*Invited Review*

# CROI 2021: Advances in Antiretroviral Therapy for HIV and Antiviral Therapy for COVID-19

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*The 2021 Conference on Retroviruses and Opportunistic Infections included advances in therapy for HIV as well as for SARS-CoV-2. Data presented on COVID-19 therapies included trials showcasing the use of monoclonal antibodies for prevention and treatment of COVID-19. Promising new data were presented on lenacapavir, an investigational HIV capsid inhibitor given as a subcutaneous injection every 6 months. Although encouraging data from settings across the globe reported achievement of 90-90-90 HIV care cascade targets, disparities exist in care engagement and viral suppression, particularly for people of color and young people with HIV. Several interventions were associated with improved care cascade outcomes. The COVID-19 pandemic has impacted HIV care engagement, but mitigation strategies can allow programs to continue to serve people with HIV during the pandemic. Studies examining the resistance patterns of existing antiretroviral therapy (ART) agents were presented, as were resistance mechanisms of novel agents such as lenacapavir and resistance patterns among individuals who seroconverted while on preexposure prophylaxis. Data from large observational cohorts were presented on patterns of ART uptake and trends in mortality and in virologic failure. Pertinent findings relating to pediatric and maternal health issues included data on dolutegravir-based ART in children and adolescents with HIV; safety and tolerability of dolutegravir-based ART in children and pregnant women; similarly high maternal viral suppression at 50 weeks postpartum in women receiving certain ART regimens; weight gain in pregnant women receiving dolutegravir plus tenofovir alafenamide/emtricitabine; and viral suppression with dolutegravir-based ART when started during the third trimester of pregnancy.*

**Keywords:** CROI, HIV, lenacapavir, antiretroviral therapy, SARS-CoV-2, COVID-19

## Clinical Trials of Initial Antiretroviral Therapy and Investigational Antiretroviral Agents

### Monoclonal Antibodies for Treatment of COVID-19 and HIV-1

Caskey presented a plenary lecture (Abstract 36) on the technology of broadly neutralizing antibodies (bNAbs) in both HIV-1 and SARS-CoV-2. She outlined how experience with bNAbs in HIV, including the technology, characterization, and engineering, influenced the rapid development of immunotherapy in SARS-CoV-2. Conversely, our accumulating knowledge of the safety, efficacy, and broad implementation of SARS-CoV-2 bNAbs can shape the future direction of this field in HIV. Treatment principles learned from HIV have been borne out in the clinical experience with SARS-CoV-2; for example, the evolution of SARS-CoV-2 variants at specific binding sites suggests this is directly in response to immune pressure. Just as we use combination therapy in HIV to avoid selection of resistance, combination monoclonal antibody (mAb) therapy in SARS-CoV-2 is also recommended to retain efficacy against emerging strains.

Notable differences between HIV and SARS-CoV-2 include the diversity and latency of HIV-1 and the inability to cure HIV-1 with natural infection, which render some of the lessons learned from SARS-CoV-2 inapplicable to future HIV strategies. Caskey reviewed ongoing trials and work with bNAbs in HIV-1 treatment, prevention, and treatment-free remission.

Data regarding mAbs used in prevention and treatment of COVID-19 were presented during session O-6. Cohen and colleagues (Abstract 121) presented data from their phase III, randomized, double-blind, placebo-controlled trial (BLAZE-2), which examined use of bamlanivimab in nursing homes for prevention of COVID-19. The investigators enrolled nursing home residents, high-risk staff, and stratified participants into prevention and treatment populations based on their baseline SARS-CoV-2 status. Median age of all participants was 51.5 to 53.5 years, median age of nursing home residents was 75 to 76 years, and 76% of participants were women.

There was an 80% reduction in risk of symptomatic COVID-19 in nursing home residents who received bamlanivimab (odds ratio [OR], 0.28; $P<$ .001). In terms of prevention of SARS-CoV-2 acquisition of infection, a 76%

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reduction in risk was observed (OR, 0.24; $P<.001$). Viral loads in the bamlanivimab group were lower than those in the placebo group, and reductions in viral load and viral shedding were faster. Ultimately, the investigators concluded that bamlanivimab can prevent SARS-CoV-2 infection and progression of symptomatic COVID-19.

O'Brien and colleagues (Abstract 123) reported on the use of an mAb cocktail consisting of casirivimab and imdevimab for prevention of COVID-19 in a phase III randomized, placebo-controlled study. Enrolled patients were SARS-CoV-2 reverse-transcriptase polymerase chain reaction (RT-PCR) and antibody negative at baseline with an exposure to a household contact with COVID-19. The primary endpoint was SARS-CoV-2 RT-PCR–confirmed infection, either symptomatic or asymptomatic. Median age of enrolled patients was 43 to 45 years, and nearly half were Latinx. Among patients who received casirivimab and imdevimab, there was a 100% reduction of symptomatic infection and a 48% reduction of any infection (symptomatic or asymptomatic). The proportion of patients with high viral loads in the upper respiratory tract was higher in the placebo group than in the treatment group, and patients in the placebo group had a higher total number of weeks with detectable viral RNA. These results suggest that casirivimab and imdevimab were effective in preventing symptomatic SARS-CoV-2 infection in exposed household contacts, as well as in decreasing overall infection rates, viral load, and duration of detectable respiratory tract viremia.

Dougan and colleagues (Abstract 122) presented data on use of bamlanivimab in addition to etesevimab for treatment of COVID-19. In their randomized double-blind, placebo-controlled trial (BLAZE-1), they enrolled high-risk adult patients in the ambulatory setting with mild or moderate COVID-19 within 3 days of SARS-CoV-2 RT-PCR positivity. The primary endpoint was either hospitalization or death due to COVID-19 by day 29. Notably, 29% to 30% of participants were Latinx; more than 75% had mild COVID-19. Mean duration of symptoms was 4 days. The primary endpoint occurred in 2.1% in the treatment group and 7% in placebo group ($P=.0004$), or a 70% reduction in the primary outcome. There were 0 deaths in the treatment arm and 10 deaths in the placebo arm. Investigators also observed decreased viral load by day 7 in the treatment group compared with the placebo group, as well as shorter median time to symptom resolution. They concluded that the combination of 1 dose of bamlanivimab and etesevimab when given early in disease course reduced hospitalizations and deaths related to COVID-19 and decreased viral load and time to symptom resolution.

Kallewaard and colleagues (Abstract 426) examined the effect of genomic variation and variant selection of SARS-CoV-2 and its effect on the activity of neutralizing mAbs. They studied bamlanivimab and etesevimab individually and in combination. They then tested the activity of mAbs against these selected variants. No variants were identified with combination therapy bamlanivimab and etesevimab. Variants E484D/K/Q, F490S, Q493R, and S949P were observed with bamlanivimab alone, and K147N, D420N, and N460K/S/T/Y were observed with etesevimab alone. These mutations were confirmed to have reduced susceptibility to the single mAb agents with at least 50-fold or greater reduction in activity. However, mAb combination therapy effectively neutralized all variants except Q493R. This supports the use of combination mAb therapy for treatment, given its robust effectiveness against variants (and current inability to rapidly assess for variants in clinical settings), as well as lower rates of emergent resistance when used in combination compared with monotherapy.

Turning to HIV, Moldt and colleagues (Abstract 425) presented studies on genotypes and phenotypes with sensitivity to bNAbs. The investigators genotyped *env* sequences and predicted sensitivity to bNAbs with high probability, with a positive predictive value of more than 75%. This holds promise for the ability to target individual viruses for future trials with specific bNAbs.

## Other COVID-19 Therapeutics

Jordans and colleagues (Abstract 124) presented research on a randomized clinical trial of convalescent plasma, of which results are consistent with prior clinical trials showing no beneficial effect of convalescent plasma on mortality[1,2] when not used in early disease.[3] In this open-label randomized clinical trial across 14 hospitals in the Netherlands, investigators examined the effect of convalescent plasma on 60-day mortality. Enrolled patients were hospitalized for COVID-19 (SARS-CoV-2 RT-PCR confirmed within 96 hours); patients who had been mechanically ventilated for longer than 96 hours and those deemed to be terminal or discharged were excluded. The study population was mostly male (72%), with a median age of 63 years and a median duration of symptoms of 10 days. There was no difference in outcome of death (adjusted hazard ratio [aHR], 0.95; $P=.95$). No difference in time to discharge (aHR, 0.88; $P=.68$), effect on viral clearance, change in antibody development, or change in cytokines was observed. Of note, most patients had already developed neutralizing antibodies to SARS-CoV-2 at baseline. The study was terminated early because of lack of benefit.

Gharbharan and colleagues presented 2 case series of convalescent plasma therapy for individuals with COVID-19 who were B-cell depleted from anti-CD20 therapy (Abstracts 391 and 392). There were 5 patients and 23 patients, respectively, in the case series who experienced prolonged symptoms from COVID-19 lasting approximately 26 days. All patients had SARS-CoV-2 detected by PCR and an absent antibody response to SARS-CoV-2. Patients were given convalescent plasma therapy containing neutralizing antibody titers of at least 1:160. In the case series of 5 patients, all experienced clinical improvement and recovered after therapy. Isolation was lifted 4 to 16 days after therapy. In the case series of 23 patients, 20 patients recovered, and 3 patients died. Among survivors, isolation was lifted after a median of 10 days. The investigators suggest that

convalescent plasma therapy should be considered in B-cell–depleted patients with COVID-19 infection.

Olender and colleagues presented combined data from 2 clinical studies of remdesivir compared with standard of care for the treatment of severe COVID-19 disease (Abstract 393). This analysis included 368 patients receiving remdesivir and 1399 patients who were receiving standard of care. Analysis populations were balanced using propensity score matching. Of note, data on concomitant corticosteroid use were not available in these studies. Clinical recovery at day 14 was greater in the remdesivir group than in the standard of care group (65% vs 57%, respectively; $P=.0017$). Mortality through day 28 was lower in the remdesivir group than in the standard of care group (12% vs 16%, respectively; $P=.026$). The mortality benefit was limited to those on low-flow oxygen at baseline (4% vs 13%, respectively; $P=.0005$) with no apparent benefit for those on room air or those receiving high-flow oxygen or invasive mechanical ventilation.

Munoz and colleagues presented interim data from an ongoing, single-arm trial of remdesivir for severe COVID-19 in children aged 18 years or younger (Abstract 617). There were 27 participants included, with a median age of 10 years and a median weight of 34 kg. Participants were hospitalized for a median of 2 days, had experienced COVID-19 symptoms for a median of 3 days, and 67% required supplemental oxygen at baseline. Of participants, 3 (11%) died due to COVID-19 and 2 (8%) discontinued remdesivir early due to adverse events (abnormal liver function tests in both cases). At the end of study follow-up, 82% were discharged from the hospital.

Corritori and colleagues presented data from a retrospective analysis of patients hospitalized with COVID-19 who were treated with favipiravir, an inhibitor of viral RNA polymerase approved for treatment of COVID-19 disease in Russia (Abstract 390). They included 940 patients: 470 patients treated with a 10-day course of favipiravir and 470 treated according to standard of care. Patients were not randomized, and treatment was open-label. Patients treated with favipiravir experienced a faster time to viral clearance compared with placebo (6 days vs 12 days, respectively; $P<.001$) and a faster time to resolution of symptoms (8 days vs 15 days, respectively; $P<.001$). The investigators noted reduced progression to critical disease and reduced mortality with favipiravir.

