Advances in Antiretroviral Therapy

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The 18th Conference on Retroviruses and Opportunistic Infections maintained its tradition of being the preeminent forum for detailing the state-of-the-art in antiretroviral therapy. There were important presentations on investigational antiretroviral drugs, clinical trials in treatment-experienced patients, and new antiretroviral strategies. Relevant data on resistance to antiretroviral drugs and pharmacokinetic interactions were discussed. There were extensive presentations on antiretroviral therapy in resource-limited settings, including large-scale clinical trials, scale-up of antiretroviral therapy, adherence, retention in care, and treatment outcomes for children and adults. Prevention of mother-to-child transmission continued to be an important part of the conference.

Investigational Drugs

GS-7340

Zolopa presented study data on GS-7340, a novel amidate prodrug of tenofovir designed to deliver high concentrations of tenofovir diphosphate to lymphatic tissues in an effort to minimize systemic exposure and toxic effects while maximizing efficacy (Markowitz et al, Abstract 152LB). Eligible participants were HIV-infected adults naive to antiretroviral therapy who had plasma HIV-1 RNA levels greater than 15,000 copies/mL and CD4+ cell counts of at least 200/µL. Participants were randomly assigned to tenofovir disproxil fumarate 300 mg daily (n = 10), GS-7340 50 mg daily (n = 10), or GS-7340 150 mg daily (n = 10). All subjects received monotherapy for 14 days. The mean baseline plasma HIV-1 RNA level was between 4.72 $\log_{10}$

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copies/mL and 5.03 $\log_{10}$ copies/mL. The primary endpoint was time-weighted average plasma HIV-1 RNA level reduction over 2 weeks of dosing.

The viral load change was greater in both the 50-mg and 150-mg GS-7340 recipients than in the tenofovir group (-0.95 $\log_{10}$ copies/mL and -1.07 $\log_{10}$ copies/mL for GS-7340 doses vs -0.54 $\log_{10}$ copies/mL for tenofovir; $P = .03$, and $P = .001$, respectively). The first-phase decay in plasma HIV-1 RNA level was statistically significantly greater in the 2 GS-7340 groups than in the tenofovir group. Both GS-7340 groups had lower plasma levels of tenofovir and higher intracellular tenofovir diphosphate levels in peripheral blood mononuclear cells (PBMCs). There were no safety concerns identified in this small study with limited follow-up. The authors noted that the lower dose of GS-7340 may allow for coformulations that are not possible with tenofovir and may reduce manufacturing costs, which could expand access to tenofovir in resource-limited settings (RLS).

Zinc-finger nucleases. Lalezari and colleagues presented data on 6 participants who received autologous CD4+ T cells that had been treated with a zinc-finger nuclease targeting the CC chemokine receptor 5 (*CCR5*) gene for disruption (Abstract 46). The participants underwent leukapheresis to collect a large volume of PBMCs, and the monocytes and CD8+ T cells were depleted. The

remaining CD4+ T cells were treated with an adenoviral vector to introduce the zinc-finger nuclease that targeted the *CCR5* gene for disruption. These cells were expanded in vitro and then infused back into the participant as a single dose.

The authors presented data on 2 dosing cohorts of 3 participants each. The participants were all men with longstanding HIV infection, were receiving antiretroviral therapy, had a plasma HIV-1 RNA level below the limit of detection, and had a CD4+ cell count in the range of 269/µL to 450/µL. There were no serious adverse events related to the infusion, but milder, infusion-related events such as fever, chills, and sweats were common. The CD4+ T-cell count increased in all 6 participants by amounts ranging from 100/µL to 500/µL. These changes generally persisted throughout follow-up, which ranged from 3 months to 12 months. The modified cells appeared to engraft and expand after infusion in 5 of the 6 participants. One participant who had high adenoviral antibody levels before infusion had modified cells that were detectable but did not appear to expand in vivo. These modified CD4+ T cells were also found in the rectal mucosa and persisted in 5 of the 6 participants.

CXC chemokine receptor 4 (CXCR4)-tropic HIV-1 is found commonly in patients with HIV infection, especially those with longstanding infection who have been treated with several different antiretroviral regimens.[1] Potential gene therapies targeting *CCR5* alone would not be sufficient to treat patients with CXCR4-tropic HIV-1. Small-molecule CXCR4 antagonists have not been developed successfully for treatment of HIV-1 infection. Wilen and colleagues presented data on using zinc-finger nucleases to disrupt the *CXCR4* gene in CD4+ T cells (Abstract 47). They were able to disrupt the *CXCR4* gene in vitro, and this did not appear

to adversely affect cell growth. They showed that these cells were protected from infection by CXCR4-tropic strains. Using a humanized mouse model, they found that mice receiving the CXCR4-disrupted cells were protected from CXCR4-tropic HIV. Dual-tropic HIV-1 species eventually emerged in these mice, suggesting that a strategy targeting *CXCR4* and *CCR5* was needed.

Oral Attachment Inhibitor

Nettles and colleagues presented data on the pharmacodynamics of BMS-663068 (Abstract 49). This compound is a prodrug of BMS-626529, which binds to gp120 and interferes with the attachment of HIV to the CD4 receptor. This was an open-label trial of 5 different dosing schemes of BMS-663068 with and without ritonavir. Each cohort enrolled 10 HIV-1-infected adults who were not receiving other antiretroviral therapy for at least 8 weeks before dosing. Two subjects were found to be ineligible after dosing began and were excluded from the analysis.

The median maximal decline in plasma HIV-1 RNA level ranged from 1.2 $\log_{10}$ copies/mL to 1.8 $\log_{10}$ copies/mL over 8 days of dosing, including all 48 subjects. There were 7 participants who were found to have HIV-1 strains that required more than 1 µmol of BMS-626529 (the active drug) to inhibit 50% of the growth and 2 additional subjects who did not have a baseline sample for analysis. When excluding these 9 subjects, the median maximal decline in plasma HIV-1 RNA level was 1.6 $\log_{10}$ copies/mL to 1.8 $\log_{10}$ copies/mL. The addition of ritonavir raised the area under the curve (AUC) and minimum plasma concentration (C_{min}) values moderately but did not appear to improve antiviral activity. There were no serious adverse events. The most common adverse events were headache and rash, which were mild to moderate. This study establishes the short-term efficacy of this compound but suggests that there are subpopulations of HIV-1 strains that are somewhat resistant to this compound. Nowicka-Sans and colleagues further characterized these subpopulations by examining the

in vitro activity of BMS-626529 in various clinical isolates (Abstract 518). They found that 27% of HIV-1 subtype B, 58% of subtype C, and 72% of subtype A isolates had 50% effective concentrations greater than 1 µmol.

Nonnucleoside Analogue Reverse Transcriptase Inhibitors

GSK2248761 is a nonnucleoside analogue reverse transcriptase inhibitor (NNRTI) that is currently in phase IIB clinical trials. Vavro and colleagues compared the in vitro activity of this compound with that of efavirenz, etravirine, and rilpivirine (Abstract 520). The compound appeared more potent than the other NNRTIs. The highest 50% inhibitory concentration (IC_{50}) was 41 nM for a strain with K103N, Y181C, and G190A mutations in reverse transcriptase. This compound was additive or synergistic with all other antiretroviral medications tested.

Integrase Inhibitor

Fenwick and colleagues presented data on BI-C, an HIV-1 integrase inhibitor that prevents the processing of the 3′ end of the viral DNA but not the strand-transfer reaction (Abstract 523). BI-C was among a series of compounds the investigators identified in a high-throughput assay. X-ray crystallography showed that these compounds bind a pocket on integrase targeted by lens epithelium-derived growth factor (LEDGF). BI-C has promising in vitro activity against a variety of isolates, including ones highly resistant to other integrase inhibitors that target the strand-transfer reaction (the integrase strand-transfer inhibitors, or INSTIs). The authors reported that this compound was moving into phase I trials.

Clinical Trials of Antiretroviral Therapy in Treatment-Naive Patients

AIDS Clinical Trials Group Study A5175

Campbell and colleagues presented data from AIDS Clinical Trials Group (ACTG) study 5175 (Abstract 149LB).

Prior presentations reported on the inferiority of once-daily administrations of atazanavir, didanosine, and lamivudine. This analysis reported on the comparison of efavirenz plus zidovudine/lamivudine versus efavirenz plus tenofovir/emtricitabine. The primary endpoint was time to treatment failure, defined as death, virologic failure (plasma HIV-1 RNA level > 1000 copies/mL at week 16 or later), or HIV disease progression. HIV-1-infected adults with a CD4+ cell count less than 300/µL and naive to antiretroviral therapy were eligible. Participants were enrolled from 12 sites in 8 RLS in addition to the United States. There were 526 and 519 participants enrolled in the tenofovir/emtricitabine and zidovudine/lamivudine groups, respectively. The study population consisted of 46% women and had extensive racial and ethnic diversity. The median baseline CD4+ cell count was 162/µL and 169/µL for the tenofovir/emtricitabine and zidovudine/lamivudine groups, respectively. The median plasma HIV-1 RNA level was 5.0 $\log_{10}$ copies/mL and 5.1 $\log_{10}$ copies/mL, respectively. There was no difference between groups in the primary endpoint or any of the components, and the CD4+ cell counts were similar between groups. At 3 years of follow-up, approximately 20% of subjects in both groups reached the primary endpoint.

There were statistically significant differences between groups in the safety analyses. The zidovudine/lamivudine group was more likely to have grade 3 or grade 4 laboratory abnormalities and more likely to require a drug substitution. The reason for drug substitution was almost entirely because of grade 3 or grade 4 anemia and neutropenia: 59 cases occurred in the zidovudine/lamivudine group compared with 0 cases in the tenofovir/emtricitabine group. These differences were more pronounced in women than in men. The authors concluded that both regimens are efficacious and that tenofovir/emtricitabine has safety advantages over zidovudine/lamivudine. Furthermore, they asserted that this safety advantage should prompt use of tenofovir/emtricitabine in popu-

lations at higher risk of adverse events, including women.

Once-Daily Raltegravir

Eron and colleagues presented data from the QDMRK study, which compared once- and twice-daily dosing of raltegravir as initial antiretroviral therapy in HIV-1-infected adults (Abstract 150LB). This was a randomized, double-blind, active-controlled clinical trial. Participants were randomly assigned to receive tenofovir/emtricitabine with raltegravir either 400 mg twice daily or 800 mg once daily. The primary objective was to show the noninferiority of once-daily to twice-daily dosing of raltegravir. The study included 770 participants (median age, 38 years; ~80% men; ~30% nonwhite).

The proportions of participants with plasma HIV-1 RNA level less than 50 copies/mL (noncompleters = failures) were 88.9% and 83.2% in the twice- and once-daily groups, respectively (overall difference between once-daily and twice-daily dosing, −5.7%; 95% confidence interval [CI], −10.7% to −0.83%). This did not exclude the noninferiority margin of −10%. In addition, the 95% CI excluded zero and established the statistical inferiority of the once-daily arm. Among those with a baseline plasma HIV-1 RNA level greater than 100,000 copies/mL, 84.2% of the twice-daily group and 74.3% of the once-daily group had levels less than 50 copies/mL (−9.9%; 95% CI, −19% to −0.8%). Among those with a baseline plasma HIV-1 RNA level of 100,000 copies/mL or less, 91.9% and 89.1%, respectively, had levels of less than 50 copies/mL (−2.7%; 95% CI, −8.3% to 2.7%). Virologic failure and development of resistance was more common in the once-daily group. These trends were similar across strata of plasma HIV-1 RNA level.

Darunavir/Ritonavir Plus Raltegravir

Taiwo and colleagues presented data from ACTG A5262, a single-arm, open-label trial of darunavir/ritonavir 800 mg/100 mg plus raltegravir 400 mg twice daily as initial antiretroviral therapy for HIV-1-infected adults (Abstract 551). This study enrolled 112 participants: 88% men, 56% nonwhite; median age, 36 years. A total of 44% had a baseline plasma HIV-1 RNA level greater than 100,000 copies/mL, and 36% had a CD4+ cell count less than 200/µL. Fifteen participants left the study before week 48, including 1 participant who died of cryptosporidiosis. At week 48, 71% had a plasma HIV-1 RNA level less than 50 copies/mL in an intent-to-treat analysis in which missing values are ignored. Twenty-eight subjects had virologic failure (a composite of early failure and confirmed plasma HIV-1 RNA detection at week 24 or later). No darunavir resistance mutations emerged, and INSTI resistance emerged in 5 subjects, all of whom had baseline plasma HIV-1 RNA levels greater than 100,000 copies/mL. Virologic failure was associated with a baseline plasma HIV-1 RNA level greater than 100,000 copies/mL and a baseline CD4+ cell count less than 200/µL.

Clinical Trials of Antiretroviral Therapy in Treatment-Experienced Patients

Dolutegravir

Eron and colleagues presented data on dolutegravir (S/GSK1349572), an investigational INSTI (Abstract 151LB). This study enrolled participants who had current or prior virologic failure with raltegravir and evidence of resistance. A prior cohort in this study received dolutegravir 50 mg once daily; this cohort received 50 mg twice daily. The results of both cohorts are presented for comparison. Participants were divided into 2 groups based on their INSTI resistance pattern (Q148H/K/R plus ≥ 1 secondary mutation, or other mutational patterns).

Subjects added dolutegravir to their existing antiretroviral therapy regimen for 11 days followed by optimization of the background regimen. They must have had 1 or more active drugs to add into the optimized background regimen to be eligible for the twice-daily cohort. The primary endpoint was a 0.7-$\log_{10}$ copy/mL reduction in plasma HIV RNA level or achievement of a plasma HIV-1 RNA level less than 400 copies/mL after 11 days. There were 27 and 24 subjects in the once- and twice-daily groups, respectively. The mean plasma HIV-1 RNA levels were 4.5 $\log_{10}$ copies/mL and 4.3 $\log_{10}$ copies/mL, respectively. The median baseline fold-changes to dolutegravir were 1.5 and 2.7, respectively.

Among subjects with the mutation pattern of Q148H/K/R plus at least 1 secondary mutation, 3 of 9 (33%) receiving once-daily dolutegravir achieved the primary endpoint, compared with 11 of 11 (100%) receiving twice-daily dosing. Among subjects with other mutational pathways, 18 of 18 (100%) receiving once-daily dosing and 12 of 13 (92%) receiving twice-daily dosing achieved the primary endpoint. The twice-daily dose has been selected for future phase III studies of dolutegravir in INSTI-experienced patients.

Second-Line Therapy After Failure of 3 Nucleoside Analogue Reverse Transcriptase Inhibitors

Mambule and colleagues randomly assigned 202 participants with failure of an initial regimen of only nucleoside analogue reverse transcriptase inhibitors (nRTIs) to receive ritonavir-boosted (/r) lopinavir plus a NNRTI with either didanosine, lamivudine, or a regimen with no nRTI (Abstract 541). The CD4+ cell count increases after 24 weeks were similar among the 3 groups, with increases of 143/µL, 124/µL, and 148/µL after 24 weeks, respectively. At week 24, 66%, 76%, and 68%, respectively, achieved a plasma HIV-1 RNA level less than 50 copies/mL.

Lopinavir/Ritonavir Alone as Second-Line Therapy

Two studies examined results of monotherapy with lopinavir/r as second-line therapy. Bartlett and colleagues presented 24-week results from ACTG 5230, a pilot study of 123 patients from 3 sites in Africa and 2 in Asia with documented virologic failure, defined as plasma HIV-1 RNA levels between 1000 copies/mL and 200,000 copies/mL,

after at least 6 months of continuous, NNRTI-based initial antiretroviral therapy (Abstract 583). At baseline, median age was 39 years, median plasma HIV-1 RNA level was 164/µL, and 76% of patients had received nevirapine-based antiretroviral therapy. These patients, having met criteria for failure of their initial regimen, were switched to lopinavir/r monotherapy as second-line treatment.

After 24 weeks of lopinavir/r 400 mg/100 mg twice daily, 107 (87%; 95% CI, 80% – 92%) remained virologically suppressed with plasma HIV RNA levels less than 400 copies/mL. HIV-1 genotypes were available for 11 of 15 participants meeting criteria for virologic failure, and 4 new major mutations were observed (2 A71T and 2 V82F). Thirteen participants for whom monotherapy was failing intensified their antiretroviral therapy with the addition of tenofovir/emtricitabine/r, and 11 (85%) achieved virologic suppression. Grade 3 or grade 4 adverse events were observed in 31 participants (25%). The authors note that the lack of a comparator group limits the utility of the findings. Long-term follow-up of the study participants will continue through antiretroviral therapy week 104, which will determine durability of the treatment response as well as outcomes for those who intensify failing monotherapy with tenofovir/emtricitabine.

Bunupuradah and colleagues presented a needed corollary to the above findings by comparing lopinavir/r monotherapy with tenofovir/lamivudine plus lopinavir/r in a randomized controlled trial of 200 patients with documented virologic failure (plasma HIV-1 RNA levels > 1000 copies/mL) of an initial NNRTI-based regimen in Thailand (Abstract 584). In an intention-to-treat analysis of 48-week outcomes, for which missing or adding tenofovir/lamivudine was treated as failure, the proportion of participants achieving virologic suppression (plasma HIV RNA level < 400 copies/mL) in the monotherapy group was 75%, compared with 86% in the tenofovir/lamivudine plus lopinavir/r group (*P* = .053). A statistically significantly lower percentage of participants receiving monotherapy had plasma HIV-1 RNA levels less than 200 copies/mL (69% vs 86%, respectively; *P* = .01) and less than 50 copies/mL (61% vs 83%, respectively; *P* < .01). Major protease inhibitor (PI) mutations (M46I, I50V) at failure were detected in 1 participant receiving monotherapy. The authors conclude that lopinavir/r alone should either not be recommended as a second-line regimen or used with caution.

Darunavir/Ritonavir, Raltegravir, Etravirine

Fagard and colleagues presented the long-term results of the TRIO (Efficacy of Darunavir/Ritonavir, Etravirine, and Raltegravir in HIV Patients with Resistant Viruses) study (Abstract 549). This was a single-arm, open-label trial enrolling patients for whom several antiretroviral regimens had failed. All participants received darunavir/r, etravirine, and raltegravir plus an investigator-selected background regimen. No participants discontinued the study regimen except for 1 participant, who discontinued raltegravir because of an adverse event at week 8. One participant died before week 96 and 2 participants withdrew consent. At week 96, 88% of participants had a plasma HIV-1 RNA level less than 50 copies/mL. Although 19 participants experienced virologic failure before week 96, failure generally occurred with low-level viremia, and virus was resuppressed without the participants changing regimens. This study supports the long-term efficacy of this combination of antiretroviral drugs in patients with prior virologic failure.

Antiretroviral Treatment Strategies

Darunavir/Ritonavir Alone

Valantin and colleagues presented week-96 data from a randomized, controlled trial of daraunavir/r alone as maintenance antiretroviral therapy (Abstract 534). This study randomly assigned 225 patients taking suppressive antiretroviral therapy to darunavir/r 600 mg/100 mg twice daily plus 2 nRTIs (triple-therapy group) or darunavir/r alone (monotherapy group). At 48 weeks, participants were changed to darunavir/r 800 mg/100 mg once daily. Participants were observed for an additional 48 weeks.

