVID-19 vaccine effectiveness against different variants among a population-based HIV cohort. They observed a substantial decrease in vaccine effectiveness among PWH during the Omicron period than in other periods. Hendricks and colleagues (Abstract 1212) presented safety outcomes from a trial of a SARS-CoV-2 mRNA vaccine trial in sub-Saharan Africa. They found that the mRNA vaccines had an acceptable safety profile in PWH, people with prior SARS-CoV-2 infection, and pregnant participants. Freitas and colleagues (Abstract 396) reported on uptake of 3 or more vaccine doses in PWH in Ontario, Canada. They found an overall high uptake, with nearly two-thirds of PWH receiving at least 3 doses of a COVID-19 vaccine, compared with about half of the general population. Although no differences by sex were observed in the uptake of the initial series, the authors observed that men were more likely than women to receive booster shots and suggested that this observation warrants further investigation. Jonas and colleagues (Abstract 1209) presented data on vaccine uptake among PWH in several regions of Tanzania. They described remarkable public health, health facility, and community efforts to promote vaccine uptake and how these efforts transformed a 0.2% vaccination rate among PWH in October 2021 to nearly all age-eligible PWH being vaccinated a year later.

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Finally, Inzaule and colleagues (Abstract 199) used World Health Organization (WHO) data from the WHO Global Clinic Platform to assess the effects of COVID-19 vaccines on mortality reduction among hospitalized PWH across multiple variant waves. They found that vaccinated PWH had a substantially reduced risk of death compared with unvaccinated PWH across the pre-Delta, Delta, and Omicron waves. However, the magnitude of the effect was less than in people who were HIV negative.

Impact of the pandemic on HIV testing, care, and outcomes. Green and colleagues (Abstract 1080) examined the effects of the pandemic on HIV testing among men who have sex with men in the Los Angeles Lesbian, Gay, Bisexual, and Transgender (LGBT) Center's health services program. As expected, they found a dramatic reduction in HIV

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testing during the transition from the prepandemic to the pandemic phase, which then increased over the subsequent 2 years but did not achieve the same levels as the prepandemic phase, even with the transition to the modern era in which SARS-CoV-2 is approaching endemicity. They noted the need to understand who is not returning for testing to ensure preventative services can reach all those in need. Hershow and colleagues (Abstract 1086) assessed the effect of the pandemic on HIV testing among people who inject drugs using data from the National HIV Behavioral Surveillance (NHBS) system. They found a reduction in the use of these services after the pandemic which was more pronounced among groups including young adults and those experiencing homelessness or incarceration. They concluded that there is an ongoing need to engage people who inject drugs in services that can provide routine HIV testing. Althoff and colleagues (Abstract 1073) presented data from NA-ACCORD (North American AIDS Cohort Collaboration on Research and Design) in which they assessed the impact of the pandemic on HIV care delivery in the US and Canada. They found that with the rapid scale-up of telemedicine, half of adults in HIV care before the pandemic were able to remain engaged and maintained a high proportion of viral suppression. PWH newly engaged in HIV care in the Spring of 2020 were also able to achieve suppression even during the height of the pandemic shutdowns. Tedaldi and colleagues (1074) presented findings consistent with this observation at 8 US-based sites. They found that although there were changes in visit type after the emergence of the pandemic, patterns returned to normal over the subsequent 2 years and there was relative maintenance of viral suppression after the pandemic. Finally, Yelverton and colleagues (Abstract 1075) analyzed EHR data from 1 university clinic and found that although telehealth users were less likely to have viral loads recorded than those utilizing in-person care, the proportion of individuals with detectable viremia was similar between groups. That is not to say that COVID-19 did not have an impact on antiretroviral therapy (ART) suppression in all settings. A study by Ssuuna and colleagues (Abstract 1207) reported on the impact of the COVID-19 lockdown in Uganda on ART disruption. They found that missed HIV care appointments increased significantly after the lockdown, with 13.5% of individuals in the Rakai Community Cohort Study reporting ART disruption following the emergence of the pandemic, especially among women and younger individuals. Viral suppression was about 4% lower (95.1 vs 91%) among those who experienced COVID-related ART disruptions than in those who did not. Taken together, these studies show the flexibility and remarkable resilience of the HIV care delivery system and emphasize the importance of telehealth mechanisms as well as the potential need for mechanisms for remote monitoring in the event of future pandemics.

Pathak and colleagues (Abstract 1072) utilized data from the US Centers for Disease Control and Prevention to investigate whether COVID-19 led to excess HIV mortality. They found significant increases in HIV mortality for several groups during 2020 to 2022 compared with 2010 to 2019; most notably there were over 3000 excess HIV deaths in 2020 to 2022 and COVID-19 was listed on nearly three-quarters of those death certificates. Interestingly, Black and Hispanic decedents were less likely to have COVID-19 identified on a death certificate, possibly due to undiagnosed infection or other indirect effects of the pandemic on excess mortality.

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Acute SARS-CoV-2 infection and vaccination in children. Rungmaitree and colleagues (Abstract 671) assessed a reduced dose of tixagevimab/

cilgavimab for COVID-19 in immunocompromised children and adolescents who were less than the typical weight cutoff for administration (40 kg). They found that this dose generated good antibody levels compared with immunocompromised children above the normal weight cutoff and compared with healthy children who had received 3 SARS-CoV-2 vaccines. They argued that their results support further study of next-generation long-acting monoclonals.

Berenguer and colleagues (Abstract 398) assessed the safety and effectiveness of SARS-CoV-2 mRNA vaccines in children in Madrid, Spain. In an analysis of over 2.8 million children, they found a modest benefit to vaccination in this group. Although those who were vaccinated were less likely to develop multisystem inflammatory syndrome in children (MIS-C), one of the most dreaded complications of COVID-19 in children, the risk was overall low in both groups.

Acute SARS-CoV-2 infection and vaccination in people who are immunocompromised. Mozaffari and colleagues (Abstract 664) reported on remdesivir use in immunocompromised patients hospitalized for COVID-19 during Omicron. They found that remdesivir continues to be efficacious in reducing mortality, irrespective of supplemental oxygen requirements. They concluded that the agent continues to be the treatment of choice for this vulnerable population.

Mozaffari and colleagues (Abstract 859) reported on outcomes of COVID-19 among hospitalized kidney transplant patients. Using data from over 800 hospitals, they observed that although the COVID-19 outcomes were worse among those with compromised renal function, these individuals were less likely to receive COVID-19-specific treatments. They proposed that this therapeutic gap could be related to concerns about drug interactions and uncertainty about the renal clearance of treatments.

Guggilla and colleagues (Abstract 858) reported on the association between immunosuppressive conditions and outcomes in patients hospitalized for COVID-19. Using EHR data from approximately 10,000 individuals, they examined conditions that included common variable immunodeficiency and complement deficiency and found that patients with primary immunodeficiencies or transplants, but not HIV infection (regardless of concurrent CD4+ cell count), had worse outcomes than immunocompetent individuals. Di Chiara and colleagues (Abstracts 861 and 862) examined these associations in children and found that, although immunocompromised children are more likely to be admitted to the hospital with acute COVID-19, once admitted, they are less likely than non-immunocompromised children to require ICU admission or ventilator support. However, in the latter comparison, the difference in hospital outcomes could be attributed to significant differences in age between the groups. These studies add further nuance to the assessment of risk related to immunocompromising conditions.

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Long COVID

There is ongoing interest in long COVID (also known as PASC[13] or post-COVID condition), which continued to be a major focus of SARS-CoV-2 research at the meeting. Antar (Abstract 137) gave a mini-lecture on the progress that has been made in the last year in understanding the biologic mechanisms of the condition. Much of the original research presented at CROI 2024 showed the direction the field is likely to take in the coming years.

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Epidemiology and Natural History

Risk factors for long COVID were investigated by many groups. However, an emerging theme in the field is that risk factors and pathogenesis of long COVID may differ by sex. Evering and colleagues (Abstract 852) examined demographic, viral, and immune factors associated with long COVID in 545 people with mild-to-moderate acute COVID-19 in the placebo arm of the ACTIV-2/A5401 trial. Among women, but not men, a higher symptom score at enrollment (which occurred within 10 days of acute COVID-19 symptom onset) was associated with an increased risk of long COVID.

An emerging theme in the field is that risk factors and pathogenesis of long COVID may differ by sex

It is unclear whether SARS-CoV-2 infection triggers accelerated weight gain in survivors. In a prospective study by Atieh and colleagues (Abstract 865), 128 adults who had a prepandemic whole-body dual-energy X-ray absorptiometry (DXA) scan, half of whom had documented COVID-19 and the other half who had never had COVID-19, were followed-up with a second DXA scan. Prior COVID-19 was associated with a decline in lean body mass regardless of long COVID status. Never-COVID participants had larger annualized increases in trunk fat and total fat, and neither group experienced changes in bone mineral density.

Pathogenesis and Immune Responses

Antigen persistence. There is emerging evidence that SARS-CoV-2 genetic material and/or antigen may persist in at least some individuals following COVID-19.[14] Peluso and colleagues (Abstract 138) used single-molecule array assays (SIMOAs) to measure SARS-CoV-2 antigens (spike, nucleocapsid [N], S1) in the plasma of individuals up to 14 months following an initial COVID-19 episode. Compared with true-negative samples collected before the pandemic, they found an increased prevalence of antigen throughout this interval, which in many cases preceded SARS-CoV-2 vaccination or reinfection; antigen persistence was strongly tied to COVID-19 illness severity; a detailed report was published following the meeting.[15] Salmon and colleagues (Abstract 347) also identified spike antigen in some plasma from people with long COVID. They found that megakaryocyte frequency in circulation is increased in people with long COVID and during severe acute COVID-19. Megakaryocytes are the bone marrow resident cells that produce platelets. They identified spike protein and SARS-CoV-2 RNA in up to 35% of circulating megakaryocytes in people with long COVID. A small percentage of circulating platelets in people with long COVID contained spike or viral double-stranded RNA, and peripheral serotonin and pathway components were reduced in people with long COVID, consistent with prior observations.[16]

Salmon and colleagues found that megakaryocyte frequency in circulation is increased in people with long COVID and during severe acute COVID-19

Human herpesviruses. Reactivation of human herpesviruses (HHVs) is a potential mechanistic driver of long COVID,[17–19] but there have been few studies of viral reactivation during the acute phase of COVID-19. Cimini and colleagues (Abstract 345) measured plasma viral loads, serology, and T-cell responses to HHV in healthy donors and people with mild COVID-19 at 3 time points during acute infection. Epstein-Barr virus (EBV) viremia was common in the infected and uninfected groups (21%-35%) and cytomegalovirus (CMV) viremia was rarer but present in both groups (0%-5%). Overall, there were no differences in HHV seroprevalence, anti-HHV antibody levels, and HHV reactivation between infected and uninfected groups. IFN production after T-cell stimulation with EBV was decreased in infected compared with uninfected participants, although no differences were observed

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between the groups after stimulation with CMV antigen. This work challenges the idea that HHV reactivation during mild acute COVID-19 is a mechanistic driver of long COVID, although leaving open the possibility that HHV reactivation may drive pathology in people with severe acute COVID-19 or in people infected without previous vaccination.

Adrenal function. Two studies of long COVID at 2 to 3 and 12 months post COVID found lower levels of untimed total serum cortisol in people with long COVID at these time points than in those with quick recovery.[17,19] However, cortisol is secreted by the adrenal glands in a diurnal fashion, with peak cortisol levels found before or just after awakening in the morning with waning levels throughout the day, so comparing untimed levels may not yield insights into adrenal function. Dalhuisen and colleagues (Abstract 855) measured total serum cortisol levels at 3-6 months post COVID in 144 people with long COVID (28 of whom may go on to develop myalgic encephalomyelitis/chronic fatigue syndrome [ME/CFS] according to the Institute of Medicine's definition which requires 6 months of symptoms)[20] and 56 people with quick recovery. The study used elements of existing surveys to estimate who is likely to develop ME/CFS but did not formally assess who did develop ME/CFS. No significant differences in cortisol between long COVID and quick recovery groups were found when samples were grouped in hourly blood draw windows. However, when the long COVID group was split into those who were likely to develop ME/CFS and those who did not develop ME/CFS, those likely to have ME/CFS had lower cortisol levels at 8:00 AM to 9:00 AM and higher cortisol levels at 9:00 AM to 10:00 AM than those with quick recovery, suggesting a delayed peak in morning cortisol awakening response in people with severe long COVID or ME/CFS. This finding needs confirmation in other studies.

Microbiome studies. The interaction of the microbiome in long COVID pathogenesis is a topic of interest, especially given the recent successful clinical trial of a synbiotic preparation of *Bifidobacteria* and prebiotics in long COVID.[21] Purpura and colleagues (Abstract 563) found a decreased abundance of butyrate-producing bacteria in people who had mild acute COVID-19 and now have long COVID characterized by fatigue, cognitive difficulty, or dysautonomia compared with people with mild COVID-19 who recovered. Butyrate is a short-chain fatty acid produced from dietary fiber by gut microbiota and is considered beneficial to gut health and barrier function.

Other biomarker profiling. Thus far, it has been difficult to identify biomarkers of long COVID that translate across patient cohorts. Marmont and colleagues (Abstract 854) quantified 57 biomarkers in 364 people diagnosed with long COVID. Biomarker profiling segregated the individuals with long COVID into 1 of 6 groups. Three groups were characterized by lower levels of inflammatory biomarkers, lower BMI, younger age, and fewer comorbidities, and 3 groups were characterized by elevated inflammatory biomarkers. One group's biomarker profile reflected tissue damage, axonal damage, and coagulation and was associated with cardiac and respiratory symptoms of long COVID, suggesting that long COVID may be comprised of distinct syndromes with different pathologies and different biomarkers.

One group's biomarker profile reflected tissue damage, axonal damage, and coagulation and was associated with cardiac and respiratory symptoms of long COVID, suggesting that long COVID may be comprised of distinct syndromes with different pathologies and different biomarkers

Many studies of RNA sequencing (RNAseq) in long COVID are now underway. One such study, by Maison and colleagues (Abstract 400), examined 28 publicly available RNAseq datasets, including 23 people with long COVID, and found that long COVID was associated with increased transcription

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of the electron transport chain and ATP synthesis genes. These associations were distinct from those distinguishing acute COVID-19 from recovered and healthy controls.

Neurologic Long COVID

There is particular focus emerging on the neurologic consequences of COVID-19, given how common neurocognitive symptoms are in people with long COVID. Identifying objective correlates of these symptoms would yield insights into the pathophysiology of the condition.

Plasma markers. McAlpine and colleagues (Abstract 568) assessed plasma biomarkers of vascular inflammation in 40 people with prior severe COVID-19 and current neurologic long COVID compared with 16 healthy controls. They found elevated levels of ADAMTS13, soluble P-selectin, serum amyloid protein, fetuin A36, sVCAM-1, and α1-acid glycoprotein in the neurologic long COVID participants compared with controls, suggesting dysfunction in leukocyte adhesion and endothelial function. Some markers were higher in long COVID participants than in acute COVID-19 participants, supporting different mechanisms in acute vs post-acute COVID-19.

Cerebrospinal fluid studies. Although there have been reports of SARS-CoV-2 antigen in the plasma of people in the weeks to months after COVID-19,[15] it remains unknown whether antigen is present in cerebrospinal fluid (CSF) in the post-acute phase of people with or without long COVID. Farhadian and colleagues (Abstract 562) used the SIMOA immunoassay to quantify SARS-Cov-2 N antigen in CSF and plasma of 31 people with neuro-long COVID, 5 people hospitalized with COVID-19, 8 people with full recovery post COVID, and 20 prepandemic never-COVID controls. No N antigen was detected in the CSF or plasma of any post-acute participant, whether in the neuro-long COVID or the full recovery group. There were also no differences between acute COVID, neuro-long COVID, or full recovery post COVID-19 in an index meant to assess the fraction of N immunoglobulin G (IgG) to total IgG in CSF and plasma, suggesting that viral persistence in CSF is not common in neuro-long COVID.

Eden and colleagues (Abstract 561) examined 37 analytes implicated in neurodegenerative diseases in the CSF of 76 people post COVID, with and without long COVID, during acute, more than 3 months, and more than 12 months post infection and in the CSF of 20 healthy controls. No significant differences were seen in CSF analytes between long COVID, recovered COVID, or healthy controls at more than 3 and more than 12 months post infection, but there were significant differences in glutamate receptor 4, cathepsin F, dipeptidyl peptidase 2, beta-hexosaminidase subunit, and 14-3-3 protein zeta/delta in acute compared with post-acute patients and controls. This adds to other reports unable to identify a clear CSF biomarker of long COVID.[22]

Imaging markers. McAlpine and colleagues (Abstract 560) assessed brain perfusion via magnetic resonance imaging with arterial spin labeling in 14 people with cognitive neuro-long COVID on average 450 days from acute COVID-19 and 6 healthy controls. They found a trend of hypoperfusion in the left greater than right parietal lobes in people with neuro-long COVID and suggest that these findings may correlate with worsened attention, semantic memory impairment, and visuospatial deficits.

