Invited Review

CROI 2017: Advances in Antiretroviral Therapy

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The 2017 Conference on Retroviruses and Opportunistic Infections (CROI) featured exciting preclinical data on investigational antiretroviral agents with good in vitro efficacy and long half-lives. Investigational medications, including bictegravir, demonstrated excellent efficacy and tolerability, as did dual-agent therapy with dolutegravir paired with rilpivirine or with lamivudine. Dolutegravir monotherapy proved inadvisable due to virologic failure and resistance. The gap between high- and low-income settings along the HIV care continuum is narrowing, with Zimbabwe, Malawi, and Zambia approaching the 90-90-90 targets established by the joint United Nations Programme on HIV/AIDS (UNAIDS), whereas communities in the Southern United States are falling behind. Innovative strategies to improve outcomes include 2-way text messaging, home-based HIV testing, peer navigation, and New York City's realignment of services into comprehensive sexual health programs. A high prevalence of resistance was documented in low- and middle-income settings and policy considerations were modeled to address increasing resistance rates. Novel resistance mutations to integrase strand transfer inhibitors and nucleoside analogue reserve transcriptase inhibitors were identified, but the clinical implications are unclear and require further investigation. Several studies provided insights on dosing and safety of antiretroviral therapy to prevent mother-to-child transmission through pharmacokinetic analysis. A special session devoted to Zika virus included a study of its effects on the central nervous system and a promising animal study of a Zika vaccine.

Keywords: CROI, HIV, AIDS, Zika, antiretroviral, therapy, treatment strategies, investigational drugs

Investigational Antiretroviral Drugs: Early Studies

HIV-1 Capsid Inhibitors

Tse and colleagues presented data on HIV capsid inhibitors that have potential for slow-release administration for use as a long-acting treatment (Abstract 38). The HIV p24 capsid protein self-assembles into hexamers that combine to form the conical capsid structure surrounding the inner viral core. GS-CA1 is a small molecule with a 50% effective concentration (EC_{50}) of 140 picomoles. During the maturation phase of the viral replication cycle, GS-CA1 interferes with the assembly and eventual disassembly of the viral capsid. It also prevents the nuclear translocation of the preintegration complex without affecting reverse transcriptase function. The binding site appears highly conserved in viral isolates. The GS-CA1 compound appears more potent in vitro than current classes of antiretroviral drugs and is active against highly resistant HIV strains. It has been formulated as a long-acting compound.

Capsid inhibitors act at multiple phases in the HIV life cycle and have the potential for use in long-acting treatment.

Other Classes

GS-PS1. Link and colleagues presented preclinical data on a novel once-daily protease inhibitor that does not require pharmacologic boosting (Abstract 433). The drug appears to have potent activity against HIV strains resistant to darunavir and atazanavir, and has a low propensity to generate resistance in vitro. The long half-life suggests its possible use as part of a once-daily single-tablet regimen for HIV treatment.

GS-9131. GS-9131 is a novel nucleoside analogue reverse transcriptase inhibitor (nRTI) with activity in vitro against HIV strains resistant to currently available nRTIs (Abstract 436). Resistance to GS-9131 emerges through a complex pathway distinct from other nRTIs. GS-9131 is a candidate for once-daily dosing and will likely be studied in individuals with limited treatment options.

UB-421. Wang and colleagues presented a phase II trial of UB-421, a monoclonal antibody that binds the CD4 receptor to prevent HIV-1 entry (Abstract 450LB). In the trial, HIV-infected adults with viral suppression were enrolled into 1 of 2 cohorts: 8 weekly doses of UB-421 10 mg/kg or 8 biweekly doses of 25 mg/kg. All participants interrupted antiretroviral therapy during the infusion period. UB-421 appeared relatively safe in this short-term trial with no emergence of anti-UB-421 antibodies. Grade 1 or 2 rash was noted in half of the participants. Participants remained virally suppressed throughout the

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infusion period with the exception of 7 subjects who had isolated plasma HIV-1 RNA measurements of 50 copies/mL to 400 copies/mL. Five participants did not restart antiretroviral therapy at the end of UB-421 dosing, and viral rebound occurred from 35 days to 62 days after the last dose. The long-term safety of blocking the human CD4 receptor needs to be evaluated carefully in future studies.

Investigational Drugs in Antiretroviral Regimens

Bictegravir

Bictegravir is an investigational once-daily integrase strand transfer inhibitor (InSTI) with a high barrier to resistance (Abstract 40). Early studies suggest a good safety profile. The major route of metabolism is through cytochrome P450 (CYP3A4) and glucuronidation with a half-life of 18 hours. Increased exposure occurred when coadministered with inhibitors of both pathways. Induction of these enzymes with rifampin led to substantial reductions of drug levels. The metabolism did not appear to be affected by moderate hepatic impairment or severe renal impairment. The coformulation of bictegravir, tenofovir alafenamide (TAF), and emtricitabine is expected to be administered without restrictions around food.

Sax and colleagues presented a randomized, placebo-controlled phase II trial of bictegravir or dolutegravir with TAF/emtricitabine for initial antiretroviral therapy (Abstract 41). The trial randomly assigned 98 participants to bictegravir (65) or to dolutegravir (33). At week 48, 97% of participants in the bictegravir arm and 91% in the dolutegravir arm had viral suppression according to the US Food and Drug Administration's (FDA) snapshot algorithm. No resistance to study medication was detected in either arm and no safety concerns were identified. Bictegravir is currently in phase III clinical development as a single-tablet regimen with TAF and emtricitabine.

Doravirine

Squires and colleagues presented details of a double-blind, randomized, placebo-controlled phase III trial in which doravirine, a novel investigational nonnucleoside analogue reverse transcriptase inhibitor (NNRTI), was compared with darunavir/ritonavir in combination with 2 open-label nRTIs (Abstract 45LB). Doravirine is dosed at 100 mg once daily without restrictions around food intake and has a low potential for drug-drug interactions. It is active against many HIV isolates with NNRTI resistance mutations. In the trial, 766 participants were randomly assigned and treated (median age, 35 years; 84% were men; 23% were black; median CD4+ cell count was 220/µL, and mean plasma HIV RNA level was 4.4 $\log_{10}$ copies/mL). At week 48, doravirine was noninferior to darunavir/ritonavir in achieving virologic suppression of 84% vs 80%, respectively (difference 3.9%; 95% confidence interval [CI], -1.6-9.4). This conclusion appeared robust in analyses of baseline CD4+ cell count and plasma HIV-1 RNA levels in subgroups. Two participants in the doravirine arm developed treatment-emergent resistance. Doravirine had favorable lipid level changes compared with darunavir/ritonavir and appeared safe, with a low discontinuation rate due to adverse effects. A separate study found that severe renal impairment did not have a clinically meaningful impact on doravirine pharmacokinetics (Abstract 430).

Elsulfavirine

Elsulfavirine is a prodrug of VM1500A, an investigational NNRTI with a half-life of 8 days. Murphy and colleagues presented results of a double-blind, placebo-controlled phase IIb trial comparing elsulfavirine 20 mg daily with efavirenz, each given with tenofovir disoproxil fumarate (TDF)/emtricitabine in 120 HIV-infected adults initiating antiretroviral therapy (Abstract 452LB). At week 48, 81% of elsulfavirine participants and 74% of efavirenz participants had HIV RNA levels below 400 copies/mL. Elsulfavirine appeared to be better tolerated than efavirenz in this trial.

Ibalizumab

Lewis and colleagues presented a single-arm clinical trial of ibalizumab, an investigational CD4 attachment inhibitor, with an optimized background regimen in highly treatment-experienced HIV-infected adults (Abstract 449LB). Eligible participants had to have resistance to at least 1 agent from each of 3 drug classes, and sensitivity to at least 1 antiretroviral drug to be used in an optimized background regimen. Forty participants were enrolled: the mean age was 51 years; 85% were men; the mean viral load was 100,287 copies/mL; the mean CD4+ cell count was 140/µL; and baseline resistance to antiretroviral therapy was extensive. Participants received a single intravenous infusion of 2000 mg ibalizumab without changing baseline antiretroviral therapy. After 14 days, participants began an optimized background regimen and ibalizumab 800 mg administered intravenously every 2 weeks. Plasma HIV RNA levels decreased more than 1 $\log_{10}$ copies/mL at day 14 in 60% of participants. At week 24, 43% of participants had a viral load below 50 copies/mL and 50% of participants had a viral load below 200 copies/mL. Serious adverse events were common, but only 1 drug-related adverse event (immune reconstitution inflammatory syndrome) led to treatment discontinuation.

Lin and colleagues reported on the safety, tolerability, and pharmacokinetics for novel dosing regimens of ibalizumab (Abstract 438). The investigators found that 800 mg every 2 weeks or 2000 mg given intramuscularly or intravenously monthly resulted in sustained antibody concentrations in the therapeutic range. These dosing regimens led to reductions in plasma HIV RNA levels similar to those seen in prior studies that used weekly subcutaneous administration.

New Antiretroviral Strategies

Dolutegravir Plus Rilpivirine

Llibre and colleagues presented 2 phase III open-label, randomized clinical trials comparing dolutegravir plus rilpivirine

with continued antiretroviral therapy in HIV-infected participants who were virally suppressed (Abstract 44LB). Enrolled participants had no history of virologic failure, no chronic hepatitis B virus infection, were on stable antiretroviral therapy for at least 6 months, and had confirmed viral suppression below 50 copies/mL. A total of 1024 participants (the mean age was 43 years, 22% were women, 20% were nonwhite, and 70% had a CD4+ count above 500 cells/µL) were randomly assigned to either of the concurrent studies. At week 48, 95% of participants in each treatment arm were virologically suppressed. The virologic suppression with dolutegravir plus rilpivirine was noninferior to continued antiretroviral therapy (–0.2%; 95% CI, –3.0%-2.5%). Those in the dolutegravir plus rilpivirine arm experienced a higher rate of adverse events leading to treatment discontinuation, but the overall rates of treatment success were high in both arms.

Switching suppressive antiretroviral treatment to dolutegravir and rilpivirine is noninferior to continued standard antiretroviral therapy.

Dolutegravir Plus Lamivudine

Several trials are investigating a 2-drug regimen of dolutegravir and lamivudine. Joly and colleagues presented a single-arm trial of this regimen as maintenance antiretroviral therapy in HIV-infected adults (Abstract 458). Participants changed existing antiretroviral therapy to dolutegravir and 2 nRTIs for 8 weeks followed by dolutegravir and lamivudine. Participants had to have had a genotype prior to antiretroviral therapy that showed no resistance, no history of viral failure with resistance, and no chronic hepatitis B virus infection. A total of 104 participants received dolutegravir and lamivudine alone: the median age was 45; 86% were men; the median CD4+ cell count was 743/µL; and the median nadir CD4+ cell count was 399/µL. At week 48, 101 of 104 (97%) had an HIV RNA level below 50 copies/mL. The authors suggested pursuing this strategy in larger trials.

