CROI 2014: Advances in Antiretroviral Therapy

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The 2014 Conference on Retroviruses and Opportunistic Infections (CROI) highlighted important advances in antiretroviral therapy, with an emphasis on HIV eradication strategies. Follow-up information about the Mississippi baby who remains free of HIV infection off antiretroviral therapy was presented, and a second baby and 1 adult may also have been cured with very early initiation of antiretroviral therapy. The HIV care cascade was again a major focus of the conference. Investigators from around the world presented data on the implementation, and limitations, of the care cascade paradigm. Scale-up of antiretroviral therapy continues and a number of presentations featured optimal ways to measure the impact of these efforts by applying lessons from implementation science and health care economics. Encouraging results from expanded prevention of mother-to-child transmission programs, especially Option B+, were highlighted. Extensive data on transmitted (primary) drug resistance in the United States and Europe were presented.

Keywords: cascade of care, CROI 2014, cure, HIV, resource limited, treatment

Clinical Studies Investigating HIV-1 Cure

Persaud and colleagues presented further data on the Mississippi child thought to be cured of HIV infection and a second baby with a possible cure (Abstract 75LB) at the 2014 Conference on Retroviruses and Opportunistic Infections (CROI), held from March 3 to 6, 2014. The Mississippi child has been described previously.[1] This child remains off antiretroviral therapy with undetectable plasma HIV-1 RNA through 41 months of age (23 months after stopping antiretroviral therapy). Trace levels of HIV-1 DNA remain in peripheral blood mononuclear cells (PBMCs), but no replication-competent virus could be found and no HIV-1 DNA could be identified in PBMCs with the sensitive droplet digital polymerase chain reaction (PCR) assay. HIV-specific cellular and humoral responses are not detectable.

The investigators also reported on a second baby who was born to a mother who did not receive prenatal antiretroviral therapy. The baby started combination antiretroviral therapy at 4 hours of life. The baby had detectable HIV-1 DNA in the peripheral blood at 4 hours of life and detectable plasma HIV-1 RNA (217 copies/mL) at 36 hours. Plasma HIV-1 RNA was undetectable by day 11 and has remained undetectable through 9 months. HIV-1 DNA was undetectable at day 6 by droplet digital PCR and has remained undetectable. HIV-1 RNA was detected at day 6 in cerebrospinal fluid obtained from a lumbar puncture during evaluation for possible sepsis. No replication-competent virus was recovered at 1, 3, and 9 months of life. Noninduced proviral genomes were detected by droplet digital PCR in stimulated T cells at 1 month, but not at 3 months or 9 months. HIV antibody status was indeterminate at 3 months and negative at 9 months. The infant remains on combination antiretroviral therapy in contrast to the Mississippi child who has remained off antiretroviral therapy. Planned clinical trials will try to replicate these observations in other infants.

Hatano and colleagues presented data on an adult who started tenofovir/emtricitabine for preexposure prophylaxis (PrEP) and was subsequently found to have had low-level plasma HIV-1 RNA at the time of PrEP initiation (Abstract 397LB). This patient was intensified to a standard 3-drug antiretroviral regimen. Two additional measurements after PrEP initiation showed detectable plasma HIV-1 RNA. All assays for HIV-1 DNA were negative. A plasma HIV outgrowth assay was negative for inducible viruses. An HIV Western blot was initially indeterminate and subsequently became negative. A treatment interruption is planned after 1 year of antiretroviral therapy.

Treatment Intensification With or Without Therapeutic HIV-1 Vaccination

Murphy and colleagues presented data on ERAMUNE-02, a pilot clinical trial that investigated whether intensification of suppressive antiretroviral therapy with maraviroc/raltegravir with or without therapeutic HIV-1 vaccination would decrease the HIV-1 latent reservoir as assessed by measuring HIV-1 DNA levels (Abstract 422). All participants underwent intensified antiretroviral therapy with maraviroc/raltegravir at baseline for 8 weeks; participants were then randomized to continue either intensified antiretroviral therapy alone (n = 14) or with therapeutic HIV-1

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vaccination (3 doses of DNA prime vaccine followed by recombinant adenovirus-5 vaccine; n = 14). Neither strategy achieved the goal of reducing HIV-1 DNA levels by at least 0.5 $\log_{10}$ copies/mL at 1 year postrandomization in at least 2 participants. Only 1 participant in the intensification alone group achieved this goal. Similarly, no change was observed in HIV-1 DNA levels in rectal biopsy tissue.

Predictors of Residual Viremia

Residual viremia (ie, viremia detected using a plasma HIV RNA assay with a sensitivity of < 1 copy/mL) has been proposed as a measure of the HIV-1 latent reservoir. Riddler and colleagues investigated predictors of residual viremia in patients with long-term suppression on antiretroviral therapy (Abstract 425LB). They examined 334 patients who maintained virologic suppression for 4 years after initiating antiretroviral therapy. They analyzed 2 plasma samples obtained approximately 4 years after antiretroviral therapy initiation using a single copy assay. Consistent with prior studies, residual viremia (plasma HIV RNA level ≥1 copy/mL) was predicted by higher pretreatment plasma HIV-1 RNA level. They also found that higher on-treatment CD8+ cell counts and lower on-treatment CD4+/CD8+ cell count ratios were predictive of detectable residual viremia, even when controlling for pretreatment plasma HIV-1 RNA levels.

Vorinostat

Prior single-dose studies of vorinostat suggested that this histone deacetylase inhibitor reactivates latent HIV-1 in vivo. Margolis and colleagues examined 5 participants who received vorinostat for 4 cycles (where 1 cycle is defined as 3 daily doses followed by 4 days off), followed by 4 weeks to 8 weeks off therapy, followed by another 4 cycles. They found that in contrast to single-dose studies of vorinostat, repeated doses did not appreciably increase histone deacetylase inhibition from baseline and expression of cellular HIV-1 RNA was not increased. These results do not support further studies of vorinostat for HIV-1 cure strategies.

Investigational Antiretroviral Therapy Agents

Entry Inhibitors

Kattenhorn and colleagues presented preclinical data on eCD4-Ig, an enhanced CD4-immunoglobulin (Ig) fusion protein consisting of the first 2 N-terminal domains of the CD4 molecule and the Fc region of human IgG1 coupled with a small C-C chemokine receptor type 5 (CCR5)-mimetic sulfopeptide (Abstract 528). This compound neutralized a wide array of viral isolates that were resistant to broadly neutralizing monoclonal antibodies. The investigators noted that this compound is a promising candidate for both the treatment and prevention of HIV-1 infection.

Inhibitors of Vif-APOBEC3 Interactions

Two abstracts presented data on targeting the interaction between APOBEC3G (apoB mRNA editing enzyme, catalytic polypeptide-like 3G; also known as A3G), a cellular cytidine deaminase that restricts HIV replication by inducing G-to-A hypermutation in viral DNA, and Vif (viral infectivity factor), a protein produced by HIV that binds A3G and targets it for proteasomal degradation. Pery and colleagues conducted a high-throughput screen to identify a lead compound that inhibits HIV regulation by increasing A3G activity and freeing it from control by Vif. Bennett and colleagues targeted Vif dimerization, which is a necessary step prior to binding A3G (Abstract 532). They have identified a compound that blocks Vif dimerization and inhibits infection of PBMCs against a broad range of viral isolates.

Clinical Trials of Initial Antiretroviral Therapy

Comparison of Non–Efavirenz-Containing Antiretroviral Regimens

Landovitz and colleagues presented data from AIDS Clinical Trials Group (ACTG) A5257, an open-label clinical trial of 3 non–efavirenz-based antiretroviral regimens (raltegravir, ritonavir-boosted [/r] atazanavir, or darunavir/r, each given with tenofovir/emtricitabine) for initial treatment of HIV-1 infection (Abstract 85). Participants (n = 1809) were randomized 1:1:1 to these 3 arms and began assigned therapy. Using a definition of +/-10%, these 3 regimens were equivalent in terms of virologic efficacy (time to confirmed plasma HIV-1 RNA level > 200 copies/mL). The regimens were not equivalent with regard to the second primary end point of time to change in randomized treatment. Participants randomized to atazanavir/r changed therapy more often than did those randomized to raltegravir or darunavir/r, which were found to be equivalent to each other (16% vs 1% and 5%, respectively). Atazanavir/r discontinuations were due to hyperbilirubinemia (as would be expected) but also to higher rates of gastrointestinal toxicities.

When looking at a preplanned comparison of time to a composite of either primary end point, raltegravir appeared superior to darunavir/r, which was in turn superior to atazanavir/r. Among 295 virologic failures across the study arms, 9 (1.5%), 18 (3%), and 4 (< 1%) participants in the atazanavir, raltegravir, and darunavir arms had treatment-emergent resistance detected during follow-up. Similar to prior studies, no protease resistance was detected at failure. For the raltegravir arm, 17 of 18 had nucleoside analogue reverse transcriptase inhibitor (nRTI) resistance and 11 of 18 had integrase strand transfer inhibitor (INSTI) resistance.

nRTI-Sparing Antiretroviral Therapy

Raffi and colleagues presented data on NEAT 001/ANRS 143 (European AIDS Treatment Network 001/French National Agency for Research on AIDS and Viral Hepatitis 143), a randomized, open-label clinical trial comparing darunavir/r given with tenofovir/emtricitabine or raltegravir for initial treatment of HIV-1 infection (Abstract 84LB). They enrolled 805 participants (88% male). The primary end point was time to virologic

failure or clinical failure (death, or new AIDS or serious non-AIDS event). Raltegravir was found to be noninferior to tenofovir/emtricitabine (17.4% vs 13.7% experienced the primary end point, respectively; difference 3.7%; 95% CI, -1.1%-8.6%). A greater decrease in creatinine clearance was found in the tenofovir/emtricitabine arm, and more treatment-emergent resistance was seen with raltegravir. The investigators concluded that darunavir/r plus raltegravir represents a reasonable, nRTI-sparing choice for first-line antiretroviral therapy.