Treatment and Prevention

Vaccination. Two studies presented at CROI add to the growing body of evidence demonstrating that pre-COVID vaccination lowers the risk of post-COVID conditions. Malden and colleagues (Abstract 847) presented an EHR study of ~161,500 vaccinated and a similar number of matched unvaccinated people. The incidence of 12 of 13 post-COVID condition-related diagnoses was lower in the vaccinated group, except for post-COVID mental

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disorders, which appeared to occur more frequently in the vaccinated group. These findings were bolstered by a similar study by Yang and colleagues (Abstract 849) of 246,500 adults with COVID-19 in South Carolina, in which pre-COVID vaccination was associated with a lower risk of 68 individual sequelae (of 132 sequelae studied). In this study, the risk of mental, behavioral, and neurodevelopmental disorders was decreased in the vaccinated group.

Acute treatment. Berry and colleagues (Abstract 657) used the HealthVerity database to investigate whether receipt of remdesivir during hospitalization for acute COVID-19 is associated with risk of developing any 1 of 16 post-COVID conditions 3 to 9 months following hospitalization. Berry and a few of his co-authors are affiliates of Gilead Sciences, which developed remdesivir. They found that remdesivir use was associated with reduced risk of several post-COVID conditions in those older and younger than 65 years and that the effect size was stronger in the younger group.

PASC in People With HIV

US-based studies examining whether long COVID is more common in people living with HIV seem to indicate that it is,[23,24] though non-US–based studies seem to indicate that it is not.[25] Two US-based electronic medical record studies were presented at CROI assessing whether PWH are more likely to experience post-COVID conditions, and both studies found a higher risk of post-COVID condition in PWH than in people without HIV. Yang and colleagues (Abstract 848) examined the incidence of 132 post-COVID sequelae in individuals (3485 PWH and 1.3 million people without HIV) in the state of South Carolina and found that HIV is associated with higher odds ratios of most sequelae studied. Horberg and colleagues (Abstract 844) matched 749 COVID-positive PWH to 2236 COVID-positive people without HIV by month of positive test, age, race, sex, and vaccination status prior to test in the Kaiser Permanente Mid-Atlantic States health system. They found that the relative risk of post-COVID condition in PWH compared with people without HIV is 1.19 (95% CI, 1.01-1.40) when post-COVID condition is defined as 1 or more of 17 conditions incident in the 30 to 180 posttest and not present in the previous 4 years. These studies are limited by the electronic medical record study design, as incident diagnoses such as abdominal pain or nonspecific chest pain may be unrelated to long COVID, and neither study matched smoking status and 1 did not match comorbidities, rates of which are often higher in PWH. Additional comparisons of the incidence of these post-COVID conditions in PWH with and without COVID-19 would help mitigate these biases.

Ocampo and colleagues (Abstract 846) investigated long COVID frequency and risk factors in a cohort of predominantly young, male Thai PWH who began ART during acute HIV infection; the vast majority had suppressed viral loads and CD4+ counts greater than 500 cells/μL. In this cohort, cognitive and blood testing were done before and after SARS-CoV-2 infection. At 1 or more years after COVID-19, 25% of 216 PWH ever experienced long COVID (WHO definition)[26] and 7% had ongoing symptoms a median of 15 months after COVID-19. Approximately half of the participants with long COVID had symptoms lasting more than 1 year. In this cohort, the number of preinfection COVID-19 vaccinations, hospitalizations for acute COVID-19, and pre-COVID anxiety were each associated with the development of long COVID. Additionally, there were no significant differences in pre- and post-COVID-19 CD4+ cell counts, cognitive test scores, or anxiety or depression scores in those who ever or never had long COVID. Although this is an excellent study of long COVID in young men who initiated ART during acute HIV infection and

In this cohort, the number of preinfection COVID-19 vaccinations, hospitalizations for acute COVID-19, and pre-COVID anxiety were each associated with the development of long COVID

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have suppressed viral loads, these findings may not apply to more diverse populations of PWH, including those who are older, are female, started on ART more than 12 months after exposure to HIV, have comorbidities, or have low CD4+ cell counts.

PASC in Children and Adolescents

The evidence for an association of anti-SARS-CoV-2 antibodies with long COVID in adults is mixed, with some studies reporting increased levels of virus-specific antibodies in people with long COVID,[19,27] and others reporting no differences or decreased levels. There are notably fewer studies of this in children with long COVID. Izquierdo-Pujol and colleagues (Abstract 853) report lower levels of anti-RBD of spike IgG and IgA and lower levels of neutralizing antibodies in a cohort of 108 children with long COVID than in 23 controls. These findings emphasize the need for additional biologic studies to understand the condition in children.

Conclusion

The research presented at CROI 2024 shows that SARS-CoV-2 infection and long COVID remain dynamic fields of investigation. These studies advanced our knowledge of acute and PASC and provide insight into the ongoing efforts to understand the epidemiology, pathophysiology, and management of these conditions, as well as the new challenges that are arising during the ongoing pandemic.

All cited abstracts appear in the CROI 2024 Abstract eBook, available online at www.CROIconference.org

The IAS–USA will identify and resolve ahead of time any possible conflicts of interest that may influence CME activities with regard to exposition or conclusion. All financial relationships with ineligible companies for the authors and planners/reviewers are below.

Financial affiliations in the past 24 months: Dr Antar reported no relevant financial relationships with ineligible companies. (Updated May 31, 2024). *Dr Peluso reported consulting income from AstraZeneca, Gilead Sciences, Inc, and Apellis Pharmaceuticals, and research support from Aerium Therapeutics and Shionogi.* (Updated June 9, 2024)

Reviewer 1 reported consulting or advisor fees from Antiva, Assembly Biosciences, Generate Biomedicines, and Gilead Sciences, Inc. (Updated March 6, 2024) *Reviewers 2 and 3 reported no relevant financial relationships with ineligible companies.* (Updated March 6, 2024)

All relevant financial relationships with ineligible companies have been mitigated.

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Invited Review

CROI 2024: The Challenges of Sustained Viral Suppression, Advanced HIV Disease, and Ending the HIV Epidemic Targets

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Abstract: *Data on the HIV care cascade demonstrated challenges in achieving Ending the HIV Epidemic (EHE) targets across all 18 EHE focus metropolitan areas, but innovative adherence interventions using point-of-care tenofovir testing and motivational interviewing support care cascade outcomes in Namibia and South Africa, respectively. Data on treatment with long-acting injectable (LAI) antiretroviral therapy (ART) demonstrated high acceptability, retention, and virologic suppression including in groups that were not well represented in clinical trials including persons born female and persons with detectable viral loads. The adjuvanted hepatitis B vaccine appeared to be safe and appeared to be superior to conventional hepatitis B vaccines in persons with HIV (PWH) who were prior nonresponders to the hepatitis B vaccine. New therapies are in the pipeline for LAI hepatitis C medication that may cure hepatitis C with 1 injection. ACTG (AIDS Clinical Trials Group) A5359 showed that long-acting cabotegravir/rilpivirine (LA CAB/RPV) can be used effectively in PWH experiencing adherence challenges to oral ART and suggested a paradigm for treating this population with an unmet medical need. Studies on resistance mutations in SARS-COV-2 show that treatment-related emergent resistance does not appear to contribute to viral rebound or have the potential for transmitted drug resistance. The data presented on HIV and maternal and pediatric health included findings from studies on the implementation of first-line dolutegravir-based ART in pregnant and postpartum women and children, along with results of a phase I/II trial involving LA CAB/RPV in adolescents. Additionally, various abstracts addressed hypertensive disorders in HIV during pregnancy and postpartum periods, as well as the intersection of HIV and mental health in women and youth.*

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Using Publicly Available Data to Look Beyond the Care Cascade

Most US cities are not on track to reach Ending the HIV Epidemic (EHE) goals by 2030. The goals are to decrease HIV incidence by 90% through the achievement of the following targets: 95% of people with HIV (PWH) linked to care; 95% retained in care; 95% virally suppressed; and preexposure prophylaxis (PrEP) for 25% of individuals at risk for HIV. Schnure and colleagues (Abstract 1177) adapted the Johns Hopkins Epidemiological and Economic Model to examine the impact of 4 interventions: increased PrEP use, improved linkage to care, increased retention, and improved rates of viral suppression, on the incidence of HIV in metropolitan areas. They considered the effect these interventions would have if they targeted 3 different populations: Black and Hispanic men who have sex with men (MSM) and are younger than 35 years old; MSM and people who inject drugs; and the general population. The model estimated that

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achievement of all 4 EHE targets by 2030 would lead to a reduction of HIV incidence by 75% (95% credible interval [CrI], 72-78) in Baltimore, 67% (95% CrI, 63-70) in Los Angeles, and 67% (95% CrI, 64-68) if applied across all 18 EHE focus metropolitan areas. Although increases in PrEP coverage and retention in care for PWH and focusing on the risk group populations had the most impact, none of the scenarios led to achieving 90% reductions in HIV incidence. These data highlight the challenges faced by EHE efforts in the US.

Although increases in PrEP coverage and retention in care for PWH and focusing on the risk group populations had the most impact, none of the scenarios led to the achievement of 90% reductions in HIV incidence

The Atlanta, Georgia, metropolitan area in the US consists of 20 counties, 4 of which are prioritized by the EHE initiative. Piske and colleagues (Abstract 1180) examined HIV incidence and prevalence, PrEP uptake, and the distribution of relevant services including PrEP, testing, syringe service programs, and HIV care sites across all 20 counties. They also surveyed 48 stakeholders who were PWH, advocates, primary care or community-based organizations, or health department employees to assess service availability, needs, and infrastructure. Their findings highlight known health disparities, such as the disproportionate impact of the epidemic among Black people, but also allow the identification of geographic variations. Five counties outside of those prioritized by EHE accounted for 16% of the Atlanta metropolitan area's new HIV diagnoses in 2021, but fewer than 9% of HIV testing sites and 7% of PrEP sites are located within these counties. Survey respondents also described challenges with access to HIV self-tests, mobile clinic testing, case management and navigation, and many other services. They also focused on the lack of staffing and infrastructure to address clients' needs. These findings suggest that an exclusive focus on EHE-prioritized counties may miss areas needing HIV prevention and care services to meet EHE goals.

De Waal and colleagues (Abstract 1046) from the IeDEA (International Epidemiology Databases to Evaluate AIDS) cohort explored trends in CD4+ T-cell count at initiation of antiretroviral therapy (ART) and prevalence of CD4+ counts less than 200 cells/μL in a global cohort of 1,355,104 PWH between 2005 and 2019. They found geographic variations in the availability of CD4+ T-cell count at ART initiation, which was available for 58%-86% of patients globally in 2005. In North America, Latin America, Asia-Pacific, and South Africa, availability remained stable at 61%-86% in 2019. In other regions of sub-Saharan Africa, including sites in East, West, Central, and Southern Africa, CD4+ T-cell count availability at initiation of ART declined to 13%-53% by 2019. The prevalence of CD4+ counts less than 200 cells/μL declined over time from 54%-90% globally in 2005 to 30%-45% in 2019. CD4+ counts less than 200 cells/μL were more common among men in sub-Saharan Africa, but not in other regions, and in those older than 45 years globally. The investigators did not speculate as to why CD4+ T-cell count measurements at initiation of ART have declined in some regions. The fact that more than one-third of individuals being tested have CD4+ counts below 200 cells/μL suggests that testing in this context is still clinically important and should be encouraged, particularly in sub-Saharan Africa.

To understand the durability of viral suppression at a national level in South Africa, Lauren and colleagues (Abstract 1200) created a unique patient identifier to allow longitudinal analysis of individual-level data within the National Health Laboratory Service, which performs viral load (VL) testing for South Africa's public-sector HIV program. They analyzed data from 2,383,871 PWH aged 15 to 59 years who had VL measurements of less than 200 copies/mL between March 2015 and September 2016, and their primary outcome was a VL suppression to less than 200 copies/mL at 6 to 18 months after the baseline suppressed VL. Overall, 73% of the cohort had VL measurements at 12 months, and 87% of those had VL suppression. Lower rates of 12-month VL monitoring were seen among those newly in care (60%) and those aged 15 to 24 years (65% for women and 67% for men). Lower rates of VL suppression at 12 months were seen in those with prebaseline VLs greater than 200 copies/mL (74%-78%) and in men aged 15 to 24 years (67%). No tests of statistical significance of these differences were performed. The authors note that overall, viral suppression in the cohort was durable and 95% had VLs less than 1000 copies/mL. However, the fact that 27% of individuals are missing the outcome measurement is a limitation. If those missing outcomes are assumed to be unsuppressed, then the overall rate of viral suppression at 12 months is 63.5%, and lower

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for those aged 15 to 24 years (56% for women and 53% for men).

Longitudinal viral suppression data in South Africa were also examined by Keene and colleagues (Abstract 1199) in a cohort of 68,888 PWH aged 15 years or older

Treatment interruptions are common, most often occur in the first 6 months after the start of ART, and lead to lower rates of viral suppression after restart

on ART and followed in 2 South African townships for at least 12 months. They used routine health data to define treatment interruptions as more than 90 days late for an expected visit or no visit within 180 days of database closure on September 30, 2022. The cumulative incidence of interruptions after 5 years on ART was 71% (95% CI, 71-72). The median number of treatment interruptions was 1 (interquartile range [IQR], 1-2) with a median time between initiation or restart to interruption of 4 months (IQR, 1-9). Most PWH in the cohort returned to care (73%; 95% CI, 72-73) after a median of 7 months. However, 1 year after restarting ART, only 29% had VL measurements less than 50 copies/mL. The investigators conclude that treatment interruption is very common, often happens within the first 6 months of ART, and is associated with much lower rates of viral suppression after restart. These data suggest that those returning to care require additional intervention and support.

Martin and colleagues (Abstract 1037) also used routine health data from the US Enhanced HIV/AIDS Reporting System (eHARS) to examine the risk for rebound viremia among PWH newly diagnosed with HIV between July 2017 and April 2023 in San Diego County, California. Their primary outcome, VL greater than 200 copies/mL after viral suppression to 50 copies/mL or less at any point after diagnosis occurred in 302 (12%) of the 2515 persons in the cohort. Survival analysis demonstrated that a shorter time to rebound viremia was seen in those with younger age at diagnosis (P=.006); Black or Hispanic race/ethnicity (P=.03); female gender (P=.005); injection drug use as an HIV transmission risk factor (P=.001); and advanced HIV at the time of diagnosis (P<.001) beyond 75 weeks of median follow-up time. Of note, the presence of low-level viremia (50-200 copies/mL) was also a predictor of rebound viremia (P<.001). The investigators suggest the development of a risk score to identify PWH at risk for rebound viremia, although it is unclear from this analysis whether the factors associated with the risk of viremia would be cumulative when combined into a risk score.

HIV Care Cascade Outcomes Among Key Populations

Several sessions examined HIV care cascade outcomes among marginalized groups or key populations. Sumner and colleagues (Abstract 1019) used data from the US Centers for Disease Control and Prevention's National HIV Surveillance System (NHHS) database to examine the impact of income and racial segregation on HIV care outcomes. They used a metric called the Index of Concentration at the Extremes (ICE), which measures the level of marginalized vs privileged persons in each census tract. To use race as an example, the metric tracks Black/White racial segregation and is the number of White persons subtracted from the number of Black persons in a census track divided by the total population. This gives a measurement from –1 to 1 where the most privileged quintile is the reference group. The investigators developed 3 ICE metrics as predictors: ICE for income, comparing persons whose income is $100,000/year or higher with those less than $25,000/year; ICE for race as described; and ICE for income and race, comparing number of White persons with income of $100,000/year or higher with Black persons with incomes less than $25,000/year. Among a cohort of 32,529 PWH who received their diagnosis in 2021, investigators found a statistically significant higher likelihood of HIV diagnosis in all 3 ICE metrics: for race, the rate ratio (RR) was 10.13; for income, the RR was 3.86; and for income and race, the RR was 5.92 (95% CI excluded 1 for all 3 metrics). Differences in linkage to care and in viral suppression were also noted by ICE, with statistically significant differences seen between quintiles 1 and 5 for income, race, and the combined income and race metric for both outcomes. These data suggest that poor care cascade outcomes are concentrated in census tracks experiencing racial and economic segregation and highlight the need for structural interventions in these communities.