Dolutegravir Monotherapy

Dolutegravir appears to have a high barrier to the emergence of resistance. Wijting and colleagues reported on a randomized clinical trial comparing dolutegravir monotherapy with continued antiretroviral therapy in HIV-infected adults with virologic suppression (Abstract 451LB). The 104 participants were randomly assigned to 1 of 2 arms: dolutegravir alone or continued antiretroviral therapy. At week 24, dolutegravir alone was noninferior to continued antiretroviral therapy: 98% on dolutegravir alone had HIV RNA levels below 200 copies/mL compared with 100% of participants receiving continued antiretroviral therapy. After week 24, the participants receiving antiretroviral therapy were allowed to change to dolutegravir alone. After 24 weeks to 48 weeks of receiving dolutegravir alone, 8 participants experienced virologic failure, including 3 who developed InSTI resistance. This suggests that this strategy may not be ready for use in clinical practice and should not be pursued in further clinical trials.

PRO140

PRO140 is an investigational monoclonal antibody that binds to human CC chemokine receptor R5 (CCR5) to prevent HIV entry (Abstract 437). Lalezari and colleagues presented findings from a study of 16 participants with CCR5-tropic HIV infection who received PRO140 in the form of 350 mg weekly subcutaneous injections alone as maintenance antiretroviral therapy. Five participants experienced virologic rebound and resumed combination antiretroviral therapy. One participant discontinued the study. Nine participants who received PRO140 alone remain virologically suppressed after 2 years of follow-up. There was no emergence of C-X-C chemokine receptor type 4 (CXCR4) using HIV-1 variants. The strategy is being investigated in other ongoing studies.

Pharmacokinetic Considerations

Tenofovir. Castillo-Mancilla and colleagues presented data on quantifying tenofovir diphosphate in dried blood spots from individuals receiving TAF as a measure of adherence over a period of several weeks to months (Abstract 405). The red blood cell concentrations were quantifiable, but at lower levels than seen in those who receive TDF. Presumably this is related to the lower tenofovir plasma concentrations observed in individuals receiving TAF as opposed to those re ceiving TDF.

Dumond and colleagues examined concentrations of tenofovir in the semen of individuals receiving TAF (Abstract 406) or TDF. Tenofovir concentrations were similar in the seminal plasma for those receiving either TAF or TDF. This finding was unexpected because TAF achieves much lower blood plasma concentrations than TDF.

Older HIV-Infected Adults. Several abstracts evaluated the pharmacokinetic profile of antiretroviral drugs in aging populations. Ahlgren and colleagues studied 99 HIV-infected adults aged 65 years and older and found they had elevated darunavir concentrations (48% higher) compared with younger controls. Concentrations of atazanavir or efavirenz, however, were similar in both groups (Abstract 431). Elliott and colleagues performed intensive dolutegravir pharmacokinetic sampling by comparing 28 HIV-infected adults aged 60 years and older with 16 HIV-infected adults younger than 60 years and found that drug exposure was not affected by age (Abstract 432).

Crushing Tablets. Roksam-Kwit and colleagues evaluated the effect on plasma concentrations of crushed fixed-dose dolutegravir/abacavir/lamivudine tablets in 22 HIV-uninfected adults (Abstract 429). The dolutegravir exposure, as measured by area under the curve (AUC), increased by 26% when the crushed tablet was given in an oral suspension, and

increased by 18% when the crushed tablet was coadministered with enteral nutrition. No appreciable difference was noted for exposure when abacavir or lamivudine crushed tablets were taken. The authors concluded that fixed-dose dolutegravir/abacavir/lamivudine could be crushed for individuals who had difficulty swallowing or with the use of an enteral feeding tube.

The HIV Care Continuum

Global Progress Toward Reaching UNAIDS 90-90-90 Targets

Exciting data about progress made on the HIV care continuum and toward reaching the UNAIDS 90-90-90 treatment goals were a highlight at this year's CROI. In the plenary session, Dr Hakim, from the University of Zimbabwe, gave the N'Galy-Mann lecture in which he detailed the history of HIV/AIDS research in Zimbabwe. Zimbabwe identified its first person living with HIV infection in 1985 and the country's initial response to the epidemic was impeded by public denial of the existence of HIV. Since 1999, Zimbabwe has developed a national AIDS policy and strategic multisectoral response, supported by a 3% tax on individual and corporate income. As a result, HIV prevalence peaked at 29% in 1986 and is now at 14%, with substantial geographic variation. Based on the Zimbabwe Population-based HIV Impact Assessment (ZIMPHIA), part of the PHIA project, a 5-year initiative to collect information related to HIV infection in approximately 15 to 20 African countries, progress toward achieving 90-90-90 targets in Zimbabwe is being made. ZIMPHIA was conducted between October 2016 and August 2016 by ICAP-Columbia with local partners and the Zimbabwe Ministry of Health, the US President's Emergency Plan for AIDS Relief (PEPFAR), and the Centers for Disease Control and Prevention (CDC). The UNAIDS 90-90-90 goals are 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 have viral suppression by 2020.

Zimbabwe, Malawi, and Namibia have all made substantial progress toward reaching UNAIDS 90-90-90 targets, but population mobility and limited availability of HIV-1 plasma RNA testing impede progress in many countries.

To date in Zimbabwe, 74.2% of HIV-infected individuals have been diagnosed, 86.8% of those diagnosed are on treatment, and 86.5% of those on treatment are virologically suppressed. These achievements are particularly impressive in light of the country's political climate and economic conditions. Hakim emphasized Zimbabwe's multifaceted research program, which includes studies with the HIV Prevention Trials Network and the AIDS Clinical Trials Group, and ongoing work to expand medical education and research capacity in the country.

Justman and colleagues (Abstract 114LB) presented additional data from Zimbabwe, Malawi, and Zambia, collected by PHIA. Representative HIV-focused households were surveyed to estimate HIV incidence and the prevalence of virologic suppression, defined as a plasma HIV-1 RNA level below 1000 copies/mL. In a survey of 76,662 adults and children, the overall response rate was 69.1%, and HIV prevalence among adults (aged 15 years to 59 years) varied dramatically by sex (9.8% of men and 14.4% of women) and by geographic location. Prevalence in the pediatric population was much lower, at 1.4% of those aged 0 years to 14 years. Most striking were the data on progress in achieving the 90-90-90 goals. In all 3 countries, 70.4% of individuals were aware of their serostatus, 87% of those individuals were on antiretroviral treatment, and 88.6% of those were virologically suppressed, with the successes largely driven by older populations. The investigators concluded that the HIV epidemic is stabilizing, or even declining in some circumstances, in the populations surveyed, and that young adults, particularly those who are unaware of their HIV serostatus, should receive targeted testing and treatment interventions to achieve the 90-90-90 goals and maintain current successes.

Olney and colleagues (Abstract 115) used data from ZIMPHIA in a mathematical model of various HIV infection care stages. The investigators predicted that Zimbabwe will achieve 2 of the 3 90-90-90 treatment goals: 90% of diagnosed individuals with HIV infection will receive antiretroviral therapy by 2020, and 90% of those individuals receiving antiretroviral therapy will become virologically suppressed by 2020. However, the goal that 90% of HIV-infected individuals will become aware of their HIV serostatus by 2020 will not be met by a substantial margin. They predicted that only 72% of HIV-infected persons in Zimbabwe would be diagnosed, and the diagnosis and linkage of an additional 11,244 individuals per year would be needed to achieve all 3 goals simultaneously; this would also require a 5% increase in overall funding.

Nguyen and colleagues (Abstract 116) also created a mathematical model to examine the clinical outcomes and cost-effectiveness of 4 strategies in Southwest Kenya. The strategies were to expand voluntary counseling and testing (VCT) to 90% of the community; to offer VCT and linkage to care to 90% of those diagnosed with HIV infection; to provide retention interventions to ensure 90% antiretroviral treatment and 90% virologic suppression for those on treatment; and to offer all 3 interventions combined. The model, using 2012 HIV care continuum data from Médecins Sans Frontières (MSF), showed that 62% of the population was tested, 57% were linked to HIV care, and 40% were virologically suppressed. The time-discrete, dynamic microsimulation model showed that if implemented in 2014, after 15 years the baseline care continuum outcomes would increase from 73% to 94% tested, from 66% to 93% linked, and from 36% to 56% suppressed, respectively, depending on the strategy implemented. Incidence would drop from 1.93 per 100 person-years without intervention to 1.10 per 100 person-years with the combined intervention. The incremental cost-effectiveness ratio was $180 per year of life saved, although this was

dependent on regional HIV prevalence estimates. Results from this model suggest that the combined strategy would be cost-effective in Southwest Kenya and other areas in Kenya where HIV prevalence is more than 3%, but might still fall short of the UNAIDS 90-90-90 treatment targets.

Data from the French National Agency for AIDS Research (ANRS) 12249 cluster randomized trial of a universal test-and-treat approach on HIV incidence in rural South Africa were used to assess 90-90-90 targets in 564 individuals for 1 year after HIV diagnosis (Abstract 1018). Twenty-two percent had migrated out of the study catchment area, 57% were diagnosed, 27% were engaged in HIV care, 12% were receiving antiretroviral treatment, and 10% were virologically suppressed. The investigators highlight that only 17% of this newly diagnosed cohort initiated antiretroviral therapy within 12 months of seroconversion in a setting where linkage to care and treatment was facilitated. These findings are concerning and highlight the challenges of reaching 90-90-90 targets in regions of high population mobility and to support those recently diagnosed as they engage in care.

Patel presented data in the SISTER (Sentinel Incidence Survey to Evaluate the Response), a novel mechanism for assessing 90-90-90 targets by embedding an incidence and virologic suppression survey into an existing, community-based HIV prevention and case management program in Namibia (Abstract 35; also see "HIV Epidemic Trends and Advances in Prevention" by Drs Liu and Buchbinder). At baseline, 64% of 461 people living with HIV infection were aware of their diagnosis, 53% were receiving antiretroviral therapy, and 43% were virologically suppressed. After 1 year, 92% of the cohort was retained, although retention for those living with HIV infection was lower (89%) than for those uninfected (93%, $P < .05$). However, achievement toward 90-90-90 targets within the cohort had improved: 99% of the 423 individuals living with HIV infection were aware of their diagnosis, 92% were receiving antiretroviral therapy, and 75% achieved virologic suppression. The investigators concluded that this type of community-based program can be used in other countries to assess progress toward achieving the 90-90-90 targets, and to promote HIV testing and linkage to care and treatment adherence.

