Invited Review

CROI 2019: Advances in Antiretroviral Therapy

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The 2019 Conference on Retroviruses and Opportunistic Infections included many exciting advances in antiretroviral therapy (ART). Investigators presented a case report of a second patient possibly cured of HIV through an allogeneic hematopoietic stem cell transplant from a CC chemokine receptor 5-Δ 32 donor. Two clinical trials of long-acting injectable cabotegravir and rilpivirine showed promising safety, efficacy, and tolerability as maintenance ART. Test-and-treat and rapid-ART-start strategies show promise in advancing progress toward the HIV care cascade 90-90-90 Joint United Nations Programme on HIV/AIDS/World Health Organization targets. However, late diagnosis and mortality after ART initiation remain high, even in the context of HIV service scale-up, and mortality from unintentional opioid overdose in people living with HIV in the United States is on the rise. In vitro studies were presented that identified and evaluated the effect of resistance-associated mutations on ART susceptibility and elucidated mechanisms of resistance. Epidemiologic data were reported on the prevalence, impact, regional variation, and changes over time of resistance-associated mutations. Decreasing regional and national rates of resistance may be a benefit of increasing use of integrase strand transfer inhibitors (InSTIs). New findings were presented on maternal and fetal health outcomes in women of reproductive potential, drug-drug interactions between hormonal contraception and ART, and further exploration of the association between InSTIs and birth defects.

Keywords: CROI, 2019, HIV, AIDS, antiretroviral, therapy, ART, treatment strategies, investigational drugs, care cascade, resistance, infants, women

Clinical Trials and Investigational Antiretroviral Agents

Possible Cure of HIV-1 Infection

Gupta and colleagues presented on a patient living in London, England, who underwent an allogeneic hematopoietic stem cell transplant (HSCT) from a donor with a homozygous CC chemokine receptor 5 (CCR5)-Δ 32 deletion to treat Hodgkin Lymphoma (Abstract 29). (Aspects of this case are also described in "CROI 2019: Advances in Basic Science Understanding of HIV" by Stevenson in this issue.) The patient was noted to have CCR5 virus before transplant. He discontinued antiretroviral therapy (ART) 17 months after transplant. All standard and ultrasensitive plasma HIV-1 RNA levels were below the limit of detection for 18 months after cessation of ART. HIV-1 DNA declined below the limit of detection measured by clinical assay. Measured using droplet-digital polymerase chain reaction testing, 1 of 8 replicate showed low-level positivity. Three quantitative viral outgrowth assays were performed and none demonstrated inducible HIV production. Anti–HIV-1 antibodies declined over time, with progressive loss of bands on Western blot, and HIV-1 specific T-cell responses also declined.

An additional case of allogeneic HSCT from a CCR5-Δ 32 donor for acute myelocytic leukemia was presented (Abstract 394). This patient discontinued ART in November 2018, with no viral rebound to date.

Investigational Antiretroviral Drugs

Capsid inhibitor. Sager and colleagues presented pharmacokinetic data on an HIV-1 capsid inhibitor delivered via subcutaneous injection (Abstract 141). GS-6207 inhibits several steps of viral replication, including capsid assembly and disassembly, nuclear transport, and virus production. Single ascending doses of GS-6207 were tested in uninfected volunteers. Pooled safety assessments, which included those for placebo recipients, did not identify any safety concerns. All adverse events were mild or moderate, including mild injection site reactions. Drug concentrations were detected 24 weeks after a single injection and most doses exceeded the 95% effective concentration for 12 weeks or longer. The investigators noted that a study in people living with HIV is ongoing.

A patient received a stem cell transplant with a CCR5-Δ 32 deletion and remains virologically suppressed without antiretroviral therapy, becoming the second after the Berlin Patient to achieve this milestone

Yant and colleagues presented on the in vitro activity of GS-6207 (Abstract 480). This compound retained activity

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against a broad range of HIV-1 resistant to other ART classes including those with Gag polymorphisms conferring resistance to maturation inhibitors. The compound also exhibits activity against HIV-2.

Maturation inhibitor. DeJesus and colleagues presented data from a phase IIa study of a maturation inhibitor, GSK-2838232 (Abstract 142). Maturation inhibitors bind Gag and prevent proteolytic cleavage between the p24 and SP1 proteins, inhibiting production of mature virions. GSK2838232 has favorable pharmacokinetic profiles when coadministered with ritonavir. This clinical trial enrolled 33 ART-naive adults living with HIV. In the first part of the trial, GSK2838232 100 mg was administered daily of cobicistat 150 mg for 10 days. After this cohort, sequential dose cohorts were enrolled starting at 200 mg daily descending to 20 mg daily, also for 10 days. The pharmacokinetic profile supported once-daily dosing of cobicistat with a half-life of 16 hours. Investigators observed robust antiviral activity with doses from 50 mg to 200 mg daily, with a maximal plasma HIV-1 decline of 1.3 to 1.7 $\log_{10}$ copies/mL, and antiviral activity continuing for 2 to 3 days after the last dose. One participant exhibited phenotypic resistance to GSK2838232 and another had virus that was not sensitive to GSK-2838232 at baseline. No safety concerns were identified. One participant harbored virus with reduced susceptibility to GSK2838232 at baseline and 2 participants had treatment emergent A364A/G *gag* mutations.

A human immunoglobulin G1 antibody targeting the V3 epitope in Env exhibits potent neutralizing activity against 60% to 70% of global HIV-1 isolates

Broadly neutralizing monoclonal antibodies. Stephenson and colleagues presented data on PGT121, a human immunoglobulin G1 antibody targeting the V3 epitope in the envelope (Env) (Abstract 145). PGT121 exhibits potent neutralizing activity against 60% to 70% of global HIV-1 isolates. Investigators enrolled 50 adults: 30 were living with HIV (half were viremic and half were virally suppressed), 43 received varying doses of PGT121, and 7 received placebo. PGT121 appeared safe, with only minimal local reactions, including when given subcutaneously. The elimination half-life was 23.5 days among individuals without HIV infection, 19 days for virally suppressed individuals living with HIV, and 13 days for viremic individuals. Among individuals with an HIV RNA level of 3.5 to 5.0 $\log_{10}$ copies/mL at baseline, 5 demonstrated a virologic response, with a median decline of 1.7 $\log_{10}$ copies/mL through day 7, and 4 participants had no response. All rebound viruses were resistant to PGT121. Two participants with baseline plasma HIV-1 RNA levels of 200 to 700 copies/mL achieved virologic suppression at 7 days and maintained suppression through 140 days and their PGT121 concentrations slowly declined to below the limit of detection; one experienced viral rebound at day 168, without resistance to PGT121, and the second remained virally suppressed. Investigators did not observe enhanced anti–HIV-1 cellular immunity as a result of antibody-antigen complexes, known as the "vaccinal effect," with broadly neutralizing monoclonal antibodies.

Clinical Trials of Investigational Initial ART and ART Switch

Injectable long-acting (LA) cabotegravir (CAB) and rilpivirine (RPV). Swindells and colleagues presented the results from ATLAS (Antiretroviral Therapy as Long-Acting Suppression), a randomized, open-label trial comparing LA injectable CAB and RPV with standard 3-drug oral ART (Abstract 139). They randomly assigned 616 participants with sustained virologic suppression on a nonnucleoside reverse transcriptase inhibitor (NNRTI), protease inhibitor (PI), or integrase strand transfer inhibitor (InSTI) with 2 nucleoside reverse transcriptase inhibitors (nRTIs) (33% women, 32% nonwhite, 26% older than 50 years). The control group continued their oral regimen through 48 weeks. The LA injectable group changed their existing ART to oral CAB and rilpivirine for 4 weeks. Those tolerating the drugs and maintaining virologic suppression changed to monthly injections of CAB and RPV. The primary endpoint was a plasma HIV-1 RNA level of 50 copies/mL or higher 48 weeks after randomization. This occurred in 1.6% of the LA group and 1.0% of the control group (difference, 0.6%; 95% confidence interval [CI], -1.2% to 2.5%). This met the prespecified definition of noninferiority. A key secondary objective was achieving a plasma HIV-1 RNA level below 50 copies/mL, according to the US Food and Drug Administration (FDA) snapshot algorithm. This was observed in 92.5% and 95.5%, respectively (difference, -3.0%; 95% CI, -6.7% to 0.7%). This also achieved noninferiority. Three participants in the LA arm discontinued because of injection site reactions. Three participants in the LA arm discontinued for lack of virologic activity,: 2 had subtype A1 virus, 1 had AG virus, all developed RPV resistance, and 1 developed CAB resistance.

Data from the FLAIR study showed noninferiority when comparing injectable cabotegravir/rilpivirine with oral dolutegravir/abacavir/lamivudine

Orkin and colleagues presented the results from FLAIR (First Long-Acting Injectable Regimen), a randomized, open-label, clinical trial that enrolled ART-naive adults (Abstract 140). There were 629 participants who started dolutegravir (DTG)/abacavir (ABC)/lamivudine (3TC) for 20 weeks. If participants maintained HIV-1 plasma RNA levels below 50 copies/mL at week 16, then they were eligible for randomization at week 20; 569 participants (22% female, 26% nonwhite, 11% older than 50 years)

were randomly assigned to continue DTG/ABC/3TC (control group) or change to LA injectable CAB and RPV. The primary endpoint was a plasma HIV-1 RNA level of 50 copies/mL or higher 48 weeks after randomization. This occurred in 2.1% of the LA group and 2.5% of the control group (difference, -0.4%; 95% CI, -2.8% to 2.1%). This met the prespecified definition of noninferiority. A key secondary objective was achieving a plasma HIV-1 RNA level below 50 copies/mL, according to the US FDA snapshot algorithm. This was observed in 93.6% and 93.3%, respectively (difference, 0.4%; 95% CI, -3.7% to 4.5%), which also achieved noninferiority. Only 2 participants in the LA arm discontinued because of injection site reactions. Four participants in the LA group discontinued because of lack of virologic activity including 3 with protocol-defined virologic failure: all 3 had subtype A1 virus, all developed CAB resistance, and 2 of 3 developed RPV resistance. These studies establish the safety, tolerability, and efficacy of monthly LA injectable CAB and RPV for maintenance therapy of HIV-1 infection. Injection site reactions were common in both trials and were reported more commonly with the initial injections. Participants expressed greater satisfaction with the injectable therapy. Further analyses are needed to determine the relationship between subtype A1 virus and the virologic failure with this regimen.

DTG/3TC. Underwood and colleagues presented an analysis of the GEMINI 1 and 2 trials, which enrolled treatment-naive adults living with HIV and randomly assigned them to DTG plus 3TC (2-drug) or a standard (3-drug) regimen (Abstract 490). The proportion of participants with target not detected on the viral load assay was compared with HIV-1 measured below the limit of the detection. The proportions achieving target not detected were similar in the 2-drug and 3-drug groups at week 48 (77% vs 73%; difference, respectively; 3.8%; 95% CI, -0.6% to 8.2%) and all earlier time points. The time to achieving target not detected was also similar in both groups.