Understanding HIV care outcomes among Hispanic/Latino persons can be challenging because most analyses ignore significant diversity within the Hispanic/

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Latino community. Morales and colleagues (Abstract 1016) also used NHHS data on birthplace and social vulnerability index by census track to differentiate data on diagnosis, linkage to care, and viral suppression amongst those identified as Hispanic/Latino in 2021. Outcomes included nonlinkage to medical care, defined as no documentation of CD4+ T-cell count or VL test within 1 month of HIV diagnosis and nonviral suppression, defined as no VL test less than 200 copies/mL within 6 months of HIV diagnosis. The investigators found that among 5056 Latino persons diagnosed with HIV in 2021, 51.5% were born in the US (excluding Puerto Rico), 17.3% in Mexico, 11.1% in South America, 10.9% in the Caribbean (including Puerto Rico and Cuba), and 9.2% in Central America. Compared with those born in the US, decreased prevalence of nonlinkage to care (adjusted prevalence ratio [aPR], 0.72; 95% CI, 0.58-0.90 and aPR, 0.78; 95% CI, 0.61-1.00, respectively), adjusting for age and gender. Lower prevalence of nonviral suppression (aPR, 0.75; 95% CI, 0.64-0.87), South America (aPR, 0.69; 95% CI, 0.57-0.84), and the Caribbean (aPR, 0.48; 95% CI, 0.30-0.77, excluding Puerto Rico and Cuba). Interestingly, neither care outcome was significantly different by social vulnerability index quartiles. These data demonstrate the significant heterogeneity in care outcomes by place of birth in this key population and suggest a focus on supporting linkage to care and viral suppression for Latinos born in the US.

A session moderated by del Rio and el Sadr (Symposium 07) on HIV care and services among refugees, displaced persons, and marginalized populations underscored the specific challenges that arise from forced migration, conflict, violence, and other factors leading to displaced persons. Tessema (Abstract 38) from the International Rescue Committee noted that, globally, more than 110 million people have been forcibly displaced from their homes, creating a need to address HIV prevention and care to ensure individual and public health among displaced persons and receiving communities. Parczewski and colleagues (Abstract 1069) from the Pomeranian Medical University in Poland discussed lessons learned from the influx of Ukrainian refugees over the past 2 years. He emphasized the need to scale up the structure for routine care, including vaccinations, mental health, and unmet medical needs, while simultaneously adjusting to the different demographics of the Ukrainian HIV epidemic. They quickly expanded their capacity to care for women, providing HIV-focused gynecologic care with interpretation services, and educating providers in the care of advanced HIV disease and multidrug-resistant (MDR) tuberculosis.

Sued and colleagues (Abstract 1182) from the Pan American Health Organization discussed challenges faced throughout Latin America with migration and displaced populations. Because the HIV prevalence among migrants in Latin America is 3 times more than the general population, Sued promotes free access to care for these communities and rapid integration of people into their receiving countries, including allowing them to work. He also stressed the importance of having migrants involved in the design of care and response programs to avoid unintentional victimization. Finally, Panfilova discussed her experiences as a refugee living with HIV who was forced to flee from Kyiv to Berlin, Germany. She works for the Teenergizer organization, which reached 10,000 young people in Ukraine in February and provides peer counseling and mental health support. Challenges their organization have noted for this community include lack of access to HIV testing because of the need for parental consent, PWH in areas occupied by Russian forces needing Russian passports to access ART, and an exacerbation of mental health issues because of the uncertainty of living in a war zone. The robust discussion that followed covered the intersection of advocacy for the human rights of dis placed persons and structures needed for HIV prevention and care.

Using Novel Interventions to Support Adherence

Several posters of note highlighted new interventions to support adherence to ART. Bikinesi and colleagues (Abstract 1198) integrated a point-of-care (POC) urine tenofovir assay into an existing enhanced adherence counseling (EAC) program across 42 HIV care clinics in Namibia. They enrolled 211 participants with a VL more than 1000 copies/mL after 1 round of EAC into an intervention that included POC urine testing at every monthly ART pick-up, with counseling tailored to the test results. If viral suppression was not achieved after

Point-of-care urine tenofovir test-informed counseling led to greater rates of viral suppression than adherence counseling alone

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3 months, an additional 9 months of POC testing plus EAC were provided. They used preintervention data as a comparison, which is a limitation of the analysis. Overall, they found that 87% of participants in the intervention attained viral suppression after 3 months, and 93% did by 9 months, which was statistically significantly different from the preintervention rates of 33% viral suppression with EAC alone (P<.001 for both). The month 3 urine POC testing was 98% sensitive but only 59% specific as a predictor of viral suppression. When asked whether they would want to use the POC urine test in future EAC, 88% of participants and 95% of providers agreed or strongly agreed, implying high acceptability of the intervention. Provided that POC urine tenofovir tests can be provided at low cost, this intervention could improve viral suppression rates over EAC alone.

Using a cluster randomized trial design, Onoya and colleagues (Abstract 1201) examined the impact of motivational interviewing training for a program on HIV treatment for lay counselors in 554 adults living with HIV in the first 12 months after diagnosis. Four clinics were randomized to the intervention training, which included recorded counseling sessions to assess the counselors' technical skills in motivational interviewing, and 4 received standard of care (SOC). Although there was no statistically significant difference in overall retention rate between the intervention and control clinics, Poisson regression revealed an increase in retention rates in the clinic proportional to increasing motivational interview skill levels of the clinic counselors. Viral suppression to less than 50 copies/mL at 12 months increased more in the intervention group (RR, 1.4; 95% CI, 1.1-1.8) than in the control group. These data suggest that a rigorous motivational interviewing training program for lay counselors can have an impact on viral suppression in the first 12 months after HIV diagnosis.

Treatment With Long-Acting Injectable ART in the "Real World"

Approved in 2021, long-acting cabotegravir/rilpivirine (LA CAB/RPV) offers an alternative for individuals facing challenges with adherence to daily oral regimens. Despite its potential, the uptake of LA CAB/RPV has been slow. One reason for delays has been insurance-related barriers. In a review of state-by-state AIDS Drug Assistance Program (ADAP) coverage presented by Zalla and colleagues (Abstract 1245), they identified a substantial disparity in insurance coverage between LA CAB/RPV and more conventional oral therapies. Their analysis revealed that only 78% of state ADAP provide coverage for LA CAB/RPV, compared with the 92%-98% coverage rates for the latest oral ART options. Furthermore, when looking at characteristics of ADAP clients from the Ryan White annual client-level report, they found that up to 20% of ADAP clients did not have access to LA CAB/RPV and that low-income, Hispanic, and American Indian/Alaskan Native people were more likely to live in states without ADAP coverage of LA CAB/RPV, emphasizing how this discrepancy in access is particularly detrimental to low-income and racially minoritized populations with HIV, who already have lower rates of viral suppression.

In hypothetical scenarios and clinical trials, LA CAB/RPV has been highly acceptable across many clinic settings and populations. Orkin and colleagues (Abstract 621) presented their work from the ILANA (Implementing Long-Acting Novel Antiretrovirals) study, a 1-year implementation research study based in the United Kingdom (UK) that examined bimonthly injectable ART in the clinic for the first 6 months followed by in the home or community in months 6 to 12. They conducted a prespecified month-4 analysis to examine feasibility and acceptability through validated implementation questionnaires. The 114 participants (55% female; 51% Black; 68% heterosexual; median time on ART, 11 years) found the injections to be feasible, acceptable, appropriate, and preferable to oral ART. Among this population, 99% of injections were given within the window, with only 5 discontinuations, and 96% of participants preferred LA CAB/RPV to oral ART.

Luc and colleagues (Abstract 622) report similar findings in a survey conducted among 150 patients in Chicago (85% aged >30 years; 24% Hispanic; 67% Black; 36% cis-female; 55% heterosexual). Among individuals receiving at least 1 dose of LA CAB/RPV, the majority (88.7%) reported switching to avoid oral medication regimens and reported a high mean HIV treatment satisfaction score of 6.7 out of 7. Although most participants expressed satisfaction with treatment, 98% experienced injection site pain, which for 47%, decreased after the initial injection. Despite LA CAB/RPV being a favorable option for many, it is noteworthy that although 61% of participants experienced unexpected improvements in aspects of their lives post initiation of LA CAB/RPV, 10% of participants (n=15) reported that an aspect of their life unexpectedly got worse.

The inclusion of a significant proportion of female participants, with 53% in the ILANA study and 36% in

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the Chicago cohort, represents critical real-world data about female preferences. Elias and colleagues (Abstract 620) conducted a scoping review to evaluate the inclusion of cis and trans women and nonbinary persons in clinical trials to evaluate LAI agents. They found that only 19% of participants in LAI studies were female. This finding is relevant given the findings of Philbin and colleagues (Abstract 1237), who surveyed 1078 women with HIV from the MACS (Multicenter AIDS Cohort Study)/WIHS (Women's Interagency Health Study) cohort and discovered a preference for LAI ART among those who were younger, living in certain cities, and who had lower self-reported (<95%) adherence to oral ART regimens. Although this preference underscores the potential of LAI ART to meet the unique needs of women, it also raises concerns about exacerbating health disparities, especially considering the current prerequisite of viral suppression for initiating LA CAB/RPV.

Addressing adherence concerns, particularly missed and late injections, is crucial for expanding LAI ART to populations that stand to benefit the most. Hill and colleagues (Abstract 624) conducted a retrospective cohort study among 287 adults (median age, 42 years; 20% Black, 38% Hispanic; 15% female at birth) receiving LAI CAB/RPV in San Diego. They collected data on demographics, risk factors for injection visit no-shows, and timing of no-show visits. They used a Cox proportional hazards regression model to discern predictors of failure to attend injection appointments or delays in receiving injections. The study identified 2803 injection visits (median, 9/participant) with late injections of 1 to 3 instances/patient, with delays spanning from 1 to 59 days. Notably, 42 of the 44 late injections were fewer than 14 days late, and in 13 out of 44 cases, an oral bridge was utilized. After adjusting for age, the factors independently correlated with delayed injections included male sex at birth (hazard ratio [HR], 9.18; 95% CI, 1.26-66.9) and younger age (HR, 0.98; 95% CI, 0.95-1.00). They found that missed clinic visits in the year before transitioning to LAI CAB/RPV were linked to at least 1 missed injection appointment, yet these missed visits did not correlate with delayed injections, underscoring the importance of having the support necessary to reschedule missed injections. Moreover, missed and late injections were not connected to detectable VLs or virologic failure.

Despite adherence challenges, "real-world" studies underscore the effectiveness of LA CAB/RPV in sustaining viral suppression levels among those initiating treatment with undetectable VLs. Eron and colleagues (Abstract 625) reported that among 278 ART-experienced individuals in the Trio Health cohort (median age, 44 years; 36% Black, 20% Hispanic; 17% female) who commenced LA CAB/RPV, viral suppression was sustained, with less than 1% experiencing virologic failure. Similarly, Liegeon and colleagues (Abstract 1236) reported a retrospective cohort analysis of 119 persons (median age, 36 years; 30% cis-women; 85% Black) with HIV referred for LAI CAB/RPV at an academic Ryan White clinic in Chicago. Among patients referred, uptake was high (71%), with a high retention rate (86% at a median of 8 months) among virally suppressed individuals. Furthermore, in a Federally Qualified Health Center setting in Washington, DC, Fessler and colleagues (Abstract 1235) detailed their efforts to establish an LA CAB/RPV program, serving 184 patients who received a total of 1096 doses. They reported that 97% of doses were administered within the prescribed treatment window with 97% virologic suppression (VL <200 copies/mL). The collective evidence from diverse sites demonstrates the efficacy of LA CAB/RPV in sustaining viral suppression beyond a clinical trial environment.

Maguire and colleagues (Abstract 626) addressed concerns regarding the risk of virologic failure associated with LA CAB/RPV in individuals with a body mass index (BMI) exceeding 30 kg/m² through a retrospective multicenter cohort study. The study spanned 5 medical centers and included 369 participants (median age, 40 years; 80% born male), 40.1% of whom had a BMI higher than 30 kg/m². Over a median treatment duration of 202 days, the incidence of HIV VL higher than 50 copies/mL was comparable between participants with a BMI higher than 30 kg/m² (4.8%) and those with a BMI lower then 30 (5.4%). Correspondingly, virologic failure rates were observed to be 0.8% in the higher BMI group compared with 1.04% in the lower BMI group, representing no significant difference in the risk of virologic failure across the different BMI categories. This study provides reassurance regarding the efficacy of LA CAB/RPV across a wide range of BMI values.

Most of the research on LA CAB/RPV has focused on individuals initiating treatment while virally suppressed, consistent with the initial clinical trials. However, Hickey and colleagues (Abstract 628) described the outcomes of a cohort of 59 patients from the Ward 86 clinic in San Francisco who commenced LA CAB/RPV therapy with a VL higher than 50 copies/mL and followed for more than 56 weeks. Notably, 70% of these patients had an initial VL of 10,000 copies/mL or higher. Late injections were frequent, with 28% occurring more than 7 days late, and 14% more than 14 days late; 3 patients were

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lost to follow-up. After 48 weeks, 81% achieved viral suppression (VL <50 copies/mL) on LA CAB/RPV alone, although the figure rose to 93% when LA CAB/RPV was combined with an additional antiretroviral agent. Nonetheless, 3 patients experienced virologic failure accompanied by the emergence of resistance, including 1 with an integrase inhibitor mutation (R263K). The success in reaching virologic suppression aligns with those reported by Fessler and colleagues (Abstract 1235), who initiated LA CAB/RPV treatment in 31 patients with a VL higher than 50 copies/mL (median, 160 copies/mL), with 94% achieving VL suppression. These studies highlight the potential for this intervention to be used in populations with adherence challenges in the clinic setting.

However, current LAI with LA CAB/RPV is only an option for those without known nonnucleoside reverse transcriptase inhibitor (NNRTI) mutations. Gandhi and colleagues (Abstract 629) explored the combination of LA lenacapavir (LEN), a capsid inhibitor administered every 6 months with LA CAB to address the treatment needs of individuals with adherence challenges and NNRTI resistance. This is a common concern in low- and middle-income countries where NNRTI resistance is extremely common. In a retrospective review, which included 4 clinics, 34 patients on LA CAB/LEN were identified (median age, 48 years; 76% cis-male; 41% Black, 38% Latinx). In this cohort, they noted an increase in virologic suppression was observed, with 94% (32/34) achieving VLs less than 75 copies/mL after commencing LEN, compared with the 47% suppression rate at baseline. This initial case series lays the groundwork for future clinical trials to assess the efficacy of the LA CAB/LEN regimen in individuals with NNRTI resistance.

Rollout of ART in Low- or Middle-Income Countries

In 2019, South Africa endorsed tenofovir/lamivudine/dolutegravir (TLD) as first-line ART, transitioning from efavirenz (EFV)-based regimens. McCluskey and col leagues (Abstract 648) describe a study in KwaZulu-Natal that assessed the efficacy, tolerability, viral suppression, and retention among individuals switching from EFV- to TLD-based ART. The cohort comprised 499 participants (80% female), with a median pretransition ART duration of 6 years. TLD was well tolerated with a discontinuation rate of less than 1%. However, only 81% of participants were virally suppressed and in care at 48 weeks, primarily due to participants being lost from care or deceased, highlighting the importance of adherence and retention efforts.

The 2015 World Health Organization (WHO) guidelines call for immediate ART (iART) initiation in all PWH irrespective of CD4+ T-cell count due to individual- and population-level benefits. Crabtree-Ramírez and colleagues (Abstract 649) explored rapid (<7 days) and early (<14 days) ART initiation rates within CCASAnet (The Caribbean, Central and South America Network for HIV Epidemiology) sites, examining associated factors and assessing survival outcomes. They retrospectively evaluated 9173 PWH, 92.7% initiated ART, with rapid initiation (≤7 days) in 37% and early initiation (≤14 days) in 49% of cases. Notably, most early and rapid ART initiations occurred in Haiti, representing 88% and 83%, respectively. Outside of Haiti, the rates of early ART varied significantly, with Argentina at 3%, Chile at 5.4%, Peru at 6.8%, Mexico at 25%, Brazil at 34%, Honduras at 44%, and Haiti at 79% overall. Factors contributing to early ART initiation included recent diagnosis, female gender, nonheterosexual HIV acquisition modes, and higher education levels. This analysis highlights the considerable diversity in ART initiation timelines across CCASAnet sites, driven by variances in health system policies and strategies, and highlights the need for further global efforts to expand rapid and early ART.

Differentiated Service Delivery

Leveraging the WHO's endorsement of multimonth dispensing (MMD), numerous sites worldwide are exploring reducing the frequency of health care visits for PWH. For example, during the COVID-19 pandemic, South Africa extended ART prescriptions from 6 to 12 months to reduce health care visits. Patten and colleagues (Abstract 1246), using data from the Aid for AIDS insurance provider, assess the impact of these changes on HIV viral suppression rates within the private health sector. Analyzing data from more than 73,000 adults (51% aged 30-44 years; ~59% female) on ART between November 2019 and November 2022. An interrupted time-series analysis identified a slight improvement in viral suppression with the 12-month prescription policy, with a reduction in virologic suppression after returning to an every-6-month prescription. These findings suggest that extended prescription periods can maintain, if not improve, viral suppression and offer options for delivery models that reduce clinic visits.