At week 96, the proportion remaining on the randomized treatment was similar between the 2 groups, 90 of 112 participants in the monotherapy group versus 91 of 113 in the triple-therapy group. The number of participants experiencing virologic failure (defined as 2 consecutive measures of plasma HIV-1 RNA level > 400 copies/mL) were 5 and 4 in the 2 groups, respectively. Participants in the darunavir/r-alone group experienced more low-level viremia than the triple-therapy group, but there was no emergence of resistance to darunavir. In an intent-to-treat analysis, the proportion with suppressed plasma HIV-1 RNA level did not differ between groups (88% vs 84%, respectively).

Predictors of Antiretroviral Therapy Response From Large Cohort Studies

Many presentations used existing cohort studies to examine potential determinants of treatment outcomes. Althoff and colleagues determined trends in plasma HIV-1 RNA levels in HIV-1-infected patients from 13 clinical cohorts participating in the North American AIDS Cohort Collaboration on Research and Design (NA-ACCORD) (Abstract 548). Investigators determined antiretroviral therapy usage at the time of the highest plasma HIV-1 RNA level per individual per year and found that, of 91,569 patients receiving care between 1997 and 2007, 77% used antiretroviral therapy at some point. The proportion of patients receiving antiretroviral therapy who achieved virologic suppression, defined as plasma HIV RNA level of 500 copies/mL or less, increased each year and reached more than 50% by 2005 to 2007.

For those receiving antiretroviral therapy, initial disparities in median plasma HIV-1 RNA level by HIV transmission group narrowed over time,

with injecting drug users having statistically significantly higher annual median levels from 1997 to 2006, and converged at a median below 500 copies/mL for all groups in 2007. Similarly, black patients consistently had a higher annual median plasma HIV-1 RNA level from 1997 to 2006 than that of white patients ($P < .01$), but disparities by all racial or ethnic categories (black, white, Hispanic, other/unknown) converged in 2007. These are encouraging data in terms of the potential for decreasing median community plasma HIV-1 RNA levels and in the diminishing disparities of those achieving virologic success during antiretroviral therapy.

Data from 18 cohorts in Europe participating in the Antiretroviral Therapy Cohort Collaboration (ART-CC) were examined by Jarrin and colleagues for differences in mortality among treated patients according to race or ethnicity and geographic origin (Abstract 558). Data on geographic origin were available for European and Canadian cohorts; origins were classified as Europe; Northern Africa and Middle East; sub-Saharan Africa; Asia; and Caribbean, South, and Central America. Data for race or ethnicity were available for Canadian and US cohorts. Thus, the investigators conducted separate analyses for Europe (n = 34,614), Canada (n = 1387 for geographic origin, and n = 1710 for race or ethnicity), and the United States (n = 7928). In Europe, HIV-infected migrants from sub-Saharan Africa and Asia had lower mortality than HIV-infected nationals, in unadjusted analysis (odds ratio [OR], 0.52; 95% CI, 0.44 – 0.61 for sub-Saharan Africa; and OR, 0.52; 95% CI, 0.33 – 0.81 for Asia). These associations remained statistically significant after adjustment for sex, age, transmission group, AIDS status, CD4+ cell count, and pre–antiretroviral therapy plasma HIV-1 RNA level. In the United States, black race was associated with higher mortality than white race (OR, 1.18; 95% CI, 1.07 – 1.31). None of the racial or ethnic categories in Canada (black, Hispanic, Asian, or indigenous) had statistically significantly different mortality from that of white Canadians in the cohort.

Two presentations examined switches to second-line antiretroviral therapy in non-RLS. The first, presented by Abgrall and colleagues, used data from the ART-CC to determine antiretroviral therapy outcomes after transition to second-line therapy for those at least 16 years of age who started antiretroviral therapy after 2002 using either PI/r or NNRTI plus at least 2 nRTIs (Abstract 578).

Of 15,008 patients, 40% switched and 16.5% interrupted initial treatment. The hazard ratio (HR) for AIDS-defining illness or death was 2.49 (95% CI, 2.21 – 2.81) for those who interrupted treatment compared with those who switched antiretroviral therapy regimens. This association remained statistically significant after adjustment for risk-transmission group, age, AIDS diagnosis, calendar year, duration of initial regimen, and many other potential confounders. Those who switched regimens for treatment failure had a higher risk of death or AIDS event (HR, 5.91; 95% CI, 3.38 – 10.33) than those who switched for regimen simplifications. Those who switched because of a physician's decision, side effect, or patient's decision also had higher risks of AIDS or death than those who switched for regimen simplification in the adjusted analysis. The investigators also found that more than 50% of switches were exchanging or adding drugs within the same antiretroviral therapy class and that most of the switches, discontinuations, or deaths occurred within the first year of antiretroviral therapy.

Hull and colleagues determined the effect of fixed-dose combination formulations of antiretroviral therapy on switches to second-line therapy among 2144 HIV-1-infected adults initiating antiretroviral therapy between 2000 and 2010 with efavirenz, atazanavir, or lopinavir-based regimens in the Canadian Observational Cohort Collaboration (CANOC) (Abstract 579). They examined the following 3 associations: (1) fixed-dose abacavir/lamivudine for patients receiving abacavir and lamivudine, (2) fixed-dose lamivudine or emtricitabine/tenofovir for those receiving tenofovir plus lamivudine or

emtricitabine, excluding those taking efavirenz, and (3) fixed-dose emtricitabine/tenofovir/efavirenz for those receiving tenofovir, efavirenz, and either lamivudine or emtricitabine.

For all 3 analyses, the use of a fixed-dose combination was inversely associated with regimen switch compared with those not using fixed-dose combinations after adjustment for age, sex, history of injection drug use, year of antiretroviral therapy start, pre–antiretroviral therapy plasma HIV-1 RNA level, and geographic location. For comparison 1, the adjusted odds ratio (aOR) for the inverse association was 0.20 (95% CI, 0.10 – 0.40); for comparison 2, aOR was 0.40 (95% CI, 0.24 – 0.68); and for comparison 3, aOR was 0.20 (95% CI, 0.15 – 0.44). Virologic suppression was also more likely when using fixed-dose combinations of abacavir/lamivudine and emtricitabine/tenofovir/efavirenz. Although this study is limited by the fact that data are derived from an observational cohort with the potential for unmeasured confounders, the findings imply that the use of fixed-dose combinations may lead to less regimen switching and, in some cases, increased likelihood of virologic suppression.

Three different cohorts determined causes of death in treated HIV infection. Ruppik and colleagues examined 459 deaths between 2005 and 2009 among 9053 Swiss HIV Cohort participants observed during that period (Abstract 789). They were able to determine cause of death in all but 11 of these individuals and found that non–AIDS-defining malignancies were the most common cause of death (19%), including hepatocellular carcinoma (2.8% of total deaths), followed by AIDS-defining illnesses (16.4%) and liver diseases excluding hepatocellular carcinoma (15%).

Kowalska and colleagues determined risk of cause-specific death over time in relationship to antiretroviral therapy exposure among HIV-1-infected patients in the EuroSIDA cohort (Abstract 790). They found that the risk of non–AIDS-related deaths (non–AIDS-related infections, liver disease, non–AIDS-defining malignancies, cardio-

vascular disease, other, and unknown) increased with cumulative exposure to antiretroviral therapy. Among 11,982 patients in antiretroviral therapy, the adjusted incidence rate ratio (aIRR) for non–AIDS-related death was lower in the first 2 years after antiretroviral therapy initiation than in years 2 to 4 of antiretroviral therapy (aIRR, 0.64; 95% CI, 0.52 – 0.80). This relationship was driven by those initiating antiretroviral therapy before 2002. The trend remained statistically significant after controlling for age when examined for the following specific causes of death: cardiovascular disease, liver-related disease, other, and unknown but not for the other causes of death.

Zhang and colleagues used data from the AIDS Therapy Evaluation Project, Netherlands (ATHENA) cohort to determine the association between CD4+ cell count and plasma HIV-1 RNA level before and after antiretroviral therapy initiation and non–AIDS-related endpoints: cardiovascular disease, renal failure, liver disease, and a combined endpoint incorporating all 3 (Abstract 791). Incidence of non–AIDS-related events was lower before than after antiretroviral therapy initiation for cardiovascular disease (0.18/100 person-years vs 0.49/100 person-years, respectively; *P* < .001) and for the combined endpoint but not for renal failure or liver disease. The investigators found that higher CD4+ cell counts were inversely associated with non–AIDS-related events both before initiation (adjusted relative risk [aRR], 0.60; 95% CI, 0.53 – 0.68) and after initiation (aRR, 0.40; 95% CI, 0.35 – 0.47). There was no statistically significant association between plasma HIV-1 RNA level before antiretroviral therapy initiation and non–AIDS-related events.

Several studies applied genome-wide association analysis to existing longitudinal cohorts, including one by McLaren and colleagues, who used samples from subjects in ACTG studies (A5202, A5142, A5095, and ACTG 384) to assess genetic influence on virologic outcomes of patients taking efavirenz or abacavir (Abstract 477). Genotypic testing was performed using whole-genome single-nucleotide polymorphism (SNP) arrays on 1622 samples from individuals taking efavirenz and 792 samples from people using abacavir. Samples were stratified by ethnicity, and approximately 500,000 SNPs were examined for association with the following 3 outcomes: (1) early virologic response (defined as plasma HIV-1 RNA level < 50 copies/mL at or before 16 weeks of antiretroviral therapy), (2) virologic relapse (plasma HIV-1 RNA level > 200 copies/mL after achieving a level < 200 copies/mL), and (3) virologic response (plasma HIV-1 RNA level < 50 copies/mL at or before 48 weeks). All subanalyses included only those individuals who did not report missed doses, and they specifically interrogated SNPs within 100 kilobases of a selected group of drug-absorption, distribution, metabolism, and elimination (ADME) genes.

Results did not show any SNP that met criteria for genomewide statistical significance ($P < 5 \times 10^{-8}$) for association with any of the outcome categories. The authors reported approximately 80% power to detect OR value greater than 2.1 for virologic failure in the efavirenz group and approximately 80% power to detect OR value greater than 3.7 for virologic failure in the abacavir group. They concluded that there were no large-effect (OR > 2) common variants found to contribute to virologic failure in this combined cohort but that common variants with modest effects or rare variants would not be discovered in this analysis and could contribute to the outcomes tested.

Treatment Outcomes Among Young Adults

A themed discussion (Session 14) covered 4 poster presentations on antiretroviral therapy use and outcomes in youth. Rudy introduced the session with an overview of epidemiology in this important group of approximately 10 million people living with HIV who are between the ages of 15 years and 24 years. In North and Latin America and in Central and Western Europe, this epidemic is driven by men who have sex with men (MSM), and in East-ern Europe and some parts of Asia, it is driven by injection drug use. In southern Africa, data suggest that the highest HIV infection risk is in women in their 20s, driven by heterosexual risk. There are also many perinatally infected adolescents who are now "aging up" into this group and who face additional challenges because of their extensive treatment experience. The Joint United Nations Programme on HIV/AIDS (UNAIDS) estimates that there are 1 million new infections each year in young adults.

Agwu and colleagues examined disparities in antiretroviral therapy utilization in a cohort of 247 non–perinatally HIV-infected youth aged 12 years to 24 years receiving care at 14 different treatment sites between 2002 and 2008 (Abstract 692). Inclusion criteria for the cohort were being antiretroviral therapy–naive and having at least 2 CD4+ cell count measurements of no more than 350/μL. The median age of the cohort was 21 years (interquartile range [IQR], 20 – 23 years), 72% were boys or men, and 68% were black. The majority (78%) were receiving care at adult HIV treatment sites. A total of 198 (69%) of the cohort initiated antiretroviral therapy.

In multivariate analysis, antiretroviral therapy initiation was associated with CD4+ cell count less than 200/μL (adjusted hazard ratio [aHR], 2.02; 95% CI, 1.40 – 2.90) and attending 4 or more outpatient HIV practitioner visits in the year after meeting treatment criteria (aHR, 2.23; 95% CI, 1.50 – 3.31). Potential predictors that were not statistically significant in the multivariate analysis included race or ethnicity, HIV acquisition risk, insurance coverage, year meeting treatment criteria, and being at an adult treatment center.

The investigators also examined risk of discontinuing first antiretroviral therapy regimen, which occurred in 117 individuals in the cohort (41%): 50 switched antiretroviral therapy regimens, and 67 discontinued antiretroviral therapy. Discontinuation of the initial antiretroviral regimen occurred statistically significantly more rapidly (within 297 days; IQR, 18 – 896 days) among those cared for at adult clinic

sites than among those cared for at pediatric sites (within 594 days; IQR, 229 – 999 days). The overall aHR for discontinuation was 2.06 (95% CI, 1.20 – 3.55) for those receiving care at adult sites compared with pediatric sites. Of those who discontinued, 67% remained in care the year following discontinuation; all 15 who received care at pediatric sites were receiving antiretroviral therapy, compared with only 78% of the 49 patients receiving care at the adult sites (*P* = .04).

Saavedra-Lozano and colleagues determined the clinical status of 74 members of the Madrid Cohort of HIV-infected children at the time of their transfer to an adult clinic (Abstract 693). The mean age at transfer was 18.9 years (range, 13 – 22 years), the mean absolute CD4+ cell count was 710/μL; 54% had plasma HIV-1 RNA levels less than 400 copies/mL; and 54% received a clinical diagnosis of lipodystrophy. The majority of the patients were receiving 1 PI and 2 nRTIs (28%) or 1 NNRTI and 2 nRTIs (27%), and 75% had received 2 or more antiretroviral regimens at the time of transfer. Thirty-nine (53%) of these patients underwent HIV-1 genotypic testing, although criteria for genotypic testing in the cohort were not provided. Of these, 21 had PI- and reverse transcriptase inhibitor–associated resistance mutations, and 3 had only PI-associated resistance mutations. The authors concluded that the patients had relatively well-preserved clinical and immunologic condition after many years of antiretroviral therapy but that prevalence of lipodystrophy and drug resistance mutations were high in the cohort.

Ryscavage and colleagues conducted a retrospective, matched case-control study comparing 46 HIV-1-infected young adults aged 17 years to 24 years with adults aged 25 years to 40 years, all newly receiving care in an adult-oriented, university-based clinic (Abstract 694). The adult control group was randomly selected from the clinic and matched 1:1 with the young adults for ethnicity, sex, pregnancy during the study period, pre–antiretroviral therapy plasma HIV-1 RNA level, and HIV genotypic susceptibility score.

The young-adult population was 54% black, 61% women, and 59% pregnant patients. The primary endpoint was achievement of virologic suppression (plasma HIV-1 RNA level < 400 copies/mL) 6 months after antiretroviral therapy initiation or after establishment of care in the clinic for those already receiving antiretroviral therapy.

The investigators found that 58.7% of young adults achieved virologic suppression at 6 months compared with 78.2% of adults (*P* = .025), and the young adults had a 6-fold higher likelihood of being lost to follow-up (LTFU, also indicates loss to follow-up) than did the adults, defined as no clinic attendance for 12 months or longer. These differences were particularly dramatic in black patients. Young-adult black patients had a statistically significantly lower probability of virologic suppression than either young nonblack patients (44% vs 77%, respectively) or nonblack adults (91%).

Lowenthal and colleagues determined the ability of a screening tool for pediatric psychosocial dysfunction, the Pediatric Symptom Checklist (PSC), and of age at antiretroviral therapy initiation to predict virologic failure of antiretroviral therapy in a cohort of HIV-infected children in Botswana (Abstract 695). They conducted a cross-sectional analysis of 8- to 16-year-old, HIV-infected children receiving care at a single site, and they translated, culturally adapted, and validated the PSC, using receiver operating characteristic (ROC) analysis to determine optimal cutoff scores. The study enrolled 635 children who had been receiving antiretroviral therapy for more than 6 months, 24% of whom met criteria for virologic failure and 17% of whom had PSC scores of more than 20, the threshold for positivity determined in the ROC analysis.

The OR for virologic failure among those with PSC scores of 20 or higher was 1.64 (95% CI, 1.04 – 2.57) compared with those with PSC scores less than 20. Initiating antiretroviral therapy at age 10 years or older was also statistically significantly associated with virologic failure (HR, 3.08; 95% CI, 2.01–4.71). Neither of the 2 associ-

ations varied statistically significantly after adjustment for sex, age, school grade, baseline or current CD4+ cell count, orphan status, or the other of the 2 predictors.

Acute Infection

Treatment of acute HIV infection. The benefit of treatment for acute HIV infection remains unclear. The following studies focused on the impact of treatment during acute or recent HIV infection in terms of treatment outcomes, viral load set point, or immune activation. Grijsen and colleagues reported results of a multicenter, open-label, randomized control trial comparing no treatment with 24 weeks or 60 weeks of temporary 4-drug antiretroviral therapy during primary HIV infection (Abstract 161). Only those patients for whom treatment was indicated were randomly assigned to 1 of the 2 treatment groups. There were 36 patients in the untreated group, 40 patients in the 24-week treatment group, and 39 in the 60-week treatment group. Patients were treated with 2 nRTIs, an NNRTI, and a PI. Primary endpoints were plasma viral load at 36 weeks after randomization or treatment interruption and total time off therapy. Subjects had serologic test results consistent with acute HIV infection in 73% of cases, and symptoms were present in 83% of cases. Antiretroviral therapy was initiated for subjects with an incident AIDS diagnosis or a CD4+ cell count less than 350/μL.

At 36 weeks after randomization or treatment interruption, the mean viral set point was statistically significantly higher in the untreated group: 4.8 $\log_{10}$ copies/mL in the untreated group compared with 3.9 $\log_{10}$ copies/mL and 4.2 $\log_{10}$ copies/mL in the 24- and 60-week treatment groups, respectively (*P* < .001). Authors also analyzed time off treatment and found that the median was 0.7 years (95% CI, 0.2 – 1.2 years) in the untreated group and 3.1 years (95% CI, 2.3 – 3.8 years) and 2.1 years (95% CI, 0.4 – 3.8 years) in the 24- and 60-week groups, respectively (*P* < .001). There was no statistically significant difference in time off treatment

between the 2 treatment groups. The authors suggested that temporary antiretroviral therapy during primary HIV infection lowers the setpoint and defers the start time for continuous antiretroviral therapy for chronic HIV infection.

Markowitz and colleagues sought to understand whether antiretroviral therapy initiated during early HIV infection and targeting entry, reverse transcriptase, integrase, and protease would improve outcomes compared with a 3-drug, PI-based regimen (Abstract 148LB). The authors presented 48-week data from a randomized, open-label trial of a 5-drug regimen compared with a 3-drug standard PI-based antiretroviral regimen initiated during acute and early HIV-1 infection. Patients were randomly assigned 1:2 to receive 3 drugs or 5 drugs. Both treatment groups received tenofovir/emtricitabine and either atazanavir/r or darunavir/r; the 5-drug group also received maraviroc and raltegravir. Data were available from 11 patients in the 3-drug group and 23 patients in the 5-drug group.

At week 48 of treatment, there were no statistically significant differences in percent of subjects with plasma HIV-1 RNA levels below detection using the single-copy assay, increase in CD4+ T cell count, or immune activation markers. There were 3 individuals in the 5-drug group for whom treatment failed to suppress viral load at 48 weeks by standard assay; this result was unexpected but not statistically significant. Researchers noted that additional studies are under way to compare the effects of the 3-drug regimen with those of the 5-drug regimen on the gastrointestinal tract and on the latent reservoir.

