

Topics in Antiviral Medicine™

A publication of the IAS–USA

Selected Highlights of the 2023 Conference on Retroviruses and Opportunistic Infections (Part 1)

**CROI 2023: Advances in Antiviral Therapy in HIV
and Viral Hepatitis** CME 445

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

The HIV Care Cascade and Equity Issues in Care Outcomes • New Data for Estimating Mortality and Causes of Death in People With HIV • Impact of the COVID-19 Pandemic on HIV Services and Outcomes • Advances in Hepatitis B Treatment and Outcomes • Hepatitis C • Updates on Antiretroviral Therapy • Updates on HIV Resistance • Selected Issues in Maternal and Pediatric Health

**CROI 2023: Epidemiologic Trends and Prevention for
HIV and Other Sexually Transmitted Infections** CME 468

Albert Y. Liu, MD, MPH; Susan P. Buchbinder, MD

Recent HIV Infections and HIV Incidence • Risk Factors for HIV Acquisition and Transmission • Partner Notification • HIV Testing • HIV Self-Testing • Effect of COVID on HIV Testing and Prevention Services • HIV Prevention Interventions • Sexually Transmitted Infections • PrEP

CROI 2023: Acute and Post-Acute COVID-19 CME 493

Anukka A. R. Antar, MD, PhD; Michael J. Peluso, MD

Acute COVID-19 • Pathogenesis and Immune Responses • Vaccines and Prevention • Post-Acute COVID-19 • Treatment Options • Vaccine Effectiveness, Uptake, and Equity • Nonpharmaceutical Interventions • Special Populations of Interest

**CROI 2023: Epidemiology, Diagnosis, and Management
of Mpox** CME 510

Jason Zucker, MD

Mpox Epidemiology • Mpox Diagnosis • Mpox Clinical Presentations and Management • Vaccination • Mpox and the Future Research Agenda

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CROI2023

Conference on Retroviruses and Opportunistic Infections

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

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

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Phone: (415) 544-9400

Website: www.iasusa.org

On the Web

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

ISSN 2161-5853 (Online)

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Grant Support

This activity is part of the IAS–USA national educational effort that is funded, in part, by charitable contributions from ineligible companies (formerly described as "commercial interests" by ACCME). Per IAS–USA policy, any effort that uses grants from ineligible companies must receive grants from several companies with competing products. Funds are pooled and distributed to activities at the sole discretion of the IAS–USA. Grantors have no input into any activity, including its content, development, or selection of topics or speakers.

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On completion of this activity, which contains 4 articles, the learner will be better able to:

- Describe the important new data presented at the 2023 Conference on Retroviruses and Opportunistic Infections on advances in antiviral therapy in HIV and viral hepatitis, and epidemiologic trends and prevention for HIV and other sexually transmitted infections
- Describe the pathogenesis and immune responses, vaccine options and preventative measures, and treatment options for acute and post-acute COVID-19
- Describe the current epidemiology of mpox, including diagnosis, clinical presentation, and treatment options

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Dr Buchbinder reported institutional grants/grants pending with Gilead Sciences, Inc., GlaxoSmithKline, and ViiV Healthcare. (Updated March 30, 2023)

Dr Gunaratne reported no relevant financial relationships. (Updated April 10, 2023)

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*Invited Review***CROI 2023: Advances in Antiviral Therapy in HIV and Viral Hepatitis**

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Abstract. Several innovative methods were presented at the 2023 Conference on Retroviruses and Opportunistic Infections (CROI) targeting different aspects of the HIV care continuum to improve testing, linkage to care, and viral suppression. Some of these approaches were directed at more vulnerable groups, such as pregnant women, adolescents, and individuals who inject drugs. In contrast was the devastating impact of the COVID-19 pandemic, with negative outcomes on HIV viral load suppression and retention in care. Data were presented on hepatitis B virus (HBV) suppression showing that tenofovir alafenamide (TAF)/emtricitabine (FTC)/bictegravir (BIC) may be superior to tenofovir disoproxil fumarate/FTC plus dolutegravir in suppressing HBV in HIV/HBV-coinfected individuals. A pilot study examining a 4-week trial of direct-acting antiviral therapy to treat hepatitis C in recently infected individuals showed lower rates of sustained virologic response at 12 weeks than longer courses. Additional data were presented on the use of long-acting cabotegravir/rilpivirine, comparing this regimen with oral TAF/FTC/BIC and the use of long-acting cabotegravir/rilpivirine in those with viremia. Data were presented on a novel strategy of lenacapavir with 2 broadly neutralizing antibodies given every 6 months as maintenance antiretroviral therapy

(ART). Data were presented on improving HIV care outcomes in adolescents, interventions to prevent mother-to-child transmission, and HIV reservoirs in children and adolescents. Data were also presented on interactions between ART and hormonal contraception, as well as ART-related weight gain and impact on pregnancy. A study examining BIC pharmacokinetics in pregnancy was presented, as well as retrospective data on outcomes of adolescents receiving TAF/FTC/BIC.

Keywords: HIV, HBV, hepatitis B, care, care continuum, antiviral therapy, ART, DAA, direct-acting antiviral, lenacapavir, long-acting antiretroviral therapy, maternal health, pediatric health

The HIV Care Cascade and Equity Issues in Care Outcomes

Medical and Structural Interventions to Improve the HIV Care Continuum

Several groups at the 2023 Conference on Retroviruses and Opportunistic Infections (CROI) presented multiple novel test and treat interventions that led to improvements in care engagement and viral suppression over time. Data were reported for infants, across a high-prevalence state in India, and among people who inject drugs (PWID) and their partners.

The utility of novel point-of-care (POC) nucleic acid test diagnostics in supporting early diagnosis and antiretroviral therapy (ART) initiation in infants was tested by Kroidl and colleagues in a cluster randomized study involving 28 maternity health centers in Mozambique and Tanzania (Abstract 132). The

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intervention arm ($n = 3295$) had POC testing and treatment at birth and at 4 to 8 weeks and 3 months of life and was compared with the control arm ($n = 13,310$), which had a dried blood spot saved at birth and POC testing and linkage to care at 4 to 8 weeks and 3 months of life. The primary outcome was a combined clinical outcome of death, hospitalization, severe medical condition, and retention in care. The investigators anticipated that recruitment of 6000 mother-infant pairs would lead to a total sample size of 224 infants with HIV. However, they found only 124 infants with HIV, 38 of whom were diagnosed at birth in the intervention arm. HIV incidence among the infants was 2.7% in Mozambique and 0.6% in Tanzania ($P < .001$ for difference), both of which are lower than regional estimates of a 4% rate of transmission. Median time to ART initiation for those infants diagnosed at birth was only 23 hours. Investigators found that, by 18 months, the rate of viral suppression to less than 1000 copies/mL was 66% in the intervention arm and 30% in the control arm ($P = .005$). They did find a difference in mortality between the intervention and control groups at 6 and 12 months; however, the difference was not significant at 18 months (adjusted hazard ratio [aHR], 0.823; 95% CI, 0.379-1.787). There was also no difference between groups in severe illness or retention at 18 months. Although the findings demonstrate that POC testing was feasible at birth, the complexity of assessing impact considering the smaller-than-anticipated sample size is limiting.

Ramien and colleagues implemented a comprehensive program of index testing that includes identification of partners, partner notification, partner testing, linkage to care, and ART initiation in Telangana, India, a high-prevalence state for HIV (Abstract 152). They reported on delays during each of these steps in the care cascade across 50 HIV testing and treatment facilities between July 2020 and January 2022. They found 9863 index cases, which led to 15,253 partners identified. The median age of partners was 32 years, 53% were women (including transgender women), and 51% were nonspousal sex partners. Telephone contact was the most common modality for partner notification (76%). The researchers were able to test for HIV in and deliver results to 13,335 (87%) of the contacts identified, of whom 2626 (20%) were diagnosed with HIV infection. Of those, 2423 (92%) initiated ART. Delays in testing and notification were found for nonspousal sex partners; the median time to notification for this group was 41 days, whereas the majority of spouses, children, and parents were identified, tested,

and notified of test results in the same day ($P < .05$). Encouragingly, once HIV testing was complete, treatment initiation did not take longer for nonspousal sex partners than for other risk groups. This approach to comprehensive index testing was successful, but the investigators noted unique challenges in engaging

Delays were found in HIV testing and notification for nonspousal partners, whereas the majority of spouses, children, and parents were identified, tested, and notified

nonspousal sex partners, which can delay ART initiation and allow for ongoing HIV transmission.

Monroe-Wise and colleagues presented data on the use of assisted partner services, whereby health care practitioners support partner identification, testing, and linkage to care for HIV and for hepatitis C virus (HCV) infections among PWID who also have HIV (Abstract 153). This process leaned heavily on peer educators and screened all partners for intimate partner violence; index partners with high risk of intimate partner violence were excluded. Of 989 index enrollments, 49% were female, 7.4% had HCV viremia, 11% reported either needle or equipment sharing in the last month, 81% were receiving ART, and 68% had viral suppression. Partners of the index patients had the following characteristics: 71% male, 90% injection drug use, 68% transactional sex, 6% with HCV viremia, and 18% with HIV. Of people with HIV among the partners, there was high awareness of status and care linkage; 76% were receiving ART, and 70% had viral suppression. Of 4705 partners mentioned by index patients, 97% were located and agreed to enroll in HIV and HCV testing. HIV and HCV prevalence varied by partner type. Among 712 sex-only partners, 25.1% tested positive for HIV and 9.2% were HCV antibody positive. Among partners who were injection and sex partners, 32.5% tested positive for HIV and 18.2% were HCV antibody positive. Injection-only partners had an HIV prevalence of 25.2% and an HCV antibody prevalence of 19.9%. Of the 597 partners with HIV, 85% were aware of their status and 358 (60%) were known to have viral suppression. Awareness and treatment of HCV was much less common; of the 393 partners with HCV, 54% were positive by polymerase chain reaction (PCR), only 26% were aware of their status, and 2% of

those had been previously treated for HCV infection. Of the 331 index patients and partners with HIV not receiving ART at enrollment, 72% were receiving ART after 6 months of follow-up. These data suggest that peer educator-led partner services for PWID can support identification and linkage to care for HIV and HCV among partners and that linkage services are impactful even for partners with HIV who know their status.

Dalal and colleagues presented findings from the rapid initiation of ART program in the Kaiser Permanente Northern California integrated health care system (Abstract 1083). Of 1409 people with HIV infection who were newly diagnosed between January 2015 and December 2020, 34% underwent rapid ART initiation within 7 days of diagnosis. After 1 year of follow-up, there were no differences in viral suppression between those with rapid ART start and those with standard (more than 7 days after diagnosis) ART start. However, the rapid ART start group had 90.2% care retention at 1 year, compared with 94.5% in the standard group ($P < .001$). Follow-up data over 6 years showed concerning trends, with lower care retention, medication adherence, and viral suppression in those with rapid ART start. Although these data are limited to a single center, they support the need for close monitoring of long-term care outcomes of rapid start programs.

Many investigators used pragmatic trial designs and other innovative strategies to deploy multicomponent interventions to improve the HIV care continuum. Interventions presented at CROI occurred at the clinic level and were also targeted at key populations, including pregnant and postpartum women, mobile individuals, youth, and PWID.

Sikombe and colleagues used a stepped-wedge cluster randomized trial design to test the impact of a clinic-level patient-centered care intervention across 24 care centers in Zambia (Abstract 201). The intervention consisted of training of clinic staff in patient-centered care; collection of patient experience data through exit interviews, with feedback of results provided to staff; and a small, facility-level performance incentive. A subset of the patients ($n = 933$) was selected for assessment of the primary outcome of HIV viral load of greater than 400 copies/mL and was representative of the population served by the clinics: 58% female and median age of 37 years. Using a mixed-effects regression of intervention effect with facility as a random effect, the intervention had no statistically significant impact on viral suppression. However, the fraction of respondents reporting a poor experience using the physician-patient communication

scale fell by 14% when the intervention had been sustained for more than 6 months. Over the course of the intervention, there was a 70% reduction in visits with a bad experience across all clinics. Among 84,954 patients, the risk difference for retention in care at 15 months was 5.9% (95% CI, 0.6-11.2) greater in the intervention arm and even more pronounced for those newly initiating ART. These data suggest that a clinic-level practice facilitation intervention focused on patient experience can significantly improve patient experience and retention in care.

HIV suppression to less than 1000 copies/mL increased from 70% at baseline to 95% at 12 months in the intervention group, with an absolute risk difference of 25%

Kabami and colleagues developed a multicomponent intervention to improve viral suppression among pregnant and postpartum individuals with HIV (Abstract 130). In a cluster randomized trial, they enrolled participants across public health facilities in southwestern Uganda between September 2019 and October 2020. The intervention included enhanced viral load counseling, which included specific training in meaning and importance of viral suppression for prevention of mother-to-child transmission (MTCT), and support from peer mothers trained in this new counseling method. POC viral load monitoring was also included in the intervention. Fourteen public health facilities were randomly assigned, with 505 individuals in the intervention arm and 355 in the control arm. The median age in both groups was 28 years, and 76% of participants were married. Viral suppression to less than 1000 copies/mL increased from 70% at baseline to 95% at 12 months in the intervention group, with an absolute risk difference of 25% (95% CI, 22%-28%; $P < .001$). A secondary endpoint of disclosure of HIV status also showed improvements, with a 10% increase in disclosure to anyone ($P = .011$) and a 10% increase in disclosure to a spouse or partner ($P = .015$). The analysis was limited by lack of endpoint ascertainment in the control group, so comparisons of viral suppression between intervention and control clinics were not possible.

Ayieko and colleagues from the SEARCH (Sustainable East Africa Research in Community Health) collaborative tested a mobile patient-centered care intervention in a randomized controlled trial in Uganda and Kenya (Abstract 200). Adults with HIV were eligible for inclusion if they spent 2 or more weeks in the last 12 months outside their home community and had either HIV viral load greater than 400 copies/mL or 2 or more missed visits in the past 12 months. Participants were randomly assigned 1:1 to standard of care (control) or a mobile intervention, which included a travel pack with a 14-day emergency ART supply in discrete packaging and packing checklist, off-site and 4- to 6-month refills, a mobility coordinator to assist with ART and care access outside of the community, and screening for travel at each visit with flexible clinic scheduling. Of 201 participants randomly assigned, 54% were female, 17% had a baseline viral load of more than 400 copies/mL, and 25% were considered highly mobile with more than 14 nights away from home in the preceding 3 months; missing 2 or more visits was the most common inclusion criterion.

Investigators monitored which components of the mobile intervention were most used by those in the intervention arm over 36 weeks and found that 100% of participants used at least 1 of the components, with the travel pack with emergency ART being the most popular. No significant difference between groups was observed in the primary outcome: viral suppression below 400 copies/mL at 48 weeks of follow-up (relative risk, 0.99; 95% CI, 0.88-1.10; $P = .595$). There was also no difference in outcomes in 3 prespecified subgroups: those with nonsuppressed viral load at baseline, highly mobile individuals, and those reporting alcohol use. However, the secondary outcome of proportion retained in care at 48 weeks was higher in the intervention arm (99%) than in the control arm (93%; relative risk, 1.06; 95% CI, 1.02-1.10; $P < .001$). The greatest effect on retention in care was seen in those with baseline nonsuppression, with 100% retained in the intervention group and 77% in the control group ($P = .013$); and in those who were highly mobile, with 98% retained in the intervention group and 81% in the control group ($P < .001$). The secondary outcome of ART possession rate, the proportion of follow-up days with ART over 48 weeks as determined by clinic refill records, was also higher in the intervention group than in the control group. These findings show that the intervention had high uptake and, although it did not have an impact on viral suppression, it did improve retention in care,

particularly for those with unsuppressed viral load and high mobility.

Naggirinya and colleagues presented data from a prospective randomized controlled trial of the mHealth tool, Call for Life, in 3 facilities in a remote district in Uganda (Abstract 202). They enrolled 15- to 24-year-olds with HIV in the program, which is an interactive voice response system that provides pill and appointment reminders, assists with symptom screening, and delivers weekly health tips. A total of 206 participants were enrolled, with baseline characteristics comparable between the intervention and standard of care groups. The primary outcome, viral suppression below 1000 copies/mL at 12 months, was 73.6% in the intervention arm and 51.9% in the standard of care arm ($P = .004$). There was no difference in retention in care at 12 months between groups. An adjusted analysis examining factors associated with detectable viral load at 12 months included female sex, having no sexual partner, and “simply forgot pills.” These findings are encouraging, particularly considering the known disparities in treatment outcomes for this age group.

Another youth-focused intervention, the Suubi+ Adherence study—a longitudinal cluster randomized trial examining the impact of an economic empowerment intervention—was reported by Kizito and colleagues (Abstract 814). The intervention included long-term child development accounts, microenterprise workshops, and 12 mentorship and educational sessions targeted at adolescents with HIV. Among 455 adolescents with HIV with a median age of 12.6 years, investigators found that adherence, as determined by pill counts, was higher in the intervention group over time. The odds ratio (OR) for adherence in a mixed-effects regression model was increased at each visit, rising to 2.05 (95% CI, 1.41-3.00) odds of adherence in the intervention arm compared with the standard of care arm by the sixth intervention visit. The success of this intervention highlights the intersection between economic empowerment and positive health behaviors such as adherence to ART.

Samet and colleagues tested a multicomponent intervention linking HIV and substance use treatment in Russia among PWID with HIV (Abstract 203). The intervention included rapid access to ART, naltrexone treatment, and strengths-based case management with a peer case manager. The investigators enrolled 225 individuals with HIV who were hospitalized at a center for addiction in Russia between September 2018 and March 2022. The control and intervention arms were well matched, with a mean age of 37 years,

60% male, 31% employed, 33% ever previously receiving ART, and a mean of 10 years since diagnosis. In the intervention group, 90% of individuals initiated ART within the study period, but only 57% received the baseline naltrexone injection and 9% received the prescribed 4 naltrexone implants. Regarding the primary outcome, 46.9% in the intervention group achieved an undetectable (<40 copies/mL) viral load at 12 months, a statistically significant difference from viral suppression in the control group (22.7%; adjusted OR [aOR], 3.04; 95% CI, 1.44-6.44). The investigators also measured the likelihood of ART initiation within 28 days, which was 73.9% in the intervention arm and 11.4% in the control arm (aOR, 23.23; 95% CI, 11.13-48.07). A combined outcome of an undetectable viral load and reported 30 days of opioid abstinence was also more common at 12 months in the intervention group than in the control group (aOR, 6.51; 95% CI, 2.08-20.40). The investigators concluded that the intervention was more effective than the standard of care in supporting ART initiation, retention in HIV care, and viral suppression, despite limitations on modalities for substance use disorder treatment in Russia.

Little is known about the impact of ART diversion (ie, when someone prescribed ART gives or sells the medication to another person with HIV without authorization from a provider) for therapeutic purposes on treatment outcomes. Kennedy and colleagues used data from the Rakai Community Cohort Study to assess the prevalence of ART diversion on a population level (Abstract 206). Of 2852 people with HIV, 9.3% reported ART diversion at some point and 6.8% reported diversion over the past year. Giving and receiving ART were the most common behaviors, with few participants reporting buying ART and none reporting selling it. Men were more likely than women to report diversion: 12.9% compared with 7.4%. Those who reported only giving ART to others rather than receiving it were more likely to have a viral load greater than 1000 copies/mL (prevalence ratio, 2.04; 95% CI, 1.14-3.36). Those who only received ART, both gave and received ART, or bought ART did not have an increased risk of detectable viral loads. Considering the association between giving ART to others and virologic failure, the investigators encourage the incorporation of messaging about ART sharing in adherence counseling.

Sustaining the HIV Care Continuum and Research in Times of Crisis

A themed discussion session highlighted the extraordinary work in maintaining HIV services occurring under

conditions of civil unrest in Haiti and Ethiopia. Marc and colleagues presented data on successful ART initiation at GHESKIO (the Haitian Study Group on Kaposi's Sarcoma and Opportunistic Infections), a nongovernmental organization providing HIV and primary care, in the context of civil unrest (Abstract 1077). Since September 2022, a political crisis in Haiti has led to armed gang control of 50% of the country and destabilization of transportation, energy, and food supplies coupled with violence and loss of many health care workers to migration. In this context, GHESKIO offers comprehensive care that includes transportation, food support, primary and vocational schools, community ART refills, and counseling based on motivational interviewing. Between December 2020 and June 2022, 246 patients initiated ART with tenofovir disoproxil fumarate (TDF), lamivudine (3TC), and dolutegravir (DTG). Of the 169 patients with 12 months of follow-up, 138 (82%) received a viral load measure-

GHESKIO offers comprehensive care that includes transportation, food support, primary and vocational schools, community ART refills, and counseling based on motivational interviewing

ment and 124 (73% of total) had a measurement of less than 200 copies/mL. Loss to follow-up occurred in 6%, and 4 patients died. The presenters attributed their success to innovative strategies of care delivery and cohesive teams with strong connections to the most marginalized communities.

Pierre and colleagues presented complementary data to the GHESKIO experience from their research in Haiti over the past 3 years (Abstract 1076). They noted many challenges in continuing their 22 ongoing research trials in this context, including the relevance of the research questions, the ethics of engaging participants, recruitment barriers of transportation and decentralized clinics, need for in-person procedures, retention, and the security, safety, and mental health of participants and staff. They propose a GHESKIO model for conduct of research under these circumstances, with an emphasis on collaborative leadership, community engagement, enhanced communication, and structural support for participants and staff. Under

these circumstances, they were able to enroll 231 individuals in a randomized controlled trial comparing ART regimens, with 93.5% of participants achieving viral suppression and only 5 lost to follow-up or discontinued. Some of the same factors that influenced engagement in care described above were cited as reasons for their success, including comprehensive social and structural support for participants and the study team.

Habte and colleagues presented data from Amhara, Ethiopia, a location where more than 50% of the region experienced violent conflict between June and December 2021 (Abstract 1078). During this time, the number of people receiving ART decreased from 146,092 to 120,967, and an emergency response task force was convened at the end of the conflict to restore HIV care services. The investigators found that 105 of the 189 health care facilities providing ART had been damaged or looted during the conflict, with 53% unable to provide ART and 76% without laboratory services. They used backup electronic medical records to identify 36,436 individuals whose ART had been interrupted and restart their medication. By April 2022, 5 months after the conflict ended, 183 of the 189 health care facilities were able to reinstate ART delivery services, and by June 2022 147,817 individuals were receiving ART in Amhara. The authors attributed the rapid reinstitution of services to strong governmental coordination, “Back to Care” campaigns at the clinician and community levels, and pairing of clinics within the conflict zone with those outside of the conflict zone for support. They plan to use similar strategies in other parts of Ethiopia currently experiencing conflict to restore HIV and other health care services.

New Data for Estimating Mortality and Causes of Death in People With HIV

CROI 2023 also highlighted encouraging data on reductions in mortality among people with HIV across the globe, and new strategies, including molecular diagnostics and verbal autopsies, were used to provide more accurate assessments of causes of death.

Data from RESPOND (the International Cohort Consortium of Infectious Disease), which represents 17 cohorts and 33,598 people with HIV across Europe and Australia, were used to determine trends in mortality between 2012 and 2019, with retrospective data used from 2012 to 2017 and prospective data from 2018 to 2019 (Abstract 870). In an analysis including 167,930 person-years of follow-up, age-adjusted, cause-specific mortality decreased over time for AIDS,

non-AIDS-defining malignancies, cardiovascular disease, liver disease, and other causes. Conditions that were associated with an adjusted incidence rate ratio

The authors attributed the rapid reinstitution of services to strong governmental coordination, “Back to Care” campaigns at the clinician and community levels, and pairing of clinics within the conflict zone with those outside of the conflict zone for support

for mortality of 2 or higher in a multivariable time-updated Poisson regression included current CD4+ count of 350 cells/μL or less and HIV viral load greater than 200 copies/mL, end-stage renal disease, cardiovascular disease, chronic untreated hepatitis C, end-stage liver disease, and being a current smoker. Limitations of this analysis include possible selection bias in the retrospective data and the fact that cause of death was unknown or missing for some participants. These findings indicate that improvements in virologic suppression or control of chronic conditions could reduce mortality in the cohorts.

Trickey and colleagues used data from ART-CC (the Antiretroviral Therapy Cohort Collaboration) to explore trends in causes of death among people with HIV between 1996 and 2020 (Abstract 156). Mortality rates in the cohort declined from 16.8 (95% CI, 15.4-18.4) per 1000 person-years between 1996 and 1999 to 7.9 (95% CI, 7.6-8.2) per 1000 person-years between 2016 and 2020. Investigators used the Coding Causes of Death in HIV (CoDe) protocol to classify death by a single cause. Investigators were able to assign causes of death to 78% of 16,832 deaths among 189,301 people with HIV during the observation period. The adjusted mortality rate ratio for AIDS-related mortality per 4 years was 0.82 (95% CI, 0.80-0.84), and adjusted mortality rate ratios for cardiovascular disease, suicide, liver disease, and non-AIDS infection all showed statistically significant declines. However, declines were not observed in central nervous system disorder, respiratory, and substance use-related mortality. These data suggest that individuals with HIV and substance use disorder deserve particular attention, along with other non-HIV-related causes,

to reduce mortality among people with HIV.

In Malawi, an estimated 62% to 86% of deaths occur in the community rather than in a medical facility, which leads to challenges in estimating HIV/AIDS-related mortality. Kalata and colleagues piloted the 2016 World Health Organization (WHO) Verbal Autopsy electronic questionnaire in 2 geographic clusters to estimate the proportion of deaths due to HIV/AIDS in the community between January and August 2022 (Abstract 872). In a sample that included approximately 260,000 individuals, they found 354 deaths during this time frame, of which 54% occurred in the community. They were able to assign cause of death using the virtual autopsy method to 91% of those 190 deaths. Of the 164 deaths occurring in a health care facility, only 52% were assigned a cause of death. Noncommunicable diseases were the primary cause of death in the community, and HIV was the second-leading cause of death (17%). In health care facilities, cause of death differed, with death from complications of malaria being most common (22%); the proportion of deaths due to HIV (5%) was much lower and the average age of decedents was younger than in the community. These findings suggest that more HIV/AIDS deaths are occurring in the community and that virtual autopsy may lead to more accurate estimates of death due to HIV/AIDS on a population level.

Data from the PHIA (Population-Based HIV Impact Assessment) project were used to estimate mortality associated with HIV using 11 nationally representative cross-sectional household surveys conducted between 2015 and 2019 (Abstract 873). The investigators compared mortality in households with and without members with HIV in the 3 years preceding the survey and found 5 countries with significantly higher death rates in households with members with HIV in Malawi, Kenya, Tanzania, Zambia, and Zimbabwe—but no differences in 6 other surveyed countries. These data suggest that, in the absence of clear cause-of-death assessments, representative surveys comparing households with and without people with HIV can provide insights into HIV-related mortality.

Sabin and colleagues analyzed mortality rates between 2000 and 2019 in the Royal Free Hospital in London among 221 people with HIV 1 year after intensive care unit (ICU) admission (Abstract 874). They found that cumulative 1-year mortality was 50% but that mortality rates differed dramatically over time. Every year led to a 7% reduction in 1-year mortality after adjustment for age, sex at birth, Acute Physiology and Chronic Health Evaluation II (APACHE II) score,

CD4+ cell count, and recent HIV diagnosis. Although this was a single-center study in a hospital that delivers specialty care for people with HIV, these data suggest that HIV status should not play a role in the choice of admission to an ICU and that overall ICU-related mortality in this population is improving over time.

Rebeiro and colleagues examined the impact of registry linkage on survival estimates among people with HIV in Brazil, Mexico, and Peru, all of which have robust mortality, ART, and CD4+ cell count and viral load electronic registry systems (Abstract 875). They found that ascertainment added 15% to the number of overall deaths in these 3 cohorts. The impact of registry linkage varied by country. In Brazil, the number of deaths increased, but survival also increased because of increased follow-up time. In Mexico, the estimated number of people who had transferred to other care facilities decreased, and estimates of mortality increased. The investigators concluded that local registry linkage can be a useful tool in reducing measurement errors in survivorship in Latin America.

Data from the CHAMPS (Child Health and Mortality Prevention Surveillance) network were used to determine causes of death in children under 5 years of age with HIV in the high-prevalence countries of Kenya, Mozambique, Sierra Leone, and South Africa using minimally invasive tissue sampling (Abstract 133). CHAMPS study methods include notification of all stillbirths and deaths in children under 5 years of age, consent and enrollment within 24 hours of death, clinical and surveillance record abstraction, verbal autopsy, minimally invasive tissue sampling, testing for various infectious pathogens including HIV and those causing tuberculosis and malaria, and an expert panel to determine cause of death based on information gathered. CHAMPS enrolled 4292 decedents between 2017 and 2021 across the 4 countries, and cause of death was determined in 3030 of these. The investigators found that only 49% of the 108 children with HIV were known to have HIV before their death, but this percentage varied across countries, from 23% in Sierra Leone to 67.9% in South Africa. The expert panel also determined that 92.6% of the deaths were preventable. The proportion of HIV-associated deaths increased over time in every country except for South Africa, and 97% of HIV-related deaths had other infectious processes in the causal chain, with bacterial infections being the most common. The adjusted cause-specific mortality rate for HIV in children under 5 years of age varied from a low of 1.2 per 1000 live births in

South Africa to a high of 6.4 per 1000 live births in Mozambique. The investigators noted that HIV-related deaths are likely underreported considering the number of HIV diagnoses made after death and that most of these deaths were avoidable, indicating that further interventions are needed.

Impact of the COVID-19 Pandemic on HIV Services and Outcomes

Several abstracts at CROI highlighted the detrimental impact of the COVID-19 pandemic on HIV services and the disproportionate effect on marginalized groups. Viguier and colleagues estimated the effect of the COVID-19 pandemic on HIV diagnoses across the United States in 2020 (Abstract 158). They used the CD4+ depletion model to develop different methods to estimate missed diagnoses in 2020. They found that

The proportion of HIV-associated deaths increased over time in every country except for South Africa, and 97% of HIV-related deaths had other infectious processes in the causal chain, with bacterial infections being the most common

there were 3100 to 3300 fewer HIV diagnoses than projected for 2020 than for 2010 through 2019. This particularly impacted women, PWID, and Hispanic and Latino individuals, who had higher levels of missed diagnoses. They concluded that the drop in HIV diagnoses in 2020 was suggested by decreases in testing during 2020, and that different subgroups were affected disproportionately by the decrease in testing. Tucker and colleagues presented data on HIV viral load suppression and racial disparities among people with HIV in New York City during the COVID-19 pandemic, studying cohorts engaged in care and those out of care (Abstract 891). Before the pandemic, the out-of-care group had lower rates of viral suppression than the in-care group, and this gap widened in 2021. The rates of viral load suppression were lower in Black and Hispanic patients, including when they reentered care in 2021. Spinelli and colleagues showed trends in decreased HIV viral load suppression in HIV clinics across the United States (Abstract 1094). They

observed slowing gains in improved viral load suppression during the pandemic, with greater impacts on PWID, women, and Black patients with HIV. Hall and colleagues examined a cohort of individuals with HIV in Saskatchewan, Canada, and found similar decreases in retention in care (58.1% in 2019 and 51.3% in 2022; $P = .02$) and trends in rates of viral load suppression (76.1% in 2019 and 68.8% in 2022; $P = .06$) (Abstract 893). Unfortunately, they observed 80 deaths, or 15.4% of the studied population; most deaths were attributed to drug overdose or complications from injection drug use. Post evaluated HIV outcomes during the pandemic for a cohort of Black people with HIV in the United Kingdom (Abstract 1095). A total of 17.5% of the cohort had either HIV viremia (with a viral load >200 copies/mL) or an interruption in ART. Nassau and colleagues reported on HIV testing in PWID in Philadelphia from 2018 to 2022 and found a decrease of 18% in recent HIV testing over that period (adjusted prevalence ratio, 0.82; 95% CI, 0.70-0.96; $P < .001$) (Abstract 1100).

Advances in Hepatitis B and C Epidemiology and Treatment

Advances in Hepatitis B Treatment and Outcomes

Taddese presented data on hepatitis B virus (HBV)-infected hepatocytes in individuals with HIV/HBV coinfection receiving tenofovir/emtricitabine (FTC) therapy (Abstract 115). They observed that HBV infection persisted in hepatocytes despite low or undetectable HBV viremia, although the proportion of infected hepatocytes decreased after exposure to tenofovir/FTC therapy. Avihingsanon and colleagues presented data on HBV viral suppression from a phase III study comparing tenofovir alafenamide (TAF)/FTC/bictegravir (BIC) with TDF/FTC plus DTG in people with HIV and HBV (Abstract 116). Those treated with TAF/FTC/BIC and with either HBV envelope antigen positivity or baseline HBV viral loads less than $8 \log_{10}$ IU/mL had significantly higher rates of HBV viral suppression (HBV DNA level <29 IU/mL) than those treated with TDF/FTC plus DTG. In their multivariate analysis, treatment with TAF/FTC/BIC was an independent predictor of HBV viral suppression, suggesting that TAF/FTC/BIC is superior to TDF/FTC plus DTG in suppressing HBV in coinfecting individuals.

Begré and colleagues compared HBV RNA and HBV core-related antigen (HBcrAg) in a matched cohort study of individuals with HIV with functional HBV

cure (defined as first quantitative HBV surface antigen [HBsAg] test result <0.05 IU/mL) and those with ongoing HBV infection receiving tenofovir (Abstract

Data were presented on the efficacy and safety of bulevirtide, an antiviral agent that inhibits HBV and HDV, in patients with HIV/HBV/HDV coinfection

586). They observed greater decreases in HBcAg in individuals receiving tenofovir therapy with functional HBV cure than in those without functional cure at 1 year ($P=.04$) and 5 years ($P=.003$). They also observed that those with functional cure were more likely to have HBV RNA undetectable at 5 years than those without functional cure ($P=.02$). The study authors concluded that HBV RNA and HBcAg could be used as predictive markers for HBV functional cure in individuals with HIV.

Wandeler analyzed HBV outcomes in patients with HIV/HBV coinfection treated with tenofovir-based ART, with a median duration of 5 years of follow-up (Abstract 587). Baseline characteristics of their cohort included median CD4+ count of 192 cells/ μ L. A total of 46% had an HBV DNA viral load greater than 2000 IU/mL, and nearly 24% had substantial fibrosis or cirrhosis. They observed regression of fibrosis (80.4%) and cirrhosis (93.8%) in this cohort, with no progression to cirrhosis and no cases of hepatocellular carcinoma. No demographic characteristics were associated with loss of HBsAg; HBsAg clearance occurred at a rate of 15.8% at 5 years. High HBV DNA level, HIV/AIDS WHO stage 3 or 4, and decreased adherence to ART (seen with detectable HIV RNA) were associated with unsuppressed HBV DNA.

Mizushima and colleagues examined acute HBV infection and serologies in HIV-negative men who have sex with men (MSM) who received HBV vaccine or were receiving tenofovir-based preexposure prophylaxis (PrEP) (Abstract 588). They defined acute HBV infection as either a positive HBsAg test result at the time of enrollment with clearance within 6 months or HBsAg or HBV core antibody (HBcAb) seroconversion during the study period. There were no cases of

HBsAg positivity or symptomatic hepatitis in those with HBV prophylaxis (vaccination or tenofovir-based PrEP). Those MSM with transient HBcAb positivity were more likely to have received HBV prophylaxis ($P = .006$). Interestingly, HBV DNA was detected in 1 out of 3 cases with transient HBcAb positivity. The study authors define this phenomenon of infection without positive or transient serology as “microinfection” and encourage further studies to determine its clinical importance.

De Ledingham and colleagues presented data on efficacy and safety of bulevirtide, an antiviral agent that inhibits HBV/hepatitis D virus (HDV) entry into cells, in patients with HIV/HBV/HDV coinfection (Abstract 589). Fourteen of 21 patients received bulevirtide alone, and 7 of 21 patients received a combination of bulevirtide and pegylated interferon gamma. All patients were also receiving TAF/FTC as part of ART. Mean HDV RNA level declined in most patients (77.7% in the bulevirtide monotherapy group, 71.4% in the bulevirtide and pegylated interferon gamma group). The investigators did not observe any adverse effect of bulevirtide on HIV viral suppression or CD4+ cell counts.

Hepatitis C

Advances in hepatitis C treatment. Martinello and colleagues presented data from the TARGET3D (Treatment of Recently Acquired Hepatitis C With the 3D Regimen or G/P) pilot study examining the efficacy of a 4-week course of glecaprevir/pibrentasvir in patients with recent HCV infection acquired within 12 months (Abstract 194). They defined recent HCV infection as either acute hepatitis within the past 12 months plus a positive HCV antibody or RNA test within 6 months of enrollment or HCV antibody seroconversion within 18 months. Those with a newly positive HCV RNA test within 6 months of enrollment and prior cure or clearance of virus were also included as recently reinfected patients. The primary endpoint studied was sustained virologic response at 12 weeks (SVR12). The study participants included 23 individuals in the United Kingdom, Australia, and New Zealand; 96% were men. A total of 70% had HIV, and 35% were cases of reinfection. A total of 74% of cases had genotype 1, 9% had genotype 3, and 4% had genotype 2. The median HCV RNA level was 5.8 \log_{10} IU/mL. The primary endpoint of SVR12 was achieved in 78% of those in the intent-to-treat group and in 82% of those in the per-protocol group. Of the 4 cases of confirmed virologic failure, 3 participants received retreatment with 12 weeks of

either sofosbuvir/velpatasvir or grazoprevir/elbasvir and 2 achieved SVR. Fully 100% of those who had an HCV RNA level of less than 6.5 log₁₀ IU/mL achieved SVR12. The median baseline HCV level in those who had virologic failure was 7.3 log₁₀ IU/mL. Overall, the study authors concluded that rates of SVR were lower in patients recently infected with HCV who were treated with 4 weeks of glecaprevir/pibrentasvir than in those treated with longer regimens (6-8 weeks).