Reaching the Last 90: Challenges of Measuring and Achieving Virologic Suppression

Several presenters addressed strategies to improve virologic monitoring in low- and middle-income countries in order to meet the 90-90-90 target of 90% virologic suppression. Peeling (Abstract 105) described innovations in plasma HIV-1 RNA measurement and scale-up, emphasizing the dramatic variation in scale-up of viral load testing. In Namibia, 91% of individuals on antiretroviral therapy have had at least 1 plasma HIV-1 RNA test and the turnaround time for results is 5 working days or less. In contrast, in Tanzania only 5% of individuals on antiretroviral therapy have ever had their plasma HIV-1 RNA level measured, and turnaround time for testing is 28 to 50 working days. Two point-of-care platforms for plasma HIV-1 RNA testing are currently available, although they are expensive and have lower throughput than the fully automated laboratory assays. More point-of-care tests are in development. Assays that use dried blood spots are useful, particularly in rural settings, but still have problems with false-positive results associated with measuring cell-associated viral RNA and proviral DNA. Peeling highlighted Uganda's plasma HIV-1 RNA testing expansion, which uses a 5-tiered laboratory network forming a hub-and-spoke model. The 100 hubs provide analysis of dried blood spot samples received from 30 spokes each, and monthly tests have increased from 10,000 to more than 70,000 in slightly over a year. Zimbabwe is pursuing a similar model, but with a focus on connectivity. All of Zimbabwe's point-of-care instruments upload data into the cloud, or Internet servers, which the Ministry of Health then accesses. The data can be used for patient care, but also to ensure quality control and stock management for individual machines. These innovative approaches can be applied in other low- and middle-income countries to expand access to plasma HIV-1 RNA level measurement.

Reynolds (Abstract 104) reviewed the limitations of immunologic monitoring, and emphasized the need for access to plasma HIV-1 RNA testing. He also highlighted the need to address the "viral load cascade," which means not just providing access to the test but ensuring that the results are acted on and alternate antiretroviral regimens are initiated as indicated. Data from the Rakai fishing communities in Uganda in 2015 showed that only 42% of the HIV-infected population had plasma HIV-1 RNA levels measured, in a setting where testing is routinely available. Reynolds estimates that only 2% to 4% of individuals in low- and middle-income countries are receiving second or third antiretroviral regimens, and reviewed data showing long delays in transitioning individuals to second regimens, even in the setting of demonstrable virologic failure. Delays in switching to second antiretroviral regimens have been associated with the development of drug resistance and mortality, and have clear implications for treatment as prevention strategies.

Three presentations focused on viremia patterns in large cohorts. Crepaz and colleagues (Abstract 31) used data from the CDC HIV National Surveillance System to expand the traditional definition of virological suppression of plasma HIV-1 RNA less than 200 copies/mL to understand virologic dynamics over time. They compared individuals whose last plasma HIV-1 RNA level in 2014 was below 200 copies/mL to those having all their measurements in 2014 be below 200 copies/mL and to those who never achieved a level below 200 copies/mL in 2014. Among the 630,965 people living with HIV infection in the United States in 2014, 57% had a last plasma HIV-1 RNA level measurement below 200 copies/mL, but only 48% achieved durable virologic suppression, with all measures below 200 copies/mL. Eight percent never achieved plasma HIV-1 RNA levels below 200 copies/mL and 32% did not have their plasma HIV-1 RNA levels assessed in 2014. Women, African-Americans, Hispanics, and those between the ages of 13 years and 24 years were less likely to achieve durable

virologic suppression than men, non-Hispanic whites, and those aged 55 years and older, respectively. These data suggest that the current continuum of care outcome measure, which relies on a single plasma HIV-1 RNA assessment, overestimates durable viral suppression by approximately 20%.

Data from 9 clinics participating in the CDC HOPS (HIV Outpatient Study) examined the opposite side of virologic dynamics (Abstract 32). Because most cases of HIV-1 transmission occur when the plasma HIV-1 RNA level is greater than 1500 copies/mL, time spent with plasma HIV-1 RNA levels greater than 1500 copies/mL represents a period of transmission risk and failure of treatment as prevention goals. Among 5873 persons followed up for a median of 5.4 years between 2000 and 2014, the percentage of person-time with plasma HIV-1 RNA greater than 1500 copies/mL decreased from 37% in 2000 to 10% in 2014 ($P < .01$). A percentage of person-time above 1500 copies/mL was also statistically significant when associated with persons aged 35 years and under and those between 35 years and 49 years than with those people aged 50 years and older, those having public insurance, and those of non-Hispanic black race compared with white. These results show encouraging trends in rates of virologic suppression over time in the United States, which may decrease the risk of HIV transmission.

Hermans and colleagues (Abstract 113) explored the risk of antiretroviral treatment failure after low-level viremia in an observational cohort of 132,782 South African people living with HIV infection and receiving treatment in 57 clinics in urban and rural settings. The researchers found that among 69,454 individuals on an initial NNRTI-based antiretroviral therapy, low-level viremia, defined as plasma HIV-1 RNA levels between 51 and 999 copies/mL, occurred in 12% of persons per year, or approximately 20% overall. The presence of low-level viremia had a statistically significant association with virologic failure, defined as 2 plasma HIV-1 RNA level measurements above 1000 copies/mL. In a stratified analysis, higher degrees of low-level viremia were associated with a greater hazard of virologic failure: those with 400 to 999 copies/mL had a hazard ratio (HR) of 5.7 (95% CI, 5.1-6.4); 200 to 399 copies/mL was associated with an HR of 3.8 (95% CI, 3.4-4.2), and 51 to 199 copies/mL was associated with an HR of 2.2 (95% CI, 2.0-2.4), compared with those whose HIV-1 RNA levels were continuously below 50 copies/mL. Even those who had low-level viremia but then had resuppression to below 50 copies/mL were still at a statistically significant increased risk of virologic failure. The investigators concluded that ongoing viral replication is a predictor of future virologic failure, and that the World Health Organization (WHO) threshold of 1000 copies/mL likely fails to identify those at high risk for virologic failure.

Strategies to Improve the HIV Care Continuum for Key Populations

Barnabas (Abstract 107) addressed the challenges of achieving engagement in all stages of the care continuum for priority populations. She first reminded the audience that vulnerability is highly context specific, and that priority populations should be defined by high regional HIV prevalence or incidence rather than by specific behavioral characteristics. For example, individuals who use injection drugs who use safe injection practices are not considered vulnerable. Achieving 90-90-90 targets is more difficult in marginalized populations because they face additional barriers of criminalization, stigma, and discrimination. These barriers are reflected in disparities in antiretroviral therapy coverage for individuals who use injection drugs, sex workers, and men who have sex with men (MSM), and in virologic suppression for postpartum women and youth. Barnabas suggested that strategies to improve the HIV care continuum for these populations must begin with involving members of the key populations and decentralizing services, simplifying treatment protocols, and integrating them with other services, such as safe injection, opioid substitution treatment, and tuberculosis treatment. The following abstracts highlight some of these successful strategies.

Postpartum Women and Infants. Two abstracts described successful strategies for engaging postpartum women and infants in care. Myer and colleagues (Abstract 24) randomly assigned 472 consecutive HIV-infected mother-infant pairs to an integrated maternal and child health service offering antiretroviral therapy for the duration of breastfeeding (intervention), or to separate adult antiretroviral treatment services and routine well baby services (local standard of care; control). Among 234 mothers in the control arm, 56% met the criteria for the combined primary outcome of maternal retention in care and viral suppression to plasma HIV-1 RNA levels below 50 copies/mL at 12 months postpartum. In the intervention arm, 77% of 234 women met the criteria for the primary outcome, for an absolute risk difference between intervention and control of 21% (95% CI, 12-30%; $P < .001$). The duration of exclusive breastfeeding was also longer in the intervention arm at a median of 3.0 months, compared with 1.4 months in the control arm ($P = .001$). The cumulative risk of mother-to-child transmission over 12 months was less than 1% and did not show a statistically significant difference between the 2 study arms. Thus, the integration of antiretroviral therapy services into a comprehensive postnatal maternal-child health platform, rather than separate services for mothers and infants, may improve engagement in care and treatment outcomes.

Integration of postpartum care with HIV treatment for mothers and rapid diagnostic testing for infants lead to improvements in engagement in care for women and children.

Jani and colleagues (Abstract 26) conducted a cluster randomized trial to assess the impact of point-of-care (POC) diagnostic testing for infants aged 4 weeks to 6 weeks. They

compared POC testing to standard of care testing using dried blood spot samples, which are sent to reference laboratories. Initiation of antiretroviral therapy within 2 months of diagnostic testing was accomplished in 89.7% of 2034 infants in the POC arm and 12.8% of infants in the standard-of-care arm ($P < .0001$). Retention in care also improved in the POC testing arm (61.6%) compared with the standard-of-care arm (42.9%; adjusted risk ratio [aRR], 1.4; 95% CI, 1.1-1.9). The investigators proposed that adoption of POC protocols for early infant testing can promote earlier antiretroviral initiation and retention in care and may contribute to achieving UNAIDS 90-90-90 targets for pediatric populations.

Adolescents and Young Adults. Adolescents and young adults are increasingly a focus of HIV care continuum interventions, because of high HIV incidence and increased risk of treatment failure in these populations. One themed discussion (Abstracts 835-838) highlighted several innovative strategies to improve UNAIDS 90-90-90 target outcomes in these key populations. Reif and colleagues evaluated a model of community cohort care in which adolescents and young adults newly diagnosed with HIV infection were consecutively enrolled in cohorts of 6 to 8 peers stratified by age (aged 10 years to 14 years, and 15 years to 20 years) (Abstract 835). The cohorts received care through monthly meetings in a community building separate from the clinic, where counseling, clinical management, and antiretroviral therapy distribution are all provided by the same nurse and caregiver each month. Fifty adolescents enrolled in this cohort were compared with a historical control group of 462 adolescents aged 13 years to 19 years who received individual care in an adolescent HIV clinic. The 12-month retention in care was 86% among those in the community cohort care, compared with 66% in the historical control cohort ($P < .001$). The community cohort care participants also reported decreased stigma, increased social support, and higher acceptance of the care model, but this was not compared directly with data from the historical control group. These data suggest that community cohort care deserves further study as a novel method to reach and engage newly diagnosed youth living with HIV infection.