Ananworanich and colleagues also investigated the effects of a 5-drug regimen on acute HIV infection (Abstract 516). The team sought to understand the impact of this regimen on HIV suppression, the viral reservoir, and restoration of immunity in the peripheral blood and sigmoid colon. A total of 20 study participants were treated for 6 months with tenofovir, emtricitabine, efavirenz, raltegravir, and maraviroc. Levels of HIV RNA and DNA were mea-

sured in the blood and sigmoid colon, and mononuclear mucosal cells and PBMCs were analyzed in 16 and 8 patients, respectively.

The authors highlighted the finding that patients with infection classified as Feibig stage III (classified as detectable HIV-1 RNA, p24 antigen positive, HIV seropositive on enzyme-linked immunosorbent assay, and negative on HIV Western blot testing) at enrollment had statistically significantly reduced numbers of CD4+CCR5+ T cells in the mononuclear mucosal cells compared with both healthy individuals and with persons with disease in Feibig stage I (defined as HIV-1 RNA detectable, p24 antigen negative, and HIV-antibody negative). The authors suggested that 5-drug treatment in early-Feibig-stage, acute HIV infection may prevent CD4+ cell depletion in the sigmoid colon and render gut and peripheral HIV RNA undetectable, thereby reducing the viral burden and promoting immune restoration.

Investigators from the University of California San Francisco (UCSF) Options Project compared the effect of antiretroviral therapy initiation during acute or early HIV infection with later antiretroviral therapy initiation on various immunologic and virologic outcomes (Abstract 517). There were 34 participants in the early-treatment group and 32 in the later-treatment group. Participants were included in the analysis if they maintained at least 2 years of viral suppression after initiation of either early or late antiretroviral therapy. The authors analyzed markers of CD4+ and CD8+ activation and found that the late-antiretroviral therapy group had statistically significantly higher levels of activated CD4+ and CD8+ T cells, statistically significantly higher proviral DNA levels, and statistically significantly higher viral reservoirs than the early-treatment group. They suggested that earlier antiretroviral therapy initiation may be associated with lower T-cell activation and smaller HIV reservoirs.

Resistance and acute HIV infection. The relevance of minor resistance variants at the time of acute infection is

unclear. Liegler and colleagues studied minor resistance variants in 6 patients from the UCSF Options Cohort who were found to have the M184V transmitted drug resistance mutation during primary HIV infection (Abstract 513). Results of population-based sequencing and quantitative minor variant assays were observed over time in individuals enrolled within 6 months of infection whose transmitted drug resistance mutation M184V had reverted to wild type after discontinuation of antiretroviral therapy.

The sensitive polymerase chain reaction (PCR)-based minor variant assay detected reversion at an average of 18 weeks compared with 28 weeks using population-based sequencing. Loss of detectable M184V (less than 0.5%) occurred at a mean of 36 weeks from infection and persisted for up to 5 years of monitoring. After M184V detection by population sequencing, loss of detectable M184V occurs rapidly at a mean of 10 weeks. The authors suggested that the rapid overgrowth of wild-type virus may indicate that reverse transcriptase 184 declines to levels that are not clinically important 1 year after reversion.

Gianella and colleagues also looked at minority resistance variants during early HIV-1 infection and compared bulk sequencing with ultra-deep sequencing on baseline blood samples of 23 recently infected individuals (Abstract 514). Several findings suggested that such minority mutants are unlikely to be transmitted to, and maintained in, the recipient host. The authors showed that ultra-deep sequencing revealed a higher frequency of resistance mutations (93.7%) than found through bulk sequencing (12.5%). Furthermore, 60% of the drug resistance mutations in the ultra-deep sequencing group were present at less than 1% (mean 0.56%; 95% CI, 0.43%–0.69%), and there was wide variability in the drug resistance mutations with repeated runs. There was no correlation between minority drug resistance mutations and negative clinical outcomes with initial antiretroviral regimens. The authors suggested that the majority of detected low-frequency

drug resistance mutations are likely to be the consequence of HIV-1 within-host diversification or evolution, or of methodology-related error.

Antiretroviral Treatment in Resource-Limited Settings

Overview

The opening session N'Galy-Mann Lecture, delivered by Harries, focused on the history of the HIV epidemic in Malawi, where HIV infection prevalence reached 14% of the general population by 1995 (Abstract 18). Harries reminded the audience that, before antiretroviral therapy availability in Malawi, 90% of adults receiving a diagnosis of stage 4 HIV disease were dead within 12 months, and half of all children receiving an HIV infection diagnosis were dead within 2 years of diagnosis. Harries and his colleagues envisioned a directly observed-therapy–like strategy for antiretroviral treatment in Malawi in August 2001, and they received resources from the Global Fund to Fight AIDS, Tuberculosis, and Malaria for antiretroviral therapy scale-up in 2002.

Scale-up emphasized simplicity and standardization of regimens to ensure ease of delivery and equity of access throughout the country, with 1 initial and 1 second-line regimen available. Monitoring and evaluation procedures were built into the efforts early on and included quarterly, in-person site visits within that program. Data from the program showed that Harries and colleagues achieved 60% coverage for antiretroviral therapy by September 2010, and the percentage of patients initiating antiretroviral therapy at World Health Organization (WHO) clinical stage 4 diminished from 25% in 2005 to 10% in 2010. The efforts have yielded results at a population scale, with overall mortality declining dramatically, whether measured by traditional registers or by nontraditional mortality measurements such as coffin sales and church funerals.[2]

Harries argued that the future will require a focus on prevention of new HIV infections, expansion of programs for prevention of mother-to-child trans-mission (PMTCT) of HIV infection, which reach only 35% of HIV-infected mothers and children, and LTFU of patients with HIV infection who have not yet initiated antiretroviral therapy. The 2010 WHO guidelines for antiretroviral therapy and PMTCT will help with these endeavors,[3,4] but the lack of access to CD4+ cell count monitoring remains a major obstacle to progress.

Harries proposed universal HIV testing and immediate antiretroviral therapy initiation, as promoted by Granich and colleagues in 2009.[5] Malawi recently adopted a policy of "antiretroviral therapy for life" with tenofovir, lamivudine, and efavirenz for all HIV-infected pregnant women regardless of CD4+ cell count. Harries acknowledged that such a program will require careful monitoring of the safety, acceptability, feasibility, and outcomes of the program, but he believes that this intervention, combined with targeted prevention interventions such as microbicides, preexposure prophylaxis (PrEP), and male circumcision should form the next salvo in the battle against the HIV epidemic in Malawi.

Sow gave a "Global Antiretroviral Therapy Update" during a workshop for new investigators and trainees (Abstract 6). He emphasized the unprecedented success of global antiretroviral therapy scale-up and highlighted challenges to continued success. These challenges include high mortality after antiretroviral therapy initiation, difficulty managing HIV infection in patients with tuberculosis coinfection, retention in care, lack of laboratory monitoring, and lack of access to second-line regimens or regimens for repeated antiretroviral therapy failure.

Sow selected 4 "top" papers of the past year, 2 that highlighted the mortality benefits of early initiation of antiretroviral therapy, even in patients receiving tuberculosis treatment,[6,7] 1 that demostrated the importance of generic antiretroviral therapy to cost savings achieved within President's Emergency Plan for AIDS Relief (PEPFAR)-supported programs,[8] and 1 that described factors associated with increased mortality in patients receiving second-line antiretroviral therapy in a cohort of 27 Médecins Sans Frontières (Doctors Without Borders, MSF)-sponsored programs.[9] Sow also emphasized the importance of the 2010 WHO guidelines for the initiation of antiretroviral therapy at CD4+ cell counts less than 350/µL and the need for treatment of HIV-associated comorbidities, such as cardiovascular disease, in RLS.

Walensky discussed several issues relevant to the cost-effectiveness of antiretroviral therapy in RLS (Abstract 74). She discussed the limitations of cost-effectiveness literature in general and the application of WHO cost-effectiveness standards to RLS. The economic value of antiretroviral therapy in RLS was first addressed in a 2006 publication, which examined the cost-effectiveness of antiretroviral therapy in Côte d'Ivoire by WHO Gross Domestic Product comparison standards.[10] Subsequent studies examined cost-effectiveness of CD4+ cell count monitoring, plasma HIV-1 RNA level monitoring, and initial and second-line antiretroviral therapy. These showed that antiretroviral therapy costs, rather than laboratory-monitoring costs, were higher in regions offering plasma HIV-1 RNA monitoring, as the viral load monitoring led to transitions to more costly second-line regimens.[11]

Walensky and colleagues also applied clinical efficacy and cost-effectiveness analysis to the 2010 WHO treatment guidelines, which recommended antiretroviral therapy initiation at CD4+ cell counts less than 350/µL, increased number of sequential antiretroviral regimens (ie, availability of second-line therapy), and replacement of stavudine with tenofovir.[12] The clinical impact model determined that the initiation of antiretroviral therapy at CD4+ cell counts less than 350/µL conferred the greatest survival benefit, followed by the availability of second-line antiretroviral therapy, followed by replacement of stavudine by tenofovir. The cost-effectiveness analysis showed that earlier initiation of antiretroviral therapy and replacement of stavudine by tenofovir would be important first steps, followed by access to second-line therapy. Overall, the introduction of all 3 WHO-recommended measures

was shown to be very cost effective, even for many RLS, with a ratio of US $2370 per life-year saved.

Advances in Antiretroviral Therapy Scale-Up and Care Delivery in Resource-Limited Settings

Several presentations highlighted new strategies for antiretroviral therapy scale-up and care delivery in RLS. Vitoria of the WHO gave an overview of current and future strategies for antiretroviral therapy optimization at the global level, and began by highlighting the dramatic success of the past decade of antiretroviral therapy scale-up (Abstract 108). He noted the 13-fold increase in access to antiretroviral therapy over the past 6 years and that 5.25 million people now receive antiretroviral therapy in low- and middle-income countries.

Antiretroviral therapy has been shown to impact country-level health indicators. Notable examples include antiretroviral therapy–associated reductions in overall mortality in South Africa and antiretroviral therapy–associated declines in tuberculosis incidence in Botswana. However, global coverage of antiretroviral therapy remains at 36% for adults with respect to the 2010 WHO guidelines criteria, 28% for children, and 53% for PMTCT in 2009, and stark inequalities in terms of drug price compared with national incomes persist. The joint UNAIDS/WHO "Treatment 2.0" initiative advocates specific strategies to catalyze the next phase of scale-up in HIV disease treatment.[13]

The strategies proposed by this initiative include (1) the promotion of fixed-dose combinations, which bring programmatic, clinical, and economic benefit; (2) potential dose reductions in antiretroviral therapy based on data from phase II trials indicating virologic outcomes were similar for several doses of many drugs[14]; (3) reformulation of existing drugs to make them easier to take and less toxic; (4) improvements in bioavailability of drugs, including alterations of crystalline forms and the potential use of nanopharmaceuticals; (5) the potential role of new

antiretroviral drugs in RLS, such as rilpivirine in a fixed-dose combination or long-acting tenofovir; and (6) new treatment strategies including induction or maintenance of monotherapy with ritonavir-boosted PIs, which have mixed results in early trials but deserve more investigation. Vitoria concluded that a combination of innovative strategies can help antiretroviral therapy scale-up move into its second decade and achieve further success.

Long and colleagues used results from a recent randomized control trial showing noninferiority of nurse versus physician management of HIV-infected patients receiving antiretroviral therapy as background for an examination of the impact of shifting the management of patients on stable antiretroviral therapy from physicians to nurses in South Africa in a routine-care setting (Abstract 43).[15] The study included patients initially managed by physicians and eligible for nurse management, as determined by stable antiretroviral therapy for longer than 6 months, undetectable plasma HIV-1 RNA level, CD4+ cell count greater than 200/μL, and less than 5% weight loss over the past 3 clinic visits. The patients were divided into 2 groups: those managed by doctors (n = 1620) and those managed by nurses (n = 540); the groups were matched for age, sex, CD4+ cell count, time on antiretroviral therapy, and antiretroviral regimen. Baseline characteristics were comparable across the 2 groups: subjects had been receiving antiretroviral therapy for a mean of 13.2 months and were receiving either stavudine/lamivudine/efavirenz or zidovudine/lamivudine/efavirenz.

Primary outcomes—LTFU, mortality, virologic rebound, and mean CD4+ cell count response—did not differ statistically significantly between the 2 groups. The cost savings were modest: a US $48 reduction per year per patient in care and responding to treatment. However, when extrapolated to the approximately 25% of South Africa's current population receiving antiretroviral therapy and eligible for nurse-managed care, this shift in care would represent a savings of more

than US $12 million annually. Long acknowledged that the study's limitations included lack of generalizability and confounding by unmeasured variables that differ between study groups, but he concluded that shifting care to nurses could result in increased treatment capacity without compromise of patient outcomes.

Bendavid and colleagues estimated the contributions that the decreasing price of initial antiretroviral therapy and increasing foreign assistance for HIV care had on antiretroviral therapy coverage in RLS (Abstract 568). The authors used data from the WHO Global Price Reporting Mechanism and the French National Agency for Research on AIDS and Viral Hepatitis (ANRS) Economics of AIDS and Access to HIV/AIDS Care in Developing Countries Project to create a price index for initial antiretroviral therapy for 13 countries in sub-Saharan Africa. The index described costs per country per year and represented 84% of Africa's estimated total number of people living with HIV or AIDS. Foreign assistance was measured as disbursements from the World Bank, the Global Fund to Fight AIDS, Tuberculosis, and Malaria, and PEPFAR, and data on antiretroviral therapy coverage was obtained from UNAIDS.

The authors found that the mean annual price of initial antiretroviral therapy dropped from US $1177 in 2003 to $96 in 2008, and antiretroviral therapy coverage increased from 5.7% to 51.2% over the same time period. Multivariate analysis, adjusting for public health expenditures, gross domestic product, HIV prevalence, and government effectiveness, showed that antiretroviral therapy coverage was associated more closely with price reductions at lower prices and that, together, price reductions and foreign assistance for HIV care explained half of the increase in antiretroviral therapy coverage observed between 2003 and 2008. The authors concluded that price reductions, even to very low levels, are unlikely to be associated with substantial additional gains in antiretroviral therapy coverage and that achievement of universal coverage

will require a substantial increase in foreign assistance and national public health expenditures for HIV care.

Retention in Care and Adherence to Antiretroviral Therapy in Resource-Limited Settings

Bangsberg discussed adherence and resistance to antiretroviral therapy (Abstract 111). He began his presentation by reminding the audience of a 2006 meta-analysis of 228 studies, which demonstrated that adherence in RLS was 77% (95% CI, 67%–86%), a level statistically significantly greater than in resource-rich countries (55%; 95% CI, 48%–61%).[16] He stressed the positive-feedback loop of social capital and its promotion of adherence as proposed by Ware and colleagues,[17] and he emphasized that the major barriers to treatment adherence in RLS—primarily structural and economic factors—can be neutralized by the protective effects of social capital.

Unfortunately, adherence does decline over time, a phenomenon well known in resource-rich settings and shown in RLS as well.[18] Recently, 2 adherence interventions in RLS showed the potential for text-message reminders to substantially increase adherence. Adherence was increased from 48% to 57% in one study and from 47% to 63% in a second study, both comparing those receiving text messages to those not receiving text messages, respectively.[19,20] Bangsberg highlighted a new monitoring technology, in which a medication dispenser records when it is opened and sends a wireless message to a central server, which then can send appropriate reminders to either patients or caregivers.[21] He noted the potential limitation to this technology is that an intervention must be made quickly because treatment interruptions longer than 3 days to 4 days are associated with loss of virologic control.[22] However, given that pharmacy-refill data can be better than CD4+ cell count monitoring at detecting virologic failure,[23] Bangsberg speculated that the costs of more effective adherence monitoring and support devices could be covered by the cost savings of improved adherence.

Bangsberg concluded with a reminder that the most important challenge in sustaining adherence success in RLS is posed by restriction in funding sources. If the time to treatment increases, which Geng and colleagues showed occurs when funding sources are unstable, then those taking antiretroviral therapy are likely to share their medications with ill family and friends.[24] This practice could erode treatment success for those undergoing antiretroviral therapy and lead to the emergence of resistance in those not "officially" receiving antiretroviral therapy but with whom the medications are shared.

Nachega introduced Session 16, "Retention and Adherence to Care in Resource-Limited Settings," with an overview of how adherence fits into the larger framework of HIV care outcomes and the demonstrated cost savings of antiretroviral therapy adherence.[25] He highlighted differences in methods of measuring adherence and mentioned the effectiveness and scalability of some of the interventions, particularly a pill-monitor and text-messaging intervention described above by Bangsberg; he noted that retention in care is also essential. Although much of the LTFU in RLS, up to 40% in some scenarios, is because of death, Nachega emphasized the need for improved methods of tracking and retention in care to improve the current situation, in which up to 50% of people can be LTFU by 24 months of antiretroviral therapy.[26]

Ahonkhai and colleagues presented results from a retrospective cohort study of 11,397 patients initiating antiretroviral therapy in South Africa between 2004 and 2008 (Abstract 1014). Median follow-up within the cohort was 2.4 years, and at study conclusion 63% of patients remained in care, 11% interrupted care but returned within 1 year, 17% were LTFU with no appointments within a year, and 9% died within the first 7 months of antiretroviral therapy. Of those who interrupted care, 84% had plasma HIV-1 RNA levels less than 400 copies/mL, and median CD4+ cell count was 257/μL upon return. Early death was predicted by

low pre–antiretroviral therapy CD4+ cell count (median, 48/μL), and male sex predicted all outcomes other than maintenance in care. Interestingly, LTFU decreased over time as the program expanded. Ahonkhai also noted that baseline risk factors did not distinguish interrupted care from LTFU, but these 2 events had strikingly different outcomes.

Braitstein and colleagues presented data from an evaluation of LTFU in programs participating in the IeDEA (International Epidemiologic Databases to Evaluate AIDS) cohort collaboration (Abstract 1015). They included data from 29 antiretroviral therapy clinics in East Africa with 43,175 eligible patients (age ≥ 18 years, and receiving antiretroviral therapy at last visit) and used a Weibull survival model with the fixed covariates of age, sex, CD4+ cell count at antiretroviral therapy initiation, and WHO stage at antiretroviral therapy initiation to explore program characteristics associated with LTFU.

The authors determined that clinics using only telephone to reach lost patients and without dedicated outreach staff have an aHR for risk of LTFU, defined as absence from the clinic for 6 months or longer, of 3.36 (95% CI, 1.72–6.57) compared with clinics using dedicated staff for LTFU-prevention outreach. Furthermore, clinics that used only public means for outreach, defined as outreach by bicycle or foot, had an aHR for LTFU of 3.12 (95% CI, 1.41–6.88) compared with those that used all available means for outreach, including the use of a private vehicle. Clinics that waited more than 30 days after a missed visit were more likely to have LTFU than those who did not (aHR, 2.32; 95% CI, 1.26–4.24).