PRO140. Dhody and colleagues presented data on PRO140 (leronlimab), an investigational monoclonal antibody that blocks binding of HIV to CCR5 (Abstract 486). They enrolled participants with prolonged viral suppression with CCR5-mediated HIV-1, measured by phenotypic testing of proviral DNA. The investigators studied a series of doses given by weekly subcutaneous injection. Participants stopped other ART 1 week after the first injection and were maintained on PRO140 alone thereafter. Investigators observed relatively high rates of virologic failure at doses of 325 mg and 525 mg. They presented interim data on the 700 mg cohort. Among 43 participants, 6 experienced viral rebound by week 12, and no additional viral rebounds were observed through week 24. No participants developed reduced susceptibility to PRO140 or altered coreceptor tropism.

Archived nRTI resistance and response to an InSTI plus 2 nRTIs. GS-US-380-4030 is an ongoing double-blinded clinical trial that enrolled 585 people living with HIV who were virally suppressed on dolutegravir (DTG) plus tenofovir disoproxil fumarate (TDF)/emtricitabine (FTC) or tenofovir alafenamide (TAF)/FTC and had no history of InSTI resistance (Abstract 551). Participants were randomly assigned to bictegravir (BIC)/TAF/FTC or DTG plus TAF/FTC. Proviral HIV-1 DNA was genotyped to characterize nRTI resistance in addition to historical resistance testing. The blinded week 12 interim results were presented. Virologic suppression was achieved in 99%. Among 30 participants harboring K65R or more than 3 thymidine analogue mutations, 97% (29/30) were virally suppressed at week 12 compared with 99% of those with any other nRTI resistance and 99% with no nRTI resistance. The data support the use of these regimens in persons with nRTI resistance. However, longer-term follow-up is needed.

Andreatta and colleagues performed a similar analysis of data from 2 studies that enrolled virally suppressed participants and randomly assigned them to BIC/TAF/FTC or a comparator regimen (Abstract 552). Participants with known nRTI resistance were excluded from these trials, but genotyping of proviral HIV-1 DNA found that 22% harbored nRTI resistance mutations, mostly M184V/I and thymidine analogue mutations. Among 70 participants with nRTI resistance detected, 67 (96%) maintained virologic suppression through 96 weeks.

Raltegravir versus efavirenz during pregnancy. Mirochnick presented a randomly assigned, open-label clinical trial of raltegravir (RAL) versus efavirenz (EFV) given with zidovudine and lamivudine in pregnant women living with HIV at 20 to 37 weeks of gestation (Abstract 39LB). Of 408 women randomly assigned, 307 were included in the primary per-protocol population with plasma HIV-1 RNA levels above 200 copies/mL and no resistance to study drugs at study entry. Women randomly assigned to RAL were more likely to achieve a plasma HIV-1 RNA level below 200 copies/mL at the time of delivery than those assigned to EFV (94% and 84%, respectively). This difference was only observed in women who were at 28 to 37 weeks of gestation at enrollment. Tolerability was very high in both groups and there was no difference in maternal or infant safety outcomes. There were 6 cases of HIV transmission to infants in the EFV group and 1 in the RAL group (P=.06), all in women who enrolled after 28 weeks of gestation. These data support the use of RAL for preventing HIV transmission during pregnancy, especially when initiating later in pregnancy.

Khoo and colleagues presented data from a randomized, open-label clinical trial of DTG versus EFV given with 2 nRTIs to women living with HIV in their third trimester of pregnancy (Abstract 40). Investigators hypothesized that a faster decline in plasma HIV-1 RNA with DTG would reduce mother-to-child transmission (MTCT) of HIV. There were 249 women included in the intention-to-treat analysis. The primary endpoint of achieving a plasma HIV-1 RNA level below 50 copies/mL at delivery was achieved in 74% in the DTG group and 43% in the EFV group (P<.0001). However, 3 MTCTs occurred, all in the DTG

group, and all likely occurred in utero. Four stillbirths occurred that were deemed unrelated to medications, all in the DTG arm.

Novel Investigational ART for Infants, Children, and Adolescents

VRC01LS in infants. McFarland and colleagues presented data on the safety and efficacy of VRC01LS a broadly neutralizing monoclonal antibody targeting the CD4 binding site, in infants born to mothers living with HIV (Abstract 45). LS refers to amino acid modifications of antibodies, methionine to leucine (L) and asparagine to serine (S), which prolong the half-life of the antibody. Investigators enrolled a cohort of non-breastfed infants who received a single subcutaneous dose of VRC01LS and a breastfed cohort that received 2 subcutaneous doses. All infants were started on ART prophylaxis and received VRC01LS within 5 days after birth. There were no grade 3 or 4 adverse events related to VRC01LS. Grade 1 or 2 local injection site reactions were noted and resolved within 24 hours. The pharmacokinetic parameters were similar to those observed in adults. Investigators concluded that administration of broadly neutralizing monoclonal antibodies is feasible in newborn infants, and future studies will examine the role

Data support the durability of viral suppression achieved by ibalizumab, a monoclonal antibody that prevents CD4 attachment

of broadly neutralizing monoclonal antibodies in treatment of infants and children.

Gaur and colleagues presented data on a single-tablet regimen of BIC/FTC/TAF in children and adolescents living with HIV (Abstract 46). Investigators enrolled 100 virally suppressed individuals on other combination ART regimens (50 adolescents aged 12-17 years and 50 children aged 6-11 years). The pharmacokinetic endpoints were presented previously. No substantial safety concerns were identified. One participant discontinued because of insomnia and anxiety. Among 75 participants who have reached week 48, 74 had plasma HIV-1 RNA levels below 50 copies/mL and no viral resistance emerged. Participants found the study drug to be palatable with an acceptable shape and size. The investigators concluded that this was a promising single-tablet regimen for children and adolescents living with HIV.

Clinical Trials in ART-Experienced Populations

Second-line therapy with DTG plus 2 nRTIs. Brown and colleagues presented additional analyses from the DAWNING (Comparative Efficacy and Safety Study of Dolutegravir and Lopinavir/Ritonavir in Second-line Treatment) study, a randomized clinical trial of DTG plus 2 nRTIs versus ritonavir-boosted lopinavir (LPV/r) plus 2 nRTIs in people whose initial NNRTI-based regimen failed (Abstract 144). The nRTI was selected based on resistance testing, and participants were required to have at least 1 nRTI with clinical activity for enrollment. Investigators analyzed the relationship between virologic efficacy, baseline nRTI resistance mutations, and choice of nRTI. nRTI resistance-associated mutations (RAMs) were present in 90% of participants; M184V/I with or without other nRTI RAMs was observed in 82% of participants. Most participants received zidovudine plus 3TC, or TDF plus 3TC or FTC. DTG was superior to LPV/r: 84% versus 70% with virologic suppression at week 48. The virologic efficacy of DTG and 2 nRTIs appeared similar for those with and without M184V/I. Among those with M184V/I, the virologic efficacy of DTG plus 2 nRTI appeared similar whether or not 3TC or FTC was used. Similar virologic efficacy was observed in those harboring K65R, and in those with 1 or more thymidine analogue mutations.

Ibalizumab. Emu and colleagues presented 96-week data on ibalizumab, a monoclonal antibody that prevents CD4 attachment, currently approved for highly treatment-experienced patients living with HIV (Abstract 485). Of the 40 participants originally enrolled, 27 were still receiving ibalizumab at week 25 when data were last presented. Of these, 22 were still receiving ibalizumab through week 96 (2 patients died, unrelated to ibalizumab; 2 withdrew consent, and 1 physician decided to discontinue). Of the 16 patients with viral suppression (HIV RNA <50 copies/mL

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at week 25), 14 maintained suppression through week 96, and 1 participant achieved viral suppression. These data support the durability of viral suppression achieved with this compound.

The HIV Care Cascade and Getting to 90-90-90

Fauci gave an impassioned description of the new US plan for ending the HIV epidemic announced by President Trump in the 2019 State of the Union speech. Fauci highlighted the tools we have at our disposal to end the epidemic, including preexposure prophylaxis (PrEP) and treatment as prevention (TasP), and described our moral obligation to set ambitious goals. The plan focuses on geographic and demographic "hot spots" in the United States. Forty-eight counties have more than 50% of new HIV diagnoses, and 7 southern states have disproportionate incidences of HIV in rural areas. Black people, people younger than 35 years, and men who have sex with men also bear a disproportionate burden of the US HIV epidemic. Fauci anticipates new resources allocated for PrEP and ART through the Centers for Disease Control and Prevention (CDC) and the Health Resources and Services Administration (HRSA) Ryan White HIV/AIDS Program.

The National Institutes of Health (NIH) will reallocate existing budget to cover implementation science work through existing Centers for AIDS Research (CFAR) locations, although there are some notable geographic discrepancies between priority areas and CFAR locations. Fauci noted that this initiative differs from prior efforts because it is being undertaken by numerous Health and Human Services agencies simultaneously and focuses on specific target populations. Although we now have the tools to end the HIV epidemic, time will tell whether the resources and political will allocated to this effort are sufficient to overcome substantial obstacles, such as access to care, the growing opioid epidemic, HIV-associated stigma, and discrimination.

Data on the HIV Care Cascade and the Implications of U=U

Throughout this section we will use the following definitions of HIV care cascade metrics. The "first 90" refers to the percentage of people living with HIV who are aware of their HIV diagnosis, and the target is 90%. The "second 90" refers to the percentage of people living with HIV who know their HIV serostatus and are receiving ART. The second 90 target is 90%, or 81% of total people living with HIV in a community. The "third 90" refers to the percentage of those on ART who have achieved viral suppression, traditionally defined as the most recent HIV RNA measurement being less than 200 copies/mL, although exceptions will be noted. The target for the third 90 is 90%, or 73% of people living with HIV in a community.

Several investigations of treatment as prevention, covered in "CROI 2019: Advances in HIV Prevention and Plans to End the Epidemic" by Buchbinder and Liu in this same issue, demonstrated an impact on the HIV care cascade. The PopART (Population Effects of Antiviral Therapy to Reduce HIV Transmission) trial (Abstract 92LB) examined differences between immediate ART and a package of prevention and linkage interventions by community HIV care practitioners, the same interventions and ART per treatment guidelines, and standard of care (SOC) in 21 urban communities in Zambia and South Africa. In addition to effects on population incidence, investigators noted that overall ART coverage met the care cascade's first 90 target in both intervention arms. There was also a statistically significant 16% increase in virologic suppression with immediate ART initiation, compared with SOC.

Wirth and colleagues presented care cascade data from the Ya Tsie study (Abstract 95), a community-level cluster randomized trial in Botswana in which a package of HIV prevention and treatment interventions led to a 30% reduction in population HIV incidence in the treatment communities. They conducted a postintervention survey in a subsample of 6 paired communities to determine care cascade outcomes in April 2018, compared with preintervention baseline (October 2013) and found statistically significant improvement in all 3 care cascade metrics between intervention and SOC communities. The first 90 increased from 84% to 93% in the intervention communities, compared with 86% to 88% in the SOC communities. For the second 90, ART coverage increased from 72% to 90% in intervention communities, compared with 76% to 86% in SOC communities. The third 90, viral suppression, increased from 70% to 88% in intervention communities, compared with 75% to 83% in SOC communities. A post hoc analysis also revealed that time to ART initiation was 367 days in SOC and 69 days in intervention communities.