Brown and colleagues (Abstract 836) examined the impact of having peers living with HIV infection on retention in care and virologic suppression for women aged 15 years to 24 years enrolled in the SEARCH (Sustainable East Africa Research in Community Health) trial. SEARCH is a test-and-treat trial that conducted a baseline census of all residents in 3 rural Kenyan communities between September 2013 and January 2014, including a detailed social network of all participants. The investigators examined retention in care, defined as not more than 90 days late to a scheduled clinic visit, and virologic suppression, defined as plasma HIV-1 RNA levels below 400 copies/mL. They found that women with social contact also living with HIV infection in any domain of their social network were more likely to be retained in care (adjusted HR [aHR], 2.63; 95% CI, 1.10-4.31) than those without social contacts living with HIV infection. Women retained in care were also more likely to achieve virologic suppression if they had a social contact living with HIV infection (adjusted odds ratio [aOR], 3.2; 95% CI, 1.1-9.8). These data suggest that strengthening social networks among young women living with HIV infection may help improve engagement at various stages in the HIV care continuum.

The IeDEA (International Epidemiologic Databases to Evaluate AIDS) collaboration examined loss to follow-up for younger adolescents aged 10 years to 14 years, older adolescents aged 15 years to 19 years, and adults aged 20 years and older at 33 participating health facilities in Kenya, Uganda, and Tanzania (Abstract 837). Loss to follow-up was defined as no clinic visit in 3 months and was statistically significantly higher for older adolescents (45%) than for younger adolescents (27%) and adults (31%). Among older adolescents, pregnant women had the highest risk of loss to follow-up (HR, 1.56; 95% CI, 1.39-1.76) compared with men, but nonpregnant women (HR, 1.36; 95% CI, 1.23-1.49) and women of unknown pregnancy status (HR, 1.28; 95% CI, 1.10-1.48) were also at higher risk than men. Recent enrollment status (2012-2014) was correlated with loss to follow-up risk across all age categories. The authors highlighted the role of pregnancy status in predicting engagement in care, but all youth require specific efforts.

Zanoni and colleagues (Abstract 838) provided one of the few bright spots regarding HIV care continuum outcomes in adolescents. Using data from CFAR CNICS (Center for AIDS Research Network of Integrated Clinical Systems), the investigators demonstrated that although those aged 18 years to 24 years had statistically significantly higher rates of current substance use and lacked health insurance compared with adults aged 50 years and older, they did not have decreased risk of retention in care or viral suppression.

Immigrants. Two presentations examined HIV care continuum outcomes for immigrant populations. Marukutira and colleagues (Abstract 1017) examined noncitizen immigrants in Botswana's Combination Prevention Project (BCPP), and found that 3% of the 48,640 people assessed for HIV serostatus within this cluster randomized trial were noncitizens. Noncitizens were more likely to be unaware of their HIV serostatus than citizens (63% vs 16%; $P < .001$). Of those aware of their serostatus, noncitizens were less likely than citizens to be receiving antiretroviral therapy (29% vs 71%; $P < .001$). The investigators suggested that Botswana's current policy of not providing antiretroviral therapy to noncitizens could limit the country's ability to achieve the UNAIDS 90-90-90 targets

Ross and colleagues (Abstract 1016) explored the same question in a different context, using electronic medical record data to examine care continuum outcomes data for undocumented immigrants receiving care in the Bronx, New York. They devised an algorithm to determine undocumented status using missing or invalid social security numbers and insurance status, and validated it with manual medical record review. They found small but statistically significant increases in the rates of retention in care, prescription of antiretroviral therapy, and virologic suppression in undocumented individuals compared with those with valid social security numbers.

These investigators suggested that providing services to undocumented people living with HIV infection would improve the overall HIV care continuum in those areas.

Innovative Interventions to Improve the HIV Care Continuum

Many presentations at the 2017 CROI covered novel, often multidomain interventions to address the HIV care continuum. A plenary session by Daskalakis (Abstract 108) offered an overview of the New York City (NYC) Department of Health and Mental Hygiene's "End the Epidemic" strategy. The current NYC care continuum data show that 94% of people living with HIV infection in NYC are diagnosed, 86% are retained in care, 82% receive antiretroviral therapy, and 74% are virologically suppressed. The "End the Epidemic" campaign is adopting various strategies to simultaneously improve the HIV care continuum and increase HIV prevention efforts throughout the city. The city's Sexually Transmitted Diseases clinics are being reconfigured into Sexual Health clinics, with expanded hours, HPV-related services such as colposcopy, and quick-start contraceptives for women. The clinics will also serve as locations where persons can receive immediate antiretroviral therapy or preexposure prophylaxis (PrEP) treatment initiation and navigation to longitudinal care. Other interventions include working closely with community-based organizations and pharmacies to facilitate rapid access to medications, and supporting antiretroviral treatment services with behavioral and housing support services, directly observed therapy, and financial incentives. Finally, Daskalakis proposed a "status-neutral model," where HIV prevention and care services are linked, and HIV testing leads to treatment engagement or prevention engagement, all of which are integrated. Implementation of the comprehensive "End the Epidemic" campaign began in the fall of 2016, and the data will be much anticipated.

Lester (Abstract 106) gave an overview of mobile technology and the evidence behind its supportive use for adherence to antiretroviral therapy, by first pointing out that cell phones have become so ubiquitous that more people globally have access to them than toothbrushes or flush toilets. Simple text messaging has become the most used data service in the world, representing an affordable and innovative opportunity for adherence intervention. Lester emphasized that using texts for one-way communication, such as adherence reminders, is less effective in randomized controlled trials. Based on the available evidence, optimization of mobile technology adherence support should include 2-way interaction, content written in simple language to avoid issues with disclosing personal health information, and weekly messaging. Lester also emphasized the need for long-term data and the challenges of phone turnover.

Lamb and colleagues (Abstract 110) incorporated support from text messaging into a cluster randomized trial of a combined intervention strategy to improve engagement and linkage to care in 10 clinics in Mozambique. The intervention included same-day CD4+ cell count assessment, point of diagnosis antiretroviral therapy counseling, and fast-track treatment initiation. Participants received text messages regarding health and appointment reminders to encourage linkage and retention, and a subset within the intervention arm received financial incentives in the form of prepaid cell phone cards. This was compared with standard of care using routine CD4+ testing with results in 2 to 4 weeks and separate counseling visits. The primary outcome of linkage to HIV care within 1 month of diagnosis and retention 12 months after diagnosis was more common in the intervention arm (relative risk [RR], 1.6; 95% CI, 1.5-1.8) than in the arm that received standard of care, but did not differ between those in the intervention arm who received financial incentives or not. The increases in linkage were greatest when individuals were linked to care on the day of diagnosis. Also, receiving care at any clinic, rather than just the clinic of diagnosis, substantially improved estimated linkage and retention. The benefits of rapid linkage to care are clear in this study, but 30% of participants still were not linked or retained at any clinic. The notable absence of any impact from the financial incentives deserves further investigation.

The I-Care Trial in South Africa (Abstract 111) compared 2 interventions with a standard-of-care model. The 2 interventions were an automated text message appointment reminder system, including 2-way check-in messages, health promotion messages, and peer navigation, with an emphasis on social modeling. Eighteen clinics were randomly assigned to 1 of the 3 study arms, and the primary outcome was retention in care, defined as at least 4 visits within 12 months for individuals receiving antiretroviral therapy and 2 visits in 12 months for individuals prior to initiating antiretroviral treatment. Participants in the peer navigation arm were more likely to be engaged in care after 12 months (odds ratio [OR], 1.83; 95% CI, 1.01-3.33) than participants in the standard-of-care arm, a difference primarily driven by retention in women. Retention in care was not statistically different between the automated text reminder system and standard of care. The investigators speculate that the personalized attention from the peer navigators is valuable, but emphasize the challenges of bringing such an intensive intervention to scale.

Rapid treatment initiation and peer navigators were both effective interventions to improve engagement and retention in care.

Mallewa and colleagues presented data from the REALITY 2x2x2 factorial open-label randomized trial (Abstract 117), which enrolled adults and children over 5 years of age with CD4+ cell counts below 100/μL who were initiating antiretroviral treatment. Participants were enrolled into standard of care (n = 908) or provision of 12 weeks of Ready-to-Use Supplementary Food (RUSF), which provided 1000 kcal/day with multivitamin and mineral supplementation (n = 897). The primary endpoint was mortality at 24 weeks. No difference between the RUSF and the standard-of-care arms was seen, and no statistically significant differences were seen in

CD4+ cell count gain or virologic suppression. Statistically significant gains in body mass index were observed (an additional 0.3 kg/m^2 in the RUSF arm at 12 weeks; P = .004) and mid-upper arm circumference (P = .03). This represents the first randomized trial of food supplementation that compared no supplementation with RUSF.

Data from the first 3 years of the HIV Prevention Trials Network 071 "PopART" Trial (Abstracts 1010 and 1011) examined the impact of a universal testing and treatment strategy using community HIV care providers to offer home-based rapid HIV testing and linkage to existing government health services. The intervention was delivered in annual rounds in 4 communities in Zambia between November 2013 and October 2016. Investigators reported UNAIDS 90-90-90 target results from the first 2 annual screening rounds, which reached 45,616 households, representing 95% of the target communities. At the end of the second round, 90% of women and 78% of men were aware of their HIV diagnosis. Of those known to be living with HIV infection, 78% of men and 79% women were receiving antiretroviral therapy. Antiretroviral therapy uptake did not vary by sex, but did increase with age: from 41% among those aged 18 years to 24 years to 82% among those aged 55 years or older. These data highlight that annual community-wide home-based testing and linkage to care, within existing governmental treatment programs, can be an effective strategy to achieve UNAIDS 90-90-90 targets, but that additional outreach for testing in men and care engagement for youth may be needed.

HIV Treatment Strategies and Outcomes

Treatment Strategies in Neonates

Obimbo provided an overview of the challenges and opportunities in treating infants living with HIV infection (Abstract 103). Gaps in the HIV care continuum for children living with HIV infection in Kenya, where only 45% of such children are diagnosed, were highlighted. Once diagnosed, the majority (91%) receive antiretroviral therapy, but only 63% of those on antiretroviral therapy achieve virologic suppression. Challenges for addressing HIV infection in neonates and infants include few available drugs, poor palatability, nonadherence, lack of fixed-dose combinations, changing pharmacokinetics associated with rapid growth, and the need for cold-chain storage. Current strategies to address these challenges include ongoing studies of lopinavir/ritonavir pellets, which seem to be well tolerated for infants already weaned from breastfeeding; raltegravir oral granules for neonates; and nevirapine. Novel interventions are needed to combat the high attrition and poor rates of virologic response in infants newly diagnosed with HIV infection.