## Investigational Antiretroviral Agents

**Capsid Inhibitor.** Lenacapavir is a first-in-class, long-acting inhibitor of HIV-1 capsid that is being developed for the prevention and treatment of HIV-1 infection. Cihlar and colleagues reviewed the mechanism, clinical development, available resistance data, and pharmacokinetic profile of lenacapavir (Abstract 22). Lutz and colleagues presented data on drug-drug interactions with oral lenacapavir (Abstract 89). They found that coadministration of lenacapavir and darunavir/cobicistat, a strong cytochrome P450 3A (CYP3A)/P-glycoprotein (P-gp) inhibitor, increased the area-under-the-curve (AUC) of lenacapavir 2-fold. When coadministered with voriconazole, a CYP3A inhibitor, lenacapavir AUC was only increased 30%. When coadministered with atazanavir/cobicistat, a CYP3A/P-gp/UGT1A1 inhibitor, lenacapavir AUC increased 300%, suggesting that glucuronidation is the primary pathway for elimination. Coadministration with rifampin, a strong inducer of CYP3A/P-gp/UGT1A1, led to an 85% reduction in lenacapavir AUC, suggesting that coadministration is not advised. Studies of coadministration of efavirenz, a moderate inducer of CYP3A, are ongoing. Based on coadministration of probe drugs, lenacapavir appears to be a moderate inducer of CYP3A. Lenacapavir pharmacokinetics were not affected by gastric acid reducers.

Segal-Maurer and colleagues presented data on the use of lenacapavir in people with HIV who were heavily treatment experienced (Abstract 127). Eligible participants had plasma HIV-1 RNA levels above 400 copies/mL, resistance to 2 or more agents from 3 of 4 main antiretroviral drug classes, and 2 or fewer fully active drugs for an optimized background regimen. The study included a randomized cohort with 24 participants receiving 2 weeks of lenacapavir monotherapy and 12 participants receiving placebo followed by initiation of lenacapavir in the placebo and an optimized background regimen for all participants. The nonrandomized cohort (n=36) initiated lenacapavir and an optimized background regimen at entry. For all participants, lenacapavir was given orally for 2 weeks followed by subcutaneous dosing every 6 months. A total of 72 participants were included: median age was 52 years, 25% were female, the median CD4+ cell count was 150/μL, and the median HIV-1 RNA level was 4.5 $\log_{10}$ copies/mL. The primary endpoint, achieving at least a 0.5 $\log_{10}$ copy/mL decline in plasma HIV-1 RNA level after 14 days in the randomized cohort, was more frequent in the lenacapavir group than in the placebo group (88% vs 17%; $P<.0001$). The mean decrease in plasma HIV-1 RNA level at day 14 was higher in the lenacapavir group than the placebo group (–1.93 $\log_{10}$ copy/mL vs –0.29 $\log_{10}$ copy/mL; $P<.0001$). Approximately 73% of participants achieved a plasma HIV-1 RNA level below 50 copies/mL by week 26. Two participants experienced virologic breakthrough after virologic suppression, with the emergence of high-level resistance to lenacapavir. However, both participants resuppressed with continuation of lenacapavir. There were no safety concerns identified in this study. Injection site reactions occurred in 46% of participants, were mostly grade 1, and generally resolved in a few days. Some participants developed nodules that lasted for months but did not lead to treatment discontinuation. This study provides strong support for the use of lenacapavir for the treatment of heavily treatment-experienced individuals with HIV.

**Maturation Inhibitors.** Spinner and colleagues presented data on GSK3640254, a next-generation HIV-1 maturation inhibitor that is dosed once daily (Abstract 126). They enrolled treatment-naive adults in a 10-day monotherapy trial

to assess the antiviral efficacy, pharmacokinetics, and preliminary safety. In the first part of the study, GSK3640254 200 mg daily decreased plasma HIV-1 RNA level by 2.01 $\log_{10}$ copies/mL, whereas there was a 0.22 $\log_{10}$ copy/mL reduction with 10 mg daily and a 0.14 $\log_{10}$ copy/mL increase with placebo. Of note, some participants receiving 200 mg daily developed resistance to GSK3640254 around day 10. For the second part of the trial, monotherapy dosing was reduced to 7 days. The investigators found that 40 mg, 80 mg, and 140 mg daily resulted in 1.18, 1.02, and 1.45 $\log_{10}$ copy/mL reductions, respectively, in plasma HIV-1 RNA level after 7 days. In pharmacokinetic analyses, GSK3640254 140 mg and 200 mg daily had similar profiles and were well above the clinical efficacy target. No safety or tolerability concerns were identified in this small study phase I study.

## Clinical Trials of Antiretroviral Therapy

**Second-Line Therapy.** Paton and colleagues presented data on a randomized clinical trial comparing antiretroviral therapy (ART) regimens for second-line therapy (Abstract 94). This trial used a factorial design to compare dolutegravir with darunavir/ritonavir and continuation of tenofovir disoproxil fumarate/lamivudine with switching to zidovudine/lamivudine in participants whose prior regimen failed. This trial used a public health approach and did not employ resistance testing or frequent viral load monitoring. There were 464 participants included (61% women, median age 34 years, median CD4+ cell count 194/μL, median plasma HIV-1 RNA level 4.4 $\log_{10}$ copies/mL). There was extensive nucleoside reverse transcriptase inhibitor (nRTI) resistance at baseline, with 50% of participants having the K65R/N mutation and 87% having M184V/I. Dolutegravir was found to be noninferior to darunavir/ritonavir, with 90% and 92% of participants, respectively, achieving the primary endpoint of plasma a HIV-1 RNA level less than 400 copies/mL at week 48 (difference, –1.5%; 95% confidence interval [CI], –6.7%-3.7%). In the dolutegravir group, 4 participants (2%) developed integrase strand transfer inhibitor (InSTI) resistance-associated mutations; no darunavir resistance-associated mutations were detected. Continuation of tenofovir disoproxil fumarate was noninferior to switching to zidovudine, with 92% and 90% of participants, respectively, achieving the primary endpoint of a plasma HIV-1 RNA level less than 400 copies/mL at week 48 (difference, 2.7%; 95% CI, –2.6-7.9%). There were no negative effects on treatment outcomes associated with nRTI resistance at baseline in any of the treatment arms. Specifically, participants with 0 active nRTIs in their assigned regimen experienced 92.4% and 93.7% suppression in the dolutegravir and darunavir groups, respectively. For those with K65R/N present at baseline, participants in the tenofovir and zidovudine groups experienced 94% and 96% virologic suppression, respectively. Similar results were seen for those with an M184V/I. These data support the use of dolutegravir for second-line therapy without the need for preswitch viral load or resistance testing. The study results also support the use of tenofovir disoproxil fumarate/lamivudine for second-line therapy, which may be preferable for patients and ART programs.

Siedner and colleagues presented data from a randomized clinical trial that examined genotypic resistance testing after failure of initial ART in sub-Saharan Africa (Abstract 95). This was an open-label pragmatic clinical trial enrolling people with HIV who had taken initial ART for at least 5 months, had an HIV RNA level above 1000 copies/mL, and had no known history of drug resistance. Participants were randomly assigned to immediate genotypic resistance testing or to standard of care, which involved adherence counseling, repeat viral load measurement, and transition to second-line therapy if HIV RNA level remained higher than 1000 copies/mL. The results of participants who received resistance testing were used to guide management. The primary outcome, a plasma HIV-1 RNA level below 200 copies/mL at 9 months, was achieved in approximately 60% of participants in both arms and was not statistically different. Overall, the results showed that resistance testing did not improve outcomes among patients whose first-line therapy failed.

**Long-Acting Cabotegravir/Rilpivirine.** Jaeger and colleagues presented week 96 data from the ATLAS-2M (Cabotegravir and Rilpivirine Every 2 Months Is Noninferior to Monthly) study, which long-acting (LA) cabotegravir (CAB) and rilpivirine (RPV) dosed every 4 weeks with every 8 weeks dosing (Abstract 401). The study enrolled virologically suppressed individuals who were receiving CAB/RPV LA every 4 weeks, those receiving a control regimen of oral ART in prior trials, and de novo participants who were suppressed on an oral regimen. Those not receiving CAB/RPV LA underwent an oral lead-in of CAB and RPV. Participants were randomly assigned to receive LA CAB/RPV every 4 or every 8 weeks. The week 48 endpoints have been previously reported.[4] At week 96, every 8-week dosing was noninferior to every 4-week dosing; the primary endpoint of virologic nonresponse (plasma HIV-1 RNA level at or above 50 copies/mL) was found in 2.1% of participants in the every 8-week arm and 1.1% of participants in the every 4-week arm (difference, 1.0%; 95% CI, –0.6-2.5%). Only 1 additional confirmed virologic failure occurred between week 48 and week 96 in a participant in the 8-week arm. In total, 9 confirmed virologic failures occurred in the 8-week arm (7 with RPV and 5 with integrase resistance-associated mutations) and 2 occurred in the 4-week arm (1 with RPV and 2 with InSTI resistance-associated mutations). There were no differences in safety outcomes between arms, and the proportion who discontinued for injection-related reasons was low in both arms (1% in the every 8-week arm and 2% in the every 4-week arm). The authors concluded that these longer-term data support the use of 8-week dosing of CAB/RPV LA for maintenance ART.

Benn and colleagues presented pooled data from 3 trials of CAB/RPV LA on the subgroup of participants aged 50 years and older (Abstract 402).

They found similar viral efficacy outcomes, safety profiles, adherence to treatment, and treatment satisfaction among participants older than 50 years and younger participants.

## The HIV Care Cascade and Disparities in Treatment Outcomes

### Predictors and Challenges in Achieving HIV Care Cascade Targets From Around the Globe

Data from cohorts and settings in North America suggest that disparities in the HIV care cascade persist, although many settings have achieved the 90-90-90 targets. Li and colleagues (Abstract 104) examined trends in timely receipt of ART in 13 United States NA-ACCORD (North American AIDS Cohort Collaboration on Research and Design) clinical cohorts between 2012 and 2018 by sociodemographic and clinical characteristics. Of the 11,853 treatment-naive people with HIV included in the analysis, 48% were men who have sex with men (MSM), 77% were younger than 50 years, 45% were black, and 15% were Latinx. Timely ART initiation, defined as within 30 days of entry into care, occurred for 56.4% of the cohort and increased significantly between 2012 (42%) and 2018 (82%). In the unadjusted analysis, decreased rates of timely ART initiation were seen in black patients compared with white patients, non-Latinx patients (aHR, 0.89; 95% CI, 0.83-0.94), and people with HIV in the South compared with those living in the West (aHR, 0.78; 95% CI, 0.69-0.88). A history of substance use disorder was also associated with decreased timely ART initiation (aHR, 0.81; 95% CI, 0.74-0.90). Disparities for black people with HIV, people with HIV living in the South, and people with HIV and a history of substance use disorder persisted in adjusted analyses. Although it does appear that overall incidence of and disparities in timely ART improved over time, these data suggest that specific populations and regions deserve particular attention.

