Invited Review

CROI 2016: Advances in Antiretroviral Therapy

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The 2016 Conference on Retroviruses and Opportunistic Infections highlighted exciting advances in antiretroviral therapy, including important data on investigational antiretroviral drugs and clinical trials. Clinical trials demonstrated benefits from a long-acting injectable coformulation given as maintenance therapy, examined intravenous and subcutaneous administration of a monoclonal antibody directed at the CD4 binding site of HIV-1, and provided novel data on tenofovir alafenamide. Several studies focused on the role of HIV drug resistance, including the significance of minority variants, transmitted drug resistance, use of resistance testing, and drug class–related resistance. Novel data on the HIV care continuum in low- and middle-income settings concentrated on differentiated HIV care delivery models and outcomes. Data on progress toward reaching World Health Organization 90-90-90 targets as well as outcomes related to expedited initiation of HIV treatment and adherence strategies were presented. Results from a trial in Malawi showed reduced rates of mother-to-child transmission among HIV-infected women who initiated antiretroviral therapy prior to pregnancy, and several studies highlighted the effect of antiretroviral therapy in pediatric populations. A special session was dedicated to the findings of studies of Ebola virus disease and treatment during the outbreak in West Africa.

Keywords: CROI, 2016, HIV, antiretroviral, drugs, therapy, clinical trials, long-acting injectable agent, resistance, care delivery, resource-constrained settings, Ebola

Investigational Antiretroviral Agents

MK-8591

At the 2016 Conference on Retroviruses and Opportunistic Infections (CROI), Grobler and colleagues presented data on MK-8591, an investigational nucleoside analogue reverse transcriptase inhibitor (nRTI) (4'-ethynyl-2-fluoro-2'-deoxyadenosine or EFdA) (Abstract 98). It is highly potent in vitro, with a 50% effective concentration (EC_{50}) of 0.2 nM. MK-8591 differs from other nRTIs in that it retains a 3'-hydroxyl group. This compound acts as a translocation inhibitor and, as a result, causes inefficient chain elongation. In a monkey model, the intracellular half-life of the phosphorylated metabolite of MK-8591 is approximately 50 hours, suggesting the potential for once-weekly dosing. This was confirmed in a model that used simian immunodeficiency virus (SIV)-infected rhesus macaques. In a phase I repeated-dose study, the investigators found that MK-8591 10 mg weekly resulted in trough concentrations that exceeded the target concentration by 2 fold and that the compound was well tolerated. An extended-release parenteral formulation that exhibits therapeutic levels for more than 180 days after a single injection is under investigation. In a separate investigation, a single dose of MK-8591 10 mg given to HIV-infected adults resulted in a 1.6 $\log_{10}$ copies/mL decline in plasma HIV-1 RNA through 10 days, with an intracellular half-life of 4.3 days and no emergence of resistance (Abstract 437LB).

BMS-986197

Krystal and colleagues presented preclinical data on BMS-986197, an investigational recombinant biologic molecule that incorporates 3 HIV entry inhibitors using small proteins derived from human fibronectin called adnectins (Abstract 97). The entry inhibitors include 2 anti–glycoprotein 41 adnectins binding at 2 different locations and an anti-CD4 adnectin joined into a single molecule. The combination of the individual components exhibits synergy in vitro and appears to have a heightened barrier to resistance. The pharmacokinetic data from a primate model support once-weekly subcutaneous dosing, and preliminary evidence of activity in vivo was observed in a humanized mouse model.

ABX-464

Scherrer and colleagues presented data on ABX-464, an investigational compound that inhibits HIV replication of Rev (Abstract 461LB). The investigators tested ascending doses in HIV-infected adults and found that the compound was tolerable with no concerning safety events. The compound exhibited modest antiretroviral activity, with 4 of 6 participants experiencing a 0.5 $\log_{10}$ copies/mL reduction in plasma HIV RNA after 14 days of dosing.

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BMS-955176

BMS-955176 is an investigational maturation inhibitor currently in phase II trials. Ray and colleagues presented data on the in vitro susceptibility of clinical isolates from individuals whose protease inhibitor (PI)-based therapy failed and a separate panel of highly PI-resistant viruses (Abstract 464). The investigators found that BMS-955176 retained activity against these viruses, suggesting that this compound will be useful for participants with highly drug-resistant HIV.

Clinical Trials of Long-Acting Injectable Agents

Injectable Cabotegravir and Rilpivirine for Maintenance Therapy

Margolis and colleagues presented results from the LATTE-2 (Long-Acting Antiretroviral Treatment Enabling–2) trial, a randomized open-label trial of the investigational long-acting integrase strand transfer inhibitor (InSTI) cabotegravir with rilpivirine in an injectable coformulation given as maintenance antiretroviral therapy (Abstract 31LB). Three hundred nine antiretroviral therapy–naive participants (92% male, 20% nonwhite, and 18% with a plasma HIV-1 RNA level > 100,000 copies/mL) initiated treatment with cabotegravir plus abacavir and lamivudine given orally for 20 weeks; rilpivirine was added for weeks 16 through 20. Virologic suppression was achieved in 91%, and 286 were then randomly assigned 2:2:1 to maintenance therapy with the injectable regimen given every 8 weeks or every 4 weeks or to continuation of the oral regimen. The primary efficacy end point was virologic suppression 32 weeks after randomization. Virologic suppression, according to the US Food and Drug Administration (FDA) Snapshot algorithm, was observed among 95% of participants who received the injectable regimen every 8 weeks, 94% of participants who received the injectable regimen every 4 weeks, and 91% in the oral dosing arm. Each of the arms receiving the injectable regimen achieved noninferiority. Among the participants with a plasma HIV-1 RNA level greater than 50 copies/mL at week 32, all continued on their randomized therapy and achieved virologic suppression at subsequent time points. Two participants developed protocol-defined virologic failure and none had emergence of resistance mutations.

A long-acting injectable coformulation for maintenance antiretroviral therapy is moving forward to phase III trials.

There were statistically significantly more grade 3 or 4 adverse events (not including injection site reactions) in the injectable arms, although most of these were deemed unrelated to study treatment. Injection site reactions (pain, swelling, and nodules) were common in the injectable treatment arms; nearly all reactions were grade 1 or 2, and the frequency declined over time. Only 2 participants (1%) withdrew because of injection site reactions. Participants in the injectable treatment arms reported a very high rate of satisfaction with their assigned treatment. This injectable combination is moving forward to phase III trials.

VRC01

Mayer and colleagues presented data on intravenous and subcutaneous administration of VRC01, a broadly active monoclonal antibody directed at the CD4 binding site of HIV-1, to 88 HIV-uninfected volunteers (Abstract 90). VRC01 was well tolerated, with 6.2% of participants experiencing adverse events (all mild) related to the study product. VRC01 exhibited a pharmacokinetic profile that supports subcutaneous dosing every 3 weeks or intravenous dosing every 2 months.

Bar and colleagues also presented data on VRC01 in HIV-infected adults (Abstract 32LB). The investigators enrolled participants who were virologically suppressed for at least 6 months, who had a current CD4+ cell count greater than 400/µL, and who had a CD4+ cell count nadir greater than 200/µL. VRC01 was administered intravenously every 3 weeks for 3 doses and antiretroviral therapy was interrupted 1 week after the first dose of VRC01. Participants were monitored weekly. Fourteen participants were enrolled; 1 participant was not evaluable because he discontinued antiretroviral therapy prior to the first infusion. All participants were men and 50% were white. The infusions were safe and well tolerated, and plasma VRC01 concentrations were in the anticipated range throughout the study. Eleven of 13 participants experienced virologic rebound by week 5 and the other 2 experienced it by week 12. Clonal analyses of virus isolated during virologic rebound suggest clonal expansion of virus with preexistent VRC01 resistance in some of the participants. The investigators suggested that future studies should examine combinations of broadly neutralizing antibodies.

Other Clinical Trials of Antiretroviral Therapy

Switching to Tenofovir Alafenamide

Gallant and colleagues presented results from a randomized, double-blind, double-dummy clinical trial of changing stably suppressed individuals taking emtricitabine and tenofovir disoproxil fumarate (TDF) to emtricitabine and tenofovir alafenamide (TAF) (Abstract 29). This trial randomly assigned 663 participants (15% female, 25% nonwhite, 46% receiving a boosted PI) to continue emtricitabine and TDF or start emtricitabine and TAF. Placebo tablets were used to mask treatment assignment, and the dose of emtricitabine and TAF depended on use of a boosted PI. The primary end point was virologic suppression at week 48, using the FDA snapshot algorithm: 94.3% for emtricitabine and TAF compared with 93% for emtricitabine and TDF (1.3%; 95% confidence interval [CI], -2.5%-5.1%) achieving noninferiority. The end points were driven by lack of data at week 48 not virologic failure. There were statistically significant improvements in renal tubular biomarkers and estimated glomerular filtration rates in the emtricitabine and TAF group compared with emtricitabine and TDF. There were statistically significant increases in bone

density with the use of emtricitabine and TAF compared with the stable bone density observed with emtricitabine and TDF. There were statistically significantly higher levels of total cholesterol, low-density lipoprotein (LDL) cholesterol, and triglycerides with emtricitabine and TAF than with emtricitabine and TDF. These results support the safety and efficacy of switching emtricitabine and TDF to emtricitabine and TAF to avoid potential renal and bone toxic effects.

Second Antiretroviral Regimens in Resource-Constrained Settings

La Rosa and colleagues presented data from the AIDS Clinical Trials Group (ACTG) A5273 trial, a randomized clinical trial of ritonavir-boosted lopinavir plus 2 nRTIs compared with boosted lopinavir plus raltegravir for individuals whose initial nonnucleoside analogue reverse transcriptase inhibitor (NNRTI)-based regimen failed (Abstract 30). This was a phase III, open-label, randomized clinical trial conducted at 15 sites in 9 countries. Five hundred twelve participants (52% female, 64% black, 81% infected with subtype C) with a median CD4+ cell count of 135/μL and plasma HIV-1 RNA level of 4.5 $\log_{10}$ copies/mL were randomly assigned to one of the study arms. The cumulative probability of virologic failure through week 48 was 10.3% in the raltegravir-containing arm and 14% in the nRTI-containing arm. This achieved noninferiority but did not demonstrate statistical superiority of raltegravir. Participants with 3 or more nRTI resistance mutations at baseline were more likely to achieve virologic suppression in each arm. The investigators suggested that baseline nRTI resistance was a marker of adherence. These data support the current World Health Organization (WHO) recommendation for boosted lopinavir plus an nRTI as a second antiretroviral regimen.

Additional Pharmacokinetic Considerations

Colbers and colleagues evaluated the pharmacokinetics of a crushed fixed dose of elvitegravir, cobicistat, emtricitabine, and TDF (Abstract 431). They found that the crushed tablet administered via feeding tube had similar pharmacokinetics to the intact tablet. The investigators concluded that it was reasonable to crush the tablet for administration. Molto and colleagues examined the effect of hemodialysis on dolutegravir concentrations (Abstract 432). The researchers found minimal removal of dolutegravir by hemodialysis and concluded that no dose adjustments are necessary in this situation.

Resistance

Transmitted Drug Resistance and Minority Variants

A themed discussion was dedicated to next-generation sequencing for detection of transmitted or linked drug resistance. Minority-level variants are defined as variants present at less than 20% of the viral population. Since minority-level variants do not uniformly lead to virologic failure in all cases, nor does all majority-level resistance lead to virologic failure, a better understanding of the breadth and clinical significance of minority-level variants is essential. The session showcased studies aimed at unraveling the highly complex nature of in vivo variant expression.

The prevalence and significance of sexual transmission of minority HIV drug resistance mutations (DRMs) is not completely understood. Chaillon presented a next-generation sequencing analysis of 31 HIV-infected, antiretroviral therapy–naive, phylogenetically and epidemiologically linked male source and recipient partners sampled within a median of 9 days (Abstract 487). Next-generation sequencing identified a total of 139 DRMs from 22 sites (9 NNRTI, 13 nRTI) at an average frequency of 3.37% (interquartile range [IQR], 0.3%-5.1%). There was no evidence of preferential sexual transmission or selection of minority DRMs. Longitudinal samples in the recipient partner showed that minority DRMs were identified only during early infection and were lost over time, suggesting a mutation-selection balance hypothesis in which deleterious mutations are efficiently purged from the population later in infection.

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InSTIs have increasingly been used as initial therapy in many settings; however, little is known about InSTI-associated transmitted drug resistance. Todesco presented analysis of 92 recently diagnosed, treatment-naive individuals with HIV infection and found InSTI-associated mutations in 7.6% (2.2%-13.0%) of all samples analyzed by Sanger sequencing and 10.9% (4.5%-17.2%) of all samples analyzed by ultradeep sequencing (Abstract 489). Although none of the classic InSTI-associated resistance mutations (positions 143, 148, and 155) were identified by either sequencing method, among men who have sex with men (MSM; n = 70), rates of InSTI-associated mutations were relatively high, with a prevalence of 10% (3.05%-17.0%) by Sanger sequencing and 14.3% (6.1%-22.5%) by ultradeep sequencing. Notably, there were 3 viruses that harbored minority variant mutations that were only detected by ultradeep sequencing (2 R263K and 1 E138K). The R263K mutation has been associated with dolutegravir failure.

In an effort to identify low-frequency transmitted drug resistance and describe the evolution of DRMs over time, Singh and colleagues applied ultradeep sequencing in a cohort of 14 acutely infected individuals with HIV subtype C virus infection (Abstract 488). Using a clinical cutoff of greater than or equal to 1% to identify low-frequency DRMs, 8 of 14 participants were found to have low-frequency DRMs associated with nRTIs, NNRTIs, PIs, or InSTIs. A subset of the samples was sequenced at additional time points to monitor for reversion,

and PI- and InSTI-associated mutations were found to revert by 7 days to 12 days; however, the NNRTI-associated K103N mutation persisted in 1 participant for nearly a year. The investigators also acknowledged that although the K65R mutation was the most common DRM, this may have been related to technical error in the context of 454 sequencing technology, which has been identified as a spurious finding in other analyses of 454 sequencing.[1]

Targeted next-generation sequencing is a powerful tool for detecting low-frequency, HIV drug–resistant mutations, but polymerase chain reaction (PCR) error and frequent in vitro recombination prevent accurate detection of linked mutations and assessment of population structure. Boltz presented promising results using a new next-generation sequencing–based ultrasensitive single-genome sequencing assay designed to minimize PCR bias, error, recombination, and resampling (Abstract 490). The ultrasensitive single-genome sequencing method utilizes primer IDs, short primers, and efficient ligation rather than primer IDs and long primers as is the case with standard methods. Using samples from a donor whose antiretroviral regimen failed, ultrasensitive single-genome sequencing was compared with standard methods and was found to accurately identify clustering and correct PCR error.