Universal test-and-treat strategies appeared to have a profound impact on the HIV care cascade in the context of the PopART, Ya Tsei, and Rakai Community Cohort studies but did not have a similar benefit at the national level in Brazil

Patel and colleagues presented data from the Rakai Community Cohort Study on the impact of a universal test-and-treat program implemented in 2013 in fishing communities around Lake Victoria in Uganda, a mobile population with a high burden of HIV (Abstract 96). Investigators previously reported dramatic improvements in the care cascade between 2013 and December 2016, surpassing all 90-90-90 targets. In this analysis, 1883 individuals with viral load data at 2 time points were included, to examine changes in virologic suppression over time. Investigators found that prevalence of durable viral suppression (HIV RNA level <400 copies/mL at both paired time points, at least 12 months apart) was 50%. Between December 2011 and December 2016, population-level viral suppression increased from 37% to 77% for women and 21% to 58% for men. Predictors of persistent viremia (HIV RNA level >400 copies/mL at both time points) were an age of 15 to 29 years, having never married, migrating into the cohort at any time during the study period, and having more than 1 sexual partner in the past year.

Data on the "real-world" impact of universal treatment implementation in Brazil suggest less favorable outcomes. Chaisson and colleagues used national surveillance and patient monitoring databases to determine ART uptake between 2014 and 2017 in Brazil, which recommended ART regardless of CD4+ cell count in December 2013, 2 years before its adoption by the World Health Organization (WHO) (Abstract 1022). Of 5750 patients newly diagnosed with HIV between 2014 and 2016, 51% had initiated ART during the observation period. Median time to ART start declined over time, from 46 days to in 2014 to 21 days in 2016. There was a statistically significant association between ART initiation within 3 months and diagnosis in either 2015 or 2016, compared with diagnosis in 2014, for patients in the public sector. However, overall ART initiation rates remained low 3 years after implementation of national test-and-treat guidelines.

Universal test-and-treat strategies appeared to have a profound impact of the HIV care cascade in the context of the PopART, Ya Tsei, and Rakai

Community Cohort studies but did not have a similar benefit at the national level in Brazil. Offering a unique and important perspective on the last step in the care cascade, Foote presented community perspectives on the Undetectable=Untransmissable (U=U) campaign (Abstract 118). Foote noted that U=U reduces stigma for people living with HIV and urged that existing resources be updated to incorporate U=U messages. She proposed specific language for practitioners for clarity and consistency (eg, using terminology like "prevents HIV" or "can't transmit" is preferred to "helps prevent HIV" or "is extremely unlikely to transmit"). Foote also urged practitioners to use morally neutral language to avoid unintentionally devaluing individuals with detectable viral loads. Finally, she highlighted areas in which messaging should be clearer, including that U=U is about sexual transmission of HIV and not transmission through breastfeeding or needle sharing and that U=U prevents HIV but not other STIs.

Rapid Start and Test-and-Treat Strategies to Get to 90-90-90

Puttkammer and colleagues examined the impact of the Haitian national "Test and Start" program, which prioritized rapid initiation of ART after HIV diagnosis and was launched in July 2016 (Abstract 1017). Data from a national electronic medical record system and HIV case-based surveillance system were used to determine time to ART initiation and retention on ART 6 and 12 months after initiation in 148,680 people living with HIV in Haiti. There were clear and sustained reductions in time to ART initiation by year of diagnosis between 2010 and 2018, with 75% initiating ART within 1 year of diagnosis in 2017 and more than 90% of individuals diagnosed in early 2018 initiating ART within the first 2 months. However, in unadjusted and multivariate models, adjusting for sociodemographic and clinical characteristics, there was a surprising association between ART initiation after the day of diagnosis and retention on ART at 6 months (adjusted model) and 12 months (unadjusted model). In the adjusted model, ART initiation between 1 and 4 weeks after diagnosis showed the greatest benefit (adjusted odds ratio [aOR], 1.31; 95% CI, 1.13, 1.51) over same-day ART initiation. Despite other studies documenting the benefits of same-day ART initiation, such as the Thai Red Cross Anonymous Clinic program highlighted in the N'Galy-Mann Lecture given by Phanuphak, these data demonstrate that the impact of same-day start may differ by context.

The SLATE (Simplified Algorithm for Treatment Eligibility) trial evaluated a clinical algorithm to determine eligibility for immediate ART in South Africa and Kenya. The SLATE algorithm assesses individuals presenting for ART initiation for possible challenges to same-day start, including signs or symptoms of illness, substance use, prior ART, other comorbidities, and lack of individual readiness for ART. The trial individually randomly assigned patients presenting for any HIV care, including HIV testing, to either the SLATE algorithm or SOC. South African data were presented last year.[1] Rosen and colleagues presented data from the Kenya sites (Abstract 1018), where 98% of individuals enrolled said they would initiate same-day ART if given a choice. However, only 55% of individuals randomly assigned to the SLATE intervention arm were eligible for same-day initiation per the algorithm, and 85% of those determined ineligible were disqualified for symptoms of tuberculosis. There was no difference in retention in care at 8 months between the 2 study arms, but loss to follow-up was high at approximately 40% of all patients. In Kenya, the majority of loss to follow-up occurred after the initiation of ART. The investigators have revised the SLATE algorithm to be less restrictive regarding eligibility for same-day ART and further studies are ongoing.

The context and structure of rapid start programs is important and there may be a disadvantage to same-day start for some individuals

Herce and colleagues (Abstract 1020) determined the impact of a universal test-and-treat program in 3 correctional facilities in Zambia and South Africa. The program was acceptable to most participants, and 86% of the 975 enrolled participants started ART, with a median time to ART start of 1 day after enrollment. As anticipated, follow-up was challenging, and 58% of participants initiating ART were transferred or released from the facility before 6 months of follow-up. Of those remaining in the facilities, 94% were still in care but only 78% had a viral load test result. Viral load suppression (HIV RNA level <1000 copies/mL) was found in 97% of those with tests completed.

Pry and colleagues at the Zambia Center for Infectious Diseases Research implemented a linkage assessment tool to examine the reasons people were declining same-day ART initiation across 3 HIV treatment facilities participating in the national test-and-treat program (Abstract 1024). Of 1274 eligible individuals, 9.9% declined same-day ART initiation and were asked about 22 potential personal, social, and structural reasons for declining. The most common barrier cited was "clinics are too crowded" (47.8%) followed by "friends and family will condemn me" (36.0%), and "people will see me getting medication" (32.6%). Demographic characteristics associated with declining same-day ART initiation included being older than 25 years, with the highest odds of declining ART in individuals older than 50 years (aOR 15.76; 95% CI, 10.57, 23.49); female sex; and receiving care in an urban or rural health clinic rather than a hospital setting. Although the study is limited by a lack of data on when and if participants initiated ART, it provides insights into the primary structural and personal barriers to same-day ART initiation. Taken in context with the data on same-day ART from Haiti and the SLATE trial above, these data suggest that the context and structure of rapid start programs is important and there may be a disadvantage to same-day start for some individuals.

New Data on HIV Treatment Outcomes and Mortality

Results from the SEARCH (Sustainable East Africa Research in Community Health) trial in Uganda were presented at the International AIDS Conference in 2018,[2] and Kamya and colleagues presented an oral abstract at CROI 2019 evaluating the impact of the SEARCH intervention on 3-year mortality (Abstract 138). SEARCH was a pair-matched randomized study of 32 rural Ugandan communities in the setting of population-based HIV testing,

The opioid epidemic disproportionately impacts people living with HIV and could affect improvements in mortality conferred by ART in the United States

comparing SOC linkage and treatment to a patient-centered test-and-treat model that included warm hand-offs, rapid ART initiation, flexible clinic hours, and mobile phone triage. This analysis examined 3-year mortality due to illness in those with baseline CD4+ cell counts less than 350 cells/μL, with 22% of the individuals identified as living with HIV. Mortality among those with CD4+ counts less than 350 cells/μL was 28% lower in the intervention communities. However, when stratified by sex, the intervention effect was only statistically significant among men. These data imply that population-based testing combined with linkage to care and rapid ART initiation can reduce mortality even for those late to care, although more data are needed to understand the sex discrepancy. Borgdorff and colleagues also presented data on mortality in the context of population-based HIV counseling, testing, and linkage programs during scale-up of HIV services in rural western Kenya (Abstract 146). Investigators pooled data from a regional health and demographic surveillance system, which used community health worker reports and confirmation of deaths with family or community members for mortality ascertainment, and results from the regional home-based counseling and testing program. All-cause mortality in the community decreased from 10.0 per 1000 in 2011 to 7.4 per 1000 in 2016. There was a statistically significant difference between age- and sex-adjusted mortality for those living with HIV ever on ART (2.8/1000), those living with HIV not reporting ART use (5.3/1000), and those without HIV (referent). Data on sex and CD4+ cell count differences in mortality are forthcoming, making direct comparison to SEARCH trial data impossible. However, these findings demonstrate that mortality rates among people living with HIV continue to decrease in this region, although they are still substantially higher than in those without HIV, even in the context of HIV service scale-up. The investigators also proposed the possibility of using population mortality as a surrogate indicator for HIV-associated mortality, which would be relevant in areas with high HIV prevalence and reliable mortality estimates.

Bosh and colleagues at the CDC presented data from the US National HIV Surveillance System assessing the rates of unintentional opioid overdose deaths (Abstract 147). They found that between 2011 and 2015, overall mortality for people living with HIV decreased by 13%, and opioid overdose–related deaths increased by 43%. These trends are more pronounced than those in the general population. Among people living with HIV, opioid overdose deaths rose from 1.2% of deaths in 2011 to 2.0% in 2015. Over the same period in the general population, opioid overdose deaths rose from below 1.0% to 1.1%. Opioid overdose deaths were much more common in individuals reporting injection drug use as their HIV transmission risk factor and in older age groups, although the rate increased across all risk factor and age categories. These data imply that the opioid epidemic disproportionately impacts people living with HIV and could affect improvements in mortality conferred by ART in the United States.

Implications of New Strategies for Laboratory Testing

The impact of CD4+ cell count measurements. As CD4+ cell count criteria for ART initiation are no longer recommended, HIV treatment programs are considering discontinuation of CD4+ cell count monitoring. Sikombe and colleagues explored the possible consequences of no CD4+ cell count monitoring, by examining mortality in people living with HIV in Zambia initiating ART without a pretreatment CD4+ cell count measurement (Abstract 148). They propose that, in their cohort, absence of pretreatment CD4+ cell count measurement is usually caused by reagent being out of stock, equipment failure, or other non–patient-associated factors, creating a natural experiment where absence of CD4+ cell count monitoring is random and its consequences can be examined. Among 33,911 individuals initiating ART, 37.7% did not have a pretreatment CD4+ cell count measured. Two-year mortality in these individuals was 11.5%, compared with 6.6% in those with a documented pretreatment CD4+ cell count measurement. After adjusting for WHO disease

CD4+ cell count monitoring at ART initiation is becoming less common, which poses a clinical challenge for the 25% of individuals presenting with advanced HIV disease

stage, sex, age, and clinic site, the hazard ratio (HR) for mortality remained elevated (HR, 1.45; 95% CI, 1.06, 1.97) in individuals who did not have pre treatment CD4+ cell count measurements, compared with those who did. Although these findings imply a potential disadvantage to the elimination of a pretreatment CD4+ cell count measurement, it is difficult to determine whether unmeasured confounders, such as clinician judgement, impacted the results.