Two studies focused on the impact of early treatment of neonates and infants. Kuhn (Abstract 27) presented data from the LEOPARD (Latency and Early Neonatal Provision of Antiretroviral Drugs) clinical trial, which is a nonrandomized trial of early neonatal diagnosis and rapid initiation of antiretroviral therapy. This analysis examined virologic response up to 48 weeks for 30 infants who were diagnosed with HIV infection at birth and initiated antiretroviral therapy within 48 hours of birth. There was wide variation in virologic response to treatment. Eight treated infants had persistently high plasma HIV-1 RNA levels, 6 had levels below limits of detection but then had rebound, and 13 had levels that declined to below limits of detection or target not detected of the assay. Three infants whose levels were below the limit of detection were HIV seronegative on HIV polymerase chain reaction (PCR) testing, and had rapid declines in plasma HIV-1 RNA after treatment initiation. Of 3 deaths in the cohort, all had plasma HIV-1 RNA levels above 100,000 copies/mL at birth. The investigators highlighted the many clinical and social challenges inherent in engaging and treating neonates, and will continue to follow the cohort to determine if reversion to PCR-negative status is a common phenomenon.

Veldsman and colleagues (Abstract 28) examined HIV-1 RNA and DNA acquired from PCR testing in 11 infants for whom treatment was initiated between 0 and 8 days of life, and found 10 of them had rapidly suppressed viral replication to below the limits of detection for most assays. This poses a diagnostic challenge for the detection of HIV persistence on antiretroviral therapy and to avoid misdiagnosis in uninfected infants.

Challenges in Antiretroviral Treatment for Adults

The "Modern ART" symposium, which concluded the conference, provided a data-driven overview of current challenges in antiretroviral treatment.

Arribas reviewed data on the potential for simplification of antiretroviral therapy (Abstract 148). The impact of archived resistance must be considered when switching from antiretroviral regimens that have a high genetic barrier to acquired drug resistance to regimens with a low barrier. However, in settings where individuals whose therapy has not previously failed and risk of archived resistance is low, simplification of regimens is possible. Duration of suppressive therapy may also affect the ability to switch to a simpler regimen. Higher rates of virologic failure and drug resistance were seen with switches from traditional protease inhibitor plus nRTI 3-drug regimens to protease inhibitor plus InSTI or protease inhibitor plus entry inhibitor 2-drug regimens. The only successful simplification trial, the GARDEL (Global AntiRetroviral Design Encompassing Lopinavir/r and Lamivudine vs LPV/r based standard therapy) study, showed equivalent rates of virologic response in those treated with lopinavir/ritonavir plus lamivudine 2-drug regimen and those treated with lopinavir/ritonavir plus 2 nRTIs. Similar challenges are seen in trials involving reductions in drug regimens in individuals who are virologically suppressed, and the only successful trials involve simplification of treatment to lamivudine plus a boosted protease inhibitor. Arribas noted that we do not truly understand the mechanism underlying the success of lamivudine plus a boosted protease inhibitor-based regimen. Newer simplification strategies with 2-drug regimens, including dolutegravir plus lamivudine or rilpivirine, show promising preliminary

results, and newer antiretroviral agents may provide more hope for monotherapy in the future.

Grinsztejn (Abstract 149) summarized requirements for an ideal antiretroviral treatment regimen to address the continuing global HIV epidemic. Improved regimens are needed for treatment of special populations with HIV infection, including those with tuberculosis coinfection, pregnant women, children, adolescents, those with acute infection, and older people. Encouraging improvements in regimen efficacy, safety, tolerability, and convenience raise the question of whether new antiretroviral regimens are needed. However, the rising prevalence of pretreatment drug resistance, described in Gupta's talk (see below), as well as the need for improved treatments for special populations suggest that we need better treatment strategies and new drugs. The recent inclusion of dolutegravir into national treatment guidelines in Botswana, Brazil, Kenya, Nigeria, and Uganda signal upcoming changes in treatment access in low- and middle-income countries. But issues of global affordability of antiretroviral treatment will remain for countries like China, where generic antiretroviral drugs are less available.

Finally, Grinsztejn demonstrated the impact of nonmedical barriers on antiretroviral treatment uptake by showing unpublished data from Pozniak and Hill that demonstrate a strong correlation between a country's global peace index score and the percentage of people in that country living with HIV infection on antiretroviral therapy. Even in the setting of newer, simplified, more tolerable, and affordable treatment options, the ideal regimen can only be delivered if structural barriers to treatment are addressed.

HIV Resistance

Increasing Prevalence of Drug Resistance Mutations in Low- and Middle-Income Countries

Gupta (Abstract 146) presented an overview of the impact of HIV-1 drug resistance in low- and middle-income countries, including unpublished data assessing the impact of pretreatment (transmitted) HIV drug resistance. Investigators assumed that current prevalence of pretreatment drug resistance is 10%, and modeling demonstrated that 16% of AIDS-related deaths, 9% of new infections, and 8% of antiretroviral treatment costs could be attributable to drug resistance. He reviewed the rising prevalence in sub-Saharan Africa of tenofovir resistance, now exceeding 50% in those whose tenofovir-based initial therapy failed. Data also show that 15% of individuals whose initial regimens with tenofovir failed also had thymidine analogue-associated mutations (TAMs), which suggest they may have had prior treatment unknown to their clinicians. Gupta advocates the use of the WHO early warning indicators for HIV-1 drug resistance and the need for routine surveillance for drug resistance, considering the increasing prevalence of pretreatment drug resistance in low- and middle-income countries. The following studies support this recommendation.

Routine surveillance for drug resistance is needed given the increasing prevalence of pretreatment drug resistance in low- and middle-income countries.

Pretreatment Drug Resistance

The Caribbean region has the second-highest HIV prevalence in the world but surveillance for drug resistance mutations in this area is limited. In an analysis of pretreatment drug resistance in Aruba (Abstract 504LB), 54% (n = 104) of all newly diagnosed persons had baseline resistance testing between 2010 and 2015 prior to antiretroviral therapy initiation. Rates of pretreatment drug resistance with any mutation among those tested was high at 33%, with prevalence of NNRTI mutations at 32%, all of which were K103N mutations. Prevalence of nRTI and protease inhibitor mutations was low (1.9% each). By 2015, prevalence of K103N was 45%. Phylogenetic analysis identified 4 clusters with K103N-associated resistance, 3 of which had epidemiologic links to neighboring countries. These results led to replacement of the WHO-recommended initial regimen of an NNRTI-based regimen with an InSTI-based regimen and reinforcement of the importance of baseline resistance testing.

From 2012 to 2016, pretreatment drug resistance among antiretroviral therapy–naive persons was evaluated in individuals recruited from 3 regions in Mexico (Tijuana, n = 668; Central Metropolitan Zone [CMZ], n = 1194; and Cancun n = 773) (Abstract 480). Pretreatment drug resistance varied by region with rates of 4.6% in Tijuana, 16.8% in the CMZ, and 15.0% in Cancun. The most widely used antiretroviral regimen in Mexico is efavirenz with tenofovir and emtricitabine. Pretreatment resistance to drugs in this regimen increased over time from 2.9% to 9.6% ($P = .0045$). K103N was the most frequent drug resistance mutation in CMZ (4.4%) and Cancun (4.2%) but not Tijuana (1.4%). However, pretreatment resistance to efavirenz increased in all 3 regions over time ($P < .05$). This study highlights the importance of regional surveillance of drug resistance mutations to accurately track the epidemic and tailor policy responses according to regional needs.

Pretreatment Drug Resistance and Effects on Viral Outcomes

Derache (Abstracts 43, 491) presented data on the prevalence and impact of pretreatment drug resistance on viral suppression in antiretroviral therapy–naive participants starting initial antiretroviral therapy in the ANRS 12249 TasP (Treatment as Prevention) study in Kwazulu-Natal, South Africa. In this cluster randomized trial of 1337 participants, prevalence of pretreatment drug resistance was 9% for the majority (>20% of the viral population) and 18% for the minority (>2% of the viral population) variants, with no difference in rates of

pretreatment drug resistance between those with recent versus chronic infection. A majority of those with pretreatment drug resistance had NNRTI mutations (73% and 61% of those with pretreatment drug resistance detected as minority and majority variants, respectively), most of which were K103N mutations. There were very low levels of nRTI mutations (mostly TAM and M184V) and even lower levels of protease inhibitor resistance mutations. Among individuals with pretreatment drug resistance, 78% had 1 resistance-associated mutation, 11% had 2, and 11% had 3 or more. Of the 837 individuals who initiated antiretroviral therapy for whom viral load outcome data were available, median time to viral suppression (HIV-1 RNA level < 50 copies/mL) was 3.61 months with a median duration of antiretroviral therapy of 1.36 years. There was a high cumulative probability of suppression by 12 months at 94.5% (95% CI, 92.7-96.0) and no difference in time to viral suppression or probability of viral suppression between those with and without pretreatment drug resistance, regardless of detection as majority or minority variants. In persons with pretreatment drug resistance, low baseline HIV-1 viral load and good adherence were predictors of viral suppression. The authors concluded that achievement and short-term durability of viral suppression despite the presence of pretreatment NNRTI resistance may be due to the ability of tenofovir with emtricitabine to suppress virus. However, the time period on antiretroviral therapy was relatively short at 18 months, and the possibility of viral breakthrough and perpetuation of pretreatment drug resistance warrants further investigation.

Drug Resistance Mutations in Antiretroviral Treatment–Naive and –Experienced Individuals

AFRICOS is a prospective cohort study of 253 adults in Uganda, Kenya, Tanzania, and Nigeria, between 2013 and 2015, who had baseline resistance testing. Participants were evaluated in a cross-sectional analysis of drug resistance mutations (Abstract 481). Seventy-four percent were antiretroviral therapy–naive and 26% were antiretroviral therapy–experienced. Prevalence of pretreatment resistance was 5% in antiretroviral therapy–naive individuals, with the majority due to K103N mutations (4.3%). In antiretroviral therapy–experienced individuals, there were high rates of resistance: 65% with NNRTI resistance, 45% with nRTI resistance, and 6% with protease inhibitor resistance. Rates of resistance with K103N and K65R mutations were 33.8% and 10.8%, respectively. There was regional variation in rates of resistance but the small sample size limits the ability to generalize findings to broader populations.

The first nationally representative study of pretreatment resistance in Cameroon was presented by Tchouwa and colleagues (Abstract 482). Participants were recruited between February 2015 and July 2015 from 24 clinics in randomly selected rural and urban regions. Of the 335 persons who had successful genotype testing, 10% had previous exposure to antiretroviral therapy. The overall rate of drug resistance mutations was 9.7%, with 13.3% in urban regions and 4.1% in rural regions. In antiretroviral therapy–naive individuals, the rate of pretreatment drug resistance was 9.8% with higher rates in urban areas (12.9%) than in rural (5.1%) areas. Ninety-three percent of major drug resistance mutations were NNRTI-associated mutations, which indicates that about 10% of individuals who start initial antiretroviral therapy in Cameroon are receiving 2 instead of 3 effective agents to treat HIV infection, increasing their risk for virologic failure and emergence of additional mutations.