Updates on hepatitis C testing and epidemiology. Silveira and colleagues presented data on the incidence of HCV infection in MSM in New York City from 2000 to 2022 (Abstract 590). The incidence of HCV infection was 0.47 per 100 person-years in MSM using PrEP, compared with 0.96 per 100 person-years in MSM with HIV infection ($P = .004$). The incidence of HCV infection in MSM not using PrEP (without HIV infection) was 0.07 per 100 person-years ($P = .01$ for comparison with MSM using PrEP). The study authors concluded that MSM using PrEP are an at-risk group for HCV acquisition and may benefit from increased testing and interventions.

Yang presented data on the optimal interval for HCV RNA testing in individuals with HIV who were identified to be at risk for HCV acquisition (either recently diagnosed with sexually transmitted infections [STIs], with prior HCV infection that had been treated or cleared, or with elevated aminotransferase levels) (Abstract 595). They calculated incidence rates and proportion of delayed viremia in this at-risk group and found that 91% of diagnoses would have been delayed if HCV RNA testing occurred every 12 months and 58.6% would have been delayed if testing occurred every 6 months. They calculated that these participants would have had more than 10,000 infectious days than if they had been screened every 3 months, with implications for ongoing HCV transmission. The authors concluded that increased intervals of HCV RNA screening for those at risk of HCV acquisition led to delay in diagnoses and potential for forward transmission.

Han and colleagues presented data on novel HCV subtypes found in 7 participants in the ACTG (AIDS Clinical Trials Group) A5360 MINMON (A Minimal Monitoring Approach for the Treatment of Hepatitis C Virus Infection) trial, including HCV genotype 4 subtypes and subtype 7c (Abstract 596). Despite all 7 participants with these novel subtypes having either NS3, NS5A, or NS5B resistance, all were able to achieve SVR12 with 12 weeks of sofosbuvir/velpatasvir.

Carson and colleagues examined changes in risk of HCV and STI acquisition among participants in the REACT (Recently Acquired HCV Infection Trial) study after antiviral treatment (Abstract 603). A total of 84% of the 212 participants identified as MSM. A total of 26% of participants reported injection drug use in the month before their enrollment, with no change in trajectory of injection drug use after HCV treatment. A total of 60% of participants had been diagnosed with an STI in the 12 months before enrollment, and their modeling showed no change in trajectories of chemsex. The incidence of HCV reinfection was 13.2 per 100 person-years, with higher rates in the groups with higher probabilities of injection drug use or chemsex. As a result, the authors concluded that treatment of individuals with newly acquired HCV is key to prevent

Treatment of individuals with newly acquired HCV is key to prevent transmission, and continued testing to detect reinfection is recommended given the persistence of behaviors after treatment

transmission and recommended continued testing to detect reinfection given persistence of behaviors after treatment. Similarly, Hage and colleagues examined behavioral risk factors of MSM with HIV who were treated for HCV infection and found that those treated with direct-acting antiviral agents had more persistent or higher-risk behaviors than counterparts treated with interferon alfa-based regimens and were at risk for HCV reinfection, emphasizing the importance of counseling and testing this patient population (Abstract 604).

HCV self-testing (HCVST) was studied by Perazzo and colleagues, who examined its feasibility in Brazil (Abstract 592). They found that 62% of participants were able to complete the self-test without help from a health care worker. Interreader agreement of the results was high at 94.4% (kappa, 0.52), and agreement between the HCVST and health care worker-conducted oral HCV rapid tests was 99.6% (kappa, 0.67). Nichols presented data on HCVST in Georgia, Malaysia, and Pakistan and found that HCV

testing was higher in the HCVST groups than in the standard of care group, in which patients were referred to an HCV testing center (Abstract 593). Linkage to care also appeared to be higher in most self-testing groups than in the standard of care group. These abstracts show the potential use and benefit of HCVST in the community.

Updates on Antiretroviral Therapy

Long-Acting Cabotegravir and Rilpivirine

Ramgopal presented data from the SOLAR (Study to Evaluate Efficacy and Safety of Cabotegravir Long Acting Plus Rilpivirine Long Acting Versus BIKTARVY® in Participants With Human Immunodeficiency Virus [HIV]-1 Who Are Virologically Suppressed) trial, a randomized clinical trial of switching patients with viral suppression on BIC/FTC/TAF to long-acting cabotegravir and rilpivirine (LA CAB/RPV) dosed every 2 months compared with continuing BIC/FTC/TAF (Abstract 191). A total of 672 participants were randomly assigned 2:1 to LA CAB/RPV and BIC/FTC/TAF; 40% of the LA CAB/RPV participants chose to start with an oral lead-in. The primary endpoint was 1 year after randomization. At that time, 1% of the LA CAB/RPV group and less than 1% of the BIC/FTC/TAF group experienced plasma HIV RNA levels greater than 50 copies/mL according to the US Food and Drug Administration (FDA) snapshot algorithm: difference 0.7%; 95% CI, -0.7% to 2.7%. This result met the protocol-defined definition of noninferiority. Three participants receiving LA CAB/RPV experienced virologic failure; all had RPV resistance-associated mutations emerge, and 2 had integrase strand transfer inhibitor (INSTI) resistance-associated mutations emerge. Most participants receiving CAB/RPV preferred the injectable regimen and reported greater treatment satisfaction.

Rubenstein and colleagues reported data on drug concentrations in patients starting every-2-month dosing of LA CAB/RPV (Abstract 195). This cohort study enrolled 58 people with HIV with viral suppression: 88% men, median age 30 years. They received CAB 900 mg/RPV 600 mg at baseline and again 1 month later; these are the standard doses when initiating every-2-month LA CAB/RPV. A subset of participants received 4 weeks of oral CAB/RPV before initiation of injectable CAB/RPV. Drug concentrations were obtained 1 month after the first dose (just prior to the second dose) and 2 months after the second dose. These concentrations were compared with those observed in the pivotal phase III trials of LA CAB/RPV.

The investigators found that RPV concentrations were similar to those observed in the comparator group. The concentrations of CAB were lower than in the comparator group, with 60% of participants having concentrations in the lowest quartile observed in the comparator group at 1 month and 77% at 3 months. The concentrations were lower in the group that did not have 4 weeks of oral dosing before receiving injectable CAB/RPV. Virologic failure occurred in 1 participant. The authors concluded that an oral lead-in should be considered before initiating every-2-month dosing of CAB/RPV. Additional data are needed to understand the clinical significance of these lower-than-expected CAB concentrations.

Felizarta and colleagues reported data on the pharmacokinetics (PK) and tolerability of intramuscular thigh administration of LA CAB/RPV as an alternative to gluteal injection (Abstract 519). They enrolled a subset of participants receiving every-8-week and

Data supported short-term thigh administration of LA CAB/RPV for those experiencing fatigue with gluteal administration, but more data are needed on long-term thigh administration

every-4-week gluteal injections in the ATLAS-2M (Long-Acting Cabotegravir and Rilpivirine Dosed Every 2 Months in Adults With HIV-1 Infection) study and changed them to thigh administration. The concentrations were generally similar in the 2 forms of administration, although many parameters were statistically significantly higher with thigh administration. Although thigh administration was generally tolerated, only 30% of participants preferred thigh administration. The authors suggested that the data supported short-term thigh administration for those experiencing fatigue with gluteal administration. They noted that more data are needed to assess long-term thigh administration of CAB/RPV.

Gandhi and colleagues presented data from a single-center study of giving LA CAB/RPV in a population experiencing numerous challenges including housing instability, active substance use, and mental health issues (Abstract 518). They initiated injectable CAB/RPV without an oral lead-in in 133 people, of whom

57 (43%) had ongoing viremia with a mean plasma HIV RNA level of 4.21 log₁₀ copies/mL. This cohort received social supports available through routine care to support adherence to the injectable regimen. Among those who started LA CAB/RPV while being virally suppressed, all remained suppressed in follow-up. Among those initiating CAB/RPV while viremic, virologic failure occurred in 2. The rest achieved viral suppression or were responding appropriately at the time of analysis. These data suggest that additional studies are needed to characterize the efficacy of this regimen in those with viremia who do not achieve viral suppression with oral ART.

Chen and colleagues investigated the use of LA CAB/RPV in patients with viremia who did not achieve viral suppression despite oral ART using the CEPAC (Cost-Effectiveness of Preventing AIDS Complications) microsimulation model (Abstract 517). They modeled the comparison between standard of care with oral InSTI-based ART, oral InSTI-based ART with wraparound services to improve adherence, and LA CAB/RPV with wraparound services. The characteristics of the modeled population were based on that reported by Gandhi and colleagues (Abstract 518). The viral suppression rates were based on the existing literature: 25% for standard of care, 49% for standard of care and wraparound services, and 60% for LA CAB/RPV with wraparound services. The model favored LA CAB/RPV, with expected gains in life expectancy and better suppression over time. These findings held in several supporting analyses in which the input parameters were varied. On the basis of these data, the authors concluded that a clinical trial was urgently needed to further characterize the efficacy of LA CAB/RPV in this population experiencing an unmet medical need.

Islatravir

Islatravir (ISL) is an investigational nucleoside reverse transcriptase (RT) translocation inhibitor. The clinical development of this compound was placed on hold because of drug-associated lymphopenia and CD4+ cell count decreases. The clinical program has since resumed using lower doses. Squires and colleagues presented detailed data on this adverse effect (Abstract 192). Data from 1420 people with HIV and 884 people without HIV were included. The mechanism of the drug adverse effect is suprathreshold accumulation of ISL triphosphate in lymphocytes leading to apoptosis. Lymphopenia is not a result of mitochondrial damage. The development of monthly oral

ISL has been discontinued. The development of daily oral and weekly oral ISL for treatment of HIV has resumed. Higher doses of ISL led to greater declines of total lymphocyte counts. For those receiving monthly dosing, the lymphocyte count returned to normal about 12 months after discontinuation; ISL has a very long terminal half-life, likely explaining the prolonged effect on lymphocytes after discontinuation. The declines were less marked with weekly dosing, and the same pattern was generally seen. For daily dosing, the investigators reviewed lymphocyte counts in a dose-ranging study of daily ISL with doravirine (DOR). They found that participants receiving 0.25 mg of ISL daily did not experience a lymphocyte decline as compared with those in an ISL-free control arm. For future studies, the daily ISL dose used will be 0.25 mg and the weekly dose will be 2 mg. Vargo and colleagues presented PK modeling supporting this weekly dose in a separate presentation (Abstract 497).

Two clinical trials investigating changing suppressive ART to daily DOR 100 mg/ISL 0.75 mg were presented (Abstracts 196 and 197). Eligible participants for both trials had viral suppression for at least 3 months, did not have chronic HBV, and had no known resistance to DOR. The first trial enrolled participants on any suppressive 2- or 3-drug regimen (Abstract 196). A total of 672 participants were randomly assigned (approximately 37% women, median age 45 years). The investigators found that DOR/ISL was noninferior to continued baseline ART, with 0% and 1.5%, respectively, having plasma HIV-1 RNA levels greater than 50 copies/mL at week 48 according to the FDA snapshot algorithm. No virologic failure occurred in the DOR/ISL arm; virologic failure with the emergence of resistance-associated mutations occurred in 3 participants in the control arm. Lower CD4+ counts were observed in the DOR/ISL arm as a result of the known drug effect on lymphocyte counts at this ISL dose. Although adverse effects were reported more commonly with DOR/ISL in this open-label trial, the drug combination appeared well tolerated.

The second trial enrolled participants with viral suppression on BIC/FTC/TAF, and the comparison with switching to DOR/ISL was blinded (Abstract 197). A total of 641 participants (approximately 30% female, median age 48 years) were randomly assigned. At week 48, DOR/ISL was found to be noninferior to BIC/FTC/TAF, with 0.6% and 0.3% having plasma HIV-1 RNA levels greater than 50 copies/mL according to the FDA snapshot regimen. Virologic failure occurred at week 12 in 1 participant receiving DOR/

ISL; ISL was not detected in plasma samples from this participant, suggesting nonadherence. CD4⁺ cell counts and lymphocyte counts were lower in the DOR/ISL groups, as discussed previously. Two cases of HBV reactivation occurred in the DOR/ISL group;

Virologic failure occurred at week 12 in 1 participant receiving doravirine/islatravir; islatravir was not detected in plasma samples from this participant, suggesting nonadherence

neither was clinically significant. The occurrence of adverse events was otherwise similar between arms. The authors concluded that these data support the efficacy and safety of DOR/ISL. The clinical development has resumed, with ISL being dosed at 0.25 mg daily.

Lenacapavir

Lenacapavir (LEN), a long-acting capsid inhibitor, was recently approved for treatment of people with HIV infection who are highly experienced with ART treatment. Ogbuagu and colleagues presented baseline factors associated with viral suppression in the CAPELLA (Study to Evaluate the Safety and Efficacy of Lenacapavir [GS-6207] in Combination With an Optimized Background Regimen in Heavily Treatment Experienced Participants Living With HIV-1 Infection With Multidrug Resistance) study (Abstract 523). There were 72 participants included in the analysis; 78% achieved a plasma HIV-1 RNA level of less than 50 copies/mL 1 year after starting LEN. The investigators examined various demographic subgroups such as sex and race. There was no appreciable difference in viral suppression rates among these subgroups. There were no discernible differences in viral suppression rates between patients having 0, 1, or 2 active drugs in the optimized background regimen (OBR). Viral suppression rates were higher when fostemsavir or ibalizumab was used in the OBR, but no statistical comparisons were presented. These data support the use of LEN in highly treatment-experienced individuals even when options for the OBR are limited. Shaik and colleagues used an existing population PK model to identify the optimal time interval for the

second dose of subcutaneous LEN (Abstract 504). Their models supported plus or minus 2 weeks around the 26-week dose (ie, second dose to be given 24 to 28 weeks after the first dose) to maintain safe and efficacious concentrations.

Current long-acting ART options involve injections monthly or every 2 months. LEN holds promise for being part of a twice-yearly ART strategy. Eron and colleagues presented data on switching individuals with virologic suppression to a combination of LEN and 2 anti-HIV broadly neutralizing antibodies (bNAbs), tepopavimab and znlirvimab (Abstract 193). Participants were required to be sensitive to both bNAbs based on phenotypic testing of archived DNA; 55 of 124 individuals (44%) assessed for eligibility met this requirement. Study participants were randomly assigned to 1 of 2 doses of znlirvimab. The protocol was originally intended for 1 year of study medications (ie, 2 every-6-month doses of LEN/bNAbs); however, an issue with the vials used to contain LEN resulted in a temporary clinical hold, and the study was truncated at 6 months (or a single dose of study medications) and the sample size reduced. Twenty-one participants (median age 44 years, 86% men) were included in the analysis. One participant withdrew before receipt of bNAbs and was removed from the analysis. Of 20 analyzable participants, 1 withdrew at week 12 and restarted ART when their plasma HIV-1 RNA level was less than 50 copies/mL. One participant had a confirmed viral rebound at week 16. The rest of the participants remained virologically suppressed. Virus could not be amplified from the participant experiencing virologic rebound. The study medications were generally tolerated, with injection reactions being common. The investigators concluded that this is a promising strategy for a twice-yearly long-acting ART regimen.

Hagins and colleagues presented additional follow-up data from the CALIBRATE (Study to Evaluate the Safety and Efficacy of Lenacapavir in Combination With Other Antiretroviral Agents in People Living With HIV) trial, which administered LEN plus FTC/TAF to treatment-naïve individuals and then randomly assigned them to various LEN regimens (Abstract 522). They found that participants maintained high suppression rates when receiving LEN subcutaneously plus oral TAF, BIC, or FTC/TAF. None of these regimens are being pursued for treatment-naïve individuals at this time, but these data provide preliminary support for possible future long-acting combinations should long-acting versions of tenofovir, BIC, or similar compounds be developed.

Rapid Initiation of ART

Dai and colleagues presented data comparing rapid initiation of ART with delayed ART (Abstract 521). Patients newly diagnosed with HIV were offered rapid initiation of ART, defined as initiation within 14 days of diagnosis. If patients accepted, they were randomly assigned to efavirenz (EFV)/TDF/3TC (group A, n = 126) or BIC/FTC/TAF (group B, n = 132). If patients deferred ART, they subsequently underwent random assignment to EFV (group C, n = 122) or BIC (group D, n = 91) regimens. The investigators found that rapid initiation of ART was associated with high rates of engagement in care: 92.6% in groups A and B combined versus 86.9% in groups C and D combined ($P = .053$). Group B had a higher rate of viral suppression than group A: 93.5% versus 74.7% ($P < .001$). These data support the paradigm of rapid initiation of ART for those newly diagnosed and the use of InSTI-based regimens for initial ART.

Second-Line Therapy

Matthews and colleagues presented data on the use of darunavir (DRV)/ritonavir (RTV) and DTG for patients for whom first-line nonnucleoside analogue RT inhibitor (NNRTI)-based therapy failed (Abstract 198). This strategy would obviate the concern about nucleoside analogue RT inhibitor (nRTI) resistance impacting the outcomes of second-line therapy. In this study, 831 participants from 14 countries were randomly assigned to DRV/RTV plus DTG, DRV/RTV plus 2 nRTIs, or DTG/TDF/FTC. The latter arm was added later in the trial based on the positive results of other trials showing the utility of DTG and 2 nRTIs in this situation.¹ Most participants received zidovudine/FTC as their nRTIs in the DRV/RTV plus 2 nRTIs arm. At week 48, the DRV/RTV plus DTG regimen was found to be noninferior to DRV/RTV plus 2 nRTIs for virologic suppression to less than 50 copies/mL. It was also found to be superior: 84.7% versus 75.4%; $-8.6%$ (95% CI, $-1.7%$ to $-15.5%$; $P = .02$). DTG/TDF/FTC and DTG was also found to be noninferior to DRV/RTV plus 2 nRTIs (84.7% vs 78%; $-6.7%$ [95% CI, $1.2%$ to $-14.4%$]), excluding the noninferiority margin of 10%. Weight gain was greater in the DTG-containing arms. The authors concluded that DRV/RTV plus DTG and DTG/TDF/FTC were viable options for second-line therapy. However, DTG/TDF/FTC is widely available and is easier to administer from a programmatic perspective.

Existing data support the use of an InSTI and 2 nRTIs for second-line therapy even in the presence of nRTI-associated resistance mutations. Sivile and

colleagues presented data on the relationship between baseline nRTIs and virologic outcomes in the VISEND (Dolutegravir With Recycled nRTIs Is Noninferior to PI-Based ART) trial (Abstract 524). In this trial, 783 people with HIV from Zambia for whom their first-line NNRTI-based regimen was failing were randomly as-

Existing data support the use of an integrase strand transfer inhibitor and 2 nRTIs for second-line therapy even in the presence of nRTI-associated resistance mutations

signed to tenofovir/3TC/DTG (TLD) (or TAF/3TC/DTG) or zidovudine/3TC/RTV-boosted atazanavir or lopinavir. The presence of nRTI mutations or K65R did not impact virologic suppression, which remained high; viral suppression was 93% in those without nRTI mutations and 95.8% in those with nRTI mutations. These data confirm the NADIA (Nucleosides and Darunavir/Dolutegravir in Africa) trial results and support the use of TLD in those for whom an NNRTI-based regimen has failed.¹

EFV induces the metabolism of DTG, and this effect can persist for several weeks after stopping EFV. Zhao and colleagues presented data on using twice-daily DTG for 2 weeks in people transitioning from EFV-based ART to TLD to overcome this drug-drug interaction (Abstract 525). In this study, 130 South African people with HIV for whom an EFV-based regimen was failing were randomly assigned to change to TLD with a second dose of DTG or to TLD with a dose of placebo. The study was not adequately powered for statistical comparisons. The investigators found that the rates of virologic suppression and adverse events were similar between arms. Six people met criteria for resistance testing. No integrase resistance was detected in any participant. The authors concluded that their data did not support the need for supplemental DTG when transitioning from EFV-based regimens to TLD. The results should be interpreted with caution because of limited sample sizes.

Novel Long-Acting ART

There were several presentations on the development of long-acting ART. Gutierrez and colleagues surveyed

3 HIV clinics through a discrete choice experiment to understand perspectives of patients in long-acting ART delivery programs (Abstract 1055). A total of 370 participants completed the discrete choice experiment (34% women or gender minority, 59% Black, 13% Latinx, and 34% homeless or unstably housed). As expected, participants preferred to have no out-of-pocket payments, short visit times, and flexible clinic schedules. They also preferred to have the injections take place in the medical clinic as opposed to pharmacies or mobile vans. Nayan and colleagues presented preclinical data on long-acting nanoformulations of BIC (Abstract 540). They developed several BIC prodrugs that are encased in nanocrystals. The new formulations appeared safe in animal models and exhibited favorable PK profiles. Dosing in rhesus macaques suggested the possibility of 6-month dosing.

HIV-2

Because HIV-2 is intrinsically resistant to many classes of ART and the availability of HIV-2 resistance testing is limited, emerging data on new antiviral therapies for HIV-2 treatment are useful. Smith and colleagues examined in vitro antiviral activity of LEN against HIV-2 using 2 different assays (Abstract 538). They also tested HIV-2 isolates resistant to RT inhibitors and InSTIs. In their single-cycle assay, they found that LEN did have antiviral activity against HIV-2, but the mean 50% inhibitory concentration (IC_{50}) for LEN was 11-fold lower against HIV-2 than against HIV-1. They found similar differences in LEN activity from their multicycle assays. RT or InSTI resistance did not affect the antiviral activity of LEN, as the IC_{50} was comparable with that of wild-type HIV-2 virus. The authors concluded that LEN has antiviral activity against HIV-2 but decreased activity compared with HIV-1, so use of LEN in people with HIV-2 would require continued monitoring.

Joly and colleagues (Abstract 539) provided some clinical and virologic outcomes for a French cohort of 24 individuals with HIV-2 treated with TAF/FTC/BIC. In this cohort, the median time since HIV-2 diagnosis was 19 years, and the median CD4+ count was 580 cells/ μ L at the time of TAF/FTC/BIC initiation. Only 3 patients had a detectable HIV-2 viral load at the time of TAF/FTC/BIC initiation. Five patients were ART naive, and 8 of 19 patients who were ART experienced had prior treatment failure. Median duration of TAF/FTC/BIC use was nearly 28 months. Median CD4+ count increased to 615 cells/ μ L, but this value was not significantly higher than that at the time of TAF/FTC/BIC initiation

($P = .29$). All patients had a viral load that was under the lower limit of detection at 40 copies/mL. Pharmacologic analysis also showed favorable PK of BIC in these patients, with the measured values at least 20-fold higher than the 90% inhibitory concentration (IC_{90}) of BIC against HIV-2. Ultimately, this small retrospective cohort showed that TAF/FTC/BIC could suppress HIV-2 viral load and increase the CD4+ cell count, as well as achieve favorable PK in the bloodstream.

Updates on HIV Resistance

Resistance to Existing Antiretroviral Drugs

Orrell conducted a prospective cohort study of 250 individuals with HIV in South Africa to examine whether tenofovir diphosphate levels in dried blood spots were linked to emergence of ART resistance (Abstract 205). These individuals were on TDF- and EFV-based regimens and had an undetectable viral load at baseline. Monthly viral loads and dried blood spots were measured. Tenofovir diphosphate levels in dried blood spots trended downward in those patients who had viral breakthrough (defined as HIV viral load >400 copies/mL). The tenofovir diphosphate levels were significantly higher in those patients with viral breakthrough whose repeat genotype was unable to amplify, as they then achieved viral suppression, than in those who were still not virologically suppressed and had a genotype that amplified and showed drug

Tenofovir diphosphate levels in dried blood spots trended downward in those patients who had viral breakthrough, defined as HIV viral load greater than 400 copies/mL

resistance ($P = .035$). The study authors concluded that tenofovir diphosphate could be used as a predictor of viral breakthrough as well as drug resistance, although notably this was in a group receiving EFV-based ART, which is no longer first-line treatment in many low- and middle-income countries.

Thomson and colleagues examined InSTI resistance in HIV-1 in a Spanish cohort from 2008 to 2021 (Abstract 573). Their analysis of resistance mutations in nearly 2700 patients showed an overall InSTI

resistance rate of 6.5% (all to first-generation InSTIs) and a second-generation InSTI resistance rate of 2.6%. Of the 174 patients with InSTI resistance, only 5 were exclusively exposed to DTG (and not to any other InSTIs). In these 5 individuals, resistance was associated with poor adherence as well as resistance to other ART classes. In new HIV diagnoses, they observed an InSTI resistance rate of 0.92%; only 0.16% of new diagnoses had virus that was resistant to DTG. Factors significantly associated with InSTI resistance included injection drug use, age 40 years or older, and concomitant resistance to other classes of antiretroviral agents. The authors concluded that these data support the use of DTG and other second-generation InSTIs as first-line ART.

Borghetti and colleagues examined an Italian cohort of people with HIV who had virologic suppression and examined the rates of virologic failure after switching to 2-drug therapy with DTG/3TC or 3-drug therapy with 2 nRTIs plus DTG (Abstract 574). Rates of virologic failure (defined as viral load ≥ 50 copies/mL on 2 consecutive checks or ≥ 200 copies/mL on 1 check) were higher in those in the 2-drug therapy group with M184V/I (HR, 4.24; $P = .017$).

Sudderuddin and colleagues examined genotyping from samples with low-level viremia, defined as 50 to 250 copies/mL, and compared them with previous samples from the same patients to determine emerging resistance over time (Abstract 575). They found 105 new cases (7.4% of samples) of drug resistance; 49.5% of these samples showed new nRTI resistance, 42.9% showed new NNRTI resistance, and 22.9% showed new protease inhibitor (PI) resistance. They noted that the low-level viremia samples showing new resistance were obtained 2.6 years after the previous samples for testing, which is a significantly longer interval than for low-level viremia samples without resistance, obtained after 1.1 years ($P < .001$). There was no change in the rate of new resistance in samples with persistent low-level viremia versus those in which the viremia was transient ($P = .14$). Only 4 new cases of integrase resistance were found. Overall, the study authors concluded that it is rare to find new or emerging resistance in low-level viremia samples and that genotyping is not recommended. They reported that genotyping in cases of low-level viremia may be helpful in certain populations such as younger individuals, when there has been a lengthy interval since earlier genotyping, if a patient has been on an NNRTI- or a PI-based regimen, or if no earlier genotyping results are available.

Loosli and colleagues examined cohorts from Canada, Europe, and South Africa to identify risk factors for InSTI resistance in patients for whom DTG-based therapy failed (Abstract 576). The overall rate of InSTI drug resistance mutations detected was 13.5%. In their regression model, presence of nRTI mutations was associated with resistance to DTG, with an OR of 6.36 to 7.74 (95% CI, 1.74-23.24). Unsurprisingly, monotherapy with DTG was associated with resistance to DTG, with an OR of 13.08 (95% CI, 3.78-45.19). The investigators also noted that a longer period of viremia (viral load area under the curve) was associated with DTG resistance (OR, 1.75; 95% CI, 0.99-3.09), so the authors cautioned to watch for resistance in patients receiving DTG in the coming years as it is rolled out globally for first-line ART.

Burdorf and colleagues examined frequency of NNRTI mutations and whether they were associated with virologic failure in pregnant women in Malawi (Abstract 577). They found that the presence of K103N even at low frequencies (under 20% of the viral population) more than doubled the risk of virologic failure (HR, 2.44 in univariate analyses; 95% CI, 1.00-5.95). This finding supports the use of InSTI-based regimens as first-line therapy in pregnant women over NNRTI-based regimens.

Kamori and colleagues examined the emergence of InSTI resistance in Tanzania after the rollout of DTG in patients who had virologic failure (Abstract 578). They observed a high baseline prevalence of drug resistance of 71.5% in samples with viremia (HIV viral

This finding supports the use of InSTI-based regimens as first-line therapy in pregnant women over NNRTI-based regimens

load ≥ 1000 copies/mL). They observed new InSTI drug resistance mutations (acquired mutations) in 5.8% of cases, including emergence of major InSTI mutations T66A, G118R, E138K, Q148K, and R263K. All those with major InSTI resistance-associated mutations (RAMs) were also observed to have RAMs to the nRTI backbone.

McCluskey and colleagues used an observational cohort in Uganda to estimate the incidence of InSTI resistance after national first-line ART regimens were transitioned to containing DTG (Abstract 579). They did not find any cases of acquired integrase resistance up to 48 weeks after transition to DTG-based regimens. Two individuals with K65R and M184V mutations still achieved viral suppression on a TDF/3TC/DTG regimen.

Aung and colleagues studied acquired drug resistance in a statewide cohort in Rhode Island of individuals receiving ART for greater than 90 days from 2004 to 2021 (Abstract 583). They found that the rate of acquired drug resistance fell from 77% in 2004 to 44% in 2021. The largest decreases were seen in nRTI resistance, which fell from 63% to 21% from 2004 to 2021, and in NNRTI resistance, with a decrease from 53% to 32% over the same 17-year period. Rates of multidrug class resistance also decreased over the study period. The level of InSTI-acquired drug resistance stayed stable at 5% between 2016 and 2021.

Resistance to New or Novel Agents

Zuze and colleagues examined rates of fostemsavir resistance in individuals with HIV in Botswana from 2013 to 2018 (notably before the use of fostemsavir or its FDA approval in 2020) (Abstract 584). They examined proviral sequences of individuals in a nationwide database that included patients who were ART naive and those who were ART experienced, along with those who had virologic failure. The overall prevalence of fostemsavir resistance-associated mutations was 13.3% (before any fostemsavir exposure). The prevalence of fostemsavir RAMs did not differ between patients who were ART naive and those who had virologic failure on ART. The most common fostemsavir RAMs observed were M434I and M475I. The prevalence of M434V was significantly higher in those with virologic failure than in those who were ART naive ($P < .01$). The study authors concluded that fostemsavir RAMs are similar in those who are ART experienced and ART naive before any fostemsavir use.

Diamond and colleagues presented data from in vitro studies showing the use of ISL and LEN together with no evidence of antagonism or cross-resistance (Abstract 585). Notably, ISL and LEN have different mechanisms of action, with ISL inhibiting nucleoside RT translocation and LEN (a capsid inhibitor) disrupting several points in viral replication. This study showed that ISL still displayed antiviral activity against HIV strains with LEN mutations, with

the IC_{50} of ISL against these strains similar to the IC_{50} against wild-type virus. ISL also retained viral activity in strains containing M184V, although the IC_{50} appeared to increase with these strains. The investigators also determined that a combination of ISL and LEN suppressed HIV-1 more effectively than either agent alone. They also observed that fewer mutations arise with the combination of ISL and LEN than with use of either agent alone. They did not observe any single mutation that significantly affected the antiviral activity of either agent. The study authors concluded that the combination of ISL and LEN could be an effective treatment regimen for HIV-1 given the ability to suppress viral breakthrough and the increased resistance barrier observed when the drugs were used in combination.

Resistance to Investigational bNABs

Selzer and colleagues examined susceptibility of HIV-1 to teropavimab and zinlirvimab, 2 bNABs used in combination with LEN, in a phase Ib study (Abstract 580). They observed susceptibility to both bNABs in 50% of participants, and at least 90% were susceptible to at least 1 bNAB. Proviral genotyping predicted phenotypic susceptibility with high specificity but low sensitivity. Taiwo and colleagues investigated the susceptibility of VRC07-523LS, a bNAB evaluated in combination with LA CAB in the ACTG A5357 study (Abstract 581). A total of 70% of their participants had virus that was susceptible to VRC07-523LS. There were no observed associations between demographic variables and susceptibility to VRC07-523LS, although there was a trend observed for decreased susceptibility in those with more recent acquisition of HIV. Moraka and colleagues examined resistance to bNABs in those with HIV seroconversion, including 76% of patients who were ART naive (Abstract 582). They found high levels of resistance to bNABs, including 100% with resistance to 2F5, PG16, PGT151, and VRC34.01. The rate of drug resistance mutations for other classes of ART was 6.6%. The study authors concluded that bNABs may be ineffective in preventing HIV-1 infection in Botswana given currently circulating resistance mutations.

Selected Issues in Maternal and Pediatric Health

Improving HIV Care Outcomes in Youth

In Abstract 125, Ferrand and colleagues presented results of a cluster randomized trial evaluating a

community-based intervention involving HIV testing, ART initiation, and adherence support with integrated HIV and sexual and reproductive health services, called CHIEDZA, to improve HIV care outcomes among youth with HIV infection in Zimbabwe at the population level. The trial was conducted over 30 months across 3 provinces, with each province randomly assigned in a 4:4 ratio to control (existing services that were mostly facility based) or to intervention clusters (a total of 24 clusters, 12 in each arm). Within each intervention cluster, weekly integrated HIV and sexual and reproductive health services were provided at a community center to cluster residents aged 16 to 24 years. A population-based outcome survey was conducted among those aged 18 to 24 years 30 months after the intervention. The primary outcome was population-level viral suppression, defined as HIV viral load less than 1000 copies/mL, among youths with HIV infection. The secondary outcomes included percentage of youths with HIV who knew their HIV diagnosis, percentage of youths knowing their positive HIV serostatus who were currently receiving ART, and percentage of youths receiving ART who were achieving viral suppression.

A total of 36,991 youths accessed the CHIEDZA intervention, representing approximately 95% of the eligible population in the intervention clusters, with a total of 78,810 visits. Of these residents, 84% had at least 1 HIV test. A total of 1539 youths who had uptake of the CHIEDZA intervention had HIV, of whom 377 (24%) were newly diagnosed; 94% had linkage to HIV care, 97% of those linked to care received ART, and 80% achieved viral suppression. The population-based survey involved 17,682 youths, of whom 29% in the intervention arm reported accessing CHIEDZA and 4% in the control arm reported accessing the intervention, representing a low level of contamination across arms. Prevalence of HIV was 5.9% in the intervention arm and 7.5% in the control arm. A significantly higher proportion of youths in the intervention arm than in the control arm had undergone HIV testing (71.1% vs 66.1%) and knew their HIV status (68.5% vs 63.1%). However, there was no statistically significant difference between the 2 arms in the primary outcome of viral suppression (40.4% vs 37.5%) among those with HIV or in the secondary outcomes. The authors concluded that although it led to high levels of HIV testing and ART, the CHIEDZA intervention did not have a population-level effect on viral suppression, which might be explained by the inability to identify youths who were at the highest risk for HIV infection. The finding

that more than half of youths with HIV remained undiagnosed underscores the urgent need for effective strategies focused on youths.

Mother-to-Child Transmission of HIV

Substantial progress has been made in lowering rates of MTCT of HIV; however, HIV infections in infants and children persist, with 150,000 children newly diagnosed with HIV infection worldwide in 2020. An important risk factor for MTCT is high maternal viral

Substantial progress has been made in lowering rates of mother-to-child transmission of HIV, but HIV infections in infants and children persist, with 150,000 children newly diagnosed worldwide in 2020

load at time of delivery. In Abstract 129, Lwilla and colleagues presented results of a cluster randomized trial, called LIFE, involving 28 obstetric health clinics in Tanzania and Mozambique designed to estimate the added contribution of POC maternal viral load testing at time of delivery in determining risk of MTCT and its effect on initiation of standard (nevirapine monotherapy) compared with enhanced postnatal antiretroviral prophylaxis (zidovudine plus nevirapine) in HIV-exposed infants. In Tanzania, the choice of postexposure antiretroviral prophylaxis follows the WHO high-risk criteria, whereas in Mozambique, universal extended postnatal antiretroviral prophylaxis is administered to all HIV-exposed infants. In intervention arm A, POC maternal viral load testing at delivery guided MTCT high-risk assessment along with clinical criteria and antenatal care history, whereas in intervention arm B (control), only clinical and antenatal care history were available to guide the classification. In Tanzania, intervention arms A and B started extended postnatal antiretroviral prophylaxis based on maternal risk factors, which included maternal viral load in arm B. In Mozambique, universal extended postnatal antiretroviral prophylaxis was administered to all HIV-exposed infants.

Overall, 6512 mothers with HIV were enrolled, with 28% diagnosed during the third trimester of pregnancy; almost all (99%) received ART, and 21.9% had viral nonsuppression at delivery. Of 6568 newborns, a total of 781 (12%) infants were considered at high risk, with 19.5% in arm A and 4.4% in arm B ($P < .001$). In arm A, 80.5% of infants were classified as high risk based only on POC maternal viral load result at delivery. An additional 609 (18.4%) infants in arm B would have been classified as at high risk had POC maternal viral load testing been available. In Tanzania, infants at high risk in arm A (with maternal POC viral load testing at delivery) were more likely to receive extended postnatal antiretroviral prophylaxis than were infants at high risk in arm B (59.8% vs 31.4%, respectively; OR, 3.75; 95% CI, 1.34-10.49). Despite available information to classify infants as at high risk at delivery, 40.2% in arm A and 68.6% in arm B did not receive extended postnatal antiretroviral prophylaxis, highlighting suboptimal linkage of infants identified as at high risk to appropriate postnatal antiretroviral prophylaxis. The authors concluded that optimizing POC maternal viral load testing could help ensure that all infants identified as at high risk get enhanced postnatal prophylaxis. The authors also suggested that universal extended postnatal prophylaxis be considered regardless of transmission risk category in geographic regions that have a high prevalence of neonates at high risk.