Transmitted Drug Resistance

Guidelines continue to recommend boosted PI–based antiretroviral therapy for those individuals found to have thymidine analogue mutations (TAMs) on baseline resistance testing, to improve the barrier to resistance. Geretti and colleagues analyzed Sanger sequences and clinical data from the UK CHIC (United Kingdom Collaborative HIV Cohort) study to examine virologic outcomes of initial antiretroviral therapy in HIV-seropositive adults with 1 or more TAMs as the sole form of transmitted drug resistance compared with those who did not have any detectable baseline resistance (Abstract 482). There were 269 participants with isolated baseline TAMs and 6330 participants with no evidence of baseline resistance based on the 2009 WHO resistance mutations list.[2] All participants were treated with an NNRTI-based or a boosted PI–based regimen. A multivariable model and Kaplan-Meier analyses showed that the risk of virologic failure was statistically significantly associated with use of a boosted PI–based regimen compared with an NNRTI-based regimen and that the presence of TAMs at baseline did not influence virologic responses to NNRTI-based regimens. At 5 years, the probability of virologic failure was 15.3% in the group that received an NNRTI-based regimen and 31.8% in the group that received a PI-based regimen. Notably, the most common sequencing result was a single TAM, and in a subgroup analysis, there was a trend toward higher rates of virologic failure among participants with more than 1 TAM at baseline in both treatment groups. Nonetheless, this analysis calls into question the guidance on the management of individuals with isolated TAMs at baseline and the investigators called for controlled studies to better inform recommendations.

Although transmitted drug resistance to NNRTI-based therapy is commonly reported, transmission of resistance to PIs is rare. Harrigan and colleagues described transmission and clustering of resistance to HIV PIs in Ontario, Canada (Abstract 491LB). After observing an unusual pattern of baseline resistance, investigators reviewed HIV sequences from all individuals in care and applied phylogenetic mapping for HIV *pol* sequencing from the first sample for which testing was available (N = 11,500). There were 49 treatment-naive participants with PI resistance in a single large cluster. Each of the participants had numerous PI resistance–associated mutations (typically 7) at the time of first pretreatment genotype test, which conferred substantial resistance to most PIs except darunavir. These mutations were also commonly accompanied by the nRTI-associated revertant mutations M41L and T215-L/S. Most cases were observed in late 2014 or in 2015. All 49 individuals were men (median age, 29 years), and all indicated that HIV exposure occurred through sex with men. This highly resistant cluster illustrates that substantial PI-associated resistance can occur with sufficient replicative fitness to circulate for many years and possibly threaten the current treatment paradigm. The investigators highlighted the importance of systematic surveillance of HIV resistance in untreated individuals.

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Transmitted Drug Resistance and Surveillance

The WHO has proposed a global standardized HIV drug resistance, monitoring, and surveillance strategy with the aim of ensuring sustainability of antiretroviral treatment programs. Avila-Rios shared results from a nationally representative pretreatment drug resistance survey in Mexico (Abstract 477). There were 264 viruses included in the study, representing a sample of 288 participants drawn from Ministry of Health clinics across the country. Pretreatment drug resistance was measured by Sanger sequencing and next-generation sequencing and based on the WHO surveillance HIV drug resistance mutation list and the Stanford calibrated population resistance tool.[2,3] Applying standard sequencing, pretreatment drug resistance to any drug was found to be 12% (95% CI, 8.4%-16.5%) and NNRTI-associated resistance was found to be the highest (6.9%), followed by nRTI-associated resistance (5.1%) and PI-associated resistance at (2.6%). The most frequent pretreatment drug resistance mutation was the K103N mutation. Additional analysis was conducted using next-generation sequencing, which showed increasing mutation frequencies as the threshold for population detection was lowered. Among individuals who had NNRTI-associated resistance at baseline, only 25% were virologically suppressed

on NNRTI-based regimens. Additionally, NNRTI-associated resistance detected in minority variants was also statistically significantly associated with failure to achieve viral suppression, which was found at a threshold as low as 5%. The investigators suggested that the integration of baseline HIV drug resistance testing could improve the efficacy of antiretroviral therapy.

Resistance Testing

Current guidelines in the United States recommend HIV resistance testing at entry into care or soon after HIV diagnosis.[4,5] There were 2 presentations from the Centers for Disease Control and Prevention (CDC) that investigated the rates of HIV resistance testing in the United States. Banez Ocfemia presented rates of genotype testing at entry into care among 1193 practitioners surveyed through the Medical Monitoring Project Provider Survey (Abstract 497). Of practitioners surveyed, 84.5% responded that they test all patients who are new to care, 8.8% responded that they test more than half (but not all), and 6.7% responded that they test half or fewer. Multivariate modeling indicated that not being an HIV specialist (compared with being an HIV specialist) and prescribing antiretroviral therapy based on CD4+ cell count (compared with prescribing antiretroviral therapy regardless of CD4+ cell count) were associated with a lower likelihood of ordering genotypic testing for all patients.

Dasgupta and colleagues analyzed data from the US National HIV Surveillance System (NHSS) for persons aged 13 years and older with HIV infection diagnosed in 2013 who were linked to care (ie, had a CD4+ cell count or a viral load test) within 3 months of diagnosis and resided in a jurisdiction with complete laboratory reporting and high reporting of nucleotide sequence data from resistance testing (Los Angeles County, California; Michigan; New York; South Carolina; Texas; and Washington). Of 9481 persons in these jurisdictions who received a diagnosis of HIV infection in 2013 and were linked to care within 3 months of diagnosis, 6181 (65%) ever received a resistance test and 4270 (69%) received a resistance test at the time of linkage to care. Substantially lower levels of drug resistance testing were observed in selected jurisdictions, among persons in areas with smaller populations (< 500,000 population size), and among men who inject drugs. The investigators highlighted the need to consider and address such differences in testing practices.

Because InSTIs are relatively new, data on InSTI resistance and resistance testing are limited. Since 2005, laboratories conducting any HIV resistance testing for residents of New York State are required to report HIV drug resistance results to the state Department of Health. Wang, on behalf of the New York State AIDS Institute, reported on rates of InSTI resistance testing and described resistance findings based on reported resistance tests between December 2009 and July 2015 (Abstract 501). There were 5627 InSTI resistance tests that were linked to the New York State HIV registry, of which 4208 (75%) had paired protease and reverse transcriptase resistance tests, and 3533 (63%) cases were stage 3 HIV infection at time of testing. Among the 4626 cases in which an InSTI resistance test was not initially performed, 63% of first InSTI resistance tests occurred 11 years or more after HIV diagnosis. Of 3515 cases of newly diagnosed HIV infection in New York State in 2014, 16% had an initial InSTI test, compared with 55% who were initially tested for protease and reverse transcriptase resistance. Multivariable logistic regression showed that the odds of having had an initial InSTI resistance test were related to race and ethnicity, transmission risk group, and region of residence. Accordingly, there were higher rates of initial InSTI resistance testing among men (18%), those of white and Hispanic race (19.1% and 19.0%, respectively), those at risk through sexual contact with MSM (21%) or sexual contact with MSM and injection drug use (22%), and residents of New York City (17.9%). Less than 1% (7/1001) of initial and 8.6% (400/4626) of noninitial InSTI resistance tests showed resistance to at least 1 of 3 InSTIs. The time from HIV diagnosis to InSTI resistance test and the proportion of individuals with advanced HIV infection suggest that, during this period, the majority of tests were ordered for long-standing cases at advanced stages of disease.

Resistance to InSTIs

There has been increasing use of InSTIs in clinical practice for treatment-naive and -experienced individuals. Lepik and colleagues performed a retrospective review of individuals cared for at the British Columbia Centre for Excellence in HIV/AIDS Drug Treatment Program from 2009 to 2015, to assess the prevalence and incidence of InSTI-associated drug resistance (Abstract 492LB). In British Columbia, Canada, the use of the InSTIs raltegravir, elvitegravir, and dolutegravir in antiretroviral regimens increased from 10% in 2009 (540 persons treated with raltegravir) to 32% in 2015 (978 persons treated with raltegravir, 500 persons treated with elvitegravir, and 1011 persons treated with dolutegravir). Among adults who had received antiretroviral therapy and had drug resistance testing performed, there were 57 individuals with intermediate- or high-level InSTI-associated resistance. The prevalence of InSTI-associated resistance per 1000 persons who were treated with antiretroviral therapy increased from 1.07 in 2009 to 6.8 in 2015 ($P < 001$, for trend; R^2, 0.99). During this period, resistance to antiretroviral drugs declined from 331 per 1000 persons treated to 285 per 1000 persons treated ($P < .001$, for trend; R^2, 0.98). Prior to 2014, all observed mutations were limited to raltegravir-associated resistance; however, in 2014 and 2015, resistance to dolutegravir and elvitegravir was observed as well. Three cases of InSTI-associated resistance emerged during therapy with dolutegravir, including 2 treatment-experienced individuals who developed the R263K mutation and 1 treatment-naive individual who was treated with an initial regimen of dolutegravir, abacavir, and lamivudine who developed the T66I mutation. The investigators pointed out that although InSTI-associated resistance remains low, it is increasing, and emerging InSTI-associated resistance is observed in treatment-naive and -experienced individuals.

There are now several FDA-approved coformulated InSTI-based regimens, including the recently approved coformulation of elvitegravir, cobicistat, emtricitabine, and TAF, which is associated with fewer renal and bone effects than have been observed with TDF.[6] Abram and colleagues presented a pooled week-48 resistance analysis of elvitegravir, cobicistat, emtricitabine, and TAF from 7 phase III clinical trials (Abstract 496). A total of 2308 participants were included in the analysis. The 7 ongoing trials included studies of treatment with elvitegravir, cobicistat, emtricitabine, and TAF in several populations: treatment-naive adults (2 trials), treatment-naive adolescents, virally suppressed individuals and virally suppressed individuals with resistance to 2 or more antiretroviral drug classes (2 switch studies), individuals with renal impairment, and individuals with HIV/hepatitis B virus (HBV) coinfection. As part of the resistance end point, participants underwent genotypic and phenotypic analysis at baseline and in the event of virologic failure or treatment discontinuation (HIV RNA level ≥400 copies/mL). Among 16 of 866 treatment-naive adults who had genotypic and phenotypic analysis, nRTI resistance–associated mutations (M184V/I, n = 7; K65R, n = 1) and primary InSTI-associated resistance mutations (T66I/A, n = 2; E92Q, n = 2; Q148R, n = 1; N155H, n = 1) emerged in 7 (0.8%). Among 2 of 50 treatment-naive adolescents who had genotypic and phenotypic testing, however, no resistance was found. Among virologically suppressed individuals, 4 of 959 had genotypic and phenotypic testing; resistance emerged in 1 individual (M184M/I), and HIV RNA was resuppressed to below 50 copies/mL before treatment discontinuation. Among 110 virologically suppressed participants with prior resistance to 2 or more antiretroviral drug classes, none met the genotypic and phenotypic analysis criteria. Among 2 of 248 renally impaired individuals who were analyzed, both had multiclass resistance detected (1 preexisting and 1 due to possible reinfection followed by resuppression of HIV RNA to < 50 copies/mL). Among 75 HBV-coinfected participants, none met the analysis criteria. The investigators pointed out that resistance at 48 weeks to 1 or more components of elvitegravir, cobicistat, emtricitabine, and TAF was rare in all studied populations, including highly treatment-experienced individuals switching to this regimen.

The InSTI dolutegravir has a high genetic barrier to resistance and has been selected in treatment-experienced individuals and in cell culture. The novel R263K substitution in integrase is a mechanism of dolutegravir resistance in InSTI treatment–naive individuals. In InSTI treatment–experienced individuals, however, resistance emerges through the accumulation of resistance substitutions for other drugs in the InSTI class. For instance, E157Q can be selected after treatment with raltegravir and can be a polymorphism present in the circulating virus as well. Anstett and colleagues investigated the effects of E157Q substitution on the emergence of R263K and its effects on enzyme biochemical function, viral infectivity, and drug resistance (Abstract 507). The E157Q and R263K substitutions were introduced into the pET15b integrase protein expression vector followed by measurement of strand transfer and DNA binding activities as well as viral infectivity and drug resistance, which were measured through the infection of TZM-bl cells and observation of luciferase production. The E157Q substitution restored impaired replication conferred by the dolutegravir resistance–associated mutation R263K, and enhanced resistance to this compound by 20 fold compared with wild-type. The investigators cautioned that because position 157 in the integrase is polymorphic, it could be present at the initiation of dolutegravir-containing therapy, which could result in a replication competent, dolutegravir-resistant virus.

NNRTIs and Barriers to Resistance

The investigational NNRTI doravirine is currently in phase III clinical trials. Lai and colleagues assessed the inhibitory quotient and the 50% inhibitory concentration (IC_{50}) of doravirine compared with rilpivirine and efavirenz in the presence of K103N, Y181C, and K103N/Y181C mutants in vitro (Abstract 506). Antiviral assays were performed using laboratory HIV-1 isolates (wild-type and mutant) and MT4-GFP cells, followed by cell infection. The infected cells were added to plates containing different NNRTIs at various concentrations. IC_{50} was calculated for each, and doravirine was found to display inhibitory quotients of 39, 26, and 21 against the K103N, Y181C, and K103N/Y181C mutants, respectively, compared with inhibitory quotients of 4.6, 1.4, and 0.8 for rilpivirine and 2.5, 60, and 1.9 for efavirenz. The investigators concluded that doravirine may have a higher barrier to resistance than rilpivirine or efavirenz.