Leeme and colleagues also explored the utility of CD4+ cell count monitoring in the era of test-and-treat strategies and viral load monitoring in Botswana (Abstract 149). Using national laboratory system data on 14,425 patients initiating ART between January 2015 and December 2017, 25% had a baseline CD4+ cell count less than 200 cells/μL. Of those with CD4+ cell counts above 200/μL at baseline, only 3.6% experienced a drop to less than 200/μL, 79% of whom remained virally suppressed. The majority (74%) of the individuals with CD4+ cell counts below 200/μL and suppressed viral loads had CD4+ cell counts above 200/μL on repeat testing. The investigators concluded that baseline CD4+ cell count testing remains important, even in a setting where a well-developed HIV care system exists, because it is important to identify those presenting to care with advanced immunosuppression. However, they questioned the utility of ongoing CD4+ cell count monitoring if viral load data are available, particularly once individuals achieve CD4+ cell counts above 200/μL.

Zaniewski and colleagues examined trends in CD4+ cell count and viral load monitoring across 6 countries supported by PEPFAR (the US President's Emergency Plan For AIDS Relief) in Southern Africa from 2005 to 2018, using data from the IeDEA (International epidemiology Databases to Evaluate AIDS) cohort (Abstract 150). Among 542,138 adults initiating ART, there was variation by country in CD4+ cell count monitoring trends, with declines in monitoring in South Africa and Malawi but not in other countries. There was also heterogeneity within the cohort in viral load testing, with South Africa, Malawi, and Zimbabwe all scaling up viral load testing. Overall, a mixed effects model adjusted for age and sex showed that CD4+ cell count measurement at ART initiation decreased over time (OR, 0.92 per year), as did presentation with a CD4+ cell count less than 200/μL (OR, 0.79 per year) and treatment failure (OR, 0.95 per year), all statistically significant differences. However, the adjusted odds of having a viral load measurement after ART initiation increased annually (OR, 1.04). These data when examined alongside data from the other 2 abstracts on CD4+ cell count measurements prior to ART initiation, suggest that monitoring of advanced disease at initiation is becoming less common. This could pose clinical challenges, considering the ongoing presence of advanced disease in a substantial proportion of individuals initiating ART, comprising 20% to 25% in the studies presented here.

New laboratory tests to monitor adherence. Phillips and colleagues presented data on the utility of dried blood spot measurements of tenofovir levels for adherence monitoring (Abstract 462). Among 137 women enrolled, reported adherence was high, with 56% of women reporting 100% adherence. However, dried blood spot tenofovir concentration had a superior area under the curve (AUC) to self-report (AUC, 0.926 vs 0.756) and a comparable AUC to plasma measurements of EFV (AUC, 0.903) and tenofovir (AUC, 0.864). Although some differences in test performance were noted among black participants, these data suggest that ART concentrations measured with dried blood spots are a strong predictor of viral suppression. This technology could be adapted as a point-of-care assay for adherence that is more accurate than self-report and less costly than measuring plasma ART concentrations.

Another novel adherence measure was evaluated by Haaland and colleagues, who used urine FTC and tenofovir concentrations to predict adherence (Abstract 465). In a study of 18 men without HIV, t urine FTC levels correlated with plasma FTC levels, but urine tenofovir levels did not correlate with plasma tenofovir levels. When daily dosing with TDF/FTC was compared with daily dosing of TAF/FTC/elvitegravir/cobicistat, urine tenofovir levels in participants receiving TAF did not correlate with adherence. Based on these data, urine FTC level could be used as a point-of-care test for adherence to ART regimens containing this medication.

Prevalence of virologic failure, low-level viremia, and viral blips after virologic suppression. Lee and colleagues examined the risk of virologic failure, low-level viremia (HIV RNA level of 51-199 copies/mL) and viral "blips" (HIV RNA level of 51-199 copies/mL followed by viral suppression) in 16,944 people living with HIV within the NA-ACCORD (North American AIDS Cohort Collaboration on Research and Design) (Abstract 97). The time between initiation of ART and viral suppression (HIV RNA level <50 copies/mL) was highly predictive of virologic failure. For those in whom it took more than 12 months to achieve virologic suppression, the difference in risk for virologic failure at 6 years was 9.84 (5.08, 19.5) compared with those who achieved virologic suppression in less than 6 months. Black persons and persons who inject drugs were also statistically more likely take more than 12 months to achieve viral suppression.

The investigators did not find any differences in risk for low-level viremia or viral blips across various clinical and demographic predictors. These findings highlight the importance of rapid suppression after ART initiation, which may be clinically important and a marker for other barriers to ART success. However, they are limited by the time frame examined (2006 to 2015), during which InSTIs were less commonly used, since this class of ART is known to achieve viral suppression more rapidly than many other initial ART options.

Novel Data on Epidemiology and Implications of Antiretroviral Drug Resistance

Characterization of Antiretroviral Drug Resistance Mutations

Mutations in the envelope glycoprotein: a potential mechanism for drug resistance outside of target genes. After long-term passage of wild-type virus in the presence of PIs, InSTIs, nRTIs, and NNRTIs, Pham and colleagues (Abstract 540) selected antiretroviral escape mutants with mutations in the Env glycoprotein and Vpu but lacking changes in the target genes. These

antiretroviral resistance mutants were identified in 2 different T-cell lines (one favoring cell-free transmission and another favoring cell-to-cell transmission) and 2 viral subtypes with different coreceptor tropism. The gp41 envelope protein mutations Env-A556T and Env-A539V exhibited multiclass drug resistance and a 4- or 5-fold change to DTG. Several of the Env mutations positions are highly conserved across HIV-1 clades, and 2 of the Env mutations (Y61H and A539V) are found in the Los Alamos National Laboratory clinical database. These findings demonstrate that *env* can contribute to broad HIV drug resistance in vitro and may be a mechanism by which drug resistance is conferred outside of target genes. Further in vitro and in vivo analyses are ongoing and may help guide the development of more effective treatment.

Van Duyne and colleagues (Abstract 168) conducted a series of in vitro experiments to determine the mechanism by which mutations in gp41 of the Env protein (Env-A556T and Env-A539V, the identification of which are described in Abstract 540) confer DTG resistance. Using a green fluorescent protein reporter virus, viruses that fluoresce with viral gene expression, the replication kinetics of these Env mutants were quantified. The Env mutants demonstrated better cell-to-cell transmission than wild type in the absence and presence of DTG. On days of peak replication, greater geometric mean fluorescence intensity was observed in Env mutant-infected cells than in wild type, implying that not only were the Env mutants better at cell-to-cell transmission but that with each episode of cell-to-cell transmission there were more transmission events per cell. The researchers hypothesized that the enhanced cell-to-cell transmission of Env-A556T and Env-A539V mutants overcomes the DTG inhibition of cell-to-cell infection, thereby conferring DTG resistance. These findings provide insight into how Env mutations in the absence of target gene mutations may confer antiretroviral drug resistance and raises the possibility that Env mutations are a precursor to development of high-level drug resistance; however, the role of these Env mutations in vivo has not been examined.

These findings provide insight into how Env mutations in the absence of target gene mutations may confer antiretroviral drug resistance and raises the possibility that Env mutations are a precursor to development of high-level drug resistance

Capsid inhibitor RAMs. Capsid inhibitors are a promising new class of antiretroviral drugs in development that have different mechanisms of action, including capsid assembly and disassembly and virion maturation. Newton and colleagues (Abstract 539) described an in vitro analysis of patient samples submitted for routine drug resistance testing and *gag* gene site-directed mutants (using previously described capsid assembly inhibitor [CAI] *gag* substitutions)[3] to 2 maturation inhibitors that target the CA-SP1 cleavage site (bevirimat and PF46396), and 1 CAI inhibitor (PF74). Susceptibility of patient isolates to CA-SP1 cleavage site inhibitors varied more than 100-fold, and CAI inhibitor susceptibility varied less than 4-fold. Sixty-one percent of patient isolates had naturally occurring polymorphisms in the QVT motif in *gag* (amino acid positions 369-371), and these isolates exhibited less CA-SP1 cleavage site inhibitor susceptibility than those without these polymorphisms. One isolate had a polymorphism (N74N/D) that was preiously associated with reduced CAI inhibitor susceptibility.

Site-directed mutants (SDMs) with single L56I, M66I, Q67H, N74D, and A105E substitutions had more than 200-fold reductions in CAI inhibitor susceptibility, and Q67H and N74D had only modest impacts. L56I, M66I, and Q67H conferred modest cross-resistance to CA-SP1 cleavage site inhibitors. SDMs conferring large reductions in PF74 susceptibility did so at an apparent cost to fitness, as these mutants had reduced replication capacity. The characterization of the effects of capsid-related sequence variations and on CAI susceptibility will help guide the development of these promising agents.

The resistance profile of the second-generation investigational HIV maturation inhibitor GSK2838232 was evaluated (Abstract 541). Two recombinant viruses, comprising *gag* and protease fragments of 2 protease-treated patients in a wild-type laboratory strain, were serially exposed to increasing concentrations of GSK2838232 to derive escape mutants whose *gag* and protease genes were fully sequenced. In all experiments an A364V substitution was observed. An SDM containing A364V was generated, demonstrating a high level of resistance to GSK2838232, as has been seen with other maturation inhibitors. The frequency of the A364V substitution was found in less than 0.1% of sequences in the Los Alamos National Laboratory HIV database. Investigators concluded that the resistance profile of GSK2838232 is consistent with previous maturation inhibitors and that preexisting resistance is expected to be low.

Fostemsavir RAMs. Fostemsavir is a prodrug of temsavir (TMR), an investigational HIV-1 attachment inhibitor being evaluated for use in highly treatment-experienced patients with limited treatment options. Saladini and colleagues characterized the *env* genotypic profile and phenotypic susceptibility to TMR among clinical isolates from patients with multidrug-resistant virus enrolled in the Italian PRESTIGIO registry (Abstract 548). Plasma samples from 24 patients were evaluated and in all but 1 sample, infectious pseudotyped viruses were generated. Three of 23 of these samples had TMR RAMs (1 with S375N and 2 with M426L). M426L showed variable reduction to TMR susceptibility. Entry inhibitor use (maraviroc, EFV) and viral tropism had no impact on TMR susceptibility.

InSTI drug resistance mutations (DRMs). Shahid and colleagues identified integrase gene mutations associated with decreased susceptibility to newer InSTIs (BIC, DTG, CAB), a challenging endeavor given low rates of failure, slow in vitro selection, and the requirement for numerous mutations to confer resistance to these agents (Abstract 143). Investigators selected clinical samples from the British Columbia Centre for Excellence database with a single mutation at 1 of 27 amino acids that differed in prevalence between InSTI-treated and ART-naive individuals. All unique amino acid permutations at these positions were identified, and representative samples were used to make recombinant viruses. Phenotypic analysis of the recombinant viruses showed that mutations at G140, Q148, and R263 were associated with the greatest log-fold change to InSTIs; extensive cross-resistance was noted among DTG, BIC, and CAB, and between RAL and elvitegravir (EVG); accumulation of amino acid substitutions led to increased fold change; additional resistance mutations to baseline double mutants G140S plus Q148H exhibited log-fold-change increases; and 2 variantsexhibited a 2-fold change for CAB but were still susceptible to DTG and BIC. Analysis was limited to subtype B virus and clinical correlations of these in vitro data are not yet available; however, this technique is an efficient way to evaluate clinically observed sequence variation and may lead to identification of emerging resistance to these newer agents.