Matovu and colleagues showed results from a randomized, controlled noninferiority trial comparing patients receiving an intervention using nurses and peer educators to support adherence to antiretroviral therapy after initiation to those receiving standard care from a physician and counselor (Abstract 1016). They randomly assigned 92 antiretroviral therapy–naive patients eligible for initial antiretroviral therapy, 50 to the intervention group and 42 to the standard-counseling

group. The authors found that the proportion of patients achieving the primary outcome, plasma HIV-1 RNA level less than 400 copies/mL, was similar in the 2 models: 91% in the standard group and 88% in the intervention group, $P = .73$. There was also no difference in a pill-count adherence measure, CD4+ cell count, or weight change over the 6-month to 12-month follow-up period, suggesting that task-shifting of follow-up care visits to nurses and peers could be effective for patients initiating antiretroviral therapy. These task-shifting findings are similar to those of Long and colleagues (Abstract 43), discussed above.

Geng and colleagues examined failure to initiate antiretroviral therapy, LTFU, and mortality among patients during the pre–antiretroviral therapy initiation period at a single site in Uganda (Abstract 1017). They assessed outcomes in the clinic and used a random-sample tracking method for 89 of the 514 patients LTFU before antiretroviral therapy initiation. Updated outcomes were ascertained for 80% of those originally LTFU in the subsample. Overall, a total of 1772 patients (58% women) met immunologic criteria for antiretroviral therapy initiation, with a median CD4+ cell count of 121/µL.

The cumulative incidence of antiretroviral therapy initiation rose slowly over the first 90 days from 20.6% at 30 days (95% CI, 18.6% – 21.9%) to 63.4% at 90 days (95% CI, 61.4% – 66.0%) but tapered off with a total cumulative incidence of antiretroviral therapy initiation at 365 days of 67.5% (95% CI, 65.1% – 69.7%). A total of 21% (95% CI, 19.3% – 22.6%) were LTFU before antiretroviral therapy initiation at 1 year, and the mortality in the subsample for whom patient tracking was implemented was 30.8% (95% CI, 22.9% – 40.6%). Extrapolating data from the subsample to the entire clinic of all antiretroviral therapy–eligible patients, 9% died before antiretroviral therapy initiation, 7% disengaged from care, 16% were in care awaiting antiretroviral therapy, and 69% initiated antiretroviral therapy. If these data can be extrapolated to the antiretroviral therapy scale-up in RLS to date, this im-

plies that more than 1 million eligible patients who presented to care have failed to initiate antiretroviral therapy.

Kohler and colleagues analyzed the results of a program change in a single site in Kenya where free trimethoprim/sulfamethoxazole prophylaxis began to be offered to all patients, regardless of CD4+ cell count (Abstract 1018). They compared 1-year retention rates among 610 individuals enrolled before the free regimen was available with retention rates among 414 subjects enrolled after. The 2 groups had no statistically significant differences in age, sex, tuberculosis prevalence, body mass index, or CD4+ cell count.

They found a statistically significantly higher retention rate (84% vs 63%, respectively) for patients ineligible for antiretroviral therapy who enrolled after the free prophylaxis was available compared with those ineligible for antiretroviral therapy who enrolled before free prophylaxis was available ($P < .001$). No statistically significant difference was observed in LTFU for those receiving antiretroviral therapy during the same time periods. The authors speculated that the improved retention rates could be the result of decreased morbidity, the perception of receiving treatment, lower costs of care, or the establishment of care-seeking habits.

Somi and colleagues presented a retrospective review of results from the Tanzanian national HIV treatment program, which scaled up from managing the care of 11,363 patients in 2004 to 197,412 patients in 2009 (Abstract 1019). The investigators used a multistage, random-sampling model to achieve a nationally representative sample of antiretroviral therapy–naive patients at least 15 years of age who initiated antiretroviral therapy between October 2004 and August 2007 in 43 health facilities. They found that young adults, 15 years to 29 years of age, were more likely to have poor baseline clinical status (CD4+ cell count <50/µL or WHO clinical stage 4) with an OR of 1.63 (95% CI, 1.35 – 1.97) after adjustment for sex and location.

Retention in care for the cohort was 70% at 12 months and 63% at 24 months. By 24 months, 8% were re-

ported dead, 4% were alive but had discontinued antiretroviral therapy, and 25% were LTFU. Poor retention was associated with being a young adult, male sex, having poor baseline clinical or functional status, or having a CD4+ cell count less than 50/µL. Notably for a program in the midst of a greater than 1000% scale-up, retention and clinical outcomes did not vary by initiation period.

Achieng and colleagues conducted an observational study to determine which components of a comprehensive clinic and community adherence and retention program were most effective in an antiretroviral therapy program in central Kenya (Abstract 1020). The study prospectively enrolled 301 patients and collected data on participation in home visits, support groups, postpharmacy counseling, and physician-conducted pill counts over the first 6 months of antiretroviral therapy, as well as the outcomes of virologic failure, antiretroviral therapy discontinuation, death, and LTFU for the first 12 months of antiretroviral therapy.

Time to treatment failure (virologic rebound, death, or LTFU) was determined by Kaplan-Meier survival analysis and was associated with participation in support groups, postpharmacy counseling, accurate pill counts, and home visits. However, in the multivariate analysis, statistically significant reductions in risk of treatment failure were observed only for accurate pill counts (aHR, 0.19; $P < .001$) and participation in support groups (aHR, 0.43; $P < .003$). The authors concluded that these 2 components are the most essential to maintain in their adherence structure and noted during the question period that the physician-conducted pill count traditionally takes less than 1 minute and is effective without requiring many resources.

Leisegang and colleagues conducted a retrospective cohort study of women receiving antiretroviral therapy in a private managed care program in South Africa to determine the impact of pregnancy on antiretroviral therapy adherence (Abstract 1021). Women were classified as never pregnant (n = 4549), pregnant at initiation of long-

term antiretroviral therapy (n = 293), or pregnant after initiating antiretroviral therapy (n = 128).

The authors found that for women who were never pregnant and women who became pregnant after initiation of antiretroviral therapy, improved treatment adherence as assessed by monthly pharmacy refills was associated with shorter time on antiretroviral therapy, older age, receiving second-line antiretroviral therapy, pregnancy, and the 6-month postpartum period. Median adherence was much lower in the group who were pregnant at antiretroviral therapy initiation (54%) than in those who were never pregnant (79%; $P < .001$). The time to antiretroviral therapy default, defined as no antiretroviral therapy claimed for at least 6 months, was also shorter in women who were pregnant at antiretroviral therapy initiation than in the never-pregnant group. The investigators concluded that adherence is improved during pregnancy and immediately postpartum for those who become pregnant while receiving antiretroviral therapy but that adherence is more difficult for women who initiate antiretroviral therapy while pregnant. They are expanding their analysis to include a larger sample to more thoroughly explore these interactions.

Outcomes of Treatment for Adults in Resource-Limited Settings

There were at least 23 presentations on treatment outcomes and predictors of response to therapy in RLS; here, we call attention to a few abstracts from the session on outcomes of second-line antiretroviral therapy in RLS. Fox and colleagues analyzed data from the IeDEA cohort to determine rates and predictors of failure of initial antiretroviral therapy and switch to second-line antiretroviral therapy in 44,204 patients in South Africa (Abstract 580). They included antiretroviral therapy–naive patients receiving NNRTI-based initial antiretroviral therapy with at least 24 weeks of follow-up. Virologic failure was defined as a plasma HIV-1 RNA level of at least 400 copies/mL, followed by a second measure at least

2 weeks later above a threshold of 400 copies/mL to 10,000 copies/mL. At baseline, median CD4+ cell count was 121/μL (IQR, 55/μL – 184/μL); 57% initiated antiretroviral therapy with stavudine/lamivudine/efavirenz; and more than 65% had disease classified as WHO clinical stage 3 or stage 4.

Median time from antiretroviral therapy initiation to treatment failure was 16 months (IQR, 12 – 24 months) for the 10% of patients who met at least 1 failure definition. The threshold chosen for the second confirmatory plasma HIV-1 RNA level elevation affected cumulative estimates of failure, increasing levels by 1.4-fold and 1.6-fold if set at 5000 copies/mL and 1000 copies/mL, respectively, when compared with a threshold of 10,000 copies/mL. Failure was predicted by lower age, male sex, nevirapine use, year initiating antiretroviral therapy, a baseline CD4+ cell count less than 25/μL, and a baseline plasma HIV-1 RNA level of 1,000,000 copies/mL or higher. Only 33% of those with documented virologic failure switched to second-line antiretroviral therapy after a median of 5.5 months after the first elevated plasma HIV-1 RNA level. Switch was predicted by low CD4+ cell count at the time of switch and CD4+ cell count decline over time. Thus, there remains a substantial delay in switching, and many of those meeting criteria for antiretroviral therapy failure do not transition to second-line antiretroviral therapy.

Some of these studies of HIV-infected adults in RLS are summarized in Table 1, which includes studies in children. Other presentations of relevance to adult outcomes of antiretroviral therapy in RLS include Abstracts 537 – 539, 541, 552, 554, 555, 557, 559 – 567, 581, and 582.

Outcomes of Treatment for Infants and Children in Resource-Limited Settings

Although data on treatment outcomes for infants and children in RLS remain limited, there were several presentations of interest at the 2011 CROI. Kuhn and colleagues presented long-term outcomes of the NEVEREST

(Nevirapine Resistance Study), a randomized, controlled trial of treatment strategies in which HIV-infected children with prior exposure to nevirapine for PMTCT were switched to nevirapine-based therapy after initial suppression with a PI-based regimen (Abstract 128). The 52-week results of this trial have already been reported,[27] but Kuhn presented follow-up data for 18 months to 53 months postrandomization. Beginning at 18 months after randomization and continuing through 48 months, children who were in the group that switched back to nevirapine-based antiretroviral therapy were less likely to have a postrandomization plasma HIV-1 RNA level greater than 50 copies/mL, the primary endpoint of the study, than were children who continued treatment with lopinavir/r-based regimens. However, when the secondary endpoint of a confirmed plasma HIV-1 RNA level greater than 1000 copies/mL was assessed, more children in the nevirapine group than in the lopinavir/r group met this endpoint.

The authors pointed out that the patterns of failure differed between the 2 groups: by 6 months, 59% of the treatment failures, as determined by plasma HIV-1 RNA levels greater than 1000 copies/mL, were detected in the nevirapine group; by 12 months, all of the treatment failures had been detected. In contrast, by 12 months, only 60% of the failures had been detected in the lopinavir/r group. Pretreatment drug resistance genotypic testing data, determined by population sequencing, showed a clear relationship between treatment failure in the nevirapine group and the presence of NNRTI mutations in the baseline genotype. The authors concluded that a switch strategy to an NNRTI-based regimen for children exposed to nevirapine for PMTCT could be employed safely in settings where plasma HIV-1 RNA level monitoring is available. They also noted that pretreatment screening for drug resistance mutations would optimize the switch strategy by screening out those for whom an NNRTI-based regimen would likely fail, offering a novel way to integrate genotypic testing into treatment-strategy studies in children.

Table **1.** Selected Studies on Failure to Initiate, Loss to Follow-Up (LTFU), and Switching to Second-Line Antiretroviral Therapy (ART) in Resource-Limited Settings

Abstract No. Study Description	Location Cohort	Study Design Participants Definitions	Key Findings Conclusions
Abstract 1014. Early death, care interruption, and LTFU in adults from a large South African community treatment program	South Africa South African Catholic Bishops Conference, Catholic Relief Services HIV treatment program (71 sites)	Retrospective cohort; n = 11,397; ≥ 15 years old; initiating ART 2004–2008; median follow-up, 2.4 years *LTFU:* missing all appointments in first 12 months after ART start *Interruption:* missing some appointments but returning to care by 12 months	• 63% remained in care, and 37% missed appointments in first year after ART start: – 11% interrupted care, 17% were LTFU, 9% died • Of interrupters: 84% had HIV-1 RNA ≤ 400 copies/mL, 88% had increase in median CD4+ count at return to care • LTFU: decreased with increasing calendar year of enrollment *Conclusion:* Baseline factors did not distinguish interrupted care from LTFU, despite very different clinical implications of these 2 outcomes.
Abstract 1015.[a] Association of program characteristics with patient LTFU in adults on ART in International Epidemiological Databases to Evaluate AIDS (IeDEA) East Africa Consortium	Uganda, Tanzania, Kenya IeDEA East Africa (29 clinics)	Retrospective cohort; n = 43,175; ≥ 18 years old; on ART at last visit; data from 2007–2009; 61% women; mean age, 38 years *LTFU:* absent from clinic ≥ 6 months	• LTFU: 16.5/100 person-years (py) (95% confidence interval [CI], 16.2–16.9/100 py) varied widely between sites (1–79.5/100 py) • Clinics without dedicated staff or with telephone-only outreach had hazard ratio (HR) 3.36 (95% CI, 1.72–6.57) for risk of LTFU compared with clinics with dedicated staff for outreach • Clinics with only public means for outreach (bicycle/walking): HR, 3.12 (95% CI, 1.41–6.88) for LTFU compared with clinics with private vehicles for outreach • Clinics that searched for patients LTFU > 30 days after a missed visit: HR, 2.32 (95% CI, 1.26–4.24) for LTFU compared with those that searched ≤ 30 days of a missed visit *Conclusion:* Patients at sites with outreach programs with dedicated staff and vehicles and early tracking of LTFU patients had lower risk of LTFU.
Abstract 1017. Failure to initiate ART, LTFU, and mortality among adult HIV-infected patients qualifying for ART in Uganda	Uganda Immune Suppression Syndrome Clinic, Mbarara (single site)	Retrospective cohort with intensive tracking of a random sample to assess outcome; n = 1772; enrolling in care and meeting criteria for ART; 2007–2009; 58% women; median CD4+ count, 121/μL *LTFU:* 60 days late for appointment	• ART start: 20.6% (95% CI, 18.6%–21.9%) at 30 days; 63.4% (95% CI, 61.4%–66.0%) at 90 days; 67.5% (95% CI, 65.1%–69.7%) at 365 days • LFTU: 21% (95% CI, 19.3%–22.6%) • 1-year mortality in subsample (n = 134) of those LTFU with outcome tracking: 30.8% (95% CI, 22.9%–40.6%) • Extrapolating subsample results to cohort: 69% initiate, 16% in care awaiting ART, 7% disengaged from care, 9% died before ART initiation *Conclusion:* Failure to initiate ART may be an important issue; more work is needed to determine and eliminate its causes.
Abstracts 680, 681. Outcomes in ART-naive children in Abidjan, Côte d'Ivoire	Côte d'Ivoire Aconda Program	Retrospective cohorts *Abstract 680:* n = 1724; ART-naive; June 2004–November 2007; median age, 54 months *Abstract 681:* n = 405; ART-naive; 2004–2009; median age, 4.5 years; median follow-up, 12 months; 28% met World Health Organization criteria for immunodeficiency	Abstract 680: • 31% of children died, transferred out, or were LTFU before ART start • Mortality rate: 13.2/100 child-years (cy) (95% CI, 10.0–13.4/100 cy) • Mortality correlated with pre-ART CD4+ count in all age strata Abstract 681: • Observed risk of a serious morbid event: 17.8/100 cy at 18 months of follow-up • Cumulative mortality: 3.62/100 cy at 18 months (95% CI, 3.5–8.1/100 cy) • LTFU: 6.36/100 cy (95% CI, 6.16–6.55/100 cy); highest for those 2–5 years of age (9.37/100 cy; 95% CI, 8.92–9.81/100 cy) *Conclusion:* Mortality is high among ART-naive children who qualify for treatment initiation, as are rates of LTFU and serious morbid events. These events may be preventable by earlier ART initiation.

Table **1**. Selected Studies on Failure to Initiate, Loss to Follow-Up (LTFU), and Switching to Second-Line Antiretroviral Therapy (ART) in Resource-Limited Settings (continued)

Abstract No. Study Description	Location Cohort	Study Design Participants Definitions	Key Findings Conclusions
Abstract 580. Rates and predictors of failure of initial regimen and switch to second-line ART in South Africa	South Africa IeDEA Southern Africa (8 programs)	Retrospective cohort; n = 44,204 (96,937 py); NNRTI-based initial ART for ≥ 24 weeks; 59% women; pre-ART median CD4+ count, 121/µL; 57% on stavudine/lamivudine/efavirenz *Virologic failure:* HIV-1 RNA ≥ 400 copies/mL after 24 weeks of ART followed by second value 400–10,000 copies/mL *Switch:* initiation of PI plus change in nRTI(s)	• 10% of patients met at least 1 definition of treatment failure • Median time from ART start to failure, 16 months (interquartile range, 12–24 months) • Failure predicted by lower age, male sex, nevirapine use, year initiating ART, baseline CD4+ count < 25/µL, and baseline HIV-1 RNA ≥ 1,000,000 copies/mL • 33% of those with virologic failure switched to second-line ART at a median 5.5 months after first elevated HIV-1 RNA • Switch predicted by low CD4+ count at time of switch and rapid CD4+ count decline over time *Conclusion:* A substantial delay in switching exists, and many of those meeting criteria for ART failure do not transition to second-line ART.
Abstract 684. Outcomes of HIV-infected and HIV-exposed children LTFU in Western Kenya	Western Kenya AIDSRelief-Kenya	Prospective tracking of random sample of children LTFU; n = 97 (of 308 meeting inclusion) *LTFU:* absent from clinic ≥ 6 months for children on ART who were HIV-exposed or had unknown HIV serostatus; absent from clinic ≥ 12 months for HIV-infected children not on ART	• Community health workers were able to locate or determine vital status for 82% of children: – 11 died: 7 on ART, 2 HIV-exposed, 2 HIV-unknown serostatus • Primary reasons for LTFU for those with known HIV serostatus: fear of family/community discrimination or disclosure issues • For HIV-exposed LTFU: 14/46 never returned because guardians had not disclosed own serostatus or fear of family/community stigma *Conclusion:* Fear of family/community discrimination was an important cause of LTFU in this cohort and should be considered in future interventions

[a]Updated data provided in oral presentation differs from the published abstract.
ART indicates antiretroviral therapy; HIV-1 RNA, plasma HIV-1 RNA level; NNRTI, nonnucleoside analogue reverse transcriptase inhibitor; nRTI, nucleoside analogue reverse transcriptase inhibitor; PI, protease inhibitor.

Malateste and colleagues described outcomes for children before antiretroviral therapy initiation in a large pediatric antiretroviral therapy program in Abidjan, Côte d'Ivoire (the Aconda Program) (Abstracts 680 and 681). One study determined the relationships between absolute CD4+ cell count and percentage and risk of death in 1724 antiretroviral therapy–naive, HIV-infected children with a median age of 54 months (Abstract 680). Of these, 528 (31%) died, transferred out of the clinic, or were LTFU before starting antiretroviral therapy. Child mortality was much higher than that observed in European countries, with an overall mortality rate per 100 child-years (cy) of 13.2 (95% CI, 10.0–13.4), and the risk of death was inversely correlated with pre–antiretroviral therapy CD4+ cell counts in all age strata. The sec-

ond study examined morbidity, mortality, and LTFU in a cohort of 405 HIV-infected children in 2 health facilities who had a median age of 4.5 years (Desmonde et al, Abstract 681). Risks were estimated using a competing risk survival analysis, with antiretroviral therapy as a competing cause of the primary outcome. The observed risk of a serious morbid event was 17.8 per 100 cy at 18 months of follow-up. Risk was lower for children previously exposed to antiretroviral therapy for PMTCT and for children under 5 years of age. Cumulative mortality was 3.62 per 100 cy at 18 months (95% CI, 3.5 – 8.1 per 100 cy). Risk of LTFU was 6.36 per 100 cy (95% CI, 6.16 – 6.55 per 100 cy), and was highest for those between 2 years and 5 years of age (9.37/100 cy; 95% CI, 8.92 – 9.81 per 100 cy). Together, these results argue

for earlier initiation of antiretroviral therapy for children in RLS, a strategy currently recommended by the WHO but still not available to many children.