Drug Resistance in Low- and Middle-Income Countries

HIV-1 drug resistance is an important cause of failure of second antiretroviral regimens in low- and middle-income countries. On behalf of the ACTG A5288 MULTI-OCTAVE (Management Using Latest Technologies to Optimize Combination Therapy After Viral Failure) Study, Wallis and colleagues shared an analysis of resistance testing from 665 cohort participants with viral failure taking a PI-based second regimen after prior exposure to nRTIs, NNRTIs, and PIs (Abstract 493LB). Participants were from 20 sites in 10 countries and underwent resistance testing and phylogenetic analysis. All participants had been exposed to nRTIs, most commonly lamivudine or emtricitabine (100%), tenofovir (84%), and zidovudine (76%). Almost all participants (99%) had prior exposure to NNRTIs, most commonly nevirapine (63%) followed by efavirenz (56%). At time of screening, tenofovir (67%) and lamivudine (90%) were the most commonly prescribed nRTIs with either ritonavir-boosted lopinavir (55%) or boosted atazanavir (43%). Very few participants had exposure to raltegravir (6%). At least 1 resistance mutation was detected in 96% (638/665) of participants. High- or intermediate-level resistance was common, and 519 participants (78%) had resistance to 1 or more drugs. Resistance to a single drug class was found in 21%, to 2 drug classes in 31%, and to all 3 drug classes (nRTI, NNRTI, and PI) in 26%. Of the 665 sequences, 461 (69%) showed susceptibility to the second

regimens (nRTI plus boosted atazanavir or lopinavir), and the majority was susceptible or had only low-level resistance to boosted darunavir (97%) and etravirine (79%). The investigators pointed out that clinical parameters were not predictive of the extent of resistance and called for objective measures of adherence and access to both resistance testing and new antiretroviral drugs to meet the needs of low- and middle-income countries.

Boender and colleagues also called for the availability of additional antiretroviral drugs to address PI-associated resistance during failure of a second HIV regimen in sub-Saharan Africa (Abstract 498). The PASER-M (PanAfrican Studies to Evaluate Resistance Monitoring) cohort enrolled participants at the time of switch to a second antiretroviral regimen and followed up the individuals over time, monitoring viral suppression and providing genotypic analysis when HIV RNA level was at or above 1000 copies/mL. The analysis revealed that although the majority of participants were able to achieve viral suppression with a second, PI-based regimen (85%) after up to 36 months of follow-up, nRTI-associated resistance was detected in 56% and major PI-associated resistance was detected in 21.9% of those whose second antiretroviral regimen failed, conveying reduced susceptibility to all available PIs. Additional drugs, including boosted darunavir, second-generation NNRTIs, and InSTIs, are needed to meet the needs of individuals who experience failure of their second antiretroviral regimen.

In many low- and middle-income countries, routine viral load testing is not yet available to guide the decision to switch from an initial to a second antiretroviral regimen. Instead, immunologic criteria are applied to estimate treatment failure. Ndembi and colleagues evaluated the accuracy of using immunologic criteria to predict treatment failure in a retrospective cohort study of individuals cared for from 2005 to 2014 at a teaching hospital in Nigeria (Abstract 502). Immunologic failure was defined as having a decrease in CD4+ cell count to pretherapy baseline level or a persistent CD4+ cell count of less than 100/μL after 6 months of therapy. A subset of individuals had viral load monitoring, and those who were found to have an HIV RNA level above 1000 copies/mL on 2 consecutive measurements underwent genotypic testing as well. Among individuals with immunologic failure who had viral load measurements, 43.9% had detectable viral loads. Among those with an HIV RNA level of 1000 copies/mL or higher, 21% did not have any drug resistance mutations. In contrast, individuals with virologic and immunologic failures showed accumulation of extensive drug resistance mutations. The use of immunologic criteria to drive the decision to switch antiretroviral therapy resulted in unnecessary switches for individuals who did not have genotypic evidence of resistance and potentially underestimated the extent of resistance as well. The investigators suggested that viral load and genotypic testing would be beneficial to guide decisions regarding switching of antiretroviral therapy.

The use of immunologic criteria to drive the decision to switch antiretroviral therapy resulted in unnecessary switches for individuals who did not have genotypic evidence of resistance and potentially underestimated the extent of resistance.

Although baseline resistance testing is recommended in resource-rich countries, because of cost and technical demands, it is not used routinely in low- and middle-income countries. Chung and colleagues presented data from a prospective randomized trial in Kenya of a simple oligonucleotide ligation assay (OLA) to detect key *pol* reverse transcriptase–associated mutations at codons 103, 181, 184, and 190 (Abstract 494LB). A total of 991 participants were enrolled in the study in 2013 and 2014 and were randomly assigned to receive pre–antiretroviral therapy OLA testing or standard of care. Those who had 1 or more baseline resistance mutations in the OLA arm were treated with ritonavir-boosted lopinavir rather than the standard NNRTI-based initial therapy. The overall prevalence of resistance was 8.3%. Although OLA testing was found to be feasible in Kenya, OLA testing and change to a boosted lopinavir–based regimen did not substantially impact the overall rate of virologic suppression. Rate of virologic failure was similar among those who received OLA testing (7.9%) and standard of care (7.5%). Considered from an alternative perspective, among individuals with resistance, the OLA strategy reduced virologic failure (13.9% vs 46.2%; $P < .005$). OLA testing was feasible in this clinical context, and although it did not impact overall viral suppression in the as-treated analysis, it did reduce virologic failure in individuals found to have resistance. OLA testing could be a useful strategy in the event that transmitted drug resistance continues to rise.

Resistance and Implications for Preexposure Prophylaxis

Antiretroviral therapy is used for treatment of HIV infection and, increasingly, for preexposure prophylaxis (PrEP) against HIV infection. TDF is a key component of HIV treatment and PrEP approaches, but little is known about the regional burden of TDF-associated resistance and the risk factors for its emergence. Gupta presented findings from an international multicenter retrospective study of individuals undergoing genotypic testing following virologic failure with initial TDF-containing antiretroviral therapy with lamivudine or emtricitabine plus either efavirenz or nevirapine (Abstract 503). Tenofovir-associated resistance was defined as the presence of the K65R/N or K70E/G/Q mutation at treatment failure. The prevalence of TDF-associated resistance among 1926 individuals with treatment failure in 36 countries was highest in low- and middle-income countries (59.8% in West and Central Africa, 55.9% in East Africa, 55.2% in Southern Africa, 39% in Asia, and 35.3% in Latin America) and lowest in high-income regions (18.8% in Western Europe and 22.6% in North America). A multiple logistic regression analysis revealed substantial independent risk factors for TDF-associated resistance across regions: a preantiretroviral therapy CD4+

cell count below 100/μL (odds ratio [OR], 1.49 [1.26-1.77]), use of lamivudine compared with emtricitabine (OR, 1.49 [1.20-1.84]), and use of efavirenz compared with nevirapine (OR, 1.46 [1.28-1.67]). The investigators concluded that TDF-associated resistance emerges in a high proportion of individuals who develop virologic failure during treatment with a TDF-containing initial antiretroviral regimen in low- and middle-income regions and urged minimization of viral failure, early detection of viral failure, and proactive switching of therapy.

Improving HIV Care Delivery and Outcomes in Low- and Middle-Income Countries

New Data on Treatment of Children in Low- and Middle-Income Countries

Two important new investigations shed light on treatment strategies for HIV-infected children in low- and middle-income countries. Njuguna and colleagues (Abstract 38) presented results from the PUSH (Pediatric Urgent Start of Highly Active Antiretroviral Treatment) trial, in which they examined initiation of antiretroviral therapy for hospitalized HIV-infected children (birth to age 12 years) on an urgent (within 48 hours of enrollment) versus poststabilization (within 7-14 days of enrollment) basis at 4 hospitals in Kenya. The researchers screened 250 children and randomly assigned 183 to 1 of the 2 arms, but a data and safety monitoring board stopped the study at their second assessment because of futility. Substantial mortality (21%) was observed at 6 months, an outcome that did not differ between study arms (hazard ratio [HR], 1.26; 95% CI, 0.67, 2.37; P = .47). There was also no statistically significant difference in incidence of immune reconstitution inflammatory syndrome (IRIS) or serious adverse events between study arms. The investigators noted that there was a high mortality rate among these children despite the fact that all of them initiated antiretroviral therapy within 2 weeks of enrollment and that timing within those 2 weeks did not make a difference, highlighting the need for diagnosis and initiation of antiretroviral treatment prior to hospitalization for children with symptomatic disease. Early initiation of antiretroviral therapy was feasible and was not associated with adverse events such as IRIS; therefore, despite the lack of impact of urgent initiation, the results of the study were supportive of rapid initiation of antiretroviral therapy for children hospitalized with HIV infection who have comorbid illness.

Murnane and colleagues presented 4-year outcomes from the NEVEREST III (Treatment Options for Protease Inhibitor-Exposed Children) study, a randomized open-label noninferiority trial of 298 children younger than 3 years in Johannesburg, South Africa, exposed to nevirapine for prevention of mother-to-child transmission (PMTCT) (Abstract 39). The children were initially treated and achieved virologic suppression with a boosted lopinavir–based regimen, then randomly assigned to continued treatment with the boosted lopinavir–based regimen or to treatment with an efavirenz-based regimen.

One-year results of the NEVEREST III trial were published and showed that efavirenz was not inferior to boosted lopinavir in children previously exposed to nevirapine for PMTCT.[7] These results, presented as 3-year outcomes in the abstract and expanded to 4-year outcomes for the oral presentation, are from an intention-to-treat analysis of a long-term observational follow-up study of 80% of the participants from the randomized control trial. At 48 months postrandomization, 22% of the children randomly assigned to the arm containing boosted lopinavir had switched to efavirenz, and 5% of the children randomly assigned to the arm containing efavirenz had switched to boosted lopinavir. There was no statistically significant difference in time to virologic failure, defined as 2 HIV RNA level measurements above 1000 copies/mL, between those who received ritonavir-boosted lopinavir (12% failure rate) and those who received efavirenz (7% failure rate; P = .21).

In secondary analyses, efavirenz did reduce the risk of having any HIV RNA level measurement above 1000 copies/mL (OR, 0.52; 95% CI, 0.28, 0.98; P = .04) and of having HIV RNA levels between 51 copies/mL and 1000 copies/mL (OR, 0.67; 95% CI, 0.51, 0.88; P = .004) over 4 years compared with boosted lopinavir. There were also statistically significantly higher CD4+ cell counts and lower risks of abnormal cholesterol and triglyceride levels among children receiving efavirenz-based regimens. The investigators concluded that switching young children from a ritonavir-boosted lopinavir–based regimen to an efavirenz-based regimen, despite nevirapine exposure for PMTCT, is feasible and has the advantages of improved palatability, once-daily dosing, lower cost, fewer interactions with antituberculosis drugs, and preserving subsequent treatment options without conferring the disadvantage of more frequent virologic failure. These findings have important implications for treatment strategies for children in low- and middle-income countries.

Switching from a ritonavir-boosted lopinavir–based regimen to an efavirenz-based regimen, despite nevirapine exposure for PMTCT, is feasible and has many advantages for young children.

New Findings Regarding the HIV Care Continuum in Low- and Middle-Income Countries

Considering the impact of various PMTCT care models on the HIV care continuum, Abrams and colleagues presented the results of the Safe Generations study (Abstract 34). This stepped-wedge trial examined the impact of transition from the PMTCT strategy Option A, in which only those pregnant women with CD4+ cell counts at or above 350/μL are eligible for lifelong antiretroviral therapy, to Option B+, in which all pregnant women are offered lifelong antiretroviral therapy. The investigators collected data from 12 facilities, 10 of which transitioned from Option A to Option B+ (1 each month over a 14-month period) and 2 of which did not (serving as

controls). Analysis was conducted using monthly facility-level cohorts. Pregnant women not taking antiretroviral therapy were enrolled as they attended their first antenatal clinic visit. As anticipated, uptake of antiretroviral therapy was significantly greater with Option B+ (94% of 1043 women) than with Option A (35% of 1272 women; $P < .0001$). Antenatal retention, defined as clinic attendance within 56 days prior to delivery, was 54% in the Option A arm and 68% in the Option B+ arm (adjusted relative risk [aRR], 1.23; 95% CI, 1.09, 1.37; $P < .001$), after adjustment for age, CD4+ cell count, gestation at first antenatal clinic visit, and known HIV serostatus. There were statistically significant variations in retention among those taking antiretroviral therapy, with improved retention in those few with CD4+ cell counts above 350/µL in Option A cohorts. Postnatal retention at 6 months after delivery was poor (37% overall) but higher in Option B+ than Option A cohorts (50% vs 26%; aRR, 1.56; 95% CI, 1.15, 1.32). The take-home message from this implementation science approach is that although Option B+ substantially increased initiation and coverage of antiretroviral therapy for pregnant women, overall retention in postnatal care was poor. It is also concerning that proportionally more women initiating antiretroviral therapy were retained in care under Option A, implying that there could be a cost to retention as more women initiate therapy under Option B+.

Although Option B+ substantially increased initiation and coverage of antiretroviral therapy among pregnant women, overall retention in postnatal care was poor.

Mugglin and colleagues used prospective data from 20 clinics in Malawi to examine the impact of the impressive national scale-up of antiretroviral therapy, from 3000 to more than 500,000 individuals from 2004 to 2014, on retention in care by age (Abstract 118). Discontinuation rates, defined as no recorded clinic visits or pharmacy refills for more than 150 days after first missed appointment and not allowing for reentry into care, were 202 per 1000 person-years of follow-up to 5234 per 1000 person-years of follow-up in the first year of therapy and lower thereafter (35/1000 person-years of follow-up to 475/1000 person-years of follow-up). Discontinuation rates improved over time, and the investigators speculated that this had to do with more tolerable antiretroviral regimens becoming available. Discontinuation rates were statistically significantly higher for children aged 0 years to 3 years and adolescents aged 15 years to 24 years, although the discontinuation rate for adolescents decreased over time. Discontinuation was also statistically more likely for women receiving antiretroviral therapy as a component of Option B+ for PMTCT than for women receiving it based on their CD4+ cell count. These data highlight the need to focus on care engagement for adolescents and pregnant women, particularly in the first year of antiretroviral therapy.