The 148 pathway, which is initiated by RAL-associated failure, compromises second-generation integrase strand transfer inhibitors more than failure of EVG-containing regimens

In a study of clinical isolates from 19 patients experiencing virologic failure on an InSTI-based regimen, Saladini and colleagues (Abstract 549) identified major InSTI RAMs in all 19 patients (T66A, E92Q, E138K/T, G140A/C/S, Y143C/R, S147G, Q148H/R, N155H, R263K). Nine had previous exposure to RAL only, 4 to EVG only, 5 to RAL and DTG, and 1 to RAL and EVG. With in vitro susceptibility testing, DTG, BIC, and CAB mutants with a Q148R substitution plus 1 or 2 additional InSTI RAMs resulted in substantially decreased susceptibility to all 3 drugs, and comparable activity to all other mutants with major InSTI RAMs was maintained. Isolates with a 148 mutation and 2 or more additional InSTI RAMs had higher than 100-fold changes to DTG, BIC, and CAB. In one patient whose DTG-based regimen failed, the R263K mutation had a 3.5-fold change for DTG and CAB but only a 1.1-fold change for BIC. These findings suggest that the 148 pathway, which is initiated by RAL-associated failure, compromises second-generation InSTIs more than failure of EVG-containing regimens.

Susceptibility to BIC and DTG of clinical isolates obtained from heavily treatment-experienced patients whose InSTI-based regimens failed enrolled in the PRESTIGIO registry was presented (Abstract 550). All 17 patients had historical genotypic tests showing primary PI, nRTI, and NNRTI RAMs, and 14% had previous exposure to DTG twice daily; 27% were on DTG twice daily, and 50% were on RAL twice daily. The primary InSTI RAMs E138A/K, Y143C/H/R, Q148H, and N155 were found in 64% of samples and all exhibited resistance to RAL and EVG with phenotypic testing; 2 showed resistance to BIC and DTG. Fifty percent of isolates had G140S plus Q148H, which conferred intermediate resistance to DTG in all isolates and to BIC in all but 1 isolate. Of isolates, 55%, 50%, 36%, and 36% exhibited sensitivity to BIC, DTG, RAL, and EVG, respectively, with median fold changes of 3.1, 6.1, more than 164.0, and more than 188.0, respectively.

Smith and colleagues (Abstract 553) noted that data on the effectiveness of InSTIs for HIV-2 treatment are limited. To date there are no published case reports or clinical studies describing the use of BIC plus TAF plus FTC to treat these patients with HIV-2. With in vitro studies, HIV-1 and HIV-2 showed comparable sensitivity to BIC in a single cycle of infection (including group O isolates of HIV-1); BIC, DTG, and CAB were equally potent against HIV-1 and HIV-2; the Q148-pathway mutants of HIV-2 showed high resistance to BIC, and N155H mutants showed modest resistance to BIC; and fold-change values for site-directed HIV-2 mutants were concordant with those reported for clinical isolates of HIV-2 from InSTI-treated patients.[4] The investigators concluded that BIC has a similar potency for HIV-2 and HIV-1. They recommended a clinical trial in West Africa to evaluate BIC plus TAF plus FTC as initial treatment for people living with HIV in West Africa, including those with HIV-2 infection.

Wei and colleagues evaluated the sequences of escape mutants exposed to high levels of CAB (Abstract 545LB). They noted that despite increasing and prolonged CAB concentrations over 1 year, no integrase gene mutations were identified, in contrast to exposure to RAL, which generated E138K and Q148R mutations. Further analysis of the escape mutants showed changes in the 3'-polypurine tract (PPT) region, which may lead to atypical cleavage of 2–long terminal repeat (LTR) circles conferring resistance to CAB. The hypothesis that alterations in 2-LTR is the mechanism by which 3'-PPT mutations confer InSTI resistance was first described by Malet and colleagues at the CROI conference in 2018.[5,6] The plausibility of this hypothesis has been questioned and alternate mechanisms for PPT-derived resistance have been proposed.[7] Further investigation into mechanisms of InSTI resistance in the

Further evaluation to assess the clinical significance of newly detected DRMs and the optimal use of deep sequencing in clinical settings is warranted

absence of target integrase gene DRMs is warranted including correlation with phenotypic and in vivo analyses.

Tenofovir RAMs. Intracellular concentrations of tenofovir with TAF are 4-fold higher than with TDF Cox and colleagues (Abstract 546) hypothesized that the higher intracellular tenofovir levels with TAF could confer decreased resistance with the tenofovir-associated DRM K65R compared with TDF. In vitro studies of clinical isolates with K65R/N mutations in the presence or absence of M184V found that at pharmacologic concentrations of TAF, viral breakthrough was inhibited in 40 of 42 K65R mutants compared with 30 of 42 K65R mutants with pharmacologic levels of TDF. Standard resistance testing does not capture the effects of a 4-fold increase in TAF on intracellular tenofovir, and if further research confirms the clinical significance of these in vitro findings, changes to TAF genotype algorithms and phenotype assays should be indicated.

Technologies to Detect DRMs

Archived genotype. Daeumer and colleagues compared deep sequencing assays with cumulative historical genotypic testing results in a cohort of patients with viral suppression but with known triple-class resistant virus (Abstract 544). Among the 195 patients evaluated, correlation between deep sequencing and historical genotypic testing varied by individual mutation, ART drug class, and assay cutoff. Using deep sequencing and a sensitivity cutoff to detect mutations in 15% of the viral population, 45% of all historical DRMs, 55% of historical nRTI DRMs, 37% of historical NNRTI DRMs, 35% of historical PI DRMs, and 22% of historical InSTI DRMs were detected. With a cutoff of 1%, 60% of all historical DRMs, 68% of historical nRTI DRMs, 49% of historical NNRTI DRMs, 55% of historical PI DRMs, and 41% of historical InSTI DRMs were detected. At a 1% cutoff, the percent of newly detected DRMs was 11% overall and 42% for InSTI DRMs and at a cutoff of 1% to 15%, the proportion of newly detected DRMs was 20% overall and 44% for InSTI DRMs. Patient characteristics, including duration of viral suppression and ART regimen, did not correlate with deep sequencing detection of historical DRMs. This study provides more insight into the applicability of deep sequencing in clinical settings, but further evaluation to assess the clinical significance of newly detected DRMs and the optimal use of this test in clinical settings is warranted.

States with higher prevalence of poor ART adherence had higher HIV-1 prevalence and HIV-1 mortality rates

Epidemiologic Studies of DRMs

National and regional epidemiologic studies. Moyo and colleagues presented the drug resistance testing results from the 5th South African National HIV Prevalence, Incidence, Behaviour, and Communication Survey, which included collection of dried blood spot samples through which HIV antibody, viral load, ART drug levels, and drug resistance testing were performed (Abstract 152). Of 24,000 individuals surveyed, 2294 tested positive for HIV, 1107 were not virally suppressed, 697 had successful drug resistance testing, and 200 had DRMs; 27% had any DRM, 19% had NNRTI DRMs, 8% had NNRTI and nRTI DRMs, and 0.5% had PI, NNRTI, and nRTI DRMs. Among individuals with ART drug–positive versus ART drug–negative samples, 56% and 23% had any DRM, 14% and 20% NNRTI DRMs only, and 41% and 2% had NNRTI and nRTI DRMs, respectively. Rates of DRMs were highest among individuals who reported taking ART medications but had negative samples (identified as "defaulters" in this study), with any DRM, NNRTI only, and NNRTI and nRTI at 76%, 56%, and 14%, respectively. For individuals reporting never taking ART medications with negative samples (assumed to be ART naive) rates were lowest, at 15% with any DRM, 15% with NNRTI DRMs only, and 0% with NNRTI and nRTI DRMs. The researchers recommend ongoing monitoring of DRMs, stronger adherence support for "defaulters," strengthening of initial ART regimens in South Africa to include InSTIs, and early switching of patients whose ART regimens are failing to alternative regimens.

The impact of social determinants of health on ART adherence, resistance, and HIV clinical outcomes in the United States was evaluated using publicly available data-bases, measuring the average proportion of days covered of all patients per state in the Symphony Health Solutions claims database, and determining rates of resistance using isolates submitted to Monogram Biosciences for routine clinical testing (Abstract 907). HIV prevalence was highest in the southern and northeast states. Mean proportion of days covered was 73%, with at least 40% of patients demonstrating poor adherence to ART in a majority of states and clustering of poor est adherence in the southern states. Across all states, 20% to 54% of isolates tested showed HIV-1 drug resistance. States with higher prevalence of poor ART adherence had higher HIV-1 prevalence and HIV-1 mortality rates. States with higher rates of resistance had higher prevalence of HIV-1 infections. Lower education level, poverty, unemployment, female sex, and nonwhite race were associated with poor ART adherence. Lower education level, unemployment, and non-white race were associated with higher prevalence of poor or suboptimal ART adherence. The regional variation and correlations among social determinants of health, adherence, resistance, and HIV-related outcomes should inform targeting of resources and interventions to promote adherence and prevent resistance.

Decreasing rates of InSTI resistance reflect the introduction of more potent InSTI agents (DTG and BIC) along with good clinical practice

Clinical isolates from Italy from 2007 to 2017 were evaluated to identify trends in InSTI resistance over time (Abstract 535). Investigators evaluated 3004 isolates from 2598 patients. The prevalence of at least 1 InSTI major resistance mutation decreased from 14% in 2007 to 5% in 2017, and the proportion of isolates with full susceptibility to RAL, EVG, DTG, and BIC all increased during that time (83%-94%, 83%-94%, 94%-98%, and 94%-98%, respectively). Decreases in rates of InSTI resistance and increases in rates of full susceptibility of InSTIs were also seen on isolates from patients on 1 InSTI plus at least 2 ART drugs from other classes and from patients on 1 InSTI and 2 nRTIs. Among InSTI-naive patients, there was no statistically significant change in rates of InSTI resistance; prevalence remained low at 0% from 2007 to 2008 and 0.6% in 2015 to 2017, and susceptibility to all InSTIs remained high (98.0%-99.7%). Among patients on 1 InSTI and another ART drug from a different class (dual therapy), rates of resistance to any InSTI and susceptibility to RAL and EVG remained stable, and rates of susceptibility to DTG and BIC decreased (from 96% to 85%). Overall prevalence of InSTI major resistance mutations was stable aside from Q148R, which decreased from 10.2% (in 2007-2008) to 1.4% (in 2015-2017). The researchers concluded that decreasing rates of InSTI resistance reflect the introduction of more potent InSTI agents (DTG and BIC) along with good clinical practice.

Pretreatment drug resistance (PDR): public health surveillance. Avila-Rios presented surveillance data on PDR from the Condesa Clinic, where approximately 70% of all new cases of HIV in Mexico City are diagnosed each year (Abstract 876). Next-generation sequencing was conducted for 2447 individuals initiating ART and diagnosed in the Condesa clinic between September 2016 and June 2018. Prevalence of DRMs to any drug, NNRTI, nRTI, PI, and InSTI were 14.8%, 9.6%, 4.5%, 1.7%, and 0.8%, respectively, with K103N the most frequent DRM identified. Genetic network analysis identified 99 clusters consisting of 2 to 20 individuals, and clustering individuals were more likely to be younger (aOR per year, 0.96), were more likely to be men (aOR, 2.3), and were less likely to reside outside of the central metropolitan area (aOR, 0.11). Among clustering individuals, 18% shared DRMs, with K103N the most commonly shared DRM. Persons sharing DRMs were most likely to be younger (aOR per year, 0.97) and were more frequently observed after 2016 (2017 aOR, 1.7; 2018 aOR, 2.0). A growth of DRM networks was observed over time, with the number of clusters of people sharing DRMs increasing from 3 to 46 to 66 in 2016, 2017, and 2018, respectively. To address the increasing prevalence of PDR and the growth of DRM networks, plans are underway to begin molecular surveillance nearly in real time, routine collection of sociodemographic and behavioral information for all persons being tested for HIV, and alliances with nongovernmental organizations to deliver focused prevention interventions.

