Advances in Antiretroviral Therapy

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The 15th Conference on Retroviruses and Opportunistic Infections maintained its place as the premier meeting for presentation of the state of the art of antiretroviral therapy. This year brought together data on new antiretroviral agents in the pipeline, updated our knowledge base of agents approved in the past year (eg, maraviroc, raltegravir, etravirine), delineated approaches to management of treatment-naive and -experienced patients and the use of drugs for prevention of maternal-to-child transmission, and refined our expanding knowledge of drug resistance. A particular highlight of this year's conference was the progress made in antiretroviral treatment and research in resource-limited settings as reflected in both the number and quality of presentations emanating from the developing world.

Investigational Agents

CCRS Antagonists

SCH 532706. Pett and colleagues presented a phase I study of the CCRS antagonist SCH 532706 in HIV-infected men (Abstract 38). The study was an open-label, nonrandomized, single-center study of 12 subjects receiving SCH 532706, 60 mg twice daily with ritonavir 100 mg daily for 10 days. The mean changes in plasma HIV RNA level at day 10 and day 15 were $-1.31 \log_{10}$ copies/mL and $-1.62 \log_{10}$ copies/mL, respectively. The drug was generally well tolerated. One serious adverse event, pericarditis, occurred 13 days after dosing was completed and was considered possibly related to the study drug. This event resolved without sequelae. The authors noted that the drug was suitable for once-daily dosing with ritonavir.

Nucleoside Analogue Reverse Transcriptase Inhibitors

Translocation-deficient reverse transcriptase inhibitors. Existing nucleoside analogue reverse transcriptase inhibitors (nRTIs) lack a 3’OH group and thus terminate the growing DNA chain once incorporated. Marchand and colleagues presented data on a new nRTI, 4’-ethynyl-2-fluorodeoxyadenosine (4’-E-2FdA) (Abstract 726a). The compound has a 3’OH group but appears to act as a chain terminator. The authors presented evidence that once the compound is incorporated into the growing DNA, translocation and resulting incorporation of the subsequent DNA base pair are inhibited. This appears to be a new mechanism within the nRTI class of compounds.

OBP-601 (4’-Ed4T). Weber and colleagues presented data on OBP-601, a new nRTI related to stavudine (Abstract 726b). The in vitro data showed that OBP-601 was active against a broad panel of recombinant viruses. Some nRTI resistance mutations conferred mild to moderate resistance. Viruses containing the Q151M mutation appeared hypersusceptible to the drug, however. The compound exerted synergy with the other antiretroviral agents tested.

3’-Azido-2’,3’-dideoxynucleosides. Sluis-Cremer presented data on 2 related compounds: 3’-azido-2’,3’-dideoxyadenosine and -dideoxyguanosine (Abstract 727). The compounds appeared to have minimal cytotoxicity or effect on mitochondria. Both compounds exhibited potent activity in vitro. The inhibitory concentration was not affected when tested against viruses containing the K65R, L74V, M184V, or 3 or more thymidine analogue-associated mutations (TAMs).

Nonnucleoside Reverse Transcriptase Inhibitors

UK-453,061. Mori and colleagues presented data on a new nonnucleoside analogue reverse transcriptase inhibitor (NNRTI), UK-453,061 (Abstract 728). This NNRTI was tested against 62 clinically derived viruses from treatment-naive patients with transmitted NNRTI resistance including viruses from a broad range of subtypes. The compound retained activity against 61 of 62 isolates, defined as a fold-change of the 50% inhibitory concentration (IC_{50}) of less than 10. The remaining virus contained the triple mutation K101E+ V106I+ Y188F/L. The compound was synergistic with the other tested drugs.

IDX899, RDEA427, and RDEA640. Richman and colleagues compared the in vitro development of resistance to efavirenz and IDX899, a new NNRTI, in a serial passage experiment (Abstract 729). High-level resistance to IDX899 took considerably longer to develop than for efavirenz (26 to 30 passages vs 8, respectively). The efavirenz-resistant viruses typically remained sensitive to IDX899, as did all single or double mutants. Similarly, Raney and colleagues presented data on the investigational NNRTIs RDEA427 and RDEA640, which were found to have minimal cytotoxicity, good activity against NNRTI-resistant virus, and a low potential for induc-

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tion of cytochrome P450 3A4 (CYP3A4) activity (Abstract 730).

Protease Inhibitors

Dimerization inhibitors. Dimerization of the 2 protease polypeptide monomers is essential for protease’s activity. Koh and colleagues presented evidence that this process can be inhibited with small molecules (Abstract 733). In fact, they found that tipranavir and darunavir acted as dimerization inhibitors at low concentrations, whereas other protease inhibitors (PIs) did not. Protease with an A28S mutation or 4 mutations (V32I, L33F, I54M, I84V) could dimerize even in the presence of these compounds. The authors concluded that these 2 PIs differ substantially from other PIs and that protease dimerization should be investigated further for drug development.

Integrase Inhibitors

Integrase-LEDGF/p75 interaction. Integration of HIV is a multistep process. Christ and colleagues presented data on the interaction of HIV integrase with the host protein LEDGF/p75 (Abstract 735). They developed a high-throughput assay to discover inhibitors of this interaction and found compounds with low micromolar activity. They consider this interaction a viable target for drug development.

Nanoparticles

TMC278. Klooster and colleagues presented data on a depot formulation of TMC278, an investigational NNRTI (Abstract 154). TMC278 was administered to 48 HIV-seronegative volunteers as a nanosuspension that slowly released drug over an extended period. Subcutaneous or intramuscular injections of TMC278 200 mg, 400 mg, or 600 mg or of placebo were studied. The intramuscular injection appeared better tolerated and not appreciably different from placebo. The TMC278 levels were detectable for approximately 12 weeks. The peak plasma level after intramuscular injection of 600 mg occurred at approximately 3 days and was comparable to that of 25 mg orally once daily. One month after intramuscular injection of 600 mg, the plasma levels were similar to that of the expected trough of 25 mg orally once daily. These results suggest the potential for once-monthly dosing.

Efavirenz/Lopinavir/Ritonavir. Destache and colleagues discussed the in vitro study of ritonavir, lopinavir, and efavirenz nanoparticles (Abstract 743). Nanoparticles are pure drug in particle size of 340 nM. These particles slowly released drug in the in vitro system. The level at day 14 for each drug was greater than 1.0 μg/mL. These results are promising for future studies of infrequent parenteral dosing of antiretroviral therapy.

Clinical Trials of Antiretroviral Therapy in Treatment-naive Subjects

Atazanavir/Ritonavir Versus Lopinavir/Ritonavir

Molina and colleagues presented data from the CASTLE study, which compared open-label, once-daily atazanavir/ritonavir to lopinavir/ritonavir soft-gel capsules, each given with fixed-dose tenofovir/emtricitabine to 883 antiretroviral therapy–naive subjects with a plasma HIV RNA level of at least 5000 copies/mL (Abstract 37). The median CD4+ counts in the atazanavir/ritonavir and lopinavir/ritonavir groups were 205 cells/μL and 204 cells/μL, respectively, and the mean plasma HIV RNA levels were 5.01 log_{10} copies/mL and 4.96 log_{10} copies/mL, respectively. The median ages were 34 years and 36 years, respectively, and 31% were women.

Seventy-eight percent of subjects who underwent randomization to atazanavir/ritonavir achieved a plasma HIV RNA level below 50 copies/mL at week 48 compared with 76% for the lopinavir/ritonavir arm (difference, 1.7%; 95% confidence interval [CI], −3.8% to 7.1%). This excluded the prespecified noninferiority boundary of −10%, and atazanavir/ritonavir was declared noninferior to lopinavir/ritonavir. No statistically significant difference occurred between arms for subjects with baseline plasma HIV RNA levels above 100,000 copies/mL (74% vs 72%). The efficacy of lopinavir/ritonavir seemed lower in subjects with lower CD4+ cell counts, however. The authors suggested that this result stemmed from increased discontinuations because of side effects from lopinavir/ritonavir among those with the lowest CD4+ counts. The authors also noted that atazanavir/ritonavir resulted in more favorable lipid profiles than lopinavir/ritonavir did, as judged by fewer subjects initiating lipid-lowering therapy on the former (2% vs 8%, respectively) and a lower proportion of subjects with a total cholesterol to high-density lipoprotein ratio greater than 5 (12% vs 20%, respectively). Overall discontinuations as a result of side effects were low in both arms (2% vs 3%, respectively).

Fixed-dose Abacavir/Lamivudine Versus Tenofovir/Emtricitabine

Only limited data directly compare the 2 once-daily fixed-dose nRTI combinations of abacavir/lamivudine and tenofovir/emtricitabine. Smith and colleagues presented data comparing fixed-dose combinations of these nRTIs, each given with once-daily lopinavir/ritonavir soft-gel capsules (Abstract 774). This was a randomized, double-blind, placebo-matched trial. No HLA-B*5701 testing was performed. The primary outcome measured was the proportion of subjects with plasma HIV RNA levels below 50 copies/mL at week 48. Missing subjects and subjects switching antiretroviral therapy counted as failures. The trial enrolled 688 subjects (median age, 38 years; 18% female). In the abacavir/lamivudine and tenofovir/emtricitabine groups, the median baseline CD4+ count was 214 cells/μL and 193 cells/μL, respectively, and the median plasma HIV RNA level was 4.90 copies/mL and 4.84 copies/mL, respectively. At week 48, 68% and 67% of subjects had plasma HIV RNA levels below 50 copies/mL (difference, −6.6% to 7.4%). This excluded the prespecified noninferiority boundary of −12%, and abacavir/lamivudine was
declared noninferior to tenofovir/emtricitabine. Fourteen subjects receiving abacavir/lamivudine discontinued early because of suspected abacavir hypersensitivity compared with 3 in the tenofovir/emtricitabine group. Three subjects discontinued tenofovir/emtricitabine because of proximal renal tubular dysfunction. Subsequent to this presentation, a separate double-blind, placebo-controlled comparison of these 2 fixed-dose combinations was partially unblended by the study’s Data and Safety Monitoring Board because of a higher rate of virologic failure among subjects randomized to abacavir/lamivudine whose prerandomization plasma HIV RNA level was greater than 100,000 copies/mL (http://www3.niaid.nih.gov/news/news-releases/2008/actg5202bulletin.htm).

**Once-daily Verus Twice-daily Dosing of Lopinavir/Ritonavir**

Gathe and colleagues presented data from an open-label, randomized controlled trial of once-daily versus twice-daily dosing of lopinavir/ritonavir given with fixed-dose tenofovir/emtricitabine (Abstract 775). They randomized 664 subjects with a mean plasma HIV RNA level of 5 log_{10} copies/mL and CD4+ count of 216 cells/μL in the 2 arms. Plasma HIV RNA level was below 50 copies/mL 48 weeks after randomization in 77% and 75% of the once- and twice-daily groups, respectively (difference, 3%; 95% confidence interval [CI], −4.8% to 8.1%). They excluded the noninferiority boundary of −12% and declared once-daily dosing of lopinavir/ritonavir noninferior to twice-daily dosing. The adverse event rate and discontinuations because of adverse events were similar between groups. Among subjects with virologic failure, no PI resistance–associated mutations were found.

**Maraviroc**

Heera and colleagues presented a detailed analysis of subjects with virologic failure during the Maraviroc in Treatment-naive Patients (MERIT) trial, which compared maraviroc to efavirenz, each given with fixed-dose zidovudine/lamivudine (Abstract 40LB). This study enrolled 724 subjects with CCR5-using virus at a screening. At the time of randomization, 25 of the 724 subjects (3.5%) were found to have dual-tropic or mixed-tropic populations. These 25 subjects were less likely to have plasma HIV RNA levels below 50 copies/mL at week 48: 6 of 11 (56%) of those randomized to efavirenz had less than 50 copies/mL at week 48, as did 14 (7%) of those who underwent randomization to maraviroc. There were 43 subjects who discontinued maraviroc because of lack of efficacy. At the time of failure, 19 of 43 had dual-tropic or mixed HIV populations. Twenty-nine of 43 patients had the M184V mutation, and 7 had other nRTI resistance mutations in addition to M184V. These mutations were more common among those whose treatment failed and who had dual-tropic or mixed-tropic HIV populations (eg, 19/19 subjects with virologic failure and dual-tropic or mixed HIV populations had M184V). Among the subjects for whom maraviroc failed and who had CCR5-using HIV, 2 had resistance to maraviroc.

**Once-daily Emtricitabine, Didanosine, and Efavirenz in HIV-infected Children and Adolescents**

Rathore and colleagues enrolled 37 children in this single-arm, open-label trial. After 144 weeks of follow-up, 24 (65%) had plasma HIV RNA levels below 50 copies/mL (Abstract 581). The CD4+ count increased a median of 308 cells/μL, and the CD4+ percentage increased by 16%. The treatment appeared generally safe and well tolerated.

**Clinical Trials in Treatment-experienced Subjects**

Table 1 lists the results of selected clinical trials in treatment-experienced subjects. The 48-week updates are presented here for clinical trials involving raltegravir, maraviroc, and etravirine. The 16-week or 24-week results for each of these trials have been presented previously.

**Vicriviroc**

Zingman and colleagues presented data on the virologic efficacy of vicriviroc, an investigational CCR5 antagonist (Abstract 59LB). This study evaluated higher doses of vicriviroc (20 mg and 30 mg daily) than had been studied in a prior trial of vicriviroc, AIDS Clinical Trials Group (ACTG) 5211 (5 mg, 10 mg, and 15 mg). This study enrolled 116 subjects (78% men) with 3-class antiretroviral experience and plasma HIV RNA levels greater than 1000 copies/mL. Subjects were required to have only CCR5-using virus. Vicriviroc (20 mg or 30 mg) or placebo was given with an optimized background regimen that was required to have a ritonavir-boosted PI. Of 39 subjects who underwent randomization to the higher dose of vicriviroc, 22 (56%) had plasma HIV RNA levels below 50 copies/mL at week 48; the same was true for 21/40 (52%) of those who underwent randomization to 20 mg and for only 5/35 (14%) of those who underwent randomization to placebo. Among subjects receiving vicriviroc, those achieving a minimum concentration greater than 100 ng/mL were more likely to have a plasma HIV RNA level below 50 copies/mL. This level was achieved more commonly among subjects receiving the 30-mg dose of vicriviroc. No safety concerns arose from this study. The 30-mg dose was chosen for subsequent phase III studies of vicriviroc.

**Apricitabine**

Cahn and colleagues presented a phase IIB study of apricitabine in treatment-experienced subjects with the M184V mutation whose antiretroviral regimen was failing (Abstract 793). Apricitabine is a cytidine analogue that retains activity against HIV with resistance to lamivudine and emtricitabine. This study randomized 50 subjects to either continue lamivudine treatment or change lamivudine to apricitabine 600 mg or 800 mg twice daily. The primary endpoint was the change in plasma HIV RNA level at day 21, as previously reported. Subjects optimized their antiretroviral regimen at day 21 according
to baseline genotype while continuing lamivudine or apricitabine. At week 24, 72% and 75% of subjects in the 2 apricitabine arms had plasma HIV RNA levels below 50 copies/mL, compared with 58% of the lamivudine subjects. This study was not powered for this endpoint, and the results did not reach statistical significance.

**Therapeutic Drug Monitoring with Subsequent Protease Inhibitor Dose Escalation**

Demeter and colleagues presented data from ACTG 5146 of a randomized, controlled trial of the effect of therapeutic drug monitoring and PI dose escalation on virologic efficacy (Abstract 35). Eligible subjects had experienced failure of at least 1 prior PI-based regimen and had a plasma HIV RNA level of 1000 copies/mL or higher. Subjects initiated a new PI-based regimen chosen according to results of resistance testing. After 2 weeks, subjects returned for testing of plasma trough PI concentration. Results of the resistance test before starting the new regimen and the trough concentration were used to calculate the value of the normalized inhibitory quotient (nIQ). Lower trough concentrations and increasing resistance lead to a lower nIQ value. An nIQ value below 1 was hypothesized to increase risk of virologic failure.