In Mozambique, Saura-Lazaro and colleagues (Abstract 1248) retrospectively analyzed data from a cohort of more than 7378 PWH (median age, 35 years; 25% adolescent; 57% female) in the Manhiça District from January 2018 to March 2021. Fifty-nine percent of

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adolescents and 62% of adults were enrolled in 3-month dose dispensing, primarily during COVID-19, and followed for a median of 11 and 10 months, respectively. Established and early enrollers had lower rates of attrition. For established adolescent enrollers, the adjusted hazard ratio (aHR) was 0.65 (95% CI, 0.54-0.78), and for adults, it was 0.50 (95% CI, 0.44-0.56); among early enrollers, adolescents had an aHR of 0.70 (95% CI, 0.58-0.85), whereas adults had an aHR of 0.63 (95% CI, 0.57-0.70). Male sex and care in lower-volume facilities were associated with increased attrition, although longer ART duration and age 45 years or older were associated with decreased attrition.

In Central Uganda's Mubende region, Mugisa and colleagues (Abstract 1247) reviewed data from 19,000 PWH (median age, 37 years; 67% female), 97% of whom were virally suppressed (VL <1000 copies/mL), using the Uganda Electronic Medical Records System. MMD participants had markedly lower odds of VL nonsuppression, with an adjusted odds ratio (aOR) of 0.09 (95% CI, 0.07-0.12). However, MMD users with advanced HIV or on second-line ART regimens had increased odds of nonsuppression, with aORs of 4.71 (95% CI, 2.82-7.86) and 2.31 (95% CI, 1.69-3.16), respectively.

These findings advocate for the strategic use of MMD and targeted support services to amplify its benefits across diverse patient cohorts, aligning with global efforts to sustain HIV treatment adherence and retention.

Advances in Hepatitis B, C, and D: Epidemiology and Treatment

Hepatitis B

Hepatitis B vaccination. Marks and colleagues (Abstract 209) presented data in a late-breaking session from the AIDS Clinical Trial Group (ACTG) 5379 (BEeHIVe) study looking at PWH who were previously hepatitis B virus (HBV) vaccine nonresponders and their response to an adjuvanted HBV vaccine with CpG (HepB-CpG). They had previously reported on the efficacy of HepB-CpG in PWH who had not previously been vaccinated.[1] They had 2 aims: to determine noninferiority based on antibody titers after 2 doses of HepB-CpG compared with 3 doses of conventional HBV vaccine and to determine superiority based on antibody titers of 3 doses of HepB-CpG compared with 3 doses of conventional HBV vaccine. Participants in the study had to have evidence of prior HBV vaccination (but not HBV infection) with HBV surface antibody (HBsAg) titers less than 10 mIU/mL within 45 days of entering the study. They also had to be on ART for longer than 56 days prior to the study with an HIV VL less than 1000 copies/mL and a CD4+ count greater than 100 cells/µL. Patients with uncontrolled diabetes with a hemoglobin A1c (HbA1c) greater than 9.0% and advanced chronic disease were excluded. They enrolled 561 patients across 41 sites in 10 countries from December 2020 through February 2023. Thirty-six percent of the participants were female at birth, and the majority of participants were non-White. Median CD4+ count was above 600 cells/µL across all groups, and 94% of participants had viral suppression (HIV VL <40 copies/mL).

Two- and 3-dose HepB-CpG vaccines were superior to the conventional 3-dose series of vaccines in PWH; in particular, 3-dose HepB-CpG was able to achieve high proportions of titers greater than 100 mIU/mL

A seroprotection response (SPR), defined as an HBsAb titer greater than 10 mIU/mL, was achieved in 99% of participants in the 3-dose HepB-CpG arm, compared with 93.1% in the 2-dose HepB-CpG arm and 80.6% of participants in the 3-dose conventional vaccine arm. In their analysis, the 2-dose HepB-CpG arm not only achieved noninferiority compared with the conventional vaccine series, it also achieved superiority with SPR differences of 12.5% (97.5% CI, 4.1-20.9). The 3-dose HepB-CpG arm had an SPR difference of 18.4% (97.5% CI, 10.4-26.2) compared with the conventional vaccine series. The proportion of patients who achieved SPR over time was very similar in the 2 HepB-CpG arms until week 24 (timing of dose 3 of HepB-CpG vaccine). A higher proportion of participants achieved SPR and more quickly, compared with the conventional vaccine. Quantitative HBsAb titers higher than 1000 mIU/mL at week 28 were achieved in 78% of participants in the 3-dose HepB-CpG arm, and 97% achieved HBsAb titers higher than 100 mIU/mL. Twenty-six percent of participants in the 2-dose HepB-CpG arm achieved titers higher than 1000 mIU/mL and 70% achieved titers higher than 100 mIU/mL. In subgroup analyses looking at responses to vaccine, 3-dose HepB-CpG was able to produce a good antibody response in older participants,

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those with diabetes, and lower CD4+ counts and detectable HIV VL (although study numbers of participants with low CD4+ counts and detectable HIV viremia were very low). No 95% CIs were reported for subgroup analyses.

No alarming safety signals or deaths were attributed to HepB-CpG vaccine. Limitations of the study as mentioned by the presenter include the low number of patients enrolled with low CD4+ counts and detectable HIV viremia, so the presented results are not generalizable to these populations. Ultimately, 2- and 3-dose HepB-CpG vaccines were superior to the conventional 3-dose series of vaccines in PWH and in particular, 3-dose HepB-CpG was able to achieve high proportions of titers greater than 100 mIU/mL. Future analyses at week 72 are forthcoming to assess the durability of the seroprotective response.

Hung (Abstract 729) presented data on the loss of HBV seroprotection in PWH in Taiwan who were randomly assigned to groups that received double doses of the 3-dose series conventional HBV vaccine vs the standard 3-dose series. During a median follow-up of about 2 years, they observed higher rates of loss of seroprotection in the standard dose group than in the double dose group (21.4% vs 10.4%; *P*=.01) and more frequent loss of seroprotection with titers greater than 100 mIU/mL (41.7% vs 20.0%; *P*<.001). If HepB-CpG vaccines are not available in more resource-limited settings, then double-dose conventional HBV remains an option to increase HBV seropositivity and protection in PWH.

HBV epidemiology. Yendewa and colleagues (Abstract 730) assessed COVID-19 clinical outcomes in persons with chronic HBV and found significantly increased rates of 90-day mortality (odds ratio [OR], 1.21; 95% CI, 1.02-1.44; *P*=.032) and intensive care unit (ICU) admission (OR, 1.39; 95% CI, 1.17-1.66; *P*<.001) compared with HBV-negative controls. COVID-19 vaccination was associated with lower odds of mortality at 30 days (OR, 0.38; 95% CI, 0.22-0.66; *P*<.001) and 90 days (OR, 0.46; 95% CI, 0.31-0.70; *P*<.001) in patients with HBV. This emphasizes the importance of COVID-19 vaccination in patients with chronic inflammatory conditions, including chronic HBV.

Avihingsanon and colleagues (Abstract 732) subgroup analyses from the ALLIANCE (Bictegravir, Emtricitabine, and Tenofovir Alafenamide Versus Dolutegravir, Emtricitabine, and Tenofovir Disoproxil Fumarate for Initial Treatment of HIV-1 and Hepatitis B Coinfection) trial looking at factors associated with more favorable HBV response with bictegravir-emtricitabine-tenofovir alafenamide (BIC/FTC/TAF) compared with DTG/FTC/tenofovir disoproxil fumarate (TDF). They previously showed better HBV outcomes, such as higher rates of HBV e-antigen (HBeAg) loss and normalization of alanine transaminase (ALT), with BIC/FTC/TAF vs DTG/FTC/TDF.[2] In their analysis, there were significantly higher rates of HBeAg loss in participants on BIC/FTC/TAF who were Asian, younger than 30 years, lower baseline HBV VL less than 8 $\log_{10}$ IU/mL, higher baseline ALT, or CD4+ counts of 200 cells/µL or higher. They also observed significantly higher rates of HBsAg loss in the BIC/FTC/TAF participants who were Asian, had good study drug adherence, baseline HBV VL less than 8 $\log_{10}$ IU/mL, or had HBV genotypes B or C. This suggests that BIC/FTC/TAF may be more beneficial than DTG/FTC/TDF in these specific subgroups.

As more PWH switch to 2-drug regimens and lose anti-HBV activity, there remains some worry that some individuals with occult HBV (positive HBcAb) may reactivate. Mezzadri and colleagues (Abstract 736) looked at the association of elevation of liver function test (LFT) in PWH with occult HBV infection after switching from 3-drug to 2-drug regimens in Italy. There was no association between occult HBV infection and LFT elevation after switching to 2-drug therapy. Clemente and colleagues (Abstract 737) showed data on HBV reactivation in those with occult HBV infection who switched to 2-drug regimens with no HBV activity (DTG/RPV or CAB/RPV). The cohort of 41 patients comprised 34 individuals with both HBcAb and HBsAb positivity and 7 individuals with isolated HBcAb positivity. One out of the 7 patients with isolated HBcAb positivity reactivated 3 months after switching to LA CAB/RPV, as evidenced by a 20-fold increase in ALT and high circulating HBV DNA.

New HBV treatments. Das and colleagues (Abstract 739) showed exciting new data on LAI tenofovir prodrugs for HBV. They observed decreased HBV VLs in HBV-infected mice for up to 6 to 10 weeks after a single intramuscular injection with the tenofovir ester prodrug. Significant levels of the prodrug were detected in the plasma and muscle tissue of the mice, and significant levels of tenofovir were detected in liver tissue. This provides a promising new vehicle for LAI HBV (and HIV) therapy.

Hepatitis D Virus

Marlowe and colleagues (Abstract 724) presented data on the first hepatitis D virus (HDV) seroprevalence study nationwide in the US by examining HBsAg-positive samples from 10 regions in the US. They found a

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rate of HDV seropositivity of 1.6% across the US, with higher prevalence in certain regions including Health and Human Services (HHS) region 8 representing the West and Great Plains states, region 5 comprising the Midwest, and region 3 representing the mid-Atlantic. Chee and colleagues (Abstract 726) presented epidemiologic data on patients infected with HIV, HBV, and HDV compared with individual who were coinfected with HIV/HBV and individuals who were monoinfected with HBV. Higher rates of HDV infection were observed among HBV/HIV-coinfected individuals than in those with HBV-monoinfection (7.4% vs 6.8%; *P*<.01). They also saw higher rates of injection drug use among those with triple infection as compared with HBV/HDV infection (27.7% vs 12.8%; *P*<.01). Those with triple infection had higher rates of cirrhosis (HR, 1.2; 95% CI, 0.85-1.69) and risk of hepatic decompensation, hepatocellular carcinoma (HCC), or liver transplant (HR, 1.72; 95% CI, 0.99-3.00) than HIV/HBV coinfected individuals.

Wyles and colleagues (Abstract 735) presented 96-week data from a Phase III study looking at entry-inhibitor bulervitide (BLV) in the treatment of HDV. One hundred and fifty patients were randomly assigned into 3 arms: arm A with no HDV treatment for the first 48 weeks followed by BLV for 96 weeks; arm B with immediate lower-dose BLV (2 mg/day) for 144 weeks; or arm C with immediate higher dose BLV (10 mg/day) for 144 weeks. They had previously published 48-week data in the *New England Journal of Medicine*. Median age was similar across arms (ranging from 41 to 44 years), with similar rates of cirrhosis (47% to 48%). They saw increased efficacy (defined as undetectable HBV DNA or ≥2 $\log_{10}$ IU/mL decrease and ALT normalization) at week 96 in all arms compared with week 48 including arm A (39% vs 2%), arm B (55% vs 45%), and arm C (56% vs 48%). No serious adverse events were observed. There were 2 patients with HIV/HBV/HDV coinfections enrolled; these 2 patients were able to reach the primary endpoint at week 96 requiring no changes to ART. BLV is a needed new therapy for treatment of HDV but more studies need to be conducted in triply infected individuals with HIV, HBV, and HDV.

Hepatitis C

New treatments. Arshad and colleagues (Abstract 161) presented exciting work on the pharmacokinetics of an LAI hepatitis C virus (HCV) antiviral agent. They coformulated the pan-genotypic antiviral regimen of glecaprevir-pibrentasvir (GLE/PIB) into an LA formula and injected these into the thigh muscles of adult rats. Subsequently, they examined the pharmacokinetics from tail vein samples and liver tissue. They observed dose-dependent increases in the area under the curve (AUC) concentration with increasing doses of the injectable formulation. At doses of 37.5 mg and 75 mg of each drug, they observed levels greater than the median trough level of oral GLE/PIB in humans; even the lowest dose of 18.75 mg maintained a level that was greater than the trough level reported in humans for 11 weeks. Plasma concentrations for each drug were improved when administered together in a fixed-dose combination. Based on pharmacokinetic modeling, they hypothesized that an ideal GLE:PIV ratio would be 3:1, similar to the current oral formulation (ratio of 300 mg:120 mg). The concentration of the drug in the liver did not appear to change when administered intramuscularly vs orally despite bypassing first-pass metabolism in the liver. They did not observe any adverse effects in the animals receiving the injectable formulations. This represents a promising and novel way to cure HCV with just 1 injection.

Levels of injectable long-acting glecaprevir and pibrentasvir exceeded the median trough level of the oral regimen in humans and were maintained above the trough for 11 weeks

Epidemiologic trends in HCV. Patel and colleagues (Abstract 160) looked at rates of HIV and HCV incidence over the last 25 years from the ALIVE (AIDS Linked to the IntraVenous Experience) cohort in Baltimore, Maryland. They observed a decrease in the prevalence of ongoing injection drug use from 89% in 1988 to 36% in 2019 (*P*<.001). They also observed increases in the uptake of harm reduction programs such as needle exchange and medication to treat opioid use disorder. They observed decreasing HIV incidence from 4.1/100 person-years in 1988 to 1992 to 0.1/100 person-years in 2017 to 2019, with an incidence rate ratio (IRR) of 0.02 (95% CI, 0.00-0.13). By contrast, after an initial decline in HCV incidence from 9.8/100 person-years from 1988 to 1992 to 1.7/100 person-years from 1999 to 2001, they observed an increase to 4.0/100 person-years from 2017 to 2019. When they adjusted IRRs for sex and age, they saw the

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IRR for HCV increase in the period of 2014 to 2019. This appeared to be driven mostly by increases in HCV incidence in individuals under the age of 40 years, as the IRR in this group from 2017 to 2019 compared with 1988 to 1992 was 1.48 (95% CI, 0.72-3.07). The study authors conclude that increased attention should be brought to HCV treatment and prevention in persons who inject drugs.

Carson and colleagues (Abstract 699) showed declining rates of HCV among PWH in Australia after direct-acting antiviral (DAA) therapy. In their cohort of 314 participants, detectable HCV VLs went from 71% at the start of enrollment to 1% at the second follow-up period from 2021 to 2023. Similar declining rates of HCV were found across the US in PWH as presented by Ma and colleagues (Abstract 698). Chen and colleagues (Abstract 701) also presented the status of their HCV program in Taiwan, which was introduced in 2018 with the availability of restriction-free DAA. They observed a decreasing prevalence of HCV in PWH from its peak in 2018 at 6.2% to 1.1% in 2023 or an 82.6% reduction; they observed a decreasing incidence from its peak at 25.9/1000 person-years in 2019 to 8.1/1000 person-years in 2022 or a 68.7% reduction.

Implementation of HCV programs. Abstracts looked at the implementation of HCV treatment programs across the world. Pollack and colleagues (Abstract 702) presented data on HCV treatment initiated through HIV and methadone clinics in Vietnam, where they observed a 93.8% sustained virologic response at post-treatment week 12 (SVR12) rate, supporting the scale-up of integrated programs in other similar settings. Lin and colleagues (Abstract 714) presented data from a center in Southwest China that employed "simultaneous start" for HIV and HCV treatment in coinfected individuals with high rates of HIV viral suppression at 12 weeks (100%) and 98.4% achieving HCV SVR at 24 weeks. Mera and colleagues (Abstract 704) presented modeling data showing significant cost-savings (projected $10 million over 20 years, or $3122/patient) of telehealth for treatment of HCV in Cherokee Nation, suggesting this could be used in rural areas. Russo and colleagues (Abstract 706) presented data from a study screening and linking new migrants in Italy with HCV care. Once informed of the program, 97.6% of the 3501 migrants consented to screening. All patients with HBV VL greater than 2000 IU/mL were connected to treatment; 88.6% of the patients with HCV RNA-positivity were linked to care, completed DAA treatment, and achieved SVR12. The authors demonstrated significant uptake in HCV screening and treatment services in a migrant population in Italy with high rates of SVR12 and linkage to treatment.

Mehta and colleagues (Abstract 697) presented data from the SToP-C (Surveillance and Treatment of Prisoners With Hepatitis C) trial, a precision-randomized trial looking at rates of SVR12 with additional adherence support in persons who inject drugs (PWID) in India. They used a prediction model using factors such as age, income, and homelessness to stratify individuals at high or low risk of treatment failure. They found that treatment support (patient navigator and some directly observed therapy) increased SVR12 in the low-risk group (adjusted RR, 1.10; *P*=.04), but treatment support did not change SVR12 rates in the high-risk group.