Geographic disparities in HIV treatment outcomes were examined in more detail in Mississippi, Alabama, and Louisiana by Rana and colleagues (Abstract 105). They used data collected in the Enhanced HIV/AIDS Reporting System (eHARS) to examine days to viral suppression among people with HIV aged 13 years or older diagnosed with HIV between 2012 and 2019. The investigators found significant decreases in days to viral suppression for all 3 states comparing data from 2012 to 2015 with data from 2016 to 2019: a decrease from 211 days to 137 days for Alabama, from 242 days to 118 days for Louisiana, and from 332 days to 168 days for Mississippi. Investigators also noted persistent geographic disparities in time to viral suppression. Some regions showed marked improvements, most notably across the entire state of Alabama and in Louisiana's public health area 1 (around New Orleans), which went from median time to viral suppression of 250 days to 86 days. These differences may reflect the impact of Medicaid expansion or regional rapid ART initiatives. Overall, these data demonstrate encouraging improvements in time to viral suppression over time but also highlight regions and populations that are falling behind, including adolescents and the Mississippi Delta and coastal regions.

Moore and colleagues estimated HIV care cascade components for MSM participating in the Engage study, a biobehavioral cross-sectional and cohort study with recruitment by respondent-driven sampling among 2503 MSM in Montreal, Toronto, and Vancouver, Canada (Abstract 776). The investigators found significant differences in HIV Care Cascade components among MSM between the 3 cities, with higher rates of undiagnosed HIV infection in Montreal (3.3%) and Toronto (3.2%) than in Vancouver (0.2%; $P$ for difference $<.001$). Percentage of MSM on ART and with unsuppressed viral load (HIV RNA level ≥200 copies/mL) also varied significantly: in Montreal 87.6% and 10.6%, in Toronto 82.6% and 4.0%, and in Vancouver 88.5% and 2.6%, respectively. Statistically significantly lower odds of unsuppressed viral load were found for residents of Vancouver than those of Montreal (adjusted OR [aOR], 0.23; 95% CI, 0.06-0.82), for those with a primary care provider (aOR, 0.11; 95% CI, 0.02-0.57), for older participants (aOR, 0.93 per year; 95% CI, 0.89-0.97), and for those diagnosed with a sexually transmitted infection (STI) (aOR, 0.12; 95% CI, 0.04-0.32). Surprisingly, lower odds of unsuppressed viral load were also seen for those with an Alcohol Use Disorders Identification Test-Concise (AUDIT-C) score indicative of high-risk drinking (aOR, 0.19; 95% CI, 0.05-0.70). Although 90-90-90 targets were achieved across all 3 cities, there are disparities both between cities and within certain populations, such as younger MSM or those without a primary care practitioner, within each location.

Encouraging data from sub-Saharan Africa show that many programs are exceeding 90-90-90 targets. Wu and colleagues used data from the 2018 to 2019 Lesotho National HIV Drug Resistance Survey to estimate retention and viral load suppression among adults (Abstract 761). This cross-sectional study randomly selected participants from 30 clinics stratified by probability proportional to size. Data were collected from separate cohorts: those initiating ART for retention and 12-month viral suppression data and those who started ART more than 48 months ago. Retention in care at 12 months was 75%, and viral suppression was high: 93.4% at 12 months and 92.1% for those followed-up for 48 months or more. However, both metrics were statistically significantly lower for participants aged 18 to 24 years; retention at 12 months was only 56% in this age group, and odds of viral suppression were greater in other age groups: 3.5 (95% CI, 2.9-4.3) in those aged 45 years and older and 1.4 (95% CI, 1.2-1.6) in those aged 24 to 44 years. The investigators noted concern for overall retention in care at 12 months, which is well below the 90-90-90 targets, and for the challenges faced by younger adults in Lesotho.

McCluskey and colleagues presented the 24-week outcomes of a prospective, observational cohort of people on ART transitioning to dolutegravir-based regimens in public clinic sites in Uganda (Abstract 399). At baseline,

95% of the 499 participants enrolled had an HIV RNA level below 50 copies/mL. Of the 448 individuals who completed the 24-week visit, only 1% had discontinued dolutegravir because of adverse effects or clinical discretion, and 96% had HIV RNA levels below 50 copies/mL. An HIV RNA level greater than 50 copies/mL at week 24 was associated with an HIV RNA level greater than 50 copies/mL at the time of switch to dolutegravir ($P<.001$). Despite treatment interruptions due to COVID-19, 86% of participants remained in care and virally suppressed 24 weeks after transition and dolutegravir was well tolerated. These data provide support for public health policies transitioning people with HIV to dolutegravir-based regimens but suggest the need for caution in those not virally suppressed before transition.

Data from the Rakai Community Cohort Study were used to examine the association between ART use and distance to clinic among men in Uganda, a group that often has lower utilization of ART than women (Abstract 659). Investigators used GPS data to estimate distance between residence and nearest possible HIV treatment center and did not find an association between distance and being initiated on ART. Increased risk of absence of ART use was seen among men who were divorced or never married compared with married men and among residents from non-fishing communities compared with fishing communities. The investigators speculated that test-and-treat programs targeted to the fishing communities in the Rakai Cohort have increased ART uptake in those groups.

## Racial Disparities and Structural Barriers in HIV Care Outcomes

Humes and colleagues (Abstract 654) used data from the NA-ACCORD study for individuals initiating ART between 2012 and 2018 in the United States to examine incidence of achieving viral suppression within 6 months over time and factors predicting disparities in attainment of viral suppression. Of 9807 people with HIV initiating ART, incidence of achieving viral suppression increased over time, from 77% between 2012 and 2013 to 83% between 2016 and 2018. Factors associated with lower rates of viral suppression in the adjusted analysis included age younger than 50 years, Northeastern and Southern geographic regions, black race, substance use disorder, history of injection drug use, and initiating ART that did not include an InSTI. The increase in viral suppression incidence over time is encouraging, but the racial, age, and substance use disorder disparities in attainment of viral suppression have clear implications for efforts to end the HIV epidemic.

Three abstracts examined care outcomes in specific racial or ethnic minorities using data from the National HIV Surveillance System (NHSS). Sembajwe and colleagues (Abstract 655) examined outcomes among American Indian and Alaska Native people in the United States in 2018 and compared data from Indian Health Services (IHS) areas with national data. They found improved linkage to care within 1 month of diagnosis and viral suppression within 6 months of diagnosis outcomes in IHS areas compared with national data for American Indian and Alaska Native people: 79.1% compared with 77.9% for linkage and 67.7% compared with 64% for viral suppression, respectively. However, both outcomes were less favorable than those seen for non-Hispanic white people in the same geographic regions.

Singh and colleagues explored data on care outcomes among Asian people with HIV in the United States in 2018, also using NHSS data (Abstract 760). Different from trends seen in other racial/ethnic groups, where younger age is often associated with poor care outcomes, they found a lower prevalence of linkage to care, retention in care, and viral suppression (HIV <200 copies/mL) in Asian people 55 years or older, compared with younger Asian people. However, of the 786 Asian people diagnosed with HIV in 2018, men aged 13 to 34 years and women aged 35 to 54 years were more likely to be diagnosed concurrently with HIV and AIDS. Overall, care cascade metrics for Asian people fell short of ending the HIV epidemic target for Asian people in the United States.

To examine structural factors and their impact on care outcomes for black people with HIV in the United States, Logan and colleagues used cross-sectional data from the NHSS, the US Census, and the Home Mortgage Disclosure Act (Abstract 656). The 3 structural factors considered were residence in a Medicaid expansion state, residence in a state where more than 50% of people with HIV receive care through the Ryan White Comprehensive AIDS Resources Emergency (CARE) Act, and residence in a census tract with redlining. A redlining index was assessed for each census tract based on the ratio of rejected mortgage applications by race. The redlining index was adjusted for loan amount, income, and sex. The investigators found a mean index of 2.0 across all census tracts, meaning that black mortgage applicants were twice as likely to be rejected for their loan as white applicants. Among 13,042 black or white people with HIV in 2017 from 42 jurisdictions with complete laboratory data, there was not a significant association between a redlining index above 2.0, race, and either linkage to care within 1 month of HIV diagnosis or viral suppression (HIV RNA level <200 copies/mL) in 2018. Black and white people with HIV who lived in a Medicaid expansion state were more likely to be linked to care within a month of diagnosis (adjusted prevalence ratio [aPR], 1.06; 99% CI, 1.02-1.10 for black people with HIV, and aPR, 1.06; 99% CI, 1.01-1.10 for white people with HIV). Residence in a state where more than 50% of people with HIV received support from the Ryan White CARE Act was also associated with linkage to care for white people with HIV, but not black people with HIV, and viral suppression for both racial groups (aPR, 1.06; 99% CI, 1.02-1.11 for black people with HIV, and aPR, 1.05; 99% CI, 1.00-1.09 for white people with HIV). Although the sample was not nationally representative, and the effect sizes of associations found for Medicaid expansion and Ryan White CARE Act participation were not very strong, this novel use of

structural variables to predict HIV care outcomes on a population level shows promise for future investigations.

Two other presentations focused on structural barriers to care in populations impacted by the HIV epidemic. Poteat and colleagues conducted a cross-sectional survey among 213 transgender women in South Africa between May and September of 2018 to explore multiple structural barriers, including hunger, homelessness, poverty, condomless sex, sex work, violence, social work, alcohol use disorder, and medical distrust, and their associations with outcomes of HIV status and inability to access ART in the prior 12 months (Abstract 657). Within the cohort, 31.6% of respondents reported living with HIV, and 31% of the 64 respondents who had taken ART reported treatment interruption. The investigators created multivariate logistic regression models for both outcomes and found that prior or current homelessness (aOR, 6.6; 95% CI, 2.6-17.0) or sex work (aOR, 6.9; 95% CI, 3.0-16.0) were both predictive of living with HIV. Homelessness was also predictive of interruption in ART (aOR, 9.1; 95% CI, 2.1-39.0). These findings suggest that experiences of homelessness may have a strong impact on risk for HIV and on opportunities for care engagement among transgender women in South Africa.

Sjöland and colleagues conducted a face-to-face survey of 316 Burmese migrants living with HIV in Chiang Mai, Thailand, to examine the association between food insecurity, income, and the HIV care outcomes of ART adherence and viral suppression (Abstract 658). The cohort had high levels of food insecurity (48.7%), with severe food insecurity in 14.2%, but also reported 96.8% adherence with 93.5% viral suppression. Food insecurity was associated with lack of viral suppression (OR, 4.13; 95% CI, 1.22-14.0) and perceived poverty (OR, 5.96; 95% CI, 2.58-13.76), suggesting that Burmese migrants face substantial income-related barriers to viral suppression. Although the overall care outcomes data for this population are encouraging, interventions to support food security and income may be useful in sustaining viral suppression.

## Interventions to Improve the HIV Care Cascade

The Deliver Health Study, presented by Barnabas and colleagues (Abstract 111), compared clinic-based ART with a fee-for-home-ART delivery and monitoring service in Pietermaritzburg, KwaZulu Natal, South Africa, from October 2019 to January 2020 during the COVID-19 lockdown. Individuals either on (62%) or initiating (36%) ART were randomly assigned to standard of care, receiving ART from the clinic (n=80), or a no-contact home delivery with a one-time fee based on participant income (n=82). The investigators found that 98% of participants who paid the fee and 100% in the home delivery arm would recommend participation to others. After a median follow-up of 47 weeks, viral suppression (HIV RNA level <100 copies/mL) was 74% in the standard of care group and 88% in the home delivery group (relative risk for viral suppression, 1.21; 95% CI, 1.02-1.42). The investigators highlighted that assessing a fee for such services seemed feasible for the participants and would make the delivery service financially sustainable from a programmatic perspective. The context of COVID-19 lockdown may have contributed to poor outcomes in the standard of care group, but the improved viral suppression outcome seen with home delivery remains notable and worthy of further exploration.