Tiendrebeogo and colleagues examined retention in care after 6 years of antiretroviral therapy and CD4+ cell count response to antiretroviral therapy by sex in an International Epidemiological Databases to Evaluate AIDS (IeDEA) cohort in West Africa (Abstract 1015). The cohort included 49,677 people living with HIV infection who initiated antiretroviral therapy, 66% of whom were women, across 9 West African countries. The probability of retention failure (ie, death or loss to follow-up) at 6 years was 50% for men and 43% for women, a statistically significant difference. This difference was more dramatic after 6 months of antiretroviral therapy. Consistent with this, women had statistically significantly greater increases in CD4+ cell count after initiation of antiretroviral therapy, with women gaining an additional 1.15/µL per month (95% CI, 1.02, 1.29) compared with men. The mean CD4+ cell count for women after 6 years of antiretroviral therapy was more than 500/µL, whereas for men it was approximately 400/µL, also a statistically significant difference.

In an overview of issues of equity between sexes throughout the HIV care continuum, Ayles (Abstract 120) discussed findings from the PopART (Population Effects of Antiretroviral Therapy to Reduce HIV Transmission) study, including that once diagnosed with HIV infection, men were equally as likely as women to be referred to HIV care and to initiate antiretroviral therapy, and other data supporting the conclusion that men are more likely than women to be lost to follow-up.[8] Ayles proposed a model of clinics tailored to address these disparities, as has been seen in Western Cape, South Africa, where there are now 8 HIV treatment centers catering specifically to men.

To assess the impact of population mobility on the success of test-and-treat initiatives to achieve population-level virologic control, Larmarange and colleagues used data from the French Agence Nationale de Recherche sur le Sida (ANRS) 12249 Antiretroviral HIV Treatment as Prevention trial, a cluster randomized proof-of-concept trial in a rural area of northern KwaZulu-Natal, South Africa (Abstract 169LB). The investigators examined data from the first 4425 individuals included in the trial, 22% of whom were living with HIV infection. To assess the impact of population mobility on the impact of treatment as prevention, residency status (defined as spending at least 4 nights per week in the city area) was computed for each individual by day using data on trial registration, migration, and death. Because this trial utilized repeated cross-sectional approaches, it can demonstrate a dynamic cascade per calendar time, which is more robust than single cross-sectional approaches that do not account for population mobility. The investigators found high levels of migration in and out throughout the study period. If a strict calendar approach was used, the prevalence of virologic suppression increased from 25% to 40% over 15 months. Only 15% of HIV-infected people entering the population were virologically suppressed, and 27% of those migrating out were virologically suppressed. However, when individual-level data presented by exposure time were used, the percentage of virologically suppressed individuals increased from approximately 20% to 50% over 30 months, demonstrating that population mobility attenuates the observed impact of

treatment-as-prevention strategies when single measurements of cross-sectional data are used. The investigators also suggested that universal test-and-treat strategies incorporate interventions to ensure continuity of care for migrants in order to maximize impact.

Progress in Reaching 90-90-90

Since the Joint United Nations Programme on HIV/AIDS (UNAIDS) announced its ambitious 90-90-90 treatment goals (that 90% of all HIV-infected individuals will be aware of their HIV serostatus, 90% of those who are aware of their serostatus will be receiving antiretroviral therapy, and 90% of those receiving antiretroviral therapy will be virally suppressed by 2020) in 2014,[9] much of the discussion regarding the HIV care continuum in low- and middle-income countries has focused on whether national treatment programs will be able to achieve these targets. Many investigators presented exciting data on progress toward these goals, and the achievements of programs in Botswana and Malawi were impressive examples of the feasibility of reaching 90-90-90.

The achievements of Option B+ programs in Botswana and Malawi were impressive examples of the feasibility of reaching 90-90-90.

Gaolathe and colleagues presented preliminary data from the Botswana Combination Prevention Project trial, a pair-matched community randomized trial underway in 30 communities in Botswana, which will offer annual surveys of incidence and uptake of HIV prevention interventions (Abstract 111). Data from a preintervention survey of 12,610 individuals (81% of eligible participants) from the 30 communities were collected; HIV testing was offered to all residents without written documentation of prior HIV infection status, and HIV RNA testing was conducted for all HIV-infected participants. Overall, 29% of participants were living with HIV infection, 83% (95% CI, 81, 85%) of whom were already aware of their serostatus and could provide documentation. Including participants who reported HIV infection without documentation, 87% were aware of their HIV serostatus. Of those who knew their HIV serostatus, 87% (95% CI, 86, 89%) were receiving antiretroviral therapy; of those, 96% had an HIV RNA level of 400 copies/mL or lower, the national criterion for virologic suppression. Based on these data, rate of virologic suppression among all those living with HIV infection was 70%, only 3 percentage points under the 90-90-90 goal of 73%. These high levels of coverage throughout the care cascade are particularly interesting because current national guidelines only provide free antiretroviral treatment to citizens with CD4+ cell counts at or below 350/μL. These data suggest that the goal of 90-90-90 is ambitious but achievable and are highly encouraging for other low- and middle-income countries.

Jahn presented data from 717 sites within the Malawi national PMTCT program, to estimate the impact of Option B+ on national levels of antiretroviral treatment coverage (Abstract 168LB). Prior to the roll out of Option B+ in 2011, approximately 49% of pregnant women were aware of their HIV serostatus, 3% were receiving antiretroviral therapy, and 2% were virologically suppressed. In 2015, after implementation of Option B+, 80% of pregnant women were aware of their HIV serostatus, 78% were receiving antiretroviral therapy, and 48% were virologically suppressed. Based on changes over the period from 2005 to 2015, the investigators predicted that women will meet the 90-90-90 goal of 81% receiving antiretroviral treatment by 2017 and that average antiretroviral treatment coverage for men and women will reach 81% by 2020. Even with these impressive gains, the goal of 90% of pregnant women being aware of their HIV serostatus has not been met, and efforts to improve perinatal counseling and HIV testing are needed.

Jahn also discussed the scale up of Option B+ in Malawi in the context of the larger national response to the HIV epidemic (Abstract 119). The success of the program is evident, with dramatic increases in the proportion of women already taking antiretroviral therapy during pregnancy: from 26% in 2012 to 53% in 2015. However, challenges to retention in care remain, with a substantial decline in engagement in care in the first 6 months of antiretroviral therapy for those treated under Option B+ and no notable improvement in rates of retention in care from 2010 to 2015. There was also a wide range of rates of retention in care by site (50%-100%), emphasizing the need for continued monitoring and evaluation as Malawi begins a universal test-and-treat strategy in 2016.

Fidler and colleagues discussed findings on population-level antiretroviral treatment coverage using data from the first round of intervention in the PopART study (Abstract 114).[10] In the PopART study, annual rounds of home-based voluntary HIV testing by community HIV care practitioners were followed by health promotion; active referral and support for retention in care by the community practitioners; and voluntary male medical circumcision, PMTCT, HIV treatment, promotion of sexual health, tuberculosis treatment, and condom provision for appropriate populations.[10] Fidler presented data on the cascade of engagement in care within the intervention arm only. Of 4139 HIV-infected men, 47% were already engaged in care and taking antiretroviral treatment. Of those referred to care, 44% had initiated treatment within 6 months, and 60% had initiated treatment within 12 months. Of 8701 women, 49% were already receiving treatment. Of those newly referred to care, 42% initiated treatment within 6 months, and 56% initiated treatment within 12 months. Of participants who were offered immediate treatment in the clinic with CD4+ cell counts of or below 500/μL, 99% accepted it. At the end of the first year of intervention, the percentage of HIV-infected individuals not taking antiretroviral treatment declined from 51% to 29%, a substantial step toward the 90-90-90 goal. However, time to initiation of treatment was still slower than wished, with only 60% of those who were eligible receiving antiretroviral treatment after 12 months of intervention.

Chiu and colleagues used an integrated set of 3 mathematical models, 2 epidemiologic and 1 cost, to identify the

most cost-effective combination of 27 potential interventions in South Africa under the current budget or with the goal of reaching the 90-90-90 targets (Abstract 115). Considering the high impact and coincidence of the tuberculosis and HIV epidemics in South Africa, the investigators incorporated 2 different tuberculosis-related scenarios: the first was the current baseline in South Africa and the second was dictated by the 90-90-90 targets for tuberculosis. Under the current budget, condom availability and male medical circumcision were cost saving, and antiretroviral therapy at current national guidelines and PMTCT both had acceptable incremental cost-effectiveness ratios of $106 and $138, respectively, per life-year saved. The cost of universal antiretroviral treatment was $243 per life-year saved, and the 90-90-90 targets for HIV care were reached only when high coverage of adherence clubs—antiretroviral treatment delivery and adherence support groups run by nonmedical personnel—was added to the model. The investigators also found that the 90-90-90 targets for tuberculosis could not be met solely by optimizing care along the HIV care continuum and required optimization of tuberculosis care as well. These data emphasize the need for a multipronged approach to the HIV and tuberculosis epidemics in South Africa and the difficult financial outlay that is still needed before these epidemics are contained and costs begin to fall.

Improved Treatment Outcomes and Assessment of Care Quality for HIV-Infected Adults in Low- and Middle-Income Countries

Mortality Within HIV Treatment Programs. CROI 2016 included data from many different settings on mortality and outcomes at various points in the HIV care continuum in low- and middle-income countries. Mooser and colleagues conducted a systematic review of 34 studies in 26 cohorts that examined outcomes for adults and children lost to follow-up in sub-Saharan Africa (Abstract 1021). Mortality in those lost to follow-up declined from 53.1% in 2003 to 19.8% in 2010 ($P = .003$), and the proportion of individuals transferred to different care sites remained stable at 26%. Notably, 31.5% of individuals were traced but not found. An increase in median CD4+ cell count from 71/μL to 138/μL at initiation of antiretroviral therapy was seen over the same time period in the 9 studies reporting these data, and this increase could be responsible for improvements in mortality rates among those lost to follow-up. The review was limited by varying definitions of loss to follow-up (ranging from several weeks to 6 months) and differences in tracing methods, but the findings are encouraging.

Bendavid and colleagues examined mortality associated with failure to progress along various stages of the HIV care cascade (Abstract 117). The researchers examined data from the ALPHA (Analyzing Longitudinal Population-based HIV/AIDS data on Africa) network, in which investigators estimated that 40% of excess deaths among HIV-infected persons occurred among those who were diagnosed but not yet in HIV care, and estimates from Western Cape, South Africa, where linkage between a death registry and clinical records was used to determine that 25% of deaths occurred among undiagnosed HIV-infected persons and that 35% of deaths occurred among those who were diagnosed but not linked to care. The researchers compared these estimates to those from individual-level mathematical models of the HIV epidemics in Rwanda, Kenya, Malawi, and South Africa, in which an estimated 25% to 40% of deaths among persons living with HIV infection were among those who had never initiated antiretroviral treatment, similar to estimates from empiric datasets. The models were then used to estimate the impact of immediate initiation of antiretroviral therapy, which led to a 6% to 14% reduction in deaths over the next 10 years, mostly derived from prevention of loss to care rather than clinical benefits or reductions in HIV transmission. These data highlight the need to streamline initiation of antiretroviral therapy if mortality rates among persons living with HIV infection are to approach those in uninfected populations.

Initiation of antiretroviral therapy must be streamlined if mortality rates among persons living with HIV infection are to approach those in uninfected populations.

Dolling and colleagues presented a retrospective analysis of the relationship between mortality after 48 weeks of antiretroviral therapy and virologic suppression from the DART (Development of Antiretroviral Therapy in Africa) study, a randomized controlled trial in Uganda and Zimbabwe that compared monitoring of CD4+ cell count and other laboratory studies every 12 weeks with clinically driven laboratory monitoring (Abstract 1027).[11] During the course of the original study, no HIV RNA testing was available in real time. For this analysis, the investigators examined HIV RNA measurements taken 6 weeks to 13 weeks prior to death among those who died after 48 weeks of antiretroviral therapy; 41% of these deaths occurred in the setting of virologic suppression (HIV RNA level ≤200 copies/mL). Death in the setting of virologic suppression was more likely to be caused by gastrointestinal illness (12% in those who were virologically suppressed vs 2% in those with an HIV RNA level >200 copies/mL; $P = .04$) or HIV-related malignancies (12% in those who were virologically suppressed vs 2% in those who were not; $P = .04$). Although individuals who died with virologic suppression had higher CD4+ cell counts (238/μL) than those who died without virologic suppression (62/μL), the 2 groups did not have a statistically significant difference in the change in CD4+ cell count over the 48 weeks prior to death. These data are concerning because, despite the achievement of virologic suppression, death from non–HIV-related causes led to substantial mortality in this cohort.

Bassett and colleagues presented a unique strategy for prediction of 1-year mortality in people newly diagnosed with HIV infection by examining the impact of self-perceived barriers to health care at the time of diagnosis (Abstract 1016). The investigators enrolled 4903 individuals newly diagnosed

with HIV infection and collected responses to a 15- to 20-minute survey on demographics, emotional health, social support, and self-perceived barriers to entering HIV care, including service delivery, financial considerations, personal health perceptions, and logistical and structural barriers to care. Participants who noted barriers to entering care were more likely to die by 12 months of follow-up, even after adjustment for known predictors of mortality such as low CD4+ cell count, age, sex, and tuberculosis coinfection (for 1-3 barriers, adjusted HR [aHR], 1.68; 95% CI, 1.20, 2.34) (for >3 barriers, aHR, 2.54; 95% CI, 1.92, 3.37). No individual barrier was more predictive than the others, and social support and mental health survey data did not impact this prediction model. The investigators concluded that screening for perceived barriers to HIV care at diagnosis could identify those at high risk for mortality and perhaps provide insights into interventions for these individuals.