744 and Rilpivirine

Margolis and colleagues presented data from the LATTE (Long-Acting Antiretroviral Therapy Treatment Enabling) study, a phase II, dose-finding clinical trial of investigational HIV INSTI GSK1265744 (also known as 744) plus 2 nRTIs versus efavirenz plus 2 nRTIs for initial treatment of HIV-1 infection (Abstract 91LB). Participants were randomized to 1 of 3 blinded doses of oral 744 (10 mg, 30 mg, or 60 mg daily) or open-label efavirenz. If their plasma HIV RNA levels were undetectable just before week 24, participants in the 744-containing arms discontinued nRTIs and initiated rilpivirine (25 mg daily). Further data on the efficacy of maintenance therapy with 744 plus rilpivirine are needed to support future clinical trials of injectable, long-acting formulations of these compounds. This trial randomized 243 participants to the 4 arms: 96% were male, 38% nonwhite.

At week 48, 82% of participants receiving 744 had undetectable HIV RNA levels by the US Federal Drug Administration (FDA) snapshot analysis versus 71% of participants receiving efavirenz. The higher failure rate in the efavirenz-containing arms was driven by higher rates of treatment discontinuation due to adverse events. A second analysis limited to those who entered the maintenance phase found similar rates of continued virologic suppression among the 4 arms. 744 appeared safe and well tolerated, although more participants in the 744-containing arms experienced headache. Drug resistance emerged in 1 participant receiving 744 and 1 participant receiving efavirenz. These data are supportive of future trials to evaluate combination injectable formulations of 744 and rilpivirine for initial treatment of HIV-1 infection.

Doravirine

Morales-Ramirez and colleagues presented data from a phase II, dose-finding clinical trial of doravirine (MK-1439), an investigational HIV nonnucleoside analogue reverse transcriptase inhibitor (NNRTI; Abstract 92LB). Participants (n = 208) were randomized to blinded treatment with doravirine (25 mg, 50 mg, 100 mg, or 200 mg once daily) or efavirenz, each given with tenofovir/emtricitabine. The primary end point was achieving plasma HIV-1 RNA levels less than 40 copies/mL at week 24. This ranged from 71% to 80% of participants in the 4 doravirine arms (76% for the 4 arms combined), with no dose-response relationship noted, and 64% in the efavirenz arm. A plasma HIV-1 RNA level less than 200 copies/mL was achieved in 88.5% of participants in the doravirine arms versus 81% in the efavirenz arm. No statistical testing was performed for these comparisons. Doravirine appeared safe and tolerable, and a lower rate of dizziness was observed in the doravirine arms than in the efavirenz arm. The investigators concluded that further studies of doravirine are warranted, and they selected a dose of 100 mg for future studies.

Clinical Trials of Antiretroviral Therapy During Acute HIV-1 Infection

Schuetz and colleagues presented data on the relationship between timing of antiretroviral therapy initiation during acute HIV-1 infection and maintenance of the mucosal barrier (Th17 cells on rectal biopsies) and T-cell activation (CD8+/CD38+/HLA-DR+ [human leukocyte antigen-D–related]; Abstract 77). They enrolled 38 participants who initiated antiretroviral therapy during acute HIV-1 infection and had rectal biopsies and blood sampling before and 6 and 12 months after initiating antiretroviral therapy. They enrolled 5 participants who initiated antiretroviral therapy during chronic HIV-1 infection and 10 HIV-uninfected controls who were sampled at 1 time point.

They found that participants who initiated antiretroviral therapy during Fiebig stage I or II (ie, prior to detectable HIV-1 antibody by enzyme-linked immunosorbent assay [ELISA]) main tained levels of Th17 cells similar to those of HIV-uninfected controls. Participants who initiated antiretroviral therapy during chronic HIV-1 infection had depleted Th17 cells, and participants who initiated therapy during Fiebig stage III (ie, detectable HIV-1 antibody by ELISA, but not by Western blot) had levels in between these groups. Fiebig I/II participants maintained levels of T-cell activation similar to those of HIV-uninfected controls at all time points. Fiebig III participants had increased T-cell activation before therapy compared with Fiebig I/II participants and HIV-uninfected controls, and similar levels at 6 months and 12 months after therapy initiation. This suggests that early initiation of antiretroviral therapy during acute HIV-1 infection prevents disruption of the mucosal barrier and associated T-cell activation.

Chéret and colleagues investigated an intensive 5-drug regimen for antiretroviral therapy during acute HIV-1 infection (Abstract 549LB). They enrolled 90 participants who initiated treatment during acute HIV-1 infection and were randomized to receive darunavir/r plus tenofovir/emtricitabine with or without maraviroc/raltegravir. They found similar decreases in the HIV-1 reservoir as measured by HIV-1 DNA for 2 years in both groups. The rates of virologic suppression were similar at 2 years. Treatment was interrupted after 2 years. One participant in each group maintained virologic suppression after treatment interruption. The investigators concluded that there was no evidence to support intensive antiretroviral regimens for treatment of acute HIV-1 infection.

Maintenance and Switch Strategies

Once-Daily Lopinavir/r Dosing in Children and Adolescents

Lyall presented data on behalf of the KONCERT team (Abstract 74LB). This clinical trial enrolled 173 children (<18 years of age and ≥15 kg in weight) who were receiving twice-daily lopinavir/r and randomized them to continue twice-daily or change to once-daily dosing. Although all children were required to have plasma HIV-1 RNA levels less than 50 copies/mL at screening, 14% of those randomized to once-daily and 5% of those randomized to twice-daily dosing had detectable plasma HIV-1 RNA at trial entry. Once-daily dosing did not achieve noninferiority with regard to virologic suppression 48 weeks after randomization (difference -6%; 90% CI, -2%-14%). Pharmacokinetic analyses showed a lower lopinavir exposure in the once-daily arm. There were no safety concerns or appreciable differences in the emergence of viral resistance. The investigators concluded that once-daily dosing of lopinavir/r in children could not be recommended based on these data.

Ritonavir-Boosted Protease Inhibitor Therapy Alone

Paton and colleagues reported on a large study of simplification to a ritonavir-boosted protease inhibitor (PI/r) alone as maintenance therapy (Abstract 550LB). They randomized 587 participants (77% male, 68% white) who had plasma HIV-1 RNA levels less than 50 copies/mL for at least 6 months and no prior virologic failure to continue current antiretroviral therapy or to change to PI/r alone. Participants were monitored for plasma HIV-1 RNA levels every 3 months. Resistance testing was obtained for participants with confirmed plasma HIV-1 RNA levels of 50 copies/mL or higher. Two nRTIs were added for participants in the PI/r arm if there were confirmed plasma HIV-1 RNA levels at this threshold. The primary end point was loss of future drug options based on resistance testing. As expected, confirmed plasma HIV-1 RNA was more common in the PI/r arm than the continuation arm (35% vs 3%, respectively; $P < .001$); 58% of the PI/r arm remained on PI/r alone through the end of the trial. Resistance was rare in both arms. Loss of future drug options was observed in 6 participants from the PI/r arm and 4 from the continuation arm ($P > .5$). Antiretroviral drug costs were substantially lower in the PI/r arm. The investigators concluded that PI/r alone was a safe and tolerable long-term management strategy for antiretroviral treatment.

Elvitegravir/Cobicistat/Emtricitabine/Tenofovir Maintenance

Two clinical trials examined the efficacy of changing suppressive antiretroviral therapy to fixed-dose elvitegravir/cobicistat/emtricitabine/tenofovir (EVG/COBI/FTC/TDF). Arribas and colleagues presented data on switching from a PI-based regimen to EVG/COBI/FTC/TDF. They randomized 443 participants (86% male, 18% nonwhite) without prior virologic failure or resistance to tenofovir or emtricitabine to continue current antiretroviral therapy or switch to EVG/COBI/FTC/TDF (Abstract 551LB). At 48 weeks postrandomization, 94% of participants in the EVG/COBI/FTC/TDF arm maintained plasma HIV-1 RNA levels less than 50 copies/mL versus 87% in the PI-based arm (difference 6.7%; 95% CI, 0.4%-13.7%; $P = .025$). EVG/COBI/FTC/TDF achieved the primary end point of noninferiority to PI-based regimens and was found to be superior in a secondary analysis. No viral resistance emerged and no safety concerns were found in either group.

Pozniak and colleagues found similar results when enrolling patients receiving an NNRTI-based regimen (Abstract 553LB). They randomized 434 participants (93% male, 22% nonwhite) without prior virologic failure or resistance to tenofovir or emtricitabine to continue current NNRTI plus tenofovir/emtricitabine or switch to EVG/COBI/FTC/TDF. At 48 weeks postrandomization, 93% of participants in the EVG/COBI/FTC/TDF arm maintained plasma HIV-1 RNA levels less than 50 copies/mL versus 88% in the NNRTI-based arm (difference 5.3%; 95% CI, 0.5%-12%), and EVG/COBI/FTC/TDF was found to be noninferior to NNRTI-based regimens. No viral resistance emerged and no safety concerns were found in either group. Based on these 2 studies, changing suppressive antiretroviral therapy to EVG/COBI/FTC/TDF appears to be safe and efficacious in this selected population without prior virologic failure or nRTI resistance.