Two interventions specifically targeted men with HIV. Kim and colleagues presented data on linkage to care for 122 men with HIV participating in a community cluster randomized trial of 2 interventions: a financial incentive for linkage to care within 6 weeks of HIV diagnosis or care re-engagement and a tablet-based decision support mobile app (Abstract 753). Overall, 75.4% of participants either initiated or resumed HIV care within 3 weeks. The decision-support intervention alone was the only arm of the trial that showed an improvement in linkage over standard of care (risk ratio, 1.86; 95% CI, 1.19-2.92). Neither the financial incentive nor a combination of the financial and decision-support interventions were significantly associated with increased linkage to care compared with standard of care.

The second intervention targeting men used a peer-support intervention to improve linkage to and retention in care (Abstract 756). Investigators conducted formative qualitative research with 76 men and 68 health care practitioners and used those findings to construct a cross-sectional survey of 2019 men aged 20 to 34 years. The investigators found that men experienced profound fear and isolation around their HIV diagnosis, they associated HIV treatment with loss of health, and they anticipated a negative clinic experience when engaging in HIV care. From these data, investigators partnered with men from their target population in a series of design workshops and cocreated a coaching model, training men with HIV on stable ART to support men newly diagnosed with HIV or lost to follow-up. Of 3848 men enrolled, 96% started or restarted ART during the pilot period between March and September 2020. The pilot period enrolled a different cohort of men each month in a stepped-wedge implementation model, and follow-up time varied by cohort from 1 to 6 months. Overall, 95% of the cohort was retained at the endpoint, and retention within the cohorts with longer follow-up times was low at month 1 (90%-93% for cohorts with 4-6 months of follow-up) but increased over time to 94% to 96%. Although the intervention had been designed to target men aged 30 years or younger, 78% of those enrolled were aged 30 to 49 years. The investigators also found that few men declined coaching when approached, disclosure of HIV status remained a dominant fear for participants, and coaches served as positive role models within the community and as allies for clinic nurses. It was also noted that coaches were more successful if they were men with HIV and that many became overburdened either with the needs of their clients, particularly if client load was high, or by unrelated tasks assigned to them within the clinic. Outreach was largely clinic based throughout the study period because of COVID-

19, but future adaptations proposed by the investigators include community outreach, group coaching in an adherence-club model, and expansion to other medical conditions such as tuberculosis or mental health.

The CoRECT (Cooperative Re-Engagement Controlled Trial) in Connecticut used a data-to-care strategy and disease intervention specialists (DISs) to facilitate relinkage to care in a randomized control trial (Abstract 740). Between November 2016 and July 2018, investigators identified 655 people with HIV who were out of care, defined as lack of viral load measurement or clinic visit in the last 6 months, and randomly assigned them to either clinic standard of care or to an intervention by a DIS to locate participants, assess barriers to care, and facilitate relinkage. Investigators did find a significant difference in the primary outcome, re-engagement in care at 90 days, between the DIS group (51.1%) and standard of care (41.9%; $P=.019$ for difference between the groups) but did not see a statistically significant difference in retention in care at 12 months or in viral suppression at 12 months between the groups. Regardless of intervention arm, those who re-engaged in care at 90 days were more likely to be retained in care at 12 months. Based on these findings, this approach could be useful to support initial re-engagement for a recently out-of-care population but should be supported by further interventions to sustain engagement.

Rodriguez-Hart and colleagues used the inclusion of gender-affirming surgery within the New York Medicaid program in 2015 to determine the impact of this intervention on viral suppression among transgender people with HIV in New York City between 2013 and 2017 (Abstract 107). Investigators found that transgender people with HIV enrolled in Medicaid had an increase in viral suppression (HIV RNA level <200 copies/mL at last test) of 13% in this timeframe. Transgender people with HIV enrolled in Medicaid who received gender-affirming surgery had a higher rate of viral suppression in 2017 (85.1%) than the overall population of transgender people with HIV enrolled in Medicaid (75.4%). This level of viral suppression was more aligned with the comparator groups: people with HIV not enrolled in Medicaid (83.2%), cisgender women (82.2%), and cisgender men (85.5%). Transgender people with HIV in Medicaid who received gender-affirming surgery showed increased viral suppression before surgery, which is often a requirement for surgery, but remained at 87.7% at 2 years postsurgery.

The investigators also noted that this population included demographic characteristics often associated with lower viral suppression: 57.3% were black, 22.2% were aged 20 to 29 years, and 44% were living in high-poverty areas. The investigators suggest that both preparing for and receiving gender-affirming surgery can lead to sustained increases in viral suppression for this population in whom opportunities for viral suppression remain low. Although the use of a Medicaid database likely leads to under-reporting of people of transgender experience because the database does not include self-identification as transgender, this database can still provide insight into the potential positive impact of gender-affirming surgery on this marginalized population.

Lopes and colleagues pooled data from 2 pragmatic cluster-randomized trials, each with incomplete recruitment and viral load data, to examine the impact of a differentiated service delivery (DSD) model providing ART refills in the community every 6 months with clinical consultation annually (Abstract 182). The trials took place in Zimbabwe and Lesotho but had the same 3 care arms: standard of care of clinic-based refills every 3 months along with clinical consultation, community-based refills every 3 months with annual consultation, and community-based refills every 6 months with annual consultation. Noninferiority analysis of 10,136 participants compared retention in care at 12 months (95% overall) and viral suppression (98% overall) in the 3 groups. The analysis was limited by lack of viral load testing in some treatment arms: 66% in the standard of care, 61.2% in the 3-month community-based refill arm, and 43.1% in the 6-month community-based refill arm. However, in the adjusted analysis, both intervention arms met criteria for noninferiority for retention in care and for viral suppression. There were also no clear differences in unscheduled visits between arms. Despite the challenges with study design, these findings indicate that a DSD model allowing for community-based refills as infrequently as every 6 months would be feasible as a cost-reduction measure.

Pearson and colleagues described clinical outcomes for people with HIV re-engaging in care or facing a lapse in care within 3 community-based, nurse-led care sites that offer immediate ART (Abstract 762). Of 260 individuals presenting to care between October 2016 and March 2020, motivations for re-engagement included loss of insurance (58%), relocation (37%), and need for STI services (17%). ART prescriptions were requested by 91.9% of those presenting to care and were provided on the same day for 93% of clients and, overall, for 99.6%. Lack of viral suppression on re-engagement was found in 143 people with HIV, and 75% of those were suppressed at their next encounter. Of the 117 with viral suppression at baseline, 94% sustained suppression at their next encounter. These data support the efforts of a community-based, nurse-led clinic offering immediate ART and suggest that this venue can also engage people with HIV not presenting for ART, such as those presenting for STI treatment.

An unblinded, randomized, controlled trial in Uganda compared rates of viral nonsuppression at 6 months among 1686 people living with HIV meeting criteria for ART initiation who were randomly assigned to nurse-initiated or to clinician-initiated ART (Abstract 758). The primary outcome of viral load nonsuppression (HIV RNA level >1000 copies/mL) after 6 months on ART was observed in 7.7% of participants, and rates of nonsuppression in the nurse-initiated ART were noninferior to the clinician-initiated arm (risk difference, 0.0018; 97.5% CI, –0.031-0.035). Baseline CD4+ cell count and

age 35 years or younger were statistically significant predictors of nonsuppression. Only 66% of participants had a viral load test result at 6 months, but attrition did not differ between study arms. These findings suggest that nurse-initiated ART is a feasible strategy for care delivery in this context.

### Differentiated Service Delivery

Nichols and colleagues examined the cost of various service delivery methods in Zimbabwe (Abstract 766). They compared cost and retention in care over 12 months of community ART refill groups (CARGs) with the traditional model of facility- or clinic-based care. The retention rates of all groups were high at more than 90%, with a numerical trend higher in the CARGs and comparable total average costs in the 3 arms ranging from $179 to $190 USD.

Okere and colleagues compared patient costs in a DSD model in ART "clubs," where antiretroviral drugs are dispensed by trained community members, compared with standard clinic-based care in a northwestern Tanzanian community (Abstract 767). They found significantly higher direct and indirect patient costs in the standard clinic-based model than with the DSD model; patient cost per year was $31.80 overall for clinic-based care ($11.70 for direct costs, $20.20 for indirect costs) and $11.90 overall for club-based care ($4.17 for direct costs, $7.71 for indirect costs) ($P<.001$). This again shows the cost-effectiveness of community-based DSD models.

Jo and colleagues observed increases in patient participation in DSD models for the first 8 months after the first COVID-19 case in Tanzania, but the interval of medication delivery was decreased because of issues in supply owing to the pandemic (Abstract 768).

Bassett and colleagues presented observational data on community pick-up points (PUPs) as an alternate to facility-based care (Abstract 769). Higher uptake of PUPs was associated with younger age, living 10 to 30 km away from a clinic, HIV stigma, and more convenient location or hours of PUPs. This information can help increase use and efficiency of PUPs in certain populations.

Hoffmann and colleagues presented a new form of differentiated care targeted at retention in care of populations recently released from incarceration in South Africa (Abstract 770). Their intervention was based on community clubs with peer-based groups meeting every 2 weeks, along with a social worker and referrals to other services if needed. The investigators observed a significantly increased proportion of participants in the intervention group who stayed in care (58% vs 32% in the standard of care arm; $P=.001$). This model could be adapted nation- and worldwide to improve rates of retention in care for individuals recently released from the criminal-legal system.

## The Impact of the COVID-19 Pandemic on HIV Treatment and Care Outcomes

An excellent overview of the impact of COVID-19 on the global HIV pandemic was provided by Kambugu (Abstract 32). He described the negative effects of COVID-19 lockdown on every part of the HIV-care cascade. Less community outreach and access to testing leads to decreases in the number of individuals diagnosed with HIV. Decreased clinic services can impact linkage to care and ART-prescription provisions. Fear of contracting COVID-19 during clinic visits can impact retention in care, and supply chain disruptions and increases in poverty can impact viral suppression. He cited concerning data from a Global Fund: More than 70% of respondents with HIV reported moderate or high levels of disruption to their service delivery during the COVID-19 pandemic. Kambugu called for systematic approaches and innovation to mitigate the impact of COVID-19, including telehealth and DSD models.

Reports from high-income countries on the impact of COVID-19 on HIV care delivery and outcomes were mixed. Data from the HOPS (HIV Outpatient Study) between January and September 2020 were used to determine the changes in HIV care encounters and predictors of decreases in engagement (Abstract 752). The investigators found that encounters of all types, including viral load testing, decreased beginning in January 2020, and the rise of telemedicine visits did not compensate for the overall decrease in the number of outpatient visits. Predictors of lack of clinic visits included female sex, Latinx ethnicity, public insurance, and older age, but none of the predictors examined predicted lack of viral suppression. These data imply that significant challenges to care engagement during COVID-19 exist for this cohort that were not compensated for by adaptations of care delivery models such as telehealth.