In the United States from 2013 to 2016 the rate of any pretreatment drug was stable and the rates of specific drug resistance mutations changed only modestly over time

Prevalence of PDR. McClung and colleagues presented US surveillance data for PDR in people diagnosed with HIV from 2013 to 2016 (Abstract 526). From 36,288 cases in 23 US jurisdictions, 40,083 sequences were analyzed. Of cases, 19.0% had at least 1 PDR mutation (PDRM) and 11.9% had NNRTI PDRMs, 6.8% had nRTI PDRMs, 4.3% had PI PDRMs, and 0.8% had InSTI PDRMs. There was a higher prevalence of PDRMs in black individuals, the northeast region, and metropolitan areas, and a lower prevalence in people aged 30 years or older and Asian individuals. From 2013 to 2016, the rate of any PDRM was stable, the rate of NNRTI PDRMs increased (11.3%-12.4%), the rate of nRTI PDRMs was stable (6.8% -6.7%), the rate of PI PDRMs decreased (4.6%-4.0%), and the rate of InSTI PDRMs increased (0.8% to 1.1%). Rates of any PDRM increased among people aged 40 to 49 years (17.4%-20.2%) and individuals reporting HIV transmission risk from injection drug use (15.7%-23.8%). Of people with HIV infection attributed to perinatal infection, 39% had PDRMs, but the sample size was small (n=71). Cases with InSTI sequences reported increased as did cases in which the InSTI sequences were reported without the PR/RT sequence.

Wang and colleagues evaluated genotypic testing results for patients aged 13 years or older diagnosed with HIV between 2013 and 2017 and reported to the New York State HIV registry (n= 15,345) (Abstract 528). Of 15,345 persons included, 59% had any resistance testing within 3 months of diagnosis, 57% had PR/RT resistance testing, 21% had initial InSTI resistance testing, and 2.5% had only InSTI testing. Resistance to 1 or more InSTI was seen in 0.7% of patients with initial InSTI testing and was the most common. Clinically significant InSTI mutations included T66A/I, E92Q, E138K/A, G140S, Y143C/R, Q148H, and N155H. The Q148H mutation was seen in 4 newly diagnosed individuals. Investigators concluded that clinicians should ensure timely ordering of resistance testing (<3 months after HIV diagnosis per clinical guidelines) and that InSTI genotypic testing should not be ordered without PR/RT genotyping. They also suggested that the observation of Q148H in 4 newly diagnosed patients suggests InSTI resistance is emerging and that InSTI testing should now be ordered in addition to PR/RT genotyping in patients newly diagnosed with HIV infection. The frequency of InSTI PDRMs is low and baseline InSTI resistance testing is not consistent with current IAS-USA guidelines,[8] but the recommendation may change if more resistance emerges with widespread InSTI use.

In Peru, baseline genotypic testing is not routinely performed before ART initiation. Rates of PDR in Peru on samples obtained before 2010 were

previously reported as 1.0% to 4.7%. HIV sequence data were obtained from 3 parent studies (2013-2017) of ART-naive cisgender men who have sex with men (n=332) and transgender women (n=144) in Lima, Peru, and consensus gene sequences of part of the HIV pol region were evaluated for DRMs (Abstract 529). Of isolates, 16.8% had any DRM (15% had 1 DRM, and 1.7% had 2 DRMs). The most frequent RAMs conferring high-level NNRTI resistance were K103N/S (7.4% of all isolates) followed by G190A/E (1.1%); 0.8% of isolates had the M184V RAM, and 1.1% had thymidine analogue mutations. Initial ART regimens in Peru are typically EFV plus 2 nRTIs; 15% of isolates showed EFV resistance (9% median-to-high resistance), 1% showed ABC resistance, and 0.9% showed FTC/3TC resistance (all with high resistance). Rates of PDR did not differ based on gender identity. Given these rates and patterns of increasing PDR, the authors recommended urgent adoption of national surveillance for PDR, change in policy to incorporate baseline ART testing, and inclusion of InSTIs in recommended initial ART.

These high rates of PDR to EFV support Swaziland's shift to the use of InSTIs in recommended initial ART regimens and public health surveillance of PDR

PDR was evaluated for patients who enrolled in the MaxART trial (MaxART: Early Access to ART for All in Swaziland), launched in 2014, through which ART was offered to all people living with HIV in the Hhohho region of Eswatini, Swaziland, regardless of CD4+ cell count and WHO clinical disease stage (Abstract 537). HIV sequences were generated for 2578 available samples; 11% had intermediate- or high-level resistance to EFV/nevirapine (NVP), the initial ART regimen offered to all participants per national guidelines at the time of the study. The prevalence of resistance to any antiretroviral drug was 24%. Dual-class resistance to nRTI and NNRTI was rare at 0.5%. EFV/NVP resistance was associated with female sex (aOR, 1.37) and younger age at initiation of treatment (aOR, 0.961 per 1-year increment). E138A, an HIV-1 subtype C polymorphism associated with RPV resistance, was detected in 13% of sequences and accounted for more than 50% of predicted resistance to NNRTIs. K103N was the next most commonly observed DRM at 7%, and minimal PI and nRTI DRMs were identi fied (<1%). These high rates of PDR to EFV support Swaziland's shift to the use of InSTIs in recommended initial ART regimens and public health surveillance of PDR.

The prevalence of PDR and its impact on treatment outcomes was assessed among patients initiating initial ART containing EFV in the ITREMA (Intensified Treatment Monitoring Strategy to Prevent Accumulation of Drug Resistance) trial in rural South Africa. The majority of patients were women (60%) and were started on a regimen of EFV/TDF/FTC (96%); 6% reported prior ART (Abstract 527). Among patients with successful sequencing (n=194), 12% had PDR, 9% of patients without evidence of prior ART had PDR, and 20% of patients with previously undisclosed ART who were found to have EFV exposure had PDR. PDR was associated with poor clinical outcomes, including an HIV RNA level above 1000 copies/mL within 48 weeks, confirmed virologic failure within 48 weeks, and loss to follow-up within 24 weeks of ART initiation.

Prevalence of drug resistance among ART-experienced individuals. The Ministry of Health of Brazil offers genotypic testing to all individuals on an InSTI-based regimen experiencing virologic failure. To characterize InSTI resistance patterns in Brazil, Veras and colleagues evaluated 1467 integrase sequences among RAL- or DTG-experienced patients from 2012 to 2018 in the National System for Genotyping Control (Abstract 533). Rates of InSTI resistance decreased from a peak of 67% resistance to RAL and 5% to DTG in 2013 to 13.7% and 0.8%, respectively, in 2018; there were no DTG-resistant isolates from individuals on DTG for initial ART. There were no demographic, clinical, or regional variations in prevalence of resistance. G140 (7%) and E138 (1%) were the most frequent InSTI RAMs identified, and subtype B (70%) was the most common subtype followed by C (14%), F (9%), and recombinant (7%) subtypes. No national or InSTI RAM transmission clusters were identified.

In the HPTN (HIV Prevention Trials Network) 074 study conducted in Indonesia, Ukraine, and Vietnam, enhanced support for medication-assisted treatment of substance use disorder and ART adherence for people with HIV (with HIV RNA levels ≥1,000 copies/mL) and active injection drug use were associated with decreased mortality and increased viral suppression.[9] HIV-seropositive index participants were asked to recruit HIV-seronegative participants. Zhang and colleagues evaluated baseline HIV drug resistance and ART use among the HIV-seropositive participants (Abstract 534). Among 502 index participants, genotypic test results were obtained for 89% (n=449). Resistance to any ART drug class was detected in 12%, of whom 54% had multiclass resistance, with the most common DRMs identified being K103N and M184V. Of the 449 patients who had genotype results available, ART drugs were detected in 51 (11%) patients, 73% of whom had 1 NNRTI drug plus 1 or 2 NRTI drugs detected, 20% had an nRTI drug detected alone, and 4% (2 patients) had a boosted PI drug with 1 or 2 nRTI drugs detected. Of participants, 61% had the CRF01_AE HIV subtype, 36% had the A1 subtype, 2% had unique recombinant forms, and 0.7% had the B subtype. Drug resistance was more frequent among individuals with detectable ART drug levels (59% vs 6%), in Indonesia (24%) compared with Ukraine (2.4%) or Vietnam (13%), and Among those who reported a history of incarceration (43% vs 11%). These high rates of DRMs and multiclass DRMs highlight the need for enhanced adherence support and use of potent ART drugs with a high genetic barrier to resistance

among people with HIV who inject drugs.

In the DAWNING study, an open-label, multinational (58 sites in Latin America, South America, Asia, Eastern Europe, and Africa), multicenter, noninferiority, randomized, phase IIIb trial, patients whose initial ART with an NNRTI plus 2 nRTIs failed who were then randomly assigned to DTG plus 2 nRTIs had superior virologic outcomes to those who were randomly assigned to LPV/r plus 2 nRTIs (84% vs 70% with HIV RNA levels <50 copies/mL at 48 week).[10] In a post hoc analysis (Abstract 144), DTG plus 2 nRTIs remained superior to LPV/r plus 2 nRTIs, in the presence of M184V/I, even when 3TC or FTC were part of the regimen (85% vs 72%). These results support updated WHO interim guidelines for the inclusion of DTG plus 2 nRTIs as a second-line treatment option for patients whose initial NNRTI- or PI-based regimen failed.[11]

Investigators concluded that hospitalized patients on initial ART longer than 6 months with CD4+ cell counts below 350/µL and HIV RNA levels of 1000 copies/mL or higher should be rapidly changed to a second-line regimen, given these high rates of treatment failure

Strategies to identify drug resistance in ART-experienced patients in low- or middle-income countries. Bossard and colleagues (Abstract 151) evaluated rates of DRMs among ART-experienced, hospitalized patients in 2 hospitals in sub-Saharan Africa: one in Kenya and one in the Democratic Republic of Congo (DRC). Per the WHO guidelines treatment failure algorithm, a patient should have 2 consecutive high viral load test results within 3 months before switching from an initial to a second-line regimen, but for hospitalized patients a faster switch may be indicated. Among the 305 patients enrolled, more than 70% were on a regimen of EFV/TDF/3TC, the majority were women (54% in Kenya and 69% in DRC), and median time on ART was more than 4 years. Rates of viral and immunologic suppression differed between sites (HIV RNA level ≥1000 copies/mL among 37% in Kenya and 71% in DRC; CD4+ cell count <100/µL among 68% in Kenya and 82% in DRC). Adherence, measured by TDF levels, was suboptimal in 56% of patients in Kenya and 47% in DRC. Among patients with HIV RNA levels of 1000 copies/mL or higher, more than 70% experienced treatment failure (dual-class, intermediate- or high-level-resistance). Of patients with HIV RNA levels of 1000 copies/mL or higher and CD4+ cell counts below 100/µL, 74% in Kenya and 85% in DRC experienced treatment failure. Of sequences, 84%, 86%, 71%, and 40% had intermediate- or high-level resistance to EFV, NVP, 3TC, and TDF, respectively (median regimen-specific genotypic sensitivity score, which assesses the number of active drugs in a regimen based on genotype, was very low at 0.5). Investigators concluded that hospitalized patients on initial ART longer than 6 months with CD4+ cell counts below 350/µL and HIV RNA levels of 1000 copies/mL or higher should be rapidly changed to a second-line regimen, given these high rates of treatment failure.