Drug Resistance Mutations in Antiretroviral Therapy–Experienced Individuals

In a study of acquired HIV-1 drug resistance in Cameroon, participants who had been on antiretroviral therapy for 12 to 24 months (ADR1 group; n = 1065) or 48 to 60 months (ADR2 group; n = 391) were recruited between February and August 2015 (Abstract 486). Resistance testing was conducted on specimens from individuals who had an HIV viral load of 1000 copies/mL or higher. A majority of participants were on a regimen of efavirenz or nevirapine with tenofovir and lamivudine (80% of ADR1 and 73% of ADR2 participants) followed by efavirenz or nevirapine with zidovudine and lamivudine (17% of ADR1 and 20% of ADR2 participants) with only 2% of ADR1 and 6% of ADR2 participants on a protease inhibitor–based regimen. Viral suppression was 72% for ADR1 individuals and 67% for ADR2 individuals, and overall prevalence of drug resistance mutations was 10% and 12%, respectively. Prevalence of any resistance mutation in persons with virologic failure (HIV RNA level ≥1000 copies/mL) was 63% and 88%, and prevalence of NNRTI-related mutations was 62% and 88% in ADR1 and ADR2 persons, respectively. The authors noted that substantial efforts will be required to achieve the UNAIDS target of 90% viral suppression in Cameroon by 2020. Improved antiretroviral therapy management and retention in care are needed, along with preventing antiretroviral therapy shortages and increasing access to viral load testing to guide antiretroviral therapy selection.

A nationwide study of Kenyans with suspected secondary antiretroviral therapy failure was conducted to estimate the need for additional options (Abstract 488). Of the 123 participants who had a successful genotype performed, 96.7% were on secondary antiretroviral therapy (ritonavir-boosted lopinavir). Median duration of treatment was 6.4 years and median duration of secondary treatment was 3.1 years. Twenty-five percent of individuals had complete loss of drug activity to available initial (NNRTI-based) and secondary (boosted protease inhibitor-based) regimens. The authors concluded there is a need for routine viral load testing for timely detection of treatment failure and access to affordable additional regimens.

Effectiveness and Cost-Effectiveness of Policy Options Address High Prevalence of Drug Resistance

Phillips and colleagues (Oral Abstract 112) modeled the effectiveness and cost-effectiveness of policy options to address increasing rates of NNRTI-associated resistance in sub-Saharan

Africa. Policy options included no change in policy, baseline resistance testing, and switch from efavirenz to dolutegravir for individuals starting antiretroviral therapy or for those currently on efavirenz as part of an initial regimen. The model was an individual-based simulation model of HIV infection transmission and the effect of antiretroviral therapy that considered drug profiles (eg, medication-specific tolerability, risk of emergence of resistance) and used data on HIV infection and demographics from sub-Saharan Africa. A cost-effectiveness analysis used a 3% per annum discount rate and a cost-effectiveness threshold of $500 per disability-adjusted life year (DALY) averted. Costs of all HIV testing and care were included with pricing of antiretroviral drugs at $38, $44, and $213 for efavirenz, dolutegravir, and atazanavir boosted with ritonavir, respectively, and $100 annually for resistance testing. In settings with prevalence of NNRTI resistance above 10%, the option to transition all persons on initial efavirenz to dolutegravir, including those with viral suppression on an efavirenz-based regimen, provided the greatest cost savings and was the most beneficial in averting more DALYs. This remained the optimal choice even when the prevalence of NNRTI resistance was less than 5%, making a transition from efavirenz to dolutegravir an appealing alternative regardless of NNRTI-resistance prevalence.

A modeling study based on the South African epidemic (Abstract 489) also found that switching to an initial dolutegravir-based regimen from an NNRTI-based one was more effective than the introduction of resistance testing. This study predicted that a switch to dolutegravir-based regimens as initial treatments would reduce the annual incidence of HIV infection by two-thirds and decrease transmitted drug resistance to less than 5% of new infections per year by 2030. The model predicts that introduction of resistance testing would also decrease annual HIV incidence by one-half and would increase K103N mutations, but to a lesser degree than current policy.

Epidemiology of Drug Resistance Mutations in High-Income Countries

HIV InSTI Resistance. Hernandez and colleagues (Abstract 478) conducted an analysis of InSTI resistance among individuals with baseline (collected ≤ 3 months after HIV diagnosis) and follow-up (collected > 3 months after HIV diagnosis) InSTI resistance testing. The individuals were diagnosed with HIV-1 infection between 2010 and 2014 and reported to the US National HIV Surveillance System (NHSS). In a convenience sample of 9 jurisdictions, 14,468 met inclusion criteria. InSTI-associated resistance was rare with an overall prevalence of 0.4% and a baseline prevalence of 0.04%. The most prevalent InSTI-associated mutations were N155H (38%), E92Q (29%), and G140S (25%). These data show that current InSTI-based regimens are effective, and the authors recommend ongoing monitoring of resistance testing and drug resistance mutations at the population level.

A decline in prevalence of drug resistance mutations was noted among 3681 antiretroviral-experienced participants enrolled in the University of North Carolina Center for AIDS Research Clinical cohort between 2000 and 2015 (Abstract 483). Prevalence and trends of drug resistance mutations from 2000 to 2015 were calculated. Resistance to any drug class and to 2 or more drug classes increased as did nRTI and NNRTI resistance between 2000 and 2005 but subsequently decreased. Protease inhibitor resistance and resistance to 3 or more drug classes remained stable between 2000 and 2005 but subsequently decreased, and InSTI resistance increased slightly between 2009 and 2015. For those initiating antiretroviral therapy between 2007 and 2015, prevalence of resistance to any drug class, NNRTI, nRTI, protease inhibitor, or InSTI was 21%, 17%, 6%, 2%, and 1%, respectively.

Koullias and colleagues (Abstract 493) conducted a cost-effectiveness analysis for baseline InSTI resistance testing for persons living in high-income settings. Using a decision-tree model of antiretroviral therapy–naive persons who presented for baseline laboratory testing, input parameters included antiretroviral therapy efficacy, quality of life, and costs of laboratory tests and treatment. Costs of the InSTI test ($250/test), dolutegravir-based antiretroviral therapy ($38,150/year), and boosted darunavir-based antiretroviral therapy ($44,400/year) were included. An incremental cost-effectiveness ratio of less than $100,000/quality-adjusted life year (QALY) was considered cost-effective. In univariate sensitivity analysis, testing for InSTI resistance at baseline was never clinically preferred regardless of InSTI resistance prevalence, even up to 100% prevalence. In multivariate sensitivity analysis with the prevalence of an InSTI pretreatment drug resistance of 0.1%, baseline testing for InSTI resistance also resulted in equivalent or worse clinical outcomes and at a higher cost than no InSTI resistance testing even at high rates of dolutegravir failure with InSTI resistance (< 17% suppression). These data do not support baseline InSTI resistance testing.

In the United States, rates of InSTI resistance are low and the test for pretreatment drug resistance is not cost-effective.

Protease Inhibitor Resistance. An analysis of participants who had completed a phase II or III clinical trial in which they received once-daily boosted darunavir showed that emergence of resistance was rare (Abstract 505). Among a total of 1686 participants, 11% (n = 184) had protocol-defined virologic failure and 182 had genotype testing for resistance at the time of failure. Only 4 of these participants had treatment-emergent protease inhibitor resistance and/or darunavir resistance–associated mutations, and only 1 lost phenotypic susceptibility to darunavir. Among 264 subjects treated with darunavir monotherapy, 34 were evaluated for resistance and only 1 had darunavir resistance mutations during treatment (L33F mutation). This study confirms the high genetic barrier to resistance of once-daily boosted darunavir.

Evolution of Resistance and Novel Resistance Mutations

Dolutegravir Monotherapy. Blanco presented a retrospective analysis of virologic outcomes in persons switched from multidrug antiretroviral therapy to dolutegravir monotherapy (Abstract 42). The 122 individuals analyzed were enrolled in 1 of 3 large international cohorts (MVZ Karlsplatz, Munich, Germany; Clinique Medicale Actuel, Montreal, Canada; Hospital Clinic, Barcelona, Spain), had suppressed HIV-1 RNA (< 50 copies/mL) at the time of switch, and had no preexisting InSTI resistance mutations. Eleven (9%) experienced virologic failure (2 consecutive HIV-1 viral loads > 50 copies/mL), of whom 9 (82%) had InSTI resistance mutations. Median time to virologic failure was 20 weeks (interquartile range [IQR], 11-28 weeks) and median time from virologic failure to emergence of InSTI resistance was 5 weeks (IQR, 3-14 weeks). In the 9 participants who experienced virologic failure on dolutegravir monotherapy, resistance patterns and pathways varied. This study, in addition to a randomized trial of dolutegravir monotherapy (Abstract 451LB), confirms that dolutegravir monotherapy is not to be recommended.

Dolutegravir monotherapy is not recommended due to high rates of virologic failure and development of resistance.

Development of Dolutegravir Resistance in an Adherent Antiretroviral Therapy–Naive Individual. Flucher and colleagues (Abstract 500LB) presented a case report of a 45-year-old man newly diagnosed with HIV infection and *Pneumocystis jirovecii* pneumonia with a high baseline viral load (1,970,000 copies/mL) and no clinically significant NNRTI or nRTI resistance mutations. Pretreatment InSTI resistance testing was not conducted. He was started on dolutegravir and tenofovir with emtricitabine and despite excellent adherence, developed virologic failure with rapid evolution of InSTI resistance culminating in a Q148K mutation (preceded by G163E, I151V, and I151M mutations). The emergence of resistance mutations was identified through sequential paired and deep sequencing analysis at 3 time points over the course of 8 days. This is the first report of dolutegravir resistance in a treatment-naive individual and indicates this is a rare but clearly important clinical phenomenon.

Archived Quasispecies with InSTI Resistance. In an interesting study of archived HIV quasispecies in individuals successfully treated with a dolutegravir-based regimen, emerging resistance mutations to dolutegravir were documented in the proviral DNA of persons despite successful viral suppression (Abstract 495). Four treatment groups were evaluated: antiretroviral therapy–naive persons initiating dolutegravir-based regimens with primary HIV infection (group 1), or chronic HIV infection (group 2), and individuals on non–dolutegravir-based antiretroviral therapy who transitioned to a dolutegravir-based regimen in the setting of viral suppression (group 3) or as a result of virologic failure (group 4). Peripheral blood mononuclear cells (PBMCs) were collected at baseline and at weeks 4, 24, and 48, and proviral DNA was analyzed for integrase gene mutations. Despite achievement or maintenance of HIV-1 RNA levels below 50 copies/mL between weeks 4 and 48, InSTI mutations that were not present at baseline emerged in the proviral DNA in 5 of the 20 participants. These mutations included R263K and M50I, which are associated with resistance to dolutegravir and bictegravir. Viral diversity also transiently decreased even in individuals who were virally suppressed for more than a decade on other treatment regimens. The results suggest that archived quasispecies continue to evolve with antiretroviral therapy. The authors have several hypotheses regarding the results: new variants were selected directly in the blood compartment through residual replication in the setting of antiretroviral therapy; the variants were not new but might preexist at very low levels; and variants were selected at very low levels in other reservoirs because of insufficient antiretroviral penetration in those compartments.