Measurement and Consequences of Adherence. Two groups of investigators presented novel data on adherence to antiretroviral therapy. Orrell and colleagues compared 6 adherence measurement techniques in 230 antiretroviral therapy–naive individuals in South Africa to determine which best predicts outcomes: electronic adherence monitoring devices (eg, a "smart" pill box), clinic-based 60-day pill counts, 3-day self-reports of adherence, average medication possession ratio (number of tablets/days in care) or gaps in medication (number of days without medication) based on pharmacy data, or a mid-dose assessment of efavirenz concentration (Abstract 1029). Electronic adherence monitoring and pharmacy refill data (average possession ratio and gaps) were most predictive of virologic failure, defined as an HIV RNA level above 40 copies/mL at week 48 of antiretroviral therapy, and the emergence of drug resistance, determined by detection of any resistance mutation (using the 2015 drug resistance mutations in HIV-1 from the IAS–USA[12]) on an HIV genotype test at week 48. Of concern, a 3-day recall self-report of adherence was not predictive of virologic failure or the emergence of resistance; pill counts were only modestly predictive, and efavirenz concentrations were predictive of resistance but not virologic failure. The investigators concluded that pharmacy refill data is an underutilized but often widely available methodology for clinically relevant and actionable measurement of adherence.

Collier and colleagues presented the results of a retrospective analysis of 307 adults who initiated a second antiretroviral regimen that included a PI and who resided within the Africa Centre's demographic surveillance area, a largely rural and socioeconomically disadvantaged region (Abstract 1030). The overall incidence of virologic failure, defined as an HIV RNA level above 1000 copies/mL after 6 months of a second antiretroviral regimen, was 21.5 per 100 person-years, with a cumulative incidence of 45% by 5 years. A modified medication possession ratio during initial and second regimens, calculated as the number of months for which a refill was submitted as a fraction of the number of months in the treatment period, was statistically significantly inversely correlated with virologic failure. The concern that nonadherence to initial and second regimens predicts virologic failure during second regimens is particularly important in low- and middle-income countries in which there is a move to increase access to initial antiretroviral regimens but in which options for third regimens are limited.

The Impact of Changing CD4+ Cell Count Thresholds. Numerous changes over the past decade in WHO and other guidelines regarding CD4+ cell count eligibility for antiretroviral therapy culminated in the most recent 2015 WHO guidelines recommending universal HIV testing and antiretroviral therapy for all individuals living with HIV infection.[13] Several groups of investigators explored the impact of changing CD4+ cell count thresholds on programs in low- and middle-income countries.

Bor and colleagues used data from the Hlabisa HIV Treatment and Care Programme in South Africa and a regression discontinuity design to estimate the impact of immediate versus delayed antiretroviral therapy for failure to meet the CD4+ cell count eligibility set point of less than 350/μL in a real-world setting (Abstract 1011). The investigators found that retention in care at 12 months was statistically more likely in those with an eligible CD4+ cell count of just below 350/μL (50%) than in those with a CD4+ cell count slightly above the threshold (32%; $P = .001$). Those with an eligible CD4+ cell count were also statistically significantly more likely to initiate antiretroviral therapy within 6 months (43% vs 18%, respectively) and to be retained in care at 18 months to 24 months. The regression discontinuity design implies that the groups are otherwise demographically and biologically similar, and these data suggest that initiation of antiretroviral therapy has a large impact on long-term retention in HIV care.

Bor and colleagues also used data from the Hlabisa cohort to inform a mathematical model to determine the number of new initiations of antiretroviral therapy South Africa could expect if a universal test-and-treat strategy were adopted nationally and CD4+ cell count thresholds for eligibility were eliminated (Abstract 1048). An estimated 40% of participants presented for treatment with CD4+ cell counts higher than 500/μL. Although 8% of those with CD4+ cell counts at or above 350/μL initiated therapy despite being over the current eligibility threshold, only 40% of those with CD4+ cell counts at or below 500/μL initiated therapy. Based on these data, the investigators estimated that 72.8% of individuals will not initiate treatment despite being eligible for it and that elimination of treatment eligibility thresholds based on CD4+ cell count will not help achieve 90-90-90 targets.

Kluberg and colleagues examined the impact of the 2011 South African Ministry of Health policy change that extended eligibility for antiretroviral therapy from those with CD4+ cell counts below 200/μL to those with counts below 350/μL on treatment delays among those with counts below 200/μL, to determine whether eligibility expansions adversely impact more immunocompromised patients (Abstract 1012). Across 17 rural clinics in KwaZulu-Natal, the rate of initiation of antiretroviral therapy increased among the newly eligible

(60% in those with CD4+ cell counts of 200/μL-349/μL; 95% CI, 20%-220%) and the previously eligible (20% in those with CD4+ cell counts < 200/μL; 95% CI, 0%-40%) in the 12 months after eligibility expansion. The investigators noted no short-term negative impact of eligibility expansion, based on the stable or increasing rates of initiation of antiretroviral therapy among those with low CD4+ cell counts.

Models for Improved Care Delivery in Low- and Middle-Income Countries

Expediting Initiation of Antiretroviral Therapy. Several well-designed randomized controlled trials and programmatic studies examined different strategies for expediting initiation of antiretroviral therapy, which should increase retention in care and decrease mortality. Rosen and colleagues presented data from the RapIT (Rapid Initiation of Antiretroviral Therapy to Promote Early HIV/AIDS Treatment in South Africa) trial, a randomized control trial of same-day treatment initiation in Johannesburg, South Africa (Abstract 28). Participants were randomly assigned to same-day treatment initiation (at time of HIV diagnosis or at first presentation to clinic if previously diagnosed) or standard of care. The trial took place in an outpatient primary care clinic and a hospital-based HIV treatment center and utilized point-of-care laboratory testing to allow immediate treatment eligibility assessment for the arm that received rapid treatment. Initiation of antiretroviral therapy within 90 days of randomization, the primary outcome measure, occurred in 72% of those in the arm that received the standard of care (n = 229) and 97% of those in the arm that received rapid treatment (n = 234; RR, 1.36; 95% CI, 1.24, 1.49). Those in the arm that received rapid treatment were also more likely to be virologically suppressed (HIV RNA level ≤400 copies/mL) at 10 months after randomization than those that received the standard of care (RR, 1.26; 95% CI, 1.05, 1.50). Other notable aspects of rapid initiation were that 4 of the 5 participants who were lost to follow-up in that arm were lost during workup for tuberculosis and that 75% initiated antiretroviral therapy on the same day, with a median time in clinic of 2.4 hours. The investigators concluded that it is possible to start nearly all patients on antiretroviral therapy within 1 month of HIV diagnosis or presentation to care, but it should be noted that the staff assigned to the arm that received rapid initiation of treatment were all research staff. Further data on how this intervention would be received in a nonresearch setting would be useful.

Investigators examined different strategies for expediting initiation of antiretroviral therapy, which should increase retention in care and decrease mortality.

Amanyire and colleagues shared findings from a stepped wedge cluster randomized trial of an intervention to reduce delays in initiation of antiretroviral therapy across 20 clinics in Uganda (Abstract 112). The intervention was implemented in randomly selected groups of 5 clinics every 6 months and included opinion leader–led teaching and coaching for practitioners, a revised counseling protocol to link adherence counseling to initiation of treatment, real-time CD4+ cell counts to assess eligibility for treatment, and regular feedback to clinics regarding delays in initiation of treatment. Overall, 12,024 individuals met eligibility criteria, although the threshold for initiation of treatment changed from a CD4+ cell count of 350/μL or below to a count of 500/μL or below during the course of study. The investigators found that in intervention clinics, 79.6% of individuals initiated treatment within 14 days of eligibility, whereas only 37.7% did so in the control group (RR, 2.11, 2.03, 2.20; $P < .0001$). There was also a statistically significant difference in the number of individuals who had initiated treatment at 90 days after eligibility (89.7% in the intervention group and 70.4% in the control group; RR, 1.27; 95% CI, 1.20, 1.30; $P < .0001$). The percentage of individuals who achieved an HIV plasma RNA level of less than 200 copies/mL 1 year after eligibility was assessed in a random sample of 437 individuals; there was no statistically significant difference between the 2 groups, unless those individuals who were missing HIV RNA measurements were excluded. There was also no statistically significant difference in adherence to medical visits between the 2 groups. The strength of this study is that the intervention is embedded within existing HIV treatment programs, which increases external generalizability, and it is hoped that further analyses of these data will show the long-term benefits of early initiation of antiretroviral treatment, which were not seen in the analysis thus far.

Hoffmann and colleagues conducted a 4-arm randomized controlled trial in Johannesburg, South Africa, of accelerated entry into HIV care after diagnosis via mobile HIV counseling and testing units, from which entry into care is often lower than when testing occurs in clinical settings (Abstract 113LB). After receiving a diagnosis of HIV infection, 2558 individuals were randomly assigned to 1 of 4 arms: 1) standard of care; 2) point-of-care CD4+ cell count testing to assess eligibility for antiretroviral therapy; 3) point-of-care CD4+ cell count testing plus care facilitation using the CDC Antiretroviral Treatment and Access to Services (ARTAS) approach; and 4) point-of-care CD4+ cell count testing plus reimbursement for transportation. The investigators did not find any statistically significant difference in the primary outcome of self-reported entry into care at 90 days between the arms, but the secondary outcome of documented entry into care at 90 days was statistically significantly more likely in the arm that included care facilitation: 38% in the arm that received care facilitation compared with 29% in the arm that received the standard of care (HR, 1.4; 95% CI, 1.1, 1.7). The same association was seen for the secondary outcome of initiation of treatment by 180 days. Only 30% of participants were eligible for treatment, but 18% of those in the arm that received care facilitation initiated treatment compared with 13% in those who received the standard of care, or more than half of those who were eligible (HR, 1.4; 95% CI, 1.1, 1.9). No statistically significant differences were seen between standard of care and the 2 other

intervention arms (point-of-care CD4+ cell count testing and point-of-care CD4+ cell count testing plus reimbursement for transportation) for any of the secondary outcomes. Hoffman noted that other studies have also shown overreporting of engagement in care, when documentation is not required, and that outcome ascertainment for engagement in care may be essential to measuring the true impact of a program. The increased contact with patients at 30 days and 60 days after testing, included even in the arm that received the standard of care, may have led to higher rates of engagement in care than those seen in traditional mobile testing programs, but many challenges remain in achieving the 90-90-90 targets for those diagnosed with HIV infection in non–clinic-based settings.

Kwarisiima and colleagues presented virologic outcomes of a streamlined care model for people living with HIV infection with CD4+ cell counts above 350/μL in rural Kenya and Uganda (Abstract 116). The streamlined model involved a patient-centered approach to care, including empathetic handling of adherence and retention issues; efficient visits with rapid 1-day to 3-day waits for initiation of antiretroviral treatment, minimal wait times, 3-month medication supplies, and nurse triage for follow-up visits; viral load counseling structured by treatment status; access to clinicians via telephone; and appointment reminders by phone or text messaging. Of 972 enrolled participants, 86% were retained in care and had an HIV RNA measurement at 48 weeks after initiation of treatment. Retention in care at 48 weeks was 90%, with no difference by CD4+ cell count strata (350/μL-500/μL compared with >500/μL). Similarly, 93% of participants had an HIV RNA level of less than 500 copies/mL, with no difference by CD4+ cell count strata. If individuals without a 48-week HIV RNA measurement, for any reason (eg, loss to follow-up, death, or study withdrawal), were classified as virologic failures, 87% of participants had an HIV RNA level below 500 copies/mL. Adverse events and regimen switches were also minimal. The investigators recommended this type of streamlined care for delivery of antiretroviral therapy to asymptomatic patients with high CD4+ cell counts.

Differentiated Models of HIV Care Delivery. Differentiated HIV care, as defined by Grimsrud (Abstract 122), is "the continuum of adaptations that can be made to HIV services with the intention of streamlined care, including [antiretroviral therapy] delivery. The objective is to provide quality, patient-centered care reflecting the preferences and expectations of [persons living with HIV infection], while reducing unnecessary burdens on the health system." Grimsrud provided an overview of various differentiated care models, and the following abstracts presented new data on potential ways to differentiate HIV care to improve outcomes and efficiency.

Roy and colleagues evaluated opportunities for streamlining care by examining visit burden and appointment patterns for stable patients taking antiretroviral therapy with CD4+ cell counts above 500/μL or above 350/μL (Abstract 1018). The investigators found that 58% of all visits were for pharmacy refills or adherence counseling without a clinical assessment and that median appointment intervals remained stable at 60 days, regardless of years taking antiretroviral therapy or CD4+ cell count. The investigators proposed that, given the growing proportion of visits (23% currently and rising over time) made by those taking antiretroviral therapy for more than 6 months with a CD4+ cell count above 500/μL, who might be considered clinically stable, increased visit spacing for these individuals or differentiated care in the form of community adherence clubs or other community-based treatment models would be feasible.

Sharp and colleagues explored the feasibility of expanding differentiated care to clinically unstable individuals who recently achieved virologic suppression after a documented treatment failure (Abstract 1031), a departure from traditional models in which only highly clinically stable individuals are considered for differentiated or de-escalated care. In Khayelitsha, South Africa, individuals with 2 consecutive HIV RNA measurements above 200 copies/mL were referred to a lay health care worker–led group support session and adherence consultation with a nurse. Participants who achieved an HIV RNA level of less than 400 copies/mL after this intervention were then referred to adherence clubs for care. In this context, adherence clubs were groups of approximately 30 individuals led by lay health care workers meeting 5 times per year for peer support, brief symptoms screening, and supply of antiretroviral medications, supplemented by an annual visit with a clinician and HIV RNA measurement. After 18 months of follow-up, 89% of 165 participants were still retained in care, and 81% remained in the adherence club model. Of note, 78% still had viral suppression (HIV RNA level <400 copies/mL) at 18 months, arguing that even those who had recently met criteria for virologic failure could achieve positive long-term outcomes through differentiated care in adherence clubs. This strategy is particularly encouraging, as it could increase capacity for antiretroviral therapy in low- and middle-income countries.