Four weeks after initiating the new regimen, 183 subjects with an nIQ value below 1 underwent randomization to either maintain the standard PI dose (standard-of-care arm) or increase the PI dose (therapeutic-drug-monitoring arm). The dose escalation was successful in raising the trough concentration (and thus the nIQ value) for all PIs except for fos-amprenavir, for which dose escalation did not change the trough concentration. The change in plasma HIV RNA level was not statistically significantly different between the 2 arms. On subgroup analysis, however, subjects with an nIQ value of 0.7 to 1.0 (i.e., less severe resistance and/or higher plasma trough concentrations) benefited from therapeutic drug monitoring (TDM) with resulting dose escalation. Black and Hispanic subjects also appeared to benefit from TDM with a greater decrease in plasma HIV RNA level with PI dose escalation. The reason for this association with race and ethnicity is unclear.

**Change from Enfuvirtide to Raltegravir**

Harris and colleagues presented observational data on patients with sustained virologic suppression (plasma HIV level RNA below 50 copies/mL) and treatment-limiting, injection-site reactions on an enfuvirtide-containing regimen (Abstract 799). All such subjects at their clinical site were offered to switch from enfuvirtide to raltegravir. Subjects were highly treatment-experienced. Thirty-six subjects made the switch and were observed with routine virologic monitoring for a median of 7 months. The plasma HIV RNA levels of 34 of 35 subjects were still below 50 copies/mL at their most recent assessment. The remaining subject had a level of 60 copies/mL. No subjects discontinued raltegravir treatment. The authors concluded that this drug substitution was safe and effective in subjects receiving enfuvirtide.

**Antiretroviral Treatment Strategies**

**Consequences of Treatment Interruption**

This year’s conference offered new insights into the consequences of strategic treatment interruptions. El-Sadr presented data on behalf of the Strategies for Management of Antiretroviral Therapy (SMART) trial investigators on the risk of opportunistic disease or death following treatment reinitiation after treatment interruption (Abstract 36). The SMART trial randomized 5472 participants with CD4+ counts above 350 cells/μL to 1 of 2 strategies: virologic suppression, which entailed continuous use of antiretroviral therapy to maintain the lowest possible plasma HIV RNA level; or drug conservation, which consisted of deferred antiretroviral therapy until CD4+ count was less than 250 cells/μL, followed by episodic potent antiretroviral therapy to raise CD4+ counts above 350 cells/μL, followed by further treatment interruption.

Enrollment in the trial was stopped on January 11, 2006, when the study group found the hazard ratio (HR) for opportunistic disease or death for the drug conservation group compared with the virologic suppression group to be 2.52 (95% CI, 1.82-3.51), representing a statistically significant increased risk in the drug conservation group. At that point, the protocol was discontinued, and all study participants who met criteria for antiretroviral initiation were encouraged to start treatment. The investigators continued to observe all participants through July 11, 2007. At the time of study modification, notable characteristics of the drug conservation compared with the virologic suppression groups, respectively, were as follows: current use of antiretroviral therapy, 36% versus 94%; plasma HIV RNA level less than 400 copies/mL, 35% versus 82%; and mean CD4+ count, 425 versus 625 cells/μL. By the study’s close, 84% of participants in the drug conservation group and 95% of participants in the virologic suppression group were receiving antiretroviral therapy. The HR for opportunistic disease or death after study modification was 1.37 (95% CI, 0.96-1.94), which had a P value for difference from the premodification HR of .02. Similar trends were observed for death, opportunistic disease alone, or major cardiovascular, renal, or hepatic disease. In subgroup analyses, participants in the drug conservation group who were on antiretroviral therapy for greater than 85% of the time after study modification had an HR for opportunistic disease or death of 0.9, compared with the virologic suppression group. This normalization of the HR did not occur among participants in the drug conservation group on antiretroviral therapy between 75% and 85% of the time, or less than 75% of the time after study modification. The investigators also noted that the proportion of participants with plasma HIV RNA levels less than 400 copies/mL in July 2007 still differed by study group: 73% for the drug conservation
Table 1. Selected Clinical Trials of Antiretroviral Drugs in Treatment-experienced Patients

<table>
<thead>
<tr>
<th>Study Name</th>
<th>Abstract No.</th>
<th>Description</th>
<th>Regimen(s) (No. Patients)</th>
<th>Population</th>
<th>Baseline CD4+ count (cells/µL)</th>
<th>Baseline HIV RNA (log₁₀ copies/mL)</th>
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<tbody>
<tr>
<td>BENCHMRK-1</td>
<td>788</td>
<td>Phase III, randomized, placebo-controlled trial of raltegravir</td>
<td>Raltegravir 400 mg bid (n = 232) or placebo with OBR (n = 118)</td>
<td>Genotypic or phenotypic resistance to at least 1 drug from all 3 current classes, plasma HIV-1 RNA &gt; 1000 copies/mL</td>
<td>153–156 (mean)</td>
<td>4.5–4.6 (mean)</td>
</tr>
<tr>
<td>BENCHMRK-2</td>
<td>789</td>
<td>Phase III, randomized, placebo-controlled trial of raltegravir</td>
<td>Raltegravir 400 mg bid (n = 230) or placebo with OBR (n = 119)</td>
<td>Genotypic or phenotypic resistance to at least 1 drug from all 3 current classes, plasma HIV-1 RNA &gt; 1000 copies/mL</td>
<td>146–163 (mean)</td>
<td>4.5–4.6 (mean)</td>
</tr>
<tr>
<td>Combined analysis of MOTIVATE 1 and MOTIVATE 2</td>
<td>792</td>
<td>Phase IIIb/III randomized, double-blind trials of maraviroc, an oral CCR5 inhibitor</td>
<td>Maraviroc 150 mg qd (n = 414) + OBR or maraviroc 150 mg bid + OBR (n = 426) vs OBR (n = 209)</td>
<td>3-class experience, plasma HIV-1 RNA &gt; 5000 copies/mL, CCR5-using virus</td>
<td>150–182 (median)</td>
<td>4.8–4.9 (mean)</td>
</tr>
<tr>
<td>DUET-1</td>
<td>790</td>
<td>Phase III randomized, placebo-controlled trial of etravirine</td>
<td>Etravirine 200 mg bid, darunavir/ritonavir + choice of nRTIs +/- enfuvirtide vs placebo, darunavir/ritonavir + choice of nRTIs +/- enfuvirtide (n = 612 total)</td>
<td>Documented NNRTI resistance, ≥ 3 primary PI resistance-associated mutations</td>
<td>106 (median)</td>
<td>4.9 (median)</td>
</tr>
<tr>
<td>DUET-2</td>
<td>791</td>
<td>Phase III randomized, placebo-controlled trial of etravirine</td>
<td>Etravirine 200 mg bid, darunavir/ritonavir + choice of nRTIs +/- enfuvirtide vs placebo, darunavir/ritonavir + choice of nRTIs +/- enfuvirtide (n = 591 total)</td>
<td>Documented NNRTI resistance, ≥ 3 primary PI resistance-associated mutations</td>
<td>105 (median)</td>
<td>4.8 (median)</td>
</tr>
<tr>
<td>VICTOR-E1</td>
<td>39LB</td>
<td>Phase II study of vicriviroc (investigational drug)</td>
<td>Vicriviroc 20 mg, vicriviroc 30 mg, or placebo with OBR containing ritonavir-boosted PI + nRTI</td>
<td>HIV-1 RNA &gt; 1000 copies/mL, 3-class experience, CCR5-using virus</td>
<td>202–226 (median)</td>
<td>4.5–4.5 (mean)</td>
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Abbreviations: bid, twice daily; OBR, optimized background regimen; qd, once daily; nRTI, nucleoside analogue reverse transcriptase inhibitor; NNRTI, nonnucleoside analogue reverse transcriptase inhibitor; PI, protease inhibitor.

group versus 84% for the virologic suppression group. Mean CD4+ counts by group also differed: 507 cells/µL, which was lower than baseline, and 648 cells/µL for the drug conservation and virologic suppression arms, respectively. The authors speculated that these differences may have led to the continued risk for opportunistic disease or death 1.5 years after study modification.

Mehandru and colleagues (Abstract 121) examined a different aspect of treatment interruption by concentrating on the effects of treatment interruption on the CD4+ T-cell population in the gastrointestinal tract. They used a trial in which 10 patients received 3 monoclonal antibodies followed by treatment interruption, and received consent from 7 of the participants to perform rectosigmoid biopsies at 3 time points: baseline (3 to 0 days before treatment interruption), 5 to 7 weeks post–treatment interruption, and 12 to 14 weeks post–treatment interruption. Of the 7 participants, 2 did not have virologic rebound after treatment interruption. Of the 5 who did, the decrease in CD4+ cell percentage in the gastrointestinal tract was more severe than the decrease in the peripheral blood. The CD4+ lymphocytes expressing the CCR5 coreceptor were preferentially targeted. The authors also found higher levels of immune activation, as measured by the percent-
<table>
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<tr>
<th>Follow-up Time (No. Weeks)</th>
<th>HIV-1 RNA Response</th>
<th>Comments</th>
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<tbody>
<tr>
<td>48</td>
<td>65% vs 31% &lt; 50 copies/mL</td>
<td>Generally well tolerated</td>
</tr>
<tr>
<td>48</td>
<td>60% vs 30% &lt; 50 copies/mL</td>
<td>Generally well tolerated</td>
</tr>
<tr>
<td>48</td>
<td>43%, 46% vs 17% &lt; 50 copies/mL</td>
<td>Generally well tolerated</td>
</tr>
<tr>
<td>48</td>
<td>60% vs 39% &lt; 50 copies/mL</td>
<td>Generally well tolerated, rash was more common with etravirine (22% vs 11%) but rarely led to discontinuation</td>
</tr>
<tr>
<td>48</td>
<td>61% vs 41% &lt; 50 copies/mL</td>
<td>Generally well tolerated, rash was more common with etravirine (17% vs 11%) but rarely led to discontinuation</td>
</tr>
<tr>
<td>48</td>
<td>52%, 56% vs 14% &lt; 50 copies/mL</td>
<td>Trough concentration of 100 ng/mL was associated with response; this was achieved more reliably in 30-mg dose</td>
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age of activated memory CD8+ T lymphocytes, in the gastrointestinal tract than in peripheral blood.

**Immune-based Treatment Strategies**

Schooley presented data from the ACTG 5197 study, a phase II, placebo-controlled trial examining the effects of treatment with an adenovirus 5 HIV Gag vaccine (Merck & Co, Inc) in HIV-infected participants before a 16-week analytic treatment interruption (Abstract 87). The vaccine was given at weeks 0, 4, and 26. Twelve weeks after the last vaccine dose, participants initiated a 16-week treatment interruption, and they were observed for a total of 250 weeks. The inclusion criteria for participants were the following: two-thirds had a nadir CD4+ count above 300 cells/μL, and one-third had a nadir CD4+ count between 200 cells/μL and 300 cells/μL; all had plasma HIV RNA levels below 50 copies/mL for at least 24 months, CD4+ cell counts greater than 500 cells/μL, and adenovirus 5 titers below 200 units. The investigators chose 2 predetermined endpoints: the time average of the area under the curve (AUC) for the plasma HIV RNA level from week 0 to 16 of treatment interruption and the mean plasma HIV RNA level at weeks 12 and 16 of treatment interruption (defined as the set point). The investigators specified that, to reject the null hypothesis, both endpoints needed to have P values less than .025 or 1 endpoint with a value less than .0125 and the other with less than .05.

The plasma HIV RNA level time-averaged AUC was 0.26 log_{10} copies/mL less in the vaccine group than the placebo group (P = .024). The set point determination was also 0.27 log_{10} copies/mL less in the vaccine group than in the placebo group (P = .059), but the 2 endpoints, taken together, did not reach statistical significance according to the prespecified cutoff level. The vaccine did stimulate CD4+ and CD8+ Gag-specific interferon gamma (IFN-γ)-producing cells but not Nef- or Pol-specific cells, and the number of CD4+ Gag-specific IFN-γ-producing cells predicted viral control.

Several groups presented data on the use of interleukin 2 (IL-2) as adjuvant therapy for HIV–infected individuals. Molina and colleagues presented 3-year, extended-follow-up data from the Interstart Agence Nationale de Recherche sur le SIDA (ANRS) 119 trial, which randomized 130 antiretroviral therapy–naïve, asymptomatic patients with CD4+ counts between 300 cells/μL and 500 cells/μL to IL-2 or no treatment (Abstract 702). In the treatment group, IL-2 was administered at a dose of 4.5 million international units subcutaneously twice daily for 5 days at weeks 0, 8, 16, and 24. The primary endpoint was a confirmed CD4+ count of less than 300 cells/μL, initiation of potent antiretroviral therapy, occurrence of an AIDS-defining illness, or death.

At 96 weeks, the rates of progression to the primary endpoint were 35% for the IL-2 arm and 59% for the placebo arm (P = .008). The researchers found that CD4+ count (HR, 0.59 per 50
and opportunistic infections demonstrated the impressive progress made over the past few years in antiretroviral treatment programs in resource-limited settings (RLS). This year’s presentations included some of the first data on response to second-line therapy in RLS, important findings on reductions in loss to follow-up and mortality, and novel information on antiretroviral resistance in RLS.

Maartens led off the discussion on Sunday with a plenary session titled “ART in Africa: Beyond the Roll-out.” He highlighted the fact that new infections in Africa continue to outpace the availability of antiretroviral treatment. Estimates from the Joint United Nations Programme on HIV/AIDS (UNAIDS) and the World Health Organization (WHO) are that 2,800,000 new HIV infections occurred in Africa in 2006 and 1,540,000 people were living with HIV on antiretroviral therapy. The same organizations note a growing funding gap between needs and availability of funding for antiretroviral treatment: a $2.8 billion gap in 2005 and $8.1 billion in 2007. High early mortality rates upon initiation of antiretroviral therapy were presented at last year’s conference, but Maartens also mentioned recent data that demonstrate high death rates among patients awaiting antiretroviral therapy in South Africa, with a 6-month survival of 50% for those with CD4+ counts less than 200/μL. Adherence to antiretroviral therapy may be higher in Africa than in North America, according to a recent meta-analysis, and missed doses are frequently the result of system failures such as lack of medications in the pharmacy or inability to pay for medications.

According to a WHO 2006 survey, first-line antiretroviral therapy in RLS is predominately with nevirapine, stavudine or zidovudine, and lamivudine. Antiretroviral substitutions for stavudine outpace all other medications, and herpes simplex virus (HSV)-2 suppression, and (2) decreases in HIV transmission: partner and family voluntary counseling and testing, and partner counseling, condom use, and circumcision.

Data from Large Clinical Cohorts

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Barnighausen and colleagues (Abstract 128) presented data on mortality from the Africa Centre catchment area of the Hlabisa subdistrict of KwaZulu Natal Province, where antiretroviral therapy roll-out began in 2004 and the estimated HIV prevalence is 21%. More than 517,856 person-years of observation were documented, and the researchers investigated the cause in 7950 deaths. The authors noted a decline in all-cause and AIDS-related mortality among 25- to 49-year-olds starting in 2004. The all-cause mortality rate per 1000 person-years of observation was 28.9 in women and 37.3 in men from 2003 to 2004, and 22.7 in women and 29.8 in men between 2005 and 2006. This represents an encouraging trend that merits further investigation, particularly as antiretroviral uptake was reported to range from 8% to 16% within the region.

Outcomes in Women and Infants After Receiving Prophylaxis Against Mother-to-Child Transmission

Weidle presented 24-week data from the Nonnucleoside Reverse Transcriptase Inhibitor Response Study Team, a multicenter cohort of women in Zambia, Kenya, and Thailand enrolled from June, 2005, to January, 2007 (Abstract 48). The cohort included 878 women initiating therapy for any reason. They were otherwise similar in sex distribution, height, and weight for age, and WHO stage. Despite these differences, nevirapine-based regimens led to significant increases in CD4+ cell percentages and decreases in plasma HIV RNA levels at 48 weeks in both groups, and there was no statistically significant difference in achievement of viral suppression (defined as HIV RNA level < 400 copies/mL in nevirapine-exposed and -unexposed children).