Barlow-Mosha and colleagues reported on a cohort of 142 children in Uganda, aged 1 year to 12 years, who had been receiving initial antiretroviral therapy for at least 1 year and were enrolled in an ongoing, randomized controlled trial (Abstract 682). The mean age of the children was 7.3 years, 44% were girls, all were on NNRTI-based regimens, the median duration of antiretroviral therapy was 50 months (IQR, 30–63 months), 37% were exposed to single-dose nevirapine for PMTCT, and 79% had disease in WHO clinical stage 2 or 3.

The authors found that median CD4+ cell percentage was 35% (IQR, 29% – 42%), and 65% had a plasma

HIV-1 RNA level below 400 copies/mL. Children exposed to single-dose nevirapine had reduced odds of achieving an undetectable plasma HIV-1 RNA level (OR, 0.36; 95% CI, 0.17–0.74). There was poor correlation between CD4+ cell percentage and having a detectable plasma HIV-1 RNA level ($r = 0.015$). As one-third of the children receiving antiretroviral therapy had detectable plasma HIV-1 RNA levels despite good immunologic response, the authors concluded that plasma HIV-1 RNA monitoring is important for early detection of treatment failure, particularly for children with prior exposure to single-dose nevirapine who are receiving nevirapine-based initial antiretroviral therapy.

Braitstein and colleagues described the results of aggressive tracking of a random sample of children LTFU in western Kenya who were HIV-infected and receiving antiretroviral therapy, HIV-infected and not receiving antiretroviral therapy, HIV-exposed, or of unknown HIV serostatus (Abstract 684). LTFU was defined as absent from the clinic for at least 6 months for children who were receiving antiretroviral therapy, HIV-exposed, or of unknown HIV serostatus, and as absent from the clinic for at least 12 months for HIV-infected children not receiving antiretroviral therapy. A total of 308 children met these inclusion criteria, and of those, the investigators randomly selected 97 children (19 from a rural district hospital and 78 from an urban hospital) for aggressive tracking by community health workers equipped with detailed patient locator information collected on the last known visit.

The community health workers were able to locate 82% of the children in the sample. Of these, 11 (11%) had died: 7 (16%) receiving antiretroviral therapy, 2 (4%) HIV-exposed, and 2 (29%) of unknown HIV serostatus. The primary reason the majority of children did not return to the clinic, of those with known HIV infection or HIV exposure, was because of fear of family or community discrimination or disclosure issues. Of children with unknown HIV serostatus, 2 were not located and 2 were confirmed dead, making these

the largest categories in this group of 7 children. The authors pointed out that the sampling of those LTFU more recently may have led to a higher rate of successful tracking than might occur when tracking children LTFU for a longer time.

Meyer-Rath and colleagues estimated the average outpatient cost of the first 2 years of outpatient antiretroviral therapy for pediatric patients in Zambia and South Africa (Abstract 685). The investigators selected 120 children in Zambia and 148 in South Africa who were initiating therapy at up to 12 years of age between 2005 and 2008 and who remained in the same clinical setting for the first 24 months of antiretroviral therapy. They determined patient outcomes (HIV serostatus, CD4+ cell count, plasma HIV-1 RNA level, and clinical condition) and resource utilization at 12 months and 24 months of antiretroviral therapy.

The median age at antiretroviral therapy initiation was 5.45 years (IQR, 2.21–8.28 years) in Zambia and 4.01 years (IQR, 1.62–7.16 years) in South Africa, and the median CD4+ cell percentages at initiation were 12.5% (IQR, 8.60%–16.40%) and 13.23% (IQR, 7.09%–17.58%) in Zambia and South Africa, respectively. The majority of patients in Zambia received either stavudine/lamivudine/nevirapine or zidovudine/lamivudine/nevirapine, and the majority of patients in South Africa received stavudine/lamivudine/efavirenz or stavudine/lamivudine plus lopinavir/r. Patients were classified as follows: in care and responding (undetectable plasma HIV-1 RNA level, acceptable CD4+ cell percentage and clinical condition); in care and not responding (detectable plasma HIV-1 RNA level, unacceptable CD4+ cell percentage or clinical condition); or no longer in care (died or LTFU).

Rates of retention in care were approximately 75% at both sites at 12 months. The average cost per year for a patient remaining in care was US $367 in year 1 and $346 in year 2 in Zambia, and US $1068 in year 1 and $707 in year 2 in South Africa. The higher costs in South Africa were attributed to the more expensive antiretroviral regi-

men and higher staff costs. The investigators highlighted that, although pediatric treatment costs approximately the same or less than adult treatment (average per adult per first year, US $448 in Zambia and US $699 in South Africa), very few young children have access to antiretroviral therapy in either country. Some of these studies of HIV-infected children in RLS are summarized in Table 1.

Strategies for Laboratory Monitoring in Resource-Limited Settings

Hosseinipour gave an overview of laboratory and clinical monitoring strategies in Session 33, "Getting the Most From Global HIV Scale-Up" (Abstract 109). She emphasized issues specific to RLS, where the poor performance characteristics of clinical and immunologic criteria to determine antiretroviral therapy failure can lead to challenges at both ends of the spectrum: premature switch to second-line therapy for patients for whom virologic control has been achieved but is not recognized because of the lack of virologic monitoring versus prolonged treatment with suboptimal antiretroviral therapy followed by the emergence of resistant virus when clinical and immunologic criteria allow for prolonged treatment without virologic suppression. Hosseinipour reviewed data from the DART (Development of Antiretroviral Therapy in Africa) trial, which showed a small but statistically significant mortality benefit to immunologic monitoring over clinical monitoring after 5 years of antiretroviral therapy.[28] A prior study of home-based antiretroviral care[29] (showed an increased risk of death or AIDS–defining events in the clinical group compared with the immunologic and virologic monitoring group but found no statistically significant difference between the immunologic- and virologic-monitoring groups for the same outcome at 3 years of follow-up.

Hosseinipour also mentioned data on monitoring strategies (Abstracts 44 and 45LB, reviewed below). She concluded that a moderate advantage to immune monitoring can be observed

primarily beyond 2 years, and although no mortality benefit to virologic monitoring has been documented, virologic monitoring is associated with increased switch to second-line therapy and decreased duration of viremia. She then reviewed studies that evaluate the WHO immunologic criteria, all of which showed low sensitivity and low positive predictive value,[30-34] and similar data for the WHO clinical criteria to identify failure.[31,32] Data from the ART-LINC (Antiretroviral Therapy in Lower Income Countries) cohort collaboration have also shown that, of individuals who met WHO criteria for treatment failure, only 24% were switched to second-line antiretroviral therapy, and failure to switch was associated with mortality.[35] Hosseinipour also discussed resistance in RLS (Abstracts 53 and 618, reviewed below under Resistance) and second-line treatment outcomes (Abstract 583, reviewed above under Clinical Trials of Antiretroviral Therapy in Treatment-Experienced Patients).

Lallemant presented data from a randomized controlled trial in Thailand, powered for noninferiority analysis, comparing the use of CD4+ cell count with the use of plasma HIV-1 RNA level monitoring to dictate changes in antiretroviral regimen (Jourdain et al, Abstract 44). Inclusion criteria were HIV-seropositive with CD4+ cell count between 50/μL and 250/μL, no coinfection with either hepatitis B virus (HBV) or hepatitis C virus (HCV), and initiating NNRTI-based antiretroviral therapy. A total of 716 people were randomly assigned to CD4+ cell count or plasma HIV-1 RNA level monitoring every 3 months, and the primary endpoint was a combination of confirmed CD4+ cell count below 50/μL, new AIDS–defining event, or death. The 2 groups were well balanced for baseline characteristics; mean age was 36 years, and median baseline CD4 + cell count was 144/μL. LTFU was minimal (7%) at the end of the study.

The risk of clinical failure was not statistically significantly different between the 2 groups—8.3% in the viral load monitoring group and 7.7% in the CD4+ cell count monitoring group—

nor was the risk of death (4.4% vs 3.5%, respectively). Anemia, CD4+ cell count less than 150/μL, plasma HIV-1 RNA levels over 10,000 copies/mL, and body mass index less than 18.5 kg/m^2 were associated with risk of clinical failure in an adjusted multivariate analysis. Median time to switch was lower in the viral load monitoring group (11.7 months) than in the CD4+ cell count monitoring group (24.7 months; P = .001 for comparison), but virologic and immunologic response at 3 years were similar in both groups. Of the 31 patients in the CD4+ cell count monitoring group, 15 switched to PI-based regimens while their HIV-1 RNA level was undetectable, and 7% of patients required a treatment substitution for toxicity, with no statistical difference between the 2 study groups. There was no statistical difference in future drug options between the 2 groups. The investigators concluded that the additional time spent using failing regimens in the CD4+ cell count monitoring group did not lead to a decrease in future drug options for those patients, but they emphasized the need for adherence support and third-line regimen availability in RLS.

Kouanfack and colleagues asked a similar question in Cameroon, using a randomized noninferiority trial to compare laboratory monitoring (plasma HIV-1 RNA level, CD4+ cell count) plus clinical monitoring every 6 months with clinical monitoring alone (Abstract 45LB). Inclusion criteria were as follows: HIV-infected, antiretroviral therapy–naive adults; WHO stage 3 or stage 4 disease or WHO stage 2 disease with total lymphocyte count less than 1200 cells/μL; and initiating antiretroviral therapy in 1 of 9 district hospitals. The primary outcome was the mean increase in CD4+ cell count after 2 years of antiretroviral therapy, and noninferiority was defined as a difference of no more than 25% in the mean increase in CD4+ cell count between the 2 groups.

Switch to second-line therapy was required for the following scenarios: persistent plasma HIV-1 RNA level above 5000 copies/mL for the laboratory-monitoring group, and persistent

WHO disease stage 3 or stage 4 or AIDS–defining event for the clinical-monitoring-only group. A total of 459 patients were randomly assigned, and characteristics were similar between the laboratory- and clinical-monitoring groups (median CD4+ cell count, 179/μL and 182/μL, respectively). Two-thirds of all patients in both groups received stavudine/lamivudine/nevirapine, and LTFU was 9% in the clinical-monitoring group and 8% in the laboratory-monitoring group.

The primary outcome analysis showed a difference in the mean change in CD4+ cell count between the 2 groups of a 31/μL decrease (clinical monitoring vs laboratory monitoring; 95% CI, 63/μL decrease to 2/μL increase). These results did not reach the noninferiority margin of a 52/μL decrease (95% CI, 58/μL decrease to 45/μL decrease), as the lower boundary of the 95% CI of the difference (62/μL decrease) was lower than that allowed to prove noninferiority (58/μL decrease). Thirteen patients in the laboratory-monitoring group were switched to second-line antiretroviral therapy because of treatment failure, compared with none switched to second-line antiretroviral therapy in the clinical-monitoring group (P < .001). There were comparable results in virologic suppression, HIV drug resistance, mortality, disease progression, adherence and toxicity between the 2 groups.

The investigators concluded that clinical monitoring was not noninferior to laboratory monitoring and that switch to second-line antiretroviral therapy was statistically significantly increased in the laboratory-monitoring group. Both conclusions support the WHO recommendation to use laboratory monitoring in RLS. However, the authors added the caveat that, because of the overall limited differences between the 2 strategies, clinical monitoring could be used within the first 2 years of scale-up to allow for financial and structural limitations in RLS.

Rawizza and colleagues used a Markov simulation model to assess the impact of CD4+ cell count monitoring compared with plasma HIV-1 RNA level monitoring to determine antiret-

roviral therapy failure on lifetime cost of care and life expectancy in Nigeria (Abstract 675). They used data from 9690 HIV-infected patients receiving care through the Harvard PEPFAR/AIDS Prevention Initiative in Nigeria. Using a Monte Carlo simulation, they determined that routine plasma HIV-1 RNA level monitoring resulted in a longer per-person life expectancy than CD4+ cell count monitoring alone: 10.0 years compared with 7.1 years, respectively. The per-person lifetime cost of virologic monitoring was US $13,545 versus the $12,192 per-person lifetime cost for CD4+ cell count monitoring, and the incremental cost-effectiveness ratio of virologic monitoring was $467 per life-year saved. The authors concluded that, considering the low sensitivity and specificity of CD4+ cell count criteria for detection of virologic failure, plasma HIV-1 RNA level monitoring is cost-effective in Nigeria. They also concluded, however, that further studies are needed to determine the additional potential cost of the emergence of viral resistance in patients in the CD4+ cell-count monitoring group with delayed identification of treatment failure.

Additional monitoring data from the DART trial were presented. Gilks and colleagues examined the correlation between CD4+ cell count and virologic suppression in 221 patients enrolled in a larger trial comparing clinical monitoring with immunologic monitoring in Africa (Abstract 676). Overall, 15% of those with immunologic monitoring and 28% of those with clinical monitoring had plasma HIV-1 RNA levels below 400 copies/mL, determined retrospectively, at the time of diagnosis of treatment failure by either immunologic or clinical criteria. In the clinical-monitoring group, only 7 of 82 patients (9%) with CD4+ cell counts of at least 250/µL at the time of switch had plasma HIV-1 RNA levels below 400 copies/mL The authors proposed that, by using a "tie breaker" CD4+ cell count of at least 250/µL, the majority of those switches that were made based on clinical or immunologic criteria yet occurred in patients with undetectable plasma HIV-1 RNA level could have been avoided.

The second DART presentation, by Kityo and colleagues, retrospectively determined virologic response to treatment in 1164 patients who continued initial antiretroviral therapy in the immunologic- or clinical-monitoring arms of the DART trial (Abstract 677). The investigators found that virologic suppression (plasma HIV-1 RNA level < 200 copies/mL) after a median of 64 months of therapy was common (933 participants, 80%) and was associated with older age, female sex, and higher pre–antiretroviral therapy CD4+ cell count. However, when a conservative estimate of overall rates of virologic suppression was used that assumed lack of suppression for those who died or switched to second-line antiretroviral therapy based on clinical or immunologic criteria, the estimated suppression rate at the end of the trial was 54.8% (95% CI, 52.5% – 57.0%). The authors argued that the low rates of virologic failure in this trial, which did not monitor virologic outcomes of antiretroviral therapy, prospectively call into question the need for virologic monitoring in RLS.

Keiser and colleagues used data from the IeDEA cohort collaboration to examine immunologic response to antiretroviral therapy and mortality in 18,706 South African patients receiving care in clinics where plasma HIV-1 RNA level monitoring is available and in 80,937 patients from sites in Zambia and Malawi where such monitoring is not available (Abstract 678). Patients at the virologic-monitoring sites had lower CD4+ cell counts at antiretroviral therapy initiation (93/µL) than patients at sites without virologic monitoring had (132/µL; $P = .001$). After 3 years of antiretroviral therapy, the median CD4+ cell count was 415/µL at sites with virologic monitoring and 372/µL at sites without ($P < .001$). At sites with virologic monitoring, the risks of death and LTFU were also lower among the patients, and the likelihood of switching to second-line antiretroviral therapy was higher (aHR, 4.44; 95% CI, 3.95 – 4.98). The authors concluded that these data, contrary to those from the DART trial reported in Abstract 677 above, support virologic

monitoring in RLS. Table 2 summarizes these studies on monitoring strategies in RLS.

Mother-to-Child Transmission of HIV Infection

Pregnancy and Prevention of Mother-to-Child Transmission

Harries, as part of his N'Galy Mann Lecture discussed above, described a proposed 2011 Malawi initiative to test all pregnant women for HIV infection and treat all who tested HIV-seropositive for life, initially with once-daily tenofovir/lamivudine/efavirenz, in the hope of creating a "Born HIV Free" generation by 2015 (Abstract 18). The approach recognizes the nation's weak health infrastructure, insufficient availability of and capacity for CD4+ cell count monitoring, and high total fertility rate, plus the desire to send a simple message to the community that antiretroviral therapy is to be taken for life. It is anticipated that this approach would be simple to implement, reduce mother-to-child transmission (MTCT), protect babies born in subsequent pregnancies, improve maternal health, reduce risk of tuberculosis, and provide treatment of HBV coinfection.

Session 146 was also dedicated to plans for PMTCT of HIV. Dryden-Peterson and colleagues reported compelling data in support of maternal highly active antiretroviral therapy from a prospective observational study of HIV-infected women who participated in the Botswana PMTCT Programme (Abstract 740). Investigators observed 427 women during pregnancy. Women with CD4+ cell counts below 250/µL were treated with antiretroviral therapy, and those with CD4+ cell counts of 250/µL or above were treated with zidovudine starting at 28 weeks gestation (and a single dose of nevirapine if the zidovudine was taken for less than 4 weeks). All HIV-exposed babies received single-dose nevirapine and zidovudine for 1 month.