Several studies looked at optimal screening for HCV in an emergency department. In the DETECT (Determining Effective Testing in Emergency Departments and Care Coordination on Treatment Outcomes) trial, Haukoos and colleagues (Abstract 707) looked at more than 147,000 patients who were offered nontargeted HCV screening (offered to all with an opt-out option) or risk-based screening. Interestingly, they found nontargeted screening was associated with higher rates of HCV diagnoses than risk-based screening (RR, 1.34; *P*=.02). Unfortunately, once these individuals were identified, there were low rates of linkage to care and low rates of SVR12, with no difference between the nontargeted screening or risk-based screening groups. The same study group then looked at linkage to care from the emergency department, as presented by Rowan and colleagues (Abstract 708) in a randomized controlled trial with a referral arm vs a referral plus linkage navigation arm with a coordinator. Linkage navigation was superior to referral alone for linkage to care, initiation, and completion of treatment. Although a higher number of participants in the linkage arm achieved SVR12, this did not achieve statistical significance. However, in individuals younger than 40 years or with recent intravenous drug use, there was no difference in outcomes, suggesting that more creative interventions are needed to link these populations to care.

HCV in pregnancy and the postpartum period. Cafardi and colleagues (Abstract 709) recruited pregnant women with a history of injection drug use and chronic HCV and looked at treatment outcomes in mothers and testing rates of infants. Fifty-two percent of patients enrolled in the study completed postpartum DAA and achieved an undetectable VL at the end of therapy. Only

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10 completed SVR12 testing but all 10 achieved SVR12 (19% of all mothers). Seventy-seven percent of infants were tested for HCV. There was 1 positive test in 23 infants, with a calculated mother-to-child transmission rate of 4%. Chappell and colleagues (Abstract 710) conducted a phase I study looking at intracellular concentrations of sofosbuvir in late second-trimester pregnant women (weeks 23 to 25 of gestation) being treated for HCV with sofosbuvir (400 mg) and velpatasvir (100 mg). They measured the levels of the active metabolite and found that concentrations were similar to nonpregnant adults in peripheral blood mononuclear cells (PBMCs) but were about 50% lower in dried blood spots. However, 100% of their participants at the final maternal visit were cured, supporting the need for further clinical trial data for HCV treatment in pregnancy. Chapell and colleagues (Abstract 711) also showed that concentrations of sofosbuvir and velapatasvir in postpartum women on treatment were very low (milk-to-plasma concentration ratios of 0.13 for sofosbuvir and 0.4 for velapatasvir) and an estimated infant daily dose of 0.7% of the adult dose. This suggests that postpartum breastfeeding women can be encouraged to get HCV treatment with minimal risk to their infants.

HCV testing. Arca-Lafuente and colleagues (Abstract 712) validated a novel POC HCV RNA test using reverse transcriptase loop-mediated isothermal amplification (RT-LAMP). Sensitivity and specificity of the RT-LAMP testing were 94% and 100%, respectively, with results in approximately 30 to 40 minutes at $6/sample. This POC testing would be a powerful diagnostic tool in challenging-to-reach populations.

Clinical outcomes after SVR. Corma-Gomez and colleagues (Abstract 715) presented a cohort of patients coinfected with HIV/HCV compared with individuals who were monoinfected with HCV after achieving SVR12 and found no difference in mortality at 7 years (87% and 87%, respectively, *P*=.861). Of note, 98% of the patients with HIV had viral suppression to less than 200 copies/mL and a median CD4+ count of 573 cells/μL. HIV was not associated with increased mortality in their multivariable analysis. Van Santen and colleagues (Abstract 716) looked at HCC rates in HIV/HCV coinfected individuals who had been treated with DAAs. They found that DAAs decrease the risk of HCC by 44% (RR, 0.56; 95% CI, 0.31-0.99), with a greater risk reduction in those with F3-level advanced fibrosis (RR, 0.23; 95% CI, 0.06-0.84) than cirrhosis (F4) (RR, 0.73; 95% CI, 0.35-1.35). The annual incidence of HCC risk was 0.46% in those with cirrhosis, above the threshold of cost-effectiveness suggesting that these individuals should continue to be screened for HCC after DAA. In the F3 group, the annual incidence of HCC risk was 0.19%, lower than the cost-effectiveness threshold for screening. Thus, the study authors suggest alternative or no screening for HCC in this group.

Grande-Garcia and colleagues (Abstract 718) examined immunologic differences in HIV/HCV coinfected patients who were treated with DAAs or spontaneously cleared HCV. Those who spontaneously cleared the infection and shifted T-cell responses toward an "aged immune system" with increased immune checkpoint molecules and cellular depletion markers associated with aging. Those patients who were treated with DAAs showed improvement in inflammation and decreased checkpoint molecules compared with pretreatment. Studies from Promsena and colleagues (Abstract 721) and Han and colleagues (Abstract 722) also showed the incidence of re-infection with HCV in MSM and emphasized the importance of targeting this group for rescreening and other prevention strategies.

Existing treatments for HCV. Kim and colleagues (Abstract 696) presented data from ACTG5380 PURGE-C (GLE/PIB Fixed-Dose Combination Treatment for Acute Hepatitis C Virus Infection), a phase II trial looking at rates of SVR12 in patients diagnosed with early HCV in the preceding 24 weeks and treated with a 4-week course of GLE/PIB. They enrolled 45 participants from Brazil and the US from November 2019 to January 2023. Ninety-eight percent of the participants were male, and the median age was 36 years. Eighty-four percent of participants were diagnosed with their first HCV infection, 51% were PWH, and 71% had genotype 1. Eighty-four percent of the study participants (38 of 45) achieved SVR12 (95% CI, 74-91). SVR12 rates did not vary between PWH and persons without HIV. Four of the remaining 6 participants who completed HCV retreatment achieved SVR12. The authors concluded that a 4-week regimen of GLE/PIB could be an acceptable treatment for early HCV.

Advances in HIV Treatment

LA CAB/RPV

LA CAB/RPV in PWH experiencing adherence challenges. Existing clinical trial data on LA CAB/RPV have been obtained from populations that are generally adherent to oral ART with sustained virologic suppression and

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no history of virologic failure. PWH who have difficulty achieving virologic suppression with oral ART may benefit from directly observed injectable LA therapy. Rana and colleagues (Abstract 212) presented data from ACTG A5359, which enrolled PWH experiencing adherence challenges evidenced by ongoing viremia despite oral ART, disengagement from routine follow-up, or intermittent viremia despite oral ART. Eligible participants were also required to be negative for HBV infection and have no documented RPV or CAB resistance-associated mutations (RAMs). People were not excluded based on CD4+ cell count, plasma HIV-1 RNA level, unstable housing, or active substance use. Participants were first observed on oral ART, provided conditional economic incentives (eg, cash payments for achieving viral suppression), and SOC adherence support. Participants achieving plasma HIV-1 RNA levels less than 50 copies/mL were randomly assigned to continue oral ART or change to injectable monthly CAB/RPV after an optional oral lead-in. The primary outcome was regimen failure defined as the earliest occurrence of confirmed virologic failure of greater than 200 copies/mL or discontinuation of randomly assigned treatment.

The data safety monitoring board recommended discontinuing the oral ART arm. Of note, 98.75% CIs were preplanned for this interim analysis. For this analysis, 434 participants were enrolled (30% female; 27% White; median age, 40 years; 68% with plasma HIV-1 RNA levels >200 copies/mL; median CD4+ count, 270 cells/μL). A total of 294 participants were randomly assigned at the time of this analysis. The primary outcome occurred in 24.1% of the LA CAB/RPV arm and 38.5% of the oral ART arm (difference, −14.5%; 98.75% CI, −29.8-0.8). Virologic failure occurred in 7.2% of the LA CAB/RPV arm and 25.4% of the oral ART arm (difference, −18.2%; 98.75% CI, −31.1 to −5.4). Permanent treatment discontinuation was similar between arms. Two of 6 confirmed virologic failures in the LA CAB/RPV arms had the emergence of new RAMs. Ninety-three percent of injections were within the protocol-specified windows of ±7 days and there were no concerning safety data. Additional detailed analyses are planned for this trial. The authors concluded that LA ART is feasible and efficacious in people with a history of virologic failure who are experiencing adherence challenges.

LA CAB/RPV is superior to continued oral ART in PWH experiencing adherence challenges

LA CAB/RPV in sub-Saharan Africa. Few data exist on the use of LA CAB/RPV in sub-Saharan Africa where there is a larger diversity of HIV subtypes and preexisting NNRTI resistance mutations are more common. Paton and colleagues (Abstract 122) presented data from the CARES (Randomized Trial of Cabotegravir and Rilpivirine Long-Acting in Africa) study[3] that enrolled adults with HIV from sub-Saharan Africa who were stably suppressed on a DTG- or NNRTI-containing regimen with no known history of virologic failure and without HBV. The study enrolled 512 participants (58% women; 99.6% Black African; median age, 42 years). Testing of archived HIV-1 DNA showed that 10% harbored mutations conferring moderate-to-high level RPV resistance and 8% harbored mutations conferring moderate-to-high level CAB resistance. Participants were randomly assigned to continue oral ART or to start LA CAB/RPV after an optional oral lead-in. Plasma HIV-1 RNA level was assessed every 24 weeks. Ninety-six percent of the scheduled injections were given within the study-mandated windows. At week 48, 96.9% of the LA CAB/RPV group and 97.3% of the oral ART group had plasma HIV-1 RNA levels of less than 50 copies/mL (difference, −0.5%; 95% CI, −3.4 to 2.4). This achieved protocol-specified noninferiority. The proportion with plasma HIV-1 RNA levels of 50 copies/mL or higher was similar between the 2 groups. Two participants receiving LA CAB/RPV had virologic failure and both had emergence of RPV and CAB resistance. The authors concluded that these results support the use of LA CAB/RPV in this setting despite the high prevalence of archived RPV and CAB RAMs.

LA CAB/RPV in PWH with viremia. Hickey and colleagues (Abstract 628) presented data on the use of LA CAB/RPV in PWH experiencing adherence challenges and ongoing viremia. These are longer-term follow-up data to previously published results.[4] There were 59 people who initiated LA CAB/RPV when having plasma HIV-1 RNA levels of 50 copies/mL or higher. Forty-eight people (81%) remained on LA CAB/RPV with plasma HIV-1 RNA level <50 copies/mL, and 1 additional person had plasma HIV-1 RNA levels of 50 to 199 copies/mL. Five (8%) discontinued LA CAB/RPV without failure and resumed oral ART. Five (8%) failed with resistance or were lost to follow-up without resuming oral ART. These results

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support further study of LA CAB/RPV in viremic individuals experiencing adherence challenges with oral ART.

LA CAB/LEN. Gandhi and colleagues (Abstract 629) presented a multiinstitution case series of PWH initiating LEN and CAB with or without RPV. Thirty-four PWH were started on this regimen for a variety of reasons including NNRTI or integrase resistance. Eleven (32%) had plasma HIV-1 RNA levels of 200 copies/mL or higher prior to starting the regimen. Thirty-two (94%) achieved plasma HIV RNA levels of less than 75 copies/mL at follow-up. The authors concluded that these data were supportive of a trial of LEN and CAB in those with ongoing viremia and NNRTI resistance.

> ***LA CAB/RPV is effective in PWH from sub-Saharan Africa, despite archived NNRTI and InSTI RAMs***

Novel Antiretroviral Agents

MK-8527. Carstens and colleagues (Abstract 115) presented data on MK-8527, an investigational nucleoside reverse transcriptase translocation inhibitor (nRTTI) with pharmacokinetics supporting weekly oral dosing. They conducted 2 phase I, single-dose monotherapy trials in adults with HIV to assess antiviral activity, safety, and tolerability. Between the 2 studies, 37 participants (57% male; 57% White) received single doses ranging from 0.25 mg to 10 mg. The plasma HIV-1 RNA level decrease over 7 days ranged from −0.8 $\log_{10}$ copies/mL to −1.66 $\log_{10}$ copies/mL. All doses except for 0.25 mg achieved the goal of greater than 1 $\log_{10}$ decline. The doses appeared to be well tolerated, with no obvious safety signals.

GS-1720 weekly integrase strand transfer inhibitor (InSTI). Fichtenbaum and colleagues (Abstract 116) presented data on GS-1720, a novel weekly oral InSTI. They conducted 2 phase I studies to assess the pharmacokinetics, safety, and antiviral activity of this compound. They presented pharmacokinetic data in adults without HIV of single and multiple doses of GS-1720 ranging from 50 mg to 1350 mg. They observed a median half-life of 9.4 days. In a separate study, they evaluated a single dose of GS-1720 ranging from 30 mg to 900 mg in adults with HIV not on ART. They enrolled 28 participants (11% female; median age, 33 years; 32% White; median VL, 4.9 $\log_{10}$ copies/mL). The plasma HIV-1 RNA levels decreased from −1.74 $\log_{10}$ copies/mL to −2.44 $\log_{10}$ copies/mL at day 11. No emergence of integrase resistance was noted among participants in the 2-dose cohorts for which data was available. At the 2 highest doses, all participants exhibited at least a 2 $\log_{10}$ decline in plasma HIV-1 RNA levels. The authors noted that there were no concerning adverse events or laboratory abnormalities felt to be related to GS-1720.

Investigational broadly neutralizing antibodies. Losos and colleagues (Abstract 117) presented data on N6-LS, a broadly neutralizing antibody (bNAb) targeting a CD4-binding site, administered as a single dose to adults with HIV. Of note, N6-LS susceptibility testing was not done prior to study entry. Sixty-two participants were enrolled (94% male; 61% White; median plasma HIV-1 RNA level, 4.4 $\log_{10}$ copies/mL). The highest dose achieved a −1.72 $\log_{10}$ decline in plasma HIV-1 RNA levels. There appeared to be a dose-response relationship with antiviral activity.

Tsibris and colleagues (Abstract 118) presented first-in-human data on SAR441236, a trispecific anti-HIV antibody targeting 3 specific HIV envelope binding sites. The study assessed the safety and pharmacokinetics of single and multiple doses in adults with HIV with viral suppression. They also examined the preliminary antiviral activity in adults with HIV not on ART. They enrolled 51 participants (90% male; median age, 48 years; 7 with HIV-1 viremia). There were no grade 3 events related to SAR441236. The pharmacokinetic analyses showed a pattern consistent with monospecific bNAbs. The clearance of SAR441236 was greater in those with viremia. They observed low-level transient antidrug antibodies after administration in a minority of participants. Only 2 viremic participants received the higher dose of SAR441236; modest antiviral activity (−0.21 and −0.55 $\log_{10}$ copies/mL) was observed.

Novel Switch Strategies

LA CAB/VRC07-523LS. Taiwo and colleagues (Abstract 119) presented data from ACTG A5357, a phase II study of VRC07-523LS, a bNAb, given with LA CAB in adults with long-term viral suppression on oral ART. They enrolled 74 participants (74% male; 51% White; median age, 54 years). Participants were required to have susceptibility to VRC07-523LS. At study entry, participants changed ART to CAB plus 2 nRTIs for 4 weeks. If remaining virally suppressed after 4 weeks, participants discontinued oral ART and started intravenous VRC07-523LS and monthly intramuscular CAB for 48 weeks. Seventy-one participants initiated VRC07-523LS and

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intramuscular CAB. The primary safety outcome was Grade 3 or 4 adverse events related to study drugs or any adverse event that led to discontinuation of study treatment. Twelve participants (17%) experienced this outcome; most of these events were related to VRC07-523LS and occurred during infusions. However, only 1 participant discontinued the study drug early due to an adverse event. The primary efficacy outcome was virologic failure defined as confirmed plasma HIV-1 RNA of 200 copies/mL or higher. This occurred in 5 (7.3%) participants. The observed viremia was generally low level (<1000 copies/mL) and often occurred after SOC vaccines. One participant with borderline susceptibility to VRC07-523LS failed with a plasma HIV-1 RNA level of 5780 copies/mL with the emergence of an R263K integrase mutation. The authors concluded that this novel combination of an LA small molecule and a bNAb should be investigated further.

LEN/dual bNAbs. Eron and colleagues (Abstract 120) presented data on LEN given with teropavimab and zenlirvimab (2 bNAbs) as maintenance ART for PWH. Prior results from this study showed sustained viral suppression over 6 months when changing from suppressive oral ART to this investigational regimen in adults with HIV who had susceptibility to both bNAbs.[5] This abstract presented data on participants who had susceptibility to 1, but not both bNAbs. Outcome data are available in 10 participants (70% male; 60% White; median age, 49 years); 4 participants received a lower dose of zenlirvimab (10 mg/kg) and 6 received a higher dose (30 mg/kg), both given with teropavimab (30 mg/kg) and LEN. Participants were observed for 6 months prior to restarting oral ART. There were no safety concerns identified in this small study. All 6 participants in the higher-dose group maintained virologic suppression. Two of 4 participants receiving the lower dose of zenlirvimab had plasma HIV-1 RNA levels of 50 copies/mL or higher. One participant has a single plasma HIV-1 RNA level of 79 copies/mL at week 26. The second participant had low-level viremia at baseline that continued while on the study drug with plasma HIV-1 RNA levels up to 112 copies/mL. The authors noted that this combination is being studied in an ongoing phase IIB trial.