Palombi and colleagues (Abstract 668) examined the effects of treatment interruption after mother-to-child-transmission (MTCT) prophylaxis with potent antiretroviral therapy during pregnancy within the Drug Resource Enhancement and Management (DREAM) Program in Mozambique. All 220 women had received zidovudine, lamivudine, and nevirapine for at least 1 month before and 6 months after delivery. The authors found that disease parameters at 12 months after treatment interruption did not differ significantly from baseline laboratory values. The CD4+ count was 496 cells/μL at baseline and 536 cells/μL at 12 months post–treatment interruption. Similar results were seen for median plasma HIV RNA level and concentrations of hemoglobin and alanine aminotransferase, supporting the safety of discontinuing potent antiretroviral therapy after delivery in women who do not meet criteria for treatment.

Selected Pediatric Clinical Trials and Outcome Studies

Prendergast and colleagues (Abstract 77LB) presented a randomized, controlled trial conducted in Durban, South Africa, of treatment strategies in HIV-infected infants. Sixty-three infants whose HIV was diagnosed by HIV polymerase chain reaction on days 1 or 28 of life underwent randomization to 1 of 3 arms: arm A, deferred therapy until CD4+ cell percentage was below 20%; arm B, immediate, continuous antiretroviral therapy from birth to 1 year; and arm C, immediate therapy with structured treatment interruptions when plasma HIV RNA level was below 50 copies/mL, with resumption when levels passed 5000 copies/mL for the first year of life, followed by treatment cessation.

Results in arm C were discouraging. Only 8 of 21 infants completed the entire structured treatment interruption protocol, and they required significantly more regimen switches for virologic failure (11 vs 2 each in arms A and B by...
Table 2. Selected Studies on Antiretroviral Treatment Outcomes from Resource-limited Settings

<table>
<thead>
<tr>
<th>Abstract No.</th>
<th>Study Description</th>
<th>Treatment Program; Location; Duration of follow up</th>
<th>Baseline Treatment Regimen(s) (No. of Patients)</th>
<th>Baseline Age; Sex; Clinical Stage; Treatment Experience</th>
</tr>
</thead>
<tbody>
<tr>
<td>126</td>
<td>Long-term CD4+ response to potent antiretroviral therapy among treatment-naive patients in several low-income countries</td>
<td>ART-LINC Collaboration; 16 countries in Africa, Latin America, Asia; 5 y (most, 2004–current)</td>
<td>2 nRTIs + 1 NNRTI, 92%; 2 nRTIs + 1 PI, 6% (n = 19,967)</td>
<td>Median age, 35 y; 60% female; 57% CDC Stage C or WHO Stage III/IV; antiretroviral therapy-naive</td>
</tr>
<tr>
<td>127</td>
<td>Evaluation of clinical and immunologic outcomes from the National Antiretroviral Therapy Program in Rwanda, 2004 to 2005</td>
<td>Rwandan National Treatment Program; Numerous sites throughout Rwanda; 1 y (2004–2005)</td>
<td>Adults: Nevirapine/lamivudine/stavudine or zidovudine, 78%; efavirenz/lamivudine/stavudine or zidovudine, 22% (n = 3194)</td>
<td>Median age, 37 y; 65% female; clinical stage, N.A.; antiretroviral therapy-naive</td>
</tr>
<tr>
<td>816</td>
<td>Initial treatment outcomes from a rural-based antiretroviral therapy scale-up program in East Africa: the UARTO cohort</td>
<td>Uganda AIDS Rural Treatment Outcomes (UARTO); Mbarara, Uganda; 18 mo</td>
<td>nRTI + NNRTI (n = 816)</td>
<td>Median age, 35 y; 71% female; clinical stage, n.a.; antiretroviral therapy-naive</td>
</tr>
<tr>
<td>822</td>
<td>2-Year virologic outcomes of an alternative AIDS care model: evaluation of a peer health worker and nurse-staffed community-based program in Uganda</td>
<td>Reach Out Mbuya Parish HIV/AIDS Initiative; Kampala, Uganda; Oct 2003–Jan 2007</td>
<td>Active on Therapy: Efavirenz/lamivudine/zidovudine, 41%; nevirapine/lamivudine/zidovudine, 28%; efavirenz/lamivudine/stavudine, 2%; nevirapine/lamivudine/stavudine, 30% (n = 258)</td>
<td>Median age range 25–44 y; 79%; 68% female; 71% WHO clinical stage III/IV; 81% antiretroviral therapy-naive</td>
</tr>
<tr>
<td>824</td>
<td>Predictors of clinical and immunologic outcomes among HIV-infected subjects on antiretroviral therapy in Tanzania</td>
<td>PEPFAR-funded HIV care program; Tanzania; 1 y (enrolled Nov 2004–Apr 2007)</td>
<td>Nevirapine/lamivudine/stavudine, 61%; efavirenz/lamivudine/stavudine, 14%; nevirapine/lamivudine/zidovudine, 10%; efavirenz/lamivudine/zidovudine, 4% (n = 6893)</td>
<td>Median age, 37 y; 71% women; clinical stage, N.A.; antiretroviral therapy-naive</td>
</tr>
<tr>
<td>835</td>
<td>Probability and predictors of survival, drop-out, or switch to a WHO standard 2nd-line antiretroviral therapy regimen in resource-limited settings with viral load monitoring availability: the DREAM program in Mozambique, Malawi, Guinea</td>
<td>DREAM program; Mozambique, Malawi, Guinea; 4545 person-years (2002–2007)</td>
<td>Nevirapine/lamivudine/stavudine, 65%; nevirapine/lamivudine/zidovudine, 31% (n = 3749)</td>
<td>Median age, 24 y; 62% female; 37% WHO clinical stage III/IV; antiretroviral therapy-naive</td>
</tr>
</tbody>
</table>

Abbreviations: ART-LINC indicates Antiretroviral Therapy in Lower Income Countries; nRTI, nucleoside analogue reverse transcriptase inhibitor; NNRTI, nonnucleoside analogue reverse transcriptase inhibitor; PI, protease inhibitor; y, year(s); CDC, US Centers for Disease Control and Prevention; WHO, World Health Organization; N.A., not available; mo, month(s); min, minute(s); Hb, hemoglobin; BMI, body mass index; wk, week(s)
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<table>
<thead>
<tr>
<th>Location; Duration of Program</th>
<th>Baseline Age; Sex; Treatment Experience</th>
<th>Baseline CD4+ Count (cells/μL); HIV-1 RNA/mL (log&lt;sub&gt;10&lt;/sub&gt; copies/mL)</th>
<th>CD4+ Response (cells/μL)</th>
<th>Plasma HIV-1 RNA Response (copies/mL)</th>
<th>Mortality</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mozambique, Malawi, and Tanzania; 1 y (enrolled Nov 2004–Apr 2007)</td>
<td>Median age, 24 y; 62% female; clinical stage III/IV; antiretroviral therapy-naive</td>
<td>114 (median) (21% missing baseline); N.A.</td>
<td>Median at 1 y, +149; 5 y, +281</td>
<td>N.A.</td>
<td>N.A.</td>
<td>CD4+ count increases among patients on antiretroviral therapy are sustained up to 5 y; baseline CD4+ count was the strongest predictor of CD4+ count trajectory.</td>
</tr>
<tr>
<td>Kampala, Uganda; Reach Out Mbuya Parish and Mbarara, Uganda; Uganda AIDS Rural Treatment Program; Rwandan National Treatment Program; 5 y (most, 2004–current)</td>
<td>Median age range 25–44 y, 77%; 62% female; median age, 7 y; 71% WHO clinical stage, N.A.; antiretroviral therapy-naive</td>
<td>141 (median); N.A.</td>
<td>Median at 6 mo, +98; 12 mo, +119</td>
<td>N.A.</td>
<td>6 mo, 3.6%; 12 mo, 4.6%</td>
<td>Lower baseline CD4+ count and CD4+ response in men; size of treatment site was inversely associated with retention in care and change in CD4+ count.</td>
</tr>
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<td>5 nRTIs + 1 PI, 6%; 2 nRTIs + 2 NNRTIs, 92%</td>
<td>2 nRTIs + 1 PI, 6%; 2 nRTIs + 1 NNRTI, 92%</td>
<td>2 nRTIs + 1 PI, 6%; 2 nRTIs + 1 NNRTI, 92%</td>
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<td>2 nRTIs + 1 PI, 6%; 2 nRTIs + 1 NNRTI, 92%</td>
<td>2 nRTIs + 1 PI, 6%; 2 nRTIs + 1 NNRTI, 92%</td>
<td>Mortality was 15.1 times higher in the first 4 mo than the next 8 mo; relative hazard of death, 2.3 for every extra 30 min travel to clinic.</td>
</tr>
<tr>
<td>133 (median); N.A.</td>
<td>Median at average follow-up of 25 mo, +197</td>
<td>&lt; 400 at average follow-up of 25 mo, 86%</td>
<td>&lt; 400 at average follow-up of 25 mo, 86%</td>
<td>6 mo, 13%; 12 mo, 16%; 24 mo, 18%</td>
<td>Virologic failure was predicted by age &lt; 25, prior antiretroviral therapy, and lack of CD4+ response; risk of not sustaining therapy and mortality higher in those with baseline CD4+ count &lt; 100, WHO stage IV, and baseline stavudine/lamivudine/efavirenz; high early mortality in first 6 mo.</td>
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<tr>
<td>81 (median); N.A.</td>
<td>Median at 12 mo, +133</td>
<td>N.A.</td>
<td>N.A.</td>
<td>12 mo, 12.1%</td>
<td>Women were less likely to die or be lost to follow-up; baseline CD4+ count &lt; 100 and baseline Hb &lt; 10 g/dL were associated with mortality.</td>
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<td>133 (median); N.A.</td>
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<tr>
<td>206 (median); 4.6 (median)</td>
<td>Median at 12 mo, +133</td>
<td>N.A.</td>
<td>N.A.</td>
<td>12 mo, 12.1%</td>
<td>Women were less likely to die or be lost to follow-up; baseline CD4+ count &lt; 100 and baseline Hb &lt; 10 g/dL were associated with mortality.</td>
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- Predictors of time to death: BMI, Hb, prescription pick-ups > 95% and age < 26 y (all inversely correlated); predictors of time to drop out of care: BMI, baseline CD4+ count, prescription pick-ups > 95%, attended visits > 95%; no significant predictors of time to switch to 2nd-line regimens. 

*(Continued on next page)*
18 months; \( P = .03 \). When comparing arm A, which represents the current standard of care in Durban, with arm B, however, the investigators found that the percentage of infants meeting criteria to start antiretroviral therapy within 1 year after diagnosis (arm A) or treatment interruption (arm B) was significantly higher in arm A (85%) than B (43%; \( P = .01 \)). Time to meeting criteria for medication restart in both arms B and C was correlated with CD4+ cell percentage at birth. Thus, providing infants continuous antiretroviral therapy for HIV diagnosed at birth for 1 year and then interrupting treatment, with or without guidance by baseline CD4+ cell percentage, may be an alternative to deferring treatment in HIV-seropositive infants.

Investigators in the United Kingdom and Uganda compared response to antiretroviral therapy in HIV-infected children in the Ugandan Mulago cohort with those in the Collaborative HIV Paediatric Study (CHIPS) cohort, which includes children treated at 54 hospitals in the United Kingdom and Ireland (Abstract 584). They found that, at antiretroviral therapy initiation, Ugandan children were older (median, 7.6 years vs 5 years; \( P < .0001 \)), had higher median plasma HIV RNA levels (5.54 vs 5.2 log_{10} copies/mL; \( P < .001 \)), had lower baseline CD4+ cell percentages (8% vs 14%; \( P < .001 \)), and had significantly lower height-and-weight-for-age z-scores (both \( P < .001 \)). They also had more advanced HIV disease by US Centers for Disease Control and Prevention (CDC) and WHO clinical staging (62% WHO III/IV vs 56%; \( P < .001 \)). Children in both cohorts had similar rates of virologic suppression, CD4+ cell percentage increases, and height response. In a multivariate logistic regression analysis adjusted for baseline differences between the cohorts, however, Ugandan children with lower baseline CD4+ cell percentages had a poorer immune response at 6 months (aOR, 0.69; 95% CI, 0.62-0.76) and a poorer weight response (aOR, 0.27; \( P < .0001 \)). The odds of virologic suppression decreased in adolescence for children in the CHIPS cohort but not for those in the Mulago cohort.

Thai investigators conducted an investigation of the safety and efficacy of a combination PI treatment with saquinavir, lopinavir, and ritonavir in children whose nRTI- or NNRTI-based regimens were failing (Abstract 586). The HIV-NAT 017 study enrolled 50 HIV-infected children in 2 sites in Thailand who were PI-naive and whose nTRI- or NNRTI-based regimens were failing. Their median age was 9.5 years, 56% were female, 14% had CDC stage C disease, and 42% had received NNRTIs in the past. All children received lopinavir/ritonavir 230 mg/m²/57.5 mg/m² plus saquinavir 50 mg/kg twice daily, and median CD4+ cell percentage rise at 96 weeks was 14% (interquartile range, 7%-19%). The percentage of children for whom plasma HIV RNA levels fell below 50 copies/mL at 96 weeks differed between the 2 study sites: 90% in Bangkok and 63.5% in Khon Kaen. Antiretroviral therapy–related adverse drug

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<td><strong>Outcomes of 2nd-line Antiretroviral Therapy Regimens</strong></td>
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<tr>
<td>Abstract 831. Lopinavir/ritonavir + 2 nRTIs as 2nd-line antiretroviral therapy in PI-naive adults in South Africa: outcomes and adverse effects</td>
<td>McComb Hospital; Durban, South Africa; Jul 2004–Feb 2007</td>
<td>Primary Regimen: All NNRTI-based</td>
<td>At time of 2nd-line treatment initiation: Median age, 38 y; 65% female; no. of prior regimens, 1, 59%; 2, 36%</td>
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<tr>
<td></td>
<td></td>
<td>Secondary Regimen: Lopinavir/ritonavir + didanosine/zidovudine, 74%; lamivudine/zidovudine, 29%; lamivudine/stavudine, 15% (n = 155)</td>
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</tr>
<tr>
<td>Abstract 832. Immunologic response to ritonavir-boosted PI-containing 2nd-line antiretroviral therapy after switching for clinical/immunologic criteria is comparable to response to 1st-line in patients with low CD4+ counts in Africa</td>
<td>Development of Antiretroviral Therapy in Africa (DART) trial; Uganda, Zimbabwe; 48 wk</td>
<td>Primary Regimen: Lamivudine/zidovudine + tenofovir, 74%; nevirapine, 16%; abacavir, 9%</td>
<td>At time of 2nd-line treatment initiation: Median age, 38 y; 59% female; 96% WHO clinical stage III–IV</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Secondary Regimen: Lopinavir/ritonavir + NNRTI ± nRTIs, 87%; nRTIs, 12% (n = 477)</td>
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events of any kind were seen in 20% of participants, with the most common being diarrhea, vomiting, and elevated triglyceride levels. No progression of HIV disease was observed.

Treatment Strategies and Addressing Loss to Follow-up

When to initiate potent antiretroviral therapy. Walensky and colleagues (Abstract 812) developed a mathematical model that incorporates published data on the South African epidemic to determine the cost-effectiveness of early initiation of antiretroviral therapy at CD4+ counts below 350 cells/μL. They modeled 3 scenarios: no antiretroviral therapy, antiretroviral therapy initiated after the CD4+ count drops below 250 cells/μL, and therapy initiated once the CD4+ count drops below 350 cells/μL. They determined that the latter scenario, “early antiretroviral therapy,” reduced the occurrence of opportunistic disease and death and extended life expectancy by 0.8 years. They also found it to cost $1200 per life-year saved, which, because its cost-effectiveness ratio was less than 1 times the South African gross domestic product per capita ($5400 in 2006), was defined by the authors as “very cost-effective.” A separate analysis, which modeled the availability of 3 lines of antiretroviral therapy and an initiation at CD4+ counts below 500 cells/μL, was also found to be very cost-effective, at $1000 per life-year saved.