Of 432 live-born babies, 262 infants were born to mothers taking antiretroviral therapy, and 170 infants were born to mothers taking zidovudine

Table 2. Selected Studies Addressing the Impact of Laboratory Monitoring Strategies to Determine Antiretroviral Therapy (ART) Treatment Response in Resource-Limited Settings (RLS)

Abstract No. Study Description	Location Name of Study	Study Design Participants Definitions	Key Findings Conclusions
Abstract 44. Randomized trial comparing CD4+ count vs virologic monitoring strategies	Thailand Perinatal HIV Prevention Trial-3	Randomized, double-blind (preswitch) trial of CD4+ count vs HIV-1 RNA monitoring every 3 months; n = 716; initiating NNRTI-based ART; median pre-ART CD4+ count, 144/µL; mean age, 36 years *Follow-up:* 3 years	• Risk of clinical failure similar: 8.3% in HIV-1 RNA group; 7.7% in CD4+ count group ($P = .74$) • Risk of death similar: 4.4% in HIV-1 RNA group; 3.5% in CD4+ count group • Median time to switch: 11.7 months in HIV-1 RNA group; 24.7 months in CD4+ count group ($P = .001$) • 15/31 patients in CD4+ count group switched when HIV-1 RNA < 50 copies/mL • No statistical difference between groups in future drug options *Conclusion:* Rates of clinical failure were low at 3 years and did not differ between the 2 monitoring strategies, nor did CD4+ count monitoring diminish future treatment options.
Abstract 45LB. Randomized trial comparing virologic, CD4+ count, and clinical monitoring to clinical monitoring alone	Cameroon Stratall ANRS 12110/ESTHER Trial (9 rural district hospitals)	Randomized, non-inferiority trial of clinical monitoring vs CD4+ count and HIV-1 RNA monitoring every 6 months; n = 459; ART-naive; World Health Organization (WHO) stage 3/4; loss to follow-up (LTFU): 9% in clinical arm, 7% in laboratory-monitoring arm *Follow-up:* 2 years	• Median CD4+ count after 2 years: 182/µL in clinical group, 179/µL in laboratory-monitoring group • Mean increase in CD4+ count between groups did not meet criteria for noninferiority (a difference ≤ 25% between groups) • 13 patients in laboratory-monitoring group switched to second-line ART, none in clinical-monitoring group • Otherwise, comparable results in virologic suppression, HIV drug resistance mutations, mortality, disease progression, adherence, and toxicity between groups *Conclusion:* Clinical monitoring was not noninferior to laboratory monitoring; laboratory monitoring was associated with higher rates of switch to second-line ART. Authors suggest the minimal overall differences make 2 years of clinical monitoring feasible, but longer follow-up period is needed.
Abstracts 676, 677. Examining virologic outcomes from a randomized trial of CD4+ count and clinical monitoring vs clinical monitoring alone	Uganda, Zimbabwe DART (Development of Antiretroviral Therapy in Africa) trial	Randomized, unblinded trial of clinical monitoring vs CD4+ count monitoring every 12 weeks; n = 3315; ART-naive, CD4+ count < 200/µL *Follow-up:* 5 years *Clinical failure:* new WHO stage 4 event or ≥ 1 WHO stage 3 event *Immunologic failure:* CD4+ count < 100/µL	• At time of treatment failure determination: 15% of those with CD4+ count monitoring and 28% of those with clinical monitoring had HIV-1 RNA < 400 copies/mL • Only 7/82 (9%) of those with CD4+ count ≥ 250/µL at time of switch had HIV-1 RNA < 400 copies/mL • Of 1174 who remained on initial ART: 80% had HIV-1 RNA < 200 copies/mL after a median of 64 months of ART • Authors argue that rates of virologic failure were low, and that use of a CD4+ count tiebreaker at a level ≥ 250/µL could avoid switches in patients with undetectable HIV-1 RNA *Conclusion:* Although overall rates of virologic suppression are high in those remaining on initial ART, if patients who switched or died are included as failures, rates of virologic "success" drop to 55%. CD4+ count monitoring is a potential strategy in RLS, but pitfalls exist.
Abstract 678. Comparing CD4+ count response to ART and mortality in programs with and without virologic monitoring in southern Africa	South Africa, Zambia, Malawi International Epidemiological Databases to Evaluate AIDS (IeDEA) cohort collaboration	Retrospective cohort South Africa (virologic monitoring): n = 18,706; pre-ART median CD4+ count, 132/µL Zambia and Malawi (no virologic monitoring): n = 80,937; pre-ART median CD4+ count, 93/µL ($P = .011$ for difference with virologic monitoring) *Follow-up:* 3 years	• After 3 years: median CD4+ count, 415/µL at sites with virologic monitoring and 372/µL at sites without ($P < .001$) • Risk of death and LTFU were lower at sites with virologic monitoring • Adjusted hazard ratio for switch to second-line ART was higher at sites with virologic monitoring than those without: 4.44; 95% CI, 3.95–4.98 *Conclusion:* These data differ from those presented above in that they support a role for virologic monitoring in RLS but are limited by the fact that they are drawn from an observational cohort, albeit a very large one.

ANRS indicates French National Agency for Research on AIDS and Viral Hepatitis; ESTHER, Ensemble pour une Solidarité Thèrapeutique Hospitalière En Réseau (Network for Therapeutic Solidarity in Hospitals); HIV-1 RNA, plasma HIV-1 RNA level; NNRTI, nonnucleoside analogue reverse transcriptase inhibitor.

alone. A total of 10 infants were infected with HIV. Only 1 HIV-infected infant (0.4%; 95% CI, 0.01%–2.3%) was born to a woman taking antiretroviral therapy, compared with 9 HIV-infected infants (5.9%; 95% CI, 2.7%–10.9%) born to women taking zidovudine alone (*P*<.001). Thai investigators Phanuphak and colleagues also reported excellent safety and efficacy of maternal triple-drug antiretroviral therapy regardless of maternal CD4+ cell count from the Thai Red Cross PMTCT Program from 2004 to 2010. The transmission rate to babies was 1% (Abstract 742).

Ciaranello and colleagues modeled combinations of treatment options within the context of scale-up of antenatal care that could result in virtual elimination of MTCT in Zimbabwe and predicted that an approach stratified by CD4+ cell count could reduce MTCT to near or less than 5% (Abstract 739). Mothers who have a CD4+ cell count less than 350/μL would be treated with antiretroviral therapy, and mothers who have a count greater than 350/μL would receive short-course zidovudine during pregnancy and extended nevirapine treatment for the infant during breast-feeding. In a talk dedicated to applying principles of cost-effectiveness to HIV care programs, Walensky addressed the issue of PMTCT and cost-effectiveness, reporting that effective programs for PMTCT are often associated with cost savings (Abstract 74).

Ekouevi and colleagues reported on maternal HIV disease progression after the interruption of triple-drug antiretroviral therapy or short-course antiretroviral treatment for PMTCT using data from 13 programs in Africa and Thailand from the MTCT-Plus Initiative (Abstract 753). Among 1027 HIV-infected pregnant women with CD4+ cell counts greater than 400/μL, investigators compared rates of CD4+ cell count decline according to PMTCT treatment: antiretroviral therapy (n = 113; 11%), single-dose nevirapine (n = 444; 43.2%), short-course antiretroviral prophylaxis (n = 353; 34.4%), or no prophylaxis (n = 117; 11.4%). After adjusting for age, country, CD4+ cell count, and WHO stage of disease at enrollment, women who received antiretroviral therapy were 3 times as likely to become antiretroviral therapy–eligible within 24 months as women receiving short-course antiretroviral prophylaxis (HR, 3.37; 95% CI, 1.96 – 5.79; *P* < .001). The authors urged consideration of lifelong antiretroviral treatment for pregnant women with CD4+ cell counts less than 500/μL.

Mother-to-Child Transmission and Breast-feeding

Maldonado presented HIV Prevention Trials Network (HPTN) 046 data comparing an extended course of daily nevirapine for infants through age 6 months with 6 weeks of nevirapine for postnatal prevention of HIV infection acquired through breast-feeding (Coovadia et al, Abstract 123LB). After 6 weeks of daily nevirapine, 1522 breast-feeding infants were randomly assigned to either continuation of daily nevirapine or placebo until 6 months postpartum. At randomization, 29% of mothers in each group were receiving antiretroviral therapy for their own health; at 6 months, this amount increased to 31% in the extended-nevirapine group and 32% in the placebo group.

At 6 months, the rate of HIV infection was statistically significantly lower in the extended-nevirapine group (1.1%) than in the placebo group (2.4%; *P* = .048); however, this difference was not observed at 9 months or 12 months. Stratification by maternal antiretroviral therapy status showed a very low rate of infant transmission (0.2%) at 6 months for the mothers receiving treatment compared with the mothers not receiving antiretroviral therapy (2.4%; *P* = .027). For mothers not receiving antiretroviral therapy, there was a statistically significant difference in infant HIV infection at 6 months (1.4% for infants receiving extended nevirapine vs 3.4% for infants receiving placebo; *P* = .027). There were no differences in mortality or serious adverse events between the extended-nevirapine- and placebo-treated infants.

Nielsen-Saines, on behalf of the HPTN 040/PACTG (Pediatric AIDS Clinical Trials Group) 1043 study, presented compelling data in support of postexposure prophylaxis (PEP) with 2- or 3-drug antiretroviral regimens instead of zidovudine alone for prevention of intrapartum HIV transmission to infants born to women not receiving antiretroviral therapy before labor (Abstract 124LB). Babies of mothers not receiving antiretroviral drugs were identified at labor or postpartum. In this international study, babies were randomly assigned within 48 hours of birth to 1 of 3 groups: zidovudine alone for 6 weeks; zidovudine for 6 weeks plus nevirapine for 3 doses in the first week; or zidovudine for 6 weeks plus lamivudine and nelfinavir for 2 weeks. All babies were formula-fed, and follow-up continued until 6 months.

Of the 1684 babies included in the analysis, 8.3% overall were infected, with 5.5% infected in utero and 2.8% infected intrapartum. Intrapartum infection in the zidovudine-alone group occurred in 4.9%, compared with 2.2% in the zidovudine-plus-nevirapine group (*P* = .045) and 2.5% in the zidovudine-plus-lamivudine-and-nelfinavir group (*P* = .034). In addition to the association with treatment regimen, maternal viral load was associated with transmission on multivariate analysis. There was statistically significantly more neutropenia in the zidovudine-plus-lamivudine-and-nelfinavir group (15%; *P* < .0001) than in the other 2 groups. For infants born to HIV-infected mothers not receiving antiretroviral drugs, investigators suggested administering 2- or 3-drug antiretroviral treatment within 48 hours of birth for infants rather than zidovudine alone.

In an effort to identify maternal antiretroviral regimens that would still prevent infection to infants but would possibly be less toxic to the mother and child during treatment, the Primeva/ANRS 135 trial studied maternal treatment with lopinavir/r monotherapy compared with lopinavir/r plus zidovudine/lamivudine (Abstract 125LB). A total of 105 women were randomly assigned in a 2:1 ratio to begin lopinavir/r monotherapy (n = 69) or treatment with lopinavir/r plus zidovudine/lamivudine (n = 36; control group) at 26 weeks' gestation; follow-up continued

until 12 weeks postpartum. All babies were treated postpartum with 4 weeks to 6 weeks of zidovudine and observed for 24 months. Changes of antiretroviral drugs because of intolerance were statistically significantly less frequent in the monotherapy group (1.4%) than in the control group (11.1%; $P = .046$). Based on an intention-to-treat analysis, the primary endpoint of plasma HIV RNA level below 200 copies/mL at week 8 of treatment was achieved at comparable rates in both groups: 88.4% of women receiving monotherapy and 94.4% of control women ($P = .5$). Monotherapy patients had statistically significantly less viral suppression (plasma HIV RNA level < 50 copies/mL) at delivery (79.7% vs 97.2% in controls; $P = .01$). Of the 105 children born, there was 1 case of transmission in the control group and none in the monotherapy group. Studies of genotoxicity, mitochondrial toxicity, cardiac toxicity, and hematologic toxicity in infants are ongoing.

Risk of HIV Transmission During Pregnancy

John-Stewart gave a presentation on transmission risk in pregnancy in which she discussed risk of acquiring HIV infection during pregnancy and postpartum, specific issues related to the pregnancy and postpartum periods, and strategies for HIV prevention during and after pregnancy (John-Stewart et al, Abstract 67). Biological changes associated with pregnancy may put pregnant women at higher risk of HIV infection. Examples include hormonal changes, immune activation, and changes in the genital mucosa. In some studies, pregnancy and lactation have been identified as cofactors influencing risk of HIV infection. John-Stewart reported historical data from Rwanda, which indicate that the risk of transmission to infants from mothers with acute HIV infection (up to 29%) is higher than transmission rates for women with chronic HIV infection (16%). As PMTCT becomes more effective, the proportion of HIV infections in children of mothers with acute HIV infection is expected to rise substantially.

Eshleman and colleagues reported on the use of a multiassay algorithm to determine recency of HIV infection in pregnant women in the PEPI (Postexposure Prophylaxis for Infants)-Malawi trial (Abstract 737). Subjects were 2561 women enrolled in the PEPI-Malawi trial who were in labor; their infants were randomly assigned to 1 of 3 postnatal infant regimens. A multiassay algorithm was performed within 3 days of delivery on samples from all women; 73 women were identified as having been recently infected. The risk of in utero transmission of HIV was found to be 17.9% among women recently infected and 6.7% in women whose infection was not recent.

Several other abstracts examined risk factors for MTCT. Tubiana and colleagues reported extremely low risk of MTCT of HIV in women starting antiretroviral therapy before pregnancy in the French Perinatal Cohort (Abstract 735). Nearly 6000 women enrolled in the ANRS French Perinatal Cohort were included in the analysis of HIV transmission risk and stratified according to when their antiretroviral treatment was initiated. The HIV transmission rate was 0.5% if treatment had begun before conception, 0.6% if initiated in the first trimester, 1.2% if initiated during the second trimester, and 2.6% if initiated after 28 weeks. When the maternal plasma HIV-1 RNA level was less than 50 copies/mL at delivery, the transmission rates dropped to 0%, 0%, 0.5%, and 0.8% in the 4 strata, respectively.

French and colleagues looked at the effect of subsequent pregnancies on MTCT risk (Abstract 736). In reviewing 9807 pregnancies in HIV-infected women in the United Kingdom and Ireland, monitored through the National Study of HIV in Pregnancy and Childhood, they found no evidence of an increased risk of MTCT in subsequent pregnancies.

Khamduang and colleagues presented data on the interrelated transmission of HIV-1 and cytomegalovirus (CMV) during gestation and delivery in the children of HIV-infected mothers (Abstract 122). Investigators sought to understand the timing of CMV transmission and its relationship to

HIV transmission, compare the risk of CMV infection in HIV-infected and -uninfected mothers, and examine risk factors for CMV transmission in HIV-infected infants. Women and infants who had participated in a clinical trial for PMTCT in Thailand were included in the study. Ninety-seven HIV-infected infants were matched 1:2 with HIV-uninfected infants by baseline maternal viral load. CMV infection was determined by CMV IgG antibody testing at 18 months and timed by CMV IgM antibody testing or CMV DNA detection in plasma or blood at birth and thereafter.

CMV infections were more common in HIV-infected infants than in HIV-uninfected infants: congenital (14% vs 3%, respectively), intrapartum (41% vs 28%, respectively), acquired (80% vs 63%, respectively), and overall (84% vs 63%, respectively). CMV infection in utero was associated with increased odds of intrauterine HIV infection (OR, 8.1; $P = .01$). Intrapartum HIV infection was associated with both congenital and intrapartum CMV infection (OR, 2.5; $P = .04$). Overall, HIV infection was associated with CMV infection (OR, 2.9; $P = .001$). In HIV-infected infants, the risk of CMV infection was statistically significantly associated with prematurity, intrapartum HIV infection, and vaginal delivery.

Effects of Antiretroviral Therapy During Pregnancy on Infant Health

Sessions 147 and 148 were dedicated to understanding the effect of antiretroviral exposure during the perinatal period on infant health. Two studies reported on PI use and preterm delivery. Sibiude and colleagues reported findings from a retrospective analysis of 13,957 singleton pregnancies in HIV-infected women of the ANRS French Cohort from 1990 to 2009 (Abstract 743). The authors reported steadily increasing rates of preterm delivery from 9.2% (1990–1993: no antiretroviral therapy available) to 9.6% (1994–1996: zidovudine available), 12.4% (1997–1999: double-nRTI therapy and some multiclass antiretroviral therapy available), and 14.3%

(2005 – 2009: routine combination antiretroviral therapy available). Analysis also revealed that for women not receiving treatment at the time of conception and who initiated PI treatment during pregnancy, the rate of preterm delivery was higher in those treated with a PI/r regimen than in those treated with a PI alone (14.4% vs 9.1%, respectively; aHR, 2.0 [1.1 – 3.9]; *P* = .03).

Powis and colleagues also reported an association between PI use and preterm delivery from a randomized control trial of 530 women comparing PI-based antiretroviral treatment with triple-nRTI antiretroviral treatment for PMTCT (Abstract 746). In contrast, González-Tomé and colleagues reported no association between any kind of antiretroviral regimen and preterm delivery in a multicentre cohort of HIV-infected pregnant women in Spain from 2000 to 2008 (Abstract 744). Of 803 babies born, 21% were born preterm, and 53% of mothers received a PI-containing regimen. Important factors that were associated with preterm birth in this cohort were illicit drug use, HCV coinfection, lack of antiretroviral therapy, and older maternal age.

Effects of Antiretroviral Therapy During Pregnancy on Child Health Outcomes

Shapiro and colleagues showed an association between increased maternal and infant mortality after completion of antiretroviral therapy and breastfeeding at 6 months postpartum in a randomized control trial of PMTCT in Botswana, the Mma Bana Study (Abstract 747). A total of 560 pregnant, HIV-infected women were randomly assigned to either a triple-nRTI regimen or lopinavir/r plus zidovudine/lamivudine initiated at 26 weeks to 34 weeks gestation and continued until weaning at 6 months postpartum. An observational group included 170 HIV-infected women who began continuous antiretroviral therapy because of low CD4+ cell counts and received nevirapine plus zidovudine/lamivudine. Mortality data were collected on all 730 women and their 709 live-born infants.

Statistically significantly more deaths occurred in mothers and infants after weaning and antiretroviral therapy cessation at 6 months than occurred during treatment. The authors urged a higher threshold for continuous maternal antiretroviral therapy and further evaluation of optimal weaning strategies.

Storfer and colleagues examined the risk of birth defects in children exposed to nevirapine according to the trimester of first exposure in the Antiretroviral Pregnancy Registry and compared risks to those of external control subjects from 1989 to 2010 (Abstract 749). Investigators reported on 2327 nevirapine-exposed pregnant enrollees in the Registry, of whom 970 were exposed to nevirapine in the first trimester (1001 babies) and 1182 were exposed starting in the second or third trimester (1201 babies). There was no association of birth defects with first-trimester exposure or with nevirapine exposure in general.

Two abstracts looked at the effects of antiretroviral drug exposure on HIV-uninfected children of HIV-infected mothers. Noguera-Julian and colleagues reported lower mitochondrial-encoded complex IV activity in antiretroviral drug–exposed, HIV-uninfected healthy infants from a prospective observational study of 135 HIV-uninfected, antiretroviral drug–exposed babies (Abstract 750). Mitochondrial DNA was measured using quantitative real-time PCR, and mitochondrial respiratory chain enzymatic activity of complex IV and mitochondrial mass were assessed from PBMCs obtained at 6 weeks and at months 3, 6, and 12. The control group included healthy infants of women with HCV infection (n = 32). A total of 87% of study women received antiretroviral therapy for a median of 34 weeks, followed by intravenous zidovudine at delivery.

Although no infant had clinical evidence of mitochondrial disease, and mitochondrial mass was similar in control and observational groups, the complex IV activity was statistically significantly lower in the antiretroviral drug–exposed children at all time points. There was a trend toward nor-

malization with age. Furthermore, an inverse relationship between complex IV activity and mitochondrial DNA levels was observed at all time points. The authors suggested that mitochondrial DNA levels may be upregulated in an effort to compensate for antiretroviral drug–related organelle damage. Williams and colleagues presented reassuring findings on a lack of association between in utero antiretroviral drug exposure and late language emergence in HIV-uninfected children born to HIV-infected women (Abstract 751).

Mother-to-Child Transmission and Resistance

Foulongne and colleagues reported on the issue of drug resistance in pregnant women in the Kesho Bora trial in South Africa (Abstract 758). This study was a randomized controlled trial comparing use of triple-drug antiretroviral therapy during pregnancy through the breastfeeding period with use of zidovudine plus single-dose nevirapine treatment stopping at delivery. The rate of resistance mutations present at follow-up was 25% in the zidovudine plus single-dose nevirapine group and 0% in the triple-drug antiretroviral therapy group. Additional analysis of resistance in infants is planned.