Triple-bNAb regimen. Juelg and colleagues (Abstract 121) presented data on a maintenance regimen of 3 bNAbs, PGDM1400, PGT121, and VRC07-523LS, in adults with HIV having viral suppression on oral ART. Participants were not screened for baseline susceptibility to the bNAbs. Twelve participants were enrolled and received up to 6 monthly infusions of the antibodies. The infusions were well tolerated. Two participants developed early virologic failure while receiving monthly infusions, 5 participants developed virologic failure during 6 months after monthly infusions ended, and 4 participants remained virally suppressed for 6 months after completion of antibody infusions. One participant was lost to follow-up prior to the end of the study while maintaining viral suppression. The author concluded that most participants were able to maintain suppression with an all-bNAb regimen.

Weekly LEN/islatravir. Colson and colleagues (Abstract 208) presented data on weekly dosing of LEN and islatravir (ISL) as maintenance ART in adults with HIV with viral suppression on daily BIC/FTC/TAF. Eligible participants were also required to be negative for HBV infection, have a CD4+ count greater than 350 cells/μL and have no prior history of virologic failure. A total of 104 participants (18% assigned female sex at birth; 50% White; median age, 40 years) were randomly assigned 1:1 to remain on daily oral ART or change to weekly oral ISL (2 mg) and LEN (300 mg). At week 24, 94.2% of participants in both arms had plasma HIV-1 RNA levels less than 50 copies/mL. One person in the ISL/LEN arm had plasma HIV-1 RNA levels of 50 copies/mL or higher at week 24 (64 copies/mL). Of note, this participant had plasma HIV-1 RNA levels less than 50 copies/mL at week 30. No one developed new resistance mutations in this study by week 24. There were no differences in CD4+ T-cell count changes or absolute lymphocyte counts between study arms. There were no safety concerns identified. The authors concluded that larger trials of this weekly, oral ART regimen are warranted.

DTG/3TC: real-world evidence. Sörstedt and colleagues (Abstract 645) presented real-world evidence on the effectiveness of DTG/3TC within a Swedish national registry. They compared the treatment outcomes of 1125 PWH switching to DTG/3TC to 1336 people switching to a 3-drug regimen. They found that those being switched to DTG/3TC were more likely to report optimal adherence prior to the switch. The rate of virologic failure (confirmed plasma HIV-1 RNA levels ≥200 copies/mL) was lower in the DTG/3TC group than in the 3-drug group. The few failures on DTG/3TC occurred within the first year after switching to DTG/3TC with none observed after 1 year, whereas the people in the 3-drug group had low but increasing rates of virologic failure over time. The authors noted the limitations of this retrospective analysis and the incomplete ability to control for bias.

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Management of PWH With Treatment Experience and MDR HIV

LEN with no other active ART agents. Ogbuagu and colleagues (Abstract 630) examined data from participants in the CAPELLA (Study to Evaluate the Safety and Efficacy of Lenacapavir [GS-6207] in Combination With an Optimized Background Regimen [OBR] in Heavily Treatment Experienced Participants Living With HIV-1 Infection With Multidrug Resistance) trial of LEN to treat MDR HIV-1 who had no fully active drugs in the OBR. The analysis included 12 participants with a median plasma HIV-1 RNA level of 4.0 $\log_{10}$ copies/mL and a CD4+ count of 175 cells/μL prior to initiating LEN; 5 had no partially active drugs in the OBR, 6 had 1 partially active drug, and 1 had 2 partially active drugs. Eight participants (67%) had plasma HIV-1 RNA levels of less than 50 copies/mL at 26, 52, and 104 weeks after initiating LEN. Three participants had the emergence of LEN resistance mutations. However, 2 were able to achieve plasma HIV-1 RNA levels of less than 50 copies/mL with no further changes to the OBR. Two others have partial viral suppression without ever achieving plasma HIV-1 RNA levels of less than 50 copies/mL. These data support the use of LEN in those with limited treatment options.

LEN/BIC. Mounzer and colleagues (Abstract 642) presented data on switching PWH on complex ART regimens to a single tablet of LEN/BIC given daily. They defined a complex regimen as having 2 or more pills daily, twice-daily dosing, or a protease inhibitor (PI) or NNRTI in combination with a class other than nRTI. Participants were required to be virally suppressed, have no prior LEN exposure, have no resistance to BIC, and be HBV negative. One hundred twenty-eight participants were assigned randomly (2:2:1) to BIC (75 mg daily)/LEN (25 mg daily); BIC (75 mg daily)/LEN (50 mg daily); or continued baseline regimen. Only 1 of 51 participants in the BIC (75 mg daily)/LEN (50 mg daily) arm had plasma HIV-1 RNA levels that were 50 copies/mL or higher at week 24. There were no safety concerns identified. The data support further study of this once-daily combination and support investigation of LA strategies of LEN and an InSTI.

Ibalizumab injections. Anstetti and colleagues (Abstract 631) examined intramuscular dosing of ibalizumab (IBA), an anti-CD4 antibody. They enrolled 6 PWH receiving intravenous IBA as part of a combination antiretroviral regimen and 14 people without HIV. Participants received the diluted intravenous IBA formulation every 14 days for 2 doses followed by intramuscular administration of undiluted IBA for 4 doses. Participants had a strong preference for the intramuscular administration and all PWH maintained viral suppression. There were no safety concerns with intramuscular administration.

BIC/FTC/TAF as second-line therapy. Pierre and colleagues (Abstract 641) presented a clinical trial enrolling PWH from Port-au-Prince, Haiti on a ritonavir-boosted PI (PI/r)-based second-line ART. Participants were required to be virally suppressed and no resistance testing was performed. Participants were allocated randomly to change to BIC/FTC/TAF or continue on the PI/r-based regimen. Two hundred ninety participants were included: 50% female, median age of 50 years. At 48 weeks, 0.7% and 2.8% of the BIC/FTC/TAF and PI/r arm had plasma HIV-1 RNA levels of 50 copies/mL or higher (difference, −2.1%; 95% CI, −6.7 to 1.2). This achieved prespecified criteria for noninferiority. There were no safety concerns in either group. The authors concluded that the data support the use of BIC/FTC/TAF in those with viral suppression with a PI/r-based second-line regimen.

Potential use of bNAbs for MDR HIV. Two studies reported on the use of bNAbs to treat MDR HIV-1 infection. Spagnuolo and colleagues (Abstract 691) reported on the susceptibility to zenlirvimab and teropavimab among people with HIV-1 infection with resistance to nRTI-, NNRTI-, InSTI-, and PI-based therapy. They tested plasma or PBMC samples from 46 people. They found that 41% were susceptible to both bNAbs, 44% were sensitive to 1 but not both bNAbs and 15% were resistant to both bNAbs. Similarly, Rai and colleagues (Abstract 690) examined infectious virus obtained from 11 participants with MDR HIV. They tested the virus against a panel of CD4 binding site and non-CD4 binding site Abs. They found that all but 1 participant were sensitive to at least 1 CD4 binding site and at least 1 non-CD4 binding site Ab. The authors from these studies concluded that clinical trials of bNAbs for people with MDR HIV should be considered given that many people remain susceptible.

Updates in Resistance to Therapies for SARS-CoV-2, Mpox, and HIV

Resistance in SARS-CoV-2

Tamura and colleagues (Abstract 135) presented data from their prospective POSITIVES (Post-Vaccination Viral Characteristics Study) cohort examining the

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relationship between SARS-CoV-2 viral rebound and resistance mutations to nirmatrelvir-ritonavir (NTV/r) and remdesivir (RDV). They looked at 79 individuals who received NTV/r and 14 individuals who received RDV, compared with a cohort of 63 untreated individuals. They collected nasal swabs 3 times a week for the first 2 weeks after SARS-CoV-2 diagnosis in these nonhospitalized patients. Treated patients were older and more likely to be immunosuppressed in this cohort.

NTV resistance mutations were more frequently observed in those who had been treated with NTV/r (9 of 79 [11%] than in 2 of 63 untreated patients [3%]; *P*-value was not mentioned). No differences in the likelihood of NTV resistance mutations in those who had virologic rebound were discerned compared with those who did not have virologic rebound (3 of 22 [14%] vs 6 of 57 [11%], respectively; *P*-value not given). They found higher rates of NTV mutations in immunosuppressed patients than in those who were not immunosuppressed (5 of 22 [23%] vs 4 of 57 [7%], respectively; *P*-value not given). NTV resistance mutations emerged at low frequencies, which they reported were under 20% of the total viral population. In 1 patient, resistance emerged with viral rebound during the peak viral load after the treatment course, but at a low frequency of 1.3% and subsequently reverted to wild-type, suggesting that this was unlikely to have been responsible for virologic rebound post treatment. This held true for 3 other NTV resistance mutations they observed in viremic patients with virologic rebound. They observed RDV resistance mutations in 2 patients who were immunosuppressed at low frequency and observed these mutations were transient, eventually reverting to wild-type. Based on this study, it appears that NTV and RDV resistance mutations that emerge during treatment are unlikely to contribute to virologic rebound. Reassuringly, mutations were observed transiently and at low frequency, suggesting they are unlikely to contribute to SARS-CoV-2 transmitted drug resistance.

NTV and RDV resistance mutations are unlikely to contribute to virologic rebound and have been observed transiently and at low frequency, and therefore are unlikely to contribute to SARS-CoV-2 transmitted drug resistance

Zhou and colleagues (Abstract 136) examined rates of SARS-CoV-2 resistance mutations in infected macaques who received NTV/r, molnupiravir (MOV), combination therapy, or no treatment. They observed increased rates of mutations, including NTV-associated resistance mutations, in the MOV-only group than in the other groups. In the combination therapy group, they did not observe increased rates of NTV-associated mutations compared with the MOV-only group. The authors postulate that the lower rate of mutations seen in the combination group is due to decreased viral replication seen with DAA therapies, and reassuringly conclude that combination therapy with MOV and NTV/r is not associated with the emergence of NTV resistance, although whether MOV-emergent resistance is clinically significant is unknown.

Resistance in Mpox

Marcelin and colleagues (Abstract 422) presented data on tecovirimat resistance in patients with mpox. They examined 2 patients admitted with severe mpox with prolonged disease courses despite tecovirimat treatment. Both patients had HIV and had CD4+ counts that were less than 200 cells/μL. The first patient developed new lesions after an initial 14-day course and was retreated with a 90-day course; no tecovirimat-associated resistance mutations were found, and plasma concentrations of tecovirimat were in the expected range. The second patient had unsuppressed HIV with a CD4+ count of 43 cells/μL and a BMI of 48.5 kg/m². This patient received tecovirimat twice daily for 14 days and then developed new lesions after the end of therapy. They were found to have low plasma concentrations below average concentrations of tecovirimat and had the emergence of 4 RAMs on genome sequencing (A290V, D294V, I327N, Y252C). Interestingly, therapeutic concentrations of tecovirimat despite monkeypox virus activity were not associated with the development of resistance mutations, whereas low concentrations of tecovirimat led to the development of resistance in advanced disease. This would support using 3-times-a-day dosing in obese patients or those with malabsorption.

Resistance to LEN

Quentin and colleagues (Abstract 682) presented data examining the use of LEN in patients including 8 patients with MDR HIV-2 and the emergence of resistance. LEN was added to these patients' OBRs. They initially saw a transient decrease in VL with viral suppression in 6 out

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of 8 patients at 3 months, but by 1 year the HIV-2 VLs were back to baseline. They observed the emergence of N73D, a capsid mutation, in 5 patients, which conferred a 30-fold decrease in LEN susceptibility compared with wild-type virus. They found the emergence of other mutations that also likely confer resistance to LEN.

Resistance to DTG in Resource-Limited Settings

Lessells and colleagues (Abstract 676) presented data on levels of HIV viremia and drug resistance in Malawi and Zambia after switching from an NNRTI-based regimen to a DTG-based regimen. At 2 years, there were low rates of viremia (defined as an HIV VL >400 copies/mL) with 4.7% of participants in Malawi and 1.8% of participants in Zambia with viremia. Viremia at the time of switch (and study entry) was highly predictive of viremia at 2 years. Five participants developed RAMs to InSTIs and only 2 had major InSTI mutations. Overall, participants switching to a DTG-based regimen achieved high levels of viral suppression and observed InSTI resistance was rare.

Kingwara and colleagues (Abstract 677) presented data looking at the frequency of RAMs to InSTIs in patients who were viremic (VL >200 copies/mL) in Kenya. They collected samples from 190 PWH on a DTG-based regimen, including 41 who were ART naive and 149 who were ART experienced. Of these individuals, 32% of the ART-naive patients and 28% of the ART-experienced patients had a VL greater than 200 copies/mL (13 participants and 42 participants, respectively). Of the genotyped samples, 8.3% of the ART-naive patients and 22.6% of the ART-experienced patients had InSTI RAMs. Five of the 31 (16.1%) ART-experienced patients had mutations that conferred high-level resistance to DTG. All 8 study participants with InSTI resistance also had nRTI and/or NNRTI mutations. This study highlights the possibility of InSTI RAMs in ART-experienced patients with viremia and cautions clinicians to have clinical suspicion for possible DTG failure in these patients.

Labhardt (Abstract 678) presented data looking at DTG resistance in Lesotho in patients changed from an NNRTI-based regimen to a DTG-based regimen with viremia (including 1 VL that had to be ≥500 copies/mL). Of the 15,000 patients who made the ART switch, only 1% met their viremia criteria, and they were able to sequence samples from 78 participants. In this cohort, DTG resistance was 10.3% (n=8), with 6 participants with high-level DTG resistance. Overall, those with viremia tended to be younger than the virally suppressed population. Those with DTG resistance were all treated at nurse-led health centers. One patient with DTG resistance had baseline decreased susceptibility to DTG before switching, and most had nRTI- and NNRTI-resistance mutations and treatment failure with nRTIs and NNRTIs. The study authors calculated that the overall risk of DTG resistance 18 months after switching from an NNRTI- to a DTG-based ART regimen was still low, at approximately 1 in 1000, but more attention and programmatic support should be provided for possible DTG resistance in sub-Saharan Africa.

Soto Ramirez and colleagues (Abstract 679) presented work from Mexico, where TAF/FTC/BIC has been the first-line therapy since 2019, similar to the US. In 100 samples sent for integrase testing, 20 had InSTI RAMs. Five of 25 patients (20%) with failure in response to first-line ART had InSTI RAMs, compared with 15 of the 75 patients (20%) with InSTI RAMs after numerous ART failures. The most common InSTI RAM observed was R263K. Interestingly, no M184V mutation was found in those with InSTI resistance.

Resistance to INSTIs in Resource-Rich Settings

Abdi and colleagues (Abstract 683) examined the S147G InSTI resistance mutation, which was selected for in DTG failures. It was also observed to emerge with other InSTI RAMs, including T97A, N155H, E138K, L74M, and Q148R.

Hikichi and colleagues (Abstract 685) showed that mutations conferring resistance to InSTIs could arise in the genome outside of integrase mutations.. They observed acquired envelope mutations that conferred resistance to InSTIs by increasing infectivity through cell-to-cell transmission. Nucleocapsid mutations also conferred resistance to InSTIs, but to a lesser degree than envelope mutations. They hypothesized this was due to nucleocapsid mutations causing earlier stages of viral replication to be accelerated before the integration steps. This group has also recently published their work on HIV-1 and InSTI mutations this year.[6]

Calvez and colleagues (Abstract 684) described InSTI mutations affecting the integration and reverse transcription steps of HIV-1 replication. They examined the InSTI resistance mutations R263K, N155H, and G140S/Q148H. R263K and N155H statistically significantly impaired reverse transcription. G140S/Q148H also impaired RT activity, but to a lesser degree. The authors suggest this may explain why some of the InSTI mutations may cause lower viral fitness.

Aziz and colleagues (Abstract 686) described real-world experience with LA CAB/RPV and observed virologic failure at higher rates than in trials. Of the 75 patients who had undetectable VLs at the time of the

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switch, they observed a 4% rate of virologic failure. The patients had been undetectable on LAI ART for up to 16 months before virologic failure. High-level InSTI mutations were observed in genotyping at virologic failure. The 3 patients who developed failure at BMIs above 25 kg/m², were injected with one-and-a-half inch needles and had been concerned about "irregular injection techniques." The authors postulate that proper injection techniques and longer needles, along with proviral genotyping may help predict virologic failure.