Loss to follow-up. Last year’s conference featured sobering news on death rates among patients lost to follow-up in resource-limited settings. This year, a poster discussion session featured 5 abstracts on loss to follow-up in Africa. The first, presented by Nash and colleagues (Abstract 838) reviewed rates of loss to follow-up in 108,056 patients and 173 programs supported by the International Center for AIDS Care and Treatment Programs (ICAP). The overall mean loss-to-follow-up rate was 140 per 1000 person-years on antiretroviral therapy. Programs that offered food support had significantly lower unadjusted and adjusted loss-to-follow-up rates than programs that did not. The authors emphasized the need for linkage care after diagnosis and prioritizing antiretroviral therapy for those with low CD4+ cell counts.

In an examination of factors associated with loss to follow-up in community clinics in South Africa, Wang and colleagues (Abstract 841) found that, over 4 sites and 1507 patients, mean time to loss to follow-up was 6 months, and 126 (8%) patients who initiated antiretroviral therapy were lost to follow-up at 6 months. Patients with lower baseline CD4+ counts (below 200 cells/μL) and pregnant women were statistically significantly

<table>
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<tr>
<th>Baseline CD4+ Count (cells/μL); HIV-1 RNA/mL (log_{10} copies/mL)</th>
<th>CD4+ Response (cells/μL)</th>
<th>Plasma HIV-1 RNA Response (copies/mL)</th>
<th>Mortality</th>
<th>Comments</th>
</tr>
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<tr>
<td>148 (median)</td>
<td>Median at 6 mo, +95</td>
<td>&lt; 50 at 6 mo, 82%</td>
<td>N.A.</td>
<td>No difference in outcome at 6 mo between patients with recycled nRTI backbones and those with new; significant difference in virologic suppression at 6 mo by sex (88% in women, 70% in men)</td>
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<tr>
<td>4.3 (median)</td>
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</table>

At start of 1st-line, 39 (median); At start of 2nd-line, 46 (median)

N.A.  48 wk, +199

Overall rate of switch to 2nd-line antiretroviral therapy was low, 7%–8%/y; of 15% of patients who had never achieved a CD4+ count increase of 50 cells/μL on 1st line, 87% had achieved this increase after 48 wk on 2nd-line antiretroviral therapy

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Bassett and colleagues presented data from McCord Hospital in Durban, South Africa, on patients eligible for antiretroviral treatment but lost to follow-up before initiation of therapy (Abstract 839). Of 501 patients eligible for antiretroviral drugs, 16.4% were lost before treatment initiation, and 32% of these were confirmed to have died. An average of 3.6 months passed between determination of antiretroviral drug eligibility and initiation of antiretroviral drug training, and those with CD4+ counts below 100 cells/μL had an aOR ratio of loss to follow-up of 1.9 (1.07-3.39; P < .05). The authors emphasized the need for linkage care after diagnosis and prioritizing antiretroviral therapy for those with low CD4+ cell counts.
more likely to be lost to follow-up \((P = .0001)\).

Two other abstracts highlighted the need for aggressive tracking of patients lost to follow-up. Muwanga and colleagues noted high rates of loss to follow-up in a large treatment center in Uganda (Abstract 840), where the loss-to-follow-up rate among those on antiretroviral therapy was 12.9% and among those not on therapy, 59.2%. The preliminary results from 36 home visits, conducted on a subset of the 50% of patients who were lost and not reachable by phone, found that 92% of the patients could be located and 58.3% had died. These deaths will significantly alter the overall clinic mortality rate, which authors plan to recalculate once home visits are completed for all patients lost to follow-up that cannot be reached by phone.

A second presentation from Geng and the East Africa IeDEA Consortium took a sampling approach to determining outcomes for patients lost to follow-up (Abstract 842). Of 5340 patients starting antiretroviral treatment in Mbarara, Uganda, after January, 2004, 728 were lost to follow-up at 3 years. A sample of 98 of those lost to follow-up was selected, and a health educator sought them out to determine their vital status, which was possible in 84% of the sample. Of those patients the health educator was able to speak with directly (47% of the total sample), 81% had resumed care in another clinic, and 50% cited difficulties with transportation as the main reason for their loss to follow-up. The authors then used mortality data among those lost to follow-up to adjust the cumulative clinic mortality rates using probability weighting. This calculation substantially increased previously reported clinic mortality rates: at 1 year, from 1.7% preadjustment to 5.4% postadjustment; at 2 years, 2.1% to 8.9%; and at 3 years, 2.6% to 10.2% overall mortality rate for the clinic.

**Advances in Laboratory Monitoring**

Many interesting presentations described new approaches to laboratory monitoring in RLS; selected abstracts are summarized here. Coutinho and colleagues presented an oral abstract on the results of a randomized controlled trial completed within the rural Ugandan Home-Based AIDS program (Abstract 125). Participants initiating therapy within the program were randomized to 1 of 3 arms: arm A, quarterly clinical monitoring by outreach workers, quarterly CD4+ cell counts and plasma HIV RNA levels; arm B, weekly clinical monitoring and quarterly CD4+ cell counts; and arm C, weekly clinical monitoring only. Of the 1116 participants randomized, 1094 initiated antiretroviral therapy, 39% of whom had WHO clinical stage III or IV disease. The median follow-up time was 3 years, and overall mortality rate was 11.2%, with 47% of deaths occurring within the first 3 months. Ninety percent of participants had an undetectable plasma HIV RNA level at 1 year. By a Cox proportional hazards model intention-to-treat analysis, the aOR for first morbidity or mortality was 1.88 (95% CI, 1.25-2.84; \(P = .002\)) for arm C compared with arm A. Of the 17 participants in arm C who switched regimens, 15 were switched based on clinical criteria but had undetectable plasma HIV RNA levels. Thus, the authors concluded that the monitoring regimens in arms A and B allowed for earlier detection of adherence challenges and should be adopted where feasible.

Investigators from the Academic Model of Prevention and Treatment of AIDS (AMPATH) clinic in Eldoret, Kenya, also examined the utility of plasma-HIV-RNA-level monitoring in RLS (Abstract 834). All adult patients attending the clinic who were adherent to the same regimen for more than 6 months but whose antiretroviral therapy was failing by CD4+ cell count criteria had their plasma HIV RNA levels tested. The authors defined treatment failure misclassification as a greater than or equal to 25% drop in CD4+ cell count with an undetectable plasma HIV RNA level. Of 112 patients who met criteria for treatment failure by decrease in CD4+ cell count, 66 had failure misclassification, with the likelihood of misclassification elevated in patients with higher CD4+ counts (OR, 2.68 per 100 cells/μL increase; 95% CI, 1.35-5.32; \(P = .006\)). The authors felt that these results strongly supported plasma-HIV-RNA-level monitoring and have implemented testing for all AMPATH patients for whom first-line antiretroviral therapy appeared to be failing.

Bassett and colleagues (Abstract 908) examined the performance of rapid point-of-care HIV testing in RLS with a high HIV prevalence by testing multiple rapid HIV-1 and -2 test kits in the outpatient department of McConn Hospital in Durban, South Africa. All patients testing seropositive were tested a second time and then referred for further determinations of plasma HIV RNA level; patients with seronegative or discordant test results were referred to the study. Of 705 patients who had seronegative rapid HIV test results, 11 (1.6%) were chronically HIV-infected on confirmatory testing. Of 15 patients with discordant rapid HIV test results, 61.5% were HIV-infected, and a total of 2.7% (95% CI, 1.7%-4.1%) of people with seronegative or discordant test results were chronically infected. The authors estimated the sensitivity of the rapid tests in this setting to be 98.8% (95% CI, 98.2%-99.5%), and the negative predictive value to be 98.4% (95% CI, 97.5-99.4%). They estimated that, based on the current rapid testing protocol and the rate of testing at the hospital, 2 HIV-infected people per week could be incorrectly told they are HIV-seronegative.

**Resistance to Antiretroviral Therapy**

Information on HIV drug resistance in RLS is critical for planning antiretroviral scale-up and assessing the need for second-line treatment regimens. This year’s conference made several contributions to this emerging body of literature. Ayoub and colleagues (Abstract 899) presented data on drug resistance in recently infected, antiretroviral therapy-naive patients in Burkina Faso, Cambodia, Cameroon, Thailand, and Vietnam. They collected a total of 280 samples from HIV-infected individuals, evenly distributed among the 5 countries, in antenatal clinics from women in their first pregnancy or with CD4+ counts above 500 cells/
μL, and in voluntary counseling and testing sites. Only 4 of the samples (1.4%, 95% CI, 0.6-3.6) had mutations that conferred resistance to 1 or more drugs by either the 2007 Stanford HIV database algorithm, the International AIDS Society-USA (IAS-USA) mutations list, or the French national AIDS trial group algorithm. Of these, all 4 had mutations that conferred resistance to NNRTIs. One sample also contained an M184V mutation, and another carried the M46I mutation.

Three abstracts presented novel data on HIV drug resistance after first-line therapy. Gupta and colleagues (Abstract 891), presented a meta-analysis of 18 clinical trials with HIV resistance data in patients for whom first-line therapy was failing in resource-rich settings, and for 2 African cohorts and 1 Thai study examining the same in RLS. The authors found that genotypic resistance to nRTIs and NNRTIs at up to 80 weeks of follow-up was more common in RLS, where first-line NNRTI-based antiretroviral regimens were used (cumulative, 7.61%, compared with 2.60% in resource-rich settings). They also noted that the prevalence of M184V, K65R, and resistance to a third agent was more common in patients initiating treatment with NNRTI-based regimens (4.0%) than in those initiating PI-based regimens (0.9%).

Kumarasamy and colleagues (Abstract 893) presented data on 95 patients in Chennai, India, whose NNRTI-based, first-line antiretroviral therapy was failing and who had HIV genotypic testing before initiating second-line treatment. Ninety percent of patients had 2 or more reverse transcriptase (RT) mutations that confer resistance to at least 1 antiretroviral medication, with M184V in 75% of patients and the NNRTI-related mutations K103N, Y181C, and G190A in 27%, 33%, and 26% of patients, respectively.

Chaplin and colleagues (Abstract 901) conducted a similar study among 304 Nigerian patients with documented virologic failure. In this sample, the prevalence of specific HIV drug-resistance-associated mutations (D67N, M41L, L210W, A98G, and V90I) varied by subtype. The TAM pathway that combines mutations at K70R, K219QE, T215F, and D67N (TAM2) predominated in this sample dominated by HIV subtype G and CRF02_AG, as opposed to the TAM1 pathway (T215Y, M41L, L210W, and D67N), which is known to be more common in HIV subtype B viruses.

Three different groups presented data on HIV drug resistance after first-line antiretroviral failure in children. In South Africa, investigators followed 278 perinatally infected children from June, 2006, to January, 2008, of whom 25% had virologic failure with plasma HIV RNA levels greater than 1000 copies/mL (Abstract 587). The average duration of treatment before failure was 10 months (interquartile range, 6-17 months), and 88% of patients with failure had at least 1 significant mutation shown on HIV genotype testing. Sixty percent of patients had dual-class resistance, but none had 3-class resistance. The most common mutations were M184V (80%) and V106M (24%). A second abstract (589) describing HIV-genotype-testing results in 35 South African children whose first- or second-line therapy was failing had a similar mutational profile with respect to M184V and V106M, but 44% of these samples carried the K103N mutation. Of 7 patients on PI-based regimens, 3 carried virus with drug-resistance-associated mutations in the protease genome. In both South African studies, patients were infected predominantly with HIV subtype C virus.

Sungkanuparph and colleagues presented data from a cohort of HIV-infected children in Bangkok, Thailand, whose initial NNRTI-based regimen led to virologic failure between January, 2000, and December, 2007 (Abstract 588). After genotype testing, most patients were found to have at least 1 resistance-associated mutation to nRTIs (52%) and NNRTIs (43%), and patients infected with virus carrying the M184V mutation had a higher prevalence of NNRTI resistance mutations than did those without M184V/I (86% vs 21%; P = .016). Appropriate second-line therapy in 47% of children will require a PI, highlighting the need for increased access to second-line antiretroviral regimens in RLS.

Mother-to-Child Transmission

Several oral presentations of noteworthy studies reported rates of MTCT of HIV in RLS. Various regimens complemented or enhanced single-dose nevirapine for infants and mothers, demonstrating initiatives geared toward reduction of MTCT and resistance in some cases (Table 3).

Black and coauthors (Abstract 657) sought to identify risk factors for MTCT in women with advanced AIDS. They presented a retrospective analysis of women who had received care at the Antenatal Antiretroviral Clinic (ANC ARV) in South Africa between August, 2004, and February, 2007, looking for predictors of MTCT. They presented 6-week follow-up data on 302 mother-infant pairs and found that the rate of MTCT was 5% and that 2 features were associated with MTCT: shorter duration of antiretroviral treatment during pregnancy and lower CD4+ cell count. For each additional week of antiretroviral treatment, the odds of transmission were reduced by 27%, and the rate of transmission for patients who received more than 7 weeks of antiretroviral treatment was 0.3%.

Two studies reported MTCT in resource-rich settings. Townsend and colleagues (Abstract 653) confirmed the value of having an undetectable viral load in their presentation of data from the United Kingdom and Ireland National Study of HIV in Pregnancy and Childhood. The overall rate of MTCT in the United Kingdom and Ireland among infants born to HIV-infected women from 2000 to 2006 was 1.1% (61/5316 subjects). No statistically significant difference occurred in MTCT rates between women on antiretroviral therapy who underwent cesarean delivery (17/2337 subjects, or 0.7%), women on antiretroviral treatment who had a vaginal delivery (45/565 subjects, or 7.9%), and those who received prophylactic zidovudine along with a cesarean delivery (0/467 subjects, or 0%). Only 3 transmissions occurred among women on antiretroviral therapy whose viral load was below 50 copies/mL (3/2202 subjects, or 0.1%).

The second study (Abstract 654)
reported rates of MTCT associated with amnioncensis in the French Perinatal HIV Cohort. Rates of amnioncensis increased from 1% before 2001 to 2.7% in the years 2001 to 2006 among HIV-infected women who delivered after 28 weeks of gestation (excluding multiples). Although a statistically nonsignificant trend toward higher rates of MTCT occurred among mothers who underwent amnioncensis, this trend was not found in women who underwent amnioncensis and were treated with antiretroviral drugs (0%). The authors pointed out that any invasive prenatal testing is yet another indication to perform HIV testing.

Pharmacokinetics and Safety of Antiretroviral Drugs in Infants and Pregnant Women

Several presentations reported results of pharmacokinetic and safety studies of various antiretroviral drugs in infants and pregnant women. Such data were reported for tenofovir (Abstracts 47LB, 627a), emtricitabine (Abstracts 626, 629), atazanavir (Abstracts 624, 625), lopinavir/ritonavir (Abstracts 628-630), and enfuvirtide (Abstract 627b).