Geng provided a summary of how to incorporate various potential interventions to improve retention in care programs in low- and middle-income countries (Abstract 121). Geng emphasized that retention in care is the driver of efficiency and effectiveness in the global antiretroviral therapy response but that barriers to retention in care often vary in intensity, nature, and effects. In a meta-analysis of individual-level data on 12,765 individuals in 26 tracing studies, 3 main categories of barriers were identified: structural, such as transportation or financial; psychosocial, such as stigma and family support; and clinic based. Comparison of those who discontinued care with those who transferred to other clinics without informing their practitioner within the IeDEA cohort found that psychosocial barriers were more commonly reported in those disengaged from care (76% vs 27%) but that clinic-based barriers

Retention in HIV care is the driver of efficiency and effectiveness in the global antiretroviral therapy response, but barriers to retention in care often vary in intensity, nature, and effects.

were more commonly reported by those who transferred clinics without informing their practitioner (33% vs 15%), with both of these differences being statistically significant. These data suggest that not all loss to follow-up is similar, and certain barriers predict lasting discontinuation more successfully. Geng argued for a personalized public health approach in which individual responses, such as those elucidated in a simple survey but that were predictive of mortality (Bassett and colleagues, Abstract 1016, described above), could dictate specific interventions if measured appropriately. Combinations of strategies could comprise a prevent-and-treat retention strategy in which intensive interventions, such as patient navigation, microclinics, or patient-empowerment initiatives, would be initially implemented and then followed by de-escalation to less intensive interventions, such as 2-way text messaging reminders. Alternatively, an induction-maintenance strategy could be employed in which low-intensity interventions are initially offered and higher-intensity interventions are applied only to those who do not remain engaged in care. Geng proposed that implementation science techniques be used to systematically collect sufficient programmatic data to measure the efficacy of various stacked interventions, rather than relying on more expensive and often impractical, sequential multiple assignment randomized controlled trials or other more traditional research techniques.

Antiretroviral Treatment in the United States: Life Expectancy, Care Cascade Outcomes, and Strategies to Improve the HIV Care Continuum

Bradley and colleagues used data from 2009 to 2013 collected by the US Medical Monitoring Project (MMP), a national surveillance system sampling data from 23,125 participants across 23 jurisdictions, to estimate the proportion of individuals in care who achieved virologic suppression, defined as having an HIV RNA level below 200 copies/mL at the last test and at all tests over the prior 12 months (Abstract 53). Increases in virologic suppression were observed over time, from 72% in 2009 to 80% in 2013 ($P < .01$, for trend); however, these gains were less pronounced among women, those aged 18 years to 29 years or 30 years to 39 years, and those of black race. The largest increase in sustained virologic suppression over the past 12 months occurred among those aged 18 years to 29 years (32% in 2009 to 51% in 2013; ($P < .01$, for trend). MSM also consistently had higher than average rates of virologic suppression at last test and sustained virologic suppression. Although there were increases in the number of individuals taking antiretroviral therapy (89% in 2009 to 94% in 2013), the rate of change in sustained virologic suppression was higher over the same time period (58% to 68%), implying that although increases in the number of people taking antiretroviral therapy contribute to this improvement, advances in antiretroviral therapy that make it more tolerable and easier to take also impact virologic suppression. The investigators cited substantial changes in national policy, such as the recommendation for universal antiretroviral treatment for everyone living with HIV infection and the elimination of wait lists in the AIDS Drug Assistance Program, as important contributing factors to improvements in virologic suppression.

Encouraging data regarding continued improvements in life expectancy for people living with HIV infection were presented by Marcus and colleagues (Abstract 54). HIV-infected individuals receiving care within the Kaiser Permanente California system from 1996 to 2011 were matched 10:1 with uninfected individuals within the same system by age, sex, medical center, and year. Mortality rates for people living with HIV infection over this time period decreased from 7077 per 100,000 person-years in 1996 to 1054 per 100,000 person-years in 2011, whereas mortality for uninfected individuals remained stable (439/100,000 person-years in 1996 to 381/100,000 person-years in 2011). Similarly, life expectancy at age 20 years for uninfected individuals remained stable (63 years in 1996 to 65 years in 2011) but increased dramatically (19 years in 1996 to 53 years in 2011) for people living with HIV infection. Many of the disparities seen in national data for people living with HIV infection were evident in this insured cohort with access to care.[14] Life expectancy was lowest among those of black race ($P = .007$, compared with those of white race) and those reporting the HIV transmission risk behavior of injection drug use ($P = .011$, compared with those in whom heterosexual sex was their risk behavior). Despite dramatic improvements in life expectancy for people living with HIV infection, it is concerning that in this cohort of insured individuals who are engaged in medical care, a 13.1-year gap (95% CI, 11.5, 14.6) remains between the HIV-infected and uninfected populations. This gap narrowed to 7.9 years for those living with HIV infection who initiated antiretroviral therapy at CD4+ cell counts at or above 500/μL. These data imply that more work is needed to ensure normal life spans for persons living with HIV infection and that early initiation of antiretroviral therapy and addressing health disparities may play a substantial role in achieving this goal.

Despite dramatic improvements in life expectancy for people living with HIV infection, a 13.1-year life expectancy gap remained between persons living with HIV infection and the uninfected population.

Yaylali and colleagues described the impact of improving HIV care and treatment and initiating PrEP in the United States. A compartmental model was used to assess the marginal benefit of adding PrEP to improvements in the existing care cascade (Abstract 1051). These data are reviewed in more detail by Buchbinder and Liu.[15]

Metsch and colleagues presented the results of a study seeking to improve engagement in care for a key population: persons who use alcohol excessively or who use recreational drugs. The HOPE (Hospital Visit as an Opportunity for Prevention and Engagement) study targeted individuals hospitalized for substance use with HIV RNA levels above 200 copies/mL and CD4+ cell counts at or below 500/μL (Abstract 27). The investigators randomly assigned 801 such individuals across

11 US hospitals to 1 of 3 arms: treatment as usual; 6 months of patient navigation; or patient navigation with contingency management, a series of conditional financial incentives providing up to $1160 for HIV care or substance use treatment visits, medication pickups, achievement of virologic suppression (HIV RNA ≤200 copies/mL), and drug-free toxicology screening results. The primary outcome was achievement of virologic suppression at 12 months, and there was no statistically significant difference in this outcome by treatment arm at 12 months: 34.1% with treatment as usual, 34.1% with 6 months of patient navigation, and 38.6% with patient navigation plus contingency management ($P = .68$). However, there was a statistically significant difference in virologic suppression at 6 months between the arm that received treatment as usual (33.6%) and the arm that received patient navigation plus contingency management (46.2%; $P = .04$). There were also statistically significant differences at 6 months, although not at 12 months, in the secondary outcome of visit to an HIV practitioner, with a benefit observed in the intervention arms; no differences were observed in rehospitalizations, death, or engagement in substance use treatment. Also of interest, the 4 sites in the Southern United States had significantly lower rates of virologic suppression at 12 months (24.1%-26.0%) than all other sites (36.4%-60.9%; $P < .0001$). Individuals of black race and those who used stimulants were also statistically significantly less likely to achieve virologic suppression than those of white race and those who used opioids, respectively. The investigators concluded that these populations are difficult to reach and that, considering the important findings after 6 months of patient navigation, a sustained intervention may be necessary for continued benefit.

Prevention and Treatment of Pediatric HIV Infections

Option B+ was a program implemented in Malawi in 2011 to offer lifelong antiretroviral therapy to all HIV-infected pregnant and breastfeeding women irrespective of their clinical or immunologic status. Begun in 2014, the NEMAPP (National Evaluation of Malawi's PMTCT Program) study applied a stratified, multistage cluster sampling schema to identify a nationally representative cohort of HIV-exposed infants aged 4 weeks to 26 weeks and their mothers to measure the effects of Option B+ on MTCT rates. Gupta (Abstract 35LB) presented data focused on the cohort of infants aged 4 weeks to 12 weeks in the NEMAPP study. Mothers were screened for HIV infection, and HIV-exposed infants were tested for HIV infection using HIV DNA PCR assays. Among 1851 HIV-infected mothers of infants aged 4 weeks to 12 weeks, antiretroviral therapy coverage was very high at 93.5% and overall MTCT was very low at 4.1%. For those who took antiretroviral therapy during pregnancy, MTCT was even lower at 2.9%. For the 6.5% of women who never started treatment at any time during pregnancy or immediately postpartum, MTCT was higher at 20.3%. The MTCT rate differed by timing of treatment initiation, ranging from 1.4% in women who initiated treatment prior to pregnancy to approximately 4% in women who initiated treatment during pregnancy.

Current US and WHO guidelines recommend TDF as a preferred antiretroviral drug for HIV-infected pregnant women.[13,16] However, there are concerns about the adverse effects of TDF on bone development, including effects on fetal bone mineral content (BMC) as a result of exposure to maternal TDF. Siberry and colleagues (Abstract 36) presented data from the P1084s substudy of the International Maternal, Pediatric, Adolescent AIDS Clinical Trials (IMPAACT) Network PROMISE (Promoting Maternal-Infant Survival Everywhere) trial. The substudy compared newborn bone mineral content, measured using dual-energy X-ray absorptiometry (DXA) scans of whole body and lumbar spine obtained within 28 days of birth, in 359 infants by exposure to maternal antiretroviral regimens at gestational ages older than 14 weeks at 8 sites in 4 African countries. The women were randomly assigned to initiate 1 of 3 antiretroviral regimens during pregnancy: arm 1) zidovudine with single-dose nevirapine plus TDF and emtricitabine; arm 2) zidovudine, lamivudine, and ritonavir-boosted lopinavir; or arm 3) TDF, emtricitabine, and ritonavir-boosted lopinavir. No adverse associations were found between infant whole-body and lumbar spine BMC measurements and maternal TDF use when arms 2 and 3 were directly compared. This is in contrast to a finding from a published US cohort study that reported a 12% lower mean newborn BMC level following maternal TDF use.[17] The PROMISE substudy also found that initiation of a triple-drug antiretroviral regimen that included boosted lopinavir during pregnancy (arms 2 and 3 compared with arm 1) was associated with lower mean whole-body BMC levels, even after adjustment for maternal and infant factors. An analysis exploring mediating factors for this finding is underway.

HIV infection has negative effects on bone accrual in children, with decreased peak bone mass and increased risk of osteoporosis and fracture later in life. Data are lacking, however, on ways to optimize antiretroviral therapy to improve bone health in children. In Abstract 40, Arpadi and colleagues examined whether preemptive switching of an initial ritonavir-boosted lopinavir–based ART to efavirenz, compared with continuing on the regimen, was associated with improved bone outcomes in HIV-infected children aged 5 years to 10 years in South Africa. The clinical trial randomly assigned 113 HIV-infected children to the efavirenz-containing arm and 106 children to the boosted lopinavir–containing arm; the children also received 2 nRTIs, excluding TDF. In addition, the study enrolled 180 HIV-uninfected children as controls. The BMC *z* score was lower in HIV-infected children than in uninfected children, even after adjustment for dietary calcium and vitamin D intake and activity level. The BMC *z* score was lower among those taking ritonavir-boosted lopinavir than those taking efavirenz (-1.07 vs -0.49; $P < .001$), and this difference persisted even after adjustment for various factors, including physical activity, dietary calcium and vitamin D intake, viral load, and CD4+ cell count. BMC *z* score was higher with increased duration on efavirenz since switch from boosted lopinavir. The investigators concluded that in addition to avoiding the adverse effects associated with boosted

lopinavir, such as dyslipidemia and lipodystrophy, switching to efavirenz offers a benefit of improved bone mass accrual in HIV-infected children.

Several studies in developing countries have shown that HIV-exposed uninfected children have higher rates of mortality compared with HIV-unexposed children, for reasons yet to be elucidated. Treatment with cotrimoxazole has been demonstrated to decrease mortality in HIV-infected children, although data from randomized clinical trials on its efficacy among HIV-exposed uninfected children are lacking. Shapiro and colleagues conducted a randomized, double-blinded study of 2848 HIV-exposed uninfected children in a nonmalarial region of Botswana who received cotrimoxazole (n = 1423) or placebo (n = 1425) from 14 days to 34 days of life through 15 months of life (Abstract 37). Follow-up visits occurred every 1 month to 3 months through 18 months, with those infants diagnosed with HIV infection after random referral to open-label cotrimoxazole. Infants were fed by formula or breastfeeding based on the preference of the mother. The data and safety monitoring board stopped the study early due to futility in showing a benefit of cotrimoxazole. Mortality rates at 18 months did not differ between the arm that received cotrimoxazole and the arm that received placebo (2.4% vs 2.64%; $P = .7$). No differences were detected between the arms for the secondary outcomes, including hospitalization, grade 3 or 4 HIV diagnosis, or grade 3 or 4 anemia, whereas grade 3 or 4 neutropenia was more common in the group that received cotrimoxazole.

A randomized trial comparing urgent with poststabilization antiretroviral therapy was conducted among 183 hospitalized antiretroviral therapy–naive, HIV-infected children aged 0 years to 12 years in 4 Kenyan hospitals (Abstract 38), to evaluate whether urgent antiretroviral therapy with immune reconstitution leads to improved or worse outcomes. In the study, which was stopped early during interim analysis by the data safety and monitoring board due to futility, the children in the urgent-treatment arm (n = 90) received antiretroviral treatment within 48 hours (median, 1 day), and those in the poststabilization-treatment arm (n = 93) received antiretroviral treatment within 7 days to 14 days (median, 8 days). A notable baseline difference included lower CD4+ cell counts in the urgent-treatment arm compared with the poststabilization-treatment arm (12.5% vs 17%; $P = .02$). Overall mortality was 61 per 100 person-years, Mortality was 69 per 100 person-years in the urgent-treatment arm compared with 53 per 100 person-years in the poststabilization-treatment arm (HR, 1.46; 95% CI, 0.67, 2.37; $P = .47$), and no difference in mortality was noted after adjustment for baseline CD4+ cell count. Additionally, no statistically significant differences in rates of IRIS and serious adverse events were detected between the 2 arms.

In hospitalized HIV-infected Kenyan children, no difference in rates of mortality, IRIS, or serious adverse events was noted between urgent initiation of antiretroviral therapy (within 48 hours) and poststabilization antiretroviral therapy (within 7-14 days).