Novel InSTI Resistance Mutations. Hachiya and colleagues (Abstract 496) identified a novel combination InSTI mutation, L74F/V75I, which conferred resistance to first-generation InSTIs and enhanced resistance to second-generation InSTIs, when combined with a major InSTI mutation. The researchers obtained clinical HIV-1 isolates from an individual whose raltegravir-based regimen had failed and who had no InSTI resistance mutations on standard InSTI genotype testing. Sequencing of the integrase region of the clinical isolates identified clinically suspected resistance mutations (L74F, V75I, I60M, and V72I). These mutations were introduced into the integrase region of an HIV-1 DNA clone and drug susceptibility assays were conducted on the recombinant virus. The combination of L74F/V75I increased resistance to raltegravir and elvitegravir; the combination of L74F/V75I with N155H and G140S/148H enhanced resistance to dolutegravir and cabotegravir. The location of the L74 and V75 residues suggest an indirect structural impact of L74F/V75I on the catalytic center of integrase. The authors concluded that these insights help explain the superior resistance profiles of second-generation InSTIs and provide additional data to guide design of future InSTIs.

Malet and colleagues (Abstract 499) also identified novel InSTI resistance mutations that are located outside of the integrase gene. A virus highly resistant to dolutegravir was selected in vitro by adding high constant concentration of dolutegravir after virus integration. Sequence analysis of this virus showed no mutation in the integrase gene but 5 mutations in the nef region. In drug susceptibility assays, these mutations conferred high resistance to dolutegravir, raltegravir, and elvitegravir. The mechanism through which these mutations cause resistance is unclear.

Novel Tenofovir Resistance Mutations in Low- and Middle-Income Settings. The use of TDF in low- and middle-income countries is increasing but data on TDF-associated drug

resistance mutations associated with nRTI failure in these settings is limited. Rhee and colleagues (Abstract 485) identified TDF regimen–associated mutations (TRAMs) by comparing the proportion of reverse transcriptase mutations in 2873 persons from low- and middle-income settings failing a WHO-recommended initial TDF-containing regimen to the proportion of reverse transcriptase mutations in a cohort of 50,803 antiretroviral therapy-naive individuals. To identify TRAMs specifically associated with TDF selection pressure, the proportion of TRAMs in persons whose TDF-containing regimen failed was compared with the proportion of these mutations found in 5085 persons with virologic failure on an initial thymidine analogue regimen. A total of 83 TRAMs were identified including 33 nRTI-associated TRAMs, 13 of which were more common in individuals receiving TDF than thymidine analogue-containing regimens. The most common of the TDF-associated mutations were K65R (40%), S68G/N (21%), Y115F (12%), K70/E/Q/T (11%), A62V (10%), and L74I (6%). Given the expansion of TDF use in these settings, the frequency of these novel TDF-associated mutations should be monitored and further evaluated to determine which may be clinically significant.

Protease Inhibitor Resistance. It has been hypothesized that mutations in the HIV-1 gag matrix or the cytoplasmic domain of gp41 reduce susceptibility to protease inhibitors but these mutations have not been consistently identified in individuals on boosted protease inhibitors with virologic failure. Manasa and colleagues (Abstract 506) evaluated whether these mutations would emerge in individuals whose boosted protease inhibitor regimens failed. The entire gag and gp41 regions were sequenced in individuals before and after boosted protease inhibitor treatment failure, and gag and gp41 sequence changes were compared with changes in a control group who failed an NNRTI-based regimen. The researchers found many mutations in the gag matrix and gp41, but no discernable difference in the mutations between the protease inhibitor and NNRTI groups.

Drug Resistance Mutations in Investigational Antiretroviral Drugs

Dapivirine, rilpivirine, and MIV-150 (a phenyl ethyl thiazole thiourea analogue) are being evaluated as agents in preexposure prophylaxis (PrEP). To characterize the resistance and cross-resistance profiles of these drugs, Giacobbi and colleagues (Abstract 501) studied their in vitro susceptibility to NNRTI resistance mutations spanning 17 codons. Rilpivirine had the best profile with activity against 19 of the 28 variants. Dapivirine and MIV-150 were each active against 15 of the 28 variants. Drug susceptibility with the G190A mutation was unchanged for all 3 agents and rilpivirine showed no resistance with K103N and Y181C mutations and low-level resistance associated with K101E. Dapivirine and MIV-150, however, exhibited decreased susceptibility with K101E, Y181C, and K103N mutations. MIV-150 exhibited high resistance with K103N and intermediate resistance with Y181C. Future studies should evaluate the clinical impact these mutations have on the efficacy of these drugs for PrEP and their use in settings with a high prevalence of NNRTI resistance.

Bictegravir is an investigational InSTI that has excellent efficacy and tolerability in clinical trials. Ragonnet-Cronin compared drug resistance susceptibility and dissociation kinetics of bictegravir with that of other InSTIs in the presence of G140S/Q148H resistance mutations (Abstract 497). In vitro phenotype testing showed bictegravir had better activity against G140S/Q148H mutants than dolutegravir, raltegravir, and elvitegravir. Bictegravir also had a longer dissociation half-life from wild-type complexes than dolutegravir, raltegravir, and elvitegravir and a longer disassociation half-life from G140S/Q148H mutant complexes than dolutegravir only (raltegravir and elvitegravir did not bind efficiently enough to make a comparison). Long dissociation times have been correlated with potent antiretroviral activity and a high barrier to resistance. These findings support the promising in vitro and clinical trial data that bictegravir has demonstrated thus far.

Prevention of Mother-to-Child Transmission

Through programs such as "Option B+" and "Treat All," access to antiretroviral therapy has greatly expanded for HIV-infected women prior to pregnancy. In utero exposure from conception to 3-drug antiretroviral therapy, however, has an increased risk of adverse birth outcomes. It is unclear whether these outcomes vary by antiretroviral regimen. Zash and colleagues described 2-year interim results from the Tsepamo study in Botswana that compared rates of adverse birth outcomes by exposure from conception to the 5 most common antiretroviral regimens (Abstract 25). Data were extracted from all consecutive births of infants (at least 24 months gestational age) at 8 maternity wards in Botswana. The analysis included 5780 births from 2014 to 2016 that had exposure to antiretroviral therapy from conception. The most common regimens were TDF, emtricitabine, and efavirenz (43%); TDF, emtricitabine, and nevirapine (13%); zidovudine, lamivudine, nevirapine (24%); TDF, emtricitabine, and ritonavir-boosted lopinavir (4%); and zidovudine, lamivudine, and ritonavir-boosted lopinavir (3%). Outcomes included stillbirth, neonatal death (defined as in-hospital mortality < 28 days), preterm birth (< 37 weeks gestational age), very preterm birth (< 32 weeks gestational age), small for gestational age (< 10th percentile weight), and very small for gestational age (< 3rd percentile weight). The combined endpoint of any adverse birth outcome was defined as having stillbirth, neonatal death, preterm birth, or small for gestational age, whereas severe birth outcome was defined as having stillbirth, neonatal death, very preterm birth, or very small for gestational age. After adjusting for maternal age, educational level, and gravida, exposure to TDF/emtricitabine/efavirenz had a lower adjusted risk ratio of combined total and severe adverse birth outcomes than the 4 other regimens. When added to the model, CD4+ cell count did not attenuate the findings. The authors recommended further investigation into mechanisms

to explain high rates of adverse birth outcomes associated with specific antiretroviral regimens.

The pharmacokinetics and safety of antiretroviral drugs and monoclonal antibodies for perinatal mother-to-child transmission (MTCT) of HIV infection were covered in a themed poster session. Schalkwijk and colleagues (Abstract 753) simulated fetal exposure of darunavir/ritonavir at term by incorporating bidirectional placental antiretroviral transfer in a previously validated physiologically-based pharmacokinetic (p-PBPK) model of pregnancy. Placental drug transfer parameters were based on an ex vivo, human cotyledon perfusion model. The simulated fetal darunavir plasma concentrations were within the range of observed cord blood concentrations of the drug in vivo. The authors concluded that these findings support the use of this model for evaluating implications of new drug dosing schedules and enhancing maternal and fetal antiretroviral treatment strategies.

Schalkwijk and colleagues presented pharmacokinetic data of rilpivirine used during pregnancy from an open-label multicenter phase IV study of antiretroviral agents in HIV-1 -infected pregnant women in Europe (PANNA [Pharmacokinetics of newly developed ANtiretroviral agents in HIV-infected pregNAnt women] Network) (Abstract 754). In this study, 16 women received rilpivirine 25 mg once daily (taken with food) as part of their antiretroviral regimen during pregnancy. The women also underwent intensive, steady-state, 24-hour pharmacokinetic testing in the third trimester and postpartum periods. In addition, whenever possible, cord blood and matching maternal blood specimens obtained at delivery were used to measure placental transfer of rilpivirine. Maternal HIV viral load was undetectable (< 50 copies/mL) near the time of delivery in all 16 women. HIV infection was not detected based on DNA PCR in 15 of 16 (96%) infants, with 1 infant's infection being unknown. There were no reports of birth defects or serious adverse events attributable to rilpivirine. The geometric mean ratios (90% CI) for the third trimester and postpartum were as follows: 0.55 (0.46-0.66) for AUC at 24 hours (AUC_{24}), 0.65 (0.55-0.76) for maximum plasma concentration (C_{max}), and 0.47 (0.38-0.58) for predose concentration (C_{0h}). Subtheraputic C_{0h} levels in the third trimester, defined as 0.04 mg/L or less, were found in 2 women, whereas no subtherapeutic levels were detected postpartum. Among 5 individuals with available data, the median (range) ratio of cord blood to maternal plasma rilpivirine concentrations was 0.5 (0.35-0.81). Based on these results, the authors recommended therapeutic drug monitoring in the third trimester to avoid subtherapeutic levels of rilpivirine.