Tenofovir and emtricitabine were found to be safe and effective for pregnant women and infants. Hirt and colleagues (Abstracts 47LB, 626) looked at the pharmacokinetics of both drugs in 35 HIV-infected pregnant women and their infants. Women were given 2 tablets of tenofovir 300 mg/emtricitabine 200 mg at initiation of labor followed by 7 days of 1 tablet of tenofovir 300 mg/emtricitabine 200 mg. Pharmacokinetic samplings took place at delivery and at 1, 2, 3, 5, 8, 12, and 24

<table>
<thead>
<tr>
<th>Abstract No. Study Description</th>
<th>Location; Treatment Program; Duration of Follow-up</th>
<th>Treatment for Mothers (No. Patients)</th>
<th>Treatment for Infants (No. Patients)</th>
<th>Breastfeeding Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abstract 43. Extended-dose nevirapine to 6 weeks of age for infants in Ethiopia, India, and Uganda: a randomized trial for prevention of HIV transmission through breastfeeding</td>
<td>Ethiopia, India, Uganda; Six Weeks of Extended Nevirapine (SWEN) Study Team; 6 mo follow-up of infants</td>
<td>Ethiopia: SD-NVP; India: SD-NVP or ZDV, or 3TC, or potent antiretroviral therapy; Uganda: SD-NVP</td>
<td>Randomized; placebo controlled; SD-NVP (n = 986) vs SD-NVP + extended NVP day 8–42 (n = 901)</td>
<td>Exclusive breastfeeding encouraged</td>
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<tr>
<td>Abstract 42LB. Extended infant postexposure prophylaxis with antiretroviral drugs significantly reduces postnatal HIV transmission: the PEPI Malawi study</td>
<td>Blantyre, Southern Malawi; The Post-Exposure Prophylaxis of Infants (PEPI) Malawi Study; 14 wk of infant treatment; 24 mo follow-up</td>
<td>Mothers received intrapartum NVP, if possible</td>
<td>Randomized; open-label; SD-NVP + 1 wk of ZDV (control arm, n = 1003) vs control + NVP days 8–98 (n = 1016) vs control + NVP/ZDV days 8–98; (n = 997); analysis excluded infants infected at birth</td>
<td>Exclusive breastfeeding until 6 mo then total wean; 98% breastfed at 14 wk; 20%–30% breastfed at 9 mo</td>
</tr>
<tr>
<td>Abstract 45b. The TEmAA ANRS 12109 phase II trial, Step 1: tolerance and viral resistance after single-dose nevirapine and short-course of tenofovir disoproxil fumarate and emtricitabine to prevent mother-to-child transmission of HIV-1</td>
<td>Ivory Coast, Cambovia, South Africa; Tenofovir/Emtricitabine for PMTCT in Africa and Asia (TEmAA) Trial; 28–38 wk of gestation until 60-d postpartum follow-up</td>
<td>HIV-infected women 28–38 wks gestation received ZDV 300 mg bid; at start of labor, all women given SD-NVP and 2 tablets TDF/FTC, followed by TDF/FTC x 7 d postpartum (n = 38)</td>
<td>Open-label, phase II trial; SD-NVP and SD-TDF/FTC, followed by 7 d ZDV (n = 39)</td>
<td>Not reported</td>
</tr>
</tbody>
</table>

Abbreviations: mo indicates month(s); SD, single-dose; NVP, nevirapine; ZDV, zidovudine; 3TC, lamivudine; wk, week(s); PMTCT, prevention of mother-to-child transmission; bid, twice daily; TDF, tenofovir; FTC, emtricitabine; d, day(s); y, year(s); h, hour(s); NFV, nelfinavir; MTCT, mother-to-child transmission; PI, protease inhibitor; RLS, resource-limited settings; TB, tuberculosis; LPV, lopinavir; AST, aspartate aminotransferase; ALT, alanine aminotransferase.
### Table

<table>
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<tr>
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<th>Infant Death</th>
<th>Resistance</th>
<th>Adverse Events</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>6 wk: SD-NVP, 5.27%; extended NVP, 2.53% (P = 0.009); 6 mo: SD-NVP, 8.98%; extended NVP, 6.91% (not statistically significant)</td>
<td>6 wk: SD-NVP, 1.59%; extended NVP, 0.91% (not statistically significant); 6 mo: SD-NVP 3.61%; extended NVP, 1.12% (P = 0.016)</td>
<td>See note 1</td>
<td></td>
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<tr>
<td>9 mo: Control, 10.1%; extended NVP, 5.2%; extended NVP/ZDV, 6.4%; 24 mo: Control, 14.5%; extended NVP, 11.2%; extended NVP/ZDV, 12.3%</td>
<td>Probability of infant death: 9 mo: Control, 8.9%; extended NVP, 6.8%; extended NVP/ZDV, 6.3% 24 mo: Control, 16.1%; extended NVP, 14%; extended NVP/ZDV, 13.4%</td>
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</table>

#### Note 1.
Abstract 44 highlights resistance analysis of Indian data. Among HIV-1 subtype C-infected infants (99), higher rates of NVP resistance were seen in infants treated with extended NVP (92%) than with SD-NVP (40%) in infants diagnosed in first 6 wk of life. Abstract 635b highlights resistance analysis from Uganda, where more genotypic resistance at 6 wk was found in extended-NVP (84%) than in SD-NVP arm (50%); phenotypic results were comparable. Resistance detected at 6 wk was more likely to persist at 6 mo in extended NVP group.

#### Note 2.
Pharmacokinetic analysis of TDF in pregnant women and their infants (Abstract 47LB) showed that 1 dose TDF 600 mg in pregnant women at initiation of labor produced the same concentrations as 300-mg dose in other adults. Intrapartum, if delay between drug uptake and delivery is > 12 h, dose should be readministered. TDF placental transfer, ~60%. Infants should receive 11–13 mg/kg tenofovir disoproxil fumarate 1 h after birth to obtain similar drug levels as adults. Pharmacokinetic analysis of FTC (Abstract 626) showed good FTC placental transfer (~80%) and that 1 mg/kg within 6 h after birth and 2 mg/kg 12 h after birth are needed to achieve neonatal concentrations comparable to necessary adult concentrations.

(Continued on next page)
who received tenofovir as part of their regimen when first-line agents were not tolerated. The mean initiation of tenofovir was at 24 weeks’ gestation. Two women stopped tenofovir, 1 because of rash and 1, nausea; no signs of tenofovir-related toxicity or birth malformations attributable to tenofovir were found in the 78 live-born infants. Pharmacokinetic data were reported (Abstract 629) on emtricitabine from the Pediatric AIDS Clinical Trials Group (PACTG) 1026 study, gathered from 18 women who took emtricitabine 200 mg daily throughout pregnancy and for 6 weeks to 12 weeks postpartum. Steady-state profiles at 12 hours and 24 hours were calculated after obtaining maternal and umbilical cord samples. Emtricitabine exposure (as determined by AUC) was lower during pregnancy than postpartum. The magnitude was small, however, suggesting that dose adjustment may not be necessary during pregnancy.

Eley and colleagues (Abstract 624) reported on the safety and pharmacokinetic data for atazanavir 300 mg/ritonavir 100 mg daily in pregnancy. Data were analyzed after 12 women completed the third-trimester pharmacokinetic studies. Values for the third-trimester atazanavir AUC and minimum plasma trough concentration (C_{min}) were approximately 40% and 21% lower than in historical controls, respectively. The investigators suggested that this dosage level may be inadequate and plan to investigate a dose increase to atazanavir/ritonavir 400 mg/100 mg once daily in the third trimester. Otherwise, the study drugs were well tolerated. The bilirubin level reached grade 3 in 5 of 18 subjects. For the 10 subjects who reached delivery, plasma HIV RNA level was below 50 copies/mL, and all infants were HIV-seronegative. All infants had normal bili-

### Table 3. Selected Studies in Mother-to-Child Transmission of HIV (cont’d)

<table>
<thead>
<tr>
<th>Abstract No.</th>
<th>Study Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Location; Treatment Program; Duration of Follow-up</td>
<td>Kisumu, Kenya; Kisumu Breastfeeding Study; treatment 24–36 wk gestation to 6 mo postpartum and follow-up 2 y postpartum</td>
</tr>
<tr>
<td>Treatment for Mothers (No. Patients)</td>
<td>Phase 1b single-arm PMTCT trial; women 24–36 wk gestation given ZDV/3TC + NVP and treated until 6 mo postpartum (n = 296)</td>
</tr>
<tr>
<td>Treatment for Infants (No. Patients)</td>
<td>SD-NVP within 72 h of delivery (n = 497 live born)</td>
</tr>
<tr>
<td>Breastfeeding Status</td>
<td>Exclusive breastfeeding encouraged until 5.5 mo followed by a rapid 2-wk wean, resulting in complete wean by 6 mo. Note: despite a rigorous counseling program on benefits of exclusive breastfeeding until 6 mo followed by complete wean, 21% of women mixed-fed before 5 mo and 14% of women continued breastfeeding past 6 mo (Abstract 645)</td>
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</table>

| Abstract 639 | Decrease in HIV-1 mother-to-child transmission in women receiving postnatal potent antiretroviral therapy: 12-month follow-up data (See also Abstract 668, 835) |
| Location; Treatment Program; Duration of Follow-up | Mozambique; The Drug Resource Enhancement against AIDS and Malnutrition (DREAM) Program; Prospective cohort; 12-mo follow-up |
| Treatment for Mothers (No. Patients) | All women enrolled in cohort began potent antiretroviral treatment at 15-wk gestation; all mothers of live-born infants (n = 341) continued until 6 mo postpartum (unless symptoms of AIDS/CD4+ count ≤ 200 cells/μL, then continued indefinitely); antiretroviral regimens include ZDV/d4T + 3TC + NVP and back-up with NFV or LPV/ritonavir |
| Treatment for Infants (No. Patients) | SD-NVP within 24 h of delivery, followed by short-course ZDV for first 4 d |
| Breastfeeding Status | Women counseled to exclusively breastfeed until 6 mo |

Abbreviations: mo indicates month(s); SD, single-dose; NVP, neviripine; ZDV, zidovudine; 3TC, lamivudine; wk, week(s); PMTCT, prevention of mother-to-child transmission; bid, twice daily; TDF, tenofovir; FTC, emtricitabine; d, day(s); y, year(s); h, hour(s); NFV, nelfinavir; MTCT, mother-to-child transmission; PI, protease inhibitor; RLS, resource-limited settings; TB, tuberculosis; LPV, lopinavir; AST, aspartate aminotransferase; ALT, alanine aminotransferase.
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<tr>
<td>Cumulative rate of MTCT:</td>
<td>Not reported</td>
<td>See note 3</td>
<td>See note 4</td>
<td>Related Abstract 646 reports on the impact of implementation of a safe water system in 2005 on diarrhea rates in infants participating in the Kisumu Breastfeeding Study</td>
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<tr>
<td>0-7 d, 2.4%</td>
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<tr>
<td>6 wk, 3.9%</td>
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<tr>
<td>3 mo, 4.1%</td>
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<tr>
<td>6 mo, 5.0%</td>
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<tr>
<td>9 mo, 5.5%</td>
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<tr>
<td>12 mo, 5.9%</td>
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<tr>
<td>18 mo, 6.7%</td>
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<tr>
<td>283/341 infants were available for follow-up at 12 mo; of these, MTCT rate was 2.8% (8/283) at 12 mo; 47 infants lost to follow-up</td>
<td>11 infants known to have died by 12 mo, of which 4 had documented HIV status (1 seropositive)</td>
<td>Not reported</td>
<td>Abstract 668 presented follow-up data regarding treatment interruption of 220 women in DREAM Study. Median values of hemoglobin, CD4+ count, HIV RNA copies/mL, AST, and ALT were comparable at enrollment and 12 mo after antiretroviral treatment was discontinued. Resistance or mortality rates not reported</td>
<td>From original cohort, 54 infants did not have HIV diagnosis at 12 mo (46 lost to follow-up and 7 known deaths without clear HIV serostatus). Relative risk reduction of maternal antiretroviral treatment during pregnancy until at least 6 mo postpartum, assuming all infants were HIV seropositive, was 54%. Leaving them out of analysis results in 93% risk reduction, assuming an expected cumulative risk of perinatal HIV infection at 12 mo of 40%</td>
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</table>

**Note 3.** Abstract 84LB analyzed resistance among infants who seroconverted and patterns of mutations based on timing of seroconversion and maternal regimen. 29/502 infants (5.8%) were HIV-infected. Infants underwent HIV testing on multiple study visits; resistance testing was done at time of initial HIV detection and at wk 14 or 24. 83% of the 29 HIV-infected infants were seropositive before 24 wk of life; 58% of HIV-infected infants had been born to women in NVP arm; 42% to women in NFV arm. Though 0/12 infants who were seropositive from birth to 2 wk were initially found to have resistance, by 6 mo 11/12 had evidence of resistance; drug resistance increased over time. At 6 mo, 24 infants were seropositive, of whom 16 had genotypic resistance including 6/14 (43%) of mothers taking NVP and 10/10 (100%) of mothers taking NFV. Of infants exposed to NVP who developed resistance, 4 had nRTI resistance and 6 had NNRTI resistance including Y181C, K103N, G190A, and K101E. HIV-seropositive infants with prior exposure to NFV had no major PI mutations. In infants who were HIV-infected within first 6 wk of life, drug resistance was initially not detected until well into breastfeeding period, suggesting that resistant virus may have been transmitted by mother, likely through transfer of antiretrovirals in breast milk. Even though all children received SD-NVP, no case of NNRTI resistance was detected among infants whose mothers were treated with NFV.

**Note 4.** Abstract 640 highlights infant adverse fetal outcomes for this study among infants born to women with CD4+ ≥ 250 cells/μL who initiated drug treatment from 34-wk gestation. Rates of low birth weight were similar in women taking NVP- vs NFV-based regimens; women taking NVP showed a trend toward decreased odds of preterm delivery. Rates of preterm delivery, low birth weight, and stillbirth in women in both drug groups were equal to or lower than WHO rates reported for RLS. Abstract 647 reports better tolerance of the NFV- than the NVP-based regimen. 440/522 enrolled women continued until 6 mo, including 62 who switched to another regimen. Of the 440 women, 263 began on NVP, of whom 41 (16%) switched to NFV or efavirenz for hepatotoxicity, rash, initiation of warfarin/TB therapy. ZDV also resulted in switches in 21/440 (5%) women, mainly because of anemia/neutropenia. No medication interruptions were made for NFV (177 women) or for 3TC-related intolerance.
rubin levels through day 14, and 1 had grade 3 at day 15. Ferreira and colleagues (Abstract 625) further explored the effect of atazanavir exposure in utero on neonates and reported on their retrospective single-center cohort of 9 infants who were exposed to ritonavir-boosted atazanavir during pregnancy. Fetal unconjugated hyperbilirubinemia correlated to maternal bilirubin concentration at delivery, suggesting placental transfer of unconjugated bilirubin; however, neonatal levels of hyperbilirubinemia were not high enough to be harmful, and none of the 3 infants born with jaundice required phototherapy. Atazanavir levels found in the cord blood of the 9 infants were therapeutic, confirming previous reports of good placental transfer.

Three abstracts (628–630) focused on the question of whether standard dosing of lopinavir/ritonavir is adequate for pregnant women, particularly in the third trimester in PI-experienced women. Cressey and colleagues (Abstract 630) reported lopinavir/ritonavir pharmacokinetic data from the IMPAACT P1032 Trial, a randomized trial of short-course intrapartum and postpartum antiretroviral therapy in Thai women. Pharmacokinetic data were available for 16 women who initiated lopinavir/ritonavir treatment at standard doses during labor and achieved lopinavir exposure at 72 hours and 30 days postpartum similar to that seen in nonpregnant US adults, suggesting that standard doses for short-course therapy among Thai women may be adequate.

Abstracts 628 and 629 reported lopinavir/ritonavir pharmacokinetic data in non-Thai populations that suggest that, although standard doses of lopinavir/ritonavir at 400 mg/100 mg twice daily achieved an adequate minimal concentration for PI-naive pregnant women, this dosage may not be adequate for PI-experienced women, particularly in the third trimester. Best and colleagues (Abstract 629) suggested a dose of lopinavir/ritonavir 600 mg/150 mg twice daily in the third trimester for all women and in the second trimester for PI-experienced women, followed by postpartum dose reduction to standard doses.

Haberl and colleagues (Abstract 627b) report on the use of enfuvirtide in 14 HIV-infected pregnant women. Indications for enfuvirtide included failure to suppress (7), late presenters (4), and cases of premature birth with incomplete transmission prophylaxis (3). All women were enfuvirtide-naive, and 50% of women were antiretroviral therapy–naive altogether. All women received enfuvirtide in addition to at least 3 other antiretroviral drugs. The mean baseline plasma HIV RNA level before receiving enfuvirtide was 75,120 copies/mL, and the mean period of exposure to enfuvirtide before caesarean delivery was 15 days, resulting in mean antenatal plasma levels of HIV RNA of 218 copies/mL. None of the 14 infants was HIV-infected, and no enfuvirtide-related adverse events were observed in mothers or infants. In infants for whom enfuvirtide concentrations were measured, the concentrations were below 200 ng/mL, revealing a lack of transplacental distribution.