Clinical Trials in Treatment-Experienced Patients

BMS-663068

BMS-663068, a prodrug of BMS-636529, is an investigational HIV-1 attachment inhibitor that binds envelope glycoprotein gp120 and prevents the binding of HIV to a CD4+ T cell. Lalezari and colleagues presented data on the antiviral efficacy and dose response for this compound versus atazanavir/r in treatment-experienced adults (Abstract 86). This trial randomized 254 adults to 1 of 4 doses of BMS-663068 (400 mg or 800 mg twice daily, 600 mg or 1200 mg daily) or atazanavir/r. Participants randomized to BMS-663068 received monotherapy for 7 days followed by the addition of tenofovir and raltegravir. Monotherapy led to a reduction in plasma HIV-1 RNA levels from 0.7 $\log_{10}$ copies/mL to 1.5 $\log_{10}$ copies/mL. Participants randomized to atazanavir/r initiated combination therapy with tenofovir and raltegravir. Participants in all arms had good virologic suppression at week 24: 69% to 80% achieved plasma HIV-1 RNA levels less than 50 copies/mL, and there were no safety concerns. The investigators concluded that further studies of this compound are warranted.

Clinical Trials to Reduce Immune Activation

Prednisolone

Kasang and colleagues investigated low-dose prednisolone for treatment of

immune activation and prevention of disease progression in untreated HIV-infected adults (Abstract 336). They randomized 336 HIV-infected adults with a CD4+ cell count higher than 300/μL to prednisolone 5 mg daily or placebo, with a 2-year follow-up period for the occurrence of an AIDS-defining event or CD4+ cell count below 200/μL. There was no difference between arms in this end point, but time to a new AIDS-defining condition was longer in the prednisolone arm. They found that prednisolone decreased soluble (s) CD14 levels and increased CD4+ cell counts and CD4+/CD8+ cell count ratios but increased plasma HIV-1 RNA levels. The investigators suggested that this therapy merited further study.

Mesalamine

Samsouk and colleagues investigated the use of mesalamine, a mucosally active antiinflammatory agent, to reduce systemic immune activation by reducing mucosal inflammation and bacterial translocation (Abstract 341). They conducted a randomized, placebo-controlled crossover trial of a once-daily, extended-release formulation of mesalamine. They enrolled 33 (100%) participants with incomplete immune restoration (approximate median CD4+ cell count = 245/μL). They found no effect of mesalamine on systemic or mucosal immune activation as measured by CD8+/CD38+/HLA-DR+ cells in the peripheral blood or on rectal biopsies. Mesalamine did not lead to a reduction in bacterial translocation as measured by sCD14 or in soluble markers of immune activation. The investigators concluded that other strategies are needed to reduce bacterial translocation and systemic immune activation.

Rifaximin

Tenorio and colleagues reported on a randomized, open-label clinical trial of rifaximin, an oral, nonabsorbable antibiotic that reduces plasma lipopolysaccharide (LPS; a marker of bacterial translocation) levels in patients with cirrhosis (Abstract 339). They randomized HIV-infected adults with suboptimal immune reconstitution (CD4+ cell count < 350/μL) despite sustained virologic suppression to receive 4 weeks of open-label rifaximin (n = 49) or no treatment (n = 24). A separate control group of HIV-uninfected adults (n = 20) provided a reference for observed results in the randomized population. They found that the rifaximin group had lower levels of immune activation than the no treatment group at week 4 (end of rifaximin treatment) but not at week 2 (2 weeks into rifaximin treatment) or week 8 (4 weeks after rifaximin treatment). Inconsistent responses were observed with the microbial translocation markers: changes in LPS and sCD14 levels were statistically significantly lower for rifaximin at week 2; no changes were observed at week 4; and changes in sCD14 levels were lower for rifaximin at week 8. Rifaximin was associated with a statistically significant, but minimal, decrease in IL-6 and C-reactive protein (CRP) levels 4 weeks after completion of rifaximin treatment. These data suggest that immune activation may be modifiable through reductions of bacterial translocation. However, the magnitude and durability of this effect were minimal, suggesting that further study of alternative treatments is warranted.

Sevelamer

Sandler and colleagues investigated the use of sevelamer to reduce microbial translocation and immune activation in HIV-infected adults (Abstract 337). Sevelamer is a nonabsorbable polymer that binds phosphate and reduces LPS by 78% in dialysis patients. The investigators enrolled 30 HIV-infected adults who received sevelamer for 8 weeks. They found that LPS and sCD14 levels were not reduced by sevelamer. Levels of low-density lipoprotein (LDL), oxidized LDL, and tissue factor were statistically significantly reduced with sevelamer, but D-dimer levels showed a small, statistically significant increase. Sevelamer did not decrease microbial translocation as hypothesized and whether its effects on LDL and oxidized LDL merit further study is unclear.

Probiotics

Stiksrud and colleagues used a different approach to reduce immune activation (Abstract 342). They attempted to alter the gut microbiota through probiotics to reduce markers of inflammation, coagulation, and microbial translocation that have been associated with all-cause mortality in other studies. The probiotic consisted of fermented skim milk supplemented with *Lactobacillus rhamnosis*, *Bifidobacterium animalis* subsp. *lactis*, and *L. acidophilus*. They enrolled 30 participants and randomized them to the probiotic (n = 14), a placebo of fermented skim milk (n = 8), or a second control of no treatment (n = 8) for 8 weeks. Levels of D-dimer, CRP, and IL-6 declined in the probiotic group but did not change appreciably in the nonprobiotic group (a combination of the placebo and no treatment groups). No change was noted in LPS or sCD14 levels. Further data on gut microbiota and immune activation by flow cytometry are pending. This pilot trial should be followed by larger studies with longer durations of follow-up.

Pharmacokinetic Considerations

Impact of HIV Infection on Intestinal Epithelial Transporters

Bendayan and colleagues investigated the intestinal mucosal expression of drug transport enzymes in HIV-infected adults not on antiretroviral therapy, HIV-infected adults with well-controlled HIV infection, and a matched control group of HIV-uninfected adults (Abstract 103). They found that the transporters studied were expressed at lower levels in HIV-infected adults than in -uninfected controls. These levels were partially restored by antiretroviral therapy. These findings were confirmed by decreased gene expression for these transporters in the HIV-infected groups. This suggests that HIV infection itself may influence drug metabolism.

Rilpivirine and Darunavir/r

Jackson and colleagues presented data on 25 HIV-infected participants initiating a once-daily combination of rilpivirine (25 mg) and darunavir/r (800 mg/100 mg; Abstract 507). They found that rilpivirine concentrations were somewhat higher in this study than in prior phase III studies of rilpivirine given with 2 nRTIs. Darunavir and ritonavir concentrations were not affected. The investigators concluded that this drug combination should be investigated in future studies. Foca and colleagues found differing results when studying HIV-infected young adults and adolescents (Abstract 508). They found that rilpivirine concentrations were similar to those observed in older adults when dosed without darunavir/r, whereas rilpivirine concentrations were threefold higher when coadministered with darunavir/r. The investigators could not conclude whether the higher rilpivirine concentrations observed with darunavir/r coadministration would impact safety and tolerability.

Lopinavir/r and Depot Medroxyprogesterone Acetate

Luque and colleagues presented data on behalf of AIDS Clinical Trials Group protocol A5283 that investigated the effect of lopinavir/r on the pharmacokinetics of depot medroxyprogesterone acetate (MPA; Abstract 514LB). They found that lopinavir/r concentrations were not affected by depot MPA. The MPA concentrations were 46% higher than in historic HIV-uninfected controls from a prior study. Depot MPA appeared safe and well tolerated. There was no evidence of ovulation in the study participants.

Antiretroviral Therapy in Pregnancy

Colber and colleagues investigated changes in darunavir/r pharmacokinetics associated with pregnancy (Abstract 887). They reported on darunavir and ritonavir concentrations observed in 15 HIV-infected pregnant women during the third trimester and at least 2 weeks postpartum. They found that darunavir trough concentrations were 64% lower in the third trimester than postpartum. The investigators noted that twice-daily dosing should be used for treatment-experienced patients during pregnancy.

Lê and colleagues reported data on 103 HIV-infected pregnant women receiving atazanavir/r (Abstract 889). They found that atazanavir concentrations were not substantially altered during pregnancy; drug concentrations were assessed during each trimester, at delivery, and postpartum. The trough concentrations were approximately 30% lower during pregnancy than postpartum, which was not thought to be clinically significant by the investigators. The virologic outcomes were excellent: 97% had plasma HIV RNA levels less than 50 copies/mL at the time of delivery, and no cases of mother-to-child transmission (MTCT) were observed. Atazanavir/r appeared safe in this population. Similar reductions of atazanavir trough concentrations during pregnancy were observed in a separate study of HIV-infected women, and these concentrations were not affected by concomitant use of tenofovir (Abstract 892).

Blonk and colleagues investigated the pharmacokinetics of raltegravir during pregnancy (Abstract 890). They found that trough concentrations were reduced by 50% during the third trimester but thought this reduction unlikely to be clinically significant. They found that raltegravir efficiently crossed the placenta into the fetal circulation.

Examining the HIV Care Cascade in Resource-Limited and Other Settings

The cascade of care for HIV, prominent at CROI 2013, was again popular this year as a metric for examining the effectiveness of HIV treatment programs.[2] Many investigators presented data on the cascade, or alternative constructions of the cascade itself, yet a few common themes emerged. In studies that examine the complete cascade from diagnosis to successful virologic suppression, substantial barriers to diagnosis and linkage to care remain, even in high-prevalence countries with active testing programs. Population mobility is a key challenge because it leads to loss to follow-up at all stages of the cascade and simultaneously contributes to overestimation of loss to follow-up when care transfers are not accounted for. As Bangsberg pointed out while leading the themed discussion Treatment Cascade and Loss to Follow-Up, without direct ascertainment of vital status for those considered lost to follow-up, mortality and transfers of care are vastly underestimated at all steps of the cascade. Despite these issues, the continued focus on the care cascade at CROI 2014 demonstrates the utility of the construct, and some of the key cascade-related findings are reviewed below.