Hermans and colleagues presented a pilot and implementation study on testing of LPV drug levels before drug resistance testing for patients in whom a second-line ART regimen is failing in low- or middle-income countries (LMICs) (Abstract 461). WHO recommends drug resistance testing in patients in whom a second-line ART regimen is failing, and if resistance is found, switching to a third-line regimen. The researchers noted that drug resistance testing is costly and that only a minority of these patients in LMICs have PI resistance (<20%).[12] In their pilot and implementation studies conducted in South Africa, LPV drug levels predicted LPV resistance with 90% sensitivity and 61% specificity, with a positive predictive value of 44% and a negative predictive value of 95%. The researchers concluded that testing of drug levels at the time of PI treatment failure would be a cost-effective strategy, to reserve costly drug resistance testing for patients most likely to have PI resistance.

Selected Issues in Maternal and Pediatric Health

The prevalence of maternal HIV/hepatitis B virus (HBV) coinfection and its impact on HIV mother-to-child transmission (MTCT) and maternal and infant clinical outcomes were evaluated by Bhattacharya and colleagues (Abstract 41). Post hoc analysis was performed on maternal-infant pair data and retrospective laboratory testing of maternal samples from HPTN 046, a randomized controlled clinical trial of HIV MTCT in sub-Saharan Africa. Of 2016 women with HIV infection included in the analysis (22% of whom were on ART), 88 (4.3%) were determined to have HBV coinfection (defined as having a positive HB surface antigen). Compared with women with HIV monoinfection, women with HIV/HBV coinfection with high HBV viremia (defined as having an HBV DNA level greater or equal to 106 IU/mL) had lower median CD4+ cell counts at baseline. High maternal HBV viremia was also associated with low birth weight and 6.75 times (95% CI, 1.86–24.50) higher risk of infant HIV infection. The research team did not find any impact of HIV/HBV coinfection on infant mortality or maternal outcomes (ie, maternal premature rupture of membranes and episiotomies) at 18 months. One limitation of this study was the lack of available HIV viral load data. The mechanism by which HBV viremia led to higher risk of HIV MTCT remains unclear.

Ntozini and colleagues conducted a community-based 2x2 factorial cluster randomized trial, known as the SHINE (Sanitation, Hygiene, Infant Nutrition Efficacy) Project, to determine whether 2 nutrition and sanitation interventions

delivered alone or in combination, compared with a SOC group, affected neurodevelopment in 323 HIV-exposed infants and children (of whom 6 had HIV infection) from 726 women with HIV infection in rural Zimbabwe (Abstract 42). The improved nutrition intervention, which researchers labeled as improved infant and young child feeding, consisted of provision of a lipid-based nutrient supplement from 6 to 18 months and feeding counseling. The improved water, sanitation, and hygiene interventions incorporated access to a pit latrine, hand washing stations, liquid soap, chlorine, a play space, and hygiene counseling. Each intervention individually did not have a significant effect, but combining them improved nutrition and improved water, sanitation, and hygiene interventions substantially and improved motor, cognitive, and language development, assessed by the Malawi Developmental Assessment Tool, in the HIV-exposed children at 2 years of age.

LNG IUDs are a safe and acceptable contraceptive option for women with HIV infection

Evans and colleagues observed a 39% higher mortality and more growth stunting among HIV-exposed children compared with HIV-unexposed children through 18 months in the SHINE trial (Abstract 790). Chasekwa and colleagues observed that the improved nutrition intervention, but not the improved water, sanitation, and hygiene interventions, reduced growth stunting and anemia in HIV-exposed children (Abstract 791). Chadna and colleagues evaluated early childhood development, assessed by several different developmental tools used widely in sub-Saharan Africa, in the SHINE trial. Outcomes at age 2 years differed between HIV-exposed and HIV-unexposed children in several but not all measures (with lower total developmental, motor, and language scores in the HIV-exposed group), emphasizing the need for studies with longer follow-up to assess whether these small differences in early childhood development lead to sustained, meaningful developmental differences in later ages (Abstract 784). Early ART in children in the first year of life is associated with improved clinical and virologic outcomes and with decreased HIV reservoir size, but there are limited data on the impact of early ART in neonates.

Tagarro and colleagues evaluated whether rapid initiation of ART within 7 days (early) versus 7 to 28 days of life (delayed) in HIV-infected neonates had any long-term clinical, virologic, and immunologic effects later in life (Abstract 44). A total of 44 infants with perinatally acquired HIV infection from 4 different cohorts were included in the analysis. The infants were included if they were 28 days of age or younger at the initiation of ART, had no ART interruptions with the first 2 years, and had at least 2 HIV viral load test results during the follow-up period. Infants who were started on triple ART as MTCT with NVP/zidovudine/3TC on day 1 and transitioned to ART within 15 days were also included.

Primary clinical endpoints were mortality and progression to AIDS, and primary virologic outcomes included time to viral suppression, time to virologic failure, and proportion of time suppressed. Viral suppression was defined as having at least 2 consecutive HIV RNA levels below 50 copies/mL, and virologic failure was defined as having at least 2 HIV RNA levels of 400 copies/mL or higher. A viral blip was defined as having an HIV RNA level between 50 and 400 copies/mL once followed by viral suppression. Time-to-event analysis using Kaplan Meier curves and flexible spine models was performed. The median follow-up period for the children was 11.5 years. At baseline, there were differences in ART regimens in those treated within 7 days and those treated at 7 to 28 days, and higher viral loads were observed in children who received early treatment.

Time to viral suppression was statistically significantly lower in those treated early, with probability of suppression decreased by 35% for each week the initiation of ART was delayed, after adjustments for ART regimen and baseline viral load at time of initiation. A linear association between age at time of ART initiation and viral suppression was observed. There were no statistically significant differences between early versus delayed ART in other long-term primary endpoints, including progression to AIDS, time to virologic failure, or proportion of time suppressed, as well as in other outcomes (eg, changes to ART regimen or time to immunologic recovery).

Interactions Between Hormone-Based Contraception and ART in Women With HIV Infection

Levonorgestrel and nonhormonal copper intrauterine devices (IUDs) are effective, long acting, and reversible contraception approaches that are underutilized by women with HIV infection, especially in LMICs with high HIV prevalence. There are limited safety data for use of IUDs in women with HIV infection. The impact of progestin on HIV viral shedding in the genital tract, used as a proxy marker for HIV transmission risk, remains unclear.

Todd and colleagues presented results from the first randomized, double-blind trial, among 199 South African women with HIV infection aged 18 to 40 years, comparing genital and plasma HIV viral load levels as well as acceptability in women using levonorgestrel IUD (LNG IUD) and those using a nonhormonal copper IUD (C-IUD) (Abstract 50). The analyses were stratified by ART status on entry into the study (those on ART and those not yet initiated on ART). The authors found no statistically significant increase in genital tract HIV viral load shedding and no statistically significant difference in detectable plasma HIV viral loads between the 2 IUD arms, with no differences noted when stratified by ART use. Of the 34 serious adverse events noted, 18% were related to IUD use.

Overall, continued use of IUDs over 24 months was 76%, with expulsions and discontinuations higher in the C-IUD group. Discontinuations of IUDs were mainly due to adverse effects including heavy bleeding, pain, and

dysmenorrhea. The authors concluded that compared with nonhormonal C-IUDs, LNG IUDs do not significantly alter genital tract and plasma HIV viral load levels and that LNG IUDs are a safe and acceptable contraceptive option for women with HIV infection.

Previous research highlighted a concern for drug-drug interactions between EFV and hormone-based contraception, with 1 study[13] showing 45% to 57% lower exposure to LNG in women with HIV infection on EFV-based ART who received standard-dose of LNG subdermal implants, resulting in suboptimal contraception protection and unintended pregnancies.

Scarsi and colleagues explored, in an open-label pharmacokinetic study, whether doubling the dose of LNG (from the standard dose of 150 mg to 300 mg) in subdermal implants would overcome the drug-drug interaction and provide effective contraception in women on EFV-based ART (Abstract 51). The investigators compared the drug plasma concentrations, computed as geometric mean ratios, over numerous visits spanning 48 weeks of 28 Ugandan women receiving EFV-based ART and double-dose LNG implants (along with C-IUDs as backup contraception) and 17 ART-naive historical controls receiving standard-dose LNG implants. Over 48 weeks, in women on EFV-based ART receiving LNG 300 mg implants, LNG concentrations were 33% to 44% lower than in the historical controls receiving standard-dose LNG. A statistically significantly lower proportion of women (46% vs 90%; $P<.05$) receiving EFV-based ART and LNG 300 mg had a level of LNG of 303 pg/mL or below (identified in prior research as a threshold at which unintended pregnancies occurred), compared with the historical controls receiving standard-dose LNG.

The investigators cautioned about the effectiveness of double-dose LNG implants as contraception in women receiving EFV-based ART, as doubling the dose of LNG still yielded suboptimal LNG levels because of the drug-drug interactions between LNG and EFV. They suggested further research into the pharmacogenetics and variability of LNG levels within individuals.

Haas and colleagues explored the role of pharmacogenetics in explaining the adverse drug-drug interactions between ART and exogenous hormones administered via vaginal rings in the ACTG (AIDS Clinical Trials Group) A5316 study (Abstract 52). ACTG A5316 is a multicenter, multi-country study that enrolled 72 women with HIV infection aged 16 years or older in one of 3 groups: those not yet on ART (designated as the control arm), those receiving EFV-based ART, or those receiving ritonavir-boosted atazanavir (ATV/r)-based ART. On the first day of the study, the women underwent insertion of a vaginal ring releasing etonogestrel (ENG)/ethinyl estradiol (EE) (120/15 mcg daily) over 21 days. Intensive, 8-hour pharmacokinetic sampling was performed for EFV and ATV/r drug levels on days 1 and 21, as was testing for ENG/EE plasma levels on days 7, 14, and 21.

It is ethical and imperative to increase representation of women of reproductive potential and pregnant women in HIV clinical research

The investigators also genotyped 17 targeted single nucleotide polymorphisms (SNPs), including SNPs that define cytochrome P450 (CYP)2B6 metabolizing genotypes as normal, intermediate, and slow (for EFV), UGT1A1 (for ATV), CYP3A4/5, CYP1A1/2, and other estrogen trait-associated SNPs (for ENG and EE). Compared with the control arm, EFV lowered median ENG concentrations at day 21 by 73%, 77%, and at least 93% in those with CYP2B6 normal, intermediate, and slow metabolizing genotypes, respectively. Similarly, EFV lowered median day 21 EE concentrations by 41% in CYP2B6 normal and intermediate metabolizers, and by 75% in CYP2B6 slow metabolizers. No association was found between the other SNPs and EE/ENG levels in the ATV/r-based ART and control arms. The investigators concluded that the CYP2B6 slow metabolizer genotype exacerbates the adverse pharmacokinetic interaction of EFV with both ENG and EE, with the purported mechanism being the enhanced induction of CYP that is mediated by exposure to higher levels of EFV. They also suggested that the interaction between EFV and hormones can be lessened, although not completely overcome, by adjusting EFV dosing in individuals based on their CYP2B6 metabolizing genotype.