Bell and coauthors (Abstract 656) presented data on the rate of reduction of plasma HIV RNA levels during the first 14 days of therapy in pregnant women, comparing nevirapine- and PI-based regimens (including 2 nRTIs) in women from 3 different centers. The authors measured plasma HIV RNA levels before treatment and at 14 days, as well as CD4+ cell counts, and found that the plasma half-life was shortest for women taking nevirapine, followed by those on lopinavir/ritonavir, then those on nelfinavir. They suggested that these data support the continued use of nevirapine in pregnant women who have a CD4+ count below 250 cells/μL.

Prevention of Mother-to-Child Transmission and Resistance

The development and transmission of resistance related to prevention of mother-to-child transmission (PMTCT) was addressed in numerous abstracts (Abstracts 44, 84LB, 631-634, 635a, 635b). Chi and colleagues reported on the reduction of NNRTI resistance mutations in women treated with a single dose of tenofovir 300 mg/emtricitabine 200 mg in addition to short-course zidovudine and intrapartum nevirapine for PMTCT. Previously released data showed a significant risk reduction, but the investigators did not test for viral subpopulations and could not comment on viral subpopulations present at levels below 25%. The results of testing 122 specimens with the oligonucleotide ligation assay to detect resistance in minority subpopulations present as low as 5% were reported (Abstract 631). The investigators found a 69% reduction in NNRTI resistance at 2 weeks postpartum (2/15 subjects vs 10/23 subjects; relative risk [RR], 0.31; 95% CI, 0.08-1.21) and a 58% reduction in NNRTI resistance at 6 weeks postpartum (8/43 subjects vs 18/41 subjects; RR, 0.42; 95% CI, 0.21-0.87).

With regard to repeated use of single-dose nevirapine PMTCT, Eshleman and colleagues (Abstract 632) found that there was no difference in the proportion of nevirapine resistance, the types of mutations detected, or the frequency of K103N in women treated with single-dose nevirapine for the first time (n = 57) versus women who had been treated with single-dose nevirapine in a subsequent pregnancy (n = 54), nor did repeat exposure influence the emergence of resistance in HIV-infected infants.

Much inquiry has been made into the issue of NNRTI resistance fading after use of single-dose nevirapine for PMTCT. In HIV-infected women who received single-dose nevirapine for PMTCT, Wind-Rotolo and colleagues (Abstract 634) demonstrated that nevirapine-resistant virus in the plasma also persisted in the resting CD4+ T-cell latent reservoir. Not surprisingly, in some cases, nevirapine-resistant virus was identified in the latent reservoir but not identified as nevirapine resistance in the concurrent plasma sample.

Mutations associated with PI resistance were less common than NNRTI- or lamivudine resistance–associated mutations in virus in women treated with pregnancy-limited antiretroviral therapy (PLAT) in the US-based Women and Infants Study Group (WITS) cohort, according to Paredes and colleagues (Abstract 635a). Their analysis included HIV-infected pregnant women who received PLAT from 1998 to
2004 (n = 146). They note that overall, mutations were fairly common; they therefore recommend genotype resistance testing in women who have received PLAT.

**Adverse Events**

Several abstracts explored adverse events in pregnant women or infants exposed to antiretroviral drugs. Masaba and colleagues (Abstract 640) presented favorable data on low-birth-weight, stillbirth, and preterm babies among women treated with nevirapine-based antiretroviral therapy and infants treated with single-dose nevirapine from the Kisumu breastfeeding study (Table 3).

Ekouevi and colleagues (Abstract 641) presented data on pregnancy outcomes among HIV-infected women who were treated with potent antiretroviral therapy within the Ditrame Plus observational cohort in Abidjan, Cote D’Ivoire. Despite lower rates of MTCT in women with advanced AIDS who were treated with antiretroviral therapy than in women on short-course antiretroviral therapy (2.3% vs 16.1%), more low-birth-weight babies were born to women treated with nevirapine-based antiretroviral treatment (22.3%) than to those who received short-course antiretroviral therapy (12.4%). Fortunately, no difference in mortality rates was found for babies in the 2 groups in the first year of life.

Toro and colleagues found similar rates of antiretroviral-associated drug toxicities and substitutions in HIV-infected antiretroviral therapy–naive pregnant women and in nonpregnant women and men participating in the MTCT-Plus Initiative (7.4, 5.8, and 4.6 toxicities per 100 patient-years, respectively; Abstract 787). Given these results, the authors suggested that antiretroviral therapy should not be delayed during pregnancy over concerns about medication side effects or toxicities.

**Antiretroviral Concentrations in Breast Milk and Breastfeeding Infants**

Corbett and colleagues (Abstract 648) looked at concentrations of antiretroviral drugs in the breast milk, maternal plasma, and infant plasma of 20 women and infant pairs participating in the Malawi-based Breastfeeding Antiretroviral and Nutrition (BAN) study at the end of 12-hour dosing intervals at 6 weeks, 12 weeks, and 24 weeks postpartum. Participating women were treated with zidovudine or stavudine, lamivudine, and either nevirapine or nelfinavir. Zidovudine and stavudine concentrations were detectable in fewer than 20% of samples. Although lamivudine was present in higher concentrations in breast milk, the ratio that was actually present in infant plasma was low (1% of breast milk). Nevirapine concentrations in breast milk were approximately 70% of maternal plasma with low exposure in infants (20% infant plasma/breast milk). Nelfinavir exposure in breast milk was lower than in maternal plasma and undetectable in infants. Such findings suggest that there is a minimal risk of toxicity of these antiretroviral drugs to breastfeeding, HIV-seronegative infants. Of all of these drugs, nevirapine produced the highest levels in infants and may predispose infants who become infected to resistance.

Lehman and colleagues (Abstract 649) presented data on serial breast milk testing in 599 breast milk samples from women participating in antiretroviral treatment for PMTCT. Samples were tested for cellular DNA, HIV, and beta-actin DNA by real-time PCR. Although the investigators found cell-free and cell-associated HIV RNA levels suppressed in the presence of antiretroviral therapy, they also reported the presence of a large reservoir of latently infected cells that were not significantly affected by antiretroviral therapy, including short-course antiretroviral treatment.

**Resistance**

**N348I**

As previously reported at last year’s conference, the N348I mutation confers dual resistance to both NNRTIs and nRTIs. Yap and colleagues (Abstract 79) further characterized the 2 related biochemical mechanisms by which this mutation confers dual resistance. Using biochemical assays, they tested the zidovudine-monophosphate (MP) excision activity of wild-type and mutant HIV RT in the presence and absence of nevirapine. The N348I mutation decreases the ability of nevirapine to inhibit HIV RT, and the rate of RT RNase H cleavage, which provides RT with more time to efficiently excise the zidovudine-MP from an RNA-DNA template-primer. The ability of nevirapine to stimulate RNase H was significantly reduced in the presence of this mutation compared with the wild-type enzyme. The effect of zidovudine-triphosphate (TP) and nevirapine combined in RNA-dependent DNA polymerization reactions, along with the combined effects of N348I on nevirapine binding, RNase H activity, and zidovudine-MP excision, resulted in efficient enzyme replication. Mutations distal from the polymerase active site and NNRTI-binding pocket can confer drug resistance.

Ehteshami and coauthors (Abstract 81) explored the mechanism behind selective increases in zidovudine resistance in the presence of both TAMs and connection domain mutations N348I and A360V by comparing N348I, A360V, TAM, and TAM/N348I/A360V mutant enzymes. Mutations N348I and A360V mechanistically complemented each other to increase zidovudine resistance in a background of TAMs.

**Q509L**

Brehm and colleagues (Abstract 80) described the mechanism of action behind increased zidovudine resistance in the presence of TAMs and mutations at the connection (A371V) and the RNase H (Q509L) domains of the HIV RT. They determined zidovudine-MP excision and RNase H cleavage product and estimated single turnover zidovudine-MP excision. Compared with TAMS alone (D67N/K70R/T215F), TAM/A371V, TAM/Q509L, and TAM/A371V/Q509L increased zidovudine-MP excision 1.7-, 2.7-, and 2.9-fold, respectively, and decreased RNase H cleavage product formation 1.3-, 2.1-, and 2.1-fold. In the presence of TAMS, HIV RT muta-
ions Q509L and A371V/Q509L result in increased zidovudine-MP excision of RNA-DNA duplexes by reducing template degradation, and they increase the efficiency of excision on short RNA-DNA duplexes.

M184V

Selection of M184V in antiretroviral therapy–naive and –experienced patients treated with entecavir for hepatitis B virus (HBV) in the setting of HIV and HBV coinfection was the subject of an important report. Audsley and colleagues reported on the emergence of the M184V mutation in both antiretroviral therapy–naive and –experienced patients who received entecavir for HBV in the setting of HBV and HIV coinfection (Abstract 63). Entecavir, a guanosine nRTI that was approved by the US Food and Drug Administration in 2005 for HBV treatment, has recently received attention for its previously unreported anti-HIV activity in vitro and in vivo. The investigators for this study reviewed the effect of entecavir on plasma HIV RNA levels in an international, multicenter retrospective cohort of 17 HIV and HBV coinfected patients who had received entecavir monotherapy. There were 17 patients, of whom 10 were antiretroviral-naive and 7 were antiretroviral-experienced. Naive patients experienced a median plasma HIV RNA level reduction of 1.0 log_{10} copies/mL after a median 113 days on entecavir, whereas antiretroviral therapy–experienced patients had a 1.1 log_{10} copies/mL drop in plasma HIV RNA level after a median of 96 days on the drug. Twelve of the patients with HIV polymerase sequencing revealed an M184V mutation in 3 antiretroviral-naive and 3 -experienced patients. Of the 3 patients with antiretroviral drug experience, all had been exposed to lamivudine. Both reduction in HBV viral load and length of time on entecavir were statistically significantly associated with selection of the M184V mutation. The authors cautioned that entecavir monotherapy should not be used in HIV and HBV coinfected patients given this selection for the M184V mutation, and they issued a reminder that all HBV-seropositive patients should undergo HIV testing before initiation of HBV therapy.

Antiretroviral Therapy–Naive Patients and Resistance

Several abstracts explored the impact of low-frequency minor drug-resistant variants or quasispecies on clinical outcome. Two (Abstracts 83, 879) examined clinical outcomes in antiretroviral treatment–naive patients who were found to have low-frequency mutants despite sensitive conventional genotypes at baseline. Another report (Abstract 892) compared reported rates of primary drug resistance with clinical treatment outcomes in antiretroviral treatment–naive patients who began standard antiretroviral therapy.

Minor Populations of Y181C

Paredes and colleagues (Abstract 83) reported additional results from the AIDS Clinical Trials Group A5095 case-cohort study (previously described as a randomized trial comparing the efficacy of 3 regimens consisting of zidovudine/lamivudine and abacavir or efavirenz or abacavir and efavirenz). The main study results revealed that triple-nRTI therapy was inferior to the efavirenz-based regimens and illustrated how baseline NNRTI resistance more than doubled the risk of virologic failure. In subjects without NNRTI resistance by bulk sequencing who met criteria for virologic failure (≥ 200 copies/mL at 16 weeks), blind assays by allele-specific PCR were performed to test for the presence of minor populations with K103N and/or Y181C. The authors then compared the prevalence of these minority NNRTI-resistant variants among virologic failures and nonfailures in the evaluable random cohort. The presence of preexisting minority Y181C mutants was associated with more than 3-fold increased risk of virologic failure to first-line efavirenz-based antiretroviral therapy, even among adherent subjects. The authors noted, however, that the mutants were present in very low levels, that their proportions overlapped in subjects with and without virologic failure, and that some subjects with Y181C mutants still achieved long-term virologic suppression on efavirenz-based antiretroviral therapy. They did not detect an association between minority K103N mutants and increased risk of virologic failure.

Metzner and colleagues also explored the prevalence and clinical significance of minority quasispecies in 220 antiretroviral therapy–naive patients in Germany (Abstract 879). Baseline samples were analyzed retrospectively in patients who had begun tenofovir/emtricitabine and either a ritonavir-boosted PI or an NNRTI. Minority variants were identified in 27 patients. The K65R, K103N, and M184V variants were detected by allele-specific, real-time PCR in 4 (1.8%), 10 (4.6%) and 17 (7.9%) patients, none of whom was identified using conventional genotyping (4 patients had 2 mutations). At 24 weeks of follow-up on antiretroviral therapy, 21 patients had a plasma HIV RNA level below 50 copies/mL, 4 were lost to follow-up, and 2 had HIV RNA levels that did not become undetectable, likely the result of nonadherence. Of those patients with K103N, only 2 had begun an NNRTI-based regimen, and they had undetectable plasma HIV RNA levels at follow-up. The authors concluded that those mutations present as quasispecies were not associated with virologic failure in patients initiating antiretroviral therapy.

Fessel and colleagues (Abstract 892) assessed all antiretroviral treatment–naive patients with wild-type HIV by standard genotypic resistance testing and compared the rates of baseline resistance with rates of virologic failure. They identified 126 patients with wild-type HIV who had received at least 6 months of antiretroviral therapy. Six (4.8%) patients experienced virologic failure because of nonadherence, and 120 patients had undetectable plasma HIV RNA levels (< 75 copies/mL). Of the 111 regimens described, 41 were ritonavir-boosted PI-based regimens and 70 were NNRTI-based regimens. Using standard genotype testing, the investigators compared local rates of primary
drug resistance of 10% to 15% with the less than 5% of virologic failure found in patients with wild-type HIV who initiated antiretroviral therapy; they concluded that this type of analysis should continue to ensure that low-frequency mutations do not compromise the utility of standard genotyping.

**Ritonavir-boosted Atazanavir Monotherapy Maintenance**

McKinnon and colleagues (Abstract 890) reviewed the genotypic resistance results of 5 patients who experienced viral rebound during the ACTG 5201 study of atazanavir/ritonavir simplified maintenance therapy. Five subjects with plasma HIV RNA levels ranging from 508 copies/mL to 21,652 copies/mL, had no major PI resistance by standard genotyping or single genome sequencing. Minor mutations were detected; however, none was identified as likely to alter susceptibility to atazanavir per the Stanford drug resistance database. All patients had resuppression on another ritonavir-boosted PI regimen. The authors encouraged further investigation of this simplified low-risk maintenance therapy.

**Protease Inhibitor Resistance and L76V**

Norton and colleagues (Abstract 854) queried a commercial database (Monogram Biosciences, Inc) to identify isolates with at least 1 PI mutation with the objective of quantifying the frequency with which the L76V mutation occurred and its effect on susceptibility to other PIs either alone or with other PI-associated mutations. The L76V mutation was present in only 3.1% of the database isolates queried and was associated with a decreased susceptibility to lopinavir, darunavir, amprenavir, and indinavir. It notably did not affect susceptibility to other PIs including atazanavir, saquinavir, tipranavir, and nelfinavir. An atomic model was proposed to explain the meaning of the L76V mutation on the nearby S2 pocket, based on the known differential penetration of various PIs at that site. The presence of other PI mutations notably increased the susceptibility to atazanavir and saquinavir. This mutation was seen in a higher incidence at the time of failure to lopinavir/ritonavir monotherapy.

De Meyer and colleagues (Abstract 874) presented detailed characterization of patients who experienced virologic failure in the darunavir/ritonavir arm of the randomized, controlled TITAN trial comparing lopinavir/ritonavir with darunavir/ritonavir in a treatment-experienced population that was naive to both darunavir/ritonavir and lopinavir/ritonavir. Ten percent of patients in the darunavir/ritonavir arm experienced virologic failure, compared with 22% of patients in the lopinavir/ritonavir arm. The following primary PI mutations developed in the darunavir/ritonavir failures: V32I in 3 patients, 147V and V76I in 2 patients, and I54L in 1 patient. Fewer virologic failures arose in the darunavir/ritonavir arm than in the lopinavir/ritonavir arm that lost susceptibility to any other PI based on phenotypic analysis and confirmatory genotypic interpretation.