Population-Based Surveillance of the HIV Care Cascade

Maina and colleagues presented data from KAIS (Kenya AIDS Indicator Survey), a countrywide, 2-stage stratified cluster sampling survey of household residents 18 months to 64 years of age from October 2012 and February 2013 (Abstract 149). KAIS offered home-based HIV testing and CD4+ cell count measurement and linkage to care for those diagnosed with HIV infection. Although the percentage of individuals ever tested for HIV infection increased from 34% in 2007 to 70% in 2012, awareness of HIV serostatus among HIV-infected individuals remained low, 47% in 2012. Prevalence in children (0.9%) was lower than that of adults (5.6%), but only 16% of children had ever been tested for HIV infection.

By Kenyan eligibility guidelines for antiretroviral therapy, 58.8% of individuals with HIV infection were eligible for treatment, but only 60.5% of those eligible were receiving treatment. Encouragingly, 75% of those receiving antiretroviral therapy were virologically suppressed to an HIV-1 plasma RNA level less than 1000 copies/mL. These country-level results highlight the fact that even in the setting of dramatic scale-up of testing and treatment, many individuals, particularly

children, are unaware of their HIV serostatus, and the drop-off in the care cascade between eligibility and antiretroviral therapy coverage seen in many other settings was also observed here.

Huerga and colleagues conducted a similar cross-sectional population-based study in Kwazulu Natal, South Africa, a population highly impacted by the HIV epidemic, with an overall HIV prevalence of 25% and women (31%) much more impacted than men (16%; Abstract 152LB). Examining the overall cascade, the investigators found that 75% of HIV-infected participants were aware of their HIV serostatus, 65% were linked to care, 57% had initiated antiretroviral therapy, 52% remained on treatment, and 49% were virologically suppressed. Of those with plasma HIV-1 RNA levels greater than 1000 copies/mL, 72% had antiretroviral drug resistance. Statistically significant sex disparities were seen in incidence, awareness of diagnosis, and antiretroviral therapy coverage, and all of these disparities were higher in women. Thus, in both Kenya and Kwazulu Natal, population-based surveys revealed challenges in diagnosis and linkage to care but good virologic response once antiretroviral therapy was initiated, demonstrating the utility of population-based surveys in directing national public health efforts.

Evaluations of Specific Steps in the HIV Care Cascade and Interventions to Improve Selected Components

Several groups presented data that shed light on specific steps in the HIV care cascade or interventions to improve specific components. Mehta and colleagues (Abstract 1063) examined the HIV care cascade for men who have sex with men (MSM; n = 12,022) and IDUs (n = 14,481) across 26 treatment sites in India. They found that few HIV-seropositive MSM (30%) and IDUs (41%) were aware of their diagnosis, which represents the most substantial barrier to engagement in care along the cascade for these vulnerable populations. Awareness of HIV serostatus was associated with receipt of and linking HIV testing to other services, such as treatment for tuberculosis, STIs, and opioid dependence.

Barnabas and colleagues (Abstract 148) addressed similar barriers of diagnosis and engagement in care with an intervention package in South Africa and Uganda that included community sensitization, household consent for home-based HIV testing, point-of-care CD4+ cell count measurement, referral to care or prevention services for individuals with negative HIV test results, and follow-up visits. They tested 96% of individuals residing in the target communities and achieved excellent results for clinic engagement (96% at 6 months after study visit), for both newly and previously diagnosed individuals with HIV infection. The intervention package appeared to be highly successful, with 65% of HIV-seropositive individuals achieving virologic suppression (up from 50% pre-intervention).

Limitations of the Current HIV Care Cascade and Its Paradigms

McNairy and colleagues (Abstract 151) pointed out limitations of the HIV cascade of care concept: each step is contingent on the prior step; outcomes of people prior to antiretroviral therapy initiation are excluded; there are many reasons for loss between cascade steps; and the time frame for movement between steps is not considered. They proposed a parallel cascade approach to follow up all patients over time and divide them into 3 outcome categories: optimal, retained or transferred to other facilities; suboptimal, retained but without optimal care or missing data; or poor, lost to follow-up or death.

They used routinely collected data from 390,603 adults across 217 facilities in sub-Saharan Africa and calculated the proportion of patients in each of the 3 categories at 3, 6, and 12 months after enrollment in care, but considering the lack of data on virologic control, they adapted cascade steps. They found that 56% of patients had an optimal outcome of care at 12 months: retained in care pre–antiretoviral treatment, on treatment, or transferred. Application of the traditional cascade to the same cohort showed only 23% of patients retained on antiretroviral treatment at 12 months. They proposed that the use of both cascades is inclusive of all patients, before and on antiretroviral therapy, and identifies those at high risk for poor outcomes over time.

Three other groups incorporated similar concepts to examine limitations to the traditional HIV care cascade. Reidy and colleagues (Abstract 1061) ascertained vital status for a subpopulation of patients in care in Kenya before and after initiation of antiretroviral therapy and found that including the additional vital status information decreased percent lost to follow-up pre–antiretroviral therapy from 38% to 12%; increased those labeled as in care from 52% to 75%, owing mostly to clinic transfers; and increased mortality from 10% to 19%. Less dramatic changes after vital status ascertainment were seen for those on antiretroviral therapy, highlighting the limitations of using routinely collected data to assess retention in the care cascade, particularly for pre–antiretroviral therapy patients.

Ahonkhai and colleagues (Abstract 1064) examined unplanned interruptions and return to care along the cascade and found that 37% of patients at a single site in Nigeria had an unplanned care interruption but returned to care at some point during the 3 years of observation. These interruptions were most common in the first year on antiretroviral therapy and at higher baseline CD4+ cell counts. Holmes and colleagues (Abstract 1065) also examined the impact of return to care on the cascade across 18 sites in Zambia. Similar to the results from Nigeria, they found that 35% of the patients classified as lost to follow-up returned to care. They observed negative consequences of these temporary interruptions, including statistically significant decreases in body mass index and CD4+ cell counts and increased rates of active tuberculosis, World Health Organization (WHO) stage III and IV HIV disease, and pregnancy upon return to care.

Data presented at CROI 2014 on the value of the HIV care cascade in other settings support the findings from resource-limited settings. Using data from the US Center for AIDS Research Network of Integrated Clinical Systems (CNICS) sites, Mugavero and colleagues found that incorporating rates of missed clinic visits improved standard prediction models for all-cause mortality that employ a retention-in-care metric of 2 visits per year (Abstract 983). Espinoza and colleagues from the US Centers for Disease Control and Prevention (CDC) found high rates of migration to a different state after diagnosis of HIV infection (11% ever migrated and 2.5% migrated within 1 year of diagnosis), implying that population mobility also impacts the HIV care cascade in non–resource-limited settings.

Antiretroviral Therapy Scale-Up in Resource-Limited Settings

Intersection Between Research, Antiretroviral Therapy Scale-Up, and Policy

Three sessions at this year's conference focused on the translation of research into capacity building, successful scale-up of antiretroviral therapy, and development of policy in resource-limited settings. Mboup (Abstract 18) began the dialogue with the 2014 N'Galy-Mann Lecture. He highlighted the success of the Senegalese HIV prevention and treatment program, which began sentinel surveillance in 1989 and initiated antiretroviral treatment in 1997, well ahead of most other countries in sub-Saharan Africa. He proposed several factors responsible for their early success, including fully engaged political leadership; national programs for control of STIs, such as registration and care for commercial sex workers; a strong strategic information system with early sentinel surveillance programs followed by expanded and ongoing behavioral surveys; and a commitment to research, leading to technology transfer and capacity strengthening through international collaboration.

The specific contributions of research to the Senegalese success story include the early development of a longitudinal cohort of commercial sex workers, established in 1985, which provided a comprehensive platform from which to examine the interaction of the simultaneous HIV-1 and HIV-2 epidemics. This foundation allowed the launch of the Senegalese Antiretroviral Access Initiative (ISAARV) in December 1997. This antiretroviral therapy treatment program was expanded to create a decentralized national system with outstanding results, including high levels of adherence, immune response to antiretroviral therapy, and virologic suppression. ISAARV continues and is now pioneering the use of dried blood spot technology for HIV-1 plasma RNA level assessment and HIV genotype testing. Mboup cited international research collaborations as being instrumental in the expansion of a small virology laboratory into an international reference and research laboratory. These collaborations are ongoing and formalized in programs such as the regional West African Platform for HIV Intervention Research (WAPHIR). Their new and ambitious goal is to establish a center of excellence in Senegal for health research. Mboup presents Senegal as a model for the benefits that early political and academic leadership and successful international partnerships can bring to scale-up efforts.

Okello's presentation (Abstract 118) further supported the need for collaboration between research and scale-up efforts by describing the translation of evidence to policy in Swaziland. Using the WHO framework for evidence-informed policy, she described how specific research findings were translated into policy, tested for impact, and adopted at a national scale. For example, a 2007 nationally representative household survey examined HIV prevalence, convincing many politicians that the high HIV prevalence seen previously in antenatal surveys was real, and a severe and generalized epidemic was present in Swaziland. Evidence from SHIMS (Swaziland HIV Incidence Measurement Survey) in 2012 revealed that 25% of 18- to 49-year-olds with CD4+ cell counts less than 350/μL were not receiving antiretroviral therapy.

After meetings with policy makers and stakeholders, a comprehensive electronic database was deployed to track HIV-infected individuals before starting antiretroviral therapy and increased funding was provided for linkage and retention in care services. This has led to reductions in loss to follow-up, particularly before initiation of antiretroviral therapy. Okello concluded with a strong recommendation that research questions be developed in partnership between researchers and policy makers to better reflect the true needs of the community, rather than the preferences of academic institutions, and balance societal priorities with economic reality.