Clinical Pharmacology and Modeling Predictions of Antiretroviral Drugs in Pregnancy and Pediatric Populations

A Themed Discussion session (Session TD-1) focused on clinical pharmacology and modeling predictions of antiretroviral drugs in pregnancy and pediatric populations. Decreased exposure to many antiretroviral drugs occurs during pregnancy as a result of physiologic variations and altered pharmacokinetics. IMPAACT P1026s is an ongoing open-label, phase IV prospective study of the pharmacokinetics and safety of antiretroviral drugs, including dolutegravir and rilpivirine, in HIV-infected pregnant women. Data on the pharmacokinetics of dolutegravir during pregnancy and postpartum as well as infant washout pharmacokinetics and safety are lacking. Mulligan and colleagues analyzed the 24-hour pharmacokinetics of dolutegravir 50 mg administered once daily to 15 HIV-infected pregnant and postpartum women in the United States as part of the IMPAACT P1026s study and examined safety and infant washout pharmacokinetics (Abstract 438). The analysis encompassed data from 9 women in their second trimester, 15 in their third trimester, and 9 at 6 weeks to 12 weeks postpartum; 10 infants were included in the infant washout analysis. The dolutegravir area under the curve (AUC) was 25% to 30% lower in the second and third trimesters of pregnancy compared with paired postpartum levels, and dolutegravir plasma concentration at 24 hours after administration was 41% lower during pregnancy than in paired postpartum values. These differences, however, were not statistically significant, and all 15 women were noted to have an undetectable viral load at the time of delivery. Moderate elevation of alanine aminotransferase levels, possibly related to dolutegravir, was detected in 1 pregnant woman, and 2 women experienced preeclampsia. All 9 infants who were tested were found to be HIV-uninfected. The elimination half-life of dolutegravir in infants was 34.5 hours, more than twice that observed in nonpregnant adults as well as in pregnant and postpartum women in this study. Congenital abnormalities were reported in 4 infants, and 4 experienced hypoglycemia. The investigators concluded that more data on dolutegravir pharmacokinetics, safety, and outcomes in pregnant women and infants are warranted before dolutegravir can be recommended for treatment during pregnancy.

Rilpivirine is a second-generation NNRTI being investigated as a potential drug for PrEP in HIV-uninfected women and for prevention of intrapartum MTCT in HIV-infected women. Using data from the IMPAACT P1026s cohort, Best (Abstract 439) presented results of a study examining concentrations of rilpivirine in the female genital tract in 24 HIV-infected pregnant and postpartum women who received rilpivirine 25 mg once daily orally as part of their care. Plasma and cervicovaginal fluid specimens were collected and measured

for rilpivirine concentrations at the following intervals during the second and third trimesters of pregnancy and at 6 weeks to 12 weeks postpartum: before the first dose and then 1 hour, 2 hours, and 4 hours after the first dose. For all samples combined, median rilpivirine concentration was 92 ng/mL (IQR, 49-147) in plasma and 70 ng/mL (IQR, 23-121) in cervicovaginal fluid, which is at least 100 times more than the protein-free 90% effective concentration for rilpivirine of 0.66 ng/mL, considered the inhibitory concentration. The investigators found that the AUC of rilpivirine in cervicovaginal fluid was similar to that in plasma over the first 4 hours of dosing during the second and third trimesters of pregnancy; however, the AUC of rilpivirine in cervicovaginal fluid was lower postpartum than during pregnancy. The investigators suggested that rilpivirine concentrations are likely to reach inhibitory concentrations in the female genital tract when the drug is administered orally and that concentrations of drug in cervicovaginal fluid may be higher during pregnancy than postpartum.

The final 2 abstracts presented in Session TD-1 pertained to pharmacokinetic modeling of antiretroviral drug clearance in pregnant women and infants. Clearance of nevirapine occurs primarily via hepatic metabolism by cytochrome P450 (CYP450) enzymes 2B6 and 3A4 (CYP2B6 and CYP3A4) and secondarily via renal excretion. Nevirapine clearance is reduced in term and premature infants because of immature CYP450 enzyme activity. Autoinduction of nevirapine clearance occurs in adults and older children, but its extent in infants is unclear. Data on the effects of immaturity of CYP450 enzyme activity and autoinduction on nevirapine clearance are crucial for selecting an optimal nevirapine dosing regimen in infants.

In Abstract 440, Mirochnick and colleagues developed a population model of existing nevirapine pharmacokinetic data and simulations to examine dosing regimens of nevirapine 6 mg/kg twice daily for term infants and nevirapine 4 mg/kg twice daily for 1 week followed by 6 mg/kg twice daily for late-term infants of 34 weeks to 37 weeks gestation to achieve a treatment target trough concentration of at least 3 µg/mL. Data were collected from 192 infants younger than 1 year who were enrolled in 1 of 5 Pediatric ACTG and HIV Prevention Trials Network protocols in the United States, Brazil, and Africa. The investigators employed software to model changes in nevirapine pharmacokinetics over time, with imputation of the effects of immaturity of CYP2B6 and CYP3A4 enzymes and rate of autoinduction on nevirapine clearance from published data. The model found that nevirapine clearance was low immediately following birth and increased substantially during the first 2 months of life. In addition, autoinduction of nevirapine clearance was proportional to the nevirapine dose size during the first 12 months of life. Nevirapine clearance was also influenced by CYP3A4 metabolism and prematurity status. The simulations confirmed that the 2 nevirapine dosing regimens achieved the treatment target trough level of at least 3 µg/mL, and these 2 regimens are currently being evaluated in the IMPAACT 1115 and 1006 studies.

In Abstract 441, Olagunju and colleagues presented results of physiologically based pharmacokinetic modeling to simulate and predict infant exposure to maternal therapeutic efavirenz from breast milk during lactation. The investigators developed a model combining whole-body physiologically based pharmacokinetic maternal and infant models and incorporated system- and drug-specific parameters for absorption, distribution, metabolism, excretion, and breastfeeding. The model involved virtual populations of breastfeeding mother-infant pairs (n = 100 per infant age group) and assumed that the mothers were receiving efavirenz 600 mg orally daily and that infants were breastfed exclusively for the first 6 months of life. The model was found to sufficiently describe efavirenz pharmacokinetics in plasma and breast milk, with prediction of breast milk, plasma pharmacokinetic parameters, and infant exposure being within 50% difference compared with clinical data. The investigators concluded that this modeling approach sufficiently predicted infant exposure to maternal therapeutic efavirenz from breast milk and emphasized that physiologically based pharmacokinetic modeling can be applied and expanded to studies of exposure to other maternal drugs during lactation.

The use of long-acting antiretroviral drugs for HIV treatment is a promising strategy among children and adolescents, offering the potential benefits of regimen simplification, cost savings, and improvement in adherence. Rajoli and colleagues applied physiologically based pharmacokinetic modeling in their study to assess the in vivo pharmacokinetics of a long-acting injectable formulation of cabotegravir and rilpivirine in children and adolescents and to ascertain appropriate dosing regimens (Abstract 442). The models incorporated in vitro pharmacokinetic data for cabotegravir and rilpivirine and were validated against published clinical data on long-acting formulations of the 2 drugs in adults. Simulations were performed for 200 virtual pediatric patients for each weight band between age 3 years and 20 years following intramuscular injections of cabotegravir and rilpivirine. The models factored in demographics, tissue size, and drug-specific parameters, including metabolism and distribution. The simulated pharmacokinetics for long-acting cabotegravir and rilpivirine in adults in the models were consistent with available clinical data. More specifically, for cabotegravir 800 mg administered intramuscularly on a quarterly basis, mean AUC was 4467 µg.h/mL and 5257 µg.h/mL, maximum concentration (C_{max}) was 3.3 µg/mL and 3.54 µg/mL, and trough concentration (C_{trough}) was 1.1 µg/mL and 1.2 µg/mL for children and adolescents and for adults, respectively. For rilpivirine 900 mg administered intramuscularly on a monthly

A long-acting injectable formulation of cabotegravir and rilpivirine adjusted for weight may be a potentially valuable dosing strategy in children and adolescents, offering benefits of regimen simplification, cost savings, and improvement in adherence.

basis, mean AUC was 74,420 ng.h/mL and 91,087 ng.h/mL, C_{max} was 168 ng/mL and 168.7 ng/mL, and C_{trough} was 79.1 ng/mL and 78.3 ng/mL for children and adolescents and for adults, respectively. The models predicted optimized doses of cabotegravir and rilpivirine administered quarterly and monthly, respectively, for all weight bands, with at least 95% of individuals achieving C_{trough} levels over the cutoff limits. The investigators concluded that long-acting injectable cabotegravir and rilpivirine adjusted for weight could be a potentially valuable dosing strategy for children and adolescents.

New Antiretroviral Drugs and Approaches for Treatment of Pediatric HIV Infection

Data on new antiretroviral drugs for the treatment of HIV-infected pediatric populations were presented in a themed discussion session (Session TD-10). Nevirapine dosing in infants for PMTCT has been well studied; however, data are lacking on optimal nevirapine dosing for treatment of HIV infection in newborn infants. Capparelli and colleagues presented results of a study that assessed safety and drug concentrations of nevirapine 6 mg/kg twice daily for the treatment of HIV-infected newborn infants (Abstract 815). Six infants born at or later than 35 weeks gestation who weighed 2 kg or more were treated with nevirapine 6 mg/kg twice daily along with lamivudine 2 mg/kg twice daily and zidovudine 4 mg/kg twice daily until 2 weeks of age or for 40 weeks gestational age, whichever occurred later. A decrease in HIV RNA was detected in all infants. No antiretroviral therapy–related adverse events were reported during the first month. At week 2, nevirapine drug concentrations ranged from 3 mcg/mL to 11 mcg/mL and were considered therapeutic levels. Based on these findings, the investigators recommended nevirapine 6 mg/kg twice daily for HIV treatment in term and near-term infants.

Data from the IMPAACT P1093 study of dolutegravir pharmacokinetics, safety, and dosing in children and adolescents were presented by Wiznia and colleagues (Abstract 816). Twenty-three treatment-experienced, InSTI-naive children between age 6 years and 12 years with an HIV RNA level at or above 1000 copies/mL were enrolled in this ongoing phase I/II open-label study. Eleven children were involved in stage 1 with intensive pharmacokinetics, and 12 children were involved in stage 2 with no pharmacokinetics, safety, and efficacy. In stage 1, dolutegravir was added to a failing antiretroviral regimen (monotherapy phase) with an optimized background regimen after intensive pharmacokinetics at day 5 to day 10 (continuation phase). In stage 2, dolutegravir plus an optimized background regimen was initiated at study entry. The primary outcome of virologic success was defined as an HIV RNA below 400 copies/mL by week 48; the secondary outcome was an HIV RNA below 50 copies/mL by week 48. The median age of the children was 10 years (range, 6-11 years). The baseline median CD4+ cell count was 645/µL (range, 466/µL-732/µL), and the baseline CD4+ cell percentage was 24% (14%-29%). Virologic success, defined as achieving an HIV RNA level below 400 copies/mL was observed in 78.3% (95% CI, 56.3%-92.5%) of the children. Increases in CD4+ cell count of 387/µL (range, 49/µL-575/µL) and in CD4+ cell percentage of 9% (7%-14%) were seen. Dolutegravir was well tolerated by the children, with no drug discontinuations because of adverse events and no severe dolutegravir-related clinical or laboratory adverse events. The investigators concluded that treatment with dolutegravir in addition to an optimized background regimen in children aged 6 years to 12 years was well tolerated and led to high rates of virologic suppression and immunologic recovery at 48 weeks.

TDF has been associated with bone and renal toxic effects. TAF is a prodrug of tenofovir that is metabolized intracellularly to tenofovir and phosphorylated to active TDF and, therefore, leads to 91% lower exposure to tenofovir in plasma than TDF. Hence, TAF 10 mg coformulated in a once-daily single-tablet regimen with elvitegravir 150 mg, cobicistat 150 mg, and emtricitabine 200 mg has the potential for better bone and renal safety and for increased antiretroviral adherence in adolescents.

Gaur and colleagues presented results from a phase II/III single-arm, open-label study on the safety, efficacy, and steady-state pharmacokinetics of TAF, elvitegravir, cobicistat, and emtricitabine in HIV-infected adolescents through 48 weeks (Abstract 817); pharmacokinetic data through 24 weeks were previously reported.[18] Fifty HIV-infected, treatment-naive adolescents between age 12 years and 18 years with an HIV RNA level at or above 1000 copies/mL, a CD4+ cell count above 100/µL, and weight at or above 35 kg were enrolled in the study. Two adolescents discontinued the study before week 48. The primary end point for this analysis was virologic success, defined as an HIV RNA level of less than 50 copies/mL at week 48. Forty-six participants (92%) achieved virologic success; the mean increase in CD4+ cell count was 224/µL. No antiretroviral drug resistance mutations were detected. Six participants (12%) experienced serious adverse events, one of which was study drug–related and resolved without drug discontinuation. No cases of proximal renal tubulopathy were reported. The most common drug-related adverse events included nausea, abdominal pain, and vomiting. The median (IQR) change in serum creatinine level at week 48 compared with baseline was an increase of 0.07 mg/dL (0.02, 0.15), which was attributed to the inhibitory effect of cobicistat on creatinine secretion by the renal tubules. There was no change in median ratio of urinary protein to creatinine at week 48 compared with baseline. Median changes in bone mineral density (BMD) in spine and total body less head (were positive through week 48, and median changes in height-age adjusted spine and total body less head *z* scores were minimal. Only 1 participant experienced a decrease of higher than 4% in BMD in spine or total body less head at week 48 compared with baseline. These positive results favor the continuation of investigations of TAF, elvitegravir, cobicistat, and emtricitabine in the treatment of HIV-infected children and adolescents.

In Abstract 819, Giacomet and colleagues presented findings on the 10-year effects of TDF on BMD in 26 HIV-infected youths aged 4.9 years to 17.9 years in a longitudinal study. Eligibility criteria included HIV infection through MTCT,

undetectable viral load, and treatment with lamivudine, stavudine, and a PI. At enrollment, stavudine was changed to TDF and PIs were changed to efavirenz. Annual DXA scans were performed for 10 years. Lumbar spine and whole skeleton BMD values were compared with those of the control group, which consisted of 201 uninfected youths aged 3 years to 25 years. Regression curves of lumbar spine and whole skeleton BMD (absolute values and *z* scores) were statistically significantly lower in HIV-infected youths compared with controls, and the difference between HIV-infected youths and controls did not change over the 10-year period. The investigators concluded that switching to a TDF-containing regimen in HIV-infected youths was not associated with normalization of BMD values, yet the strategy did not lead to further decline in BMD over the long term.