In Abstract 131, Kankasa and colleagues evaluated the efficacy and safety of an intervention combining POC maternal viral load testing and extended infant postnatal prophylaxis in preventing postnatal HIV transmission through breastfeeding in Zambia and Burkina Faso. A total of 1506 breastfed HIV-exposed uninfected infants and their mothers with HIV (98.4% of whom were receiving ART) were randomly assigned to the standard of care arm ($n = 753$), which consisted of prevention of MTCT according to the local WHO guidelines in each country, or the intervention arm ($n = 753$). The intervention consisted of POC viral load testing in mothers, with a viral load greater than 1000 copies/mL prompting immediate initiation of 3TC prophylaxis in infants until 12 months or until 8 weeks after stopping breastfeeding. The primary outcome was infant HIV infection at 12 months. In the intervention arm, 102 infants received 3TC prophylaxis guided by POC maternal viral load testing, with a median time of 0 days (IQR, 0-1) after testing. At 12 months, 76% of the mothers continued breastfeeding. The period of high risk for HIV transmission (defined as the period with maternal viral load >1000 copies/

mL and no infant postnatal prophylaxis) was shorter in the intervention arm than in the control arm (0.55/100 person-days vs 6.54/100 person-days, respectively). During the 12-month follow-up period, there was 1 case of HIV transmission in the intervention arm compared with 6 in the control arm, translating to HIV transmission rates of 0.2 per 100 person-years and 1.2 per 100 person-years, respectively, with the difference not being statistically significant. The frequency of serious adverse events was similar in the 2 arms. Overall, the study showed that the intervention integrating maternal POC viral load testing and same-day infant postnatal prophylaxis initiation for nonsuppressed maternal viral load was safe and significantly decreased the period of high risk for HIV transmission, although that did not translate into a significant reduction in HIV transmission to infants at 12 months.

Surveillance data on 49,824 HIV-exposed infants born between 2018 and 2021 to mothers with an HIV diagnosis prior to delivery in the Western Cape, South Africa, were presented in Abstract 778. Despite high maternal ART coverage, with 90% of the mothers receiving any ART during pregnancy and 86% in the year following delivery, MTCT of HIV remains a concern. A total of 925 (2%) infants were diagnosed with HIV. At delivery, 74% of the mothers had viral suppression (defined as viral load <100 copies/mL). Most of the MTCT was attributed to breastfeeding. The authors highlighted the need for interventions to improve maternal viral suppression and lower MTCT in pregnancy and breastfeeding.

HIV Reservoirs in Children and Youth

Niesar and colleagues characterized the proviral reservoirs in children in Botswana with HIV clade C infection who had started ART at birth and were administered dual bNABs (Abstract 141). The children were enrolled in the Early Infant Treatment cohort, in which they received ART continuously from birth. Those children who were on ART for at least 96 weeks with HIV viral load of less than 40 copies/mL for at least 24 weeks then transitioned to the Tatelo (Dual bNAB Treatment in Children) trial, in which they received ART in addition to dual bNABs VRC01-LS and 10-1074 administered every 4 weeks for at least 2 months, after which ART was discontinued. A total of 25 children received VRC01-LS and 10-1074 treatment. Of these 25 children, 11 (44%) maintained HIV suppression (defined as HIV RNA level <400 copies/mL) through 24 weeks (controllers) and 14 (56%) developed viral rebound with a level of at least 400 copies/mL

(rebounders). Viral reservoir analysis involved droplet-based digital PCR, full-length individual proviral sequencing, and matched integration site and proviral sequencing. Based on testing of 592 available proviral genomes, lower viral reservoirs at birth were detected in controllers than in rebounders. There were no significant detectable differences in proviral reservoir size in controllers before and after bNAb treatment. In comparison, high frequencies of intact and defective proviruses were detected in rebounders at birth, which increased during the period between initiation of bNAb treatment and viral rebound.

Limited data are available on whether early ART initiation during acute HIV infection reduces viral reservoirs, improves immune reconstitution, and leads to improved long-term HIV control in youths

Limited data are available on whether early ART initiation during acute HIV infection reduces viral reservoirs, improves immune reconstitution, and leads to improved long-term HIV control in youths. Abstract 457 described results of the Adolescent Trials Network (ATN) 147 study, which evaluated HIV plasma RNA PCR, HIV DNA droplet-based digital PCR based on peripheral blood mononuclear cells, and HIV antibody based on Western blot over 24 months in a mixed-effect model among 103 youths aged 12 to 24 years who were newly diagnosed with HIV infection in 2 US cities. Youths were classified as having acute infection if they had Fiebig stage I to V based on HIV Western blot at baseline, and nonacute infection if they had Fiebig stage VI. Of 103 youths, 35% had acute HIV infection and the remaining 65% had nonacute infection; 78% started ART within 48 hours of HIV diagnosis, and 88% began treatment within 1 week. Baseline HIV RNA viral load was higher in youths with acute HIV infection than in those with nonacute infection. Overall, early initiation of ART led to sustained viral suppression (defined as <20 copies/mL) in 68% of youths by 12 months and 72% by 24 months, with significant reductions in HIV DNA and antibody levels. HIV RNA viral suppression was similar

between youths with acute and nonacute HIV infection within 4 months of ART initiation. HIV DNA level decrease over 24 months was similar in youths with acute and nonacute infections who achieved viral suppression. Overall, negative or indeterminate Western blot occurred in 32% of the children at 12 months and 34% at 24 months, with youths with acute HIV infection receiving ART being more likely to have a negative or indeterminate western blot at 12 and 24 months (OR, 14.8; 95% CI, 4.76-45.93). However, HIV RNA viral suppression was not significantly associated with having a negative or indeterminate western blot.

In Abstract 458, Cotugno and colleagues evaluated the safety of leukapheresis to provide in-depth characterization of the latent reservoir from peripheral blood mononuclear cells collected from 9 children (mean age, 18.6 years; age range, 12-26 years) with perinatal HIV infection and early ART initiation within the first year of life. Leukapheresis was found to be well tolerated in all 9 children; no adverse events related to the procedure were reported. The authors suggested that multiomics analysis within integration sites of intact HIV proviruses could provide important insights into the viral reservoir reactivation potential in these children.

Interactions Between ART and Hormonal Contraception in Women

In Abstract 526, Ndlovu and colleagues presented data from the EPIC (Evaluation of Pharmacokinetic Drug-Drug Interactions Between Contraceptives and Doravirine-Containing ART) study on the safety, tolerability, and efficacy of DOR in women with HIV who received concomitant ART and hormonal contraception in South Africa. Women who had viral suppression on their existing first-line ART underwent an oral DOR lead-in period of at least 6 weeks before switching from their existing ART to DOR-based ART (DOR, 3TC, and TDF). The women selected 1 of the following contraception methods: intramuscular depomedroxyprogesterone acetate (DMPA), etonogestrel implant, or copper intrauterine device. A fourth comparison group included women on DTG-based ART who received concomitant DMPA for contraception. A total of 89 women have been enrolled to date. Of the 194 adverse events reported, 6% were found to be related to DOR, with headaches (2%) and nausea (1%) being most commonly reported. All the adverse events attributable to DOR were of grade 1 severity, except for 1 case of grade 2 diarrhea. Among the women receiving DOR, only 1 reported dissatisfaction with the ART, and more than 90% of the women had greater than 76% adherence as measured

by pill count. By the end of the study, 52 of 60 women (87%) in the DOR-based ART groups had sustained viral suppression. The authors concluded that changing from first-line regimens to DOR-containing ART was safe, tolerable, and effective in achieving sustained viral suppression in women who are concomitantly receiving hormonal contraceptives, and that DOR-containing ART may be an alternative option for those living in resource-limited settings who have intolerance or other contraindications to DTG-containing ART.

Matovu Kiweewa and colleagues previously published data from the BONE:CARE study showing that concurrent DMPA contraceptive use led to double the loss of bone mineral density over 24 months in women with HIV who started TDF-containing ART in Uganda.² In the follow-up phase IV open-label hybrid randomized and quasi-experimental intervention study called BONE:STAR described in Abstract 685, the researchers found that among women receiving TDF-containing ART, switching to a TAF-containing ART (in this study, BIC/FTC/TAF) was associated with significant improvement in mean percentage bone mineral density, as measured by dual energy X-ray absorptiometry, over 12 months. Compared with women who changed to TAF-containing ART and used nonhormonal contraception, the women receiving concomitant DMPA and TAF-containing ART had lower bone mineral density Z-scores at baseline and at all follow-up time points. The authors noted that alternative contraceptive methods could be developed for women who are unable to use nonhormonal contraception and emphasized the need for additional research on the clinical impact of lowered bone mineral density in women receiving concomitant DMPA and ART.

Antepartum Weight Gain and Adverse Pregnancy Outcomes

The International Maternal Pediatric Adolescent AIDS Clinical Trials (IMPAACT) Network 2010 VESTED (Virologic Efficacy and Safety of ART Combinations With TAF/TDF, EFV, and DTG) trial was an open-label, randomized phase III trial that compared the safety and efficacy of DTG- and EFV-based regimens in pregnant women with HIV in 9 countries. In the trial, 643 pregnant women between 14 and 28 weeks of gestation were randomly assigned to receive 1 of the following 3 ART regimens: (1) DTG plus FTC/TAF, (2) DTG plus FTC/TDF, and (3) EFV/FTC/TDF. IMPAACT 2010 VESTED showed previously that low antepartum weight gain (defined as <0.18 kg/wk) was associated with a higher risk of adverse pregnancy outcomes (defined as a

composite outcome of stillbirth, preterm delivery, or small for gestational age <10th percentile) than normal weight gain (HR, 1.4; 95% CI, 1.04-2.00), with rates of adverse pregnancy outcomes differing by assigned ART arm. Low weight gain was most frequent in women in the EFV/FTC/TDF arm (30%), compared to 24% in the DTG plus FTC/TDF arm and 15% in the DTG plus FTC/TAF arm.³ In Abstract 774, Hoffman and colleagues conducted an exploratory causal mediation analysis to further evaluate whether antepartum weight change mediated the differences in adverse pregnancy outcomes found by ART arm. The frequency of adverse pregnancy outcomes was lowest in women in the DTG plus FTC/TAF arm (24%), compared with the EFV/FTC/TDF (32%) and DTG plus FTC/TDF (33%) arms. In the comparisons between arms, the

Changing from first-line regimens to DOR-containing ART was safe, tolerable, and effective in achieving sustained viral suppression in women who are concomitantly receiving hormonal contraceptives

percentage of risk of adverse pregnancy outcome risk differences mediated by weight change was +31% for DTG plus FTC/TAF versus EFV/FTC/TDF, +11% for DTG plus FTC/TAF versus DTG plus FTC/TDF, and -2% for DTG plus FTC/TDF versus EFV/FTC/TDF. These risk differences were similar in the multivariable models after adjusting for baseline gestational age, body mass index, CD4+ T-cell count, country, and age. The authors concluded that up to one-third of observed differences in adverse pregnancy outcomes between the randomly assigned arms appear to be mediated by ART-related weight change and highlighted the need for further research on the role of antepartum weight gain and on other ART-related mechanisms associated with adverse pregnancy outcomes in women with HIV.

HIV Drug Resistance in Perinatal HIV Transmission

Abstract 779 concerned patterns of HIV drug resistance in the 4 mother-infant pairs with perinatal transmission of HIV in the IMPAACT 2010 VESTED trial. The mother-infant pairs were followed up during the postpartum period through 50 weeks; most (90.3%) of the

infants were breastfed. Perinatal transmission of HIV to the infant was observed in 4 of 617 (0.6%) mother-infant pairs, with 3 in the DTG-based ART arm and 1 in the EFV-based ART arm. All 4 women had received EFV/3TC/TDF or EFV/FTC/TDF for 1 to 7 days before study enrollment; all infants were breastfed and received nevirapine with or without zidovudine for prophylaxis. HIV transmission was thought likely to have occurred in utero in 2 mother-infant pairs and during breastfeeding (1 early and 1 possibly during the weaning period) in the other 2 pairs. NNRTI drug resistance was detected, with NNRTI mutations acquired or selected in 2 mothers who switched from initial EFV-based ART to DTG-based ART and in 2 and possibly 3 infants from nevirapine prophylaxis. Although 3 cases of HIV transmission occurred in women who received DTG-based ART, the investigators did not detect DTG HIV drug resistance or prevalent mutations in the 3'-polypurine tract, which can confer DTG resistance. The authors concluded that DTG-based ART was associated with low rates of perinatal HIV transmission along with low rates of DTG drug resistance. The authors suggested evaluating alternative antiretroviral prophylaxis regimens for infants with a higher barrier of resistance given that most of the infants who became infected with HIV acquired viral resistance to NNRTIs.

Antiretroviral Therapy During Pregnancy

An advantage of physiologically based pharmacokinetic (PBPK) models is the integration of physiologic changes during pregnancy and drug-specific features to predict the concentration exposure, including absorption, distribution, metabolism, and excretion, during pregnancy. Results of a maternal-fetal PBPK model for LA CAB and LA RPV during pregnancy were presented in Abstract 782. The model included assumptions that the first 3 doses of the drugs were injected during the second trimester and the last 3 doses were administered during the third trimester of pregnancy. The simulations using the maternal-fetal PBPK model showed that after the first loading dose injection, the trough concentrations were reduced by 29.5% and 23.0% during pregnancy compared with during nonpregnancy for LA CAB and LA RPV, respectively. After the sixth injection, the trough concentrations were 31.1% and 29.2% lower for CAB and RPV, respectively. The predicted decrease in plasma concentrations in the second and third trimesters for LA CAB and LA RPV was attributed to the projected induction of UGT1A1 and CYP3A4 enzymes during

these trimesters. The authors cautioned that there are limited clinical data on use of LA CAB and LA RPV in pregnant women, and recommended that prospective clinical trials of LA CAB and LA RPV be conducted to further evaluate PK during the second and third trimesters of pregnancy.

Data on the PK of BIC in pregnancy are limited. Abstract 783 described preliminary PK results of BIC and related virologic outcomes in pregnancy compared with the postpartum period as part of the IMPAACT 2026 trial, an ongoing, nonrandomized, open-label,


Viral suppression, defined as a viral load of less than 50 copies/mL, was detected in all 7 children with available data for viral testing at all visits after 48 weeks of treatment

parallel-group, phase IV prospective study involving pregnant women with HIV. Intensive steady-state PK sampling of BIC at a dose of 50 mg orally once daily was performed in 27 women during the second and third trimesters and the postpartum period. Total exposures to BIC were found to be lower during pregnancy than in the postpartum period, with the area under the plasma concentration-time curve from time 0 to the end of the dosing interval (AUC_{τ}) 49% and 56% lower and maximum plasma concentration 39% and 50% lower in the second and third trimesters, respectively, compared with paired data from the postpartum period. However, all concentrations at 24 hours were above the BIC protein-adjusted 95% effective concentration value of approximately 0.162 $\mu\text{g/mL}$. Viral suppression in the women was sustained in pregnancy and the postpartum period, and no cases of HIV transmission to the infant were detected to date.

Antiretroviral Therapy in Children and Adolescents

Data on the PK of coformulated FTC/TAF with cobicistat-boosted PIs in young children with HIV are limited. In Abstract 829, Vieira and colleagues presented interim results on steady-state PK, safety, and efficacy in 9 virally suppressed children weighing 14 kg to less than 25 kg and taking once-daily FTC/TAF (120 mg/15 mg) and DRV in a multicenter, open-label, multicohort

phase II/III study. Eligibility criteria included age of at least 3 years, baseline CD4+ count of at least 200 cells/ μ L, baseline estimated glomerular filtration rate of at least 90 mL/min/1.73 m², and receipt of FTC/TAF for at least 48 weeks. Steady-state PK data showed that exposures to DRV, cobicistat, FTC, TAF, and tenofovir were within the range of exposures observed in an adult population PK analysis in a phase III study. Viral suppression defined as a viral load of less than 50 copies/mL was detected in all 7 children with available data for viral testing (100%) at all visits after 48 weeks of treatment. The ART regimen was also found to be safe and well tolerated, with the most common adverse events being vomiting and anemia and no serious adverse events or adverse events leading to study discontinuation or death. The authors noted that these findings support continued study of FTC/TAF in combination with cobicistat-boosted PIs as ART in young children with HIV.

Currently, BIC/FTC/TAF is approved for use as ART for children with HIV weighing at least 25 kg. Abstract 830 described results for risk of virologic failure and acquired genotypic resistance from a retrospective study of 300 children and adolescents under 18 years of age receiving BIC/FTC/TAF in France. At baseline, most of the children (93.3%) were ART experienced, 85% had prior exposure to INSTIs, mostly DTG, and 63.4% had viral suppression. A total of 23 (38.3%) children experienced virologic failure (defined as failure to achieve plasma viral load <50 copies/mL within 3 months of BIC/FTC/TAF initiation or viral rebound with viral load \geq 50 copies/mL). Virologic failure was more common in children with higher median plasma viral load at baseline. No emergence of HIV drug RAMs was seen in children with virologic failure. As a result of adherence counseling, viral suppression was attained at the last visit in 81.7% of the children, including in 12 of 23 (52.2%) of the children with virologic failure classification, therefore obviating the need for ART change. BIC/FTC/TAF was well tolerated, with no discontinuation due to drug-associated adverse effects. 

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Financial relationships with ineligible companies within the past 24 months: Dr Gunaratne reported no relevant financial relationships (Updated April 10, 2023). Dr Tieu reported receiving grant support awarded to her institution from Gilead Sciences, Inc. (Updated April 12, 2023). Dr Wilkin reported serving as a consultant to GlaxoSmithKline/ViiV Healthcare and Merck and Co., Inc., and receiving grant support awarded to his institution from GlaxoSmithKline/ViiV Healthcare and Merck and Co., Inc. (Updated April 10, 2023). Dr Taylor reported no relevant financial relationships (Updated April 10, 2023).

Reviewer 1 reported serving as a consultant or receiving advisor fees from Antiva, Assembly Biosciences, Generate Biomedicines, and IGM Biosciences, and receiving fees for participation in review activities, eg, data monitoring boards, statistical analysis, or endpoint adjudication committees with Gilead Sciences, Inc. (Updated March 30, 2023). Reviewers 2 and 3 reported no relevant financial relationships with ineligible companies (Updated April 30, 2023).

All relevant financial relationships with ineligible companies have been mitigated.

Additional References Cited in Text

1. Paton NI, Musaaazi J, Kityo C, et al. Dolutegravir or darunavir in combination with zidovudine or tenofovir to treat HIV. *N Engl J Med*. 2021;385(4):330-341. doi:10.1056/NEJMoa2101609
2. Kiweewa-Matovu F, Kiwanuka N, Nabwana M, et al. Intramuscular depot medroxyprogesterone acetate accentuates bone loss associated with tenofovir disoproxil fumarate-containing antiretroviral therapy initiation in young women living with HIV (the BONE: CARE study): a prospective cohort study in Uganda. *Lancet Glob Health*. 2022;10(5):e694-e704. doi:10.1016/S2214-109X(22)00080-8
3. Hoffman RM, Ziembra L, Brummel S, et al. Antepartum weigh gain and adverse pregnancy outcomes in IMPAACT 2010 [CROI Abstract 176]. Abstracts from the virtual 2021 Conference on Retroviruses and Opportunistic Infections. *Top Antivir Med*. 2021;29(1):55-56.

Top Antivir Med. 2023;31(3):445-467
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*Invited Review***CROI 2023: Epidemiologic Trends and Prevention for HIV and Other Sexually Transmitted Infections****Albert Y. Liu, MD, MPH; Susan P. Buchbinder, MD**

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Abstract. *At the 2023 Conference on Retroviruses and Opportunistic Infections (CROI), several investigators used tests of recent HIV infection to track which populations are currently most heavily impacted by HIV and to estimate HIV infection rates in those populations. Assisted partner notification for HIV was successfully applied for spouses of persons with HIV and sexual and injection partners of people who inject drugs; however, delays in linkage to care were seen for non-spousal partners in one study. Lack of awareness of HIV positive status remains an issue in various populations; several presentations focused on novel strategies for improving HIV testing uptake in these populations. Doxycycline administered as 200 mg post sexual exposure significantly reduced the risk of syphilis, chlamydia, and gonorrhea infection in men who have sex with men but did not prevent bacterial sexually transmitted infections in cisgender women; reasons for this discrepancy are currently being explored. Although oral HIV pre-exposure prophylaxis (PrEP) is increasingly being used in populations in greatest need of prevention tools, PrEP uptake and persistence remain low in a number of key populations, including people who inject drugs. Several innovative delivery models show early promise in addressing gaps along the PrEP continuum. The successful use of injectable cabotegravir PrEP in several populations was presented at this conference, although uptake remains low globally. The pipeline of novel long-acting and rapid-onset PrEP agents appears to be robust, including implants, vaginal rings, and topical inserts, with several presentations focusing on preclinical and early clinical trials.*

Keywords: HIV, testing, prevention, transmission, PrEP, PEP, STI, doxycycline, doxy-PEP

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Recent HIV Infections and HIV Incidence

The Recent Infection Testing Algorithm (RITA) is a tool that differentiates recent from chronic HIV infection. Suthar and colleagues used the RITA algorithm to compare factors associated with HIV infection with those associated with recent infection in Cambodia (Abstract 848). Of more than 53,000 individuals tested for HIV infection from August 2020 to August 2022 in 68 facilities, 6868 (13%) tested HIV positive, and 192 of these (3.1%) tested RITA-recent. Compared with the general population, men who have sex with men (MSM) had a nearly 2-fold higher adjusted odds for testing RITA-recent than for being newly diagnosed with longer-term HIV infection (adjusted odd ratio [aOR], 27.4 vs 15.5, respectively). Transgender women (TGW) were also substantially more likely to be deemed recently infected than for being newly diagnosed (aOR, 19.2 vs 11.0, respectively), as were entertainment workers (aOR, 6.1 vs 3.5, respectively). Persons who inject drugs (PWID) were less likely to test RITA-recent than newly diagnosed (aOR, 13.9 vs 26.3, respectively). These data might suggest that MSM, TGW, and entertainment workers are acquiring their infections more recently than other groups, and PWID may have HIV for longer periods of time prior to being diagnosed. The authors suggest that these data may help point to populations in need of greater prevention and testing interventions.

Recency testing was also used by Stephens and colleagues to understand patterns of HIV acquisition and testing in Malawi (Abstract 849). Of more than 8300 newly diagnosed persons aged 15 to 24 years diagnosed from September 2019 to March 2022 across 251 sites in Malawi, 4.9% were recently infected overall, although 8.2% of diagnoses among breastfeeding women were recent. Most males aged 15 to 18 years (>50%) and females aged 15 to 16 years (55%) reported they had never previously tested for HIV, although the largest proportion of recent infections were in persons aged 17 to 18 years (7.3%). These data suggest that most young people with HIV in Malawi have been infected for longer than 12 months at the time of diagnosis. Improved HIV testing

uptake and prevention interventions are needed among this population.

Saito and colleagues examined recency testing paired

Most young people living with HIV in Malawi have been infected more than 12 months at the time of diagnosis

with partner notification services in 60 health facilities in all 5 provinces in Rwanda (Abstract 199). From August 2021 to October 2022, data were analyzed on routine recency testing and sexual partner notification at these sites. Recent infections using the rapid test for recency assays (RTRI) were designated as less than 6 to 12 months in duration, and long-term infections were those designated to be greater than 12 months in duration. Of the 1238 index cases aged 15 years and older, 7.9% were found to be recent. Recent cases were more likely than long-term cases to be younger than 35 years (72% vs 60%; $P = .008$), female (79% vs 62%; $P = .001$), single (38% vs 30%; $P = .008$), and a female sex worker (FSW) (20% vs 8%; $P = .001$). Overall, 45% of the sexual contacts listed were tested, and the HIV prevalence in this group was 15.5% (20% among recently infected index cases vs 15.1% among long-term infected index cases). The recency yield was 4% among sexual contacts linked to recently infected index cases vs 0.8% among sexual contacts linked to long-term infected persons ($P = .045$). These data found that newly diagnosed index cases with recent infection were more likely than those with long-term infection to have sexual contacts with recent infection. The authors suggest that HIV recency testing paired with partner notification provides important opportunities to identify new infections earlier and tailor prevention efforts to groups at high risk.

Poirot and colleagues reported on the impact of returning recency test results on intimate partner violence (IPV) in Rwanda (Abstract 940). The authors point out that the President's Emergency Plan for AIDS Relief (PEPFAR) does not recommend returning recency results to persons newly diagnosed with HIV due in part to lack of safety information about whether such information might trigger IPV. They conducted a prospective cohort study of newly diagnosed persons with HIV from August 2021 to October 2022 in 60 health facilities in Rwanda. Over a 6-month period, persons were asked at 4 study visits about experiences of control, economic, emotional,

physical, or sexual violence from a current partner in the prior 4 weeks. Of 932 persons newly diagnosed with HIV who had IPV data from 1 or more visits after return of recency test results, they found higher rates of IPV at baseline before HIV diagnosis compared with after HIV diagnosis (29.8% vs 17.6%; $P < .001$). Prevalence of IPV did not increase after return of HIV recent infection test results (17.6% vs 16.1%; $P = .40$), nor did they see a difference in IPV between those with recent vs longer-term infection. One participant did report that their recency result was a reason for the violence they experienced, although there were other reasons as well. The authors conclude that programs returning results can adopt strategies to mitigate IPV risks.

Hallmark and colleagues reported on HIV time-space alerts among PWID and MSM in the United States from 2018 to 2021 (Abstract 851). The Centers for Disease Control and Prevention (CDC) issues alerts when the number of diagnoses in the most recent 12-month period is greater than 2 standard deviations and more than 2 diagnoses above the mean in the preceding 12-month period, as a way of potentially identifying clusters or outbreaks of HIV. During this period, the CDC issued 308 quarterly alerts in 4.9% of counties for PWID and 777 quarterly alerts among 14.2% of counties for MSM. Alerts among PWID occurred in a higher percentage of large central metro areas (41.2%), whereas for MSM, a higher percentage of alerts occurred in large fringe (29.1%) and medium (27.4%) metro areas. There were steep declines in alerts, especially among MSM, in the period immediately following the start of the COVID-19 pandemic, likely due to decreased testing. These numbers rebounded for MSM but not for PWID. Numerous subsequent alerts occurred in 29.9% of counties with alerts among PWID and 19.3% of counties with alerts among MSM. The authors raise concerns about the occurrence of alerts for PWID among 41% of central metro areas, which may suggest expanding transmission among PWID in these urban areas as well as sustained alerts in many counties.

Torres and colleagues used RITA testing to calculate an annualized HIV infection rate among MSM and TGW seeking HIV testing who were not on preexposure prophylaxis (PrEP) or postexposure prophylaxis (PEP) at 6 sites in Brazil and 12 sites in Peru (Abstract 850). They enrolled more than 7000 participants into the study, with 97% acceptance rate of those who were eligible. HIV prevalence was 10.0% in Brazil and 20.7% in Peru. Overall annualized incidence was 3.3 per 100 person-years in Brazil and 7.6 per 100 person-years in Peru. Incidence was highest in 18 to 24 year olds in both countries (4.1 per 100 person-years in Brazil and 10.5 per 100 person-years

in Peru). Transgender women had a higher incidence in Brazil than MSM (4.0 vs 3.3 per 100 person-years, respectively), whereas in Peru, MSM had a higher infection rates than TGW (8.2 vs 5.7 per 100 person-years, respectively). These data highlight the urgency of expanding PrEP services to young MSM and TGW in both countries.

McFall and colleagues reported on HIV incidence among MSM and PWID attending care centers in India

Overall annualized HIV incidence among men who have sex with men and transgender women was 3.3 per 100 person-years in Brazil and 7.6 per 100 person-years in Peru

from 2014 to July 2022 (Abstract 863). In this study, clients who were HIV negative on their first test and had 1 or more subsequent tests were included. The study enrolled more than 5700 MSM and more than 7300 PWID. The HIV incidence rate was 1.9 per 100 person-years among MSM and 4.1 per 100 person-years among PWID. These high infection rates occurred despite being engaged in a community-based clinic where prevention services are free. The authors called for more focus on prevention for key populations in low- and middle-income countries, including long-acting PrEP.

Risk Factors for HIV Acquisition and Transmission

Tate and colleagues presented data from the National HIV Behavioral Surveillance (NHBS) survey of PWID in San Francisco to characterize the status of the HIV epidemic for this population (Abstract 864). Despite decreases in new HIV infections overall in San Francisco during this time, new diagnoses among PWID rose by 48%, accounting for 27% of all new diagnoses in San Francisco in 2021. Of the 95-95-95 targets for the proportion of people diagnosed, proportion on antiretroviral treatment (ART), and proportion virally suppressed, the NHBS survey suggested that none of these landmarks had yet been met. In NHBS in San Francisco in 2022, 80% of PWID with HIV knew their HIV status, 92% of these were on ART, and 71% of these were fully virally suppressed. Of the PWID with

a new HIV-positive test result, 75% had had a health-care visit in the previous 12 months, and only 22% of them had been offered an HIV test. Participants with new HIV positive test results tended to be Black/African American (42%), male (50%), heterosexual (83%), and over age 50 years (50%). The authors suggest that San Francisco is not on course to get to zero HIV infections among PWID, with substantial progress needed to reach the 95-95-95 2030 goals. They called for increased HIV testing of PWID in health care settings, as well as more support for PWID with HIV to achieve viral suppression.

Goodreau and colleagues reported on changes in sexual practices among cis-gender MSM who were not on PrEP, as reported in the American Men's Internet Survey from 2014 to 2019 (Abstract 866). They found that young (15 to 24 years old) MSM not on PrEP saw a 5 percentage point year-on-year increase in condomless anal sex; this year-on-year percentage increase was 13 percentage points for young Hispanic MSM. Most of this sexual practice was with partners of perceived negative or unknown status, so this is not attributable to undetectable equals untransmittable (U=U). The authors call for more messaging around risk for MSM who cannot or do not want to take PrEP.

Edu and colleagues modeled the potential impact of persons with low-level viremia (51-1000 viral copies/mL) on HIV transmission, using data from Population-based HIV Impact Assessment (PHIA) surveys in 14 sub-Saharan African countries from 2015 to 2019 (Abstract 868). They found that persons with low-level viremia were not more likely to report high-risk behavior than those with undetectable viral loads, but that persons with undiagnosed HIV and those diagnosed but untreated were more likely to report high-risk behavior. In their model, undiagnosed and diagnosed but untreated persons with HIV contributed to 72% of transmissions, and less than 1% of transmissions occurred from persons with low-level viremia. The authors call for improved HIV testing and linkage services to address this source of new HIV infections.

Kroidland and colleagues report ecologic data on changes in HIV incidence following mass drug administration to eliminate lymphatic filariasis (*Wuchereria [W] bancrofti* infection) in southwest Tanzania (Abstract 869). Previously, *W bancrofti* was associated with a 2.3-fold increase in HIV incidence. The Tanzanian government distributed ivermectin and albendazole once annually from 2009 to 2015, resulting in a reduction of *W bancrofti* prevalence from 35.1% to 1.7%. The same individuals whose data were collected from 2007 to 2011

were revisited in 2019 and screened for *W bancrofti* and HIV. Among those who were *W. bancrofti* uninfected, HIV incidence declined only from 0.72 to 0.64 per 100 person-years over this period. However, among those who were originally *W bancrofti* infected, HIV incidence decreased from 1.9 to 0.76 per 100 person-years. The authors postulate that treatment of *W bancrofti* led to this more substantial decline in HIV incidence.

Singogo and colleagues reported on venue-based vs clinic-based recruitment for HIV testing in Malawi (Abstract 1087). They conducted cross-sectional biobehavioral surveys of representative samples of individuals seeking care in government clinics (n=2313) and social venue patrons (n = 1802) from January to

Among persons who inject drugs in San Francisco with a new HIV-positive test result, 75% had had a healthcare visit in the previous 12 months but only 22% of them had been offered an HIV test

March of 2022. Clinics were randomly selected from government clinics providing HIV testing, and venues were randomly sampled from urban and rural strata, with an oversampling of rural venues. They found that compared with the clinic population, the venue population was more likely to be male (69% vs 28%), aged greater than 25 years (61% vs 51%), unmarried (62% vs 40%), drink alcohol daily (44% vs 8%), have more sexual partners in the last year (mean, 16 vs 2), report a new sex partner in the past 4 weeks (42% vs 15%), and report transactional sex (52% vs 12%). HIV prevalence was higher among the venue population (19% vs 9%), although more than three-quarters in each group were virally suppressed. At venues, HIV prevalence among women increased from 0% among 15 to 17 year olds to 43% among 18 to 21 year olds. At venues, factors associated with HIV infection included being female (39% vs 10%), having a new partner in the past 4 weeks (28% vs 13%), and transactional sex (25% vs 12%). Acute (0% vs 0.6%) and recent infections (4.7% vs 9.7%) were uncommon in clinics and in venues, respectively. The authors suggest that outreach to venues, particularly to young women, is important for HIV prevention and viral suppression.

Partner Notification

Parthasarathy and colleagues presented data from the high-burden state of Telengana in India (Abstract 152). With 2.3 million persons with HIV, India has the second-highest HIV burden in the world. The team contacted spouses, nonspousal sex partners, and children or parents of 9863 index cases. Of the 15,253 contacts reached, median age was 32 years and 47% were male. Overall, 33% were spouses, 51% were nonspousal sex partners, and 16% were children or parents of the index case. Of this group, 87% received test results, 20% were found to be HIV positive, and 92% of them initiated anti-retroviral therapy (ART). However, the speed with which they were notified and began ART was substantially longer for nonspousal sex partners than spouses. The vast majority of spouses received same-day testing and notification of test results, and 31% of the nonspousal sex partners took more than 1 week for testing and notification of test results. Of this 31%, the median delay was 41 days (interquartile range, 17-92 days). In evaluating time of initial contact to beginning ART, 75% of spouses achieved this on the same day or within 1 week, but this was only true of 43% of sex partners. The authors point to the importance and success of index testing but highlight the need for more expedited methods for the nonspousal sex partners of index persons.

Monroe-Wise and colleagues presented data from a study of Assisted Partner Services (APS) in Kenya (Abstract 153). They pointed out that PWID have a 22-fold higher prevalence of HIV infection than the general population, similar to that seen in MSM, but that there are substantial barriers to HIV testing and care for this population. The team used community-embedded peer educators to locate persons with HIV infection in the community, locate their injecting and sexual partners, and find the people with HIV and partners testing positive for HIV or hepatitis C virus (HCV) after 6 months for follow-up interviews. The team found 485 women and 504 men with HIV. These PWID had been injecting for an average of 5.4 years, and 10.8% reported sharing equipment in the past month. Of this group, 16.4% were HCV positive and 67.9% were HIV virally suppressed. Nearly three-quarters reported 1 to 5 sexual partners, with the remainder reporting 6 or more. Of the 4705 partners reported, 97% were located and 100% of these were enrolled in the study, a testament to the skill of the peer educators. Of these, 70.5% were injecting partners, 18% were sexual partners, and 11.5% were injecting and sexual partners. Among the partners, HCV prevalence was 18%, HIV prevalence was 18%, and 69.9% of these were

virally suppressed. HIV prevalence was highest (32.5%) in participants who were sexual and injecting partners. Of the partners found to have HIV, 85% were known to be positive, 91% of those were on ART, but only 77% of those were virally suppressed. Only 26% of HCV-positive partners were known to be HCV positive, and only 2% of those who were PCR positive had been previously treated. The authors calculated that the number needed to interview to find a partner with HIV was 11.24, but to find a partner with HIV who was either unaware of their status, not on ART, or not virally suppressed was 4.14. On follow-up, of 189 of the index participants not virally suppressed at baseline, 71.9% were virally suppressed at 6 months; 71.8% of partners not virally suppressed at baseline were suppressed at 6 months. Of those reporting IPV at baseline, 22% reported IPV at 6 months, and 4% of those reporting no IPV at enrollment reported IPV at 6 months, although none attributed the IPV to study procedures. This appeared to be a successful program to identify and link to care PWID and their injecting and sexual partners.

HIV Testing

Singh and colleagues presented data from 21 jurisdictions in the National HIV Surveillance System on the proportion of persons who tested positive who had ever had a previous HIV negative test from 2014 to 2019 (Abstract 934). They found that for all races and ethnicities, the proportion who ever had a previous negative HIV test before HIV diagnosis decreased significantly (from 63% to 54%; estimated annual percent change [EAPC], -2.7). This decrease was greatest for Hispanic/Latino persons (from 63% to 52%; EAPC, -3.2), then White persons (from 68% to 57%; EAPC, -3.0), and then Black/African Americans (from 62% to 54%; EAPC, -2.2). Significant decreases occurred for males and females among Black/African American persons, but males only among Latino and White persons. The authors postulate that this decrease in HIV testing before diagnosis may be associated with trends in uptake of HIV testing and prevention strategies, reminding us that at least annual HIV testing should be promoted among all persons with HIV risk factors.

Patel and colleagues evaluated the association between the amount of HIV testing and the areas with greatest needs for HIV testing, as defined by the rate of persons with undiagnosed HIV infection in 2019 (Abstract 935). They found a significant association between the amount of testing and the areas with greatest needs for testing (Rho, 0.59; $P < .001$), but found that jurisdictional

associations varied. For instance, those with the greatest need (higher undiagnosed HIV infection per capita and lower CDC-funded HIV tests per capita) included Miami-Dade County, FL; Prince George's County, MD; Hudson County, NJ; Bronx County, NY; and Hamilton County, OH. Those with the lowest need (lower undiagnosed HIV infection per capita and higher CDC-funded HIV tests per capita) were San Francisco County, CA; Tarrant County, TX; Suffolk County, MA; and Missouri and Alabama. The authors suggest that those areas with greater unfulfilled testing needs could use these data to identify gaps and barriers to their testing services and improve or expand upon their testing programs. Those with fewer unfulfilled needs may also be areas with more robust PrEP programs, which may both increase knowledge of HIV serostatus and increase the number of HIV tests being done.

Guardiola and colleagues reported on directed screening for HIV infection in 10 emergency departments (EDs) in Catalonia, Spain (Abstract 942). They recommended HIV testing in the EDs for any of 6 specific clinical scenarios: presence of sexually transmitted infection (STI), PEP, chemsex, mononucleosis-like syndrome, and community pneumonia or herpes zoster in those under the age of 65 years. After 60 weeks of follow-up from June 2021 through August 2022, 6180 HIV tests were performed with 55 new HIV diagnoses (0.9%) identified. Persons reporting chemsex had an HIV seroprevalence of 5.4%, and patients with community-acquired pneumonia or mononucleosis-like syndromes had an HIV prevalence close to 2%. The authors suggest that these clinical scenarios provide efficient criteria for ED screening.