**Enfuvirtide and Resistance**

Several abstracts focused on resistance mutations developing during treatment with the fusion inhibitor enfuvirtide. Poveda and colleagues (Abstract 850) presented the details of clonal analysis of a total of 23 plasma samples from 10 patients who experienced virologic failure on enfuvirtide. They performed clonal analysis and analyzed the Rev response element and the gp41 open-reading frame. The high-affinity Rev binding site was highly conserved and was not modified after the selection of enfuvirtide-associated resistance mutations. Mutations V38A and V38E statistically significantly altered the secondary structure of the high-affinity Rev binding site; this alteration in the critical region of the Rev response element could potentially interfere with HIV-1 replication. The authors hypothesized that such impairment could confer virologic and immunologic benefits in the setting of incomplete viral suppression on enfuvirtide.

Svicher and colleagues (Abstract 851) analyzed 181 sequences of HIV-1 gp41 and observed 88 enfuvirtide-treated patients clinically from baseline to week 48. They identified 3 Rev mutations, of which 2 (E57A and N86S) were statistically significantly correlated with known enfuvirtide-resistance mutations (Q40H and L45M in gp41; bootstrap, 0.78; P < .05). The E57A Rev mutation in particular was associated with increased viremia (P = .006) and a loss of CD4+ cells (P = .04) from baseline to week 48. The Rev N86S mutation at baseline was predictive of on-treatment development of enfuvirtide mutations Q40H + L45M (P = .01). Consequently, the question raised was whether Rev mutations may be driving the evolution of enfuvirtide resistance.

**CCR5 Antagonists**

In vivo evidence of evolution of CXCR4 tropic virus from CCR5-tropic virus. HIV coreceptor switching and emergence occurs in approximately 50% of treatment-experienced patients. Patel and colleagues (Abstract 245) characterized env genes to understand the evolutionary pathway from CCR5 to CXCR4 usage, utilizing phylogenetic and phenotypic analysis of env gene. They found patterns that were consistent with accumulations of mutations over time, with evolution occurring from CCR5- to mixed-tropic to CXCR4-tropic Env.

**Enhanced Sensitivity Tropism Assay**

Hunt and colleagues (Abstract 864) reported on the improved detection of preexisting minority CXCR4 mutants using a modified assay with enhanced sensitivity for CXCR4-using variants. HIV-infected patients (n = 57) with drug-resistant viremia (> 1000 copies/mL) on a non-CCR5-inhibitor–based regimen were tested by the standard tropism assay and a new modified, more sensitive assay every 4 months. The standard assay, which picks up as little as 10% minority X4 populations, found 70% R5, 26% dual-mixed, and 4% X4 virus at baseline. At 1 year, 15% of those originally identified by standard assay as R5 were reclassified as dual-mixed tropic by the standard assay. Of the viruses that were reclassified at 1
year, 60% were persistently identified as dual-mixed via the enhanced sensitivity assay (which detects 0.1%-0.3% X4 populations). The more sensitive assay was also associated with reclassification of viruses at 1 year; however, reclassification took place in only 15% of those with R5-tropic virus at baseline. Further correlation of these findings with clinical outcomes is needed.

Changes in the V3 loop sequence were found to be associated with maraviroc treatment failure in patients enrolled in the MOTIVATE 1 and 2 trials. Clonal analysis of V3 loop sequencese at baseline was compared with that at week 24 in 35 patients who experienced virologic failure on maraviroc as the result of a change in tropism or phenotypic resistance (Abstract 871). All cases of phenotypic resistance of the CCR5-tropic virus to maraviroc were associated with mutations in the V3 loop.

Two abstracts presented conflicting results regarding a recently developed assay for identification of CXCR4- versus CCR5-tropic viruses (Abstracts 919 and 920a). One assay (SensiTROP, Pathway Diagnostics) was reported by its developers to have good ability to detect and quantify the amount of both CXCR4-tropic and CCR5-tropic HIV virus (Abstract 919). The assay uses heteroduplex tracking technology to detect CXCR4-tropic virus with numerous mutations in the V3 loop by forming heteroduplexes with the CCR5 V3 probes. This process was then modified to allow separation, detection, and quantitation of the CCR5-CCR5 homoduplex DNA hybrids and CXCR4-CCR5 heteroduplex DNA hybrids. Using this assay, the authors reported the ability to quantify X4-R5 DNA mixtures down to a level of 5% (interassay coefficient, 1.8%-16.9%), to determine X4:R5 ratios when the plasma HIV RNA level is more than 1000 copies/mL, and to accurately detect CXCR4-tropic HIV when present at only 1% of the amount of CCR5-tropic virus.

In contrast, Tressler and colleagues (Abstract 920a), presented a less favorable assessment of the same assay (SensiTROP) compared with another assay (Trofile, Monogram Biosciences, Inc). They calculated values for the sensitivity and specificity of the SensiTROP assay relative to the Trofile by retesting stored samples in a blinded manner from 100 HIV-infected, treatment-experienced patients who had participated in the maraviroc Expanded Access program with the SensiTROP assay. To determine the sensitivity, specificity, positive predictive value, and negative predictive value, the authors considered samples that tested as R5 at baseline and screening to be true positives (n = 40) and samples that tested dual-mixed or X4 at baseline to be non-R5 (n = 39) per their Trofile assay results. The SensiTROP assay identified only 19 of 39 non-R5 viruses; the authors determined a non-R5 detection sensitivity of 42.4% and a specificity of 92.5% for this test. The utility of this assay was questioned given its failure to identify dual-mixed or X4 virus in more than 50% of samples.

### Integrase Inhibitors

Hackett and colleagues (Abstract 872) explored integrase inhibitor polymorphisms with the objective of understanding pathways to resistance, potential group subtype effects, and the prevalence of resistance-associated mutations. Analysis included phylogenetic analysis of 1265 integrase inhibitor–naïve subjects from diverse continents, of which 1200 were identified as group M, 100 as group O, and 4 as group N strains. Of 288 amino acids, 42% were polymorphic at a level of 1% or greater. They noted that the catalytic regions were highly conserved and that residues 148 and 155 were associated with primary resistance. Some known resistance mutations were identified as naturally occurring polymorphisms including V72I (55%), L74M (5% of group M), T97A (5%), T112I (11% of group M and 35% of group O), V151I (2%), K156N (1%), E157Q (4%), V165 (5%), and I203M (3%).

In terms of resistance testing for the integrase inhibitors, Abstracts 881 and 882 presented data on novel resistance testing methods from 2 manufacturers. Smith and colleagues presented data on integrase genotypic reagents for analysis of 81 diverse HIV-1 strains including subtypes A, B, C, D, F, G, CRF01, and CRF02 (Abstract 881) from diverse nations. Using the “Celera” prototype HIV-1 integrase genotyping reagents, they amplified the catalytic core domain of the integrase in 83 of 84 samples (98%). Although they found many polymorphisms in this key domain, no polymorphisms were located in resistance-associated codons. Henry and colleagues (Abstract 882) presented their data on a novel phenotypic drug susceptibility assay based on the generation of recombinant HIV-1 using yeast recombinant cloning technology.

### Etravirine and Resistance

Several abstracts presented analyses of cohorts with heavy NNRTI exposure for prevalence of mutations and eligibility for etravirine as second-line therapy (Abstracts 865-868). Sungkanuparph and colleagues (Abstract 865) analyzed the mutational patterns in a cohort of 158 HIV-infected patients in Thailand for whom treatment with NNRTI-based regimens had failed (84.2% nevirapine, 15.8% efavirenz). Etravirine-associated mutations were found in 82.9% of patients, including 59.5% Y181C/I/V, 33.5% G190A/S, 8.4% V179D/F, 4.4% V106I, 0.8% V90I, 0.8% A98G, 0.8% L100I, and 0.8% K101E/P. Of 131 patients with etravirine-associated mutations, 92 (70.2%) had fewer than 3. The majority of these 92 etravirine-eligible patients also had at least 2 active nRTIs available to them based on genotype results (69 subjects, or 75%). Such findings beg routine use of genotype testing to assist with second-line therapy selection in resource-poor settings and suggest that etravirine-based therapy is a hopeful option for second-line therapy despite NNRTI-based treatment exposure in such settings.

Likewise, Picchio and colleagues (Abstract 866) presented an analysis of HIV genotypic data to determine the preponderance of isolates that would be eligible for etravirine (fewer than 3 etravirine-associated resistance mutations). The investigators reviewed a large clinical database (Virco Lab, Inc) of samples submitted from 1999 until
2007 and found 89,113 samples that met the definition for NNRTI resistance based on the IAS-USA mutation list. Of these, 40% had no etravirine associated mutations, 36.7%, 16%, and 7.3% harbored 1, 2, and 3 or more etravirine-associated resistance mutations, respectively. The 4 most frequently occurring etravirine-associated mutations, in descending order of frequency, were Y181C, G190A, K101E, and L101I. Overall, only 7.3% of clinical isolates with known NNRTI resistance harbored 3 or more etravirine-associated mutations. The authors did not comment on any knowledge of whether samples were collected on or off therapy or whether patients with multiple resistance-test results with different NNRTI mutations were pooled in any way. They also noted that 95,019 samples met the criteria for NNRTI resistance based on the commercial biologic cutoff values that yielded similar results, which were not presented.

In a Nigerian cohort (Abstract 867) of patients with predominantly non-subtype-B HIV (CRF02, 45%; G, 43%; A, 5%; CRF06, 4%; recombinant, 3%; other, 2%), 214 patients with virologic failure on an NNRTI-based regimen had genotypic analysis. In 32% of samples, there were no etravirine-associated mutations. There were 1, 2, and 3 or more mutations in 35%, 23%, and 10%, respectively, and the presence of etravirine mutations was found to be statistically significantly associated with length of time on NNRTI-based therapy. The 4 most frequently identified etravirine-associated mutations in the cohort were Y181C, G190A, A98G, and K101E.

Llibre and colleagues (Abstract 868) also found that a high degree of etravirine resistance was rare in their analysis of 1586 Spanish Resistance Laboratory samples with at least 1 NNRTI-associated resistance mutation based on the IAS-USA list. Only 1.14% of samples had more than 3 etravirine-associated resistance mutations, and 8.2% of samples had more than 2 such mutations.

Winters and colleagues presented virtual phenotype (a genotype interpretation) predictions of etravirine drug susceptibility and clinical (Virco Lab, Inc) cutoff values (Abstract 873). They based their analysis on clinical isolates with drug-susceptibility phenotypes, viral genotypes, and a clinical regression model developed from data from the DUET trials. Ultimately, they defined 2 clinical cutoff levels, corresponding to predicted fold-change values associated with 20% or 80% loss of the response of subjects infected with HIV-1 wild-type strains. The virtual phenotype predicting etravirine resistance ranged from a 0.9 fold-change for wild-type isolates to a 200-fold change. Based on their analysis, they found a 20% and 80% loss of etravirine response in patients with 1.6 and 27.6 etravirine fold-changes in susceptibility, respectively.

Patients receiving etravirine with an etravirine fold-change of less than 20% (n = 355), 20% to 80% (n = 413), and more than 80% (n = 85) had median reductions in plasma HIV RNA levels of −2.6 log10, −2.3 log10, and −1.3 log10 copies/mL, and 38%, 24%, and 15%, respectively, had plasma HIV RNA levels below 50 copies/mL at 8 weeks. By week 24, these same patients, defined by their baseline clinical cutoff category, had plasma HIV RNA levels below 50 copies/mL in 55%, 37%, and 26%, respectively.

### Adherence and Resistance by Antiretroviral Class

Gardner and colleagues (Abstract 777) presented an adherence analysis by class of antiretroviral therapy from the FIRST study, a prospective, randomized, antiretroviral-therapy-strategy trial for 903 antiretroviral-therapy-naive patients, of which 446 were on an NNRTI-based regimen and 457 were on a PI-based regimen. Adherence was assessed at 7 days, 1 month, 4 months, and then every 4 months thereafter. Genotypic testing was also performed at virologic failure (plasma HIV RNA levels above 1000 copies/mL). Patients were observed for a median of 5 years, and the mean baseline CD4+ count was 211 cells/μL.

Increased NNRTI resistance was associated with decreased adherence in the NNRTI arm but not the PI-regimen arm. Hazard ratios for resistance in the NNRTI arm based on level of reported adherence were 2.3 (range, 1.4-3.7) for people with 80% to 99% adherence, and 6.5 (range, 2.9-10.7) in the 80% adherent group compared with the 100% adherent people. The median time to virologic failure, however, was 1.2 years on the PI-based regimen as opposed to 3.0 years on the NNRTI-based regimen. Though both arms had similar rates of overall resistance at virologic failure (28%, NNRTI arm; 30%, PI arm), only 8% of patients in the PI-based arm had PI resistance, whereas 25% of patients had NNRTI resistance in the NNRTI-based treatment arm. The bulk of resistance identified in patients on the PI strategy was nRTI-associated. Although the study confirms the association between adherence, NNRTI-based regimens, and resistance, the authors acknowledged that the study failed to obtain information on differential adherence, which could explain some of the findings.

Cozzi-Lepri and colleagues (Abstract 894) also reviewed the incidence of resistance by class in their large United Kingdom cohort of antiretroviral therapy-naive patients who had initiated continuous antiretroviral therapy consisting of 2 nRTIs plus either an NNRTI (n = 5080) or a ritonavir-boosted PI (n = 929) between 1998 and 2005. Of the 1016 patients who experienced the first virologic failure, 564 (56%) had genotypic results recorded. At 7 years, the rate of resistance was 19% for at least 1 nRTI mutation, 17% for at least 1 NNRTI mutation, and 3% for at least 1 major PI mutation. Detection of class-specific mutations was less likely in patients who initiated PI-based regimens than in those on NNRTI-based regimens. No difference was found in the rate of nRTI mutations associated with PI- versus NNRTI-based regimens.

### Treatment Interruption and Resistance

Danel and colleagues (Abstract 778) analyzed data from the Truvacan Trial, a fixed-cycle trial of 2-months-off, 4-months-on antiretroviral therapy in patients with high pretreatment CD4+ cell counts in West Africa. Originally, a 3-arm trial comparing continuous therapy...
with CD4+ cell count–guided therapy and a cycle of antiretroviral treatment of 2 months off then 4 months on, the CD4+ cell count–guided arm was terminated because of high rates of morbidity. Results of the remaining 2 arms were analyzed comparing mortality, severe HIV-related morbidity, and percentage of patients with a CD4+ count greater than 350 cells/μL at 24 months.

Of the 435 patients who underwent randomization to continuous versus 2-months-off, 4-months-on therapy with zidovudine/lamivudine/efavirenz, the incidence of mortality was 0.45 per 100 person-years in the continuous group versus 0.45 per 100 person-years in the 2-months-off, 4-months-on treatment group, and the incidence of severe HIV-associated morbidity was 6.8 per 100 person-years in the continuous therapy arm and 9.1 per 100 person-years in the fixed-cycle therapy arm. At 24 months, 94% of patients in the continuous therapy arm reached a CD4+ count of 350 cells/μL or greater, as did 85% of patients in the 2-months-off, 4-months-on treatment group.

The authors noted important secondary analyses. Short-term cost was lower in the 2-months-off, 4-months-on treatment group (P < .001); however, this cost savings came in exchange for increased resistance in the 2-months-off, 4-months-on antiretroviral therapy group (21% vs 9% of patients with at least 1 resistance mutation; P = .007). Of resistance mutations, 62% were NNRTI- and 23% were lamivudine/emtricitabine-associated. Although clinically noninferior, the 2-months-off, 4-months-on therapy regimen led to unacceptable resistance rates.

**Treatment Interruption and Minority Drug-Resistant Viral Populations**

Wang and colleagues (Abstract 877) analyzed 14,779 viral genomes from plasma samples taken at several time points after treatment interruption of up to 59 weeks from 3 patients using the parallel allele-specific sequencing assay. Low-level virus replication during nonsuppressive antiretroviral therapy was different from that found in viruses during high levels of replication. After treatment interruption, minority drug-resistant viruses increased in the high-level viral replication grouping and persisted for more than 9 weeks before being replaced by single-drug-resistant viruses and finally by wild-type viruses.