Finally, Bertozzi (Abstract 120) offered an excellent global perspective on the impact of scale-up on the 10-year anniversary of the President's Emergency Plan for AIDS Relief (PEPFAR) and the Global Fund to Fight AIDS, Tuberculosis and Malaria. He discussed the need for better metrics of success, pointing out the essential flaw in using antiretroviral therapy coverage over time as a measure of success of either of these programs, because the numerator, the number of people living with antiretroviral therapy, accumulates and the denominator includes those without antiretroviral therapy, who are at high risk for death. More appropriate metrics include decreases in HIV incidence in high-prevalence countries, which have occurred across PEPFAR focus and nonfocus countries, and decreases in the number of AIDS-related deaths, which correlate with PEPFAR funding status. Bertozzi cited work by Bendavid and colleagues, presented first at CROI 2012, which demonstrated statistically significant reductions in overall age-adjusted mortality for adults in PEPFAR focus countries versus nonfocus countries.[2]

Bertozzi made a compelling argument that to truly examine the impact of funding for scale-up of antiretroviral therapy requires facility-level data on relevant outcomes, such as the percentage of patients starting antiretroviral

therapy at CD4+ cell counts higher than 200/μL, retained at 12 months, and virologically suppressed. Further, he demonstrated that clinic performance data on costs per patient treated can be highly misleading because receiving treatment without achieving virologic suppression is highly cost-inefficient and instead proposed that clinics be examined by the cost per year per patient retained in care and virologically suppressed. Similar arguments apply to the way performance is assessed for HIV testing and counseling programs. Bertozzi's take home points were that performance must be measured at the clinic or facility level for effective intervention and that metrics must be outcome-focused, rather than coverage-focused, to be relevant to the health of the patient.

The utility of this approach was later highlighted by Geng and colleagues (Abstract 1060), who examined the comparative effectiveness of antiretroviral therapy in HIV care programs in East Africa. Using program-based estimates of mortality derived from an approach to sampling that sought definitive outcomes for a subsample of patients lost to follow-up, they found dramatic differences in mortality by program, 22.5% in Tanzania to 4.9% in Uganda. There is a need for deeper understanding of health care organizations, patients, and communities to ensure the effectiveness of all HIV care programs. These are important insights at a time when international funding streams for HIV prevention and treatment programs are diminishing and thoughts increasingly turn to returns on investment.

Adult Antiretroviral Therapy Outcomes in Resource-Limited Settings

Bärnighausen and colleagues (Abstract 150) presented data regarding the impact of antiretroviral therapy scale-up on life expectancy in a full population cohort of 90,000 individuals in KwaZulu-Natal, a region of South Africa with an HIV prevalence of 30%. Concurrent increases in antiretroviral therapy coverage and adult life expectancy (from 50 years in 2004 to 61 years in 2012) of the entire cohort have been observed, whereas life expectancy for those without HIV infection has remained stable. This implies that life expectancy gains are due to the scale-up of antiretroviral therapy and that a focus on scale-up has not had a negative impact on the health of the HIV-uninfected population. Further examination of these data demonstrates that adult life expectancy increased much more rapidly in women (from 52 years in 2005 to 65 years in 2012) than men (from 48 years to 55 years over the same time frame). Women access antiretroviral therapy at higher rates in KwaZulu-Natal, a difference not fully explained by enrollments in programs for the prevention of mother-to-child transmission (PMTCT). Lower proportions of engagement in care by men appear to be driving the difference in HIV-related deaths, and studies are under way to understand the sex disparity.

A multinational collaboration in Latin America, the Caribbean, Central and South America Network for HIV Epidemiology (CCASAnet), examined predictors of virologic failure of first-line antiretroviral therapy and major regimen change within their network (Abstract 563). Cumulative incidence of virologic failure and major regimen change 5 years after the start of treatment were 27% and 14%, respectively. Younger age (20 years vs 40 years), prior AIDS, initiation of antiretroviral therapy in earlier calendar years, and treatment initiation with PI-based regimens were all associated with virologic failure. Investigators speculated that the lack of a major regimen change in patients with virologic failure might reflect scarcity of second-line antiretroviral therapy options.

Boender and colleagues (Abstract 570) presented data on long-term outcomes of second-line antiretroviral therapy in the setting of antiretroviral resistance from 13 sites in sub-Saharan Africa participating in the prospective, observational PASER (Pan-African Studies to Evaluate Resistance) study. They found that 54% of the 243 patients starting second-line therapy with a boosted PI had a partially active second-line regimen, defined as a genotypic sensitivity score less than 3, but that this was not statistically significantly associated with failure of the second-line regimen at 12 months or 24 months or the subsequent emergence of PI resistance on second-line therapy. At 24 months, only 15% of patients retained in care experienced virologic failure on second-line antiretroviral therapy. Thus, failure rates for both first- and second-line antiretroviral therapy appear to be lower in resource-limited than in non–resource-limited settings or comparable between the two, and many of the predictors of failure (male sex, young age) are similar between the two, implying that strategies should be adapted in both settings to address these higher-risk groups up front.

Strategies for Antiretroviral Therapy in Infants and Children in Resource-Limited Settings

Coovadia and colleagues (Abstract 72) presented data from the NEVEREST (Nevirapine Resistance) 3 study, which enrolled infants exposed to nevirapine for PMTCT, initiated antiretroviral therapy with a lopinavir/r-based regimen until virologic suppression was achieved, and then randomized them to switch to an efavirenz-based regimen or stay on the lopinavir/r-based regimen. They found that overall rates of virologic failure after 48 weeks of follow-up—defined as any measurement of plasma HIV-1 RNA level greater than 50 copies/mL or 2 measurements greater than 1000 copies/mL—were low and did not differ between the 2 arms. The study was designed as a noninferiority trial with a 10% bound, but the efavirenz group had a superior outcome for the greater than 50 copies/mL definition of virologic failure. For children exposed to nevirapine-based PMTCT, transition to efavirenz after successful virologic suppression with a PI appears to be a safe option, and this strategy could be considered in resource-limited settings as it is less costly, is more palatable, and preserves other antiretroviral regimen options.

Three studies examined the impact of antiretroviral therapy initiation in infants. Tejiokem and colleagues (Abstract 923) presented data from an ongoing cohort of 210 HIV-infected children in Cameroon who were diagnosed with plasma HIV-1 RNA and DNA at less than 7 months of age, and 91% of whom started antiretroviral therapy at a median age of 4.1 months. At a median age of 19.1 months, 18% had no detectable HIV antibody by ELISA, demonstrating a high rate of seroreversion in these infants. Of the persistently HIV-seronegative infants (n = 9), they found variable levels of HIV-1 RNA and DNA, indicating variability in the HIV reservoir in these children. Failure to interpret these results correctly could lead to misdiagnosis or discontinuation of treatment in these children, and further studies are needed to determine whether these early-treated infants have the potential for HIV control.

In a relevant study in a non–resource-limited setting, Persaud and colleagues examined the impact of virologic control by 1 year of age on HIV-1 reservoir size in children (Abstract 72). Eligible study participants included those patients from PHACS AMP (Pediatric HIV/AIDS Cohort Study Adolescent Master Protocol) who maintained virologic suppression throughout the study period, defined as no 2 consecutive plasma HIV-1 RNA levels of 400 copies/mL or greater. Children who achieved virologic suppression before 1 year of age had a statistically significantly lower median proviral load (4.2 copies per million PBMCs) than those achieving suppression between 1 year and 5 years of age (19.4 copies per million PBMCs) and at greater than 5 years of age (70.7 copies per million PBMCs). Despite this, levels of immune activation, measured by sCD14, TNF-α, GMCSF, IL-β, and IL-8, remained elevated in all 3 groups and were statistically significantly higher than the same parameters in perinatally HIV-exposed, -uninfected youth. Those achieving virologic control earlier than 1 year of age had high rates of seronegativity (86%) correlating with decreased proviral reservoirs. Early virologic suppression is therefore associated with decreased proviral load and seronegativity but does not reverse the chronic immune activation associated with HIV infection.

Shiau and colleagues combined data from 3 clinical trials: FInHDER (Finding Infants with HIV Disease), NEVEREST 2, and NEVEREST 3 (Abstract 924). They compared viral dynamics after initiation of antiretroviral therapy between those subjects starting treatment at less than 6 months of age and those starting between 6 months and 24 months of age. Using FInHDER data, they found that age at treatment initiation of less than 6 months was statistically significantly associated with improved virologic suppression at 6 months on antiretroviral therapy (55% vs 33% in those starting treatment at <6 months and at 6 months to 24 months of age, respectively). In the NEVEREST 2 and 3 trials, those initiating antiretroviral therapy at less than 6 months were also more likely than those initiating between 6 months and 24 months of age to have suppressed plasma HIV-1 RNA levels at 52 weeks postrandomization, regardless of whether the trial dictated a switch to a nevirapine-based regimen or they remained on lopinavir/r. These studies demonstrate that antiretroviral therapy initiation at less than 6 months of age leads to better virologic control and may contribute to increased seroreversion and reduction of the HIV reservoir in infants.

Prevention of PMTCT

Implementation of PMTCT Programs

New data on the efficacy, implementation, and scale-up of PMTCT programs in resource-limited settings were presented at this year's conference. Two oral presentations provided data on the implementation of Option B+ for PMTCT in Africa (Abstracts 158, 159). The WHO has promoted a set of strategies for PMTCT: Option A provides antiretroviral therapy guided by CD4+ cell count or prophylactic antiretroviral therapy during pregnancy and extended infant prophylaxis with nevirapine; Option B+ provides lifelong antiretroviral therapy to pregnant and lactating women, irrespective of maternal CD4+ cell count, and shortens the duration of infant antiretroviral therapy prophylaxis. In Session S8, Option B+ was described as substantially simplifying PMTCT implementation and allowing for broad scale-up. Overviews of the benefits and challenges of Option B+ implementation in Malawi (Abstract 158) and Uganda (Abstract 159) show gains in access to antiretroviral therapy for pregnant women, with early surveillance data suggesting a trend toward reduced perinatal HIV-1 transmission. Further information on Option B+ implementation was presented in poster format (Abstracts 882, 883).