WHO guidelines recommend a brief course of antiretroviral treatment (a "tail") for women after single-dose nevirapine treatment for PMTCT. Two abstracts presented data in favor of this practice. McMahon and colleagues found a trend toward superior outcomes in prevention of emergence of resistance after single-dose nevirapine administration for PMTCT with a 21-day tail compared with a 7-day tail of either tenofovir/emtricitabine, zidovudine/lamivudine, or lopinavir/ritonavir (Abstract 759). Ngo-Giang-Huong and colleagues showed that 1 week of treatment with zidovudine plus lamivudine after exposure to single-dose nevirapine virtually eliminated the emergence of nevirapine resistance mutations at 7-day, 10-day, and 1-month follow-up analysis of 117 women who participated in the Thai PHPT (Perinatal HIV Prevention Trial)-5 (Abstract 760).

Fogel, on behalf of colleagues in the PEPI-Malawi Study, reported cases of multidrug-resistant HIV infection detected in breast-feeding infants whose mothers began antiretroviral therapy postpartum (Abstract 761). Infant HIV genotypic analyses were available for 37 HIV-infected babies whose mothers initiated postpartum treatment with stavudine, lamivudine, and nevirapine. Thirty (81.1%) of the 37 infants had NNRTI resistance, and 11 (29.7%) of the infants had multiclass resistance. Earlier postpartum antiretroviral therapy use was statistically significantly associated with multiclass resistance (P =.0009). This was observed only in infants who were exclusively breast-fed.

Resistance

Resistance in Resource-Limited Settings

As part of global antiretroviral therapy scale-up, the WHO recommends programmatic assessment informed by surveillance of acquired drug resistance (ADR) and transmitted drug resistance (TDR) to help inform best practices and minimize emergence of HIV drug resistance. Bertagnolio, on behalf of the WHO, reported on 2 major surveillance initiatives from RLS (Abstract 52). The ADR report consisted of surveys from 16 resource-limited sites from 2002 to 2010. The survey results represent 2150 patients who initiated antiretroviral therapy (and were either treatment naive or experienced at initiation) at 15 sites in Burundi, India, Malawi, Mozambique, and Nigeria. Nearly three-fourths of patients were taking stavudine/ lamivudine/NNRTI (74%), 22% were taking zidovudine/lamivudine/NNRTI, 3.2% were taking tenofovir/lamivudine/ NNRTI, and 0.8% used other regimens. A total of 90% of patients had virologic suppression (HIV RNA level < 1000 copies/mL) at 12 months. There were 128 patients (10%) in whom genotypic analysis was performed because of a plasma HIV RNA level greater than 1000 copies/mL at 12 months. Analysis of patients with baseline genotypic testing results (n = 1503) revealed the following resistance pattern: 6%

any resistance, 5% NNRTI resistance, 2.7% nRTI resistance, 2% double-class resistance, and 0.5% PI resistance; 77% had subtype-C HIV. The most common mutations were Y181/C/I, K103N/S, and M184I/V. Of the 128 individuals for whom antiretroviral therapy failed at 12 months, 67% had any drug resistance, 65% had NNRTI resistance, 55% had nRTI resistance, 55% had double-class resistance, and 3% had any PI resistance. The most common mutations conferred resistance to nevirapine, efavirenz, and lamivudine.

The authors noted that a statistically significant proportion of patients also had 3 or more thymidine analogue–associated mutations (TAMs) (4.7%) and the K65R mutation (5%). Such mutations would negatively impact effectiveness of the second-line regimens that contain tenofovir or zidovudine. Of patients who were retained in care and alive, 90% had viral load suppression (plasma HIV RNA level < 1000 copies/mL), which dropped to 70% when including LTFU and patients discontinuing treatment in the analysis. A total of 75% of clinics were able to meet a goal of having 70% of patients suppressed at 12 months. These results are similar to resource-rich-setting cohorts. The authors pointed out that, given the patterns of resistance, a second-line regimen including PI/r plus tenofovir or zidovudine should be effective at the population level.

Bertagnolio and colleagues also reported surveys of TDR in recently infected, antiretroviral therapy–naive populations. Age less than 24 years, first pregnancy, first HIV risk–defining event within the past 3 years, and CD4+ cell count greater than 500/µL were used as surrogates for recent infection. Results represent geographic areas as opposed to specific clinics or nations. There were 41 surveys from 20 countries during 2005 to 2007. The majority of surveys were from sites in Africa, Asia, and Mexico. Truncated sequential sampling was used to classify prevalence of TDR as low (less than 5%), moderate (5% – 15%), or high (> 15%). The results showed that 81% of sites had low levels of TDR and 17% of sites showed moderate levels of TDR,

mainly to NNRTIs (12%) and some to nRTIs (7%). No surveys showed moderate levels of PI resistance, but all reported low levels. Bertognolio pointed out those geographic areas with moderate resistance that warrant additional attention.

Additional abstracts dedicated to understanding resistance across the globe were presented in Session 119 (Abstracts 619 – 626). Dross and colleagues illustrated the impact of TDR on antiretroviral efficacy, reporting on nevirapine- and lamivudine-resistant HIV-1 detected in antiretroviral therapy–naive Kenyans initiating NNRTI-based antiretroviral therapy (Abstract 620). Of 400 treatment-naive adults who began nevirapine-based antiretroviral therapy, 42 had virologic failure at follow-up. Genotypic testing of baseline blood samples showed mutations associated with nevirapine resistance or with lamivudine resistance in 26% of patients with virologic failure.

Yang and colleagues reported on the global surveillance of TDR in 330 plasma or dried blood spot samples from PEPFAR-supported countries including Botswana, China, Kenya, Malawi, Tanzania, and Vietnam (Abstract 619). All sites showed TDR of less than 5% except for the site in Ho Chi Minh City, which had a moderate level of resistance (5% – 15%). The authors urged further understanding of this concerning trend.

Rates of TDR in Kampala, Uganda (Abstract 621), and Mexico City (Abstract 623) were also reported to be moderate at 5% to 15%, whereas investigators from Brazil reported rates of TDR ranging from moderate to high (> 15%) in some areas (Abstract 624). Hamers and colleagues compared rates of drug resistance to year of antiretroviral therapy scale-up in sub-Saharan Africa. Earlier year of scale-up was more strongly associated with prevalence of drug resistance (Abstract 622).

Viral Load Monitoring in Resource-Limited Settings

Reynolds and colleagues reported on the effect of routine viral load monitoring on the rate of accumulated

genotypic evidence of resistance to commonly used antiretroviral drugs in Uganda (Abstract 53). A cross-sectional, observational study in infectious diseases clinics of Kampala, Uganda, compared a cohort of 559 antiretroviral-naive patients who had CD4+ cell count and viral load monitoring every 6 months with 998 clinic patients who had been receiving antiretroviral therapy and had CD4+ cell count monitoring only. Viral load monitoring was performed at the end of 36 months to 40 months in all patients in the CD4+ cell count-only group, and genotypic analysis was also performed if the plasma HIV RNA level was greater than 2000 copies/mL. In the viral load–monitoring group, viral loads were assessed at months 12, 24, and 36, with genotypic testing of patients with levels exceeding 2000 copies/mL. Mutations were classified according to the IAS–USA panel listing[36] and the Stanford University HIV Drug Resistance Database (www.hivdb.stanford.edu).

At 36 months, the viral load–monitoring group showed 57% resistance to NNRTI; 43% had the M184V mutation, 7% had K65R, and 7% had a single TAM. The immunologic-monitoring group showed 90% resistance to NNRTI; 87% had the M184V mutation, 1% had the K65R mutation, 43% had a single TAM, 23% had 2 TAMs, and 10% had 3 or more TAMs. Viral load monitoring was associated with reduced resistance in all categories. The most dramatic reduction in resistance mutations in the viral load–monitoring group was in the TAMs. Only 23% of the participants in the viral load–monitoring group had 4 or more etravirine mutations, compared with 40% in the immunologic-monitoring group.

The additional resistance that accumulated during immunologic monitoring has implications for the effectiveness of second-line regimens. Gupta and colleagues echoed these findings, showing a rapid accumulation of TAMs in the absence of viral load monitoring with nevirapine-based or triple-nRTI regimens. This information has serious implications for the use of zidovudine, abacavir, or tenofovir in second-line antiretroviral regimens (Abstract 618).

Nonnucleoside Analogue Reverse Transcriptase Inhibitor Resistance

Session 114 was dedicated to new insights in resistance to NNRTIs. In an effort to explain the association of the E138K rilpivirine-associated mutation with the M184I mutation (rather than M184V), Hu and Kuritzkes created recombinant viruses carrying E138K plus M184I or M184V mutations and compared relative infectivity and fitness profiles (Abstract 594). The E138K/M184I virus had higher relative infectivity than the E138K/M184V recombinant in the presence of a second-generation NNRTI. Drug-susceptibility data showed that the E138K/M184I virus also had a greater fold-increase in the IC_{50} for etravirine, efavirenz, and lamivudine than the E138K/M184V virus. The authors concluded the E138K/M184I combination confers a meaningful replication advantage and higher levels of resistance to etravirine and lamivudine compared with the E138K/M184V double-mutant. This may explain why the E138K/M184I combination was observed in patients with virologic failure in trials of rilpivirine.

Mackie and colleagues examined the prevalence and clinical importance of baseline polymorphisms in antiretroviral-naive subjects initiating NNRTI-based antiretroviral therapy (Abstract 595). Baseline genotypic testing results were obtained from the UK HIV drug resistance database and linked to clinical cases. There were 2058 subjects included in the analysis, of whom 1704 initiated efavirenz-based antiretroviral regimens and 354 initiated nevirapine-based therapy. Reverse transcriptase polymorphisms of interest included those on codons 90 to 108, 135 to 138, 179 to 190, and 225 to 348. A total of 40% of subjects were identified as having at least 1 polymorphism at baseline. Neither single nor double polymorphisms had an effect on plasma HIV RNA level reduction at week 4 or on achieving a plasma HIV RNA level less than 200 copies/mL at week 24 compared with wild-type virus.

Geretti and colleagues analyzed the virologic outcomes of patients who interrupted and restarted NNRTI-based antiretroviral therapy in the SMART (Strategies for the Management of Antiretroviral Therapy) study (Abstract 596). They compared virologic outcomes with respect to the modality of treatment interruption, *Cytochrome P450 2B6/constitutive androstane receptor (CYP2B6/CAR)* host genotype, NNRTI clearance rates, and presence of drug resistance mutations as detected by allele-specific PCR and ultra-deep sequencing. Of the 132 subjects who underwent interruption of an NNRTI-based regimen (60.6% with efavirenz, 38.6% with nevirapine, and 0.8% with delavirdine), 63 discontinued nRTIs and the NNRTI simultaneously, and 69 either continued nRTIs alone or switched to nRTIs plus a PI. Median plasma nevirapine levels were 0.96 ng/mL (IQR, 0.5 – 3.2 ng/mL) after a median of 32 days and 16 ng/mL (IQR, 9 – 55 ng/mL) for efavirenz after a median of 30 days.

The *CYP2B6/CAR* genotype was predictive of efavirenz concentrations, with the highest levels observed in the TT/CC profile ($P = .02$). Major nRTI resistance was detected in 20% of patients and major NNRTI resistance was detected in 11% of patients by bulk sequencing and slightly more by allele-specific PCR, 24% and 16%, respectively. Although 81% of patients with suppressed viremia who interrupted and then restarted NNRTI-based antiretroviral treatment regained viral suppression, 19% did not. Predictors of virologic suppression at 12 months to 18 months after restarting antiretroviral treatment included simultaneous interruption of antiretroviral therapy (as opposed to stagger-switch), longer duration of treatment interruption, and older age. The authors issued caution regarding the risk of resistance with treatment interruptions, suggesting the use of stagger-switch methods rather than simultaneous interruption. They proposed additional studies to better understand the possible utility of *CYP2B6/CAR* genotypic testing as a predictor of delayed NNRTI clearance.

Cozzi-Lepri and colleagues reported an analysis of predictors of virologic response to etravirine-containing antiretroviral regimens in the EuroSIDA

cohort (Abstract 598). There were 320 patients identified as having initiated etravirine-containing antiretroviral regimens from 2001 to 2009, of whom 68% had at least 1 genotypic test before treatment. Expert-based interpretation of resistance was calculated based on the 3 most frequently used expert calculations for resistance: the ANRS score (http://www.hivfrench resistance.org), the Stanford University database score (http://hivdb.stanford.edu/), and the Rega score (http://regaweb.med.kuleuven.be/) as well as 2 etravirine-specific scores developed by the commercial firms Tibotec and Monogram.

There were 399 person-years of follow-up and 42 cases of virologic failure (10.5/100 person-years; 95% CI, 7.7 – 14.0 per 100 person-years). The ANRS score was the only interpretation instrument that was statistically significantly associated with risk of virologic failure caused by resistance. An increased risk of failure was observed for patients with K101E, and the K103N mutation was independently associated with a reduced risk of failure. The authors pointed out the uncertainty in predictions of antiviral activity for etravirine in clinical practice and urged further elucidation of the possible relationship between the K103N mutation and etravirine hypersusceptibility.

Protease Inhibitor Resistance

Novel insight into the emergence of drug resistance mutations in protease was the subject of Session 115 (Abstracts 599–605). Fun and colleagues presented data on how the genetic barrier to resistance is decreased by *gag* polymorphisms (Abstract 603). The investigators performed in vitro selections with molecular clones of HIV subtypes B, C, and AG in the presence of increasing darunavir concentrations, and they monitored *gag* and protease genes over time. The investigators reported that in 5 of 5 cultures with HIV subtype AG, a mutation occurred at the NC/p1 cleavage site at *gag* codon 437. The *gag* 437 mutation corresponds with a 5- to 7-fold decreased suscepti-

bility to darunavir compared with the parental AG virus.

Larrouy and colleagues reported on the positive impact of the HIV-1 *gag* CS A431V mutation on virologic response to darunavir/r in treatment-experienced patients (Abstract 604). The A431V *gag* CS mutation was associated with short-term virologic response. The investigators hypothesized that a specific *gag* CS mutation might not have the same impact on virologic outcome, according to the PI used, and could have a direct impact on PI susceptibility in an inhibitor-specific manner.

Depatureaux and colleagues reported on protease-region resistance mutations in the highly diverse HIV-1 group O in both treatment-naive and on-treatment individuals infected with HIV-1 group O virus (Abstract 605). Logistic regression analysis revealed a statistically significant association with lopinavir/r treatment and the following mutations: I15I, G48M, L63K, and T74S ($P < .005$).

CC Chemokine Receptor 5 Antagonist Resistance

Session 113 was dedicated to coreceptor usage and resistance to CCR5 inhibitors. Putcharoen and colleagues described kinetics and mechanism of resistance of vicriviroc-resistant HIV-1 subtype B clinical isolates from subjects in the ACTG 5211 trial (Abstract 589). Pseudoviruses were constructed that expressed cloned or uncloned HIV-1 envelope obtained at baseline and at virologic failure in 3 subjects in whom resistance to the investigational drug vicriviroc emerged. Resistant viruses had slower entry kinetics than wild-type virus, and in the presence of the investigational small-molecule coreceptor antagonist TAK-779, the entry kinetics were restored to wild-type level, suggesting that vicriviroc-resistant viruses use drug-bound CCR5 for entry. Vicriviroc-resistant virus was also shown to be cross-resistant to maraviroc and TAK-779. Additionally, the authors showed how vicriviroc-resistant viruses are inhibited by monoclonal antibodies directed against the CCR5

N-terminal domain and second extracellular loop (ECL2), suggesting that the resistant envelope may have adapted to utilize drug-bound receptor by more efficient utilization of the N-terminus and ECL2 regions of the CCR5.

Similarly, Jubb and colleagues also described how maraviroc-resistant viruses use the ECL2 and the N-terminal domain of CCR5 (Abstract 590). Svicher and colleagues showed an association between dual tropism and signature mutations in the V3 bridging sheet domain of HIV-1 gp120 and how these mutations modulate the interaction at the CCR5 N-terminus (Abstract 591). The study analyzed 498 V3 and 242 gp120 sequences from 740 HIV-1 subtype B–infected patients from the Los Alamos Database. Three V3 determinants—T2M, I26R, and I12V—were statistically significantly associated with phenotypically defined dual tropism. These determinants occurred in negligible amounts in pure R5 and X4 viruses (0%, 0%, and 2%, respectively) but at much higher rates in dual-mixed virus (9.3%, 4.9%, and 14.2%, respectively; $P < .001$). The mutations I12V and I26R both decreased N-terminus binding affinity for gp120.

Other mutations associated with dual-mixed virus outside the V3 loop include T102S, M105V, and R398Q, all of which are in the gp120 bridging domain. These mutations were present at 15.8%, 16.7%, and 33.3%, respectively, in dual-mixed virus, compared with less than 3% in pure R5 or X4 virus. The authors pointed out that dual-tropic viruses represent HIV species that are structurally different from pure R5 and X4 viruses, as opposed to being just a mixture.

Coakley and colleagues described a comparison between V3-sequencing-based prediction and coreceptor tropism as determined by an enhanced-sensitivity coreceptor tropism assay (Monogram Biosciences) (Abstract 592). Both tests were performed on 4 distinct patient groups: an HIV acute-seroconversion cohort (n = 69), an early-treatment-naive cohort (n = 271), a treatment-naive cohort of participants in ACTG 384 (n = 221), and a late-treatment-experienced group

(n = 587). Compared with the enhanced-sensitivity tropism assay, V3 sequencing showed increasing sensitivity with disease stage: 18%, 34%, 43%, and 62%, respectively, in the 4 patient groups. There was also a strong inverse correlation of average sensitivity compared with CD4+ cell count ($R^2 = -.98$; $P = .01$). The authors concluded that V3 sequencing for prediction of CXCR4 virus in treatment-naive individuals is inadequate, given its lack of sensitivity in this group.

The role of ultra-deep sequencing in the use of maraviroc was explored by Heera and colleagues (Abstract 593). Ultra-deep sequencing was performed on specimens from treatment-experienced patients who participated in the combined maraviroc-treated groups of the MOTIVATE (Maraviroc Versus Optimized Therapy in Viremic Antiretroviral Treatment–Experienced Patients) trials, of whom 674 patients had been identified as having R5 virus and 215 as having non-R5 virus by the original coreceptor tropism assay (Monogram Biosciences). Both the relative percentage of X4 virus and the absolute count of virus were determined via ultra-deep sequencing. Multivariate analysis of predictors of achieving a plasma HIV RNA level of less than 50 copies/mL at 48 weeks revealed that baseline CD4+ cell count, activity of background drugs, and the absolute X4 viral load by ultra-deep sequencing were independent predictors of long-term maraviroc responses. Patients with X4 HIV RNA levels of less than 5300 copies/mL had a response rate of 65%, which increased to 71% if the CD4+ cell count was greater than 70/µL. Other studies of the utility of ultra-deep sequencing as well as other assays for predicting CCR5 coreceptor antagonist success were presented in Session 126 (Abstracts 666 – 671).

Raltegravir Resistance

Session 116 highlighted resistance issues with the INSTI class. The role of T97A in the presence of Y143C/R was explored by Reigadas and colleagues, who performed in vitro assays comparing wild-type integrase with integrases containing the mutation T97A alone or with Y143C/R (Abstract 606). Site-directed mutagenesis experiments were performed on expression vectors harboring the integrase gene, and the T97A mutation was introduced. Both wild-type and mutated integrase genes were expressed in bacteria and purified. Strains were studied in the presence and absence of raltegravir. Virus with the T97A mutation alone was as susceptible as wild-type virus, but the combination of T97A and Y143C or Y143R resulted in severely impaired susceptibility to raltegravir compared with Y143C or Y143R alone. This finding is consistent with previous clinical observations.