Giaquinto and colleagues examined the pharmacokinetics, safety, and efficacy of maraviroc in addition to optimized background therapy in 103 R5-tropic HIV–infected, treatment-experienced children in an open-label, 2-stage trial (Abstract 818). Dose finding was assessed in stage 1, and safety and efficacy were evaluated in stage 2. The children were assigned to 1 of 4 age and formulation groups, with maraviroc dosed twice daily. At the start of the study, the maraviroc dose was based on body surface area and the optimized background therapy that the children were receiving, and the dose was adjusted and pharmacokinetics reevaluated if average concentration was below 100 ng/mL at week 2. Maraviroc was generally well tolerated, with most treatment-emergent adverse events being of grade 1 severity and no grade 3 or 4 treatment-emergent or serious adverse events being related to maraviroc. Fourteen children experienced grade 3 or 4 laboratory abnormalities, with the most common being grade 3 neutropenia. The safety profile of maraviroc in these children was considered to be comparable to that in adults. The children experienced a median decrease in HIV RNA of over 1 $\log_{10}$ copy/mL at week 48, with 48% of the children achieving an HIV RNA of less than 48 copies/mL. All children in the study had an increase in CD4+ cell count and percentage.

Optimizing the PMTCT Cascade

Gupta and colleagues presented more data on the roll-out of Malawi's Option B+ program from 2011 to 2015, with full decentralization of HIV treatment services and integration with PMTCT programs (Abstract 789). Using quarterly reports collected from all sites on cohorts receiving antiretroviral therapy, the investigators described the marked increase in the number of active sites offering antiretroviral therapy, from 303 to 704, and the rise in the percentage of antenatal clinics offering antiretroviral therapy, from 37% to 98% between 2012 and 2015. There was rapid integration of PMTCT and HIV treatment services, with 94% of sites providing services to those receiving antiretroviral therapy under Option B+ or in general between 2014 and 2015, and redistribution to smaller rural health facilities. Antiretroviral therapy coverage among HIV-infected pregnant women substantially increased from 22% to 95% between 2014 and 2015. There was a slight decrease in the proportion of sites with retention rates of higher than 80%, from 56% to 49% during the 4 years of the Option B+ program.

In Abstract 790, Aliyu and colleagues presented the results of a cluster randomized study to evaluate whether an intervention that offers a package of services improves maternal initiation of antiretroviral therapy and retention in care compared with standard of care in mother-infant pairs postpartum across 12 pair-matched sites in rural Nigeria. The intervention sites received the standard of care in addition to expanded service options, point-of-care CD4+ cell count testing, integrated maternal and infant services, and active involvement of male partners and peer mentors. The investigators found that the mothers who received the intervention were 3.3 times more likely to initiate treatment and 9 to 10 times more likely to be retained in care at 6 weeks and 12 weeks postpartum compared with women who received the standard of care.

In Abstract 791, Fayorsey and colleagues described the MIR4HEALTH (Maternal-Infant Retention for Health) trial, a randomized study examining the efficacy of a combination package of lay counselor–led interventions compared with standard of care to improve retention in PMTCT care in Kenya. Three hundred forty HIV-infected pregnant women initiating antenatal care were randomly assigned to 1 of 2 arms: 1) active patient follow-up, which involved individualized health education led by a lay counselor, phone and short message service (SMS) appointment reminders, home visits, physical tracing after missed visits, and support for retention and adherence (n = 170); or 2) standard of care, which involved routine PMTCT and postnatal HIV care according to Kenyan national guidelines (n = 170). The primary end point was attrition at 6 months postpartum, defined as the proportion of mother-infant pairs not retained in care as a result of loss to follow-up, pregnancy loss, or mother or infant death. Approximately one-third of the women were known to be HIV-infected, with a median (IQR) gestational age of 24 weeks (range, 17-28 weeks); median (IQR) CD4+ cell count was 426/µL (274/µL-601/µL). In intent-to-treat analysis, a statistically significantly lower attrition of mother-infant pairs was noted in the intervention arm than in the arm that recieved the standard of care (18.8% vs 28.2%; $P = .04$). Factors associated with lower attrition at 6 months postpartum were older age, known HIV infection at baseline, and disclosure of HIV serostatus to a partner. Nine infants tested positive for HIV infection on a PCR assay, with no statistically significant difference between the 2 arms. These findings highlight that a combination package of lay counselor–led interventions can result in a reduction in attrition in mother-infant pairs receiving PMTCT care in settings with high HIV prevalence.

Clouse and colleagues used an existing national laboratory database to ascertain the frequency of "clinic shopping" or switching of medical care postpartum among 312 women who had initiated antiretroviral therapy during pregnancy in 7 clinics in a South African province and were considered lost to follow-up (no documented clinic visit in more than 3

months) (Abstract 792). Women were categorized as having continued HIV care if they accessed care after initiating antiretroviral therapy at a new facility, as demonstrated by at least 1 HIV viral load or CD4+ cell count test on record in the database. Women were considered to be "clinic shoppers" if they received care at a new facility within the same region as the clinic in which they initiated antiretroviral therapy. Of the 284 women with available records who were considered lost to follow-up, a high proportion (37%) were actually in continued HIV care. Of these, 67% were clinic shoppers and 33% received care outside the province. The study findings emphasize the potential flaws in estimations of retention in care and highlight the importance of developing a national health database that can link patients and records by a unique identifier.

Retention rates among HIV-infected pregnant women enrolled in the Option B+ program in Malawi have ranged from 67% to 78%. Hoffman and colleagues conducted a case-control study of HIV-infected pregnant women who began antiretroviral therapy as part of Option B+, to examine sociodemographic characteristics, disclosure of HIV serostatus to partners, pre–antiretroviral therapy education, and knowledge regarding Option B+ among women retained in the program (Abstract 793). The study included 50 women who defaulted and were out of care from Option B+ for more than 60 days and 153 controls who were retained in Option B+ for at least 12 months. More than 80% of the women initiated antiretroviral therapy at a median (IQR) gestational age of 24 weeks (range, 16-28 weeks); of these, 91% defaulted and were out of care at 3 months postpartum. Women who were retained in care (controls) were more likely to disclose their HIV serostatus to their primary partner compared with those who defaulted (100% vs 78%; $P < .001$). In a multivariate analysis controlled for age, education, and travel time to the clinic, the odds of retention were higher among women who were aware of their partner's HIV serostatus (OR, 4.07; 95% CI, 1.51, 10.94) and had more knowledge about Option B+ (OR, 1.60; 95% CI, 1.15-2.23; $P = .004$). To enhance retention of HIV-infected pregnant women in Option B+ in Malawi, the investigators recommended interventions to help encourage disclosure of HIV serostatus to partners and improve education about the importance of the Option B+ program for maternal and child health.

Ebola Update

A special session was dedicated to the devastating Ebola outbreak in West Africa (2013-2016). According to the WHO, there have been more than 28,000 Ebola infections and 11,316 deaths from the Ebola virus, including 500 to 1000 health care workers.[19] There is a crucial need for vaccine development and treatment strategies to prevent or mitigate the severity of Ebola virus infections. Two presentations from the PREVAIL (Partnership for Research on Ebola Vaccines in Liberia) trial were dedicated to vaccines and immune-based therapy.

Bolay presented findings from a randomized controlled trial of the safety and immunogenicity of 2 Ebola vaccines in a phase II study of uninfected volunteers who were enrolled in the context of the Ebola outbreak in Liberia (Abstract 76LB). Uninfected volunteers were randomly assigned to receive 1 of 2 candidate vaccines or a placebo. The 2 candidate vaccines were a vesicular stomatitis virus (VSV)-based vaccine, rVSV-deltaG-ZEBOV GP, in which the gene encoding the G envelope glycoprotein of VSV is replaced with the envelope glycoprotein of the Ebola virus, and a recombinant chimpanzee adenovirus type-3–based vaccine, ChAd3-EBO-Z, which contains a DNA fragment insert that encodes the Ebola virus glycoprotein. There were 500 participants in each of the vaccine arms and 250 participants in each of the 2 associated placebo arms. Study end points included safety and immunogenicity. At baseline, 6.3% of study participants had antibodies to Ebola virus infection despite no prior knowledge of infection. The percentages of participants who were diagnosed with HIV infection and syphilis at baseline were 5.2% and 5.1%, respectively. Overall, attendance of follow-up visits exceeded 98%. Both vaccines were well tolerated, with only minor site reactions and transient decreases in neutrophils that did not persist beyond the first week of follow-up. Immunogenicity was measured by enzyme-linked immunosorbent assay (ELISA). Excluding those individuals who were antibody positive at baseline, an antibody response at month 1 was noted in more than 85% of participants in each of the vaccine arms and fewer than 10% of participants in the placebo arm ($P < .001$).

Davey presented results from the PREVAIL II trial, a randomized controlled trial of an investigational treatment that comprises 3 monoclonal antibodies (ZMapp™) for acute Ebola virus infection (Abstract 77LB). Having demonstrated promising results in nonhuman primate models, the treatment was introduced in this trial during the latter half of the Ebola virus epidemic in 2014 and 2015. Individuals with acute Ebola virus infection from sites in Liberia, Sierra Leone, Guinea, and the United States were randomly assigned 1:1 to 3 infusions of the treatment plus standard of care or to standard of care alone. The study was conducted over 10 months and was stopped due to extinction of the Ebola virus and subsequent decreased enrollment. Instead of including 100 participants in each arm as originally planned, 36 participants were enrolled in each arm. One participant in the control arm was lost to follow-up. There were 21 deaths overall, of which 13 occurred in the control arm (mortality of 37.1%) and 8 occurred in the arm that recieved treatment plus standard of care (22.2%). Although there was a trend toward superiority in the treatment arm, the posterior probability of superiority was only 91.2% and fell short of the predefined statistically significant threshold for declaring efficacy (set at ≥97.5%).

Little is known about the clinical sequelae after Ebola virus infection in survivors. Two presentations outlined long-term sequelae, the presence of asymptomatic infections, and characteristics of Ebola virus in semen (Abstracts 73LB and 74LB). Etard and colleagues described long-term clinical sequelae, psychosocial consequences, and viral clearance rates among a cohort of survivors in Guinea (Abstract 73LB).

Guinean adult and child Ebola survivors were enrolled (n = 475) in the survivor cohort for 2 years of follow-up. Several long-term symptoms were reported including muscle and joint aches, headache, fatigue, abdominal pain, anorexia, and ocular symptoms. The most severe findings in the cohort involved abnormal eye exam results in 19% of survivors; there were cases of uveitis, episcleritis, keratitis, and cataracts. Anemia (hemoglobin level < 10 g/dL) was the most common lab abnormality. Semen analysis from 107 men revealed a 6% positivity rate, and the viral RNA persisted in semen for 9 months in 1 individual. Additionally, depression was a prominent disorder among survivors (25% of men and 18% of women).

Similarly, Fallah and colleagues from the PREVAIL III trial in Liberia presented data on the natural history of Ebola virus disease among survivors (Abstract 74LB). The analysis from the ongoing PREVAIL III cohort study included follow-up of more than 1000 survivors of Ebola virus disease and more than 1000 close contacts. Common persisting symptoms and exam findings among survivors included ocular, musculoskeletal, and neurologic abnormalities. In particular, uveitis was a prominent finding. The issue of detection of persistent Ebola virus in semen was also examined in this study. Of 97 male survivors, 38% had viral RNA detected in the semen at least once, and in some men the viral RNA was detectable intermittently. The longest period of time between Ebola virus disease and continued Ebola virus detection in the semen was 18 months.

In an effort to better characterize the dynamics of Ebola virus clearance in semen, Sissoko and colleagues studied rates of Ebola virus clearance in a prospective cohort study of male Ebola survivors in Guinea (Abstract 75LB). Of 26 men included in the analysis, 73% were found to have Ebola virus in semen, detected by RNA PCR assay at the initial analysis, and the rate of viral clearance in semen was slow. Ebola virus was present in the semen of 1 participant at 334 days after initial disease onset. Using individual patient data, investigators modeled the likelihood of a positive result for Ebola RNA in semen and suggested that 50% would have detectable Ebola virus in semen at 108 days and 10% would have detectable virus in semen at 325 days. Additional studies are needed to understand the potential significance of persistent Ebola virus in semen in terms of transmission risk, so that proper counseling can be provided.

Although Ebola virus is most known for the severity of its clinical presentation and high mortality rates, several studies documented evidence of asymptomatic infection. Richardson and colleagues described evidence of asymptomatic Ebola infection that was found in the quarantined hot spot of Kono, Sierra Leone (Abstract 72LB). The performance characteristics of the ELISA tests to detect Ebola exposure and the estimated proportion of asymptomatic Ebola infection in the population were examined. Serum samples from 30 survivors and 132 uninfected controls who underwent testing for Ebola antiglycoprotein and antinucleoprotein were analyzed. Receiver operator curves were constructed, and the assays were found to be comparable. The Ebola antiglycoprotein ELISA, found to have 96.7% sensitivity and 97.7% specificity at a cutoff of 4700 U/μL, was selected for use during the second phase of the study. Volunteers who had not reported Ebola illness from quarantined households underwent Ebola antiglycoprotein testing. Of 207 volunteers, there were 12 seropositive individuals who had not had any symptoms. After combining known infections with asymptomatic infections, 25% of infections were found to be asymptomatic. The findings raised questions about appropriate screening for exposure and whether people with asymptomatic infections should be evaluated for clinical sequelae or ongoing risk for transmitting the virus.

Ebola virus disease has particularly impacted health care workers, resulting in fragmented local health care systems. Ndawinz and colleagues reported on the impact of the Ebola virus epidemic on HIV care in Sierra Leone (Abstract 910). During 2014, 360 health care workers were infected with Ebola virus, and over this same period, there was a substantial decline in the number of patients receiving antiretroviral therapy in Sierra Leone.

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