Antinori and colleagues presented encouraging data from ICONA (Italian Cohort of Antiretroviral-Naive Patients) cohort participants, comparing viral suppression before and during Italy's COVID-19 lockdown (Abstract 748). The investigators found an increased risk of an HIV RNA level 50 copies/mL or higher after adjustment for nationality, sex, HIV clinical variables, or geographic location (aHR, 1.44; 95% CI, 1.20-1.72). However, in an on-treatment analysis and a sensitivity analysis that adjusted for missing data through inverse probability of weighting, there was not a statistically significant difference between an HIV RNA level above 50 copies/mL in 2019 and 2020. The investigators concluded that, despite the devastating impact of COVID-19 on Italy, the data suggest that absolute risk for virologic failure remained low for cohort participants.

Data from low- and middle-income countries demonstrated significant resilience of HIV programs to COVID-19–related impacts and some successful mitigation strategies, including multimonth prescriptions and community-based delivery mechanisms. Joseph and colleagues described the experience of GHESKIO (Haitian Group for the Study of Kaposi's Sarcoma and Opportunistic Infections), an HIV treatment center serving more than 13,000 people with HIV receiving ART in Port-au-Prince, Haiti, with community-based ART and laboratory testing, a strategy they adopted to deliver care during civil unrest beginning in September

2019 and expanded during the COVID-19 pandemic (Abstract 185). Services offered included nurse-staffed community distribution points, where people with HIV could pick up ART prescriptions and have viral load testing, and home delivery of ART through community health workers. Beginning in May 2019, all people with HIV served by GHESKIO were offered either in-clinic or community-based services at the time of each encounter, regardless of venue. The number of community distribution points increased from 1 in May 2019 to 9 in November 2019. The investigators examined trends in use of the non-clinic-based services between May 1, 2019, and January 27, 2021, with a particular focus on the period of civil unrest (September 2019-February 2020) and COVID-19 (March 2020-January 2021). They found 16,234 patients who completed at least 1 visit during the observation period. Before the beginning of civil unrest, only 2% of people with HIV elected to receive non-clinic-based services. During the period of civil unrest, 15% received nonclinic visits, and during the COVID-19 pandemic, 30% received nonclinic visits, with the vast majority of nonclinic visits in both timeframes occurring at the community distribution points. During the COVID-19 pandemic, 18.9% of patients received care solely from nonclinic sites. Predictors of having 1 or more nonclinic visit included male sex, higher education and income, age younger than 18 years, longer duration on ART, nonsingle status, and living in a neighborhood on lockdown during the time of civil unrest. Although more data on HIV care outcomes would be helpful to determine the efficacy of this intervention, these data demonstrate that many patients chose nonclinic-based services during times when continuity of care was jeopardized.

Harris and colleagues reported HIV care cascade data before and during the COVID-19 pandemic in 11 African countries and across 1059 HIV care sites (Abstract 186). The investigators examined care cascade data across 4 quarters: Q1, October to December 2019; Q2, January to March 2020; Q3, April to June 2020; and Q4, July to September 2020. The number of individuals receiving an HIV test declined at most sites between Q2 and Q3 but increased overall from 20,525 to 23,478 across all sites with a stable 4% positivity rate. Similarly, ART initiation also declined between Q2 and Q3 but showed an overall increase from 23,169 to 24,665 between Q1 and Q4. The proportion of individuals receiving 3 or more months of ART increased from 51% in Q1 to 80% in Q4. The number of participants currently on ART increased in each quarter, as did the percentage of individuals achieving virologic suppression (87.5% in Q1 and 90.1% in Q4), which improved as access to viral load testing expanded. These findings are encouraging and suggest that, although HIV testing and ART initiation were impacted early on by the COVID-19 pandemic, these care metrics rebounded quickly. A dramatic increase in multimonth prescription delivery did not appear to impact the number of individuals on ART or achieving viral suppression, which improved throughout the pandemic.

Fernandez and colleagues used the President's Emergency Plan for AIDS Relief (PEPFAR) monitoring and evaluation data across 18 countries in sub-Saharan African to estimate the proportion of interruptions in treatment in 2 timeframes: before COVID-19 Q1, October to December 2019, and during COVID-19 Q3, April to June 2020 (Abstract 738). They found that the proportion of potential interruptions in ART was similar before and during COVID: 4.9% in Q1 before COVID and 5.3% in Q3 during the pandemic. However, men were statistically more likely to have loss to follow-up for more than three months or death than women during the pandemic (Q3).

Nasuuna and colleagues described interventions by the Infectious Disease Institute (IDI) to mitigate the impact of the COVID-19 pandemic on the 215,427 people with HIV in Kampala, Uganda (Abstract 729). During the nationwide lockdown from March to June 2020, IDI contacted people with HIV by phone to support ART delivery and offer services to ensure continuity of ART, including home or specified community point delivery of ART, transfer of ART to the facility nearest to them, and pickup of ART by a nonpatient designee. IDI also provided transportation for their health care workers to and from IDI facilities to ensure that care facilities remained open. Of those in care, 55% missed an appointment during the lockdown. However, 95.3% received an ART refill through the mechanisms described above, including 25% receiving multimonth refills. Refills were received at their usual facility for the majority (86%) of patients, in the community for 8%, and outside of the region for 5%. These data imply that, although in-person care was impacted by the lockdown in Uganda, the vast majority of patients still had access to ART.

Finally, Lee and colleagues shared novel data on the impact of HIV status on those hospitalized with COVID-19 (Abstract 142). The investigators conducted a matched, retrospective study comparing outcomes of hospitalized people with HIV and COVID-19 with those hospitalized with COVID-19 but not with HIV. Prior data from national datasets in the United Kingdom suggest that people with HIV hospitalized with COVID-19 may have an increased risk of mortality, but studies may have been limited by lack of HIV-related data and inability to match for known confounders. This investigation included data from 6 hospital trusts across England from February to May 2020 and matched 69 hospitalized people with HIV and COVID-19 with 181 people hospitalized with COVID-19 without HIV by hospital site, COVID-19 test date, age, sex, and the index of multiple deprivation decile, a countrywide metric that can act as surrogate for socioeconomic deprivation. Primary outcomes were time from COVID-19 diagnosis to improvement from baseline by 2 or more points on an ordinal clinical ranking scale or to discharge from the hospital. The investigators found that people with HIV had a hazard ratio (HR) of 0.57 (95% CI, 0.39-0.85) for the primary outcome compared with matched controls without HIV. However, the effect size was attenuated after adjustment, with baseline frailty

and malignancy being predictors of poor outcomes among people with HIV. In a secondary analysis, proportion of death or requirement for mechanical ventilation did not differ between people with HIV and the matched control group. Although the investigators noted these data were gathered early in the COVID-19 pandemic, before more widespread use of COVID-19–specific therapies for hospitalized patients such as dexamethasone or remdesivir, their findings suggest that underlying comorbidities, rather than HIV itself, may be the primary driver of poor outcomes for people with HIV and COVID-19.

## Insights From ART Through Observational Studies

Arribas presented an overview of the paradigm shift from triple-drug ART to the more varied ART options available today (Abstract 45). They reviewed earlier meta-analyses, looking at triple therapy versus dual therapy, dual therapy versus monotherapy, and then explored clinical trials such as GEMINI (Genomic Medicine for Ill Neonates and Infants). They also reviewed the data behind the question of dual therapy in treatment-naive patients and concerns about drug resistance, as well as dual therapy as a maintenance regimen. Finally, they reviewed the long-acting options for dual therapy.

Observational studies can provide valuable real-life data and longitudinal lessons about ART. Burgos-Cibrian and colleagues from Spain presented an analysis of a multicenter prospective cohort of more than 900 patients with propensity matching, looking at the outcomes of people with advanced HIV and AIDS (Abstract 405). They included ART-naive individuals with advanced HIV or AIDS (defined as CD4+ cell count <200/μL or diagnosis of an AIDS-defining illness) who started ART with a 2 nRTI backbone regimen and a third drug. Primary outcome was mortality at 3 years, with secondary outcomes of virologic effectiveness (HIV RNA level ≤200 copies/mL) and immune reconstitution (CD4+ cell count >350/μL). A plurality of patients was on protease inhibitor (PI)-based regimens (44.9%), followed by nonnucleoside reverse transcriptase inhibitor (NNRTI)-based regimens (29.6%) and InSTI-based regimens (25.6%). Median CD4+ cell count of studied patients was 101/μL at baseline, and more than 30% of participants were classified with AIDS-defining illness. Median follow-up was 5 years, with 5695 person-years of follow-up. Mortality rates at 3 years trended numerically lower for individuals on InSTI-based regimens (2.6% at 3 years) than on NNRTI-based regimens (4%) or PI-based regimens (6.1%), but was not statistically significant. In those with an AIDS-defining illness, this trend was more marked, with a 5.8% mortality rate for those on InSTI-based regimens, 9.1% for those on NNRTI-based regimens, and 14.6% for those on PI-based regimens. InSTI-based regimens trended towards decreased association with mortality (HR, 0.53; 95% CI, 0.25-1.14). Individuals on InSTI-based regimens also reached the end-points of virologic suppression and immune reconstitution faster than those on NNRTI- or PI-based regimens.

Mounzer and colleagues (Abstract 406) presented data from a longitudinal OPERA (Observational Pharmaco-Epidemiology Research & Analysis) cohort of 961 treatment-naive people with advanced HIV (CD4+ cell count <200/μL) on 3-drug regimens. The investigators compared effectiveness of various 3-drug regimens and examined outcomes such as virologic suppression (HIV RNA level <50 copies/mL) and treatment discontinuation. Most patients were taking bictegravir/tenofovir alafenamide/emtricitabine (n=416), followed by dolutegravir (n=271), cobicistat-boosted elvitegravir (n=168), and boosted darunavir (n=106). Participants taking bictegravir/tenofovir alafenamide/emtricitabine were less likely to discontinue treatment. Of the cohort, 70% achieved immune reconstitution (CD4+ cell count 200/μL), but there was no difference in immune reconstitution among 3-drug regimens (*P*=.52). Participants taking bictegravir/tenofovir alafenamide/emtricitabine were numerically more likely to be virologically suppressed (HIV RNA level <200 copies/mL) than those taking boosted darunavir, but there was no statistically significant difference between bictegravir/tenofovir alafenamide/emtricitabine and dolutegravir- or cobicistat-boosted elvitegravir-containing regimens.

Nandakumar and colleagues assessed the incidence of viral load blips in individuals taking dolutegravir- or efavirenz-based regimens in Thailand (Abstract 407). They enrolled participants with acute HIV infection and measured viral loads at weeks 2, 4, 8, 12, and then every 12 weeks. Viral blip was defined as that which occurred in a participant who had achieved viral suppression who subsequently had an HIV RNA level of 20 copies/mL or above, followed by an undetectable viral load. Of the 324 participants, 280 were taking an efavirenz-based regimen, and 44 were taking a dolutegravir-based regimen. Overall incidence of viral blips was 11.5 per 100 person-years, with no difference in incidence between the dolutegravir or efavirenz groups. The dolutegravir group had a higher overall rate of viral blips, but this was not statistically significant, and the range of viral blips was higher in the dolutegravir group. However, the study authors noted that the median time to viral suppression was much shorter in the dolutegravir group (8 weeks) than the efavirenz group (23 weeks), which could have led to longer time to develop blips, explaining the higher rate of blips in the dolutegravir group.