Kailembo and colleagues reported on factors associated with lack of awareness of HIV infection among Tanzanians with HIV (Abstract 936). Using data from the Tanzania HIV Impact Survey conducted in 2016 to 2017, they found that of 1779 survey participants with HIV, 39% were unaware of their HIV status. On multivariable analysis, factors associated with unawareness included male sex (adjusted prevalence ratio [aPR], 1.47), younger age (15-24 years compared with those 50 years or older; aPR, 1.43), having low HIV knowledge (aPR, 1.2), and not using condoms (aPR, 1.42). Widowed persons were significantly less likely to be unaware of positive status (aPR, 0.74). The authors state that this reinforces the need for targeted interventions to increase safe and ethical index testing, social network testing, and HIV self-testing, with a focus on young adults and men.

Leslie and colleagues reported on the prevalence of overreporting of recent HIV testing and underreporting of positive HIV serostatus based on a population-based

survey conducted in a rural setting of Ehlanzeni District in South Africa (Abstract 937). They found that 69% reported recent testing, but reporting was confirmed in only 34% of survey respondents after correcting for potential under-documentation. They also found that HIV prevalence was estimated at 16% based on self-report but was actually 28% in this population. They suggest that survey-based measures must be interpreted with caution, given the inaccuracies found in this survey.

Shaikh and colleagues point to the importance of offering non-HIV services for TGW as a method for increasing HIV testing (Abstract 941). They evaluated data from 3 clinics in India from February 2021 to July 2022. During this time, 2276 individuals registered at the clinics, 87% of whom identified as a TGW, and 54% of whom had never received services through the government's targeted interventions program. The most utilized service was laser therapy, followed by HIV services. Of 883 clients screened for HIV, 48 were newly diagnosed with HIV infection, although only 20 completed confirmatory testing and 13 initiated ART. The authors concluded that integrating non-HIV services desired by the community enabled these clinics to reach clients not previously engaged in local or national HIV programming and served as an entry point to HIV testing and care. Additional efforts are needed to increase confirmatory testing and ART initiation.

Polk and colleagues reported on the impact of the mpox outbreak on increased HIV testing and diagnosis in a large integrated health care system (Abstract 944). They reported on 17 EDs and 44 Urgent Care clinics across the Charlotte region in North Carolina in the period pre-mpox (July 2021 to June 2022) to testing during the mpox outbreak (July 2022–October 2022). Overall, total HIV tests increased from 2.3 per 1000 encounters per month to 3.8 per 1000 encounters per month ($P < .05$) and the total number of new diagnoses per month increased from 1.4 to 3.9 ($P < .05$). They plan to use this information to continue to educate clinicians in these settings on the need and opportunities for HIV testing.

Armstrong-Hough and colleagues reported on a randomized controlled trial to increase HIV testing uptake among household contacts of persons with tuberculosis (TB) (Abstract 1050). They point out that up to half of household contacts decline HIV test offers during routine TB contact investigation in Uganda and South Africa. Community health workers visited the homes of TB index patients to screen contacts for TB symptoms and to offer free, optional oral HIV testing. Households were randomly assigned 1:1 to standard-of-care or a socio-behavioral intervention to make HIV testing the

norm. In total, 328 contacts in 99 index patient households were randomly assigned to the intervention and 224 contacts in 86 patient households were randomly assigned to the standard-of-care arm. Completion of HIV testing was higher in the intervention than the control arm (98% vs 92%; $P = .006$). Out of these tests, 2.1% of those tested in the intervention arm were found to be HIV positive, as were 0.6% in the control arm ($P = .22$). Community health workers reported that the norming strategy took equivalent or less time than the standard strategy. These results suggest that this simple, brief strategy could increase HIV testing uptake among contacts of persons diagnosed with TB.

Using community health workers to normalize HIV testing is a simple, brief strategy that could increase HIV testing uptake among contacts of persons diagnosed with tuberculosis

Terwilliger and colleagues reported on attempts to isolate HIV from municipal wastewater (Abstract 947). They used samples from 6 wastewater treatment plants in the Houston area, and were able to identify DNA, but not RNA in these samples. They suggest that wastewater monitoring could be a new tool to understand the epidemiology of HIV in near real time.

HIV Self-Testing

Ekwunife and colleagues evaluated the impact of removal of subsidies for HIV online self-testing kit ordering in Kenya (Abstract 930). They evaluated periods before subsidy removal (cost of oral-fluid and blood-based kits was \$2.30 USD) to periods after subsidy removal (cost of oral-fluid tests was \$4.30 USD and cost of blood-based kits was \$6.90 USD), using sales of an emergency contraceptive product during those periods as a control. They found that ordering of oral-fluid self-test kits declined 1.5-fold after subsidy removal (with 357 fewer test kits per month), and blood-based self-collection kits declined by 27-fold (with 226 fewer test kits per month) compared with the control. These data suggest that subsidies are effective at increasing the demand for HIV self-test kits.

Pines and colleagues evaluated PWID willingness

to use and deliver HIV self-test kits to peers at the San Diego-Tijuana border region (Abstract 932). Of the 539 HIV-negative PWID completing the survey, 81% stated that they would want to use HIV self-test kits, with more than 90% reporting reasons that they would be able to test for HIV more regularly, that it would be more convenient than going to a clinic or community-based organization, and that it would give them more privacy and confidentiality. Of the 19% stating they would not want to use self-test kits, 24% each reported that they would be worried that self-tests are less accurate, that they would be worried about using the test incorrectly, and that they would be worried about misinterpreting

Online ordering of oral-fluid self-test kits in Kenya declined 1.5-fold after subsidy removal, and blood-based self-collection kits declined by 27-fold, highlighting the importance of subsidies in increasing the demand of HIV self-test kits

the test results. Individual characteristics associated with willingness to use self-test kits included more years of education (aPR, 1.02), prior HIV testing (aPR, 1.24), prior HIV self-test kit use (aPR, 1.27), and hazardous alcohol consumption (aPR, 1.12). The following were less likely to want to use a self-test kit: persons who injected drugs several times per day in the past 6 months (aPR, 0.87); receptive syringe sharing (aPR, 0.92); and perceived HIV risk (aPR, 0.83). Among the 366 participants who consented to the social network substudy, willingness to distribute self-test kits was increased with years of education (aPR, 1.02), prior HIV testing (aPR, 1.27), prior HIV self-test kit use (aPR, 1.25), willingness to use self-test kits themselves (aPR, 8.31), network size (aPR, 1.04), proportion of network that ever had unstable housing (aPR, 1.5), proportion of network that had ever been detained or arrested (aPR, 1.57), and proportion of network that offered drugs or encouraged drug use (aPR, 1.29). Those who reported a higher proportion of the network with whom they were very close were less likely to be willing to distribute HIV self-test kits (aPR, 0.8). The authors conclude that there is high potential for HIV self-test kits and their distribution among PWID, which could address undertesting in this population.

Effect of COVID on HIV Testing and Prevention Services

Viguerie and colleagues attempted to isolate the effect of COVID-19-related disruption of HIV testing on HIV diagnoses in the United States in 2020 (Abstract 158). Prior to 2020, the US saw a 2% to 3% annual decline in new diagnoses per year, but found a 17% decline in 2021. The authors wanted to differentiate decreased diagnoses because of decreased testing vs decreased infections due to behavior changes related to COVID-19 (eg, social distancing). Using 3 different mathematical techniques, they found that 3200 to 3300 new HIV diagnoses were missed in the US in 2020 due to decreased testing, or approximately 18% fewer diagnoses than expected. The absolute number of missed infections was highest among persons assigned male at birth, MSM, persons in the South, and Black persons. However, the proportion of missed infections was highest in Hispanic/Latino persons (22%), females at birth (24%), heterosexuals (24%), and MSM/PWID (30%). These are likely the lower bound of estimates for missed infections because they do not take into account either very new missed infections or very old missed infections. These data suggest that the substantial decrease in new HIV diagnoses in 2020 in the US were not attributable to incidence changes, but rather decreases in HIV testing services.

Nassau and colleagues presented data on changes in prevention services for PWID in Philadelphia in 2022 compared with 2018 to assess the impact of COVID-19 on service disruption (Abstract 1100). Using data from NHBS, they compared HIV testing, medical care, syringe service program access, drug treatment, and PrEP use in the year prior to interview. There were baseline differences in the participants sampled in the 2 years by age, race/ethnicity, housing stability, and primary injecting drug. After adjusting for these differences, they found an 18% decrease in recent HIV testing was observed between these 2 times (aPR, 0.82; $P < .001$). Although a significantly smaller proportion of PWID accessed each service in 2022 than in 2018, they did not see statistically significant differences in access to HIV services in adjusted models. PrEP awareness was higher in 2022 (approximately 38% in 2018 vs 54% in 2022; $P = .001$); however, this did not translate into improved PrEP use (both arms $<5%$). The authors concluded that harm reduction services should be co-located with HIV prevention and care services in nontraditional, nonclinical settings.

HIV Prevention Interventions

Cowan and colleagues presented the results of the Amethyst trial, a cluster randomized trial investigating the effect of risk-differentiated care for FSW in Zimbabwe (Abstract 123). In southern Africa, FSW have a high burden of HIV, and although community-led FSW programs in Asia have shown benefit on HIV and STI incidence, these interventions have not been widely used nor tested in Africa. The investigators nested this study into a larger study, the Sisters' study (not described in

The substantial decrease in new HIV diagnoses in 2020 in the US was not attributable to incidence changes, but rather decreases in HIV testing services

the presentation). The Amethyst intervention consisted of a peer educator providing risk-differentiated peer support, as well as self-help groups, although few of these groups took place. The intensity of the intervention varied depending on the amount of risk reported by the FSW (ie, risk determined by age under 25 years, new to sex work [ie, for <6 months], high client burden of >10 per week, inconsistent condom use, problematic drinking and/or drugs, and problematic violence). In all, 22 clusters were randomly assigned in a 1:1 ratio to the Sisters' program alone or the Sisters' program with Amethyst. Outcomes were assessed after 28 months using respondent-driven sampling in all 22 clusters. In total, approximately 2200 FSW were recruited from each arm, and more than 2100 per arm contributed to the final analysis. There was no significant difference in the proportion of HIV-negative FSW with risk of HIV acquisition (defined as condomless sex by Y chromosome or gonorrhea on vaginal specimen without adequate PrEP use [700 fmol/punch on dried blood spot]); 92.1% of the intervention group and 92.2% of the control group were at risk for HIV acquisition. However, there was a significant decrease in the risk of HIV transmission from FSW with HIV (defined as condomless sex as described above in someone not virally suppressed); 5.8% of the intervention arm vs 10.4% of the control arm ($P < .001$). The results for FSW at risk for HIV infection were disappointing, and more is needed to determine how to

reach this population with effective interventions. The authors also concluded that self-report did not correlate well with biomarkers, either for condomless sex or for PrEP use.

Buchbinder and colleagues presented interim data from the Mosaico trial, a phase III trial of a combination adenovirus 26 mosaic vaccine and a mosaic and clade C gp140 vaccine among 3887 MSM and transgender persons in the US, Latin America, and Europe (Special Session 1). This trial had a novel design in how PrEP was handled: participants were first navigated to low- or no-cost PrEP, and if they declined PrEP, were offered to be screened for the study. Participants were not on PrEP when they enrolled, but if they were counseled and offered PrEP throughout the trial, and if they took up PrEP, remained in the trial. PrEP uptake was approximately 10% by month 24 in the study. The vaccine had no effect on HIV infection rates, which were 4.1 per 100 person-years in both arms in the modified intent-to-treat analysis. HIV infection rates were highest among younger study participants and participants enrolled in Latin America. This presentation was followed by a presentation by Corey, who laid out the future of HIV vaccine research, which is focused on many strategies to develop vaccines that induce broadly neutralizing antibodies as well as infusion of broadly neutralizing antibodies.

Sexually Transmitted Infections

Several studies evaluated the use of doxycycline-PEP (doxy-PEP) for the prevention of STI. Haaland and colleagues presented on the mucosal pharmacology of doxycycline following oral dosing in 11 men and 9 women (Abstract 118). They conducted a single-dose pharmacology study in which participants were administered 200 mg of a delayed release formulation of doxycycline hyclate and a single dose of tenofovir alafenamide/emtricitabine/bictegravir, followed by collection of rectal or vaginal and cervical biopsies and urethral swabs at 24 hours, and blood and rectal or vaginal swabs for up to 7 days. Rectal secretion doxycycline concentrations peaked at 48 hours, compared with 8 hours in vaginal secretions, and 4 hours in plasma. Doxycycline exposure in mucosal secretions was higher than in plasma, with an area-under-the-curve ratio of 2.17 for rectal secretions to plasma and 1.72 for vaginal secretions to plasma. Additionally, plasma and rectal doxycycline concentrations did not differ between men and women. The maximum concentration (C_{max}) of doxycycline in mucosal secretions reached 10- to 20-times (x) the minimum inhibitory concentration (MIC) for *Chlamydia*

trachomatis; these concentrations remained above the MIC for about 4 days and above 4x the MIC for up to 2 days after dosing. For *Treponema pallidum*, C_{max} reached 7x to 12x the MIC and remained above the MIC for approximately 3 days and above 4x MIC for up to 2 days. For *Neisseria gonorrhoeae*, C_{max} only reached 3x to 5x the MIC, remained above the MIC for approximately 2 days but above 4x MIC for less than 12 hours. Tissue concentrations of doxycycline were 3x to 9x the MIC for *Chlamydia trachomatis* and *Treponema pallidum* but only 1x to 2x MIC for *Neisseria gonorrhoeae*, and doxycycline concentrations in male urethral secretions were 11x to 18x MIC for *Chlamydia trachomatis* and *Treponema pallidum* but only 4x MIC for *Neisseria gonorrhoeae*. These findings suggest that doxycycline efficiently distributes to mucosal sites and persists at concentrations exceeding reported MIC values for *Chlamydia trachomatis* and *Treponema pallidum* to a greater extent than for sensitive *Neisseria gonorrhoeae*.

Molina and colleagues reported results from the ANRS 174 DoxyVAC study, an open-label randomized trial to prevent STIs among MSM on PrEP (Abstract 119). Participants who had an STI in the past 12 months were randomly assigned in a 2x2 factorial design to receive doxy-PEP (200 mg doxycycline taken within 24-72 hours post sex) or no PEP in a 2:1 ratio, and 2 injections of the 4CmenB vaccine or no vaccine in 1:1 ratio. Based on results from the DoxyPEP trial¹ demonstrating a 65% reduction in STI incidence, in September 2022, the DoxyVAC Data Safety Monitoring Board requested an unblinded analysis of 502 participants enrolled from January 2021 to July 2022. At baseline, the median age was 39 years, 81% were White, and participants had a median of 42 months of PrEP use and 10 sex partners in the last 3 months. There was no interaction between doxy-PEP and the 4CmenB vaccine for the primary endpoints. The incidence of first episode of chlamydia or syphilis was 5.6 vs 35.4 per 100 person-years in the doxy-PEP vs no PEP arms (adjusted hazard ratio [aHR], 0.16; 95% confidence interval [CI], 0.08-0.30), with an 89% reduction in time to first chlamydia and 79% reduction in time to first syphilis. There were also significant reductions in time to first gonorrhea (aHR, 0.49; 95% CI, 0.32-0.76) and *Mycoplasma genitalium* (aHR, 0.55; 95% CI, 0.34-0.89) infection with doxy-PEP. Among 65 cultures available for gonorrhea resistance testing, 100% (7/7) were tetracycline resistant at baseline, with no difference between arms during follow-up (67% and 81% tetracycline resistant in the doxy-PEP and no-PEP arms, respectively). No chlamydia resistance was observed among samples tested. In a microbiome analysis, there was no difference

in methicillin-resistant *Staphylococcus aureus* (MRSA) in throat swabs or extended spectrum beta-lactamase (ESBL) *Escherichia coli* in anal swabs between arms. For the 4CmenB vaccine evaluation, the incidence of first episode of gonorrhea was 9.8 vs 19.7 per 100 person-years in the 4CmenB vaccine vs no vaccine arms (aHR, 0.49; 95% CI, 0.27-0.88). There were no drug-related serious adverse events reported for either doxycycline or 4CmenB; drug-related adverse events were uncommon in those receiving doxy-PEP and were mostly gastroin-

In the DoxyVAC study among men who have sex with men, doxycycline postexposure prophylaxis given within 72 hours after sex reduced chlamydia, syphilis, and gonorrhea incidence by 89%, 79%, and 51%, respectively, and the 4CmenB vaccine reduced gonorrhea by 51%

testinal events; approximately one-third of participants receiving 4CmenB had a drug-related adverse event, mostly pain at the injection site, which was short lived.

Luetkemeyer and colleagues examined antimicrobial resistance among MSM and transgender women in the DoxyPEP trial¹ (Abstract 120). In this study, 637 participants were randomly assigned 2:1 to receive 200 mg doxycycline within 72 hours of condomless sex or no doxycycline. Among 320 gonorrhea cases detected at baseline and follow-up, 49% of cases had culture collected, and of those, 42% had culture growth. At baseline, 4 of 17 gonorrhea cases (24%) had tetracycline resistance, and during follow-up, 6 of 20 cases (30%) had tetracycline resistance in the doxy-PEP arm, compared with 11% in the standard-of-care arm, suggesting that doxy-PEP may be less protective against gonorrhea strains with existing tetracycline resistance. Doxy-PEP was associated with a 14% absolute reduction in *Staphylococcus aureus* colonization and an 8% absolute increase in doxycycline resistance compared with baseline. MRSA prevalence was low (6%) and was unchanged with doxy-PEP use. For nonpathogenic *Neisseria* species, which may serve as a reservoir for drug-resistant genes that can transmit to pathogenic bacteria, nearly two-thirds of isolates had preexisting doxycycline resistance; however, there were

no significant changes associated with doxy-PEP use. Luetkemeyer recommended longer-term monitoring during doxy-PEP implementation to understand the trajectory and clinical importance of microbial susceptibility patterns associated with doxy-PEP.

Stewart and colleagues reported results on doxycycline PEP among 449 cisgender women in Kenya (Abstract 121). Participants taking daily oral PrEP were randomly assigned 1:1 to receive 200 mg doxycycline hyclate taken within 72 hours of sex or standard of care and followed for 12 months. The median age was 24 years, and the median time on PrEP was 7 months; the prevalence of STIs at baseline was 18%. Retention was high in the cohort, and women assigned to doxy-PEP reported coverage of 78% of sex acts. The overall STI incidence was 27 per 100 person-years. There were 109 incident STI events detected: 50 in the doxy-PEP arm, and 59 in the standard-of-care arm (relative risk [RR], 0.88; 95% CI, 0.60-1.29; $P = .51$), and results were also not statistically significant for chlamydia and gonorrhea alone. When censoring follow-up once participants became pregnant, there was no difference in STI incidence rates between arms (RR, 0.91; 95% CI, 0.62-1.35); results were also similar in subgroup analyses by age, hormonal contraception use, transactional sex, and STI detected at baseline. There were no severe adverse reactions related to doxycycline use and no incident HIV infections in either arm; however, 4 participants reported social harms related to doxy-PEP use. High levels of tetracycline-resistant *Neisseria gonorrhoeae* (100%; 6/6 samples) were detected at baseline and at follow-up visits (100%; 22/22 samples). There was no resistance to *Chlamydia trachomatis* detected among

In a doxycycline postexposure prophylaxis study among cisgender women in Kenya, there was no impact of doxycycline postexposure prophylaxis on incident STIs

66 samples tested. The researchers proposed several possible explanations for the negative results, including: (1) anatomy: whether endocervical tissue may differ from urethral, rectal, and pharyngeal tissues; (2) resistance: high levels of gonorrhea resistance were observed in Kenya; however, there are no known cases of resistance chlamydia globally; and (3) adherence: although the trial was designed to maximize adherence, and self-reported adherence was high, it was imperfect in the study. Given

the high burden of STIs among cisgender women, they highlighted the need for effective STI prevention interventions in this population.

Traeger and colleagues modeled the potential impact and efficiency of prescribing doxy-PEP among people with or at risk of HIV infection, using data from a Boston-based lesbian, gay, bisexual, transgender, queer, and intersex (LGBTQI+) health center (Abstract 122). They tested 10 different hypothetical strategies for targeting doxy-PEP, 3 of which targeted populations: (1) all persons accessing care; (2) persons with HIV and PrEP users; (3) PrEP users only; and 7 of which included only persons with a diagnosed bacterial STI in the past 12 months: (1) any STI; (2) rectal STI; (3) 2 STIs in past 12 months; (4) 2 STIs in past 6 months; (5) 2 STIs in the same visit; (6) syphilis; and (7) gonorrhea). They then applied a counterfactual using efficacy data from the US DoxyPEP study to assess the number of persons requiring doxy-PEP, the number of STIs averted, and the number needed to treat (NNT) for a year to avert 1 STI. They drew data from more than 10,000 patients followed up for more than 28,000 person-years from 2015 to 2020. They found that treating population groups averted more STIs, but at the cost of requiring treatment of larger populations of patients. Most efficient was treating persons with previous STIs. For example, using doxy-PEP just for persons with an STI in the previous year would require treating 41% of the cohort but averting 42% of the infections. The NNT was lowest for averting chlamydia and gonorrhea for persons with 2 STIs in the past 12 months (2.8 and 4.1, respectively), 2 STIs in the past 6 months (2.5 and 3.6, respectively), and 2 concurrent STIs (2.5 and 3.4, respectively). For syphilis, the most efficient strategy was to treat persons with prior syphilis infection (NNT, 6.0). The authors concluded that guidelines should incorporate having a recent STI diagnosis as an indication for doxy-PEP, recognizing that treating a larger population would reduce more infections, but at the cost of treating a larger proportion of people. They also recommended that persons with an STI, regardless of whether they had HIV or were on PrEP, be offered doxy-PEP, as restricting to these 2 subpopulations did not improve the NNT. They further suggested that local epidemiology could be used to target specific STIs. For example, treating persons with prior syphilis with doxy-PEP would require that only 9% of the population be treated while averting 25% of syphilis cases. They recognize that there are numerous assumptions with their model, including the population on which it is based, so different results could come from other populations.

Atkins and colleagues reported on the incidence of syphilis, HIV, and HCV among people reporting sex work

from a Birmingham, Alabama-based AIDS service organization from May 2008 to June 2022 (Abstract 1025). Of more than 20,000 clients served, 950 (4.6%) reported sex work in the prior 5 years. Sex work was associated with older age (mean, 32 years vs 31 years; $P = .002$), being a cis-gender woman (45.8% vs 42.5%; $P < .001$), and identifying as non-Hispanic White (71.5% vs 44.2%; $P < .001$). Persons reporting sex work were also more likely to report injection drug use (57% vs 8%), other drug use (19% vs 3%), having a PWID partner (41% vs 5%), and sharing noninjection drug equipment (12% vs 1%). Sex work was associated with 3.42x the odds of syphilis diagnosis and 1.75x the odds of HCV diagnosis. Among the subgroup of MSM, sex work was associated with 4.57x the odds of HCV diagnosis and 2.49x the odds of HIV diagnosis. The authors concluded that targeted prevention and treatment programming is needed for persons reporting sex work.

Brown and colleagues reported on patterns of STI among TGW with and without HIV in 6 eastern and southern cities in the US (Abstract 1027). Of 1018 TGW studied, median age was 31 years, 29% self-identified as Black and 27% as Latinx, and 27% had HIV. TGW with HIV were significantly more likely to be diagnosed than TGW without HIV with 1 or more bacterial STIs (aPR, 1.96) including syphilis (aPR, 2.7) and to have herpes simplex virus (HSV)-2 IgG antibody (aPR, 1.53). Among TGW without HIV, correlates of having 1 or more bacterial STIs included being from Baltimore/Washington DC (aPR, 2.3), being Black (aPR, 5.47) or Latino (aPR, 3.87), self-identifying as genderqueer/nonbinary (aPR, 1.68), and having more than 1 sex partner (aPR, 1.87); having non-cisgender male partners exclusively was associated with decreased risk (aPR, 0.10). Among TGW with HIV, having one or more bacterial infections was less likely with increasing age (aPR, 0.91), hazardous alcohol use (aPR, 0.54), and having a lifetime history of sexual violence (aPR, 0.60). The authors concluded that the prevalence and correlates of bacterial STIs differs substantially between TGW with and without HIV, highlighting differential needs of these populations. They speculated that the relative lack of individual level correlates of bacterial STIs among TGW living with HIV may suggest macro-level factors in conferring risk among this population and called for an effort to elucidate the drivers of bacterial STIs among TGW to facilitate more targeted prevention and treatment strategies optimally suited for these populations.

Moscicki and colleagues reported on rates of STIs among young people with perinatally acquired HIV and those exposed perinatally but without HIV in the US-based Pediatric HIV/AIDS Cohort Study network

(Abstract 1028). Youth in this cohort study were screened annually for chlamydia, gonorrhea, and trichomoniasis; young women were also tested for human papilloma virus (HPV). The incidence of gonorrhea, chlamydia, trichomoniasis, and HPV among youth with HIV was 49, 111, 75, and 135 per 1000 person-years, respectively; the rates for youth without HIV were 33, 95, 54, and 52 per 1000 person-years, respectively. The authors concluded that rates of gonorrhea, chlamydia, and trichomoniasis were high and similar between these 2 populations, underscoring the need for STI prevention strategies, including promotion of condom use and counseling, which clinicians may mistakenly believe has already happened. They also called for robust triage for cervical abnormalities in young women with HIV to avoid over-referral to colposcopy.

Syndromic management substantially underestimates the prevalence of STIs. Truong and colleagues reported on the prevalence of chlamydia and gonorrhea among adolescents in Kisumu, Kenya (Abstract 1026). They reported on STI testing among 1159 boys and girls aged 15 to 19 years on whom STI testing had interpretable results. Overall prevalence was 9.6%, and higher among

Syndromic management substantially underestimates the prevalence of STIs

girls (odd ratio [OR], 2.13; $P < .001$), those reporting last sexual activity 1 month ago or more recently (OR, 1.69; $P = .01$), having more than 1 partner (OR, 2.14; $P = .19$), having experienced forced sexual contact (OR, 1.6; $P = .02$), having engaged in transactional sex (OR, 1.68; $P = .01$), and having ever experienced STI symptoms (OR, 1.77; $P = .007$), although the latter was only reported by 13.8% of youth diagnosed with an STI. The authors point out that undiagnosed or misdiagnosed STIs can result in onward transmission and impact the reproductive health of adolescents; they suggest STI testing should be made available for adolescents with risk factors.

PrEP

Long-Acting Injectable PrEP

Marzinke and colleagues evaluated cabotegravir (CAB) pharmacology among participants with delayed injections in the HIV Prevention Trials Network (HPTN) 084 study (Abstract 159). This is an ongoing phase III trial

that demonstrated the superiority of long-acting injectable CAB (CAB-LA) compared with daily oral tenofovir disoproxil fumarate/emtricitabine (TDF/FTC) in individuals assigned female at birth. In the injection phase of the study, the first 2 injections were administered 4 weeks apart, followed by injections given every 8 weeks thereafter. The CAB-LA regimen was targeted to achieve concentrations greater than 4x the protein-adjusted 90% inhibitory concentration (PA-IC₉₀) (0.664 µg/mL) in 80% of individuals, and more than 8x the PA-IC₉₀ (1.33 µg/mL) in 50% of individuals. They classified delayed injections as type 1 if the second injection occurred 8 to 14 weeks after the first injection and as type 2 if any subsequent injection took place 12 to 18 weeks after the last injection. Among 1614 participants randomly assigned to the CAB-LA arm, 194 participants (12%) had at least 1 delayed injection, with a total of 224 delays observed: 19 type 1 and 205 type 2 delays. For type 1 delays in which the second injection was given 8 to 10 weeks after the first injection, 100% and 91% had CAB trough concentrations more than 4x the PA-IC₉₀ and more than 8x the PA-IC₉₀, respectively; however, 75% were less than 4x the PA-IC₉₀ when the interval was 12 to 14 weeks between injections. For type 2 delays in which the injection was administered 12 to 14 weeks apart, 98% and 87% of CAB trough concentrations were more than 4x the PA-IC₉₀ and more than 8x the PA-IC₉₀, respectively; 90% and 62% remained more than 4x the PA-IC₉₀ and more than 8x the PA-IC₉₀ when the injections were 16 to 18 weeks apart. Participants with a body mass index less than the median of 26.3 kg/m² were more likely to have concentrations more than 8x the PA-IC₉₀ following a delay. One participant seroconverted in the setting of delayed injections in the blinded phase of HPTN 084, with HIV first detected after a 16.1-week delay between the 8th

There may be up to 6 weeks of forgiveness in persons assigned female at birth who received delayed long-acting cabotegravir

and 9th injections; the CAB concentration was less than 4x the PA-IC₉₀ at the first HIV-positive visit. In parallel with these analyses, population pharmacokinetic modeling was conducted using data from 16 clinical trials and nearly 24,000 injection events and demonstrated that CAB concentrations were 28% lower after the first injection but 32% higher at steady state among women than

among men. Additionally, CAB concentrations were 30% lower after the first injection and 5% lower at steady state among participants with body mass index at or above 30 kg/m² vs below 30 kg/m². These data suggest that there may be up to 6 weeks of forgiveness in persons assigned female at birth who received delayed CAB-LA injections.

Eshleman and colleagues described the long-acting early viral inhibition (LEVI) syndrome occurring in individuals with early HIV infection in the setting of CAB-LA PrEP (Abstract 160). Among the 2282 cisgender men and TGW randomly assigned to CAB-LA PrEP in the HPTN 083 trial, 6 infections occurred despite on-time injections, 16 infections occurred with no CAB exposure within the past 6 months, 4 had HIV infection at enrollment, 3 were infected while receiving oral CAB, 3 were infected after 1 or more delayed injections, and 2 were infected near the time of CAB reinitiation. In these cases, HIV rapid tests and antigen/antibody tests often failed to detect HIV infection in the setting of CAB-LA PrEP, and viral suppression and delayed or diminished antibody expression can persist for months after infection. In HPTN 083, detection of infection was delayed in approximately half of the CAB arm infections but was rarely observed when infection occurred over 6 months after CAB administration. She presented a case study from HPTN 083 in which there was a 3-month delay in detecting HIV infection by antigen/antibody testing (qualitative RNA was positive at the first HIV positive visit with viral load of 6.1 copies/mL). Although genotyping failed at the first HIV-positive visit, integrase strand transfer inhibitor (InSTI) resistance was detected at a visit 9 months later. This participant had assay reversion in which rapid, antigen/antibody, and qualitative RNA test results switched from reactive to nonreactive and back to reactive during the first year after infection. Eshleman compared acute HIV infection (AHI) as a phase of natural HIV infection to infections occurring in the setting of LEVI (infection during PrEP use or initiation of PrEP during acute/early infection). Although viral replication in AHI is explosive and associated with various symptoms, viral replication in the setting of LEVI is smoldering and symptoms are usually minimal or variable. Assay reversion is rare in AHI but common in LEVI. Although AHI usually lasts 1 to 2 weeks until antibody detection, LEVI can persist for months after the antiviral agent is discontinued. Viral transmission is very likely during AHI, but it is unlikely during LEVI. Drug resistance is unlikely in AHI but can emerge early in the LEVI syndrome when viral load is low. In HPTN 083, InSTI resistance emerged in 10 of 18 cases when CAB was administered within 6 months of the first HIV-positive visit; however, InSTI resistance was not observed

when the first HIV-positive visit occurred more than 6 months after the last CAB injection. In most cases, retrospective testing using a sensitive RNA assay detected HIV infection prior to the emergence of InSTI resistance. RNA testing can be used to screen for HIV infection in individuals on CAB-LA PrEP, as recommended by the US Centers for Disease Control and Prevention and in the

In the long-acting early viral inhibition syndrome among individuals with early HIV infection in the setting of long-acting cabotegravir, viral replication is smoldering, assay reversion is common, and the syndrome can persist for months

US Food and Drug Administration package insert, and the pros and cons of RNA screening are being evaluated in the ongoing HPTN 083 and 084 open-label studies.

Scott and colleagues presented data on HIV incidence and prevention efficacy of CAB-LA PrEP among US Black men and TGW who have sex with men in HPTN 083 (Abstract 161). Among 1698 participants enrolled at US sites, 844 (50%) self-identified as Black (or mixed race including Black), most were MSM (93%), and the median age was 27 years; a lower proportion of Black vs non-Black participants had a college education or higher (68% vs 83%). At enrollment, Black and non-Black participants reported a similar number of sex partners in the past month (median, 2), Black participants were less likely to report recreational drug use in the past 6 months (63% vs 73%); however, prevalent STIs were more common among Black participants at baseline (syphilis, 4% vs 1.9%; rectal gonorrhea, 5.7% vs 3.4%; urine gonorrhea, 1.1% vs 0.4%). Among Black MSM and transgender women, HIV incidence was 2.11 per 100 person-years in the TDF/FTC arm (15 infections) and 0.58/100 person-years in the CAB-LA arm (4 infections), with a hazard ratio (HR) of 0.28 (95% CI, 0.096-0.834). Among non-Black MSM and transgender women, HIV incidence was 0.63 per 100 person-years in the TDF/FTC arm (5 infections) and 0/100 person-years in the CAB-LA arm (0 infections), with HR of 0.086 (95% CI, 0.004-2.060). Adherence to TDF/FTC was somewhat lower among Black vs non-Black participants using dried-blood spot assessments, with 65% of Black vs 81% of non-Black participants having drug levels consistent

with taking 4 or more doses per week. On-time CAB-LA injections were high among Black and non-Black participants (83% vs 90%), and injection site reactions were slightly less common among Black participants (56% vs 65%). These findings highlight the potential of CAB-LA to increase access to PrEP and address continued racial disparities in HIV incidence in the US.

Clement and colleagues reported on PrEP product choice among HPTN 083 participants enrolled in the US (Abstract 994). In the open-label extension of this study, participants were offered the choice of open-label CAB-LA or daily oral TDF/FTC. Among 803 participants in whom regimen choice data were available, 96% chose CAB-LA and 4% chose TDF/FTC. Choice did not differ by age, cohort, race, ethnicity, or education status. The most common reasons for choosing CAB-LA included preferring injections and/or not liking pills (70%), superiority of CAB-LA to TDF/FTC for HIV prevention (15%), and CAB being more convenient, discreet, or easier to adhere to (5%); the most common reasons for choosing TDF/FTC included not liking injections and/or preferring pills (52%), potential adverse effects of TDF/FTC are better understood or preferable to those of CAB-LA (12%), concerns about resistance if injectable PrEP fails (21%), and scheduling constraints or difficulties with visits (12%).

Brown and colleagues reported on bone mineral density (BMD) changes with CAB-LA or TDF/FTC PrEP in MSM and TGW in HPTN 083 (Abstract 987). Among 254 participants (median age, 27 years) who received at least 10 bimonthly injections over 18 months from enrollment, BMD was 0.2 to 0.6 standard deviations lower than an age-, sex-, and race-matched population at baseline, with 15% having a Z-score 2.0 or lower at the lumbar spine, femoral neck, or total hip. BMD decreased by 0.5%

Among Black men who have sex with men and transgender women in the HPTN 083 study, long-acting cabotegravir was highly efficacious when compared with daily oral tenofovir disoproxil/emtricitabine

to 1.0% in the TDF/FTC arm and increased 0.5% to 1.5% in the CAB-LA arm. After adjusting for age and race, BMD was significantly higher among participants receiving CAB-LA than those receiving TDF/FTC (Z-score difference, 0.09-0.20 at week 105). The researchers suggest that individuals interested in PrEP and at higher risk of

fracture because of older age, lower BMD, or other osteoporosis risk factors may consider CAB-LA to maintain bone health.

Hosek and colleagues reported on the safety, tolerability, and acceptability of CAB-LA in African female adolescents enrolled in the HPTN 084-01 study (Abstract 162). This single-arm, open-label, phase IIb safety study enrolled 55 adolescents below the age of 18 years in Uganda, Zimbabwe, and South Africa. The mean age of participants was 16 years; 25% had 1 or more sex partners with HIV, 22% reported transactional sex, 31% had chlamydia, and 36% reported significant depressive symptoms at baseline. Three participants had neuropsychiatric events (depression, anxiety, and suicidal behavior/attempt) during follow-up, all of which resolved with counseling. Among 55 participants enrolled, 2 discontinued during the oral CAB lead-in phase due to unrelated adverse events, and 53 participants entered the injection phase. There were no product-related serious adverse events, no product discontinuations due to adverse events, and no incident HIV infections during follow-up. CAB-LA injections were well tolerated, with only 17% reporting injection-site reactions at week 5 that decreased over time, and no participants discontinued injections early due to intolerability. Adherence to injections was very high, with only 1 participant discontinuing injections due to pregnancy, and 100% of expected injections given over 33 weeks of injection phase follow-up.

Among African female adolescents in the HPTN 084-01 study, adherence to long-acting cabotegravir injections was very high and injections were well tolerated, with most participants choosing long-acting cabotegravir over oral tenofovir disoproxil/emtricitabine in the open-label extension

When asked what they liked about the injectable method, participants liked that CAB-LA protected them against HIV (55%), was easier to use than other methods (42%), provided longer-term protection than other methods (23%), and can be used discreetly (19%). Overall, 36% did not have any concerns about the injectable method; however, some raised concerns that injections may be painful (28%), may cause harmful adverse effects

(19%), and once injected, cannot be reversed (13%). After completing the injection phase, most participants (92%) chose to continue CAB-LA over oral TDF/FTC when given a choice in the HPTN 084 open-label extension.