Huang and colleagues also looked at integrase codon 143. Using isolates from virus submitted for drug resistance testing, the authors identified and studied 75 viruses containing amino acid substitutions (Abstract 607). In addition to the well-known Y143R/C mutations, Y143H/G/S mutations were also identified. Fold-change in susceptibility with Y143R was 25 and fold-changes with any of the other substitutions ranged from 2 to 8. Apart from Y143R, all the other substitutions required secondary mutations to confer large reductions in raltegravir susceptibility.

Preexposure Prophylaxis and Resistance

PrEP was covered extensively at the conference. Resistance in the context of PrEP during the iPrEx (Chemoprophylaxis for HIV Prevention in Men) study was examined by Liegler and colleagues (Abstract 97LB). Data were presented from the interim iPrEx study's analysis on the presence of resistance mutations in samples from patients at the time of first evidence of seroconversion, tested using both bulk sequencing (genotypic or phenotypic assays) and a novel quantitative minor variant assay (lower limit of detection, 0.5%) for detection of K65R, K70E, M184V, and M184I mutations. There were 100 participants who were infected during the study, for whom 91 samples were successfully tested.

Of those tested, 58 seroconversions occurred in the placebo group and 33 in the emtricitabine/tenofovir (PrEP)-treated group. The majority of HIV subtypes were B. Minor resistance-associated mutations were detected in 2 samples from the placebo group: 1 with K65R and the other with M184V. There were no minor variant mutations in any of the seroconversions from the treatment group. Most of the seroconversions in the PrEP group did not have positive PrEP-drug levels, and the 3 subjects with detectable drug had extremely low levels and did not show minor drug-resistant variants. There were 3 individuals who were HIV-seronegative at entry but later found to be undergoing acute HIV infection, of whom 2 were from the PrEP arm: 1 found to have an M184V mutation and the other an M184I mutation. In these 2 individuals, the mutant subpopulations became undetectable by population sequencing by 9 weeks and 12 weeks after discontinuing PrEP.

Viral Load Monitoring and Resistance Testing

Metzner discussed the current state-of-the-art and future directions for viral load assays, drug resistance mutations testing, and the goal of expanded access to technology for RLS (Abstract 72). With regard to viral load detection, the increasing sensitivity of commercially available assays to a detection level of 20 copies/mL, or perhaps in the future to 1 copy/mL, raises questions about the importance of low-level viremia at different levels in relation to risk of resistance, need for antiretroviral drug adjustment, and immune activation.

Session 124 provided insight into novel HIV quantification methods through nucleic acid amplification. Yukl and colleagues explored modification of a well-known commercial real-time PCR assay to detect plasma HIV-1 RNA levels less than 1 copy/mL (Abstract 656). Investigators reported that mean plasma viral load correlated inversely ($R = -0.78$; $P = .028$) with total duration of viral suppression (plasma HIV RNA levels < 40 copies/mL) and suggested that residual viremia may

decay slowly over years of treatment (Abstract 656).

Innovations in genotypic drug resistance testing were also discussed, such as testing of other areas of the HIV genome, or even whole HIV-1 genome sequencing. At this point, there is no evidence that whole-genome sequencing is superior to sequencing of protease and reverse transcriptase; however, whole-genome sequencing could offer increased options for combining of antiretroviral drugs and enhance current methods of epidemiology. Whole-genome sequencing would require effective algorithms to be developed for the prediction of the clinical relevance of various mutations.

The role of minority drug resistance mutation assays compared with bulk sequencing was also emphasized. Metzner described data comparing the presence of minority drug resistance mutations in the Zurich Primary HIV Cohort with that of a chronically infected group from the Swiss Cohort Study. Results showed that minority variants with the K103N mutation were detected at equal rates in both groups (4%) but that M184V variants were present at higher rates in the primary-HIV-infection cohort (8%) than in the chronically HIV-infected cohort (2.5%), suggesting that the M184V virus is less fit and less likely to persist over time.

The impact of NNRTI-associated minority resistance variants on virologic success for treatment-naive patients beginning initial NNRTI-based regimens was illustrated in a meta-analysis of 10 studies and 985 subjects covered by Li and colleagues (Abstract 614). Patients with baseline NNRTI-associated minority resistance variants had a statistically significantly higher risk of viral failure, regardless of adherence, than patients without such variants. The importance of minority resistance variants appears to vary by drug class. Further study will be needed to understand their impact on clinical care.

The design and application of feasible resistance mutations testing methods for use in RLS is of crucial importance. Several abstracts at the conference illustrated methods for resistance mutation analysis in RLS (Session 125, Abstracts 662 – 664).

Pharmacokinetic Considerations

Tenofovir/Emtricitabine for Preexposure Prophylaxis

Anderson and colleagues evaluated drug concentrations in plasma and PBMCs in 16 HIV-uninfected adults given a single tablet of fixed-dose tenofovir/emtricitabine (Abstract 641). They found that the tenofovir diphosphate concentrations in PBMCs were approximately 35% of those achieved in primate models of HIV transmission and that the tenofovir diphosphate concentrations in plasma were similar to those in the primary models. As expected, concentrations of both drugs were much lower than steady-state concentrations in HIV-1-infected patients receiving long-term therapy. The authors note that the low concentrations of tenofovir diphosphate are concerning for episodic administration of tenofovir/emtricitabine as used for PrEP of HIV-1 transmission.

Raltegravir-Based Antiretroviral Therapy

Miro and colleagues reported on the antiviral and pharmacokinetic properties of raltegravir-based regimens for HIV-1-infected, solid-organ transplant recipients (Abstract 644). There were 15 subjects whose regimens were switched to raltegravir plus tenofovir/emtricitabine or abacavir/lamivudine. All participants had continued virologic control, and this regimen switch allowed for standard dosing of immunosuppressant medications. The authors found no statistically significant pharmacokinetic interactions between raltegravir and cyclosporine or mycophenolic acid.

Pharmacokinetic Properties of Newly Available and Investigational Compounds

The compound TBR-652 is an investigational antagonist of CCR5 and CC chemokine receptor 2 (CCR2) virus that has demonstrated in vivo antiviral activity. Martin and colleagues reported on the pharmacokinetic profiles in several animal models (Abstract 627). There was good bioavailability and a long plasma half-life (approximately 35 hours) in all the species examined.

Telaprevir is a nonstructural protein 3 (NS3)/4A protease inhibitor that was recently approved by the US Food and Drug Administration (FDA) for the treatment of HCV infection. It is both a substrate and an inhibitor of cytochrome P450 3A (CYP3A). The current dose is 750 mg every 8 hours. Garg and colleagues attempted to enhance the pharmacokinetic profile of telaprevir by adding ritonavir (Abstract 629). Two dosing schemes, telaprevir 250 mg/ritonavir 100 mg twice daily and telaprevir 750 mg/ritonavir 100 mg twice daily, were administered to healthy volunteers, and the pharmacokinetic properties were compared with those of the standard dose. Neither of the ritonavir regimens achieved adequate trough levels of telaprevir. Moreover, the addition of ritonavir did not appear to change the pharmacokinetic profile of telaprevir.

Rilpivirine is a NNRTI recently approved by the FDA for the treatment of HIV infection. Crauwels and colleagues evaluated the pharmacokinetic profiles of rilpivirine after switching from efavirenz (Abstract 630). They found that rilpivirine concentrations were reduced after switching from efavirenz compared with a control period of rilpivirine administration before efavirenz dosing. This effect lessened over time but was still somewhat apparent up to 28 days after efavirenz administration. The authors concluded, however, that none of the observed drug concentrations was low enough to be concerning for virologic breakthrough and that this switch should be safe in clinical practice.

Once-Daily Maraviroc Dosing

Taylor and colleagues investigated the pharmacokinetic profile of maraviroc dosed once daily with darunavir/r (Abstract 636). They compared the maximal concentration and trough concentration of 20 subjects receiv-

ing maraviroc 300 mg once daily plus once-daily darunavir/r with those of 13 subjects receiving maraviroc 300 mg twice daily plus fixed-dose tenofovir/emtricitabine. They found that maximal concentrations (at 2 hours post–maraviroc dosing in both groups) and trough concentrations (at 24 hours and 12 hours post–maraviroc dosing, respectively) were similar in the 2 groups.

Neuroleptic Drugs

Okulicz and colleagues evaluated the virologic outcomes of 21 patients receiving antiepileptic drugs that induce the CYP3A4 enzymes: phenytoin, carbamazepine, and phenobarbital (Abstract 646). Their comparison included 85 patients receiving other neuroleptic drugs as a control group. The authors found the risk of virologic failure was much higher for patients receiving the enzyme-inducing antiepileptic drugs; 10 of 17 patients (59%) had virologic failure compared with 20 of 75 patients (27%) taking other neuroleptic drugs. They noted that this difference has important implications for RLS, where, in general, only enzyme-inducing antiepileptic drugs are available for treatment of seizure disorders.

Efavirenz in the Second and Third Trimesters of Pregnancy

Efavirenz is teratogenic when taken early in pregnancy but is recommended as initial therapy by the WHO for HIV-1-infected women after the first trimester. Cressey and colleagues compared the pharmacokinetics of efavirenz in HIV-1-infected women during the third trimester of pregnancy with pharmacokinetics at 6 weeks to 12 weeks postpartum (Abstract 754). They found slightly higher efavirenz clearance and lower trough concentrations during the third trimester than at the postpartum points. The authors felt that the magnitude of this change was enough to warrant a change in efavirenz dosing during pregnancy. It is important to note the majority of the women in this study were Thai and these results may not generalize to other populations.

Antiretroviral Therapy and Breast-feeding

Liotta and colleagues presented data on drug concentrations in infants being breast-fed by HIV-1-infected women receiving antiretroviral therapy (Abstract 757). They had 38 paired maternal and infant samples from patients at 1 month to 6 months postpartum. Nevirapine was present at therapeutic concentrations in all infant samples tested. Lamivudine was detectable in most infant samples. Lopinavir, stavudine, and zidovudine were detected much less commonly. The authors concluded that direct administration of nevirapine to infants during breast-feeding was likely not necessary.

Rifabutin and Lopinavir/Ritonavir

Naiker and colleagues evaluated 2 dosing schemes for rifabutin when administered with lopinavir/r (Abstract 650). They enrolled 16 HIV-1-infected patients being treated for tuberculosis. All patients received rifabutin 300 mg daily for 4 weeks along with other standard initial tuberculosis drugs, after which a lopinavir/r-based regimen was added. Patients were randomly assigned to a reduced dose of rifabutin (either 150 mg daily or 150 mg 3 times per week). Participants receiving 150 mg 3 times weekly had rifabutin drug levels that were appreciably lower than levels before the initiation of lopinavr/r. The group receiving rifabutin 150 mg daily had levels that were similar to or slightly higher than those observed before lopinavir/r dosing, and they had peak rifabutin concentrations that were within the therapeutic range. There were no safety concerns in any of the groups. The authors suggested that rifabutin should be administered at 150 mg daily when dosed with lopinavir/r, not at the currently accepted dosage of 150 mg 3 times weekly.

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References

1. Wilkin TJ, Goetz MB, Leduc R, et al. Re-analysis of coreceptor tropism in HIV-1-infected adults using a phenotypic assay with enhanced sensitivity. *Clin Infect Dis*. 2011;52:925-928.
2. Mwagomba B, Zachariah R, Massaquoi M, et al. Mortality reduction associated with HIV/AIDS care and antiretroviral treatment in rural Malawi: evidence from registers, coffin sales and funerals. *PLoS One*. 2010;5:e10452.
3. World Health Organization. Antiretroviral therapy for HIV infection in adults and adolescents: Recommendations for a public health approach: 2010 revision. http://www.who.int/hiv/pub/arv/adult2010/en/index.html. Accessed May 20, 2011.
4. World Health Organization. Antiretroviral drugs for treating pregnant women ande preventing HIV infection in infants: Recommendations for a public health approach (2010 version). http://www.who.int/hiv/pub/mtct/antiretroviral2010/en/. Accessed May 20, 2011.
5. Granich RM, Gilks CF, Dye C, De Cock KM, Williams BG. Universal voluntary HIV testing with immediate antiretroviral therapy as a strategy for elimination of HIV transmission: a mathematical model. *Lancet*. 2009;373:48-57.
6. Severe P, Juste MA, Ambroise A, et al. Early versus standard antiretroviral therapy for HIV-infected adults in Haiti. *N Engl J Med*. 2010;363:257-265.
7. Abdool Karim SS, Naidoo K, Grobler A, et al. Timing of initiation of antiretroviral drugs during tuberculosis therapy. *N Engl J Med*. 2010;362:697-706.
8. Holmes CB, Coggin W, Jamieson D, et al. Use of generic antiretroviral agents and cost savings in PEPFAR treatment programs. *JAMA*. 2010;304:313-320.
9. Pujades-Rodríguez M, Balkan S, Arnould L, Brinkhof MA, Calmy A. Treatment failure and mortality factors in patients receiving second-line HIV therapy in resource-limited countries. *JAMA*. 2010;304:303-312.
10. Goldie SJ, Yazdanpanah Y, Losina E, et al. Cost-effectiveness of HIV treatment in resource-poor settings—the case of Côte d'Ivoire. *N Engl J Med*. 2006;355:1141-1153.

11. Walensky RP, Ciaranello AL, Park JE, Freedberg KA. Cost-effectiveness of laboratory monitoring in sub-Saharan Africa: a review of the current literature. *Clin Infect Dis*. 2010;51:85-92.

12. Walensky RP, Wood R, Ciaranello AL, et al. Scaling up the 2010 World Health Organization HIV treatment guidelines in resource-limited settings: a model-based analysis. *PLoS Med*. 2010;7:e1000382.

13. Hirnschall G, Schwartländer B. Treatment 2.0: catalysing the next phase of scale-up [published online ahead of print February 24, 2011]. *Lancet*. 2011;doi:10.1016/S0140-6736(11)60247-X.

14. Hill A, Ananworanich J, Calmy A. Dose optimisation: a strategy to improve tolerability and lower antiretroviral drug prices in low and middle income countries. *Open Infect Dis J*. 2010;4:85-91.

15. Sanne I, Orrell C, Fox MP, et al. Nurse versus doctor management of HIV-infected patients receiving antiretroviral therapy (CIPRA-SA): a randomised non-inferiority trial. *Lancet*. 2010;376:33-40.

16. Mills EJ, Nachega JB, Buchan I, et al. Adherence to antiretroviral therapy in sub-Saharan Africa and North America: a meta-analysis. *JAMA*. 2006;296:679-690.1

17. Ware NC, Idoko J, Kaaya S, et al. Explaining adherence success in sub-Saharan Africa: an ethnographic study. *PLoS Med*. 2009;6:e11.

18. Byakika-Tusiime J, Crane J, Oyugi JH, et al. Longitudinal antiretroviral adherence in HIV+ Ugandan parents and their children initiating HAART in the MTCT-Plus family treatment model: role of depression in declining adherence over time. *AIDS Behav*. 2009;13 Suppl 1:82-91.

19. Lester RT, Ritvo P, Mills EJ, et al. Effects of a mobile phone short message service on antiretroviral treatment adherence in Kenya (WelTel Kenya1): a randomised trial. *Lancet*. 2010;376:1838-1845.

20. Pop-Eleches C, Thirumurthy H, Habyarimana JP, et al. Mobile phone technologies improve adherence to antiretroviral treatment in a resource-limited setting: a randomized controlled trial of text message reminders. *AIDS*. 2011;25:825-834.

21. Haberer JE, Kahane J, Kigozi I, et al. Real-time adherence monitoring for HIV antiretroviral therapy. *AIDS Behav*. 2010;14:1340-1346.

22. Parienti JJ, Das-Douglas M, Massari V, et al. Not all missed doses are the same: sustained NNRTI treatment interruptions predict HIV rebound at low-to-moderate adherence levels. *PLoS One*. 2008;3:e278

23. Bisson GP, Gross R, Bellamy S, et al. Pharmacy refill adherence compared with CD4 count changes for monitoring HIV-infected adults on antiretroviral therapy. *PLoS Med*. 2008;5:e109.

24. Geng EH, Bwana MB, Kabakyenga J, et al. Diminishing availability of publicly funded slots for antiretroviral initiation among HIV-infected ART-eligible patients in Uganda. *PLoS One*. 2010;5:e14098.

25. Nachega JB, Leisegang R, Bishai D, et al. Association of antiretroviral therapy adherence and health care costs. *Ann Intern Med*. 2010;152:18-25.

26. Rosen S, Fox MP, Gill CJ. Patient retention in antiretroviral therapy programs in sub-Saharan Africa: a systematic review. *PLoS Med*. 2007;4:e298.

27. Coovadia A, Abrams EJ, Stehlau R, et al. Reuse of nevirapine in exposed HIV-infected children after protease inhibitor-based viral suppression: a randomized controlled trial. *JAMA*. 2010;304:1082-1090.

28. Mugyenyi P, Walker AS, Hakim J, et al. Routine versus clinically driven laboratory monitoring of HIV antiretroviral therapy in Africa (DART): a randomised non-inferiority trial. *Lancet*. 2010;375:123-131.

29. Coutinho A, Mermin J, Ekwaru J, et al. Utility of routine viral load CD4 cell count, and clinical monitoring among HIV-infected adults in Uganda: a randomized trial. [Abstract 125.] 15th Conference on Retroviruses and Opportunistic Infections (CROI). February 3-6, 2008; Boston, MA.

30. Reynolds SJ, Nakigozi G, Newell K, et al. Failure of immunologic criteria to appropriately identify antiretroviral treatment failure in Uganda. *AIDS*. 2009;23:697-700.

31. Mee P, Fielding KL, Charalambous S, Churchyard GJ, Grant AD. Evaluation of the WHO criteria for antiretroviral treatment failure among adults in South Africa. *AIDS*. 2008;22:1971-1977.

32. Chaiwarith R, Wachirakaphan C, Kotarathititum W, Praparatanaphan J, Sirisanthana T, Supparatpinyo K. Sensitivity and specificity of using CD4+ measurement and clinical evaluation to determine antiretroviral treatment failure in Thailand. *Int J Infect Dis*. 2007;11:413-416.

33. Keiser O, MacPhail P, Boulle A, et al. Accuracy of WHO CD4 cell count criteria for virological failure of antiretroviral therapy. *Trop Med Int Health*. 2009;14:1220-1225.

34. Moore DM, Awor A, Downing R, et al. CD4+ T-cell count monitoring does not accurately identify HIV-infected adults with virologic failure receiving antiretroviral therapy. *JAIDS*. 2008;49:477-484.

35. Keiser O, Tweya H, Boulle A, et al. Switching to second-line antiretroviral therapy in resource-limited settings: comparison of programmes with and without viral load monitoring. *AIDS*. 2009;23:1867-1874.

36. Johnson VA, Brun-Vézinet F, Clotet B, et al. Update of the drug resistance mutations in HIV-1: December 2010. *Top HIV Med*. 2010;18:156-163.