Colby and colleagues used ultrasensitive assays to see if residual viremia in the presence of undetectable viral load on commercial testing (reflective of the presence of HIV from reservoirs) was present in people with acute HIV infection who initiated ART in Thailand (Abstract 408). The investigators enrolled participants who were diagnosed with acute HIV infection who initiated ART immediately and were virally suppressed at weeks 24 and 48. Most participants were taking an efavirenz-based regimen (73%), and 26.5% were taking an InSTI-based regimen; the median CD4+ cell count at diagnosis was 364/μL. A majority of the participants had detectable viremia on the ultrasensitive assay despite being

undetectable on a commercial assay. Those with high viral load at baseline (HIV RNA level >6 $\log_{10}$ copies/mL), advanced HIV disease at diagnosis, and longer time to viral suppression (>16 weeks) were more likely to have detectable viremia by ultrasensitive assay (*P* values <.001, <.001, and .003, respectively).

Ma and colleagues presented data on the entire Centers for AIDS Research (CFAR) Network of Integrated Clinical Systems (CNICS) cohort from January 2018 to December 2019 and examined ART regimen by class (Abstract 409). This cohort consisted of nearly 15,000 people: 96% were on ART, 61% were nonwhite race, and 55% were MSM. InSTI-based regimen comprised the majority of ART in use (72%); 39% of participants on InSTI-based regimens were on a bictegravir-containing regimen, and 37% were on a dolutegravir-containing regimen, and 69% of participants were on a tenofovir alafenamide-containing regimen. There were 458 treatment-naive individuals initiating ART, 93% on an InSTI-based regimen (73% bictegravir based, 23% dolutegravir based). Overall, this shows the national trends of InSTI-based regimens being the most used and the use of tenofovir alafenamide instead of tenofovir disoproxil fumarate in most regimens.

Davy-Mendez and colleagues examined the (CNICS) cohort and rates of virologic failure (HIV RNA level >200 copies/mL after 24 weeks of ART) in patients initiating ART and categorized these failures into 5 separate scenarios (Abstract 410). Of participants, 33% were started on an InSTI-based regimen, 37% on an NNRTI-based regimen, and 21% on a boosted PI-based regimen. The overall rates of virologic failure in the cohort were 21.5% at 2 years and 37.4% at 8 years. Higher rates of virologic failure were associated with female sex (subdistribution HR [sHR], 1.3), black race (sHR, 1.45), and lower baseline CD4+ cell count (*P*<.05 for all mentioned variables). Patients on a NNRTI-based regimen had a statistically significant higher risk of virologic failure leading to an ART-regimen switch than those on an InSTI-based regimen (sHR, 2.48; 95% CI, 1.51-4.09). Davy-Mendez and colleagues then presented data from the same cohort on use of second ART, which was defined as a new ART agent more than 8 months after ART initiation in individuals with an HIV RNA level above 200 copies/mL (Abstract 411). The rate of overall virologic failure in these individuals was quite high at 48.9%. The majority of participants were switched to an InSTI-based regimen, followed by a PI-based regimen. There was no significant difference in time to virologic failure based on ART class.

## HIV Resistance

### Resistance Patterns of Existing Agents

Krystal presented data from a study of resistance patterns to temsavir, the active agent of the HIV-1 attachment inhibitor fostemsavir, along with ibalizumab and maraviroc, given the common involvement of envelope glycoprotein gp120 in their activity (Abstract 422). The investigators examined envelope structures from participants who experienced virologic failure in the BRIGHTE (Fostemsavir in Adults with Multidrug-Resistant HIV-1 Infection[5]) trial and did not find any cross-resistance between fostemsavir and ibalizumab, suggesting there is no overlap in resistance patterns. The investigators also examined envelope sequences[6] from participants in the MOTIVATE (Maraviroc for Previously Treated Patients with R5 HIV-1 Infection) trial. Maraviroc samples still retained susceptibility to temsavir, and a majority of participants whose treatment with maraviroc failed had virologic success (a >1 $\log_{10}$ copy/mL decrease in viral load) with fostemsavir. From these samples, the investigators inferred there is no correlation between resistance to maraviroc and ibalizumab and resistance to temsavir.

Hikichi and colleagues reported on mutations in *env* (gp41) and resistance to ART (Abstract 424). The investigators previously showed that HIV can develop *env* mutations that can confer resistance to dolutegravir. They observed mutant variants with *env* mutations emerging in primary isolates independent of drug class, and some of these mutations conferred broad resistance to multiple ART classes, including InSTIs, nRTIs, NNRTIs, and PIs. Their experiments also suggested that these mutations are able to overcome ART by increasing viral cell-to-cell transmission. The investigators also examined isolates of individuals whose raltegravir-containing regimens failed and found *env* mutations similar to observed *env* mutations in their prior experiments in the absence of any specific integrase mutations. This raises the possibility of viral mutations that can confer resistance outside of specific drug-resistance mutations (DRMs).

Santoro and colleagues examined the importance of M184V on virologic success in a retrospective study that included participants who were virally suppressed (HIV RNA level ≤50 copies/mL) with a prior genotype and were switched to lamivudine/dolutegravir (Abstract 429). Median time to virologic suppression was 5.4 years, and median number of prior virologic failures was 0. This cohort had a rate of 6.9% prevalence of prior M184V (37 of 533 individuals); the median time of most recent M184V before the switch was 11 years. The investigators did not find a statistically significant increase in virologic failure in participants with M184V compared with those without M184V, but they did observe a numerical increase: 5.4% virologic failure in the group with M184V versus 2.6% in the group without M184V at 1 year, and 9.2% versus 4.4% at 2 years in these groups, respectively (*P*=.345). When groups were stratified by M184V detected 5 or fewer years, M184V detected more than 5 years before the switch, and no M184V, the investigators found there was a statistically significant increase in virologic failure, with 20%, 0%, and 2.6% at 1 year, respectively, and 20%, 5%, and 4.4% at 2 years, respectively (*P*=.007). Although the probability of virologic failure was not an increased difference after switching to lamivudine/dolutegravir, despite the presence of M184V, the numerical increase is concerning, and the recent

presence of M184V within the last 5 years appears to lead to a statistically higher rate of virologic failure. Despite this study's limitations (small sample size and retrospective design), it should give pause to those considering a switch to lamivudine/dolutegravir in the presence of prior M184V detection.

The question of transmitted drug resistance (TDR) and its role in the use of bictegravir/emtricitabine/tenofovir alafenamide was studied by Acosta and colleagues (Abstract 430). They analyzed population sequencing and next-generation sequencing of individuals enrolled in Gilead studies 1489 and 1490, 2 phase III randomized, double-blind, active-controlled studies comparing bictegravir/emtricitabine/tenofovir alafenamide with dolutegravir/abacavir/lamivudine and bictegravir/emtricitabine/tenofovir alafenamide with dolutegravir plus tenofovir alafenamide/emtricitabine, respectively. Of note, patients with nRTI DRMs conferring resistance to tenofovir alafenamide, emtricitabine, lamivudine, or abacavir were excluded from this study. The rate of TDR prevalence was 19.5%; most prevalent were NNRTI mutations (14.1%) followed by PI mutations (3.5%), nRTI (2.7%), and InSTI (1.3%) mutations. The investigators did not find a statistical difference in virologic success by week 144 (98% in those with TDR vs 97% without TDR). One participant had Q148H plus G140S and K70R and K103N but was virally suppressed at week 4 through week 144 on bictegravir/emtricitabine/tenofovir alafenamide. Participants who were not virologically suppressed (HIV RNA level ≥200 copies/mL, or did not resuppress to <50 copies/mL) underwent resistance testing; no emerging resistance was observed to emtricitabine, lamivudine, tenofovir alafenamide, abacavir, bictegravir, or dolutegravir.

Brown and colleagues presented data from the SESOTHO trial supporting the switch to second-line ART for individuals with low-level viremia (HIV RNA level 100-999 copies/mL) in Lesotho (Abstract 431). They found high rates of nRTI resistance (84%) and NNRTI resistance (86%) in their cohort. Additionally, 84% of these individuals had mutations that conferred high-level resistance to at least 2 drugs in their current ART regimen, and this persisted with 81% of individuals in the control group with resistance to at least 2 of their initial ART drugs. Given this information, the investigators suggest changing the viral threshold stated by the World Health Organization (WHO) as indication for a switch to alternate ART (currently HIV RNA level of 1000 copies/mL).

Cheung and colleagues conducted studies examining integrase mutations and confirmed that viruses with Q148H (which has a detrimental effect on viral fitness) without an accompanying G140S were rendered unable to propagate (Abstract 432). T97A, E138K, and G140S individual mutations conferred resistance to elvitegravir but not to other InSTIs. G140S plus Q148H conferred complete resistance to raltegravir and elvitegravir, and reduced activity of bictegravir, cabotegravir, and dolutegravir. Adding T97A to G140S plus Q148H conferred significant resistance to dolutegravir (>100-fold reduction), cabotegravir (>100-fold reduction), and bictegravir (47.7-fold reduction); E138K with G140S plus Q148H conferred some resistance to bictegravir, cabotegravir, and dolutegravir. All 4 mutations together (T97A/E138K/G140S/Q148H) conferred complete resistance to all InSTIs. These experiments correlated with the resistance scores from Stanford's HIV drug resistance database.

### Resistance Patterns in PrEP

Chohan and colleagues examined emerging HIV drug mutations in people who seroconverted while taking preexposure prophylaxis (PrEP) in Kenya through a national protocol (Abstract 427). The investigators reported 67 seroconversions from a population of approximately 25,000 people on PrEP, 11 (20%) of whom were noted within 6 weeks of starting PrEP. Genotyping was conducted on 30 samples, and none had K65R or K70E, 5 (17%) had M184V, and 9 (30%) had NNRTI mutations, such as K101E, K103N, V106I, G190A, and Y181C. This suggests the importance of monitoring for drug resistance in individuals who seroconvert while taking PrEP to ensure they are on a virally active regimen.

Cox and colleagues presented an ultrasensitive drug-resistance analysis from participants who seroconverted in the DISCOVER (Study to Evaluate the Safety and Efficacy of Emtricitabine and Tenofovir Alafenamide Fixed-Dose Combination Once Daily for Pre-Exposure Prophylaxis in Men and Transgender Women Who Have Sex With Men and Are at Risk of HIV-1 Infection) trial,[7] which studied the use of tenofovir alafenamide/emtricitabine or tenofovir disoproxil fumarate/emtricitabine for PrEP (Abstract 428). The investigators observed a rate of 0.5%, or 27 patients, who seroconverted while on PrEP. Genotyping and ultrasensitive analyses were conducted on the samples from participants with an HIV RNA level above 400 copies/mL; 4 of 20 (20%) participants had M184V by population sequencing but were suspected to have HIV infection at baseline, all in the tenofovir disoproxil fumarate group. With ultrasensitive testing, 1 additional participant had M184V in the tenofovir alafenamide group, with mutation present at the rate of 2%. Likely transmitted DRMs were observed in participants taking InSTIs (T66A, E92G, Y143C, Q148R, N155H), PIs (M46I), and NNRTIs (V90I, B106I, K103N, Y188L). Most of the mutations seen were detected in patients with suspected HIV-1 infection at baseline.