Efficacy of PMTCT

In a secondary analysis of PROMOTE (Prevention of Malaria and HIV Disease in Tororo, Uganda) study data (Abstract 69), investigators compared the efficacy and safety of lopinavir/r versus efavirenz in pregnant and breastfeeding Ugandan women. The parent study was an open-label trial assessing the efficacy of these 2 antiretroviral therapy strategies in reducing incidence of placental malaria. HIV-1–infected, treatment-naive pregnant women (n = 389) were randomized to receive either lopinavir/r or efavirenz in combination with zidovudine/lamivudine; maternal antiretroviral therapy was administered between 30 weeks gestation and delivery. Infants received either zidovudine or nevirapine prophylaxis and women were advised to breast-feed for 1 year after delivery. All women in the study also received bed nets and trimethoprim/sulfamethoxazole.

Baseline characteristics were similar between arms with a median viral load of 4 $\log_{10}$ copies/mL and CD4+ cell count greater than 350/mL. Viral suppression was defined as plasma HIV RNA levels less than 400 copies/mL. Using a noninferiority threshold of 11%, there were no differences in virologic suppression between arms at 8 weeks; at the time of delivery, women in the efavirenz arm were statistically significantly more likely to achieve virologic suppression (98% vs 86%, respectively; $P < .001$).

Postpartum, no statistically significant differences in virologic suppression were seen between study arms at weeks 24 and 48. CD4+ cell count recovery was greater in the lopinavir/r arm, both at delivery and 24 weeks postpartum. There were substantially more grade 1 or 2 gastrointestinal adverse effects such as nausea and diarrhea in the lopinavir/r arm but no differences in terms of grade 3 or 4 adverse events. There was no clear explanation for the differences seen in virologic suppression at time of delivery. Additional data from this study was presented in poster format (Abstract 867). Overall HIV-1 transmission rate was 0.5%; the 2 transmission events occurred in the lopinavir/r arm. However, HIV-free survival at end of study did not differ between study arms. These data support the current WHO guidelines, which recommend treatment with efavirenz for pregnant and breast-feeding women.

The ANRS 12174 study team presented data on postnatal prevention of HIV-1 infection (Abstract 70). Describing the breast-feeding period as the Achilles heel of PMTCT, the study randomized HIV-exposed but -uninfected infants to 2 preventive strategies: infant lopinavir/r versus lamivudine for the duration of breast-feeding. The study was conducted in 4 countries in sub-Saharan Africa. Inclusion criteria included maternal CD4+ cell count greater than 350/μL (thus ineligible for maternal antiretroviral therapy under local guidelines), history of maternal receipt of PMTCT treatment, and infant HIV PCR assay negative at day 7. Infants (n = 1273) received prophylaxis between 7 days and 50 weeks of age and were tested for infection quarterly. Women were counseled to exclusively breast-feed for 6 months, followed by partial breast-feeding up to week 50. The primary end point was HIV infection by week 50; secondary end points included death, HIV-free survival, and adverse events. Retention at week 50 was greater than 90%.

Baseline characteristics were similar between study arms. Median maternal CD4+ cell count was 529/μL but only 44% of subjects had undetectable plasma HIV-1 RNA. Median duration of breast-feeding was 41 weeks. Adherence was estimated at greater than 90% by bottle weighing, and infants received antiretroviral therapy during approximately 75% of breast-feeding time; there was slightly higher adherence to lamivudine than lopinavir/r (92.5% vs 90%, respectively; $P < .01$). Rates of HIV-1 transmission were 1.4% versus 1.5% in the lopinavir/r and the lamivudine arms, respectively ($P = .83$). More than half of new infections occurred later than 6 months postpartum. Mortality rates were 3.0% and 2.5% in the lopinavir/r and the lamivudine arms, respectively ($P = .57$). More than 30% of children experienced severe adverse events, most of which were hematologic. The investigators concluded that infant prophylaxis is a safe and effective intervention that allows women to breast-feed up to 12 months with a low risk of HIV-1 transmission to the infant.

A Ugandan study compared the efficacy of Option A (n = 1015) versus Option B+ (n = 586) for PMTCT (Abstract 885). Infants were tested for HIV infection using DNA PCR at 6 weeks to 12 weeks of age. Rates of transmission were 2.9% and 1.9% for Option A and Option B+, respectively, but this difference was not statistically significant. The rate of transmission was lower (1.1%) in women who qualified for antiretroviral therapy due to immunologic or clinical criteria.

Adherence was found to be associated with reduced HIV transmission during breast-feeding in the BAN (Breast-feeding, Antiretrovirals, and Nutrition) study (Abstract 880). The study, conducted in Malawi, randomized mother-infant pairs to receive maternal antiretroviral therapy or infant antiretroviral therapy prophylaxis during breast-feeding. Efficacy results have been published previously and showed similar rates of transmission in both arms.[3] In this study, the investigators analyzed the association between adherence to either strategy and HIV-transmission risk. Adherence was measured using pill count, suspension bottle weight, and maternal self-report. The primary end point was infection at 36 weeks of age in infants confirmed to be HIV-uninfected at 5 weeks of age (n = 1477). Adherence greater than 90% on pill or bottle weight count was associated with a 56% relative risk reduction in postpartum HIV transmission (95% CI, 12%-78%).

Toxicity of PMTCT

New data on infant toxicity of antiretroviral therapy–based PMTCT was presented at the conference. Data from the US-based SMARTT (Surveillance Monitoring for Antiretroviral Therapy Toxicity) study within PHACS showed an association between in utero tenofovir exposure and loss of bone mineral density (Abstract 71). HIV-infected pregnant women and their -uninfected infants were enrolled beginning in 2011. The investigators included infants with a gestational age greater than 36 weeks at delivery and compared infants that were not exposed to tenofovir (n = 69) with infants exposed to more than 8 weeks of tenofovir in the third trimester (n = 74).

The primary outcome was assessed using whole body bone mineral content at 2 weeks of age by dual-energy x-ray absorptiometry (DEXA) scanning. Baseline characteristics differed substantially between the exposed and unexposed groups: nonexposure to tenofovir was strongly associated with younger maternal age, being an unmarried mother, substance abuse in the mother, lower use of a PI/r-based regimen, and female sex of infant. A surprisingly high (21%) proportion of women in the non-tenofovir arm received triple-nucleoside regimens during pregnancy. Results of DEXA scanning showed a mean whole bone mineral content of 63.8 g versus 56.0 g in the non-tenofovir versus tenofovir groups, respectively (12.2% lower in the tenofovir group; difference of 6.4 g after multivariate analysis). There was no association between maternal CD4+ cell count or viral load and infant bone mineral content. No fractures were observed in any of the infants. The clinical ramifications of these findings are as of yet unclear, and more follow-up of exposed infants is planned.

A number of abstracts reported on toxicities associated with PMTCT. In an analysis of ANRS observational and randomized studies (Abstract 862), further evidence of the association between in utero zidovudine exposure and cardiac abnormalities was presented. Zidovudine exposure in the first trimester was associated with an adjusted odds ratio (aOR) of 2.2 (CI, 1.3-2.7) for the development of congenital heart disease, mostly ventricular septal defects. In a randomized study nested within the larger observational cohort, zidovudine exposure in the third trimester of pregnancy was associated with ventricular length shortening in girls but not in boys.

Additional data from the SMARTT PHACS surveillance study (Abstract 863LB) showed an overall congenital anomaly rate of 6.7% in antiretroviral therapy–exposed, HIV-uninfected children between 2007 and 2011 (n = 2580). Most anomalies were cardiac or musculoskeletal. In adjusted models, only atazanavir and the rarely used combination of stavudine and didanosine were associated with an increased risk of congenital anomalies.

A comprehensive review (Abstract 160) of the challenges of accurate tracking of antiretroviral therapy toxicities in HIV-exposed, -uninfected infants was presented in a themed discussion session. The presentation summarized existing data on known associations between in utero antiretroviral therapy exposure and the development of birth defects, birth outcomes, growth, and neurodevelopment.

Antiretroviral Therapy Pharmacokinetics During Breast-Feeding

Two poster abstracts determined the concentration of NNRTIs in breast milk. Etravirine was found in high concentrations in breast milk in a study conducted in 9 HIV-1–infected pregnant women on suppressive antiretroviral therapy (Abstract 891). Etravirine was added to the suppressive regimen and pharmacokinetic data were obtained in the immediate postpartum period. Etravirine concentrations in breast milk exceeded plasma concentrations. Despite plasma viral suppression in all women, 2 women had detectable HIV-1 RNA in breast milk. In a Nigerian study of 51 HIV-1–seropositive, breast-feeding mothers, the relationship of efavirenz concentration in breast milk and in infants was found to be associated with polymorphisms in the CYP2B6 (rs3745274) gene (Abstract 888).

Characteristics and Clinical Outcomes in Pregnant Women

Researchers from South Africa presented data on maternal mortality in different PMTCT eras (Abstract 67). They performed a retrospective review of maternal deaths occurring between 1997 and 2012 at a single referral hospital in Soweto, South Africa. On average, 22,000 deliveries are performed annually at the site, and HIV prevalence in pregnant women was 23.6% in 2012. Four time periods were defined: 1997 to 2002, during which no PMTCT treatment was available; 2003 to 2008, when single-dose nevirapine was introduced; 2009 to 2011, when zidovudine prophylaxis was introduced; and 2011 to 2012, when pregnant women began to be treated with antiretroviral therapy.