Hazra and colleagues reported on a breakthrough HIV-1 infection in the setting of real-world CAB-LA PrEP administration (Abstract 981). This was a 28-year-old gender-diverse patient assigned male at birth who had HIV-1 detected 91 days after transitioning from TAF/FTC to CAB-LA, despite on-time dosing. He reported condomless oral and anal sex with a primary partner and 20 to 30 unique partners monthly, had recently engaged in anal fisting, and was also diagnosed with syphilis and mpox in the 6 months prior to HIV infection. The primary partner had HIV resistant to nucleoside reverse transcriptase inhibitors (nRTIs) (K65R, Y118I) and InSTIs (E92G) and had an undetectable HIV-1 RNA for more than 24 months on treatment. The patient had on-time injections at days 0, 27, and 91; on day 91, the HIV-1/HIV-2 antigen/antibody was nonreactive, but an HIV RNA-PCR test was detected at 1.48 log₁₀ copies/mL. At repeat testing on day 100, his HIV-1/HIV-2 antigen/antibody test was reactive, HIV-1 antibody was detected on differentiation assay, and HIV RNA-PCR was detected at 1.30 log₁₀ copies/mL, and standard HIV-1 sequencing was unable to be performed. HIV DNA qualitative PCR was below the lower limit of quantitation and HIV-1 proviral DNA resistance could not be performed. Plasma CAB concentration on day 128 (37 days following the most recent injection) was 1180 ng/mL. The patient was started on a fully suppressive ART regimen (darunavir/cobicistat + dolutegravir) with undetectable RNA at day 128. This case highlights diagnostic and management challenges in the setting of CAB-LA PrEP failure and the need to better understand HIV-1 reservoirs in breakthrough infections.

Novel PrEP and PEP Agents

Young and colleagues presented data on an ultra-LA in situ forming implant (ISFI) with CAB (Abstract 991). This implant, comprised of a biodegradable-polymer, water-miscible solvent, and CAB, generates a liquid syringeal suspension that undergoes a phase inversion when injected into the subcutaneous space and releases drug over time via diffusion. Although this ISFI is biodegradable, it can also be removed early if needed, and can also be co-formulated to include multiple drugs in a single injection. Prior studies demonstrate the safety, ultra-LA pharmacokinetics (PK), and complete protection after several simian human immunodeficiency virus (SHIV) rectal challenges in female macaques. In this study, the researchers demonstrated that CAB plasma concentrations following 50 to 100 µL injections in mice were well

above the PK benchmark of protection ($4\times$ PA-IC₉₀) for 11 to 12 months. When the implant was removed after 180 days, CAB plasma concentrations declined substantially, but complete CAB elimination was not achieved. After 180 days, the CAB ISFIs were easily retrievable, with 25% CAB remaining and 15% polymer remaining across all doses. When co-formulated with barium sulfate to assess implant migration, the ISFIs were visible with X-ray imaging for more than 210 days after a single injection with minimal implant migration. Young highlighted some potential benefits of ISFIs, including ability to be self-administered as a subcutaneous injection, reduced dosing frequency, reversibility, and potential for a shorter PK tail after removal.

Grattoni and colleagues presented data on an ultra-LA refillable islatravir implant tested in nonhuman primates (Abstract 165). They developed a titanium implant that uses a silicon nano-fluidic membrane to control drug release from a reservoir. This nanochannel acts like an hourglass and uses an electrostatic interaction to allow for sustained islatravir release at a constant rate, and the implant has ports that can be loaded and refilled transcutaneously. This implant was inserted into 4 rhesus macaques and achieved sustained islatravir and islatravir triphosphate concentrations in plasma, peripheral blood mononuclear cells (PBMCs), and rectal tissue over 12 to 20 months, with no changes in safety parameters, including levels of creatinine, aspartate aminotransferase, alanine aminotransferase, and lymphocyte, and CD4+ and CD8+ cell counts. In a repeated challenge model with SHIV (SHIVSF162P3), the implant provided 100% protection to 10 weekly rectal or vaginal challenges in 6 male and 6 female macaques, respectively, whereas all control animals became infected. The implants were well tolerated; however, mild swelling was noted within the first 15 days of implantation and some local tissue inflammation was observed. Although none of the implants had migrated, the researchers noted that 1 implant flipped and turned upside down, which resulted in severe inflammation at the implant site, suggesting that directionality of release is key to tolerability of the implant.

Daly and colleagues evaluated the safety and vaginal efficacy of a biodegradable islatravir implant in female pigtailed macaques (Abstract 989). This matchstick-sized implant consists of an extruded tube with polycaprolactone walls loaded with islatravir. Two implants were inserted into arms of 6 macaques and safety and PK were assessed over 5 weeks, followed by twice weekly vaginal SHIV challenges for 6 weeks; 1 islatravir implant was then removed to assess efficacy at a lower dose, and procedures were repeated. There were minimal implant-site reactions over 33 weeks, with only 1 of 12 implants with

mild erythema, and no sign of inflammation or necrosis in skin biopsies after implant removal. Plasma islatravir concentrations were similar to once-daily dosing in humans, with 2 implants corresponding to 0.75 mg oral islatravir, and 1 implant corresponding to 0.25 mg oral islatravir. Overall, 5 of 6 animals were protected from repeated vaginal SHIV challenges, with clinically relevant plasma islatravir levels (median, 1.4-3.9 nM); the 1 breakthrough infection was associated with low plasma islatravir concentrations (median, 0.8 nM).

Bunge and colleagues reported on the safety of the dapivirine vaginal ring during pregnancy in the DELIVER/Microbicide Trials Network (MTN) 042 study (Abstract 127). This study was conducted in a stepwise fashion enrolling 1 of 3 cohorts at a time, beginning with later gestational age to minimize risks of drug exposure. Cohort 1 included women at 36 to 38 weeks gestation; cohort 2 at 30 to 35 weeks; and cohort 3 at 12 to 29 weeks. Data from cohort 1 (150 participants) and cohort 2 (157 participants) were presented in which participants were randomly assigned 2:1 to use either the monthly dapivirine ring or daily oral TDF/FTC until delivery; pregnancy outcomes were reported up to 6 weeks post delivery and compared with local background rates obtained through a systematic chart review. For both cohorts, the most common outcome was a full-term birth (≥ 37 weeks), 98% in cohort 1 and 94% in cohort 2. There was 1 stillbirth in cohort 1 (in the TDF/FTC arm) and 1 stillbirth in cohort 2 (in the dapivirine arm), with a rate lower than background. In both cohorts, pregnancy complications were rare, with hypertensive disorders of pregnancy being the most commonly reported, and similar to local background rates. In cohort 2, there was 1 case of chorioamnionitis in the dapivirine ring arm. No HIV seroconversions have been observed to date, and there have been no maternal deaths. There were 2 infant deaths, 1 in each cohort, assessed as not re-

In a safety study of the dapivirine vaginal ring during pregnancy, complications were rare and similar to local background rates

lated to study product. With approval of an independent review panel, enrollment into cohort 3 began in July 2022 and was completed in January 2023.

Owor and colleagues reported on dapivirine ring safety and drug detection in 197 breastfeeding mother-infant pairs in the MTN-043 study (Abstract 785). In this open-label trial, exclusively breastfeeding mother-infant

pairs were randomized 3:1 to receive the dapivirine ring or oral PrEP for 12 weeks. Most adverse events were mild or moderate, and only a few serious adverse events or grade 3 or higher events occurred among mothers and infants, all of which were assessed as unrelated to study product. Similar to prior studies, dapivirine concentrations in breast milk were higher than in maternal plasma; however, infant plasma concentrations remained extremely low, with drug detected in 5% to 15% of samples, and mean dapivirine concentrations ranging from 10.7 to 14.5 pg/mL. In the oral PrEP arm, tenofovir diphosphate (TFV-DP) concentrations from infant dried blood spots were all below the lower limit of quantitation. These data support updates to World Health Organization and national guidelines to include breastfeeding people in recommendations for the dapivirine vaginal ring for HIV prevention.

Riddler and colleagues presented data on the safety and PK of a fast-dissolving tenofovir alafenamide/eligivitegravir (TAF/EVG) insert administered rectally in the MTN-039 study (Abstract 164). Prior studies in nonhuman primates have demonstrated the efficacy of this insert in vaginal and rectal simian HIV challenge models. In this 2-period study, 23 participants (17 male, 6 female) were enrolled and received rectal administration of one TAF/EVG insert (20/16 mg), followed by a washout period, then rectal administration of 2 inserts. The TAF/EVG insert was well tolerated, with 17 adverse events reported for 9 participants, and only 1 related adverse event of mild anal erythema. EVG, TAF, and TFV were present in plasma at 1 hour after insertion, at concentrations substantially lower than that seen with oral dosing. EVG was present in rectal tissue at 2 hours and exceeded 1 ng/mg at most time points, but decreased by 24 hours. TFV concentrations in rectal fluid and tissue were high, with sustained levels in the majority of participants for 48 to 72 hours, and almost all participants had TFV-DP concentrations in rectal tissue from 2 to 72 hours that exceeded levels observed in the HPTN 066 PK study with daily oral TDF dosing. In an ex vivo challenge model, compared with baseline, the postdose cumulative log₁₀ copies/mL HIV 24 levels were significantly reduced through 72 hours for both 1 and 2 inserts ($P < .032$ and $P < .020$, respectively). These results support the continued evaluation of the TAF/EVG insert for rectal protection.

Makarova and colleagues evaluated the window of PEP efficacy of TAF/EVG inserts against SHIV vaginal infection in pigtailed macaques (Abstract 990). Prior studies demonstrated the TAF/EVG insert provided 92% and 100% efficacy against vaginal SHIV exposure when given 4 hours before and 4 hours after exposure, respectively. In this study, TAF/EVG inserts were administered 8

or 24 hours after 13 weekly vaginal SHIV exposures. The 8-hour PEP insert protected 5 of 6 macaques (94% efficacy), and the 24-hour PEP insert provided 77% efficacy. These results extend the window of high postexposure

In animals with lenacapavir plasma concentrations above the rhesus-adjusted target exposure of 70 nM, lenacapavir demonstrated complete protection and was superior to the untreated group

protection of the insert to 8 hours and support the clinical development of the TAF/EVG insert for on-demand PEP against HIV.

Bekerman and colleagues evaluated the PK and efficacy of the HIV capsid inhibitor lenacapavir in macaques (Abstract 992). Based on in vitro testing in activated human and rhesus PBMCs, lenacapavir was predicted to be 4.4-fold less potent against SHIV vs HIV. After a single high-dose SHIV rectal challenge, 3 of 11 treated animals became infected (27%) vs 10 of 16 untreated controls (63%). In animals with lenacapavir plasma concentrations above the rhesus-adjusted target exposure of 70 nM, lenacapavir demonstrated complete protection and was superior to the untreated group ($P = .012$). These data support the ongoing phase III clinical studies of LA lenacapavir for HIV PrEP.

Oral PrEP in Cisgender and Transgender Women

Marrazzo and colleagues presented pooled data on real-world PrEP effectiveness among 6296 cisgender women enrolled across 11 TDF/FTC demonstration projects in 6 counties over an 8-year period (2012-2020) (Abstract 163). Most participants were enrolled in Africa, with 21% from India. The mean age was 25 years, half were married, one-quarter had a primary education or less, 44% had 1 or more children, and 21% reported commercial sex work. There were only 32 incident HIV infections across all studies, with an HIV incidence of 0.72 (95% CI, 0.51-1.01) per 100 person-years. Adherence was assessed in a subset of 237 participants with objective adherence data (drug levels in dried blood spots or plasma) and 2887 participants with subjective data (electronic pill-cap monitoring, pill counts, or self-report). Substantially higher adherence was reported with subjective vs objective adherence measures, and overall adherence declined over time by both measures. Using group-based

trajectory modeling to identify longitudinal patterns of adherence, the researchers found that 17% of women had consistently daily adherence, 22% had consistently high (4-6 doses/week) adherence, 39% had high but declining adherence, and 21% had consistently low (<2 doses/week) adherence. HIV incidence was 0 and 0.13 per 100 person-years in the consistently daily and consistently high groups, respectively; 0.49 per 100 person-years in the high but declining group; and 1.27 per 100 person-years in the consistently low group. Unlike prior PK modeling studies suggesting high adherence (6-7 doses/week) is required for high efficacy in women, these findings suggest that the effectiveness of TDF/FTC was similar in cisgender women who demonstrated consistently high (>4 tablets/week) or daily (7 tablets/week) adherence.

Remera and colleagues evaluated the effectiveness of PrEP among FSWs in Rwanda (Abstract 993). In a retrospective cohort study of 2544 HIV-negative FSWs seen in 22 health facilities in Kigali, Rwanda, 45% participated in the PrEP program. At 12 months, 79% of FSWs were retained in the PrEP program and 64% not on PrEP were retained in the HIV prevention program. Overall, 0.56% of FSWs in the PrEP program and 1.69% of those not in the PrEP program became HIV positive, resulting in a 69% lower risk of HIV infection among FSWs actively followed in the PrEP program (aOR, 0.31; 95% CI, 0.11-0.87).

Hiransuthikul and colleagues evaluated drug-drug interactions between feminizing hormone therapy (FHT) and oral TAF/FTC PrEP among 20 transgender women in the iFact 3 study (Abstract 996). TGWs who had not received injectable FHT within the past 3 months were enrolled and prescribed estradiol valerate and cyproterone acetate at baseline until week 9; PrEP was initiated at week 3 until week 12, and intensive PK sampling was performed at week 3 (FHT only), week 9 (FHT + PrEP), and week 12 (PrEP only). Plasma estradiol, FTC, and tenofovir exposures trended lower when TAF/FTC was administered with FHT, however the areas under the curve and C_{max} geometric mean ratios of FTC and TFV were between 0.92 and 1.14, within the bioequivalence range, indicating no clinically significant drug-drug interactions from FHT toward TAF/FTC PrEP. The geometric mean ratio for area under the curve and C_{max} for estradiol at week 31 and week 9 was 0.80 (90% CI, 0.72-0.90; $P = .002$) and 1.11 (90% CI, 257; $P = .23$).

PrEP in Pregnancy

Gómez and colleagues evaluated perinatal outcomes following maternal PrEP use in a subsample of women enrolled in a cluster randomized controlled trial in Kenya

(Abstract 766). They included 3608 mother-infant pairs in the analysis, including a random sample of 103 PrEP initiators who had detectable TFV-DP in pregnancy (18% of all PrEP initiators), and 3505 women who were unexposed to PrEP. Compared with those not exposed to PrEP, PrEP-exposed women were slightly older (median age, 27 years vs 24 years), were more likely to have a partner living with HIV (30% vs 2%), were less likely to be primigravida (11% vs 28%), and were more likely to have an STI diagnosis (8% vs 2%). Compared with PrEP unexposed women, women with confirmed PrEP exposure during pregnancy experienced similar frequencies of stillbirth (4% vs 3%; aPR, 1.1; 95% CI, 0.1-9.4), preterm birth (16% vs 19%; aPR, 0.9; 95% CI, 0.6-1.5), small for gestational age (13% vs 10%; aPR, 1.4; 95% CI, 0.8-2.5), and neonatal death (1% vs 2%; aPR, 0.7; 95% CI, 0.1-5.0). At 9 months post partum, there was no association between prenatal PrEP exposure and frequency of underweight ($P = .68$), stunting ($P = .38$), or wasting ($P = .80$). Similar to prior data that relied on self-reported PrEP use, the researchers found no difference in adverse perinatal outcomes among women with prenatal PrEP exposure confirmed with a pharmacologic measure.

Nyemba and colleagues presented data on the integration of PrEP into an antenatal care for pregnant women in South Africa (Abstract 768). Among 1200 women

There was no difference in adverse perinatal outcomes among women with prenatal preexposure prophylaxis exposure confirmed with a pharmacologic measure

without HIV enrolled in the PrEP-PP (Pre-exposure Prophylaxis in Pregnancy & Postpartum) study at their first antenatal visit, 1013 (84%) accepted a PrEP prescription at baseline, and 829 (69%) returned at 1 month and had confirmed to have initiated PrEP. Among the 829 who initiated PrEP, PrEP continuation was 58% at 3 months, 42% at 6 months, and 35% at 9 months. Less than half of women continued PrEP after 6 months when in the postpartum period, and more than half of the 187 women who initially declined PrEP at enrollment initiated PrEP later ($n = 104$; 56%). These results highlight the need for interventions to improve PrEP continuation, particularly during the postpartum period.

Within the same study, Voux and colleagues conducted a randomized controlled trial to evaluate the impact of point-of-care STI testing on PrEP use in pregnancy

(Abstract 970). Pregnant women seen at a regular antenatal care visit were offered PrEP and randomly assigned to standard-of-care (syndromic STI management) or point-of-care STI testing with self-collected vaginal swabs tested for *Chlamydia trachomatis*, *Neisseria gonorrhoeae*, and *Trichomonas vaginalis*. Among 268 pregnant women enrolled, 28% of women in the intervention arm were diagnosed with 1 or more STIs and 20% of women in the standard-of-care arm were treated for a symptomatic STI. Overall, 64% initiated PrEP at baseline, 67% in the intervention and 62% in the standard-of-care arm ($P = .42$). PrEP initiation was higher among STI-diagnosed/symptomatic women than among undiagnosed/asymptomatic women (adjusted relative risk [aRR], 1.24; 95% CI, 1.04-1.47), and PrEP persistence at 1 month was somewhat higher among STI-diagnosed/symptomatic women (aRR, 1.14; 95% CI, 0.98-1.33). These findings highlight the importance of integrated STI testing and care in PrEP programs among pregnant women.

Mogaka and colleagues reported on the acceptability of STI testing and expedited partner therapy among pregnant women initiating PrEP at 5 antenatal clinics in Kenya (Abstract 767). From February to September 2022, women were offered syphilis (RPR or rapid test) and chlamydia and gonorrhea testing using a rapid assay for *Chlamydia trachomatis* and *Neisseria gonorrhoeae* with same-day results and immediate directly observed treatment and expedited partner therapy provided to women diagnosed with chlamydia or gonorrhea. Among 177 women offered STI testing, 93% accepted testing, with 12% testing positive for an STI (chlamydia, 7%; gonorrhea, 4%; syphilis, 2%). The frequency of STIs was higher among those younger than 20 years of age than among women 20 years of age or older (25% vs 8%; $P = .009$), and the STIs were often asymptomatic. Among those testing positive for chlamydia or gonorrhea, 94% accepted same-day treatment and expedited partner therapy, with all male partners accepting treatment within 1 month and no social harms reported. These findings suggest that same-day STI testing with expedited partner therapy may be a high-yield intervention, which can benefit women and their infants and partners.

Anand and colleagues evaluated PrEP continuation among peri-conception, pregnant, and lactating women in Kenya (Abstract 769). In the Partners Scale-up Project, a stepped wedge cluster-randomized trial of PrEP delivery in 25 public HIV clinics in Kenya, 2640 women initiated PrEP, most of whom (80%) were in serodifferent relationships; 44% reported inconsistent condom use and 12% reported multiple sexual partners. At baseline, 11% were pregnant and 16% were breastfeeding, and among non-pregnant women at baseline, 15% were actively trying

to conceive, 25% had future pregnancy intention, and 33% had no pregnancy intention. PrEP continuation at 1, 3, and 6 months was 59%, 45%, and 36%, respectively, and was higher among those actively trying to conceive vs those with future or no plans to conceive ($P < .01$), whereas PrEP continuation did not differ by breastfeeding or pregnancy status.

Pintye and colleagues evaluated PrEP adherence among 198 women who initiated PrEP during pregnancy in the PrIMA (PrEP Implementation for Mothers in Antenatal Care) study, a cluster randomized trial in 20 antenatal clinics in Kenya (Abstract 771). Among 454 visits where participants continued with PrEP, 94% reported any PrEP use in the last 30 days. Among dried blood spots from these visits, 48% had detectable TFV-DP, of which 28% had TFV-DP concentrations indicating fewer than 2 doses/week, 64% indicating 2 to 6 doses/week, and 8% indicating 7 doses/week. Having detectable TFV-DP exposure at follow-up visits was more likely during the pregnant vs postpartum period (69% vs 31%; aRR, 1.87; 95% CI, 1.38-2.53), among women with a primary partner with HIV than among those with an HIV-negative primary partner (aRR, 2.03; 95% CI, 1.33-3.09), and was lower among those who had experienced PrEP adverse effects (aRR, 0.68; 95% CI, 0.47-0.99). These results point to the need for interventions to support adherence in the postpartum period and to increase knowledge of partner HIV status.

From the same study, Marwa and colleagues reported on HIV risk perception and PrEP use among 2249 Kenyan women during and after pregnancy (Abstract 773). Using a validated risk score to predict HIV acquisition among perinatal women, they identified 617 women (27%) at high HIV risk, corresponding to 8.9 HIV infections per 100 person-years; of these, most women (57%) perceived themselves to be at low risk for HIV. Women who perceived high risk were more likely to have a partner known to have HIV (21% vs 5%; prevalence ratio, 1.5) and more likely to initiate PrEP (40% vs 18%; prevalence ratio, 2.2). Additionally, perceived high HIV risk was associated with age older than 24 years, prior pregnancy, polygamous marriages, and syphilis diagnosis during pregnancy. Among 9 women who acquired HIV during follow-up, only 4 had high perceived HIV risk and only 3 reported ever taking PrEP, all of whom discontinued PrEP prior to seroconversion. The researchers suggest that improving knowledge of partner HIV status in PrEP delivery programs may help improve risk perception and encourage PrEP uptake, particularly among younger women.

Also in the PrIMA cohort, Wu and colleagues reported on the correlation between hair and dried blood spot PrEP levels during pregnancy and post partum (Abstract

770). They evaluated 34 hair-dried blood spot paired samples, with 12 from pregnancy visits at a median of 32 weeks gestation and 22 from postpartum visits at a median of 3.5 months after birth. Tenofovir levels in hair were strongly correlated with TFV-DP levels in dried blood spot ($r = 0.77$; $P < .001$), with stronger correlation during the postpartum period ($r = 0.82$) compared with pregnancy ($r = 0.57$). Based on dried blood spot benchmarks from the IMPAACT 2009 study in pregnant and postpartum women, 44% of dried blood spot samples had TFV-DP levels consistent with 2 or more doses per week, and 41% of hair samples had tenofovir levels consistent with 2 or more doses per week based on benchmarks in nonpregnant women. These results suggest that unlike blood-based measures, which are more influenced by physiologic changes during pregnancy, hair metrics may not need adjustment for PK differences in the perinatal period.

Tenofovir Adherence Assays

Ngure and colleagues assessed the acceptability and feasibility of a point-of-care urine-based tenofovir adherence assay among women in Kenya (Abstract 973). They conducted in-depth interviews with 20 women on PrEP enrolled in the point-of-care assay arm of the PUMA (Point-of-care Urine Monitoring of Adherence) study and their 8 clinicians. Most participants reported less worry of acquiring HIV due to a positive urine assay result and believed the urine assay improves PrEP adherence since they always wanted to receive positive results. Clinicians reported that real-time feedback facilitates counseling tailored to individual needs, but stated that the test would be more feasible if test kits were widely available and marketed for clinical use. Some participants reported embarrassment with providing a urine sample, and clinicians reported concerns that the kit not measuring long-term adherence may affect retention of clients with low adherence. Overall results suggest the point-of-care urine tenofovir assay to be highly acceptable and feasible for women on PrEP and their clinicians.

Mustanski and colleagues evaluated the predictive value of the urine point-of-care tenofovir test among 73 young MSM PrEP users in the RADAR cohort (Abstract 979). Self-reported adherence was over-reported (87% for ≥ 4 doses in the last 7 days) compared with urine tenofovir (69%) and FTC-triphosphate (68%) and TFV-DP (67%) in dried blood spot. Urine TFV and dried blood spot FTC-TP performed similarly well in predicting longer-term adherence, with positive and negative predictive values of 94% and 93% for dried blood spot FTC-TP and 91% and 87% for urine TFV, respectively, compared with dried blood spot TFV-DP. In multivariable analyses, the

urine assay was significantly predictive of TFV-DP in dried blood spot (OR, 30.2; $P < .001$). These findings support the utility of the urine point-of-care tenofovir test in real-world clinical settings.

Trends in the PrEP Continuum

Zhu and colleagues reported on trends in oral and injectable PrEP use in the US (Abstract 980). Using the IQVIA Real-World Data–Longitudinal Prescription Database, they assessed trends in PrEP prescriptions from January 2013 through September 2022. From 2013 to 2020, the number of persons prescribed branded TDF/FTC increased, then decreased markedly after TAF/FTC and generic TDF/FTC became available. By September 2022, 50% were prescribed generic TDF/FTC, 45% TAF/FTC, and only 3.8% branded TDF/FTC. From January 2022 through August 2022, a total of 1951 persons picked up a CAB-LA prescription, of which 84% received a prescription for a second dose within 1 month of the first prescription. A larger proportion of women were prescribed CAB-LA than oral PrEP, with women accounting for 13% of injectable PrEP prescriptions, but only 7% of oral PrEP prescriptions. These findings highlight the need to better understand reasons for low uptake of CAB-LA.

Hoover and colleagues evaluated trends in PrEP prescriptions in the US among persons enrolled in Medicaid by race and ethnicity from 2015 to 2020 (Abstract 986). Based on Centers for Medicare and Medicaid Services data for all 50 states and the District of Columbia, the number of Medicaid enrollees prescribed PrEP increased from 7932 in 2015 to 41,325 in 2020, with an EAPC of 31%. In 2020, 23% of Medicaid enrollees prescribed PrEP were Black, 18% were Hispanic, 40% were White, and 19% were women. From 2015 to 2020, racial and ethnic disparities in PrEP use increased among men, and more men continue to use PrEP than do women, with only 2976 Black women prescribed PrEP in 2020. The researchers call for interventions to increase PrEP use in populations with high rates of HIV diagnoses, particularly in Black cisgender women and transgender women.

Huang and colleagues assessed trends in PrEP use among US veterans using Veterans Health Administration (VHA) services between 2017 and 2022 (Abstract 997). The number of VHA patients prescribed PrEP increased from 1910 in 2017 to 6023 in 2022, with an EAPC of 23%. During this period, the number of Black veterans prescribed PrEP increased from 373 in 2017 to 1491 in 2022, with an EAPC of 27%, and the proportion of Black persons who comprised PrEP users increased from 20% to 25%. As PrEP prescriptions from the VHA are excluded from the IQVIA database, these data fill an important gap in monitoring PrEP use in the US.

Suprasert and colleagues reported on trends in PrEP use among PWID in San Francisco from 2018 to 2022 (Abstract 983). From 2019 to 2021, new HIV infections among PWID rose by 48% and now account for 27% of new HIV diagnoses in San Francisco. In 2022, the NHBS surveyed 479 PWID, of whom 81% experienced homelessness in the past year, 77% had a usual source of health care, and 75% had health care visits in the past year. Only 55% were aware of PrEP, 5.9% discussed PrEP with a health care practitioner, and 1.5% used PrEP in the past 12 months. These PrEP indicators were comparable or significantly worse than those of 2018: 54% had heard of PrEP ($P = .796$), 13% had discussed PrEP with a practitioner ($P < .001$), and 2.9% had used PrEP ($P = .147$). Factors associated with low PrEP awareness among PWID in 2022 were Black race/ethnicity, household income below the federal poverty level, and not testing for HIV, hepatitis C, or STIs. In contrast, among MSM surveyed in 2021, 66% had discussed PrEP with a practitioner and 65% had used PrEP in the past year. The researchers suggest that public health interventions to increase HIV testing and PrEP discussions from health care practitioners for PWID may have the greatest potential to improve PrEP uptake among PWID.

Factors Influencing PrEP Engagement

Andrzejewski and colleagues examined barriers to and facilitators of retention in PrEP care among 170 transgender women enrolled in the iMPRePT (iTAB plus

From 2018 to 2022, preexposure prophylaxis use among persons who inject drugs in San Francisco remained very low: 1.5% in 2022 and 2.9% in 2018

Motivational Interviewing for PrEP Adherence in Transgender Individuals) demonstration project (Abstract 985). Compared with participants who were retained at 24 weeks, those not retained were more likely to report engaging in sex work (18% vs 7%) and substantial/severe drug use (18% vs 8%) and were less likely to be taking gender-affirming hormone treatment (56% vs 71%). In qualitative interviews, 2 subcategories of sex work emerged: “non-survival sex work,” in which individuals had stable housing, sought clients from online sources, accessed gender-affirming hormones through practitioners, and had little difficulty staying in PrEP care, and

“survival sex work,” in which individuals had unstable housing, sought street-based clients, used black-market hormones, and had more difficulty staying in PrEP care. TGW cited financial incentives as a strategy to help with retention in PrEP care and highlighted the importance of privacy and discretion when working with TGW engaged in sex work. Additionally, TGW often prioritized medical gender affirmation over PrEP, although acknowledging that taking PrEP could facilitate adherence to gender-affirming hormones, and PrEP made TGW feel safer during sex work. Substance use was seen as a barrier to PrEP care for some TGW, often in the context of sex work.

Javanbakht and colleagues evaluated the role of methamphetamine use on PrEP care engagement among MSM enrolled in the mSTUDY, a cohort study of substance use and HIV in racial/ethnic minority MSM (Abstract 982). Among 149 participants (48% Black, 36% Latinx) who reported PrEP use in this cohort, lapses in PrEP use and inconsistent care engagement were reported in 26% of visits. Inconsistent PrEP care was associated with unemployment ($P < .01$), gonorrhea positivity ($P = .04$), and higher levels of methamphetamine use for the participant and the partner ($P < .01$). In a multivariable analysis, inconsistent engagement in PrEP care was nearly 4x higher when both the participant and their partner reported methamphetamine use (aOR, 3.82; 95% CI, 1.8-8.0) than in visits where no methamphetamine use was reported by the participant or partner.

Lankowski and colleagues reported on retention-in-care rates among Peruvian MSM and TGW enrolled in a real-world PrEP program (Abstract 1071.5). In PrEP PERU, a multi-site cohort study evaluating PrEP implementation in 4 nongovernment clinics in Lima, Peru, TDF/FTC PrEP is provided free of charge, and participants pay for laboratory testing plus a small service fee for clinic visits. Among 351 participants who initiated PrEP between January 2017 and March 2020, 91% attended at least 1 PrEP follow-up visit and 77% attended at least 2 PrEP follow-up visits within 6 months. Additionally, 85% of participants had favorable adherence, defined as having proportion of days covered above 0.8 based on pharmacy records. Age 30 years or older, bisexual identity, and higher income were associated with retention in care but not adherence; those who cited a healthcare practitioner recommendation as a motivator to taking PrEP were more likely to be retained in care and have higher adherence. Overall, there were 6 confirmed HIV seroconversions over 510 person-years of follow-up (HIV incidence, 1.2/100 person-years).

Mugwanya and colleagues assessed appropriateness of PrEP discontinuations in a large PrEP program in Kenya (Abstract 1074). They interviewed 300 clients (63%

female, 42% in a serodifferent partnership) in the Partners Scale-Up Project, a large cluster-randomized trial of PrEP delivery integrated in public HIV clinics within Kenya's national PrEP roll-out program. At PrEP initiation, 85% had high perceived risk of acquiring HIV, and 57% had used PrEP for at least 3 months. Nearly three-quarters of all PrEP discontinuations were appropriately aligned with self-reported low HIV risk states, and less than 1% of discontinuations were attributed to clinic-level factors such as wait time and staff attitudes. Additionally, nearly all clients were satisfied with their HIV prevention choice at the time of the survey. The researchers suggest that using client-level PrEP continuation rates alone without considering dynamic individual risk and use of other prevention options is not an appropriate measure of real-world PrEP program success.

Wu and colleagues reported on the alignment of PrEP use with HIV risk among young women and their male partners in Uganda (Abstract 998). From 2018 to 2021, 88 young women and 125 male partners were enrolled

Inconsistent engagement in pre-exposure prophylaxis care was nearly 4-times higher when both the participant and their partner reported methamphetamine use

in linked longitudinal studies, with a median age of 24 years for men and 20 years for women. In women and men, PrEP refills were more common when they or their partners self-reported multiple sex partners.

Zia and colleagues evaluated structural influences on the PrEP continuum among adolescent girls and young women (AGYW) in postabortive care in Kenya (Abstract 1073). Among 6877 AGYW seen across 14 postabortion clinics in Kenya, 25% were offered PrEP and 14% accepted PrEP. Most clinics were private (57%), had low client flow (57%), had some but not all clinicians trained (57%), had engaged leadership (64%), and had challenges with staff numbers (86%) and space (57%). Most AGYW were seen in postabortion clinics that had experienced PrEP commodities stock-outs (75%), had high clinic volume (63%), and had highly engaged administrative leadership (56%). Frequency of PrEP offers and uptake was higher in clinics that never experienced PrEP or HIV medication stock-outs, in public vs private clinics, and in clinics in which all clinicians were trained and had sufficient staffing for PrEP delivery. These findings point to the importance of investing in human resources and PrEP/HIV commodities

to facilitate greater PrEP coverage in AGYW.

Ntabadde and colleagues reported on the PrEP continuum among Lake Victoria fisherfolk in Southern Uganda, a community with 40% HIV prevalence (Abstract 1072). Among 1401 HIV-seronegative participants assessed between 2018 and 2020 as part of surveillance in the Rakai Community Cohort study, 97% reported ever receiving an HIV test result, 86% had heard of PrEP, and 40% were eligible for PrEP, but only 14.5% ever used PrEP. PrEP discontinuation was reported by nearly half (48%) of individuals who had ever used PrEP. PrEP use was associated with a higher perceived HIV risk, having more sexual partners, and a recent HIV test in the past year. Additionally, women who engaged in transactional sex and those who reported intimate partner violence were also more likely to report PrEP use.

Thomas and colleagues evaluated the effect of intimate partner violence on adherence to PrEP and ART in HIV-serodifferent couples in Uganda (Abstract 984). Among 149 heterosexual couples enrolled, 81% were married or cohabitating, and 64% of partners with HIV were female. Low adherence was more common when PrEP or ART users reported intimate partner violence. Ashipala and colleagues evaluated the relationship between depression and PrEP use among key populations in Namibia (Abstract 1075). In surveys of 500 PrEP users (including MSM, male sex workers, AGYW, and FSW) accessing services at 13 health care facilities in Namibia, 11% and 5% had Patient Health Questionnaire (PHQ-9) scores suggesting moderate and acute depression, respectively; 3 in 10 clients reported suicidal ideation; and 6 in 10 screened as having a potential alcohol use disorder. Depression was associated with PrEP holidays, defined as taking a break from PrEP for at least 3 consecutive days ($P = .03$) and missing pills on weekends ($P = .02$). PrEP holidays were also associated with alcohol use disorder ($P = .010$) and illicit drug use ($P < .01$). These results suggest that clients accessing PrEP services in these settings may be at greater risk for mental health issues and highlight the need for tailored interventions in key populations facing mental health challenges.

Novel PrEP and PEP Delivery Models

Kakande and colleagues presented the results of a cluster-randomized trial of a dynamic choice HIV prevention intervention delivered by community health workers in southwest Uganda and western Kenya (Abstract 124). They randomly assigned 16 villages 1:1 to the dynamic choice intervention or to a standard-of-care control condition that included referral to HIV prevention services at local health facilities. The dynamic choice intervention allowed participants to choose their preferred

product (PrEP or PEP pill in pocket), service location (clinic, home/community site, phone/virtual visit), HIV testing (rapid test, self-test), and refill frequency (up to 3 months for PrEP refills). Persons in the intervention arm also had access to patient-centered care, including phone access to clinicians 24 hours a day, 7 days a week; structured assessments of barriers to prevention services with development of personalized plans; referral to clinics with integrated reproductive health and STI services; and referrals for treatment for trauma and gender-based violence. They screened approximately 500 persons per arm and enrolled approximately 200 persons per arm; lack of risk was the primary reason for non-enrollment. The primary outcome was self-reported PrEP and PEP use. In the intervention arm, 58% chose PrEP at least once and 58% chose PEP at least once. From baseline to week 48, PrEP selection increased from 40% to 48% and PEP selection declined from 46% to 25%. Condom choice increased over time. Self-testing increased from 52% at baseline to 71% at week 48. Nearly all people chose off-site locations for prevention services at each visit. The average proportion of follow-up covered with PrEP or PEP was 28% in the intervention group and 0.5% in the control arm ($P < .001$). During periods of HIV risk, PrEP or PEP uptake was 36.6% of follow-up time in the intervention arm, compared with 0.9% in the control arm ($P < .001$). This represents a substantial improvement in the intervention compared with the control. Next, the investigators plan to integrate long-acting injectable cabotegravir as PrEP as one of the intervention choices.

Koss and colleagues presented results of an individually randomized trial of the same dynamic choice prevention intervention implemented in outpatient departments

In a cluster randomized trial of dynamic choice HIV prevention, preexposure prophylaxis or post-exposure prophylaxis uptake was 36.6% of follow-up time in the intervention arm compared with 0.9% in the control arm during periods of risk ($P < .001$)

in rural Kenya and Uganda (Abstract 975). Overall, 403 participants (61% women; median age, 27 years) enrolled in the study, with 197 in the dynamic choice prevention

arm and 206 in the standard-of-care arm. In the dynamic choice prevention arm, 86% ever chose PrEP and 15% chose PEP over 48 weeks; the choice of HIV self-testing increased from 26% to 51%, and choice of out-of-facility visits increased from 8% to 52% during follow-up. The proportion of follow-up time covered by PrEP or PEP was 47.5% in the dynamic choice prevention arm and 18% in the standard-of-care arm (29% difference; $P < .001$), with similar results among men and women. When follow-up was restricted to time of self-reported risk of HIV exposure, PrEP or PEP coverage was 65% in the dynamic choice arm and 26% in the standard-of-care arm (39% difference; $P < .001$). The researchers are currently studying a dynamic choice model offering a product choice of CAB LA, oral PrEP, and PEP.