Significance of Archived Resistance

De Miguel Buckley and colleagues (Abstract 693) examined rates of virologic suppression for PWH on DTG/3TC who had a historical M184V mutation and whether next-generation sequencing (NGS) would help with treatment decisions. They conducted a subanalysis on their VOLVER (Virologic Outcomes of Lamivudine/Dolutegravir in Virologically Suppressed Subjects With Expected or Confirmed Resistance to Lamivudine) clinical trial of patients who were switched to DTG/3TC with a prior history of 3TC resistance and looked at NGS of proviral DNA of the patients at baseline (patients in VOLVER were switched to DTG/3TC only if their enrollment proviral DNA did not have M184V). Nearly 20% of participants had M184V on NGS sequencing of proviral DNA; however, rates of viral suppression on DTG/3TC at week 48 were comparable: 90.8% in those without mutations and 90.5% in those with M184V in NGS. NGS detection of M184V did not appear to be associated with virologic suppression and the authors concluded that this should not be used in deciding to switch patients to DTG/3TC.

Asante-Appiah and colleagues (Abstract 694) examined viral suppression rates for ISL and doravirine (DOR) in patients with proviral DNA showing RT mutations in 2 of their studies. At baseline, 18.3% of the experimental group (DOR/ISL) in study P017 had nRTI RAMs and 33.1% had NNRTI RAMs. Similarly, 18.8% of their experimental group had nRTI RAMs in study P018 and 33.9% had NNRTI RAMs. The most common nRTI RAMs were V118I and M184V, and the most common NNRTI RAMs were mutations at V179V/A/D/E/I/L/M/N/T and K103N/R/S. No participants with archived M184V developed viremia on DOR/ISL. Furthermore, 0.7% of their participants with archived NNRTI RAMs developed viremia with VLs greater than 200 copies/mL, but these participants had undetectable ISL levels suggesting nonadherence to ISL. Also, 1% had low-level viremia (between 50 and 200 copies/mL) after the switch. The study authors concluded that archived M184V or archived NNRTI RAMswere not associated with virologic failure on DOR/ISL.

D'Antoni and colleagues (Abstract 695) conducted analyses of archived mutations in patients who had switched to BIC/FTC/TAF over several time points. They found that 48.5% of these RAMs were fluctuating (including most frequently K103N and M184V), underscoring that proviral genotyping at 1 point in time is not reflective of the entire HIV reservoir.

Resistance to bNAbs

Masurov and Herschhorn (Abstract 689) presented a new ultrasensitive HIV-1 cell-to-cell transmission assay that could detect the neutralization of bNAbs, thus enhancing our ability to understand resistance to bNAbs in future patients. Rai and colleagues (Abstract 690) looked at resistance to 8 bNAbs in 11 patients with MDR-HIV. They found all the study participants were resistant to at least 2 of the 8 bNAbs (average resistance was to 4 bNAbs) However, they found almost all participants were sensitive to at least 1 envelope-binding site bNAb, making this a potential therapeutic target for those with MDR-HIV. Spagnuolo and colleagues (Abstract 691) also presented data on teropavimab and zinlirvimab (bNAbs targeting envelope spike sites) resistance in MDR HIV-1. They analyzed participants in their PRESTIGIO (Prospective Registry-Based Cohort of People With HIV-1 Resistant to Reverse Transcriptase, Protease, and Integrase Inhibitors) trial and found that 76% were phenotypically susceptible to teropavimab and 50% to zinlirvimab, and 41% were phenotypically sensitive to both.

Selected Issues in Maternal and Pediatric Health

DTG-Based ART in Pregnant Women and Postpartum

Many countries in sub-Saharan Africa have shifted to first-line DTG-based ART. Although high rates of sustained viral suppression have been demonstrated in adults and children on DTG-based ART, there are limited data regarding pregnant and postpartum women. Abrams and colleagues (Abstract 182) presented results from ORCHID (Obesogenic Origins of Maternal and Child Metabolic Health Involving Dolutegravir), a prospective observational study of metabolic health among pregnant women with HIV in South Africa. The study enrolled 595 pregnant women with HIV at less than 18 weeks gestational age, 463 who were already

receiving TDF/FTC/DTG (continuers), and 132 who initiated the DTG-based ART less than 14 days before enrollment (initiators). ART and VL testing were provided through routine HIV clinical services. High rates of viral suppression were observed among the pregnant women. At baseline, among all the women, 79% of VL measures were less than 50 copies/mL, 14% were between 50 and 1000 copies/mL, and 7% were greater than 1000 copies/mL. Analysis of viral trajectories from enrollment through 24 weeks postpartum revealed that 94% of all women had at least 1 VL measurement that was less than 50 copies/mL. Of these, 84% remained virally suppressed, although 10% experienced at least 1 viral episode with a VL between 50 and 1000 copies/mL, and 8% had at least 1 episode with a VL exceeding 1000 copies/mL (with initiators having a higher proportion at 13% compared to continuers at 6%). The proportion of VL measurements with viral suppression increased from 79% at enrollment to 91% during the second and third trimesters and 6 and 12 weeks postpartum, but decreased to 85% by 24 weeks postpartum. By 24 weeks postpartum, 10% of 173 of the VL measurements were greater than 1000 copies/mL, with higher rates among initiators than continuers. In multivariable analyses, having a VL of greater than 1000 copies/mL at enrollment was associated with a higher risk of having a viral episode with a VL greater than 1000 copies/mL after achieving viral suppression. Conversely, older age and having a baseline CD4+ count greater than 500 cells/µL were associated with a lower risk. The authors concluded that although high rates of sustained viral suppression were observed in pregnant and postpartum women on DTG-based ART, viremia in the postpartum period remains a concern, with a negative health impact on women and their infants.

Hypertension Disorders in HIV During Pregnancy and Postpartum

In a post hoc analysis of blood pressure data from the IMPAACT (International Maternal Pediatric Adolescent AIDS Clinical Trials Network) 2010/VESTED (Virologic Efficacy and Safety of ART Combinations With TAF/TDF, EFV, and DTG) study, Hoffman and colleagues (Abstract 183) characterized the incidence of elevated blood pressure and hypertensive disorders among 626 pregnant and postpartum women living with HIV who were on DTG-based ART. Conducted at 22 sites in 9 countries, the IMPAACT 2010/VESTED study randomly assigned women at 14 to 28 weeks gestational age to initiate 1 of 3 ART regimens: (1) DTG/FTC/TAF; (2) DTG/FTC/TDF; or (3) EFV/FTC/TDF, and followed them for 50 weeks postpartum. Overall, the incidence of elevated blood pressure (defined as having ≥2 blood pressure readings of 130-139 mm Hg/80-89 mm Hg) was high, with 46% in the DTG plus FTC/TAF arm, 44% in the DTG plus FTC/TDF arm, and 40% in the EFV/FTC/TDF arm. The overall incidence of mild (140-159 mm Hg/90-99 mm Hg) or moderate (160-179 mm Hg/100-109 mm Hg) hypertension or hypertension requiring antihypertensive medications was low, with no cases of severe hypertension (≥180/110 mm Hg) seen. The incidence of gestational hypertension, characterized by onset at 20 weeks gestation or later and resolution within 12 weeks postpartum, was low. Preeclampsia was diagnosed in 8 women, although 1 woman developed eclampsia, with no significant differences observed among the ART groups. Although not statistically significant, there was a trend towards an increased hazard of incident elevated blood pressure or gestational/nongestational hypertension among women on DTG-based ART compared to those on EFV-based ART; these hazard ratios were similar when adjusted for weight. Irrespective of the ART treatment arm, for every 5 kg weight gain, there was approximately a 16%-22% increase in the hazard of elevated blood pressure and mild or worse hypertension. The authors concluded that prioritizing healthy weight gain and identifying and effectively managing hypertension during pregnancy and postpartum are crucial, especially considering the advantages of DTG-based ART in promoting healthier antepartum weight gain and reducing adverse pregnancy outcomes.

Prioritizing weight gain and effectively managing hypertension during pregnancy and postpartum are crucial

Rittenhouse and colleagues (Abstract 913) explored the relationship between HIV and preeclampsia, a major cause of maternal and fetal morbidity and mortality, among 3796 pregnant women in Zambia, utilizing combined data from 3 studies. Among the 3796 women included in the analysis, 40% were living with HIV although 60% did not have HIV. Overall, 3.7% of all women were diagnosed with preeclampsia, including 2.0% of the women with HIV and 4.8% of those without HIV. Among women with HIV, 72% were on ART before

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conception, and 38% had detectable VLs at enrollment. After adjusting for maternal age, nulliparity, and study enrollment period, HIV infection was associated with a reduced risk of preeclampsia. This reduced risk persisted when considering preconception ART exposure, detectable VL at enrollment, and CD4+ T-cell count at enrollment. The researchers proposed further investigation is needed to determine whether the relative immune suppression associated with maternal HIV may confer protection against preeclampsia.

Data have shown that women initiating DTG-based ART experience higher rates of weight gain and obesity,[7] with DTG associated with increased gestational weight gain compared to EFV during pregnancy.[8] Jacobson and colleagues (Abstract 910) compared the prevalence of hypertensive disorders in pregnant women based on HIV serostatus and type of ART regimen at conception (DTG vs EFV-based ART) using data from the Botswana-based Tsepamo Birth Outcomes Surveillance Study. The researchers observed that the prevalence of chronic hypertension was similar across all ART and HIV serostatus groups, with rates of 4.4%, 4.4%, and 4.6% in the DTG, EFV, and without HIV groups, respectively. In addition, the prevalence of gestational hypertension was similar across groups, with rates of 10.2%, 8.1%, and 11.7% in the DTG, EFV, and without HIV groups, respectively. Compared to the DTG-based ART group, the risk of gestational pregnancy was 20% lower in the EFV-based ART group and 20% higher in the group of women without HIV. The authors highlighted that more research is needed to understand if these observed differences are mediated by early weight gain in pregnancy and the impact of hypertensive disorders of pregnancy on adverse pregnancy outcomes.

Jao and colleagues (Abstract 916) observed no association between DTG use and changes in blood pressure during pregnancy and postpartum in women in South Africa. Of the 1894 pregnant women included in the study, 797 had HIV, although 1097 did not have HIV. All women with HIV were receiving treatment with TDF/3TC/DTG. The women underwent serial standardized blood pressure assessments throughout pregnancy and up to 6 weeks postpartum. Mean systolic and diastolic blood pressure levels were similar throughout pregnancy up to 6 weeks postpartum, irrespective of HIV status. During pregnancy and through 6 weeks postpartum, 11% of all women experienced incident hypertension, with no difference by HIV status or duration of DTG use among the women with HIV.

Collins and colleagues (Abstract 912) investigated the impact of pregnancy history on the development of non-AIDS comorbidities (NACMs) in 759 reproductive-age women aged 18 to 45 years, with or without HIV, who were enrolled in STAR (Study of Treatment And Reproductive Outcomes), a longitudinal cohort in 6 Southern US sites. Overall, 75% of the women identified as Black, and 43% reported a history of smoking. Of the 759 women, 473 (62%) had HIV, with a median CD4+ count of 669 cells/μL, and with 77% achieving undetectable VLs of less than 200 copies/mL. The 12 NACMs included obesity, psychiatric illness, anemia, lung disease, bone disease, hypertension, cardiovascular disease, liver disease, diabetes, kidney disease, dyslipidemia, and non-AIDS-related cancer. The study showed a high overall burden of the 12 NACMs, which increased with age and was higher in women with HIV compared with those who did not have HIV (mean NACM burden, 2.5 vs 2.2). After adjusting for HIV status and age, pregnancy history was found to be significantly associated with the mean NACM burden (mean NACM burden, 2.2, 2.0, and 2.6 among women with 0, 1 to 2, or 3 or more pregnancies, respectively). Although the distribution of prevalent NACMs varied by HIV serostatus, HIV infection did not alter the effect of age-adjusted pregnancy history on NACM burden.

Malaba and colleagues (Abstract 918) presented results comparing blood pressure levels and incident hypertension in pregnant and postpartum women with HIV in South Africa and Uganda as part of the DolPHIN-2 (Dolutegravir in Pregnant HIV Mothers and Their Neonates) trial, which included pregnant women at least 28 weeks gestation who were randomly assigned to receive TDF/3TC/FTC with DTG or EFV as first-line therapy. The women were followed through 72 weeks postpartum. The analysis found no significant associations between DTG use and systolic and diastolic blood pressure or weight changes through the 72-week postpartum period. Although 4 women had hypertension at enrollment, 23 women developed hypertension at 6 weeks postpartum. During the follow-up period, 8 women changed treatment assignments for reasons unrelated to blood pressure or weight gain. No association between DTG vs EFV and incident hypertension was observed during pregnancy and postpartum.

HIV Reservoirs in Children

Latent HIV-1 reservoirs are established early during primary infection in resting memory CD4+ T-cells, which impedes the possibility of achieving ART-free remission and cure. Very early initiation of ART would restrict the size of HIV-1 reservoirs, as in the case of the Mississippi Baby, in which administration of ART at 30 hours

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through 18 months of age led to ART-free remission for 27 months.[9,10] To investigate the proof of concept that initiating ART very early could sufficiently reduce HIV-1 reservoirs to enable ART-free remission, Persaud and colleagues (Abstract 184) evaluated 6 neonates who received very early initiation of ART and underwent analytic treatment interruption (ATI) in the IMPAACT P1115 study. The study enrolled 54 neonates with confirmed in-utero HIV-1 infection who began ART within 48 hours of birth and received ART. Eligibility for ATI was based on the following criteria: sustained virologic suppression with no detectable plasma HIV-1 RNA level from 48 weeks onward; absence of HIV-1 DNA; normal CD4+ count; and negative HIV-1 antibody status. Among the 6 children who met eligibility for ATI and discontinued ART, the median age was 5.5 years. Four of the 6 children achieved remission, defined as no confirmed plasma HIV-1 RNA level above the assay's limit of detection for at least 48 weeks off ART. Two children experienced viral rebound at 3 and 8 weeks. One child maintained remission for 80 weeks during ATI, after which viral rebound occurred; 3 children remain off of ART (>48 weeks, >52 weeks, and >64 weeks). Two of the 3 children who experienced viral rebound developed acute retroviral syndrome (ARS). The authors highlighted that very early ART of neonates with in-utero HIV-1 infection led to sustained remission for at least 48 weeks but cautioned the need for close monitoring for the occurrence of ARS during ATI.

Kakkar and colleagues (Abstract 955) examined the impact of cytomegalovirus (CMV) coinfection on HIV reservoir size and T-cell subset distribution in 225 Canadian children and young adults with HIV. In the study, 85% of the children were immunoglobulin G (IgG) seropositive for CMV at baseline. No significant association was found between CMV coinfection and HIV reservoir size. However, the investigators observed that CMV coinfection was associated with an alteration in the naive-memory-effector profile of CD4+ and CD8+ T cells; this change was independent of achieving sustained virologic suppression, indicating that CMV coinfection may influence the differentiation and maturation of CD4+ and CD8+ T cells in children with HIV, despite having effective viral control.

Genotypic Resistance Testing and Monitoring in Children

Brown and colleagues (Abstract 185) presented results from the GIVE MOVE (Genotype-Informed Versus Empiric Management of Viremia) trial compared genotypic resistance testing-informed management with usual care on viral resuppression and clinical treatment outcomes in children and adolescents with HIV in Tanzania and Lesotho. In the open-label trial, 284 children and adolescents who had recent viremia (≥400 copies/mL) while taking ART were randomly assigned to receive genotypic resistance testing (GRT) with expert recommendation on ART choice informed by genotype (GRT arm) or repeat VL testing and empiric decision-making guidelines (usual care arm). At baseline, 5% were receiving NNRTI-based ART, 36% were receiving PI-based ART, and 60% were receiving integrase inhibitor-based ART. Median duration on ART was 6 years (IQR, 3-10). No statistically significant difference in the composite primary endpoint (death, hospitalization, a new WHO clinical stage 4 event, no documented viral resuppression to <50 copies/mL at 36 weeks) was observed between the 2 arms (47% in the GRT arm vs 52% in the usual care arm). GRT-informed care did not improve rates of viral resuppression or clinical treatment outcomes in children and adolescents with viremia while on ART. The authors suggest caution against the widespread adoption of GRT without additional selection criteria to guide its application.