There were a total of 589 deaths during the 15-year study period. Of the women who died and had been tested for HIV infection prior to death, 70.7% were HIV-infected. Even during the most recent time period, only 22.9% of HIV-infected women eligible for antiretroviral therapy received treatment at the time of death. Median age at death for HIV-1–infected women was 29.3 years; 75.8% had accessed prenatal care at least once during their pregnancy; and median baseline CD4+ cell count was 71/μL. Eighty percent of deaths occurred postpartum and most of these occurred within 1 week postpartum. The leading causes of death in HIV-infected women were non–pregnancy-related infections, seen in 64.2% of deaths, followed by various obstetric and medical disorders and obstetric hemorrhage. Non–pregnancy-related infections were predominantly respiratory, including community-acquired pneumonia and tuberculosis. HIV-related infections remain the leading cause of maternal deaths in South Africa. These findings were attributed to late presentation, delays in starting antiretroviral therapy, and lack of adherence support.

A high incidence of acute HIV infection during pregnancy was observed in a prospective study conducted in Kenya (Abstract 68). The study enrolled HIV-seronegative women (n = 1304) presenting for antenatal care in a high-prevalence setting (26% HIV seroprevalence among women presenting for antenatal care). Pooled nucleic acid amplification testing was performed at enrollment and every 1 month to 3 months. Subjects were also screened for other STIs. Median age of subjects was 22 years; 78% were married; 7% reported a history of STIs; and only 1% reported having an HIV-1–infected partner. The investigators identified 24 new infections: 10 were detected at enrollment and 14 were seen at follow-up. The overall incidence rate was 2.34 (CI, 0.54-4.34). In the multivariate analysis, a diagnosis of incident HIV infection was most strongly associated with a diagnosis of syphilis (odds ratio [OR], 10.0; 95% CI, 2-46) and bacterial vaginosis (OR, 2.6; 95% CI, 1.2-5.8). The high incidence rates during pregnancy speak to the need for increased prevention efforts, surveillance of seroconversion, and STI screening and treatment in high-risk, high-prevalence populations.

Data from the IeDEA (International Epidemiologic Databases to Evaluate AIDS) collaboration was reviewed to determine the incidence of pregnancy among women receiving antiretroviral therapy (Abstract 868). Included in the analysis were 75,403 woman-years of follow-up. The crude pregnancy rate was 1.3 pregnancies per 100 woman-years. Pregnancy incidence was noted to be highest in the first year of starting antiretroviral therapy. Further analysis of this cohort (Abstract 869) evaluated the effect of pregnancy on retention within antiretroviral therapy programs. Of 12,861 women included in the analysis, 6.7% became pregnant during

48 months of follow-up. Pregnancy was associated with a decreased risk of AIDS or death and of loss to follow-up. The investigators acknowledged that some ascertainment bias and underreporting of pregnancy may have altered the results.

The efficacy of preconception antiretroviral therapy on virologic suppression was evaluated in a study conducted in Cape Town, South Africa (Abstract 874). The investigators enrolled women who were receiving antiretroviral therapy prior to conception (n = 210). Median duration of treatment was 2.7 years and 70% of women received NNRTI-based therapy. The investigators found that 24% of subjects had plasma HIV RNA levels greater than 50 copies/mL and 13% had plasma HIV RNA levels greater than 1000 copies/mL at presentation to antenatal care. The investigators raised concern that availability of antiretroviral therapy prior to conception may not guarantee effective suppression and optimal PMTCT.

Transmitted Drug Resistance

Surveillance data from the United States show a high prevalence of transmitted drug resistance (TDR; Abstract 87). The investigators compared commercially available gene sequencing with the more sensitive mutation-specific PCR assay to detect drug resistance mutations (DRMs). The analysis focused on 5 mutations thought to represent sentinel markers of TDR, namely, M41L, K103N, Y181C, M184V, and K65R. The data analyzed was part of the CDC VAHRS (Variant, Atypical, and Resistant HIV Surveillance) program. The population included antiretroviral treatment–naive, newly diagnosed subjects who underwent genotype testing within 3 months of diagnosis between 2009 and 2011 (n = 1070). The population was 86% male, 54% black, and 71% MSM.

The overall prevalence of any TDR was 7.9% by conventional sequencing and 13.6% with sensitive sequencing. All 5 sentinel mutations were underestimated by conventional sequencing. In particular, the K65R, Y181C, and M184V DRMs were detected 2 to 5 times more frequently using the sensitive assay. K103N was the most commonly detected DRM, found in 7.0% of specimens using commercial sequencing and in 8.4% using the sensitive assay. Blacks and whites were statistically significantly more likely to have TDR than Hispanics. MSM and women who have sex with men had equivalent rates (approximately 15%) of TDR. TDR rates were highest in the northwest and southeast regions of the United States, but no differences in the prevalence of TDR were noted across different population densities.

There was a strong association between age at infection, recent infection, and prevalence of TDR. In the 13- to 19-year-old age group, 59% of infections were determined to be recent (within 6 months) and the prevalence of TDR was 23.1%. Among the older age groups (40- to 59-year-olds), approximately 25% of infections were considered recent and prevalence of TDR was 17%. However, there were no differences in rates of TDR between recently and non–recently infected subjects within age groups. The investigators believe that this observation suggests that decay of transmitted mutations does not explain the high prevalence of TDRs observed in the younger age groups. Minority variants were more prevalent in older subjects. The clinical implications of low-frequency variants, particularly in recent infections, remain unclear. The investigators did not have access to treatment response data in this surveillance study.

Additional surveillance data on TDR in the United States were presented in poster format (Abstract 579). Sequences from newly diagnosed persons during 2008 to 2011 were analyzed and prevalence of TDR was compared between the overall sample (n = 16,985) and those reporting MSM as transmission risk category (n = 10,894). Prevalence of any TDR was 16.7% overall and 17.4% in MSM. There were no differences observed by ethnicity, but higher rates of TDR were seen in young MSM than older MSM (18.6% vs 15.9%, respectively; CI, 1.05-1.32).

Data from the ANRS show stable rates of TDR in France (Abstract 582). Newly infected subjects diagnosed between 2010 and 2012 (n = 796) underwent bulk genotypic sequencing. The overall prevalence of TDR was 10.7%; drug class–specific TDR was detected as follows: nRTIs 5.2%, NNRTIs 7.3%, and PIs 2.0%. Of note, prevalence of TDR for the second-generation NNRTIs rilpivirine and etravirine was 3.3% and for INSTIs 1.5%. Resistance was more common in subtype B virus and in MSM. The investigators noted that the overall prevalence of TDR in France has not changed since 1996 and that more than 95% of sequenced viruses are susceptible to WHO first-line antiretroviral regimens. Additional data on low-frequency drug-resistant variants in the ANRS database were presented (Abstract 605).

An analysis of data from the Dutch ATHENA (AIDS Therapy Evaluation in the Netherlands) cohort suggests that a single transmitted thymidine analogue–associated mutation (TAM) does not compromise the efficacy of first-line antiretroviral therapy (Abstract 577). The investigators used data from treatment-naive MSM diagnosed between 2002 and 2012 with HIV-1 infection (n = 2314). Subjects were classified into 3 groups based on pretreatment genotype: presence of 1 TAM; presence of a single non-TAM DRM or more than 2 DRMs; or no DRMs. Only 4% of the cohort had a single TAM. No differences were seen in time to virologic failure between the single TAM and wild type groups (hazard ratio [HR], 1.04; CI, 0.58-1.86).

A Spanish study retrospectively analyzed the prevalence of low-frequency DRMs in patients with advanced HIV disease initiating first-line antiretroviral therapy (Abstract 602). 454-pyrosequencing was performed on stored samples from subjects with pretreatment CD4+ cell counts lower than 100/μL and wild type virus on commercial sequencing (n = 145). DRMs were detected in 41% of subjects in pretreatment stored specimens using the sensitive assay. The presence of DRMs was associated with a marginal overall increase in risk of virologic failure

(HR, 2.0; CI, 1.0-4.3); no increased risk was seen in subjects treated with PI-based regimens.

Cross-sectional data from the European SPREAD (Strategy to Control SPREAD of HIV Drug Resistance) surveillance program showed no circulating signature mutations conferring INSTI resistance prior to the clinical introduction of this class of antiretroviral drugs (Abstract 580) in a random sample of sequences from newly diagnosed subjects in 2006 and 2007 (n = 300). Despite the absence of any identified major INSTI DRMs, polymorphisms known to contribute to the emergence of INSTI resistance were detected in 4% of specimens using commercial sequencing and in 12.5% of specimens using 454-pyrosequencing. The investigators suggested that transmitted INSTI resistance will increase with the expanded use of these agents.

An industry database confirms an increasing prevalence of NNRTI resistance but low levels of other drug class resistance (Abstract 578). Sequences from treatment-naive individuals enrolled in phase III studies between 2000 and 2013 were included in the analysis (n = 2516). Over this time period, NNRTI mutations increased in prevalence from 1.9% to 7.8%. TAMs were detected at a frequency of 2.2% in 2013; mutations at M184V/I and K65R were rare (0.1% at all time points). In the subset of subjects in whom integrase sequencing was performed (n = 1617), HIV-1 integrase resistance mutations were found in 0.07%, with the T97A substitution accounting for 1.2% of polymorphisms.