Shahmanesh and colleagues reported results of a trial of community-based sexual reproductive health and peer support among youth in rural Kwazulu Natal, South Africa (Abstract 976). In this 2x2 factorial trial, 1743 participants aged 16 to 29 years were randomly assigned to 1 of 4 groups: (1) enhanced standard of care comprised of mobile adolescent youth friendly services (AYFS) including condoms, universal test and treat, and PrEP; (2) sexual and reproductive health (SRH), which included home-based self-collected specimens for STI testing and referral to AYFS for integrated SRH and HIV prevention; (3) peer support, which included referral to peer navigator for a needs assessment to tailor health and support; and (4) SRH plus peer support. Overall, 43% of participants were linked to AYFS by 60 days, and 21% were eligible and started PrEP. Among 832 participants assigned to SRH, 29% of women and 16% of men had an STI. Although SRH increased linkage to AYFS within 60 days (aOR, 1.61; 95% CI, 1.32-1.95), peer support had no effect on linkage to AYFS. At 12 months, 19% tested positive for HIV, of which 185 (82%) had a suppressed HIV viral load. After adjustment for age, sex, and rural/urban area, there was no difference in transmissible HIV by either intervention.

Bardon and colleagues assessed the effects of 6-month PrEP dispensing on sexual behaviors in Kenya (Abstract 977). In the JiPime-JiPrEP trial, 495 participants, including women and men in serodifferent relationships and single women, were randomly assigned to 6-month PrEP dispensing with interim HIV self-testing and biannual clinic visits or standard-of-care 3-month PrEP dispensing with clinic-based HIV testing and quarterly clinic visits. Results from this study were previously presented that demonstrated that biannual clinic visits supported with 6-monthly PrEP dispensing resulted in non-inferior PrEP continuation outcomes, including HIV testing, PrEP refills, and PrEP adherence. In this secondary analysis, the

researchers evaluated whether sexual behaviors differed between the intervention and standard-of-care arms at 6 and 12 months of follow-up. They found that inconsistent condom use and number of sex partners in the past month did not differ between arms at either point, further emphasizing the safety of this differentiated service delivery model and supporting its use to help simplify PrEP delivery in Kenya and similar settings.

Roche and colleagues presented data from a pilot study extension of pharmacy-based PrEP delivery in Kenya (Abstract 978). In this stepped care-delivery model, pharmacists are trained to screen for PrEP and PEP eligibility using a standardized checklist, with a remote clinician available for support. In a 6-month extension of a pilot study, PEP services were added to the model, and the patient fee was eliminated. During this period, 12 participating pharmacies were able to initiate 670 clients on PrEP and 161 on PEP, many of whom were young, unmarried men not in known serodifferent relationships. Among those who initiated PEP, 37% returned and tested HIV negative, and 20% transitioned to PrEP after PEP completion. At 4 months, 51% were still on PrEP, and PrEP continuation, defined as having refilled PrEP at least once at a pharmacy over the 6-month period, was 73%. Acceptability of pharmacy delivered PrEP was high, with 96% to 100% of clients and clinicians reporting they liked getting or delivering PrEP/PEP at a pharmacy, and 94% to 100% agreed that pharmacies are a good way to reach people who are at risk for HIV. The research team will soon be launching a community randomized clinical trial of pharmacy-based PrEP/PEP delivery across 60 pharmacies.

Kuo and colleagues reported on client preferences for PrEP refills at facilities vs pharmacies in Kenya (Abstract 1091). Clients initiating PrEP at 2 public health facilities in Kenya were given the option to refill PrEP at a public clinic for free or at 1 of 3 nearby private pharmacies for a fee of 300 KES (approximately \$2.50 USD). Among 106 clients enrolled, 55% preferred getting refills at public clinics and 45% preferred a private pharmacy location. Over 292 client-months of follow-up, 44 clients (42%) refilled PrEP at least once, with only 3 clients (3%) refilling PrEP at a pilot pharmacy. In in-depth interviews, clients already engaged in clinic-based PrEP services preferred delivery in this setting and had perceived concerns with pharmacy-delivered PrEP, including mistrust of pharmacy providers, perceived lower quality of services, lack of privacy, and increased client costs. The investigators recommend additional research to understand drivers of PrEP refill location choice and implementation strategies that might facilitate clients in selecting their preferred refill site. Kuo and colleagues also assessed the costs

of providing pharmacy-initiated PrEP in Kenya through time-and-motion studies (Abstract 1090). The median financial cost of pharmacy-based PrEP delivery was \$7.70 per month at initiation and \$19.86 per 3 months at continuation visits, with PrEP drugs accounting for the greatest proportion (61%) of costs. They found that financial costs of pharmacy-based PrEP delivery may be comparable to facility-based PrEP delivery and that improved efficiencies may further decrease costs.

Bassett and colleagues presented data from a pilot randomized clinical trial assessing the uptake of contraception and PrEP in 3 hair salons in Durban, South Africa (Abstract 999). In this model, a stylist introduces the study and refers potentially interested participants to a nurse who provides HIV, STI, and pregnancy testing, risk-reduction counseling, and dispenses contraception (oral or injectable) and oral PrEP. Among 97 female intervention participants enrolled in the study, 70% report going to the salon at least every 2 months, with 43% spending at least 2 hours at the salon during their visit. Overall, 31% of women thought their primary sex partner had other partners, 8% reported intimate partner violence, and 36% were diagnosed with an STI. Uptake of contraception was 89%, and uptake of PrEP was 37%. In a multivariable model, only intimate partner violence was associated with PrEP uptake (aOR, 1.54; 95% CI, 1.7-140; $P = .02$). Future directions include incorporating injectable PrEP as a prevention option.

Silverberg and colleagues conducted a cluster randomized trial leveraging electronic health record data to increase PrEP uptake (Abstract 1089). Adult primary care practitioners within Kaiser Permanente San Francisco were randomly assigned to usual care (60 practitioners, including 6 HIV practitioners) or a low-intensity clinical decision support intervention (61 practitioners, including 6 HIV practitioners) in which providers were notified via a secure email message prior to an upcoming visit when a patient had an elevated HIV risk prediction (3-year risk of HIV, $\geq 0.2\%$). There was a nonsignificant increase in PrEP linkage in the intervention arm vs control condition (6% vs 4.5%; hazard ratio [HR], 1.32; 95% CI, 0.84-2.06); however, PrEP linkage was increased in the intervention arm among HIV practitioners (HR, 2.59; 95% CI, 1.30-5.16). The researchers suggest that more intensive interventions may be needed for practitioners less familiar with PrEP and HIV care.

Fisher and colleagues presented results of a PEP-in-pocket (PIP) program of on-demand HIV PEP in 2 HIV prevention clinics in Toronto, Canada (Abstract 972). Patients referred for PrEP or PEP were offered a full 28-day prescription for PEP if they reported a low-frequency (0-4 per year) of higher-risk HIV exposures of

any type. Patients receiving PIP were provided counseling on when to initiate medications and where to seek follow-up care. From January 2016 to December 2022, 111 people were prescribed PIP, of which 35 initiated PIP for sexual exposures (16 used PIP once, 19 used PIP more than once). Overall, a total of 69 PIP courses were initiated, with 98.6% follow-up at 6 months, and no HIV seroconversions detected. Switching between PIP and PrEP was common, with 29% of participants switching from PrEP to PIP, and 31% switching from PIP to PrEP.

Modeling the Impact and Cost-Effectiveness of PrEP and PEP

Stansfield and colleagues compared the population impact of expanding PrEP use in South Africa based on 3 HIV transmission models (Abstract 969). Synthesis is a stochastic, individual-based model targeting PrEP to 9% of adults with a PrEP indication; EMOD-HIV is a stochastic, individual-based model targeting PrEP to 3.5% adults at high risk and 20.5% at low risk; and Them-bisa is a deterministic, compartmental model targeting PrEP to 22% of women and 32% of men at high risk. In baseline scenarios, HIV prevalence was about 17% in all models and median PrEP coverage remained below 2%. Expanding PrEP coverage to 5% with CAB-LA by 2027 may avert 46% of new infections over 20 years in the Synthesis model, 35% in the EMOD-HIV model, and 12% in the Them-bisa model. Increasing PrEP coverage to 20% may increase the impact by 12 percentage points (Synthesis), 18 percentage points (EMOD-HIV), and 23 percentage points (Them-bisa). Compared with 5% CAB coverage, achieving 5% coverage with oral TDF/FTC would be expected to reduce impact on new infections averted by 16 percentage points (Synthesis), 21 percentage points (EMOD-HIV), and 3 percentage points (Them-bisa). They projected that 5% CAB-LA coverage would be highly efficient in 2 models with 14 (Synthesis) and 13 (EMOD-HIV) additional person-years on CAB-LA needed to prevent 1 infection. They concluded that expanding PrEP access with CAB-LA in South Africa may be highly effective and efficient if it is used during periods of substantial risk.

Cox and colleagues assessed the impact of HIV self-testing vs provider HIV testing for PrEP scale-up in Kenya (Abstract 1051). In the EMOD-HIV model, they compared 4 HIV testing scenarios: (1) provider-administered nucleic acid technique (NAT); (2) clinician-administered rapid diagnostic tests detecting antibodies (Ab-RDT); (3) capillary whole blood-based HIV self-testing (blood HIVST); and (4) oral-fluid HIV self-test (oral HIVST). In all testing scenarios, PrEP coverage was about 29%, which was projected to avert 50% of HIV infections


and 14% of HIV-related deaths over a 20-year period. The percentage of HIV infections with PrEP-associated nRTI-associated resistance was 0.5% and 0.7% in the blood and oral HIVST scenarios, respectively, compared with 0.1% and 0.2% in the NAT and Ab-RDT scenarios, respectively, due to a low projected number of people with HIV inappropriately started on PrEP. They attributed the low population prevalence of nRTI resistance across testing scenarios to the reduction in HIV and HIV-related drug resistance in the PrEP scenarios compared with the no PrEP scenario.

Milali and colleagues evaluated the cost-effectiveness of a dual prevention pill for contraception and HIV prophylaxis in sub-Saharan Africa (Abstract 967). Using an agent-based model in Kenya, Zimbabwe, and South Africa, they found the dual prevention pill likely to be a cost-effective alternative to oral PrEP among users needing contraception and likely cost-saving in sex workers and serodifferent couples not currently on oral PrEP. They also found that the dual prevention pill is unlikely to be cost-effective in oral contraceptive users aged 25 to 49 years without further targeting of subgroups at higher risk of HIV, and could be net harmful if it reduced contraceptive adherence. They highlight the need for effective counseling and decision-support tools to facilitate informed choice and effective use of the dual prevention pill.

Phillips and colleagues assessed the potential cost-effectiveness of availability of community tenofovir-lamivudine-dolutegravir (TLD) for HIV PEP and treatment in sub-Saharan Africa (Abstract 968). Using the HIV Synthesis model, they evaluated the impact of

Expanding preexposure prophylaxis access with long-acting cabotegravir in South Africa may be highly effective and efficient if it is used during periods of substantial risk

making TLD widely and freely available in communities without prescription (along with HIV self-tests, condoms, and emergency contraception) as a strategy to enhance PEP access. In the short term (over 3 years), they projected that community TLD availability would increase PEP and PrEP use by 10% among people with a PrEP/PEP indication, and a mean of 3% to 4% increase

in the percent of people living with HIV who are on ART. In the longer term (over 20 or 50 years), community TLD availability increased viral suppression among people with HIV by 4% and reduced HIV incidence by 36% over 20 years. There was not predicted to be a detrimental effect on prevalence of integrase resistance. Overall costs were lower with community TLD in 97% of setting scenarios, with a \$24 million saving per year over 50 years due to fewer people requiring ART and lower ART-related clinic visits. 

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Financial relationships with ineligible companies within the past 24 months: Dr Liu reported institutional grants/grants pending with Gilead Sciences, Inc., and ViiV Healthcare; non-cash provision of medicines, equipment,

or administrative support with Gilead Sciences, Inc. (Updated April 11, 2023). Dr Buchbinder reported institutional grants/grants pending with Gilead Sciences, Inc., GlaxoSmithKline, and ViiV Healthcare (Updated March 30, 2023).

Reviewer 1 reported serving as a consultant or receiving advisor fees from Antiva, Assembly Biosciences, Generate Biomedicines, and IGM Biosciences, and receiving fees for participation in review activities, eg, data monitoring boards, statistical analysis, or endpoint adjudication committees with Gilead Sciences, Inc. (Updated March 30, 2023). Reviewers 2 and 3 reported no relevant financial relationships with ineligible companies (Updated April 30, 2023).

All relevant financial relationships with ineligible companies have been mitigated.

Additional Reference Cited in Text

1. Luetkemeyer AF, Donnell D, Dombrowski JC, et al. Postexposure doxycycline to prevent bacterial sexually transmitted infections. *N Engl J Med*. 2023;388(14):1296-1306. doi:10.1056/NEJMoa2211934

Top Antivir Med. 2023;31(3):468-492.

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*Invited Review***CROI 2023: Acute and Post-Acute COVID-19****Annukka A. R. Antar, MD, PhD¹; Michael J. Peluso, MD²**¹Johns Hopkins University, Baltimore, Maryland; and ²University of California, San Francisco

Abstract. *Studies of acute and post-acute COVID-19 were presented at the 2023 Conference on Retroviruses and Opportunistic Infections (CROI). Early treatment with ensitrelvir, a novel protease inhibitor, hastened viral clearance and symptom resolution during coronavirus disease 2019 (COVID-19) and appeared to reduce the prevalence of long COVID symptoms. The development of novel agents against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), including those with broader sarbecovirus activity such as anti-angiotensin-converting enzyme 2 monoclonal antibodies, is underway. A growing understanding of the pathophysiology of long COVID has provided several potential therapeutic targets for individuals experiencing this condition. Efforts to understand COVID-19 in people with HIV have led to novel insights into the biology and natural history of SARS-CoV-2 coinfection in this vulnerable subpopulation. These and other studies are summarized herein.*

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

The emergence of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pandemic in early 2020 disrupted all aspects of life around the globe, had a major impact on preexisting research activities,

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and led to the rapid implementation of new scientific endeavors to understand the epidemiology, natural history, pathophysiology, and management of coronavirus disease 2019 (COVID-19) and, more recently, its post-acute consequences. Many HIV and infectious diseases scientists have led these efforts. This article highlights new research on acute and post-acute SARS-CoV-2 infection, including in people with HIV, presented at the 2023 Conference on Retroviruses and Opportunistic Infections (CROI).

Acute COVID-19**Epidemiology and Natural History of COVID-19**

The risk factors for poor outcomes in acute COVID-19 have become clear. These include older age; medical comorbidities such as diabetes, obesity, and pregnancy; not being previously vaccinated against SARS-CoV-2; and lack of treatment during the acute phase of the infection.¹⁻³ However, questions remain about the risk of severe disease with recent and emerging Omicron subvariants. Cloherty and colleagues examined clinical outcomes by SARS-CoV-2 variant in Chicago and demonstrated attenuation of severity with Omicron subvariants compared with prior variants of concern (VOCs) (Abstract 889). Hospitalization and death rates were highest with the Delta variant, and those rates continued to decline when Omicron subvariants were prevalent.

Over the past 3 years, several groups developed in-hospital risk prediction algorithms to aid in clinician decision-making and counseling during hospitalization for COVID-19.^{4,5} Parczewski and colleagues incorporated an artificial neural networks (ANN) analysis of computed tomography (CT) chest scans into a prediction model that also included laboratory and clinical variables, to identify the best predictors of poor hospital outcomes (Abstract 731). They identified an ANN-assigned percentage of lung involvement of greater than 50% and age over 80 years as the most significant risk factors predicting poor hospital

outcomes from acute COVID-19. This suggests that the addition of ANN-analyzed chest CT scan scores could improve automated risk prediction models.

Two studies further validated the use of nucleocapsid (N)-antigen levels in the peripheral circulation as a biomarker predicting severe outcomes from COVID-19. Jain showed that higher N-antigen levels in blood during early hospitalization were associated with elevated risk for death within 90 days (hazard ratio [HR], 4.4; 95% confidence interval [CI], 3.2-5.9) and reduced incidence of sustained recovery through day 90 (Abstract 728). This suggests a pathogenic role for viremia, and importantly it identifies a group of hospitalized people who did not have high oxygen requirements but were still at high risk for poor outcomes. Studying the placebo arm of the ACTIV-2 trial, Jilg and colleagues evaluated the association of anti-spike immunoglobulin G (IgG) and N-antigen in plasma with clinical outcomes in 229 nonhospitalized people with mild to moderate COVID-19 at risk for severe outcomes (Abstract 283). They found that absence of anti-spike antibody and higher levels of plasma N-antigen predicted hospitalization or death and delayed symptom improvement in COVID-19 outpatients. Taken together, these studies show a potential role for measurement of these biomarkers in some individuals during the acute phase of infection.

Pathogenesis and Immune Responses

Several groups described interactions between SARS-CoV-2 and the innate immune system. Bouhaddou and colleagues profiled mRNA, protein, phosphorylation, and virus–host protein–protein interactions in Calu-3 cells after infection with several VOCs (Abstract 108). VOCs alter viral RNA and protein production, evolve altered N phosphorylation, and differentially regulate host inflammatory responses. Most VOCs antagonize interferon-stimulated gene (ISG) induction, and the Omicron subvariant BA.5 showed a strengthened antagonism of innate immunity compared with subvariant BA.1. This may be the reason why Suryawanshi and colleagues found that subvariant BA.5 replicated to higher titers and more frequently led to lethal infection in keratin 18 (K18)-human (h) angiotensin-converting enzyme 2 (ACE2) mice (Abstract 275). Similarly, Shi and colleagues demonstrated that Omicron strains exhibited resistance to type I and type III interferons in primary nasal epithelial cells and provided evidence that this may be related to a novel route of cellular entry compared with older variants (Abstract 232). Puray-Chavez and colleagues showed that SARS-CoV-2 is restricted by basally active cyclic GMP–AMP synthase

(cGAS)–stimulator of interferon genes (STING), a DNA sensing pathway that underlies the basally high interferon pathway activity seen in airway-derived cells lines that do not support SARS-CoV-2 replication despite ACE2 cell surface expression (Abstract 224). Together, this work demonstrates that interferons, shown to be

Fc-receptor–mediated infection of myeloid cells by SARS-CoV-2 may be responsible for the late production of proinflammatory cytokines that characterizes severe COVID-19

a determinant of acute COVID-19 disease severity,^{1,6} are important for restriction of SARS-CoV-2 replication, and that new variants are evolving resistance to host interferon responses.

The role of natural killer (NK) and dendritic cells in SARS-CoV-2 pathogenesis is still being investigated. Balachandran and colleagues provided evidence with a nonhuman primate model that NK cells are important for clearance of virus from the pharynx and lung, with peak NK cell activity 10 days post infection (Abstract 340). Saini and colleagues extended this narrative into humans by demonstrating that COVID-19 hospitalization is associated with dysfunctional NK cells with low expression of CD16 (Abstract 341). They found that Siglec-9-defined NK cell subpopulations are highly cytotoxic against SARS-CoV-2.

Pickering and colleagues provided evidence to support the hypothesis that Fc-receptor–mediated infection of myeloid cells by SARS-CoV-2 may be responsible for the late production of proinflammatory cytokines that characterizes severe COVID-19 (Abstract 231). They used a THP-1 human leukemia monocytic cell model system to show that spike receptor-binding domain (S-RBD)-specific monoclonal antibodies promoted infection of monocytes at sub-neutralizing concentrations and provided evidence for productive infection of primary macrophages via this mechanism. Cai and colleagues also used in vitro systems to demonstrate that plasmacytoid dendritic cells (pDCs) can sense SARS-CoV-2 infected cells, and that direct contact between infected cells and pDCs is required for type I interferon production (Abstract 342).

Many viruses evolve mechanisms to evade host restriction factors or to repurpose host cell machinery to support replication. Shi and colleagues demonstrated that subsequent SARS-CoV-2 variants become increasingly more efficient at downregulating BST2/tetherin, a transmembrane protein that prevents release of viruses after assembly in the host cell (Abstract 223). This downregulation of BST2 is due to mutations in spike that route BST2 for lysosomal degradation.

Two groups investigated the importance of SARS-CoV-2 nonstructural protein 6 (NSP6) in viral pathogenesis. Chen and Serra-Moreno showed that SARS-CoV-2 uses NSP6 to remodel endosomal membranes, recruit them to perinuclear locations, and generate replication organelles required for efficient viral replication (Abstract 234). Taha and colleagues used a novel replicon system to characterize Omicron replication independent of spike and found that mutations in NSP6 lead to lower viral replication (Abstract 233).

Treatment Options

The development, testing, and authorization of therapeutics for COVID-19 proceeded at a rapid pace in the first years of the pandemic but have since slowed. Treatment guidelines have not substantially changed in the past year, with the exception of the removal of authorized monoclonal antibody products, which are predicted to have no activity against currently circulating Omicron subvariants. Excitingly, several abstracts reported on novel therapeutics in the pipeline, whereas other abstracts provided a deeper characterization of current therapeutics. Chew presented a detailed summary of the state of COVID-19 outpatient therapeutics (Abstract 31).

Protease inhibitors. Uehara and colleagues reported phase III results from SCORPIO-SR (Efficacy and Safety of Ensitrelvir in Patients With Mild-to-Moderate COVID-19: A Protocol for a Multicenter, Randomized, Double-Blind, Placebo-Controlled, Phase 3 Study), a multicenter, randomized, double-blinded, placebo-controlled trial of ensitrelvir in people with mild-to-moderate COVID-19 within 5 days of symptom onset (Abstract 166). Ensitrelvir is a novel oral SARS-CoV-2 3C-like (3CL) protease inhibitor that does not require ritonavir boosting and has an active emergency use authorization (EUA) in Japan. In this population of mostly vaccinated people infected with Omicron

subvariants, ensitrelvir was safe and well tolerated. Compared with those receiving placebo, participants receiving ensitrelvir within 72 hours of symptom onset experienced shortened duration of symptoms and shortened duration of infectious viral shedding from the upper respiratory tract by approximately 1 day each. Ensitrelvir treatment during acute COVID-19 was also associated with decreased incidence of long COVID, as discussed below.

Tong and colleagues demonstrated that pomotrelvir, another investigational protease inhibitor, retains broad in vitro activity against all SARS-CoV-2 isolates

SCORPIO-SR results demonstrate that ensitrelvir in vaccinated people with mild-to-moderate COVID-19 within 72 hours of symptom onset is associated with shortened duration of symptoms, shortened duration of viral shedding, and decreased incidence of long COVID

to date, including 5 Omicron subvariants, and it has a favorable resistance profile (Abstract 551). They additionally showed in vitro additivity when pomotrelvir is combined with remdesivir or molnupiravir, but not nirmatrelvir, likely because they share the same binding site. This observation suggests that combination therapy with antivirals may be worthy of consideration in the future.

Nirmatrelvir/ritonavir remains the first-line agent for outpatient COVID-19 therapy due to its effectiveness and oral formulation. Henderson and colleagues used data from a large academic health system to demonstrate that the use of nirmatrelvir/ritonavir was associated with a 98% relative reduction in age-adjusted risk for hospitalization within 14 days of diagnosis, compared with no therapy in outpatients diagnosed with COVID-19 (Abstract 172). This is even greater than the 89% relative risk reduction observed in the clinical trial.⁷ In a multivariate regression model predicting COVID-19 hospitalization, the effect of treatment with nirmatrelvir/ritonavir was similar to that conferred by young age (approximately 20 years), demonstrating the remarkable impact of this agent.

Butt and colleagues investigated approximately 8000 propensity-matched people from the US Veterans Affairs (VA) health system and found that nirmatrelvir/ritonavir use was associated with a modest reduction in hospitalization and death among nonhospitalized people at high risk of progression to severe disease (Abstract 569). The clearest benefit was seen in those who were older, unvaccinated, or asymptomatic at baseline. Despite these data establishing the clear benefits of this agent, Shen and colleagues showed that, although it is increasing, the uptake of nirmatrelvir/ritonavir in people diagnosed with COVID-19 in the outpatient setting remains low (Abstract 567).

One reason clinicians and patients remain wary of nirmatrelvir/ritonavir is reports of symptom and virus rebound after completion of the 5-day course of treatment. Li presented a detailed summary of what is known about symptom and viral rebound with and without antiviral therapy (Abstract 32). He highlighted that rebound phenomena are common in untreated patients and that the field currently lacks a direct comparison of rebound in people who have and have not received nirmatrelvir/ritonavir. Perelson and colleagues expanded on a previous viral dynamics model and predicted that extending the treatment duration of nirmatrelvir/ritonavir to 10 days or initiating a second 5-day treatment course 1 day after symptoms reappear would not prevent rebound (Abstract 568). Deo and colleagues characterized symptom and viral rebound in the untreated and placebo arms of the ACTIV-2 trial, enrolling primarily unvaccinated people in the pre-Omicron era (Abstract 171). They found that 1 in 4 participants had symptom rebound, and 1 in 8 had high-level viral rebound, though having both simultaneously was uncommon, providing strong evidence that symptom and viral rebound are common without treatment.

Nucleoside and nucleotide analogues. Remdesivir, a nucleotide prodrug of an adenosine analogue, was one of the first antiviral therapies to enter phase III clinical trials for SARS-CoV-2 infection. It remains the only antiviral drug approved by the US Food and Drug Administration (FDA) for the treatment of COVID-19. However, because remdesivir must be administered intravenously or intramuscularly, its use in the outpatient setting has been limited. Using a mouse model, Carlin and colleagues presented promising data on the therapeutic effectiveness of 1-O-octadecyl-2-O-benzyl-sn-glycerol-3-phospho-RVn (V2043), an oral prodrug of remdesivir, and identified modifications

to V2043 that improved its potency (Abstract 543). Hedskog and colleagues showed that remdesivir retains excellent potency against all recent Omicron subvariants (Abstract 562). Using a novel replicon system, Han and colleagues demonstrated that common RNA-dependent RNA polymerase (Nsp12) mutations in VOCs do not decrease the potency of remdesivir (Abstract 962). Work from Mozaffari and colleagues used data from more than 700 hospitals to show that early hospital use of remdesivir is associated with significant reductions in mortality in all people, including immunocompromised people at 14 and 28 days across all levels of severity and all VOCs (Abstracts 556-557).

Molnupiravir, an oral prodrug of β -D-N4-hydroxycytidine, is less effective in reducing hospitalization in at-risk outpatients with COVID-19 than nirmatrelvir/ritonavir or remdesivir, and in the US it is currently an alternate therapy used only if nirmatrelvir/ritonavir or remdesivir are not available or appropriate.⁸ Using data from the VA health system, Butt and colleagues found that molnupiravir was not associated with significant reduction in hospitalization or death within 30 days of diagnosis compared with no therapy (Abstract 570). Efforts are needed to further define the role this agent should play in the management of COVID-19.

Monoclonal antibody therapy. Although monoclonal antibody (mAb) products have been removed from the arsenal of treatments for COVID-19 due to loss of efficacy against currently circulating Omicron subvariants,⁸ efforts are underway to develop products that target invariant regions of SARS-CoV-2. Ruiz and colleagues isolated 2 novel pan-sarbecovirus mAbs that potentially bind highly divergent SARS-related coronaviruses, including sarbecoviruses that do not use ACE2 as a receptor (Abstract 309). One of these displays broad and potent neutralizing activity. Guenthoer and colleagues isolated 2 further novel spike-specific mAbs that target a functionally constrained region of RBD and a conserved region in spike subdomain 1 (SD1) that show breadth and potency across VOCs (Abstract 310). Bieniasz and colleagues identified anti-ACE2 antibodies that represent a promising, broadly potent, pan-sarbecovirus therapeutic (Abstract 107, discussed further below). Using data from an ACTIV-2 clinical trial of amubarvimab and romlusevimab, Choudhary and colleagues provided evidence that dual active mAbs resulted in faster viral clearance and lower rates of resistance than single active mAbs, lending support to the development and use of dual active mAb

therapeutics (Abstract 168). Bender Ignacio and colleagues presented results from ACTIV-2 demonstrating safety and tolerability of intramuscular administration of combination mAbs in the thigh, which could lower barriers to outpatient implementation of mAb treatment in the future (Abstract 571).

Interferon therapy. Glenn and colleagues presented data on the use of pegylated interferon lambda from a phase III study of more than 1900 mostly vaccinated but high-risk, nonhospitalized participants in TOGETHER, an adaptive, multicenter, randomized, placebo-controlled trial (Abstract 167). A single subcutaneous injection of peginterferon lambda was associated with a 58% risk reduction of hospitalization or emergency department visit if administered within 3 days of symptom onset. More rapid viral clearance was seen in those treated with peginterferon lambda, and adverse effects were similar to placebo. Fischer and colleagues presented phase II inhaled interferon- β 1A (SNG001) results from approximately 220 participants in ACTIV-2 (Abstract 169). This agent was shown to be safe, but it did not accelerate the clearance of nasopharyngeal SARS-CoV-2 RNA over 2 weeks and was not associated with more rapid symptom recovery. There was a nonsignificant trend toward fewer hospitalizations in the treatment group, but the trial was not powered to detect a difference in risk of hospitalization.

Miscellaneous approved drugs. Provocative data from the COVID-OUT phase III, blinded, placebo-controlled trial suggested that metformin, a widely available and commonly used oral agent for prediabetes and diabetes, may be of benefit in acute COVID-19. Having already demonstrated a modest reduction in risk of emergency department visits, hospitalization, and death with metformin,⁹ Bramante and colleagues presented self-collected nasal viral RNA data from days 1, 5, and 10 of the trial (Abstract 170). Trial participants taking metformin were more likely to have undetectable viral RNA at days 5 and 10 than those taking placebo (odds ratio [OR], 1.355; 95% CI, 1.054-1.742). Metformin is thought to work by inhibiting mammalian target of rapamycin (mTOR)-dependent viral translation and inhibiting Nod-like receptor family pyrin domain containing 3 (NLRP3) inflammasome activation.¹⁰ Naggie and colleagues from ACTIV-6 presented results from a randomized trial comparing ivermectin and placebo in mild-to-moderate COVID-19, demonstrating no difference in time to recovery (Abstract 572).

Perez-Zsolt and colleagues showed that plitidepsin, a clinically approved antitumor agent that blocks eukaryotic translation elongation factor 1A (eEF1A), inhibits the synthesis of all SARS-CoV-2 proteins and the formation of viral particles (Abstract 548). Plitidepsin has a less potent effect on the cellular proteome, likely because of compensatory upregulation of eukaryotic initiation factor 4A2 (eIF4A2) and eIF2S3. They also demonstrated that plitidepsin inhibits replication of other RNA-dependent, nonintegrated DNA viruses such as Zika, hepatitis C virus, and herpes simplex virus, suggesting that it could be developed and evaluated for a variety of viral indications.

Miscellaneous drugs in development. Several new compounds are in development as COVID-19 therapeutics. Miller and colleagues reported that BIT225, an investigational HIV-1 compound that targets SARS-CoV-2 envelope protein, protected against death and

In a phase III RCT of more than 1900 mostly vaccinated but high-risk, nonhospitalized participants, a single subcutaneous injection of peginterferon lambda was associated with a 58% risk reduction of hospitalization or emergency department visit if administered within 3 days of symptom onset

reduced inflammatory and viral markers in a mouse model of COVID-19 (Abstract 552). Xing and colleagues showed that spike ACE2 inhibitor (SAI)⁴, a promising small molecule inhibitor of spike-RBD-ACE2 binding, inhibited cell entry, remained potent against several VOCs, and inhibited SARS-CoV-2 replication in lung tissue in a mouse model of COVID-19 (Abstract 547).

Two studies evaluated zotatifin, an inhibitor of eIF4A, which is a host RNA helicase required for SARS-CoV-2 replication. Zotatifin can be administered intravenously or subcutaneously. Using this agent, Patick and colleagues demonstrated in vitro inhibition of translation and replication in SARS-CoV-2 variants, Middle East respiratory syndrome coronavirus (MERS-CoV), severe acute respiratory syndrome

coronavirus 1 (SARS-CoV-1), and human coronavirus 229E (HCoV-229E). They also demonstrated its synergy with other therapeutics in cell culture (Abstract

High-affinity anti-ACE2 antibodies with potent pan-sarbecovirus activity were identified...resistance to these antibodies was rare and had only subtle effects on potency

544). Warner and colleagues demonstrated safety and tolerability of zotatifin in PROPEL, a phase Ib clinical trial on people with mild-to-moderate COVID-19 (Abstract 545). Du and colleagues demonstrated that PAV-104, a pan-viral inhibitor of a subset of host protein assembly machinery, inhibits replication of several SARS-CoV-2 variants in primary airway epithelial cells at a step post entry by interfering with N oligomerization and blocking viral assembly and release (Abstract 549). Taken together, these studies emphasize the ongoing development of treatments for SARS-CoV-2 that target novel pathways and may ultimately broaden the armamentarium of available treatments for COVID-19.

Vaccines and Prevention

The first SARS-CoV-2 vaccines outside of a clinical trial were administered in December 2020 as a result of a breathtakingly rapid global effort. COVID-19 vaccinations were estimated to prevent more than 14 million deaths globally in the first year of the vaccination campaign.¹¹ However, much work remains, including distributing vaccines equitably, developing a new generation of vaccines for future VOCs, developing on-demand, self-administered prophylactic agents, understanding the correlates of sterilizing immunity, developing evidence-based vaccination schedules, combating misinformation, understanding vaccine effectiveness in special populations, and determining which nonpharmaceutical interventions are most effective and when best to implement them. A variety of research presented at CROI 2023 addressed these issues.

Prophylactics Under Development

Although the SARS-CoV-2 spike protein evolves in

response to selective pressure, the human SARS-CoV-2 receptor ACE2 cannot evolve rapidly and thus represents an attractive target for antibody and drug development.

Bieniasz and colleagues identified high-affinity anti-ACE2 antibodies with potent pan-sarbecovirus activity, presented the mechanism for their effectiveness (steric clash at the SARS-CoV-2 spike-RBD-ACE2 binding site), demonstrated their effectiveness against several human polymorphisms of ACE2, and showed almost sterile protection of the lung when used for prophylaxis in a mouse model (Abstract 107). Importantly, they showed that endogenous ACE2 activity is not affected by these antibodies and that antibody binding does not trigger ACE2 internalization. Resistance to these antibodies was rare and had only subtle effects on potency. This work complemented other efforts described above to develop pan-sarbecovirus prophylactic or therapeutic agents for future SARS-CoV-2 variants or future new emerging sarbecoviruses (Abstracts 309-310).

Monoclonal antibodies have been the mainstay for those who need prophylactic agents in addition to or instead of vaccination, especially in populations with immune compromise or dysfunction, yet neither mAbs nor vaccines deliver sterilizing immunity,

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and both require administration in a health care setting. An on-demand, self-administered prophylactic with sterilizing immunity would be a practical and beneficial agent for people at elevated risk of severe COVID-19 to take prior to entering a high-risk setting. Neary and colleagues reported that intranasal nafamostat was protective against airborne transmission of SARS-CoV-2 in a Syrian golden hamster model (Abstract 553). Nafamostat inhibits transmembrane serine protease 2 (TMPRSS2), the host cell surface serine protease that mediates the cleavage of spike that is required for virus–host cell fusion and entry.

Although intravenous (IV) nafamostat did not show efficacy in a phase IIa clinical trial of people with moderate-to-severe COVID-19 pneumonia, its half-life is short after IV administration and, like other therapeutics, it may have more beneficial effects when given early or prophylactically. Nabeta and colleagues demonstrated the safety of intranasal Q-griffithsin (Q-GRFT) in a phase I clinical trial (Abstract 554). Q-GRFT is an engineered oxidation-resistant variant of griffithsin, an algal antiviral that binds oligomannose residues in glycoproteins on viral envelopes. The researchers showed that nasopharyngeal fluids from people treated with intranasal Q-GRFT neutralized the Omicron BA.5 subvariant, as well as MERS-CoV.

Vaccine Effectiveness, Uptake, and Equity

People with hybrid immunity (induced by a combination of infection and vaccination) have the highest protection against severe acute COVID-19 outcomes.¹² Mayer-Blackwell and colleagues tracked SARS-CoV-2 spike-specific T cells over time in people recovering from COVID-19 who were subsequently vaccinated and found that mRNA vaccination broadened the postinfection memory response by expanding low-abundance clonotypes (Abstract 360). However, the recalled memory clonotypes from infection predominated. People who were hospitalized with COVID-19 developed greater spike-reactive CD4+ T-cell diversity that persisted after vaccines than people who had mild-to-moderate COVID-19. The investigators also identified vaccine-reactive CD8+ T-cell clonotypes present in nasal mucosa that were also present in the blood after booster dosing. Pérez-Caballero and colleagues showed that, among people with hybrid immunity, those who had infection prior to vaccination had broader and higher magnitude T-cell responses to numerous SARS-CoV-2 peptides than people who had vaccination prior to infection (Abstract 345).

Henderson and colleagues used data from an academic health system during the Delta and Omicron waves, and found that people with 3 vaccine doses compared with those with none had a 71% relative risk reduction for hospitalization within 14 days of diagnosis, with risk higher in the Delta era and in older people (Abstract 172). There was a 28% relative increase in risk after 180 days since the last vaccine dose; those most at increased risk were aged 75 years or older. Older age was the most influential overall predictor of hospitalization.

Although the rapid development of COVID-19 vaccines was a success story, the distribution of vaccines

left much to be desired. As of March 2023, only 28% of people in low-income countries have received at least 1 dose of a COVID-19 vaccine.¹³ One of the many reasons for this inequity is the restricted access to intellectual property for mRNA vaccines.¹⁴ In a meta-analysis of 35 clinical trials in healthy nonpregnant adults, Venkatesh and colleagues demonstrated that protein subunit vaccines, many of which are patent-free and could be mass produced, have similar neutralizing antibody titers to mRNA vaccines (Abstract 356). Lee and colleagues presented data from nearly 24 million Taiwanese people demonstrating that a protein subunit vaccine (MVC-COV1901; Medigen) was similarly effective at preventing severe COVID-19 and death as the BNT162b2 mRNA vaccine (Pfizer-BioNTech) (Abstract 355). People who received AZD1222 (AstraZeneca, a

Evidence presented demonstrated that protein subunit vaccines, many of which are patent-free and could be mass produced, have similar neutralizing antibody titers to mRNA vaccines and are similarly effective at preventing severe COVID-19 and death as mRNA vaccines

replication-deficient chimpanzee adenovirus vectored vaccine) as a primary series, regardless of which vaccine they received as a booster (mRNA, AZD1222, or protein subunit), had significantly lower protection against severe COVID-19 and death than those who received an mRNA vaccine or the protein subunit primary series.