DTG-Based ART in Pediatric Populations

Mujuru and colleagues (Abstract 186) presented extended follow-up efficacy and safety data from the ODYSSEY (Once-Daily DTG-Based ART in Young People vs Standard Therapy) trial, which previously demonstrated 96-week superior efficacy of DTG+2 nRTI treatment compared with non-DTG SOC treatment in children starting first-line or second-line ART. In total, 792 children aged 3 months to less than 18 years were enrolled and randomly assigned to groups in the trial, with 383 children starting first-line ART (189 DTG, 194 SOC) and 409 receiving second-line ART (203 DTG, 206 SOC). Of the 707 children contacted, 97% (n=683) participated in the extended follow-up. The primary endpoints were virologic (defined as a VL ≥400 copies/mL after 36 weeks) or clinical failure (defined as any new or recurrent severe WHO grade 3 or 4 event or death due to any cause). Children in the SOC arm were switched to DTG-based ART based on country guidelines and clinician decision-making. By 192 weeks, a higher proportion of children in the SOC arm experienced virologic or clinical failure compared with the DTG arm (34% vs 20%; treatment difference, –13.3%; 95% CI, –19.2 to –6.5) and by 240 weeks (34% vs 21%; treatment difference, –13.8%; 95% CI, –19.8 to –7.0). By 192 weeks, 13% of the SOC arm had switched to DTG without prior treatment failure, increasing to 42% by 240 weeks. By the end of

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the extended follow-up period, nearly all (99%) of the SOC arm had transitioned to DTG. Among the children in the SOC arm who were virally suppressed before the switch, 93% remained virally suppressed after changing to DTG. Among the children in the SOC arm who had VLs greater than 400 copies/mL preswitch, 83% achieved viral suppression following the transition to DTG. There were no statistically significant differences in serious or severe adverse events, although children in the SOC arm experienced a higher rate of ART-modifying adverse events compared with the DTG arm (21% vs 7%; *P*=.008). In addition, lower total cholesterol levels were observed in the DTG arm compared to the SOC arm, a difference that was maintained for up to 192 weeks. The results of this study provide support for the transition to DTG-based ART in children. The authors calculated that 1 treatment failure could be averted for every 8 children treated with DTG-based ART vs non-DTG-based ART.

Extended follow-up efficacy and safety data support the transition to dolutegravir-based ART in children

In Malawi, first- and second-line treatment for children with HIV had transitioned from PI- or NNRTI-based ART to DTG-based ART in 2020; by 2023, 99.9% of children with HIV on ART were receiving DTG-based treatment, thereby necessitating monitoring for DTG resistance mutations. Bello and colleagues (Abstract 187) characterized the prevalence and drug resistance patterns in children in Malawi using cross-sectional survey data from 19 clinics in Malawi from 2022 to 2023. The analysis included children aged 2 to 14 years who received DTG-based ART for at least 9 months and returned to the clinic after virologic failure with VLs greater than 1000 copies/mL after receiving intensive adherence counseling. A total of 302 children received re-testing for HIV VL, of whom 133 (44.0%) remained virally unsuppressed with VLs greater than 1000 copies/mL and had genotyping for drug resistance mutations. The median time since ART initiation was 5.6 years, although the median time on DTG-based ART was 1.5 years; 88.7% were considered treatment-experienced at the initiation of DTG-based ART. The overall prevalence of any drug resistance mutation was 74.4%, with 65.5% to any NNRTI, 42.2% to any nRTI, 16.3% to any InSTI, and 5.0% to any PI. High-level DTG resistance among children with virologic failure was 13.5%, which was higher than the 8.5% observed among adults in the same survey. The most common major DTG RAMs were R263K, E138K/A, S147G, and G118R. The finding of a relatively high prevalence of DTG RAMs raises concern for future effective treatments for children with HIV, given the limited availability of convenient alternative ART options in this population.

Sakoi-Mosetlhi and colleagues (Abstract 981) presented data from a small study involving 48 infants diagnosed with HIV who received early ART within 7 days post delivery in Botswana and showed no improvement in viral suppression in children who received DTG-based ART compared to lopinavir/ritonavir (LPV/r)-based ART through 24 weeks of follow-up. The authors highlighted caregiver-reported adherence challenges in some infants and the need for the availability of LA medications to overcome these barriers.

Labhardt and colleagues (Abstract 982) presented findings that drew from longitudinal data from 2 cohorts comprising 2126 children and adolescents from Lesotho, more than 95% achieved viral suppression with VLs less than 1000 copies/mL and over 90% less than 50 copies/mL 2 years after transitioning from NNRTI- to DTG-based ART. The researchers noted a correlation between preART transition viremia and viremia level of 50 copies/mL or higher and 1000 copies/mL or higher at 24 months. Nevertheless, most of these children (84.4% of those with preART transition viremia with VLs ≥50 copies/mL and 81.9% of those with preART transition viremia ≥1000 copies/mL) attained viral suppression at 24 months.

Novitsky and colleagues (Abstract 983) presented 24-month viral outcome data among youth with HIV in Kenya, comparing those with and without a provider-initiated change to DTG-based ART. Among the 445 children, the median age was 17 years, and the median time on ART was 11 years. Most of the children (86%) received DTG-based ART; 14% remained on other non-DTG-based ART (2% NNRTI-based and 98% PI-based ART). Among the 342 children on DTG-based ART, 92% were virally suppressed at 24 months, with 23% experiencing a VL greater than 1000 copies/mL at any time during follow-up. By contrast, among the 53 children on non-DTG-based ART, 81% had viral suppression at 24 months, with 53% experiencing a VL greater than 1000 copies/mL at any follow-up time point. Analysis of sequence data from 91 samples available from 59 children on DTG-based ART at time points with a VL

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greater than 1000 copies/mL revealed no major INSTI RAMs. The authors concluded that the absence of major InSTI RAMs upon virologic failure was reassuring, but advised close monitoring of ART adherence, VL, and drug resistance.

Desmonde and colleagues (Abstract 984) described the transition to DTG-based ART among children in 6 global regions within the multiregional IeDEA cohort. The study showed a successful scale-up of DTG-based ART, with 61,234 children followed at sites where DTG was available. Access to DTG was found to be unequal, with delayed access observed in the Asia-Pacific region compared to sub-Saharan Africa. In addition, there was delayed transitioning to DTG for those on PI-based ART, and girls in sub-Saharan Africa were less likely to have access to DTG compared to males. Furthermore, increased access to DTG was noted among those who were older or those with undetectable baseline VL.

Data support the use of long-acting cabotegravir and long-acting rilpivirine every 2 months in adolescents with virologic suppression

LAI ART in Children

Gaur and colleagues (Abstract 188) presented safety and pharmacokinetic data from the IMPAACT 2017 MOCHA (More Options for Children and Adolescents), which focused on treatment with LA CAB/RPV in adolescents with HIV. IMPAACT 2017 is a phase I/II open-label trial that enrolled adolescents aged 12 to 18 years with HIV who weighed at least 35 kg and were virologically suppressed on prestudy ART. In 1 cohort, 144 participants were switched from prestudy ART to 4 weeks of oral CAB plus RPV, followed by a lead-in phase with 2 intramuscular injections of 600 mg LA CAB and 900 mg LA RPV given 4 weeks apart, followed by maintenance dosing with injections every 8 weeks, similar to adult dosing. The median age of the participants was 15 years, and the median weight was 48 kg. More than one-third (35%) reported an injection site reaction, with most resolving within 7 days and being mild (grade 1) in severity. Only 2 participants (1%) experienced a study drug-related grade 3 or higher adverse event (ie, injection site pain and abscess, injection site abscess); both continued in the study. No deaths or adverse events leading to discontinuation of the study drug were observed. There were no serious adverse events attributed to the study drug. Over 24 weeks, 11% experienced a grade 3 or greater adverse event, the most frequent being an increase in blood creatine phosphokinase and systolic blood pressure, which were not considered related to the study drug. One unintended pregnancy in a participant resulted in a healthy live birth at term. Most of the participants (96.5%) had sustained viral suppression with VLs less than 50 copies/mL at week 24, with no confirmed episodes of virologic failure (defined as 2 consecutive VLs ≥200 copies/mL) were observed through 24 weeks. The median (5%, 95%) week 24 predose CAB and RPV concentrations were comparable to those in adults. Based on these findings, the authors concluded that the data from the IMPAACT 2017 MOCHA study support the use of LA CAB plus RPV every 2 months in adolescents with virologic suppression.

Lowenthal and colleagues (Abstract 949) reported that most adolescents (99%) in the study expressed a preference for LAI ART over daily oral medications, with the primary reasons cited being convenience and burden reduction, with decreased adherence-related stress and increased privacy related to LAI ART.

Impact of HIV and Mental Health in Women and Youth

The impact of HIV and mental health in women and youth with HIV was evaluated in several abstracts. Mental health issues, including depression, are prevalent among youths with HIV and are associated with negative health outcomes.[11] Ayieko and colleagues (Abstract 189) presented the results of SEARCH-Youth (Strategic Antiretroviral Therapy and HIV Testing for Youth in Rural Africa), a clinic cluster-randomized trial assessing a life-stage intervention, in reducing the prevalence of depressive symptoms in youth with HIV. The study involved 28 public health clinics providing HIV services to youth aged 15 to 24 years in rural Kenya and Uganda; the facilities were randomly assigned to intervention and control clinics. SEARCH Youth was previously shown to increase viral suppression in participants in the intervention clinics compared to those in the control clinics by 10% after 2 years of follow-up.[12] The intervention clinics implemented life-stage-based assessments during routine visits, along with flexible clinic access and rapid VL testing, while the control clinics followed local standard practices. The life-stage assessments facilitated discussions between providers

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and youth to identify life events and issues, prompting actions including referrals for mental health counseling. Depression was assessed using the Patient Health Questionnaire-9 (PHQ-9) during Year 3, with a score of 5 or higher indicating at least mild depression and a score of 10 or higher indicating moderate to severe depression. The analysis included 662 participants in the intervention arm and 572 in the control arm, with a median follow-up period of 3.8 years. Overall, a lower proportion of participants in the intervention arm experienced depressive symptoms compared to the control arm (53% vs 73%; relative risk [RR], 0.72; 95% CI, 0.59-0.89). There was a nonsignificant trend to risk reduction for at least mild (RR, 0.45; 95% CI, 0.13-1.57) or moderate-severe (RR, 0.48; 95% CI, 0.10-2.29) depression in the intervention arm compared to the control arm. In the subgroup comparison, the greatest risk reduction for any depressive symptoms in the intervention arm was among participants reengaging in care. Factors associated with increased odds of at least mild depression included feeling sexual pressure, physical threats, and recent life events (eg, sickness or family death), although feeling supported was found to be associated with decreased odds. The authors concluded that life stage-based discussions facilitated by the intervention helped providers and youth identify and address challenges, build resilience against depression, and enhance care engagement and adherence to ART.

There have been reports and studies suggesting a potential association between the use of DTG and depression or other neuropsychiatric side effects. Moabi and colleagues (Abstract 921) reported a high prevalence of depression and anxiety in women with and without HIV in Botswana from 2021 to 2023, a period that was impacted by the COVID-19 pandemic. Women with HIV received DTG-based ART. Overall, 13% of all women had scores consistent with moderate/severe depression and 8% with moderate/severe anxiety, with no statistically significant difference based on HIV serostatus. Additionally, 16% of all women displayed probable depression (defined as a PHQ-9 score of 9 or higher); 15% exhibited probable anxiety (defined as a General Anxiety Disorder-7 score of 8 or higher); and 15% reported suicidal ideation. Although there was a numerically higher prevalence among women with HIV, these differences did not reach statistical significance. Overall, 22% of all women were referred for mental health services.

Van der Wekken-Pas and colleagues (Abstract 922) compared rates of depression, anxiety, and sleep disorders longitudinally in 268 pregnant and postpartum women receiving DTG and EFV, 2 medications associated with neuropsychiatric symptoms. The DolPHIN-2 study was an open-label trial that enrolled and randomized South African and Ugandan women presenting late in pregnancy with untreated HIV infection to receive a DTG- or EFV-based regimen. The researchers observed no significant differences between EFV or DTG-based regimens in terms of rates of depression or anxiety or sleep quality scores. However, overall, they found elevated rates of depression, with 25% of all women having possible/probable depression and poor sleep quality, particularly during the time of HIV diagnosis and transition into motherhood. The investigators emphasized the importance of providing mental health support during the peripartum period for women diagnosed with HIV during pregnancy.

Mental health support for women diagnosed with HIV during pregnancy is essential

PrEP During Pregnancy and Birth Outcomes

Chi and colleagues (Abstract 931) reported the uptake of daily oral FTC/TDF PrEP, maternal safety, and pregnancy outcomes from the PrEP Comparison Component of the IMPAACT 2009 trial. The study enrolled 350 pregnant women aged 16 to 24 years at less than 32 weeks gestation in Malawi, South Africa, Uganda, and Zimbabwe. Women were given the choice to initiate or decline daily oral FTC-TDF for PrEP at enrollment and were followed during pregnancy and for up to 6 months postpartum. A total of 9% of participants experienced at least 1 adverse event with grade 3 or greater through delivery, with a higher proportion among the women who started PrEP (11.2%; 95% CI, 7.4-15.9) compared to those who declined PrEP (4.3%; 95% CI, 1.4-9.7). Most of these adverse events were complications of pregnancy or delivery and none were considered related to PrEP use. There were no cases of HIV seroconversion during pregnancy. Overall, 24% of the women experienced adverse pregnancy outcomes, with no statistical difference observed between the groups. The authors concluded that daily oral FTC/TDF is a safe PrEP modality in pregnancy.

Gomez and colleagues (Abstract 939) investigated the impact of prenatal oral TDF-based PrEP exposure on child neurodevelopment among 648 mother-child pairs

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without HIV in Western Kenya. There were no differences in neurodevelopment, as assessed by the Malawi Developmental Assessment Tool, from 36 to 48 months observed by prenatal PrEP exposure. The results bolster an expanding body of research supporting the safety of prenatal PrEP use and provide insights into neurodevelopmental outcomes in PrEP-exposed children.

All abstracts cited in the text appear in the CROI 2024 Abstract eBook, available online at www.CROIconference.org

The IAS–USA will identify and resolve ahead of time any possible conflicts of interest that may influence CME activities with regard to exposition or conclusion. All financial relationships with ineligible companies for the authors and planners/reviewers are below.

Financial affiliations in the past 24 months: Dr Gunaratne reported no relevant financial relationships with ineligible companies. (Updated July 18, 2024) *Dr Zucker reported no relevant financial relationships with ineligible companies.* (Updated July 18, 2024) *Dr Tieu reported grant support from GSK and Shionogi.* (Updated July 18, 2024) *Dr Wilkin reported serving as a consultant to ViiV Healthcare and Merck and Co, Inc; grants/grants pending to his institution from Merck and Co, Inc.* (Updated July 18, 2024) *Dr Taylor reported no relevant financial relationships with ineligible companies.* (Updated July 18, 2024)

Reviewer 1 reported consulting or advisor fees from Antiva, Assembly Biosciences, Generate Biomedicines, and Gilead Sciences, Inc. (Updated March 6, 2024) *Reviewers 2 and 3 reported no relevant financial relationships with ineligible companies.* (Updated March 6, 2024)

All relevant financial relationships with ineligible companies have been mitigated.

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In Memoriam

The IAS–USA is deeply saddened by the passing of John P. Phair, MD, on February 19, 2024.

Dr Phair, Professor of Medicine, Emeritus, Northwestern University Medical School, Chicago, IL, was the first recipient of the International AIDS Society–USA (IAS–USA) Lifetime Leadership Award. He was honored on April 19, 2010, at the IAS–USA annual continuing medical education course in Chicago, IL.

The IAS–USA Lifetime Leadership Award, in the area of scientific and academic mentorship and leadership, was presented to recognize and pay tribute to those individuals who have made substantial and lasting contributions to the field of HIV medicine and research and to HIV physician education and training to improve the treatment and care for HIV-infected people.

Dr Phair was recognized for his outstanding knowledge, exemplary leadership, and inspiration to researchers and clinicians in the field of HIV. He was also recognized for 18 years of noteworthy and sustained contributions as chair of the IAS–USA Improving the Management of HIV Disease annual continuing medical education course in Chicago.

Dr Phair has played a prominent part in the field of HIV, serving as a role model through his remarkable service, research, and teaching. Following his graduation from Yale University, Dr Phair attended the University of Cincinnati College of Medicine. He trained in internal medicine and infectious disease at Yale New Haven Hospital and joined the faculty of the University of Cincinnati College of Medicine in 1967. He was recognized for his important contributions to leadership while heading the Division of Infectious Disease and the Samuel J. Sackett Laboratories at the Feinberg School of Medicine at Northwestern University from 1976 until 2000. Among his notable achievements, he has worked with the National Institutes of Health-National Institute of Allergy and Infectious Diseases–funded Multicenter AIDS Cohort Study (MACS), now in its 27th year, clarifying the natural history of HIV infection. He established the NIAID-funded Chicago Adult AIDS Clinical Trials Unit in 1987 and served as Chair of the Executive Committee of the Adult AIDS Clinical Trials Group during the period when therapy moved from its infancy to its current level of effectiveness. Dr Phair chaired the NIAID AIDS Research Advisory Committee from 2000 to 2002. He received the prestigious John Phillips Memorial Award from the American College of Physicians for distinguished contributions in clinical medicine in 2005.

Guidelines for Authors and Contributors

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

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

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

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

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

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

Cases From the Field. *Topics in Antiviral Medicine*™ invites submission of case reports accompanied by a scholarly literature review of the topic. Each case report should be 1500 to 3000 words (excluding references, tables, and figures), include numbered references, and seek to teach an important lesson for practitioners relating to HIV, hepatitis viruses, SARS-CoV-2, or other viral infections and their related conditions.

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

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

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

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1. International Committee of Medical Journal Editors. Recommendations for the conduct, reporting, editing, and publication of scholarly work in medical journals. Accessed August 12, 2024. http://www.icmje.org