In an oral presentation, investigators presented data on patterns of TDR between partner-pairs with virologically linked infections (Abstract 88). The investigators hypothesized that drug resistant–virus would be underrepresented in the recipient partner because of impaired replication capacity. Subject pairs had been enrolled since 1992 in the Seattle Primary Infection Cohort. Forty index subjects whose date of seroconversion was well estimated were enrolled. There were 36 confirmed transmissions within partner-pairs, of which 31 yielded specimens for analysis. 454-pyrosequencing was performed on a number of plasma and PBMC specimens from the 31 partner-pairs included in the analysis. The majority of subjects were white MSM. Twenty-two percent of index subjects reported any history of antiretroviral therapy and only 4% were on treatment at the time of the transmission event.

Presence of DRMs was defined as a frequency of mutation higher than 1%. DRMs were detected in 41% of subject pairs. When DRMs were observed at a frequency higher than 15% in the transmitter, they were also observed at a correspondingly high frequency in the recipient, both in plasma and PBMCs. In this context, there was 100% overlap between mutations identified in the transmitter and the recipient. Of note, none of the subjects with high-frequency mutations reported antiretroviral therapy use. Among pairs with detected low-level DRMs (< 14%), there was no correspondence between transmitter and recipient DRMs. Further, most mutations were detected in PBMCs and not in plasma. The investigators concluded that DRMs are efficiently transmitted only when detected at high concentrations in the transmitter.

Acquired Drug Resistance

Failure of First- and Second-Line Antiretroviral Therapy

Investigators from Kenya found high rates of resistance among patients prescribed second-line regimens containing lopinavir/r (Abstract 584). All patients (n = 401) had failed a previous first-line antiretroviral regimen and had been on a lopinavir/r-based regimen for at least 6 months. Twenty-four percent of subjects had plasma HIV RNA levels greater than 1000 copies/mL at a median of 1.9 years on second-line therapy. In these subjects, 182 genotypes were available for analysis, including both plasma and PBMC sequences. In plasma specimens, rates of viral resistance were 78% for any resistance, 67% for nRTI resistance, 73% for NNRTI resistance, and 8% for PI resistance. Archived resistance mutations were seen in 84% of available sequencing from subjects with detectable plasma HIV RNA levels less than 1000 copies/mL.

A study from Nigeria estimated that second-line treatment failure cannot be successfully managed within current WHO guidelines (Abstract 585). Genotype susceptibility scores were calculated for participants failing either lopinavir/r- or atazanavir-based second-line therapy; a score of less than 2 was defined as a lack of further treatment options. Of patients receiving second-line antiretroviral therapy (n = 936), 6% had evidence of viral failure with a plasma HIV-1 RNA level greater than 1000 copies/mL (n = 56). Mean viral load at failure was 5.1 $\log_{10}$ copies/mL. The following DRMs were detected at failure: K103N (22.4%), M184V (20.4%), M41L (20.4%), M46I (19.4%), and I54V (15.3%). Thirty-two percent of patients had no WHO treatment options at failure. However, complete loss of all treatment options occurred in only 1 patient. Nine sequences contained no mutations at failure.

An analysis from China evaluated the risk of acquired drug resistance and mortality in patients receiving nevirapine-based antiretroviral therapy between 2003 and 2005 (Abstract 589). Patients received nevirapine in combination with either zidovudine and didanosine or stavudine and didanosine (n = 517). At a median follow-up of 58 months, 78% of patients had experienced treatment failure, and of those 56% had DRMs. Fifteen percent mortality was observed. No information was provided on adherence to these regimens, which are not recommended first-line regimens by current guidelines.

nRTI Resistance

In an oral presentation, investigators described a novel silent mutation that allows HIV-1 subtype B to overcome the fitness cost associated with TAMs (Abstract 89). Silent, or synonymous, mutations alter the genetic code at a specific codon without altering the resulting amino acid sequence. Synonymous

mutations associated with the presence of TAMs were identified at positions K65K and K66K. The investigators hypothesized that the TAMs D67N and K70R cause a viral fitness defect via the insertion of a homopolymeric nucleotide sequence upstream from the mutation and showed that by inserting a synonymous mutation, the virus is able to mitigate this fitness defect.

NNRTI Resistance

In the ANRS EASIER trial, investigators determined the prevalence of second-generation NNRTI resistance in subjects with a history of first-generation NNRTI failure who achieved virologic suppression on a subsequent regimen (n = 169; Abstract 591). Sequencing was performed on HIV-1 DNA extracted from whole blood specimens. Amplification was successful in 76% of patients, and 95% of sequences were HIV-1 subtype B. Rilpivirine DRMs were detected in 31% of patients. The most frequent mutations were at the 181, 101, and 138 positions of reverse transcriptase. Etravirine mutations were detected in 4% of subjects. Emtricitabine and tenofovir mutations were found in 56% and 9% of patients, respectively. The investigators noted that resistance to any component of the fixed-dose combination rilpivirine/emtricitabine/tenofovir was seen in 69% of patients. They recommended that pretreated patients with a history of failure on first-generation NNRTIs not be treated with rilpivirine-based therapy.

High rates of NNRTI resistance were detected in patients interrupting suppressive NNRTI-based therapy (Abstract 593). In a retrospective analysis from the UK HIV Drug Resistance Database, subjects were included if they were on a suppressive first-generation NNRTI regimen; had evidence of consistent suppression to plasma HIV RNA levels less than 200 copies/mL after 6 months of therapy; had no evidence of NNRTI resistance on prior genotypes; and underwent treatment interruption. Of the subjects with a genotype determined after treatment interruption (n = 208), 12% had 1 or more NNRTI DRMs at a median of 12 months following treatment interruption. The DRM at K103N was found in 64% and at G190A in 12% of patients. There were no differences observed between those receiving a "nucleoside tail" and those who did not, but the numbers in the nucleoside tail group were small. Only 13% of patients with treatment interruption underwent genotype testing, suggesting that the population studied may have had a higher pretest probability of resistance.

Resistance to second-generation NNRTIs was observed with moderate frequency in patients failing first-generation NNRTI–based therapy in PEPFAR programs in sub-Saharan Africa (Abstract 592). Subjects with available sequences had subtype A or D HIV-1 infection (n = 215). DRMs at position 138 of reverse transcriptase were detected in 13.8% of subjects. The investigators suggested that first-generation NNRTIs may induce mutations associated with second-generation NNRTIs in patients with non-B subtypes.

Investigators analyzed the rate of decay of the DRM at K103N in subjects previously failing efavirenz-based therapy (Abstract 604). At the time of analysis, subjects were virologically suppressed on a PI-based regimen with plasma HIV RNA levels less than 50 copies/mL (n = 28). Proviral DNA was isolated from PBMCs and sequenced. Duration of suppression was not associated with decay of K103N, which was detected in approximately 50% of subjects at all time points, for up to 11 years of follow-up. Log_{10} viral load at efavirenz failure was associated with an OR of 2.6 (CI, 1.0-6.4) for detection of K103N per log_{10} copy/mL increase.

Integrase Resistance

Integrase resistance was rare in treatment-naive subjects enrolled in an industry trial of EVG/COBI/FTC/TDF (Abstract 587). Week 144 data shows that INSTI DRMs emerged in 2.6% of the subjects enrolled (n = 701). The most frequent DRMs were E92Q (n = 9), N155H (n = 5), Q148R (n = 3), T66I (n = 2), and T97A (n = 1). Emergent nRTI resistance mutations observed included M184VI (n = 17) and K65R (n = 5).

Using clinical specimens and site-directed mutagenesis, investigators determined the mechanism of resistance conferred by mutations at position 148 of HIV integrase (Abstract 595). Patient-derived viruses (n = 210) containing the raltegravir and elvitegravir DRMs Q148H/K/R displayed reduced susceptibility to dolutegravir (IC_{50} fold change of 4.6). The largest reductions in dolutegravir susceptibility were observed with the Q148K substitution. All patient viruses contained additional mutations to those seen at the 148 position. By site-directed mutagenesis, substitutions at the 148 position alone did not reduce dolutegravir susceptibility. The addition of mutations at position 140 were associated with reduced susceptibility to dolutegravir, as were mutations at positions 74, 92, 97, and 138.

Maraviroc Resistance and Tropism

Proviral DNA from aviremic subjects was used to guide a switch to maraviroc-based therapy (Abstract 607). In this study, HIV-1–infected adults on suppressive antiretroviral therapy (plasma HIV-1 RNA levels < 50 copies/mL) for longer than 6 months who required a change of regimen because of drug toxicity were included in the analysis (n = 134). Of these, 88 (85%) had R5 tropic virus; 74 switched to a regimen of maraviroc plus 2 nRTIs; and 61 reached the 24-week analysis time point. At 24 weeks, 51 subjects (84%) remained virologically suppressed. Four of the 10 subjects who did not achieve virologic suppression at week 24 had evidence of viral resistance, 2 with X4 tropic virus.

Resistance During Tenofovir/Emtricitabine PrEP

Data on HIV resistance among participants in the VOICE (Vaginal and Oral Interventions to Control the Epidemic) PrEP trial were presented, confirming a high risk of resistance when PrEP is used during acute infection (Abstract 594). A total of 368 women were diagnosed with HIV-1 infection during the trial. Of these, 212 seroconverters were exposed to tenofovir. There was no

evidence of tenofovir resistance in any of the women exposed to tenofovir-containing PrEP. In 1 subject randomized to tenofovir/emtricitabine, the M184V DRM emerged after 309 days on product. Twenty-two subjects were retroactively found to be infected at enrollment, 9 of whom were in the tenofovir/emtricitabine arm. In 2 (22%) of these subjects, the M184V DRM emerged within 1 month of product use. Overall adherence in the VOICE trial was low, suggesting that the true incidence of resistance with PrEP may be underestimated. Increased surveillance of acute or recent infection is essential to assure the safety of PrEP.

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A list of all cited abstracts appears on pages 632-638 of this issue. Abstracts are published in *Top Antivir Med.* 2014;22(e-1):1-570, a special online issue available at www.iasusa.org/pub.

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