### Resistan ce Patterns of Novel Agents

Diamond and colleagues presented the resistance profile of MK-8507, an investigational once-weekly NNRTI currently being studied using in vitro assays (Abstract 129). This new agent is planned to be combined with islatravir, a nucleoside reverse transcriptase translocation inhibitor (NRTTI). In resistance studies, the most common mutation observed was V106A with subtype B in combination with other NNRTI DRMs. Virus strains with mutations resulting from selective pressure experiments were not commonly found in the general population (<2% prevalence). MK-8507 appears to have a similar potency and resistance profile to doravirine and rilpivirine but a

superior profile to efavirenz, maintaining activity against K103N, Y181C, and G190A, making it an attractive future once-weekly NNRTI option.

Bester and colleagues studied structural changes in HIV leading to resistance to lenacapavir (GS-6207). Lenacapavir is a long-acting HIV-1 capsid inhibitor currently in development (Abstract 420). Prior assays have determined capsid inhibitor mutations at M66I, Q67H, and N74D. The authors examined the structure, determining that these mutations inhibit the binding of GS-6207 by 3 different mechanisms causing interference at structural sites. The investigators hope to then provide the basis for developing capsid inhibitors that can escape these mechanisms.

VanderVeen presented data from a study on the effect of the above mutations of lenacapavir on HIV-1 viral replication (Abstract 128). The investigators performed single- and multicycle assays, examining susceptibility of mutant viruses to lenacapavir, and isolated 7 mutations in the presence of lenacapavir. These were not found in individuals naive to lenacapavir. M66I most greatly decreased susceptibility to lenacapavir, with a greater than 2000-fold reduction, but retained only 1.5% of the replication capacity of wild-type virus. Q67H, which decreased susceptibility to lenacapavir by 4.6-fold, retained 58% of the replication capacity of wild-type virus. This phenotype was consistent in multiple replications and multicycle assays. In multicycle assays, M66I and M66I plus Q67H mutant viruses were not detected, meaning they had no measurable infectivity. Lenacapavir retained full activity in treatment-naive individuals and in individuals with DRMs to PIs. Conversely, those with mutations to lenacapavir still retained susceptibility to PIs. Ultimately, mutations conferring the greatest resistance to lenacapavir led to mutant virus that was most impaired in terms of replication capacity.

Jeffrey and colleagues examined the resistance profile of GSK3640254 (GSK'254), a maturation inhibitor currently in development and phase IIb evaluation. Prior maturation inhibitors are rendered ineffective with mutations in *gag*, particularly V362I and 369 to 370 (Abstract 421). The investigators compared activity of GSK'254 against mutant viruses to that of a prior maturation inhibitor, GSK2141795 (GSK'795). They observed increased potency of GSK'254 compared with GSK' 795. Viruses with *gag* mutations V362I, V370A, or R286K/V370A were equally inhibited by GSK'254 as wild-type virus strains and able to inhibit p25 cleavage in Gag protein in mutant viruses compared with wild-type. GSK'254 was less potent against viruses with A364V, and its ability to inhibit p25 cleavage in Gag was reduced by 10-fold.

### Advances in Resistance Testing With Clinical Relevance

Li and colleagues presented data on DRMs in HIV proviral assays (Abstract 437). They found that defective proviral sequences are less sensitive because they have increased DRMs, specifically hypermutations. Hypermutated sequences have early stop codons, so they do not get translated into protein and, therefore, become defective and do not contribute to treatment failure. For future effective proviral drug resistance interpretations, hypermutations need to be removed; otherwise, they are overly sensitive for nonclinically significant mutations. D'Antoni and colleagues presented data showing the variability of genotyping from multiple blood draws (Abstract 438). They found a mean reproducibility of 80% with standard deviation of 25%, which highlights variability in genotyping assays to reliably detect mutations.

## ART in Children and Women With HIV

In a plenary lecture (Abstract 47), Archary provided an overview of ART drugs in treatment and prophylaxis of HIV in neonates and infants. Data on safety, dosing, and formulations of antiretroviral drugs in this age group are limited, particularly among neonates and preterm neonates. The speaker emphasized the importance of ART simplification and optimization, such as use of fixed-dose combinations and aligning neonatal and infant ART with childhood ART regimens. He also discussed the future landscape of ART for this age group, including new drugs such as islatravir and doravirine, with long-acting formulations and novel delivery mechanisms, such as bNAbs and long-acting injectable drugs that are in the pipeline.

In Abstract 174, Turkova presented results of the ODYSSEY (PENTA 20) trial, a multisite randomized noninferiority trial comparing efficacy and safe ty of dolutegravir plus 2 nRTIs (n= 350) with standard of care (n=357) in 707 children initiating first- or second-line ART in sub-Saharan Africa, Thailand, and Europe (Abstract 174). Children younger than 18 years and weighing at least 14 kg were enrolled and followed-up longitudinally, with a median follow-up period of 142 weeks. The primary outcome was a composite endpoint of time to virologic failure (defined as lack of virologic response, $<1$ $\log_{10}$ copies/mL decrease at week 24, HIV RNA level ≥400 copies/mL at 2 timepoints after week 36) or clinical failure (death from any cause or any new or recurrent WHO grade 3 or 4 adverse event) by 96 weeks. The age of the children ranged from 2.9 to 18 years, with a median age of 12.2 years. Almost one-quarter (22%) of the children had a baseline CD4+ cell count of less than 200/μL. Among children in the standard of care arm, 311 initiated ART (92% receiving efavirenz) and 396 children received second-line ART (72% receiving lopinavir/ritonavir and 25% receiving atazanavir/ritonavir). Fewer children in the dolutegravir arm (n=48; 14%) met the composite outcome of treatment failure by 96 weeks, than those in the standard of care arm (n=75; 22%), with a difference of –7.7% (95% CI, –13.2-[–2.3]; $P$= .006). Furthermore, 40 children in the dolutegravir arm and 67 children in the standard of care arm experienced virologic failure; 8 children in each arm experienced WHO grade 3 or 4 adverse events or death. There was no statistically significant difference in treatment effects between children initiating first- and second-line ART or by sex, weight, age, or baseline CD4+

cell count or viral load. Fewer children assigned to the dolutegravir arm (n=13; 4%) than to the standard of care arm (n=32; 9%) changed ART regimen during the follow-up period ($P$=.004); 2 in the dolutegravir arm and 21 in the standard of care arm changed ART because of treatment failure. The proportion of children with an HIV RNA level below 50 copies/mL and changes in CD4+ cell count and CD4 percentage from baseline at 48 and 96 weeks was similar across both arms. There were no statistically significant differences in serious adverse events between the 2 arms. At 96 weeks, weight, height, and body mass index measurements were slightly higher in children receiving dolutegravir than in those receiving standard of care, whereas mean change in total cholesterol, specifically low-density lipoprotein cholesterol level, was lower in those receiving dolutegravir (–5 mg/dL; 95% CI, –8-[–2]) than in those receiving standard of care (10 mg/dL; 95% CI, 7-13) ($P$<.001). The investigators concluded that dolutegravir-based ART was superior to standard NNRTI- and PI-based ART in children and adolescents taking first- or second-line ART, with lower treatment failure by 96 weeks and no safety concerns in those receiving dolutegravir. These findings support updated WHO recommendations of dolutegravir-based ART as the preferred regimen for children weighing at least 14 kg who are starting first- or second-line ART.

Similar findings were noted in a study conducted among 2245 children and adolescents with HIV aged 18 years or younger (median age, 8 years) in Lusaka, Zambia (Abstract 600). Children who received dolutegravir-based regimens had significantly lower odds of having viremia (HIV RNA level >1000 copies/mL) than those who received NNRTI- or PI-containing ART (OR, 0.15; $P$<.001).

Malaba and colleagues presented final results from the DolPHIN-2 (Dolutegravir versus Efavirenz in Women Starting HIV Therapy in Late Pregnancy) randomized, open-label trial that compared 268 pregnant, previously untreated women with HIV initiating dolutegravir- or efavirenz-based ART (with a 2-nRTI backbone) in their third trimester to 72 weeks postpartum in South Africa and Uganda (Abstract 175). Previously, dolutegravir-based ART was reported to be associated with superior virologic suppression over efavirenz-based ART in the first 26 weeks and at delivery. In the intent-to-treat cohort of 250 women (125 in each arm), at 72 weeks from randomization 116 (92.8%) women receiving dolutegravir-based ART experienced significantly more rapid viral suppression (HIV RNA level <50 copies/mL) than women receiving efavirenz-based ART (median time to viral suppression was 4-14 weeks [IQR, 4.00-5.14] and 12-14 weeks [IQR, 10.71-13.29], respectively; aHR, 1.93; 95% CI, 1.47-2.53). Virologic failure, defined as failure to achieve an HIV RNA level below 50 copies/mL by 24 weeks postpartum or virologic response with 2 subsequent HIV RNA levels above 1000 copies/mL, was found in 3 (2.4%) women in the dolutegravir arm and 8 (6.4%) women in the efavirenz arm. Both regimens were safe and well tolerated. Specifically, 2.2% of women experienced drug-related serious adverse events in the dolutegravir arm and 3.8% in the efavirenz arm; no infant drug-related serious adverse events were reported across both arms. In total, HIV infection was detected in 4 infants, with 3 in utero transmissions in the dolutegravir arm and 1 postpartum transmission in the efavirenz arm despite maternal viral suppression from delivery and serial negative tests in the infant, raising the concern for potential transmission during breastfeeding despite viral suppression.

Further results from the IMPAACT (International Maternal Pediatric Adolescent AIDS Clinical Trials Network) 2010 trial were presented (Abstracts 176 and 177). IMPAACT 2010 is a randomized, open-label trial conducted in 643 ART-naive women with HIV in 9 different countries who were randomly assigned at 14 to 28 weeks gestation to start to 1 of 3 regimens: dolutegravir plus emtricitabine/tenofovir alafenamide fumarate (n=217), dolutegravir plus emtricitabine/tenofovir disoproxil fumarate (n=215), or efavirenz/emtricitabine/tenofovir disoproxil fumarate (n=211). Overall, the median age of the women in the trial was 26.6 years, the baseline median CD4+ cell count was 466/µL, and the baseline median HIV RNA level was 903 copies/mL.

Suboptimal and excessive gestational weight gain during pregnancy are associated with adverse pregnancy outcomes,[8] with low weight gain associated with increased risk of maternal and perinatal death, and excessive weight gain associated with severe adverse birth outcomes. Previous reports have noted that dolutegravir-containing ART, particularly in combination with tenofovir alafenamide, leads to significant weight gain in pregnant and nonpregnant women,[9] and efavirenz- and tenofovir disoproxil fumarate-containing ART are associated with low weight gain during pregnancy.[10]

Hoffman and colleagues conducted secondary analyses of the IMPAACT 2010 study data to assess the association between antepartum weight gain and adverse pregnancy outcomes by different ART regimens (Abstract 176). Average weekly weight gain was lowest among women taking efavirenz/tenofovir disoproxil/emtricitabine/fumarate (0.291 kg), followed by dolutegravir plus tenofovir alafenamide/emtricitabine (0.378 kg) and dolutegravir plus tenofovir disoproxil fumarate/emtricitabine (0.319 kg) ($P$<.001). Higher average weight gain was significantly associated with a lower risk of any adverse pregnancy outcome across the 3 treatment arms (HR, 0.50; 95% CI, 0.25-0.97; $P$=.04). However, low weight gain, but not high weight gain, was associated with adverse pregnancy outcomes. The highest weight gain was reported in women receiving dolutegravir plus tenofovir alafenamide/emtricitabine (12.7%), followed by dolutegravir plus tenofovir disoproxil fumarate/emtricitabine (9.95%) and efavirenz/tenofovir disoproxil fumarate/emtricitabine (6.3%). The lowest weight gain was noted in women receiving efavirenz/tenofovir disoproxil fumarate/emtricitabine (30.0%), compared with dolutegravir plus tenofovir alafenamide/emtricitabine (15.0%) and dolutegravir plus tenofovir disoproxil fumarate/emtricitabine (23.6%).