Best and colleagues presented pharmacokinetic data of elvitegravir/cobicistat in pregnancy and postpartum (Abstract 755) from the ongoing IMPAACT (International Maternal Pediatric Adolescent AIDS Clinical Trials Network) P1026s pharmacokinetics and safety study of antiretroviral drugs in HIV-infected pregnant women. The study collected intensive, steady-state, 24-hour pharmacokinetic profiles of elvitegravir and cobicistat dosed at 150 mg and 150 mg once daily, respectively, during the second and third trimesters of pregnancy and 6 weeks to 12 weeks postpartum. In addition, infant washout samples after delivery were examined in infants with birth weight of more than 1000 grams who had no severe malformations or medical conditions. A total of 29 women were enrolled, with pharmokinetic data available for 16 women in the second trimester, 20 women in the third trimester, and 15 women in the postpartum period. Washout sample data were available for 16 infants. HIV RNA level was undetectable (< 50 copies/mL) for 14 of 19 women (74%); 20 of 26 infants (77%) tested HIV seronegative with data for 6 infants indeterminate or pending to date. Two infants experienced congenital malformations (1 with microcephaly, amniotic band syndrome, and intrauterine growth restriction, and 1 with ulnar postaxial polydactyly). The researchers found lower exposure and higher clearance of elvitegravir and cobicistat in the second and third trimesters than in the postpartum period. In infants, the median IQR for half-life of elvitegravir was 7.4 hours (5.9-8.8), similar to that in postpartum women and control groups of nonpregnant adults. Cobicistat was not detected in any of the infant washout samples. The authors cautioned that more pharmacokinetic, safety, and outcome data of elvitegravir and cobicistat in HIV-infected pregnant women are needed before its use during pregnancy can be endorsed.

Balogun and colleagues examined the effect of protease inhibitor–based antiretroviral therapy on estradiol (E2) levels in pregnancy and whether E2 levels are associated with adverse birth outcomes (Abstract 756). In a prospective cohort study of 96 HIV-infected pregnant women in Canada, plasma samples at early (12 weeks-18 weeks), mid (24 weeks-28 weeks), and late (34 weeks-38 weeks) gestation were collected from the following groups: 55 women on protease inhibitor–based antiretroviral therapy; 8 women on protease inhibitor–sparing regimens; and a matched control group of 49 women who were HIV-uninfected.

Maternal and cord plasma specimens were collected. In addition to E2, sex hormone binding globulin (SHBG), and dehydroepiandrosterone sulfate (DHEAS, an E2 precursor) were measured. The researchers found a significant increase in E2 plasma levels from mid to late gestation and at delivery in the women on protease inhibitor–based antiretroviral therapy. This association was not detected in women on protease inhibitor–sparing regimens or in the control group. Similarly, cord E2, DHEAS, and index levels of E2 and SHBG were significantly higher in women on protease inhibitor–based antiretroviral therapy than in the matched uninfected controls. Furthermore, E2 and DHEAS levels in cord plasma were positively correlated ($r = 0.06$; $P < .0001$) in women on protease inhibitor–based antiretroviral therapy. An inverse correlation between cord E2 levels and fetal growth restriction (measured by birth weight percentile) was found in women on protease inhibitor–based antiretroviral therapy ($r = -0.47$); this association was not detected in women with protease inhibitor–sparing regimens and in women in the control group.

Clarke and colleagues presented a dose-finding, pharmacokinetic, and safety study of raltegravir in HIV-1-exposed neonates during the first 6 weeks of life (Abstract 757). Twenty-six HIV-1–exposed neonates were enrolled in cohort 2 in the IMPAACT P1110 study. They were naive to raltegravir

and received the following dosing regimen: 1.5 mg/kg daily within 48 hours of life through day 7, followed by 3 mg/kg twice daily on days 8 to 28, and 6 mg/kg twice daily thereafter. Pharmacokinetic and 6-week safety data were available for analysis for 25 infants. Following the first dose at 1.5 mg/kg daily, the geometric mean (GM) AUC_{24} for raltegravir was 38.2 mg*h/L, and the trough concentration (C_{trough}) was 948 ng/mL (target trough >33 ng/mL). During treatment with 3 mg/kg of raltegravir twice daily during days 15 to 18, the GM AUC at 12 hours (AUC_{12}) was 14.3 mg*h/L and C_{trough} was 176.1 ng/mL. There were no reports of adverse events related to raltegravir and no infants were found to be HIV-infected. The researchers concluded that daily treatment with raltegravir was safe and well tolerated through the first 6 weeks of life, and that the data support the raltegravir dosing schedule outlined in the study in infants.

Bekker and colleagues presented pharmacokinetic and safety data of nevirapine prophylaxis in 40 HIV-exposed infants with low birth weight (<2500 g) in South Africa as part of the IMPAACT P1106 study (Abstract 758). The infants received nevirapine 2 mg/kg once daily from birth to 14 days of age, followed by 4 mg/kg once daily. Mean birth weight was 1675 g (range, 950 g-2460 g). Pharmacokinetic samples were collected at study enrollment and at 4, 6, 10, 16, and 24 weeks of age. Of 27 infants with available nevirapine C_{trough} levels (representing 94 observations), mean C_{trough} of nevirapine across all study visits was 1.87 µg/mL (range, <0.02-10.69 nevirapine g/mL). In 6/94 (6%) observations, nevirapine trough concentrations were below 0.1 µg/mL, which is the target prophylaxis C_{trough}. All samples below target levels were from later visits when the infants had been discharged to home and were receiving nevirapine from a caregiver. At the first visit, higher C_{trough} of nevirapine was associated with lower gestational age ($r = -0.47$; $P = .02$), whereas subsequent drug concentrations over the study period decreased with increasing postnatal age across all visits ($r = -0.45$; $P < .001$). No adverse events were attributable to nevirapine.

Anugulruengkitt and colleagues examined safety and drug concentrations in 94 high-risk HIV-exposed neonates receiving antiretroviral prophylaxis with zidovudine/lamivudine/nevirapine for 6 weeks after birth in a prospective cohort study in Thailand (Abstract 759). Thirty-one neonates received zidovudine and lamivudine twice daily for 6 weeks, and nevirapine 4 mg/kg once daily for 6 weeks. This group of 31 infants was compared with 63 infants who received zidovudine for 4 weeks. The investigators found no significant difference in rates of adverse events, anemia, neutropenia, and elevations in transaminase levels between the 2 groups. All infants were HIV-uninfected at age 4 months. Of 18 infants with available data, high plasma concentrations of nevirapine were achieved at weeks 1, 2, and 4 (GM concentrations of 3075, 2109, and 1438 ng/mL, respectively); all infants achieved nevirapine concentrations above 100 ng/mL during the first 4 weeks.

Cunningham and colleagues reported the safety and pharmacokinetic results of VRC01, an HIV-neutralizing monoclonal antibody, in 27 HIV-exposed newborns (Abstract 760). In the ongoing, prospective, multicenter, open-label study, 27 HIV-exposed infants at high risk of HIV transmission received a single 20 mg/kg (low dose) or 40 mg/kg (high dose) subcutaneous dose of VRC01 (13 in the low-dose group vs 14 in the high-dose group) within 72 hours of birth. All infants also received antiretroviral prophylaxis to prevent MTCT according to local standard-of-care guidelines. Safety data were presented for 27 infants, whereas pharmacokinetic data were presented for 13 of the 14 infants in the high-dose group and 12 of the 13 infants in the low-dose group. VRC01 was well tolerated with no serious systemic reactions. Local reactions (ie, erythema, induration, bruising, edema) were present in 6 infants (46%) in the low-dose group and 11 infants (75%) in the high-dose group; the local reactions were not considered serious and most resolved within 4 hours of injection. The pharmacokinetic data for the low-dose group showed circulating VRC01 through day 28 that was close to but below the target in 9 of the 12 infants (75%). Mean concentration after 28 days (C_{28d}) in infants receiving the 20 mg/kg dose was 39.33 mcg/mL, whereas mean C_{28d} in infants receiving the 40 mg/kg dose was 75.22 mcg/mL. The mean half-life of VRC01 at the 20 mg/kg dose was 19.73 days. The authors concluded that the half-life of VRC01 allows for administration on a monthly basis for infants who are at risk for HIV transmission through breastfeeding.

The half-life of VRC01 monoclonal antibodies allows for monthly administration for infants at risk for HIV transmission through breastfeeding.

Zika Virus

The outbreak of Zika virus in 2015 to 2016 prompted a themed discussion that featured presentations on the persistence of Zika RNA in bodily fluids, a promising novel messenger RNA (mRNA) Zika vaccine, an animal model of neurologic consequences of Zika virus, and laboratory testing patterns for the virus in the United States (Abstracts 1054, 1055LB, 1056LB, 1057LB). (A summary of the presentation of Zika RNA in bodily fluids [Abstract 1055LB] appears in the "Basic Science Review" by Dr Stephenson.)

Hogan and colleagues presented data on a novel Zika virus vaccine using an mRNA platform (Abstract 1057LB). The researchers have developed a nucleoside-modified, purified mRNA-lipid nanoprotein (LNP) vaccine that encodes for Zika surface proteins and efficiently elicits neutralizing antibody responses. A single low-dose immunization in mice and rhesus macaques delivered high and sustained neutralizing antibody responses and complete protection from Zika virus weeks to months after vaccination. This is a promising vaccine candidate as it appears to require only a single, low-dose immunization. The mRNA-LNP platform has a favorable safety profile and lends itself to manufacturing scalability and rapid vaccine development for diverse pathogens.

Mavigner and colleagues (Abstract 1056LB) discussed the neurologic changes in the brain and spinal cord in rhesus macaques that were postnatally infected with Zika virus. Questions remain concerning the effects of Zika infection during infancy. Viral loads in the plasma and tissues (including spleen, lymph nodes, brain, and spinal cord) were measured by quantitative polymerase chain reaction (qPCR). The animals also underwent neuroimaging including structural T1-weighted magnetic resonance imaging (MRI), resting-state functional connectivity (rs-fc) MRI, and diffusion tensor imaging (DTI). Zika virus was not detected in the urine, saliva, or cerebrospinal fluid (CSF) of these animals postmortem. In 33% of animals, Zika RNA was detected within the brain (frontal, parietal, and occipital cortices) and the spinal cord (cauda equina). Neuroimaging also showed changes with brain atrophy, decreases in rs-fc, and abnormal white matter connections using DTI. These results suggest that postnatal Zika infection can cross the blood brain barrier into the central nervous system and cause both structural and functional changes.

Volpe and colleagues (Abstract 1054) presented an analysis of 11,129 Zika virus test results obtained in the United States from June 2016 to September 2016. Ninety-four percent of nucleic acid tests were negative, 3% were positive, and 3% were discordant between urine and serum. Not surprisingly, there was significant regional variation in testing, with 48% of tests coming from Florida with a positivity rate of 2%. Montana and Rhode Island sent only 1 test each during that time and had a positivity rate of 100%.

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Additional Suggested Readings

Wensing AM, Calvez V, Gunthard HF, et al. 2017 update of the drug resistance mutations in HIV-1. *Top Antivir Med*. 2017;24(4):132-133.

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