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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

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HIV Care Continuum and Treatment Outcomes

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 several 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 Kroide and colleagues in a cluster randomized study involving 28 maternity health centers in Mozambique and Tanzania (Abstract 132). The 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 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 both patient experience and retention in care.

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 and 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 PLWH 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 the Haitian Study Group on Kaposi's Sarcoma and Opportunistic Infections (GHESKIO), a Haitian 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 measurement 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, another 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 reinitiate ART delivery services, and by June 2022 147,817 individuals were receiving ART in Ahmara. The authors attributed the rapid reinitiation 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 the International Cohort Consortium of Infectious Disease (RESPOND), 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 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 the ARTCC (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 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 Population-based HIV Impact Assessment (PHIA) 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+ 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.

Rebiero 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+ 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 Child Health and Mortality Prevention Surveillance (CHAMPS) 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 most 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. Viguerie 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 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 hepatitis B (Abstract 116). Those treated with TAF/FTC/BIC and with either hepatitis B e 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 coinfected 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 hepatitis B surface antigen [HBsAg] test result <0.05 IU/mL) and those with ongoing HBV infection receiving tenofovir (Abstract 586). They observed greater decreases in HbcrAg 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 HBcrAg 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/μL. 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 Ledinghen 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+ 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 $\log_{10}$ IU/mL achieved SVR12. The median baseline HCV level in those who had virologic failure was 7.3 $\log_{10}$ 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. Silvera 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 MINMON (A Minimal Monitoring Approach for the Treatment of Hepatitis C Virus Infection) (AIDS Clinical Trials Group [ACTG] A5360), 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) 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 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).

Hepatitis C 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.

Rubinstein 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 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 $\log_{10}$ 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 translocation inhibitor. The clinical development of this compound was placed on hold because of drug-associated lymphopenia and CD4+ 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 supratherapeutic 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 hepatitis B, 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+ 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; 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. Obuagu 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 +/- 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 every2 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), teropavimab and zinlirvimab (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 zinlirvimab. 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-naive 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-naive 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 reverse transcriptase inhibitor (NNRTI)–based therapy failed (Abstract 198). This strategy would obviate the concern about nucleoside analogue reverse transcriptase 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 assigned 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 to 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/μL 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/μL, 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+ 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 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 dolutegravir (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 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.

Novitsky 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 reverse transcriptase 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 2FS, 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 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) versus 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 such 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) underwent randomization 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 day (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. 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.

Kiweewa Matovu 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 (ie, 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 Clinical Trials Network (IMPAACT) 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+FTC/TDF arm and 15% in the DTG+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 percentage of risk of adverse pregnancy outcome risk differences mediated by weight change was +31% for DTG+FTC/TAF vs. EFV/FTC/TDF, +11% for DTG+FTC/TAF vs. DTG+FTC/TDF, and -2% for DTG+FTC/TDF vs. EFV/FTC/TDF. These risk differences were similar in the multivariable models after adjusting for baseline gestational age, body mass index, T cell CD4 count, country, and age. The authors concluded that up to one-third of observed differences in adverse pregnancy outcomes between the randomized 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 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 CAB and 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 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 long-acting CAB and RPV in pregnant women, and recommended that prospective clinical trials of LA CAB and 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, 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_{tau}) 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 Concentration at 24 Hours (C_{24}) concentrations were above the BIC protein-adjusted 95% effective concentration value of approximately 0.162 μg/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/µL, baseline estimated glomerular filtration rate of at least 90 mL/min/1.73 m^2, 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 ≥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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