Chinula and colleagues presented final results from the IMPAACT 2010 trial (Abstract 177). No significant differences through 50 weeks postpartum of maternal or infant grade 3 or greater adverse events were reported among the 3 arms. Adverse pregnancy outcome was lowest in women receiving dolutegravir plus tenofovir alafenamide/emtricitabine. Infant mortality was significantly higher in those whose mothers received efavirenz/tenofovir disoproxil fumarate/emtricitabine (6.9%) than those who received dolutegravir-based regimens (2.0%; *P*=.008). Maternal HIV viral suppression (HIV RNA level <200 copies/mL) at 50 weeks postpartum was similarly high across the 3 arms, with 96.3% in the combined dolutegravir arms and 96.4% in the efavirenz arm. Virologic failure (having 2 consecutive HIV RNA levels of 200 copies/mL or higher, at or after 24 weeks after enrollment) was significantly higher in the efavirenz-based arm (10.4%) than in the dolutegravir-based arms (4.1% for dolutegravir + tenofovir disoproxil fumarate/emtricitabine; 5.1% for dolutegravir + tenofovir alafenamide/emtricitabine; *P*=.012). ART interruptions and changes in regimen as a result of virologic failure or drug resistance were more frequent in women receiving efavirenz-based ART. HIV infection occurred in 4 infants who had been breastfed and received antiretroviral prophylaxis, with 2 infections in the dolutegravir plus tenofovir alafenamide/emtricitabine arm, 1 in the dolutegravir plus tenofovir disoproxil fumarate/emtricitabine arm, and 1 in the efavirenz/tenofovir disoproxil fumarate/emtricitabine arm. These study findings provide support for the use of dolutegravir and tenofovir alafenamide in treating women with HIV during pregnancy and postpartum.

Pharmacokinetic, safety, and virologic efficacy data of doravirine, a novel NNRTI that has activity against wild-type HIV-1 and variants with common NNRTI viral mutations such as K103N, Y181C, and G190A, were evaluated through 24 weeks in the open-label IMPAACT 2014 study among 45 adolescents with HIV aged 12 to 18 years and weighing at least 45 kg (Abstract 604). The once-daily fixed dose combination regimen consisted of doravirine 100 mg/lamivudine 300 mg/tenofovir disoproxil fumarate 300 mg. The regimen was found to be safe and well tolerated through 24 weeks. In children who were virally suppressed on stable ART, there were no virologic failures detected, and viral suppression, defined as an HIV RNA level below 50 copies/mL, was high at 95.3% (95% CI, 84.2-99.4).

## Broadly Neutralizing Antibodies for HIV Treatment in Children

The development of bNAbs, such as VRC01 and next-generation bNAbs, provides a potential novel approach for prevention and treatment of HIV-1 infection, with their breadth and potency against diverse strains.[11] The pharmacokinetics of bNAbs, which suppress HIV viral load and may deplete viral reservoirs in children, were discussed (Abstract 608). Yang and colleagues presented safety and pharmacokinetic data of intravenous VRC01LS (a bNAb variant of VRC01 directed against the CD4-binding site of the HIV-1 Env protein with 2 amino acid changes in the Fc region that extends the serum half-life) and 10-1074 (a bNAb that targets the base of the V3 loop of HIV-1 gp120) administered as dual therapy every 4 weeks to children with HIV who received early ART (from <7 days through ≥96 weeks of life) and had HIV RNA levels below 40 copies/mL for at least 24 weeks before enrollment (Abstract 609). The safety and tolerability profiles were favorable, with no infusion reactions, expedited adverse events, or grade 3 or 4 events related to dual bNAb administration reported through 32 weeks. The population half-life was 38 days for VRC01LS (which is lower than the half-life of 71 days reported in healthy adults) and 16 days for 10-1074. The investigators concluded that dual intravenous infusions of VRC01LS and 10-1074 in children achieved concentrations similar to levels seen in those who receive single bNAb infusions, with monthly dosing of VRC01LS at 15 mg/kg and 10-1074 at 30 mg/kg reaching target steady state concentrations.

Capparelli and colleagues described a composite population pharmacokinetic, 2-compartment model of VRC01LS in 21 HIV-exposed infants and 49 adults without HIV to help optimize dosing of VRC01LS for use as HIV prophylaxis and treatment in infants (Abstract 608). The infants received a weight-adjusted dose (80 mg for weight <4.5 kg and 100 mg for weight ≥4.5 kg) of VRC01LS subcutaneously within the first 4 days of life, with infants who were breastfed receiving a second dose subcutaneously 12 weeks later. The adults received 1 or 3 doses of VRC01LS intravenously (range, 5-40 mg/kg) or subcutaneously (5 mg/kg). The population pharmacokinetic model showed slow elimination of VRC01LS in infants and adults, supporting a dosing schedule of every 12 weeks.

## Pharmacokinetic Considerations for ART

### Drug-Drug Interactions Between ART and Hormonal Contraceptives

Scarsi and colleagues presented the partial results of AIDS Clinical Trials Group (ACTG) protocol A5375, which is investigating drug-drug interactions between emergency contraceptives and ART (Abstract 91). Prior studies have shown that efavirenz reduces levonorgestrel concentrations by 56%. Some guidelines recommend doubling the dose of levonorgestrel, but this has not been examined in clinical trials. A5375 enrolled women with HIV on efavirenz-based ART. Women were randomly assigned to a standard dose (n=17) or double dose (n=35) of levonorgestrel. The crucial pharmacokinetic parameter for levonorgestrel effectiveness is not clear. Double-dose levonorgestrel increased various pharmacokinetic parameters from 51% to 133% compared with standard dose, but the trough concentrations and AUC measurements were generally lower than in historic controls without HIV. No safety concerns were identified. The investigators concluded that these data support current recommendations for a double dose of levonorgestrel for women on efavirenz.

Nakalema and colleagues investigated potential drug-drug interactions between rilpivirine-based ART and levonorgestrel or etonogestrel contraceptive implants (Abstract 368). They enrolled women on efavirenz-based ART who transitioned to rilpivirine-based ART and a historic control group of women with HIV not on ART receiving contraceptive implants. The investigators found that levonorgestrel and etonogestrel concentrations were 16% to 29% higher among women receiving rilpivirine than historic controls. These differences were not thought to be clinically significant.

### Pharmacokinetic Measures of Adherence

Several presentations reported on the use of drug concentrations in dried blood spots (DBSs), a longer-term measurement of adherence and drug exposure, to predict viral outcomes of ART. Castillo-Mancilla and colleagues presented data from 433 participants receiving tenofovir disoproxil fumarate/emtricitabine plus a third agent who provided 677 paired assessments of DBSs and plasma HIV RNA (Abstract 92). The investigators prior work showed that tenofovir diphosphate concentrations in DBSs predicted HIV viremia. In this analysis, they found that emtricitabine triphosphate concentrations also predicted HIV viremia.

Odayar and colleagues evaluated tenofovir diphosphate concentrations in DBSs obtained from postpartum women with HIV (Abstract 93). The investigators performed a nested case-control study comparing women with detectable plasma HIV RNA (n=61) with those with persistent viral suppression (n=20). A total of 365 paired DBSs and plasma HIV RNA measurements were included. There was a clear dose response with lower tenofovir diphosphate concentrations being associated with future viremia. This suggests that this assay could be used to identify women in need of intervention to prevent viral rebound.

Finally, Robbins and colleagues enrolled 250 adults with HIV in South Africa with documented ART adherence challenges (Abstract 398). The investigators collected monthly DBSs and plasma HIV RNA levels. There were 21 participants who developed viral breakthrough; their tenofovir diphosphate concentrations in DBSs were consistent with fewer than 2 tenofovir doses per week, compared with 4 to 6 doses per week for those with no viral breakthrough. The investigators identified a cutoff of 400 fmol/punch that predicted a 32-times greater odds of developing viral breakthrough 1 month later. Ongoing studies are using this adherence biomarker to provide real-time feedback to clinicians and patients.

Several presentations investigated the use of urine assays to measure tenofovir concentrations. The urine tenofovir test assays for recent intake of tenofovir disoproxil fumarate as opposed to DBS assays. Phillips and colleagues evaluated a point-of-care urine tenofovir assay compared with ART adherence by self-report (Abstract 183). They found that the urine tenofovir assay was better able to predict ongoing viremia than did self-reported adherence. This could potentially identify individuals in need of adherence interventions. Sevenler and colleagues presented promising data on a new lateral flow assay that can provide semiquantitative results measuring urine tenofovir concentrations (Abstract 352). They studied people receiving tenofovir disoproxil fumarate and found a strong correlation between the assay readout and known tenofovir concentrations in urine samples.

Niu and colleagues investigated assay results as a function of time from last dose of tenofovir disoproxil fumarate (Abstract 353). They found the semiquantitative result (using visual score) and the fully quantitative result (optical readings) were highly correlated with the time since last dosing. They suggested that this could be a useful point-of-care measurement of recent tenofovir dosing.

Spinelli and colleagues investigated the use of a urine tenofovir assay in individuals receiving tenofovir alafenamide (Abstract 354). Plasma tenofovir levels are lower in individuals receiving tenofovir alafenamide than those receiving tenofovir disoproxil fumarate. The investigators used stored urine specimens from a study of participants receiving tenofovir alafenamide by directly observed therapies and identified an assay cutoff to reliably identify recent nonadherence while minimizing misclassifying adherent individuals as nonadherent. Investigators from the same group found that urine tenofovir levels were approximately 74% lower for individuals receiving tenofovir alafenamide than those receiving tenofovir disoproxil fumarate (Abstract 355).

### Gender-Affirming Hormonal Therapy in Adolescents

Yager and colleagues investigated the effects of daily use of tenofovir disoproxil fumarate/emtricitabine on the pharmacokinetics of gender-affirming hormonal therapy for young transgender men and women (Abstract 366). The investigators found that hormonal pharmacokinetics were not altered by the addition of tenofovir disoproxil fumarate/emtricitabine, and study participants maintained concentrations above target ranges recommended by the Endocrine Society. This provides reassuring data that tenofovir disoproxil fumarate/emtricitabine as PrEP will not adversely impact HIV-prevention efficacy. Additional analyses from this study found that receiving estradiol by intramuscular injection was associated with lower concentrations of tenofovir diphosphate and emtricitabine triphosphate in peripheral blood mononuclear cells than receiving estradiol orally (Abstract 367). The mechanism for this difference was unclear.

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*Financial affiliations in the past 12 months: Dr Gunaratne has no relevant financial affiliations to disclose. (Updated April 15, 2021) Dr Tieu has received grant support awarded to her institution from Gilead Science, Inc. (Updated May 17, 2021) Dr Wilkin has served as a consultant to Merck & Co., Inc/ViiV Healthcare and has received grant support awarded to his institution from Merck & Co.,*

*Inc/ViiV Healthcare. (Updated May 12, 2021) Dr Taylor has no relevant financial affiliations to disclose. (Updated May 12, 2021)*

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