Several groups examined factors associated with low vaccine uptake. Liang and colleagues examined county-level COVID-19 booster coverage by age group in southeastern US states and found that counties with higher racial housing segregation had lower percentages of booster coverage across age groups (Abstract 1006). Hoffman and colleagues examined correlates of COVID-19 vaccine update in Malawian adults and found that older age, having children, greater educational attainment, confidence in vaccine safety, and belief that its benefits outweighed its risks positively

correlated with up-to-date COVID-19 vaccination status (Abstract 1018).

Nonpharmaceutical Interventions

Numerous studies have demonstrated that lockdowns with high adherence reduced SARS-CoV-2 transmission early in the COVID-19 pandemic. However, it remains difficult to study the comparative effectiveness of different nonpharmaceutical interventions, given that these were often implemented simultaneously and without control groups. Thiebaut and

Although vaccines elicited equally strong anti-spike IgG in people with HIV compared with people who were HIV seronegative, the median neutralizing titers after the second dose were lower among people with HIV

colleagues used 3 models to examine interventions in France and demonstrated that all nonpharmaceutical interventions studied effectively reduced viral transmission, but the effectiveness of lockdown interventions decreased with time, potentially due to decreased adherence or enforcement (Abstract 1008). Nonpharmaceutical interventions are needed to contain deadly airborne respiratory pathogen epidemics if vaccine coverage is low, and rapid vaccine rollout is essential. Stuart and colleagues used the open-source COVID-19 Agent-based Simulator (Covasim) to define time intervals for ideal deployment of variant-chasing vaccines (Abstract 1015). They described an ideal variant-containing strategy of global monitoring for highly immune-evading virulent variants paired with temporary nonpharmaceutical interventions, to buy time during rapid rollout of variant-specific or broad and potent vaccines.

Special Populations of Interest

Acute SARS-CoV-2 infection and vaccination in people with HIV. Recent work from the UK Biobank demonstrated differences in regional brain volume in the thalamus, caudate, putamen, ventral striatum, and hippocampus between people who went on to acquire SARS-CoV-2 infection and people who did not acquire

SARS-CoV-2 infection.¹⁵ Paul and colleagues evaluated brain volumes using 3 Tesla magnetic resonance imaging (MRI) and neurobehavioral characteristics among 112 Thai men who have sex with men with HIV enrolled in the RV254/SEARCH010 cohort (Abstract 188). Using a machine learning algorithm, they found that a collection of volumetric features, particularly in right hemisphere regions that are implicated in impulsivity and risk-taking behavior, were associated with subsequent SARS-CoV-2 infection. Their findings were generally consistent with those of the UK Biobank study.

Several studies addressed the pathophysiology of acute COVID-19 in people with HIV. Augello and colleagues evaluated 18 HIV seropositive and 18 HIV seronegative individuals hospitalized with COVID-19 pneumonia a median of 10 days after symptom onset (Abstract 344). They found that people with HIV were more likely to have SARS-CoV-2 RNAemia, greater systemic inflammation, and worse disease severity, and they concluded that the data showed a link between HIV-related T cell dysfunction and poor control over circulating SARS-CoV-2. These observations are potentially important as evidence that additional measures to reduce the viral burden or improve immune control during early infection might be warranted in people with HIV. There may also be implications for the post-acute phase of COVID-19, because some early factors can predict longer-term clinical outcomes.¹⁶

Kolossváry and colleagues studied participants in the REPRIEVE (Randomized Trial to Prevent Vascular Events in HIV) trial and identified certain proteins in the granzyme family that predicted the development of moderate to severe COVID-19 (Abstract 274). They suggested that baseline immune dysregulation may relate to the severity of acute infection through these physiologic mechanisms. In another REPRIEVE analysis, Schnittman and colleagues compared 2181 donors who were SARS-CoV-2 negative with 283 individuals who were SARS-CoV-2 positive (most of whom had asymptomatic infection) and determined that among people with HIV, high body mass index (BMI) and low CD4 nadir were associated with unique SARS-CoV-2 humoral signatures. In this analysis, high BMI was associated with a hyperinflammatory response and low CD4 nadir was associated with dysfunctional antibody class switching. (Abstract 348). The authors suggested that these observations could explain more severe COVID-19 among people with HIV. Abela and colleagues leveraged the Swiss

HIV Cohort Study to identify that certain preexisting immunity to human coronaviruses was associated with reduced susceptibility to SARS-CoV-2 infection (Abstract 352). They also identified a weaker overall SARS-CoV-2 antibody response in those with HIV infection.

Several studies addressed issues related to SARS-CoV-2 vaccination in people with HIV. Matveev and colleagues evaluated immune responses to booster doses in people with HIV on ART who were older than 55 years of age (Abstract 369). They found that although vaccines elicited equally strong anti-spike IgG in people with HIV compared with people who were HIV seronegative, the median neutralizing titers after the second dose were lower among people with HIV. However, these differences resolved following a third dose. This study, as well as another study by Duncan and colleagues, did not find an impact of SARS-CoV-2 mRNA vaccination on the HIV reservoir (Abstract 370). Nowak and colleagues showed that responses to BNT162b2 vaccination in people with HIV correlated with the presence of certain gut microbiota populations, providing evidence that characteristics of the microbiome may predict the strength of vaccine responses (Abstract 372).

Liu and colleagues examined the effectiveness of different COVID-19 vaccines and the evolution of antibody responses in 1496 adult Taiwanese people with HIV who had received a third dose of a SARS-CoV-2 vaccine (Abstract 1020). They found similar effectiveness of a third dose of mRNA-1273 (Moderna) 100 µg or 50 µg, BNT162b2, and MVC-COV1901 (Medigen protein subunit vaccine) in preventing SARS-CoV-2 infection or seroconversion of anti-N IgG. People with HIV with CD4+ T-cell counts less than 200/µL and plasma viral load greater than 200 copies/µL had reduced antibody responses. Matsali and colleagues analyzed live-virus neutralizing activity against Omicron subvariants BA.5, BQ.1.1, and XBB.1 together with T-cell responses after the bivalent third booster shot—that is, a fifth vaccine—in 48 people with HIV with CD4+ T-cell count nadirs more than 200 cells/µL with and without hybrid immunity stratified by CD4+ T-cell count (Abstract 364). They found that hybrid immunity was associated with greater neutralizing responses against BA.5 but not against BQ.1.1 and XBB.1, which currently predominate. This fifth shot elicited strong neutralization against BA.5 and retained cross-neutralization against BQ.1.1 and XBB.1, although levels were 3-fold to 4-fold lower. There was no effect on

T-cell mediated responses.

Many people wonder whether they will have a reaction to a COVID-19 vaccine after infection. Tapley and colleagues examined a safety subset of 1267 unvaccinated people with HIV from the COVID-19 Prevention Network (CoVPN) 3008 (UBUNTU) phase III efficacy trial of the mRNA-1273 vaccine, of whom 73% had evidence of prior SARS-CoV-2 infection (Abstract 1013). Overall, 43% of people with HIV reported local or systemic reactions in the first 7 days after the first vaccination, with maximum severity of mild (62%), moderate (36%), or severe (3%). Women and people with CD4+ counts above 500 cells/µL had increased odds of moderate or severe reactivity. Spinelli and colleagues found that 7% of surveyed people with HIV in the US in the Center for AIDS Research (CFAR) Network of Integrated Clinical Systems (CNICS) cohort from February 2021 to April 2022 were not vaccinated and probably or definitely had no desire to receive one (Abstract 1011). Factors associated with vaccine hesitancy included age less than 30 years old, viral load greater than 200 copies/µL, female sex at birth, and Black race rather than White race, with vaccine hesitancy decreasing with time over the observation period.

Acute SARS-CoV-2 infection and vaccination in children and adolescents. Several abstracts addressed SARS-CoV-2 infection in children and adolescents. Tagarro and colleagues studied more than 1700 children from

Comorbidities such as asthma and chronic neurologic and cardiac conditions, but not diabetes or cancer, were associated with more severe outcomes from COVID-19 in a pediatric population

hospitals in Spain and Colombia (Abstract 835). They identified that comorbidities such as asthma and chronic neurologic and cardiac conditions, but not diabetes or cancer, were associated with more severe outcomes from COVID-19 in this pediatric population. Such individuals were at higher risk of death, mechanical ventilation, and pediatric intensive care unit admission.

Antiviral treatment options for children with COVID-19 remain limited. Bernardi and colleagues studied a high-risk pediatric population in Rome who had received nirmatrelvir/ritonavir, and found that this therapy was safe and effective (Abstract 834). Among 40 children treated, there were only 5 adverse events (nausea, increased creatine phosphokinase level, and metallic taste). The mean time of viral shedding was 13 days, and 1 patient was persistently positive for 56 days. Notably, 4 children received a longer (10-day) course due to viral persistence and severe comorbidities.

Several studies addressed SARS-CoV-2 vaccination in children. Milligan and colleagues reported on a study of vaccines in infant rhesus macaques and found that mRNA- and protein-based vaccines induced antibody responses and protected against severe lung disease on SARS-CoV-2 challenge at 1 year (Abstract 840). The protein-based vaccine induced higher titers of neutralizing antibodies, but the mRNA vaccines induced greater spike-specific T-cell responses. The authors concluded that either approach is likely to be efficacious in children. If so, this would mirror efficacy data in adults discussed previously. Di Chiara and colleagues conducted a multicenter, prospective, observational study evaluating immune responses to mRNA vaccines in 82 Italian children, 60 of whom had confirmed COVID-19 before vaccination (Abstract 841). The magnitude of the antibody response was higher in children with prior SARS-CoV-2 infection than in those without preexisting immunity, and levels of antibodies decayed between 1 and 6 months post vaccination. Chemaitelly and colleagues evaluated the BNT162b2 vaccine in adolescents and found that compared with a 10 µg dose, a 30 µg dose was associated with 23% higher effectiveness against infection with Omicron subvariants in adolescents who were infection naive (Abstract 842). They noted that this higher dose of BNT162b2 conferred similar improvement in protection as the mRNA-1273 vaccine, which is also a 3-fold higher dose.

Acute SARS-CoV-2 infection and vaccination in pregnant individuals. Two groups reported SARS-CoV-2 antibody responses in pregnancy. Lacourse and colleagues examined 71 people with SARS-CoV-2 infection during pregnancy and found that maternal and cord blood SARS-CoV-2 antibody binding and neutralizing responses were higher among those who had been vaccinated prior to infection than among those who were unvaccinated prior to infection (Abstract

794). Approximately 18% of people who had been unvaccinated prior to SARS-CoV-2 infection during pregnancy did not have sustained neutralizing antibodies by the time of delivery, and 100% of those with hybrid immunity had neutralizing antibodies. Govindaraj and colleagues examined people with an mRNA vaccine primary series during pregnancy and found that neutralizing antibody titers to Omicron subvariants were lower than those to pre-Omicron variants (Abstract 796). Pregnant individuals remain an important subpopulation for further study of COVID-19 pathogenesis, and efforts are underway to continue to characterize the impact of SARS-CoV-2 infection and vaccination in pregnant individuals and their offspring.

Acute SARS-CoV-2 infection and vaccination in people who are immunocompromised. It is postulated that VOCs arise in immunocompromised hosts who inadvertently maintain prolonged replication of SARS-CoV-2 in the presence of the selective pressure of

The bivalent booster was negatively associated with breakthrough infection and hospitalization in immune competent populations and in those with mild immune dysfunction, but its effectiveness was reduced in people with moderate-to-severe immune dysfunction

exogenous or endogenous SARS-CoV-2-specific antibodies. Kim and colleagues investigated viral kinetics with weekly saliva testing in an immunocompromised cohort (70% in active chemotherapy and 30% with solid organ transplant) (Abstract 726). The median duration of shedding of culture-positive virus was 4 weeks. Having received 3 or more vaccinations was associated with shorter shedding duration, and people receiving B-cell depleting therapy generally shed viable virus for longer. Ferré and colleagues sequenced the viral genomes of more than 700 people and reported higher frequency of minority nonsynonymous mutations in most genes of all variants studied in people who were immunocompromised (Abstract 354). This provides

additional support for the hypothesis that viral evolution can occur in the immunocompromised population.

Several groups reported vaccine effectiveness in populations with and without immune dysfunction. Sun and colleagues presented data on COVID-19 bivalent booster effectiveness in people with immune dysfunction in the N3C (National COVID Cohort Collaborative). (Abstract 214). The bivalent booster was negatively associated with breakthrough infection and hospitalization in immune competent populations and in those with mild immune dysfunction, but its effectiveness was reduced in people with moderate-to-severe immune dysfunction. Liu and colleagues examined longitudinal anti-spike IgG titers in people on anti-CD20 (B-cell depleting) therapy and found that the likelihood of mounting antibody responses increased with a third primary dose or with time after anti-CD20 administration (Abstract 368). Rocco and colleagues found that people with idiopathic CD4+ lymphopenia and absolute CD4+ counts above 100 cells/ μ L mounted similar humoral and cellular immune responses to healthy controls, and people with idiopathic CD4+ lymphopenia and CD4+ counts below 100 cells/ μ L had impaired vaccine immunity (Abstract 367). Taken together, these data will help people with immune dysfunction and their clinicians make informed decisions about best strategies for prevention of severe COVID-19.

Post-Acute COVID-19

There is growing recognition that SARS-CoV-2 infection can affect long-term health.¹⁷ Major efforts are now underway to understand the post-acute sequelae of SARS-CoV-2 infection (PASC, or long COVID), which include incident medical diagnoses potentially caused by SARS-CoV-2 infection, as well as persistent, unexplained, and sometimes debilitating symptoms.¹⁸ Peluso provided an overview of the current state of knowledge on long COVID syndromes, including epidemiology, natural history, biology, and the potential for therapeutics (Abstract 33). Several studies presented at CROI 2023 provided additional insight into these topics.

Epidemiology and Natural History

Adding to observations that long COVID affects a substantial proportion of individuals recovering from SARS-CoV-2 infection,^{19,20} Berry and colleagues studied the incidence of long COVID in nearly 45,000 patients previously hospitalized for COVID-19 (Abstract 718).

More than 27,000 patients experienced 1 or more long COVID symptoms between 90 and 270 days post hospitalization. Electronic health records most commonly captured neuropsychiatric symptoms, dyspnea, fatigue, and joint pain in this population. However, other important symptoms of long COVID such as dysautonomia and protracted disturbances in taste and smell were infrequently captured by the International Classification of Diseases (ICD)-10 codes. This led the authors to conclude that this incidence is likely to be an underestimate in addition to the fact that individuals may be unlikely to seek care for all relevant symptoms. Malambo and colleagues described long COVID in post-COVID-19 clinics in Zambia, demonstrating that this condition continues to be observed in many populations, including those outside the high-resource settings where it was initially described (Abstract 719).

Identification of objective biomarkers of long COVID symptoms remains a priority for the field.¹⁸

Efforts are now underway to confirm the clinical observation that there are different syndromic phenotypes of long COVID, which are possibly driven by different biologic processes

McAlpine and colleagues correlated symptoms of long COVID with objectively measurable defects (Abstract 493). The authors applied the Research Domain Criteria (RDoC) to better understand neuropsychiatric alterations in people with neurologic long COVID symptoms. In addition to providing support for the observation that these individuals exhibit impairment in executive functioning, processing speed, attention, and verbal fluency, among other symptoms, they observed novel alterations in motor and negative valence systems that warrant further investigation. Dziarski and colleagues also observed impairment in processing speed at 1 month post infection, which improved by 4 months in a highly vaccinated cohort (Abstract 495). Brew and colleagues assessed individuals for up to 2 years following initial SARS-CoV-2 infection and found that olfactory performance declined over time, especially among those exhibiting initial impairment (Abstract 715). In another study, Brew and colleagues

identified several potential MRI-based biomarkers of blood–brain barrier impairment, neuronal and axonal injury, and excitotoxicity in individuals with post-COVID-19 neurocognitive symptoms (Abstract 492). They saw variable improvement in these parameters over 10 months of follow-up and suggested that these markers might be useful in future studies. De Bree and colleagues identified early elevations in plasma levels of IL-1 β and sCD14 measured within the first 4 weeks as potential biomarkers for long COVID at 6 months (Abstract 710). Taken together, these studies contribute to a growing literature tying subjective symptoms of long COVID to objective biomarker or physiologic measurements.

Efforts are now underway to confirm the clinical observation that there are different syndromic phenotypes of long COVID,²¹ which are possibly driven by different biologic processes.¹⁸ Mateu and colleagues performed a hierarchical cluster analysis and identified 3 clusters of increasing severity in the Spanish King cohort study (Abstract 723). These included a milder cluster in which fatigue and dyspnea were dominant, followed by a more moderate cluster that also included headache, arthralgia, chest pain, and neurocognitive symptoms, followed by the most symptomatic cluster, which also included tachycardia, neurosensitive symptoms, and cough. Importantly, only a small proportion (7.6%) of individuals achieved recovery at 2 years of follow-up. An additional analysis of the same cohort presented by Nevot and colleagues identified 5 clusters to guide biologic analyses (discussed further below) (Abstract 711). These observations are generally consistent with symptom-based phenotypes described from smaller cohort studies.^{22,23}

Pathogenesis and Immune Responses

The pathophysiology of long COVID remains incompletely understood. Potential mechanisms include persistence of SARS-CoV-2 viral antigens (including subgenomic RNA and protein), immune dysregulation, reactivation of latent herpesviruses (eg, Epstein-Barr virus), microbial translocation, autoimmunity, microvascular dysfunction, and mitochondrial dysfunction, among others.^{18,24} A number of studies advanced our understanding of the potential contribution of each of these mechanisms.

One of the most pressing questions for the field is whether persistence of SARS-CoV-2 antigen contributes to long COVID. Peluso and colleagues presented a study using the single molecule array (Simoa) platform to investigate persistence of SARS-CoV-2

proteins in the plasma of individuals during the post-acute phase (Abstract 282). They found that 24% of individuals studied had at least 1 antigen detected during at least 1 time point up to 14 months after infection, but antigen was detected only sporadically in most individuals. Antigen persistence was strongly associated with hospitalization during acute infection, and appeared more prevalent among those consistently reporting high numbers (>8) symptoms. In complementary work, Eden and colleagues reported on the lack of persistent antigen in the cerebrospinal fluid following SARS-CoV-2 infection; though this does not rule out viral persistence in central nervous system tissue, it suggests that viral persistence may not be easily measurable in cerebrospinal fluid (CSF) (Abstract 189). Although the prevalence of antigen detection was much lower than previously reported,²⁵ this phenomenon may drive at least some cases of long COVID and is likely to remain an area of intense investigation.

Inflammation has been consistently identified in individuals with long COVID compared with those who have fully recovered.^{18,24} Several studies evaluated

Cytomegalovirus serostatus is an important protective factor with regard to post-COVID-19 neurocognitive symptoms

immune responses and potential dysregulation in the post-acute phase. De Bree and colleagues assessed inflammatory markers during the early post-acute phase (4 weeks) and at 24 weeks post COVID-19. Compared with healthy controls, they found that people with prior SARS-CoV-2 infection had ongoing elevations in IL-6, IL-10, IL-17, and IL-1B (Abstract 710). They further observed that early immune dysregulation was an important determinant of long COVID, and that C-reactive protein level elevations at week 24 were associated with ongoing symptoms. Nevot and colleagues identified differential expression of 14 cytokines when comparing 5 symptomatic clusters of long COVID with individuals who had fully recovered and uninfected controls (Abstract 711). This study provided an initial approach by which

cluster analyses might be paired with biomarker analyses to better understand the biology underlying certain phenotypes of long COVID. Mouchati and colleagues demonstrated that PASC is associated with increased zonulin, a marker of gut permeability, consistent with prior observations suggesting that microbial translocation could be an important driver of post-COVID-19 inflammation among those with long COVID symptoms (Abstract 288).²⁶ McAlpine and colleagues presented data from a study of neurologic aspects of long COVID (Abstract 190). Although they did not identify significant differences in the CSF of those with PASC compared with prepandemic controls, there were clinical and demographic differences between the 2 groups that may have biased against identification of an effect. Furthermore, they identified elevations in certain soluble markers of inflammation and glial fibrillary acid protein (GFAP) in plasma, consistent with prior observations in other cohorts.²⁷

Several studies further explored long-term humoral and cellular immune responses following SARS-CoV-2 infection. Yin and colleagues presented new cytometry by time-of-flight (CyTOF) data comparing 27 individuals who consistently met the case definition of long COVID with 16 individuals who reported complete recovery over an 8-month period prior to receipt of any SARS-CoV-2 vaccine (Abstract 346). Among those with long COVID, the researchers found higher levels of markers of tissue homing on CD4+ T cells and immune exhaustion on CD8+ T cells, which they suggested might represent indirect evidence of tissue antigen persistence. They also found a dissociation between the humoral and cellular immune responses in these individuals. For example, SARS-CoV-2-specific CD4+ and CD8+ T-cell responses directly correlated with anti-RBD antibodies in those reporting full recovery, but not in those with long COVID. The authors suggested that discoordination between the 2 arms of the adaptive immune system might drive long COVID.

Building on prior work demonstrating the potential role of human herpesviruses in long COVID,^{16,28,29} Peluso and colleagues identified cytomegalovirus (CMV) serostatus as an important protective factor with regard to post-COVID-19 neurocognitive symptoms (Abstract 273). This observation stands in contrast to prior findings that high-level immune responses to and serologic evidence suggesting reactivation of Epstein Barr virus, another human herpesvirus, are associated with increased odds of

long COVID. The reason for this surprising observation was unclear, but the authors suggested that it could relate to CMV-specific immunoregulatory cytokines (eg, virus-specific IL-10), differential anatomic compartmentalization of these viruses in relation to SARS-CoV-2, or enhancement of immune responses in those who are CMV seropositive. Further work will be needed to determine if this observation can be confirmed in other cohorts, including in those with prepandemic serologies that can be assessed.

Acute COVID-19 is known to be associated with the generation of autoantibodies, especially in those with more severe acute illness.³⁰ Using electronic health record data from a large health network, Hileman and colleagues compared individuals with COVID-19 with propensity score-matched controls (Abstract 712). They observed that autoimmune diseases, although rare in both groups, were more likely to be diagnosed in the first year after COVID-19 than in age- and sex-matched comparators. Although conditions like rheumatoid arthritis, psoriasis, and type 1 diabetes mellitus had the highest incidence after COVID-19, conditions such as polyarteritis nodosa, reactive arthritis, and antineutrophil cytoplasmic antibody (ANCA)-associated vasculitides had the highest risk ratios. This adds to the growing literature suggesting an increased risk of autoimmune conditions in the post-acute period.³¹ However, whether autoimmunity is a driver of unexplained symptoms (ie, long COVID) remains unclear.

There has been much recent attention on the role of platelet dysregulation, clotting dysfunction, and endothelial dysfunction driving microvascular abnormalities in long COVID.³² Zisis and colleagues used Endopat testing to show that long COVID is associated with arterial stiffness, and that the lowest arterial elasticity scores were more strongly associated with cardiopulmonary symptoms than neurocognitive or other systemic symptoms (Abstract 714). Durieux and colleagues extended this observation and showed that sex was an important modifier of this relationship, demonstrating that women were disproportionately affected (Abstract 717).

Dirajlal-Fargo and colleagues showed differences in oxygen consumption and oxidative stress in individuals with long COVID compared with those without COVID-19 and those who fully recovered (Abstract 285). This observation builds on prior work that showed an association between decreased mitochondrial health and neuropsychiatric symptoms in the post-acute phase.³³

Treatment and Prevention

Acute-phase treatment and long COVID outcomes.

An important unanswered question is whether treatment during the acute phase of COVID-19 has an impact on long COVID outcomes. Uehara and colleagues presented data from a phase III, double-blind, randomized trial of ensitrelvir, a SARS-CoV-2 3CL protease inhibitor approved in Japan (also discussed above) (Abstract 166). The study is notable because it is one of the first clinical trials to prospectively assess symptomatology during the acute phase of COVID-19 and in the post-acute phase, at 3 and 6 months post infection. In addition to reducing the duration of acute symptoms by approximately 1 day and accelerating viral clearance, the authors observed a 25% reduction in the presence of any long COVID symptoms and 26% reduction in neurologic symptoms at 6 months among those who received ensitrelvir compared with those receiving placebo. This finding was more dramatic when the population was restricted to individuals who had the highest baseline symptom scores, in whom the researchers identified a 45% reduction in any long COVID symptoms and 33% reduction in neurologic symptoms. Most symptoms appear to have been reduced by 20% to 70% compared with placebo, with reduction in smell disorder, difficulty concentrating, and insomnia achieving statistical significance. In support of this observation, a retrospective analysis of data from a single center presented by Antoni found that early outpatient treatment with antivirals or monoclonal antibodies was associated with 50% to 60% lower odds of symptoms at 3 months, although the data were potentially biased by a low survey response rate and potentially important clinical differences between groups (Abstract 733).

In contrast, related work presented by Evering and colleagues from the ACTIV-2 study did not identify an effect of early therapy with amubarvimab and romlusevimab on long COVID symptoms or on quality of life at 36 weeks in high-risk outpatients with mild-to-moderate COVID-19, despite an improvement in early differences in death and hospitalization (Abstract 721).

As an extension of their analysis showing benefit of metformin treatment during the acute phase, Bramante and colleagues showed a potential benefit over the long term (Abstract 170). The same trial participants were followed up with surveys every 30 days through 10 months. The team described a 42% reduction in long COVID through month 10 among participants taking metformin titrated over 14 days

during acute infection compared with those receiving placebo. This provocative observation may be related to inhibition of viral translation, or to other metabolic effects of metformin that warrant further investigation. Ultimately, more data will be needed to answer the important question of whether early treatment improves long COVID clinical outcomes.

Treatment of established long COVID. There is no standard of care for established long COVID, and most treatment is focused on ruling out conditions that might mimic long COVID and on trying to optimize symptoms. Importantly, each of the mechanisms that has been proposed as a potential contributor to long COVID is potentially targetable using antivirals, monoclonal antibodies, and various forms of immunotherapy. Limited data were presented on the treatment of established long COVID, except for a study by Augustin and colleagues that did not find an effect of therapeutic SARS-CoV-2 vaccination in those with established symptoms (Abstract 720). Further work focused on therapeutics in the post-acute phase is urgently needed to address long COVID in those who already have it.

Special Populations of Interest

PASC in people with HIV. Preexisting HIV infection could potentially alter the risk of developing long COVID.³⁴ Two large studies leveraging electronic health records showed concerning trends among people with HIV recovering from SARS-CoV-2 infection.

People with HIV had significantly higher odds of incident diabetes, heart disease, malignancy, thrombosis, and mental health disorders than HIV-seronegative people 28 or more days post COVID

Yendewa and colleagues presented an analysis from the TriNetX health research database, which includes 69 health care organizations within the US (Abstract 724). They found that people with HIV had significantly higher odds of incident diabetes, heart disease, malignancy, thrombosis, and mental health disorders than

HIV-seronegative people at least 28 days post COVID. They also observed that among people with HIV, vaccination was protective. In a complementary study working with data from the N3C cohort, Liang and colleagues compared people with HIV who had a history of SARS-CoV-2 infection with contemporary controls who were HIV seropositive who did not have SARS-CoV-2 infection during the study period (Abstract 884). They found a higher risk of pulmonary, renal, neuropsychiatric, and cardiovascular complications among people with HIV following SARS-CoV-2 infection. This observation addressed the criticism of prior studies that compared people with HIV with people who were HIV seronegative without accounting for the fact that people with HIV may have a higher likelihood of developing complications attributed to PASC independent of SARS-CoV-2 infection. Taken together, these studies suggest that there is additional risk of SARS-CoV-2 coinfection beyond the risks of HIV alone.

Other, smaller cohort studies did not clearly identify longer-term complications of SARS-CoV-2 infection among people with HIV evaluated prospectively. For example, Ocampo and colleagues evaluated young people with HIV in Thailand who were mostly vaccinated, who were on stable ART, and who had few comorbidities (Abstract 494). They found no major clinical adverse events following COVID-19 and observed that cognitive and mood parameters, which are sometimes part of long COVID syndromes, remained stable after COVID-19.


Antar and colleagues conducted a US-based, nationwide, fully remote, prospective observational cohort study to compare HIV seropositive and seronegative people with and without SARS-CoV-2 infection (Abstract 722). They found that although people with HIV were more likely to report long COVID at 2 months following infection, this was not the case at 4 to 6 months. They identified a negative correlation between cortisol and post-acute memory problems, and positive correlations between C5a, TIM-3, and TGF-beta levels, and pain, anxiety, and muscle aches, respectively. Dziarski and colleagues performed detailed neurocognitive testing in the same cohort and observed that differences in neurocognitive scores between people with HIV and people who were HIV seronegative post COVID appeared to be primarily attributable to HIV status (Abstract 495). Similarly, Durstenfeld and colleagues found that exercise capacity measured on cardiopulmonary exercise testing was reduced among people with HIV independent of SARS-CoV-2 infection status or subjective long

COVID symptoms (Abstract 666). Taken together, the data suggest that people with HIV may be at higher risk of post-COVID complications and face at least equivalent risks of developing long COVID, but they are not necessarily at higher risk of persistent long COVID symptoms. Further work will be needed to understand long COVID epidemiology, natural history, and biology in this subpopulation.

PASC in children and adolescents. Several studies addressed manifestations of long COVID in children and adolescents, a population in which this condition has received relatively little attention. Moraleda and colleagues evaluated children at 1 year post hospitalization with a history of multisystem inflammatory syndrome in children (MIS-C), comparing those hospitalized with COVID-19 with those with surgical peritonitis (Abstract 837). They found that symptom frequency was highest in those with MIS-C, and that 88% of children studied following this condition had symptoms at 1 year. The most common symptoms were headache, fatigue, insomnia, and concentration problems. Fatigue and concentration problems were also common among those hospitalized for COVID-19 who did not meet criteria for MIS-C. In contrast, Tagarro and colleagues did not find that symptoms were significantly different in children hospitalized for COVID compared with those hospitalized for other reasons (Abstract 836). The most common symptoms in both groups were fatigue, headache, poor appetite, abdominal pain, and heart rate variability. Longer hospital admission was generally associated with persistent symptoms.

Izquierdo-Pujol and colleagues performed immunophenotyping of peripheral blood mononuclear cells in children with long COVID and compared them with 23 controls who did not experience long COVID symptoms (Abstract 838). They identified differences in memory B-cell populations that suggested viral antigen persistence and differences in CD4+ effector memory T cells re-expressing CD45RA (TEMRA) that could be related to autoimmune phenomena, but they did not find significant differences in levels of 42 biomarkers between groups. Maddaloni and colleagues found potential dysregulation of immune responses in children for up to 6 months post COVID, regardless of long COVID symptoms (Abstract 839). Specifically, they identified overexpression of factors in the NLRP3 inflammasome pathway and suggested that prolonged activation of this pathway might be a driver of long COVID symptoms.

Conclusion

Work presented at CROI 2023 was at the cutting edge of our understanding of SARS-CoV-2, COVID-19, and long COVID. The studies described herein advanced our knowledge of the epidemiology, natural history, pathophysiology, and management of the acute and post-acute phases of SARS-CoV-2 infection and are expected to shape the field over the next several years. 

All cited abstracts appear in the virtual CROI 2023 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 continuing medical education (CME) activities with regard to exposition or conclusion. All financial relationships with ineligible companies for the authors and planners/reviewers are listed below.

Financial relationships with ineligible companies within the past 24 months: Dr Antar reported no financial relationships with ineligible companies (Updated March 21, 2023). Dr Peluso reported consulting income from AstraZeneca and Gilead Sciences, Inc. (Updated March 29, 2023).

Reviewer 1 reported serving as a consultant or receiving advisor fees from Antiva, Assembly Biosciences, Generate Biomedicines, and IGM Biosciences, and receiving fees for participation in review activities, eg, data monitoring boards, statistical analysis, or endpoint adjudication committees with Gilead Sciences, Inc. (Updated March 30, 2023). Reviewers 2 and 3 reported no relevant financial relationships with ineligible companies (Updated April 30, 2023).

All relevant financial relationships with ineligible companies have been mitigated.

Additional References Cited in Text

1. Gao YD, Ding M, Dong X, et al. Risk factors for severe and critically ill COVID-19 patients: a review. *Allergy*. 2021;76(2):428-455. doi:10.1111/all.14657
2. Tenforde MW, Self WH, Gaglani M, et al. Effectiveness of mRNA vaccination in preventing COVID-19-associated invasive mechanical ventilation and death—United States, March 2021–January 2022. *MMWR Morb Mortal Wkly Rep*. 2022;71(12):459-465. doi:10.15585/mmwr.mm7112e1

3. Lewnard JA, McLaughlin JM, Malden D, et al. Effectiveness of nirmatrelvir-ritonavir in preventing hospital admissions and deaths in people with COVID-19: a cohort study in a large US health-care system. *Lancet Infect Dis*. 2023 March 15 (Online ahead of print). doi:10.1016/S1473-3099(23)00118-4
4. Wongvibulsin S, Garibaldi BT, Antar AAR, et al. Development of evere COVID-19 adaptive risk predictor (SCARP), a calculator to predict severe disease or death in hospitalized patients with COVID-19. *Ann Intern Med*. 2021;174(6):777-785. doi:10.7326/M20-6754
5. Buttia C, Llanaj E, Raeisi-Dehkordi H, et al. Prognostic models in COVID-19 infection that predict severity: a systematic review. *Eur J Epidemiol*. 2023;1-18. doi:10.1007/s10654-023-00973-x
6. Bastard P, Rosen LB, Zhang Q, et al. Autoantibodies against type I IFNs in patients with life-threatening COVID-19. *Science*. 2020;370(6515). doi:10.1126/science.abd4585
7. Hammond J, Leister-Tebbe H, Gardner A, et al. Oral nirmatrelvir for high-risk, nonhospitalized adults with COVID-19. *N Engl J Med*. 2022;386(15):1397-1408. doi:10.1056/NEJMoa2118542
8. COVID-19 Treatment Guidelines. Antiviral agents, including antibody products summary recommendations. Accessed May 10, 2023. <https://www.covid19treatmentguidelines.nih.gov/therapies/antivirals-including-antibody-products/summary-recommendations/>
9. Bramante CT, Huling JD, Tignanelli CJ, et al. Randomized trial of metformin, ivermectin, and fluvoxamine for COVID-19. *N Engl J Med*. 2022;387(7):599-610. doi:10.1056/NEJMoa2201662
10. Xian H, Liu Y, Rundberg NA, et al. Metformin inhibition of mitochondrial ATP and DNA synthesis abrogates NLRP3 inflammasome activation and pulmonary inflammation. *Immunity*. 2021;54(7):1463-1477. doi:10.1016/j.immuni.2021.05.004
11. Watson OJ, Barnsley G, Toor J, Hogan AB, Winskill P, Ghani AC. Global impact of the first year of COVID-19 vaccination: a mathematical modelling study. *Lancet Infect Dis*. 2022;22(9):1293-1302. doi:10.1016/S1473-3099(22)00320-6
12. Bobrovitz N, Ware H, Ma X, et al. Protective effectiveness of previous SARS-CoV-2 infection and hybrid immunity against the omicron variant and severe disease: a systematic review and meta-regression. *Lancet Infect Dis*. 2023;23(5):556-567. doi:10.1016/S1473-3099(22)00801-5
13. Mathieu E, Ritchie H, Ortiz-Ospina E, et al. Coronavirus (COVID-19) vaccinations. *Our World in Data*. Accessed May 10, 2023. https://ourworldindata.org/covid-vaccinations?country=OWID_WRL
14. Kunyenje CA, Chirwa GC, Mboma SM, et al. COVID-19 vaccine inequity in African low-income countries. *Front Public Health*. 2023;11:1087662. doi:10.3389/fpubh.2023.1087662
15. Douaud G, Lee S, Alfaro-Almagro F, et al. SARS-CoV-2 is associated with changes in brain structure in UK Biobank 1. *Nature*. 2022;604(7907):697-707. doi:10.1038/s41586-022-04569-5

16. Su Y, Yuan D, Chen DG, et al. Multiple early factors anticipate post-acute COVID-19 sequelae. *Cell*. 2022;185(5):881-895. doi:10.1016/j.cell.2022.01.014
17. Nalbandian A, Sehgal K, Gupta A, et al. Post-acute COVID-19 syndrome. *Nat Med*. 2021;27(4):601-615. doi:10.1038/s41591-021-01283-z
18. Peluso MJ, Deeks SG. Early clues regarding the pathogenesis of long-COVID. *Trends Immunol*. 2022;43(4):268-270. doi:10.1016/j.it.2022.02.008
19. Wulf-Hanson S, Abbafati C, Aerts JG, et al. Estimated global proportions of individuals with persistent fatigue, cognitive, and respiratory symptom clusters following symptomatic COVID-19 in 2020 and 2021. *JAMA*. 2022;328(16):1604-1615. doi:10.1001/jama.2022.18931
20. Perlis RH, Santillana M, Ognyanova K, et al. Prevalence and correlates of long COVID symptoms among US adults. *JAMA Netw Open*. 2022;5(10):e2238804. doi:10.1001/jamanetworkopen.2022.38804
21. Zhang H, Zang C, Xu Z, et al. Data-driven identification of post-acute SARS-CoV-2 infection subphenotypes. *Nat Med*. 2023;29(1):226-235. doi:10.1038/s41591-022-02116-3
22. Peluso MJ, Kelly JD, Lu S, et al. Persistence, magnitude, and patterns of postacute symptoms and quality of life following onset of SARS-CoV-2 infection: cohort description and approaches for measurement. *Open Forum Infect Dis*. 2022;9(2):ofab640. doi:10.1093/ofid/ofab640
23. Kenny G, McCann K, O'Brien C, et al. Identification of distinct long COVID clinical phenotypes through cluster analysis of self-reported symptoms. *Open Forum Infect Dis*. 2022;9(4):ofac060. doi:10.1093/ofid/ofac060
24. Davis HE, McCorkell L, Vogel JM, Topol EJ. Long COVID: major findings, mechanisms and recommendations. *Nat Rev Microbiol*. 2023;21(3):133-146. doi:10.1038/s41579-022-00846-2
25. Swank Z, Senussi Y, Manickas-Hill Z, et al. Persistent circulating severe acute respiratory syndrome coronavirus 2 spike is associated with post-acute coronavirus disease 2019 sequelae. *Clin Infect Dis*. 2023;76(3):e487-e490. doi:10.1093/cid/ciac722
26. Giron LB, Peluso MJ, Ding J, et al. Markers of fungal translocation are elevated during post-acute sequelae of SARS-CoV-2 and induce NF-kappaB signaling. *JCI Insight*. 2022;7(15):160989. doi:10.1172/jci.insight.160989
27. Peluso MJ, Sans HM, Forman CA, et al. Plasma markers of neurologic injury and inflammation in people with self-reported neurologic postacute sequelae of SARS-CoV-2 infection. *Neurol Neuroimmunol Neuroinflamm*. 2022;9(5):e200003. doi:10.1212/NXI.0000000000200003
28. Gold JE, Okyay RA, Licht WE, Hurley DJ. Investigation of long COVID prevalence and its relationship to Epstein-Barr virus reactivation. *Pathogens*. 2021;10(6):10060763. doi:10.3390/pathogens10060763
29. Peluso MJ, Deveau TM, Munter SE, et al. Chronic viral coinfections differentially affect the likelihood of developing long COVID. *J Clin Invest*. 2023;133(3):163669. doi:10.1172/JCI163669
30. Chang SE, Feng A, Meng W, et al. New-onset IgG autoantibodies in hospitalized patients with COVID-19. *Nat Commun*. 2021;12(1):5417. doi:10.1038/s41467-021-25509-3
31. Roessler M, Tesch F, Batram M, et al. Post-COVID-19-associated morbidity in children, adolescents, and adults: a matched cohort study including more than 157,000 individuals with COVID-19 in Germany. *PLoS Med*. 2022;19(11):e1004122. doi:10.1371/journal.pmed.1004122
32. Pretorius E, Venter C, Laubscher GJ, et al. Prevalence of symptoms, comorbidities, fibrin amyloid microclots and platelet pathology in individuals with long COVID/post-acute sequelae of COVID-19 (PASC). *Cardiovasc Diabetol*. 2022;21(1):148. doi:10.1186/s12933-022-01579-5
33. Peluso MJ, Deeks SG, Mustapic M, et al. SARS-CoV-2 and mitochondrial proteins in neural-derived exosomes of COVID-19. *Ann Neurol*. 2022;91(6):772-781. doi:10.1002/ana.26350
34. Peluso MJ, Spinelli MA, Deveau TM, et al. Post-acute sequelae and adaptive immune responses in people with HIV recovering from SARS-CoV-2 infection. *AIDS*. 2022;36(12):F7-F16. doi:10.1097/QAD.0000000000003338

Top Antivir Med. 2023;31(3):493-509.