Issues in ART and Reproduction

In the Symposium on ART and Reproduction, the speakers provided updates on ART use in women of reproductive potential and the potential impact of ART drugs on maternal health and pregnancy outcomes, including birth defects. Mofenson underscored that although there are currently 32 ART drugs approved for HIV treatment in adults, there are limited data on the safety of these drugs for clinical use in pregnancy; most have received regulatory approval with only animal data available to assess potential adverse drug effects on the fetus (Abstract 59).

She also discussed the difficulty of accurately determining associations between drug exposures and outcomes with low incidence rates such as birth defects. She stressed that research on fetal effects associated with ART drugs should differentiate between the first trimester of pregnancy and the preconception period, as the exposure to a drug in the latter period would be crucial to assess. She described various caveats to the current data on birth defects associated with ART drugs. These data are often collected after regulatory approval of the drugs, and timing of drug exposure in relation to conception is often difficult to ascertain from cases reported to pharmacovigilance registries. Mofenson emphasized the importance of active, prospective surveillance of birth outcomes as new ART drugs are introduced into the market and the need to weigh considerations for both the mother and the child, balancing the risks of adverse effects to the fetus with the benefits to the mother.

Gandhi reviewed HIV treatment options for women of reproductive potential and pregnant women in high-income countries in (Abstract 60). She summarized current ART guidelines for women of reproductive potential who desire pregnancy, as well as for pregnant women. She discussed the pharmacokinetic issues of ART drugs during pregnancy: changes in absorption, distribution, metabolism, and elimination of drugs, as well as safety, tolerability, and efficacy considerations for different ART regimens. Gandhi also discussed PrEP considerations in women, emphasizing that TDF/FTC is generally safe for use in pregnant women as HIV PrEP, and briefly summarized drug-drug interactions between contraceptives and ART. She concluded that it is ethical and imperative to increase representation of women of reproductive potential and pregnant women in HIV clinical research.

Mukui gave an overview of the public health policy and programmatic considerations for ART implementation in women of reproductive potential in LMICs, with some examples from Kenya (Abstract 61). She highlighted key issues that should be addressed, such as concerns for safety and efficacy of ART drugs in women of reproductive age, expanding access to comprehensive family planning services that include contraception, improving in-country pharmacovigilance and surveillance systems for adverse drug effects affecting maternal and fetal outcomes, and balancing an individualized approach to health care, with specific understanding of a woman's reproductive and other health desires and choices, with a broader public health approach to program implementation.

Lyerly reiterated the substantial evidence gaps in HIV research resulting from underrepresentation of women in studies, including women who become pregnant while on ART (Abstract 62). She discussed the implications, such as gaps in knowledge about dosing of drugs, safety to the fetus, and maternal and neonatal health outcomes. She highlighted the challenges that may hinder research in women of reproductive potential, including legal and regulatory issues, myths and misunderstandings about what research is permissible within a regulatory environment, a "protectionist" culture with women being perceived as "vulnerable," insufficient training and experience in conducting research in this population, and misallocated research funding that is more focused on child health outcomes than on the women themselves.

Sex Differences in Safety of ART and in HIV Treatment Outcomes

In a Themed Poster Discussion, studies exploring whether there are differences in ART outcomes, drug exposure, and safety by biologic sex in individuals with HIV infection were presented. Godfrey and colleagues analyzed data from ACTG A5288, an open-label intervention trial in individuals with HIV infection in LMICs whose second-line ART failed (Abstract 518). Women were less likely to have viral suppression at week 48 and more likely to experience failure of third-line ART with a boosted PI (with emergence of resistance) and to experience grade 3 or 4 signs and symptoms than men. The investigators stressed the importance of further research into ART drug exposure and tolerability in women in HIV infection in LMICs.

Differences in immune activation patterns by sex in individuals with HIV infection on ART who are virally suppressed in the observational AFRICOS Study (African Cohort Study) were noted by Son and colleagues (Abstract 517). Significantly higher levels of specific immune activation markers, such as interferon-γ-induced protein 10 and soluble CD25, were observed in women with HIV infection than in men, although these differences by sex were not seen in HIV-negative individuals.

Thompson and colleagues conducted a pooled analysis of data from 7 randomized clinical trials to investigate the safety and efficacy of TAF compared with TDF in 779 cisgender women with HIV infection who initiated or switched to TAF from TDF for HIV treatment (Abstract 519). The investigators found that women who initiated TAF experienced fewer declines in bone mineral density, and those who were changed to TAF from TDF had improvements in bone mineral density. Women who were started on TAF had fewer declines in estimated glomerular filtration rate and renal tubular proteinuria, and those who switched to TAF exhibited improvements in these renal tubular markers compared with women on TDF. Women who initiated or switched to TAF had similar rates of viral suppression through week 96 to those on TDF, with overall comparable safety and tolerability profiles for TAF and TDF. These findings in women were similar to those observed in men. A nested case-control study of drug resistance that emerged during breastfeeding among mother-infant pairs enrolled in the PROMISE (Promoting Maternal and Infant Survival Everywhere) 1077BF trial included 48 transmitting mothers and their HIV-infected infants (in utero or peripartum infections, 37 infections acquired during breastfeeding, and 254 controls who were nontransmitting mothers matched by delivery date and clinical site (Abstract 769). Drug resistance was more prevalent among women who transmitted through breastfeeding (30%) than with in utero or peripartum transmission (4%). In logistic regression, risk of MTCT was associated with higher viral load and no antepartum triple-drug ART regimen, but maternal DRMs were not. DRMs were more likely in infants infected through breastfeeding (54%) than in utero or peripartum (13%). Among infants with longitudinal geno typic data (n=46), 8 infants with wild-type virus at birth developed DRMs in in the in utero cohort compared with 1 in the breastfeeding cohort. Investgators concluded that drug resistance does not appear to be the driver of MTCT, but with accumulation of DRMs during infancy, exploration of alternate treatment regimens for mothers and infants is warranted.

InSTIs and Birth Defects

The observational TSEPAMO study in Botswana previously reported preliminary results of neural tube birth defects in 4 of 596 (0.67%; 95% CI, 0.26%–1.7%) infants of women receiving DTG-containing ART and 14 of 11,300 (0.12%;

95% CI, 0.07%-0.21%) infants of women receiving non–DTG-containing ART preconception.[14,15] Following these results, the WHO, US FDA, and other international regulatory agencies in 2018 issued alerts on a possible increased risk of neural tube defects in infants born to women with HIV infection receiving DTG as part of their ART at the time of conception.[16,17] Several posters examining associations between InSTIs, including DTG, and neural tube defects were presented. Barlow-Mosha and colleagues analyzed 69,767 births from a hospital-based birth defect surveillance program from 4 hospitals in Kampala, Uganda, and found that neural tube defects (prevalence, 8.9/10,000 births; 6.8–11.4) were a common congenital malformation affecting births (Abstract 743). No statistically significant difference in the prevalence of neural tube defects was seen by HIV serostatus of the mother. With 9.6% of the infants delivered by women with HIV infection and 80% of women with HIV infection receiving EFV-based ART, 16% NVP-based ART, 0.02% InSTI-based ART, and 3.7% other ART regimens, the investigators did not find an association between ART regimen and increased risk for neural tube defects.

Sibiude and colleagues evaluated data from 808 HIV-infected mother-infant pairs exposed to InSTIs in the multicenter French Perinatal Cohort study, and data from 7318 matched unexposed pairs (Abstract 744). Exposure to InSTIs was categorized in one of 3 groups: 1) ongoing at conception; 2) initiated during pregnancy as initial ART; and 3) initiated during pregnancy as second-line ART. Among 301 infants exposed to InSTIs at conception (218 to RAL, 41 to DTG, and 42 to EVG), a birth defect rate of 5.5% was observed, which was not significantly different from the rates seen in infants with exposure when InSTIs were initiated during therapy as initial ART (2.7%; 5/183) or as second-line ART (2.7%; 9/324). No neural tube defects were found among infants exposed to InSTIs at conception; birth defects were noted in only 2 infants exposed to DTG. Compared with the rate among matched infants who were not exposed to InSTIs, the birth defect rate among infants exposed to InSTIs at conception did not differ significantly (5.7% of exposed vs 2.9% of unexposed).

Cumulative pregnancy outcome data from women with HIV infection receiving RAL through May 2018 were analyzed from 3 sources: a Merck safety database and 2 pregnancy outcome cohorts (National Surveillance of HIV in Pregnancy and Childhood and the French Perinatal Cohort) (Abstract 745). The reports of pregnancy outcome were categorized as prospective if RAL exposure was reported before there was knowledge of the pregnancy outcome, and as retrospective if RAL exposure was reported after pregnancy outcome was known. Among 1991 prospective reports of RAL exposure in pregnancy (55% were during the first trimester, with 66% of these exposures occurring during the periconception period, defined as within 28 days of conception), there were no cases of neural tube defects reported. Among 435 retrospective reports, a total of 4 cases of neural tube defects (1 case of anencephaly, 1 case of encephalocele, and 2 cases of myelomeningocele) were reported; however, only 1 case of myelomeningocele was reported among live births following exposure to RAL during the periconception period. The investigators concluded that the data do not support an association between neural tube defects and exposure to RAL during the periconception period.

Hill and colleagues analyzed 4 pharmacovigilance databases for reports of neural tube defects associated with 4 InSTIs (DTG, RAL, EVG, BIC), 2 PIs (darunavir, atazanavir) and 2 NNRTIs (NVP, EFV) through August 2018 (Abstract 746). Neural tube defects were reported for all drugs except BIC. Seven cases of neural tube defects were reported for DTG in the WHO VigiAccess database and 6 cases were reported in the US FDA Adverse Event Reporting System database, whereas no cases were reported in the European EudraVigilance and UK Medicines Health Regulatory Authority databases. Investigators cautioned about the limitations of using pharmacovigilance databases to ascertain associations between neural tube defects and specific drug exposures, because of the inability to obtain accurate denominator data. Reporting of adverse drug reactions is not systematic, there is often overlap for reporting of drugs for the same patient because of ART consisting of several drugs leading to duplications, and timing of drug exposure relative to conception in the reports is frequently uncertain.

Serum folate concentrations were measured in 486 women with HIV infection randomly assigned to initiate treatment with DTG- or EFV-containing ART in the ongoing South African ADVANCE trial, to determine whether ART regimen affects folate levels, which could contribute to risk of neural tube defects (Abstract 749). Women on EFV-based ART had declines in mean serum folate concentrations over 24 months, and pregnant women treated with EFV-containing ART had lower mean folate concentrations than women treated with DTG-containing ART. Birth outcomes were also analyzed, with 16 live births, 1 infant death, 1 spontaneous abortion, and 2 congenital abnormalities (naevus flammeus and umbilical hernia); 19 elective abortions have been reported to date.

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