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*Invited Review***CROI 2023: Epidemiology, Diagnosis, and Management of Mpox****Jason Zucker, MD**

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Abstract. *The 2023 Conference on Retroviruses and Opportunistic Infections (CROI) emphasized emerging infectious diseases such as COVID-19 and mpox. Despite emerging from countries in which it was endemic only 9 months before the conference, mpox was well covered, with more than 60 presentations addressing various topics. There was a focus on the rapid development and implementation of tests to reduce the time to diagnosis, as well as multiplex panels to increase the accuracy of differential diagnosis. Presenters also highlighted the ability to diagnose mpox from multiple compartments, such as with rectal and pharyngeal swabs, and provided crucial information on the duration of positivity that may impact isolation requirements. Clinical experiences were described, including risk factors for severe disease and syndemic management. High rates of concomitant sexually transmitted infection (STI) were reported. Finally, prevention was a key topic, with presenters pointing to the contributions of individual behavioral changes and vaccine efficacy to reducing new cases.*

Keywords: mpox, testing, vaccination, prevention, modified vaccinia Ankara, monkeypox virus, MVA, tecovirimat

In 2022, mpox, formerly a disease endemic to West and Central Africa, quickly spread to more than 100 countries worldwide, resulting in more than 85,000 cases. At the 2023 Conference on Retroviruses and Opportunistic Infections (CROI), Brooks from the Centers for Disease Control and Prevention opened a special session

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on the mpox outbreak by providing an overview of the current understanding of the disease (Abstract 39). He emphasized the strong evidence suggesting sexual transmission among gay, bisexual, and other men who have sex with men (gbMSM) and cited recent literature indicating transmission up to 4 days before symptom

Epidemiology plays a vital role in managing emerging infectious diseases by providing insights into strategies for diagnosing, managing, controlling, and preventing disease

onset. Brooks also noted the rapid and significant decline in mpox cases, due partly to behavioral changes, and early data on vaccine effectiveness.

Brooks closed his presentation by emphasizing that there is still much to learn about mpox; mpox remains a public health threat worldwide and it is crucial to continue monitoring the situation closely for a possible resurgence. Finally, better understanding and management of this emerging infectious disease will require the completion of randomized clinical trials of possible treatments, increased vaccination among individuals with a higher likelihood of disease acquisition, and establishment of the durability of immunity from vaccination and natural infection.

Mpox Epidemiology

Epidemiology plays a vital role in managing emerging infectious diseases by providing insights into strategies for diagnosing, managing, controlling, and preventing disease. Stored samples can provide clues to when outbreaks start and how disease spreads. For example, the Netherlands reported its first mpox case on May

10, 2022; however, the impact of undiagnosed prior infection was unknown. Hoornenborg and colleagues presented data from analysis of stored anorectal samples positive for gonorrhea or chlamydia from 2 large sexual health centers in the Netherlands (Abstract 897). They retrospectively tested samples from February 14 to May 18, 2022; among 401 samples, only 2 samples from the first week of May were positive for monkeypox virus (MPXV). This timing coincides with the appearance of the first cases across Europe, suggesting that the outbreak expanded quickly and highlighting how quickly disease can spread within sexual networks.

The 2022 mpox outbreak primarily affected adult gbMSM, with a small number of cases occurring in women and children. During the session on epidemiology and prevention of mpox and SARS-CoV-2 infection, Sachdev and colleagues presented work on determining the rate of transmission of mpox to pediatric household contacts (children aged <16 years) in California using contact tracing data (Abstract 209). They identified 79 index cases with 129 total contacts, of whom 18 developed symptoms and 6 were confirmed or presumed positive. Among the 6 pediatric patients, the overall secondary attack rate was 4.7%, but all of the pediatric patients were under age 10 years, and the secondary attack rate of children under age 10 years was 7.1%. Only 14% of contacts received postexposure prophylaxis. Among those who received it, there were no infections. Factors associated with household transmission included delayed diagnosis of the index cases and lack of prevention precautions at home. Crucially, no tertiary transmission was identified among children attending day care while symptomatic. These data, which are consistent with the results of previous African studies, provide crucial details about the risk of household exposure and the potential benefit of postexposure prophylaxis.¹ This information can also constitute the foundation of an evidence base for day care centers and schools developing exposure protocols.

The spread of mpox was characterized by rapid expansion and then a rapid decline in cases. At CROI, the underlying factors contributing to this decline were explored in several sessions. Panovska-Griffiths and colleagues identified the time elapsed between symptom onset and diagnosis as a crucial variable in modeling the rapid decline of mpox (Abstract 925). Using data from the United Kingdom to model the mpox outbreak, they quantified the impact of delayed diagnosis on disease transmission dynamics. Their analysis revealed a significant decrease in the average delay from symptom onset to presentation for health care, from 22 days in

May 2022 to 7 days by August 2022. Further, they demonstrated that the rapid decline in cases might be partly attributable to improved diagnostic practices, highlighting the importance of timely and accurate diagnosis in public health emergencies.

Ghosn presented data on MPXV sequence diversity in Paris (Abstract 236). They sequenced samples from 148 individuals with mpox and compared the epidemic isolates with reference strains (preepidemic strains). They found 32 mutational patterns, including epidemic strain-specific mutational patterns. One profile closely resembled the clade III preepidemic viruses in a patient returning from Asia, suggesting the ongoing introduction of nonepidemic mpox and highlighting the need to continue considering mpox in the differential diagnosis outside of the current outbreak.

Mpox Diagnosis

Diagnostic Developments

Timely and accurate diagnosis is essential in disease outbreaks to enable public health officials to track the spread of the disease and implement appropriate control measures. However, one of the earliest challenges in the mpox outbreak was the limited availability of diagnostic testing. To address these challenges, sites developed local diagnostics with unique and improved performance characteristics.

Kagan and colleagues reported on the development of a single test that can simultaneously detect orthopoxvirus (OPXV) and MPXV in lesion specimens (Abstract 955). The test had excellent performance, with 100% detection and 100% specificity among unrelated pathogens, and could detect MPXV at levels as low as 100 copies/mL. However, in 9 cases samples were OPXV positive and MPXV negative, and subsequent sequencing revealed a *crmB* gene deletion that removed the MPXV probe target region.² By including 2 targets in a single well, their test improved throughput by avoiding tiered testing, thus increasing capacity, and simultaneously preventing missed diagnoses caused by genomic deletions.

Obermeier and colleagues described the rapid development of a multiplex polymerase chain reaction (PCR) assay targeting both OPXV and MPXV (Abstract 954). This locally created assay was developed by the end of May 2022, early in the outbreak. It could detect MPXV in skin lesions and from genital, rectal, and oropharyngeal swabs. The assay demonstrated excellent performance, and despite the receipt of more than 2000 samples, 95%

were tested within 24 hours. The development of rapid diagnostic tools is critical for clinicians asking patients to isolate while awaiting results and facilitates the implementation of public health interventions to prevent the propagation of outbreaks.

Diagnostic Dilemmas

The US Food and Drug Administration has approved only tests using samples from lesional swabs. However, several case reports have indicated that patients may have positive mucosal swabs (rectum and pharynx) without skin lesions and sometimes without any symptoms.³⁻⁵ Matic and colleagues showed that viral loads were

Timely and accurate diagnosis is essential in disease outbreaks to enable public health officials to track the spread of the disease and implement appropriate control measures

highest in skin lesions, particularly genital lesions, and rectal swabs, using cycle threshold (Ct) values (Abstract 953). Urine, throat, whole blood, and nasopharyngeal swabs frequently had detectable virus, but with higher Ct values (lower estimated viral loads) than with skin lesion swabs, although Ct values were still consistent with possible infectivity.⁶ Hoornenberg presented data from the Amsterdam Centre for Sexual Health showing lower Ct values from lesion and rectal swabs than from throat swabs (Abstract 911). However, in the experience of Matic and colleagues, submitting multiple specimen types did not improve diagnostic yield when skin lesions were present (Abstract 953). These findings suggest that nonlesion swabs may provide important diagnostic information for patients without skin lesions. Furthermore, the elevated viral loads on genital lesion and rectal swabs support the hypothesis that sexual transmission was a significant driver of the recent outbreak.

Diagnostic Testing and Duration of Infection

Testing for mpox is critical for monitoring viral shedding, which can provide valuable information about the duration of infection. In a cohort of 21 patients tested longitudinally, Tan and colleagues investigated the weekly shedding of MPXV (Abstract 292). They found that 95% of rectal swabs and 76% of semen samples

were PCR positive at the final sampling time point (median, 34.5 days). In an observational study, Lescure and colleagues found that some patients had PCR-positive samples after day 14, including in 30% of rectal samples, even when symptoms and active lesions had already resolved (Abstract 737). Although further analysis is needed to correlate detectable DNA with infectivity, these findings suggest that infectivity could persist even after skin lesions have completely healed. Larger samples, viral cultures, and contact tracing studies are necessary to better define the duration of infectivity, which can guide public health recommendations and help clinicians counsel patients on when it is safe to resume sexual activity.

Mpox Clinical Presentations and Management

Missed Opportunities

Diagnostic testing is beneficial only if patients and practitioners recognize the need for testing during a patient encounter. Ogale and colleagues analyzed a cross-sectional online survey called the American Men's Internet Survey (AMIS), focusing on gbMSM (Abstract 950). Of the 842 individuals surveyed in the mpox supplement released in August 2022, forty-seven of 52 gbMSM with recent rash and HIV and sexually transmitted infection (STI) testing did not undergo mpox testing. This worrisome finding was common in older participants (>40 years of age), individuals living in the South, non-Hispanic White individuals, those without HIV, those with more than 2 sex partners, and those engaging in condomless anal sex. Atkins and colleagues identified barriers to testing in the same AMIS survey, including low self-testing efficacy, lack of knowledge of testing sites, inconvenient hours, and high testing costs (Abstract 951). Most individuals seeking care with symptoms consistent with mpox did not undergo testing, indicating the urgent need for increased awareness and access to mpox testing. These studies highlight the need to integrate mpox testing with HIV and STI testing. Disparities in mpox testing mirror those of other epidemics, emphasizing the need for targeted efforts and mpox-neutral approaches.

An mpox-neutral approach can be facilitated by use of a multiplex panel to routinely test for infection when screening individuals for ulcerative diseases. Titanji presented a promising solution involving a novel multiplex PCR assay that can detect MPXV, herpes simplex virus, and varicella zoster virus in clinical specimens (Abstract

952). Use of this panel can help identify coinfections during mpox outbreaks and detect cases early, when the infection is not initially considered. The assay is easy to use, rapid, and reliable and may improve the overall diagnosis and management of vesicular and ulcerative lesions.

Mpox Clinical Presentations

The results of several studies also supported and expanded on the finding that individuals with untreated or uncontrolled HIV are at a higher risk of complications and severe or fatal mpox

Orkin presented a highly discussed global case series that sheds light on the impact of mpox on individuals with HIV and CD4+ counts less than 350 cells/ μ L (Abstract 173). The study gathered data from 19 countries using a standardized case report form and included 382 participants. The results revealed a 30% mortality rate among individuals with a CD4+ count less than 100 cells/ μ L and a viral load greater than 10,000 copies/mL ($4 \log_{10}$ copies/mL). Additionally, participants with a CD4+ count less than 200 cells/ μ L experienced more complications, including severe necrotizing lesions, disseminated infection (including pulmonary nodules), and secondary bacterial infections. The findings suggest that mpox in people with HIV who have low CD4+ counts and elevated viral loads can be a severe, disfiguring, and life-threatening opportunistic infection that should be considered an AIDS-defining illness. These results underscore the importance of making vaccination available to those at greatest risk of severe complications and developing studies of specific antiviral agents in this population. This work was published in *Lancet* concurrently with the presentation.⁷

The results of several studies also supported and expanded on the finding that individuals with untreated or uncontrolled HIV are at a higher risk of complications and severe or fatal mpox. Garcia and colleagues described and provided graphic images for a case series from New York City of 11 patients with HIV with low CD4+ counts (median, 30 cells/ μ L; range, 3-153 cells/ μ L) who presented with severe manifestations including burnlike

lesions, globe collapse, airway edema, and gastrointestinal ulcers and bleeding (Abstract 735). Although time to antiviral therapy was not reported, most of these patients received several antiviral therapies and despite those efforts, had a median hospitalization length of 57 days, with a 45% mortality rate.

Cholli and colleagues found that CD4+ count less than 200 cells/ μ L was the most common risk factor for severe or fatal mpox in the US (Abstract 912). Silva and colleagues demonstrated a similar finding in Brazil (Abstract 905). All patients with severe complications had HIV, and all patients with a CD4+ count less than 200 cells/ μ L required hospitalization. Similarly, Garneau and colleagues demonstrated that in Baltimore, individuals with a CD4+ count less than 350 cells/ μ L had higher odds of hospitalization (odds ratio, 29; 95% CI, 3.95-213) and reported that patients hospitalized with mpox often required surgical evaluation and had an increased mortality rate (Abstract 907). These findings were consistent with the work of Philpott and colleagues, which showed individuals with a CD4+ count less than 350 cells/ μ L (relative risk, 3.2; 95% CI, 2.1-5.1) and those not actively engaged in care to have higher rates of hospitalization (relative risk, 2.4; 95% CI, 1.3-4.2) (Abstract 903).

Vaidya and colleagues found that in California, individuals with unsuppressed viral loads and low CD4+ counts were more likely to be hospitalized for mpox if they lived in areas with limited access to a healthy lifestyle based on the Healthy Places Index (Abstract 902). Similarly, Corma-Gomez and colleagues found that patients with uncontrolled HIV, as indicated by a viral load greater than 1000 copies/mL, had higher rates of severe mpox using a composite outcome of severe disease (Abstract 904). Aldred and colleagues also showed that individuals with a viral load greater than 200 copies/ μ L had a higher rate of hospitalization and more

At the onset of the outbreak, mpox was observed to have high rates of coinfection with STIs

frequent complications in Atlanta (Abstract 906). Taken together, these findings highlight the importance of improving public health strategies designed to improve the HIV care continuum and help more patients with HIV access services, treatment, and vaccination.

The studies reported above used various outcomes and composite outcomes to describe the “severity” of

mpox infection without a standardized clinical severity score. Standardized clinical severity scores facilitate quantitative comparison of disease severity between groups of patients to illuminate factors associated with severe illness and facilitate evaluation of interventions and treatment efficacy. Zucker and colleagues presented their development and pilot testing of an mpox severity scoring system (MPOX-SSS) (Abstract 738). An iteratively developed 7-element score could be calculated retrospectively for 172 of 200 patients. They found higher scores in patients treated with tecovirimat, those with a CD4+ count less than 200 cells/ μ L, and those who presented more than 3 days after symptom onset. The score showed change over time in a subset of patients. The tool has potential usefulness for evaluating treatment options but requires further validation in more extensive observational and randomized clinical trials.

Mpox and Coinfections

At the onset of the outbreak, mpox was observed to have high rates of coinfection with STIs. Management of these overlapping outbreaks, known as syndemic management, can improve overall health outcomes.

Polk and colleagues described the implementation of a protocol for coinfection testing in a large integrated health care system that included HIV testing at the time of mpox testing in 17 emergency departments and 44 urgent care centers (Abstract 944). This protocol increased HIV testing (from 2.3 to 3.8 tests per 1000 visits; $P = .01$) and new diagnoses (from 1.4 to 3.9 new HIV diagnoses per month; $P = .02$), and 27 of 41 patients newly diagnosed with HIV during this period had concurrent mpox testing. These results highlight the potential benefits of decision support interventions that can increase testing for HIV in an outbreak setting.

In Texas, Monterosso and colleagues used mpox reporting to identify individuals with undiagnosed HIV or lost to follow-up from HIV care, allowing them to confirm their status and receive expedited care services (Abstract 895). Their work demonstrates the potential synergy between HIV services and mpox testing and treatment and the importance of innovative data-to-care initiatives in ending the HIV epidemic.

In London, Girometti and colleagues reported that concurrent STI rates were 31% among individuals with HIV and mpox attending a sexual health clinic (Abstract 736). In Denver, in a case-control study of patients tested for OPXV, Carlson and colleagues found that patients who tested positive were more likely to have had an STI in the preceding year or 6 months or to have one

concurrently at the time of diagnosis (Abstract 1033). Niehaus and colleagues reported that at the Duke University Health System, most patients who were tested for mpox did not receive comprehensive STI testing but that rates of STI positivity were high when it was performed (Abstract 1035). They emphasized the need for improved STI screening in individuals being screened for mpox and suggested that an electronic medical record order set may be one strategy to improve comprehensive STI testing. These abstracts further support the need for syndemic management, ensuring that facilities offer and perform concurrent HIV, STI, and mpox testing.

Mpox Treatment

During the special session on mpox, Issacs discussed molecular pathogenesis and therapeutic targets (Abstract 40). He described the unique replication cycle of MPXV, which replicates entirely in the cytoplasm of the cell, unlike most DNA viruses, which replicate in the nucleus. He discussed the relationship between the current outbreak strain and the strain in Nigeria in 2017, highlighting missed opportunities to get ahead of this outbreak. He described mutational differences that may explain the virulence differences between the clade I and clade II viruses. He also reviewed the limited data on mpox therapeutics, including vaccinia immunoglobulin, DNA polymerase inhibitors cidofovir and brincidofovir, and tecovirimat, a novel viral protein inhibitor. Issacs emphasized that tecovirimat, which results in an attenuated virus that spreads poorly, still requires the immune system to clear the virus. Furthermore, tecovirimat has a low barrier to resistance, with a single nucleotide change leading to resistance. Combined, these 2 factors may explain why we continue to see such severe disease in immunocompromised patients despite treatment.

Regarding antiviral treatment, human data on the efficacy of tecovirimat are limited. Yazdanpanah presented an observational study of 122 patients, 21 of whom received tecovirimat (Abstract 737). They found that patients receiving tecovirimat were less likely to have lesion resolution by day 14, and that one-third of the patients treated with tecovirimat still had active lesions or complications on day 28. However, this finding was confounded by the fact that tecovirimat was more likely to be administered to patients who presented with complications or more severe disease and those who were admitted to the hospital, consistent with guidelines.

Mpox Treatment Equity

One challenge to achieving equity in mpox treatment is the use of investigational drugs that require treatment

equity, it is essential to ensure that services are available in safety-net clinics and that all eligible patients are offered treatment. Karmarkar and colleagues reviewed 465 cases of mpox in a safety-net sexual health clinic in King County, Washington (Abstract 913). Of the 404 patients with treatment data, 77% received tecovirimat, with no significant differences observed among race and ethnicity categories. However, the proportion of patients who received tecovirimat varied depending on the diagnosis site, with clinics with fewer resources being less likely to prescribe tecovirimat.

The rapid rise and fall of the mpox outbreak has sparked discussion of how the outbreak was successfully contained and the lessons learned for managing future emerging infectious diseases

Another strategy to improve equity in the treatment of mpox is using telehealth services to provide access to tecovirimat. Mgbako and colleagues demonstrated the effectiveness of a telehealth model in providing tecovirimat access to patients when prescriber capacity was limited (Abstract 1102). As of August 2022, the telehealth model had provided tecovirimat to 69 patients, who constituted 83% of all patients treated at their site. However, although the telehealth model improved access for some patients, telehealth was not available to patients without a smart device. Furthermore, despite the high prevalence of STI (and HIV) coinfection in individuals with mpox, as previously highlighted, 40% of patients did not receive any STI testing in this telehealth model.

Mpox Immunology

Benet and colleagues studied outpatients diagnosed with mpox during the 2022 outbreak in Barcelona, Spain (Abstract 378). The aim of the study was to evaluate the time from symptom onset to viral DNA clearance and disease severity by analyzing antibody responses. Samples were collected at diagnosis and weekly for 1 month, and then at 91 and 180 days. The authors found that 90% of participants had detectable levels of IgG, and the breadth of IgG titers between people with and

without HIV was similar. A rapid and strong polyclonal response was associated with milder presentations and a shorter time to viral clearance. However, individuals with HIV had lower and less durable IgG responses at 21 and 91 days after mpox diagnosis, with many patients losing their IgG response. This loss of IgG after infection may put individuals with HIV at increased likelihood of reinfection, highlighting the need to reconsider vaccination policies for people with HIV after infection.

Mpox Prevention

The rapid rise and fall of the mpox outbreak has sparked discussion of how the outbreak was successfully contained and the lessons learned for managing future emerging infectious diseases. Research on the strategies implemented, such as individual behavioral change, vaccination, and immunity, was presented at CROI 2023. By studying the trajectory of the mpox outbreak, we can better prepare for and respond to future outbreaks of mpox as well as other emerging infectious diseases.

Behavioral Changes

During the special session on mpox, Brooks highlighted the AMIS, which reported that gbMSM were taking proactive measures to protect themselves and their partners from mpox (Abstract 39). These measures included a 48% reduction in sexual partners, a 50% reduction in one-time sexual encounters, and a 49% reduction in sex with partners met on mobile apps or in sex venues. Phillips and colleagues corroborated these findings in their study of individuals living in Illinois (n = 469) that drew on the Keeping it LITE trial, which examined factors associated with HIV infection in young adults (Abstract 898). Notably, a greater proportion of participants (68%) reduced their number of sexual partners than in the AMIS. Additionally, individuals used 2 unique strategies to protect themselves: reducing sexual activity and using protection methods such as having sex with their clothes on. These findings underscore the importance of harm reduction methods over abstinence-only messaging in promoting safer sexual behavior during outbreaks. Although similar findings were reported in the United States, Rossotti and colleagues conducted a study comparing the sexual behaviors of 435 users of preexposure prophylaxis before and during the mpox outbreak in Italy (Abstract 899). Surprisingly, most participants did not alter the frequency of their sexual activity, the number of sexual partners, or the use of condoms, and only a minority of participants (26%) received 2 doses of vaccine. Nevertheless, the outbreak decreased dramatically in Italy,

leading the authors to hypothesize that factors such as the saturation of priority groups or hesitance to get tested and face mandatory quarantine measures may have played a role in the rapid decline of cases.

Vaccination

As widespread mpox vaccination is relatively new, it is essential to measure the effectiveness and durability of vaccination. Moreover, with the US Food and Drug Administration's Emergency Use Authorization for administering pediatric vaccination and intradermal doses for adults, knowing the vaccine's short- and long-term efficacy and safety is of utmost importance. Although

Although data are now accruing, the rapid onset of the mpox outbreak led policymakers to make decisions based on limited data

studies are ongoing, early data presented at CROI show promise for the role of vaccination in preventing or stopping future mpox outbreaks.

During the special session on the mpox virus outbreak, Frey discussed the history of vaccination from smallpox to mpox, including the development of modified vaccinia Ankara (MVA) (Abstract 41). She explained the differences between smallpox and mpox and the risks associated with replicating vaccines, such as accidental spread and serious complications. She highlighted the benefits of the MVA vaccine, which does not replicate and produce infectious virus. These benefits include safety and 100% seroconversion after the second dose with neutralizing antibodies that are non-inferior to those of live attenuated replicating virus. Frey also discussed the potential of intradermal injection, showing that the lower intradermal dose was immunologically noninferior to the subcutaneous dose, though associated with more erythema and induration. Finally, she reviewed the early data suggesting that mpox incidence estimates were higher among the unvaccinated than among those who received the vaccine. For those receiving 2 doses of the vaccine, the incidence rate ratio was 9.6 (95% CI, 6.9-13.2), with no difference between subcutaneous and intradermal administration.

Although data are now accruing, the rapid onset of the mpox outbreak led policymakers to make deci-

sions based on limited data. One of the earliest decisions was to pursue dose-sparing strategies for MVA vaccination without evidence of vaccine efficacy. As vaccine efficacy data were limited, modeling became a critical tool with which to evaluate potential efficacy and scenarios using dose-sparing strategies. Dimitrov and colleagues simulated high and low vaccine efficacy of fractional dose vaccine effectiveness (Abstract 1002). They found that in the context of a limited vaccine supply, as long as the fractional dose vaccination retains moderate effectiveness, there is a net benefit to providing smaller intradermal doses to more people over full subcutaneous doses to fewer people. These findings support the decision made in many countries and jurisdictions.

Vaccine Effectiveness

During the session on epidemiology and prevention of mpox and SARS-CoV-2 infection, Titanji and colleagues offered valuable insights into vaccine effectiveness (Abstract 207). Currently the evidence on vaccine effectiveness is limited to a World Health Organization survey in 1988 that estimated first-generation vaccine efficacy at 85% and a recent UK Health Security Agency study that suggested an efficacy of 78% after the first dose; a Centers for Disease Control and Prevention study indicated that unvaccinated individuals had a 10-fold greater likelihood of mpox infection. Titanji conducted a retrospective, test-negative case-control study among US military personnel (2003-2017) to investigate the effectiveness of the mpox vaccine. Among 1007 military personnel tested for nonvariola orthopox virus, 21% had prior smallpox vaccination with a median time from vaccination of 13 years, and 30% (298) tested positive. They estimated a vaccine effectiveness of 66% for first-generation smallpox vaccines and 72% for second-generation smallpox vaccines. Although the study population was unique, with a reliable data source, it relied on prior and older vaccinia vaccinations.

During the same session, Ghosn shared data from the DOXYVAC (Combined Prevention of Sexually Transmitted Infections in Men Who Have Sex With Men and Using Oral Tenofovir Disoproxil Fumarate/Emtricitabine for HIV Pre-Exposure Prophylaxis) trial, which was conducted to evaluate the impact of doxycycline for postexposure prophylaxis and meningitis B vaccine for gonorrhea prevention in individuals at increased likelihood of STIs (Abstract 208). Among the 472 study participants, there were 77 cases of mpox. Mpox was more likely to occur in younger participants, those with more sexual partners, those engaging in condomless

anal intercourse, and those who did not receive vaccination for smallpox during childhood. After vaccination was recommended, the incidence rate of mpox decreased significantly, with an incidence rate ratio of 0.010. However, multivariate analysis showed that although the number of individuals having more than 10 sexual partners in the preceding 3 months decreased after the outbreak, this change in sexual behavior had a limited impact on mpox incidence in this population.

Vaccine Immunology

At the onset of the mpox outbreak, the availability of the MVA vaccine was severely restricted, and several countries opted for a dose-sparing approach, employing intradermal dosing to increase the number of doses available. Before this outbreak, there was limited information on the efficacy of the dose-sparing approach. Although a National Institutes of Health–funded study on this strategy is ongoing, several researchers presented preliminary findings at CROI 2023.

Mazzotta and colleagues evaluated the immune response to MVA vaccination, reporting on the first dose response to subcutaneous versus intradermal dosing (Abstract 375). In a population in which most people (81%) received intradermal dosing, intradermal dosing was associated with a higher rate of systemic and local self-reported adverse events; however, intradermal dosing was also associated with an elevated immunologic response, including elevated levels of IgG and neutralizing antibodies. Although humoral immunity is essential to vaccine effectiveness, T cell responses are also important. Mazzotta and colleagues also examined humoral and T cell responses after MVA vaccination, comparing responses among individuals with and without HIV and those with and without prior smallpox vaccination (Abstract 374). The first dose of MVA vaccination elicited a humoral response that was more robust in those individuals who had previously been vaccinated for smallpox and greater in those who did not have HIV. In fact, among people with HIV, less than half seroconverted after the first shot. On the other hand, the T cell responses were diminished in those with prior smallpox vaccination. These findings strongly suggest that all patients, regardless of prior vaccination or HIV status, would benefit from at least a 2-shot vaccination series. Although this study describes only responses up to 4 weeks after the last dose, longer follow-up is needed to understand the long-term durability of humoral and cellular immune responses to vaccination.

To better understand the impact of hybrid routes of immunization, it is important to investigate the effects

of switching to intradermal dosing after initial subcutaneous administration of MVA. Moschese and colleagues evaluated the neutralization titers induced by a hybrid vaccination schedule (first dose subcutaneous, second dose intradermal) in 35 patients with available samples at 3 time points: baseline, week 4, and week 12 (Abstract 377). Although all patients had neutralizing antibodies, 29% experienced a decline in titer from 4 weeks after subcutaneous vaccination to 8 weeks after intradermal vaccination. Further research is needed to determine whether this finding is unique to the hybrid vaccination schedule and whether it has any clinical implications.

Oom described the rapid development of an observational mpox vaccine study that started enrolling before the end of July 2022 and has enrolled more than 100 patients to date (Abstract 1001). Among the enrolled

Since the beginning of the mpox vaccination planning, concerns have been raised regarding the inequitable distribution of vaccines, which may result in wider disparities in mpox infection and outcomes

individuals, 58% had received a hybrid vaccination strategy, 24% had received intradermal dosing for both doses, and 20% had a history of prior smallpox vaccination. Although this study is planned to span 3 years and is still early in its course, results of initial analysis are consistent with those reported in other studies presented at CROI, including the finding that individuals with HIV and preserved CD4+ counts respond well to the vaccine and that participants with a history of smallpox immunization have higher antibody titers. The researchers aim to follow the enrolled individuals for up to 3 years, providing insights into the vaccine's immunologic effects over time.

Mpox Serologic Testing

Although serology has limited utility in acute infections, it can be valuable in epidemiologic research. Kurpitz and colleagues developed a novel immunoassay that measures vaccine response and distinguishes between MPXV infection and previous vaccination (Abstract 379). This development has important implications for future epidemiologic studies, which can employ this test to establish the prevalence of MPXV infection and

detect asymptomatic community transmission, particularly in settings where many vulnerable individuals are vaccinated.

Mpox Vaccination Equity


Since the beginning of the mpox vaccination planning, concerns have been raised regarding the inequitable distribution of vaccines, which may result in wider disparities in mpox infection and outcomes. Knowledge and attitudes toward vaccination may influence vaccination rates. In a survey conducted by Castel and colleagues involving 249 people with HIV receiving care at 14 sites in Washington, DC, 90% had heard of mpox (Abstract 1004). Of the 201 people with HIV who had heard of mpox and answered vaccination questions, 21% were vaccinated, 39% planned to be vaccinated, and 39% did not plan to be vaccinated. Notably, young MSM were more likely to be vaccinated than non-MSM and females with HIV. Given the potential for more severe disease in individuals with HIV, this finding suggests that offering education and vaccination to all people with HIV may help avoid inequitable vaccine distribution.

Woodhouse and colleagues reported significant vaccination disparities at a southeastern clinic, where White and privately insured patients were more likely to receive the vaccine than Black and non-privately insured patients, respectively; only one-third of individuals with a recent STI received the vaccine (Abstract 1003). The authors suggested that early flags such as current prior STI status could have alerted practitioners to the need for vaccination. Similarly, Mara and colleagues in San Francisco found that among people without mpox, only 42% of those with HIV and 65% of those using pre-exposure prophylaxis were vaccinated (Abstract 1000). Additionally, Black individuals, transgender women, and people experiencing homelessness were less likely to be vaccinated, highlighting the need for targeted outreach to reduce disparities and ensure equitable vaccine distribution.

Mpox and the Future Research Agenda

In the special session on the mpox outbreak, all of the speakers highlighted the need for future investment in MPXV research, including more genetic sequencing to determine whether any mutations have enhanced human transmission or pathogenesis. There is much to be learned about transmission, including presymptomatic transmission and duration of infectivity from different compartments. Treatment including evidence-based

supportive care options, the effectiveness of tecovirimat during this outbreak, and the roles of vaccinia immunoglobulin, cidofovir, and brincidofovir all require further study. Finally, further research on the MVA vaccine used in this outbreak is needed to better understand vaccine efficacy, durability, and effectiveness.

To help answer the question of effectiveness, tecovirimat prescribers should consider referring patients to a clinical trial for treatment. In the US, clinicians can refer patients to the STOMP (Study of Tecovirimat for Human Monkeypox Virus) clinical trial,⁹ in the United Kingdom clinicians can refer patients to the PLATINUM (Placebo-Controlled Randomised Trial of Tecovirimat in Non-hospitalised Monkeypox Patients) trial,¹⁰ and in Brazil clinicians can refer patients to the UNITY (Assessment of the Efficacy and Safety of Tecovirimat in Patients With Monkeypox Virus Disease) trial.¹¹ 

Acknowledgments: The author is grateful to Jacob McLean, Shauna Gunaratne, and Joseph Cherabie for their review and feedback.

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Additional References Cited in Text

1. Nolen LD, Osadebe L, Katomba J, et al. Extended human-to-human transmission during a monkeypox outbreak in the Democratic Republic of the Congo. *Emerg Infect Dis.* 2016;22(6):1014-1021. doi:10.3201/eid2206.150579
2. Garrigues JM, Hemarajata P, Lucero B, et al. Identification of human monkeypox virus genome deletions that impact diagnostic assays. *J Clin Microbiol.* 2022;60(12):e0165522. Epub 2022 Nov 29. doi:10.1128/jcm.01655-22
3. Contag CA, Lu J, Renfro ZT, et al. Retrospective screening of clinical samples for monkeypox virus DNA, California, USA, 2022. *Emerg Infect Dis.* 2023;29(4):848-850. Epub 2023 Mar 14. doi:10.3201/eid2904.221576
4. Yakubovsky M, Shasha D, Reich S, et al. Mpox presenting as proctitis in men who have sex with men. *Clin Infect Dis.* 2023;76(3):528-530. doi:10.1093/cid/ciac737
5. Meyerowitz EA, Gendlina I, Desai VJ, et al. Anorectal testing for mpox virus infection in men who have sex with men with and without proctitis. *Clin Infect Dis.* 2023;76(5):934-937. doi:10.1093/cid/ciac825
6. Lim CK, McKenzie C, Deerain J, et al. Correlation between monkeypox viral load and infectious virus in clinical specimens. *J Clin Virol.* 2023;161:105421. Epub 2023 Mar 3. doi:10.1016/j.jcv.2023.105421
7. Mitja O, Alemany A, Marks M, et al. Mpox in people with advanced HIV infection: a global case series. *Lancet.* 2023;401(10380):939-949. Epub 2023 Feb 21. doi:10.1016/S0140-6736(23)00273-8
8. Payne AB, Ray LC, Cole MM, et al. Reduced risk for mpox after receipt of 1 or 2 doses of JYNNEOS vaccine compared with risk among unvaccinated persons—43 U.S. Jurisdictions, July 31–October 1, 2022. *MMWR Morb Mortal Wkly Rep.* 2022;71(49):1560-1564. doi:10.15585/mmwr.mm7149a5
9. STOMP. Study of tecovirimat for human monkeypox virus. Accessed May 10, 2023. <https://www.stompt-pox.org/main>
10. PLATINUM. Placebo-controlled randomised trial of tecovirimat in non-hospitalized monkeypox patients. Accessed May 10, 2023. <https://www.platinumtrial.ox.ac.uk/>
11. ClinicalTrials.gov. Assessment of the efficacy and safety of tecovirimat in patients with monkeypox virus disease (UNITY). Accessed May 10, 2023. <https://clinicaltrials.gov/ct2/show/NCT05597735>

Top Antivir Med. 2023;31(3):510-519.

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