**PI Probability Estimations and Resistance Testing in Heavily Treatment-experienced Patients**

King and colleagues (Abstract 773) presented a small proof-of-concept study of probability estimations for PI resistance to aid in the selection of antiretroviral regimens in treatment-experienced patients as an alternative to exclusive use of phenotypic testing. Twenty-three subjects with PI resistance (median, 34-fold change) underwent randomization to either a regimen chosen based on phenotypic analysis alone or a regimen chosen using the probability-estimations approach. The authors defined the probability-estimations method as an integration of expected drug exposure with susceptibility testing to estimate each patient’s probability of achieving trough concentrations above the protein-binding IC50 level. They observed patients serially after randomization and found that changes in plasma HIV RNA levels at weeks 4, 8, and 15 were not statistically different between the 2 arms.

**Nonsubtype-B HIV-1 Infections**

Several abstracts highlighted resistance issues in nonsubtype-B viruses. Differences in polymorphisms resulted in substantial structural changes in CRF01_AE compared with subtype B virus (Abstract 900). Using crystallographic techniques, the protease p1-p6 substrate structure of CRF01_AE was compared with that of nonsubtype-B virus. The CRF01_AE subtype showed a significant change in the flap-hinge region of protease and revealed a unique interaction at key sites that was not seen in the subtype B structure. Such sequence polymorphisms in the CRF01_AE subtype confer substantial structural changes within protease compared with the subtype B protease structure.

Chaplin and colleagues (Abstract 901) presented subtype, genotype, and resistance patterns from a Nigerian panel of 304 patients with virologic failure after more than 6 months of antiretroviral therapy. Based on pol sequencing in 214 patients, the following subtypes were identified: 43% CRF02, 43% subtype G, 5% subtype A, 4% CRF06, and 5% other. Substantial differences in TAM development were found in these subtypes that differed from the pattern seen most frequently in subtype B virus. Subtype B virus develops TAMs via the “TAM1” pathway (T215Y, M41L, L210W, D67N, confers more cross resistance to didanosine and tenofovir and occurs more frequently) or the “TAM2” pathway (K70R, K219QE, T215F, D67N, which confers less cross resistance). In contrast, investigators found that TAM2 mutations were twice as common as TAM1 in subtype G and that M41L and L210W were quite uncommon in the panel overall and particularly low in subtype CRF02 than in other subtypes.

Investigators from the Aquitaine cohort presented an analysis of the relationship between recent seroconversion, HIV-1 subtype, and transmission of resistance among patients identified in their southwestern French cohort between 1996 and 2006 (Abstract 902). Reverse transcriptase and protease sequences as well as phylogenetic analysis were obtained. The authors identified 263 patients as recent seroconverters within 18 months, of which 84.4% clustered with subtype B and 15.6% clustered with nonsubtype-B virus. Twenty-four clusters of transmission were identified, of which 22 were subtype B and only 1 nonsubtype B. The frequency of segregation into clusters was higher within the B sequences than within the nonsubtype-B sequences (35.1% vs 4.9%; P < .0002). Three clusters with resistant isolates were identified, and the prevalence of resistance in clustering viruses was 12.5% versus 14.7% in nonclustering isolates. The high frequency of segregation into clusters suggested forward transmission events in subtype-B-infected patients and suggested that such a pat-
tern could result in high transmission rates of drug-resistant strains.

**HIV-2 and Resistance**

Rodes and colleagues (Abstract 885) reported on resistance outcomes in 22 HIV-2-infected patients who started antiretroviral therapy and were followed for 12 months. Notably, 15 of 22 patients received triple-nRTI therapy (zidovudine/lamivudine/abacavir), and the others received nevirapine/zidovudine/lamivudine and indinavir/abacavir/didanosine regimens. At 12 months, 19 of 22 (86%) patients experienced treatment failure of these regimens. Of failures, 84% developed M184V mutations, 3 had virus that developed K65R in the absence of tenofovir exposure, and there were no Q151M mutations. The authors noted how quickly and differently RT mutations form in HIV-2 compared with HIV-1, and they urged caution and careful selection of drug-treatment combinations and treatment strategies in HIV-2-infected patients.

Roquebert and colleagues (Abstract 886) examined the in vitro susceptibility of HIV-2 to the integrase inhibitors raltegravir and the investigational agent elvitegravir using the ANRS trial assay method in 50 patients enrolled in the French HIV-2 cohort. Despite 40% heterogeneity between HIV-1 and HIV-2 integrase genes, phenotypic susceptibility to the integrase inhibitor was similar in both viruses, suggesting that these integrase inhibitors could be useful therapeutic options in HIV-2-infected people.

**Resistance Testing from Dried Blood Samples**

Youngpairoj and colleagues presented promising findings regarding the use of dried blood samples stored for 1 year at 4°C (Abstract 927). Previously, the group showed that resistance genotypes generated from dried blood samples were highly concordant with those obtained from plasma. Realizing that storage of samples below −20°C is often not feasible in RLS, the authors tested the hypothesis that dried blood samples could be genotyped efficiently after storage at 4°C for 1 year.

The investigators described their method of storage for 40 dried blood samples analyzed from HIV-1 subtype-B-infected people. A small quantity of blood from each specimen was stored onto 903 filter paper cards, which were dried overnight at room temperature and stored in a sealed plastic bag with dessicant. At 1 year, resistance testing was done, and a real-time PCR assay was performed to amplify a smaller pol fragment; a nested PCR step was used. Only 23 of 40 specimens could be successfully genotyped using standard resistance testing, however, when the specimens were tested using the in-house reverse transcriptase–nested PCR assay, 38 of the 40 specimens were successfully genotyped. They attributed this improvement in genotyping to their in-house nested PCR protocol with quality-controlled reagents to overcome possible losses in the HIV-1 RNA integrity. Such methods could prove very useful in RLS.

**Acute HIV Infection**

**Treatment of Acute HIV Infection**

Methods of treatment in acute HIV infection were reported in several presentations. Most data were drawn from cohorts of patients with acute HIV infection and were therefore somewhat limited by selection bias. Results were conflicting; some presentations concluded that there was a lack of benefit in terms of CD4+ cell count (Abstracts 694, 697) and viral load (Abstracts 693, 697). In contrast, Abstracts 695, 696, and 698 highlighted favorable CD4+ or viral load outcomes associated with early initiation of antiretroviral treatment.

**Studies Showing Early Treatment Is Not Beneficial**

**Setpoint or viral load.** Recent nonrandomized trials of treatment of acute and recent HIV seroconversion have failed to show a clinical benefit. Given the known differences in the immunologic picture of acute versus recent HIV, there may be a treatment benefit associated with viral suppression on antiretroviral therapy in very early, acute HIV seroconversions.

Volberding and colleagues (Abstract 693) reviewed the results of ACTG 371 and compared the degree of viral suppression after treatment with a PI-based regimen among subjects acutely infected with HIV-1 (estimated infection within 14 days) with that of subjects who have been infected recently (estimated infection in the prior 14 to 180 days). Patients were treated until their plasma HIV RNA level was undetectable for at least 52 weeks, at which point treatment was interrupted until either the HIV RNA level was greater than 5000 copies/mL on 3 or more occasions or more than 50,000 copies/mL on more than 2 occasions followed by reinitiation of treatment until the HIV RNA level was again undetectable for at least 52 weeks. Of the 73 patients (28 acute infections, 45 recent infections) who entered treatment interruption, 40% overall sustained a plasma HIV RNA level below 5000 copies/mL after 24 weeks of treatment interruption. However, no statistically significant difference in outcome was seen when the authors compared those who began in the setting of acute infection with those who began treatment in the setting of recent infection.

**CD4+ decline.** Desquibel and colleagues reported data from the French ANRS PRIMO cohort of subjects acutely infected with HIV-1 (within 2 months of infection). The cohort included 73 patients who received antiretroviral therapy for 6 months to 24 months after enrollment and 149 patients who remained untreated for 3 months or more (Abstract 694). Because the analysis was nonrandomized, the authors created a propensity score to correct for selection bias. They reported the time to CD4+ count decline below 350 cells/µL from baseline and generated Kaplan-Meier curves. Sixty-three patients in each group were matched by propensity score. The proportion of individuals who maintained a CD4+ count greater than 350 cells/µL 36 months after baseline did not differ between the 2 groups. It was concluded, therefore, that relatively short-course
antiretroviral therapy did not confer a statistically significant benefit in preventing or delaying a CD4+ count decline to below 350 cells/µL.

Pantazis and colleagues (Abstract 697) reported a lack of beneficial effect on both CD4+ cell count and viral load set point in their analysis of 348 patients who received transient early antiretroviral treatment within 6 months of seroconversion compared with 675 patients who deferred treatment in the Concerted Action on SeroConversion to AIDS and Death in Europe (CASCADE) cohort. Both viral load set points (P = .43) and AIDS rates were similar between the early and deferred groups at follow-up.

Immune Modulator in Addition to Antiretroviral Therapy During Acute HIV

Markowitz and colleagues shared the results of a multicenter, 48-week, open-label, randomized phase II study of 4 weeks of cyclosporine A in addition to PI-based antiretroviral therapy in patients with acute or recent HIV infection. Fifty-six patients underwent randomization 2:1 to cyclosporine plus antiretroviral treatment versus antiretroviral treatment alone. There were no statistically significant differences in mean time to a plasma HIV RNA level below 50 copies/mL, CD4+ cell count at weeks 12, 24, and 48, or change from baseline CD4+ cell count. Thus, 4 weeks of cyclosporine A in addition to antiretroviral therapy did not add any immunologic or virologic benefit in acutely or recently HIV-infected patients.

Studies Showing Early Treatment of Acute HIV Is Beneficial

CD4+ count and viral load. From their observational multicenter cohort, Prazuck and colleagues presented favorable long-term effects on CD4+ count and viral load in acutely infected patients who began antiretroviral treatment very early after seroconversion (Abstract 695). All patients were enrolled within 10 weeks of estimated seroconversion and “self-decided” to initiate antiretroviral therapy. Twenty patients were in the treatment group (treated for 1-7 years; median, 2.3 years) and 18 patients in the untreated group. The CD4+ counts and plasma HIV RNA levels at serial intervals were compared. Untreated patients experienced a median monthly loss in CD4+ cells that was twice as high as in the treated group following cessation. Statistically significant differences were found between the proportions of treated and untreated patients whose HIV RNA levels remained below 400 copies/mL at weeks 48 (42.1% vs 56%), 96 (36% vs 0%), and 144 (31% vs 0%), with P < .001 after treatment cessation. The HIV RNA levels of 25% of treated patients were able to stay below 50 copies/mL at 144 weeks after treatment interruption in patients with acute HIV who underwent early antiretroviral treatment for 24 or 60 weeks (n = 57; HIV RNA level, 4.0 log_{10} copies/mL) than in untreated patients (n = 11; HIV RNA level, 4.9 log_{10} copies/mL; P < .005). Statistically significantly higher CD4+ counts were seen in treated patients at 36 weeks after treatment cessation than in untreated patients (581 vs 349 cells/µL; P < .05).

Coinfection with GB Virus C Slows HIV

Many studies have suggested that GB virus C (GBV-C) has a beneficial effect on HIV pathogenesis. Giret and colleagues (Abstract 273) demonstrated the association between GBV-C viremia and lower T-cell activation in their cohort of recently infected patients. Of the 40 patients enrolled in the Serologic Testing Algorithm for Recent HIV Seroconversion (STARHS), 24 were GBV-C infected. Two known markers of T-cell activation, CD38+ CD8+ T cells and CCR5+ CD8+ T cells (r = 0.65; P < .01), were highly correlated. The authors further demonstrated that GBV-C-infected subjects had a lower percentage of all of these T-cell activation markers. This mechanism may help explain the observed protection against progression to immunodeficiency by this virus.

Race, Ethnicity, and Sex as Predictors of Virologic Outcomes and Mortality

Palella and colleagues (Abstract 530) analyzed mortality risk in 2383 patients from the HIV Outpatient Study (HOPS) in 7 US cities from 1999 to 2005. Participants had a mean follow-up time of 5.9 years. They noted increased death rates among people with public compared with nonpublic insurance: 4.0 vs 1.3 deaths/100 person-years, respectively. Non-Hispanic blacks also had higher death rates (3.3 deaths/100 person-years) than those of nonblacks or Hispanics (1.9 deaths/100 person-years). In a multivariate analysis that controlled for other known HIV-related mortality risks, having public insurance, being of non-Hispanic black ethnicity, being of older age, and having a lower CD4+ cell count at antiretroviral therapy initiation were all associated with increased mortality risk.

The virologic outcomes of African Americans (AAs) versus European Americans (EAs) initiating therapy between 1996 and 2004 were examined in 1794 participants (900 AA; 894 EA) in the TriService AIDS Clinical Consortium HIV Natural History Study, a longitudinal US military cohort launched in 1987 (Abstract 809). Though most baseline parameters were similar, AAs had lower CD4+ counts at diagnosis than did EAs (mean, 478 vs 552 cells/µL, respectively; P < .0001) and lower CD4+ counts at initiation of antiretroviral therapy (mean, 333 vs 367 cells/µL; P = .004). The authors completed a multivariate logistic regression analysis and found the odds of having a plasma HIV RNA level below 400 copies/mL at 6 months after antiretroviral initiation to be 0.5 for AAs compared with EAs (95% CI, 0.4-0.7; P < .001), after adjustment for age, sex, military rank, baseline plasma HIV RNA level and CD4+ count, prior AIDS events, prior antiretroviral use, antiretroviral regimen, hepatitis B coinfection, he-
moglobin level, and year of antiretroviral initiation.

Lemly and colleagues (Abstract 810) used a retrospective cohort of people receiving HIV care at a center in Nashville, Tennessee, to establish race, ethnicity, and sex differences in antiretroviral therapy use and mortality within the cohort. Unadjusted all-cause mortality rates did not differ significantly by sex but did differ between blacks and nonblacks (49 vs 31 deaths/1000 person-years; P < .001.) After adjusting for baseline clinical and demographic characteristics, death was associated with female sex, black race, and having injection drug use as an HIV risk factor. Both women and blacks were also less likely to be receiving antiretroviral therapy, even among persons with a baseline CD4+ count below 200 cells/μL.

In the Netherlands, ATHENA Cohort investigators took a slightly different approach (Abstract 817) by selecting patients initiating antiretroviral therapy between January, 1996, and May, 2005, and stratifying participants’ CD4+ cell count restoration by region of origin. Of 4348 eligible patients, 2970 (68%) were from Western Europe or North America, 751 (17%) from sub-Saharan Africa, 157 (4%) from Southeast Asia, and 470 (11%) from Latin America or the Caribbean. The median increase in CD4+ cell count after 5 years of antiretroviral therapy was higher in patients from Western Europe or North America (560 cells/μL) than in patients from sub-Saharan Africa (320 cells/μL; P value for difference .004.) There were no significant differences in patients from other regions. The estimated mean increases in CD4+ count were also higher in women than in men (an additional 27 cells/μL/year from 0-6 months; P = .04; and 11 cells/μL/year from 6-36 months; P = .008.)

Outcome Data from Large Randomized Control Trials and Longitudinal Cohort Studies

Riddler and colleagues (Abstract 776) examined the effect of baseline demographic and clinical parameters on treatment outcomes among participants in the Adult ACTG A5142 trial. This trial randomized 753 treatment-naive, HIV-infected people to the class sparing regimens of efavirenz plus 2 nRTIs, lopinavir/ritonavir plus 2 nRTIs, or efavirenz plus lopinavir/ritonavir. In a multivariate hazards analysis, a shorter time to virologic failure was inversely associated with age (HR, 0.81 per 10-year increase; 95% CI, 0.69-0.94; P = .005), female sex (HR, 0.75 for men vs women; 95% CI, 0.53-0.99; P = .046), baseline CD4+ count (HR, 0.88; 95% CI, 0.79-0.99; P = .03), and race (HR, 0.64 nonblack vs black as referent; 95% CI, 0.48-0.85; P = .002). For women, the risk of virologic failure was lowest and the time to treatment-limiting toxicity was longest in the lopinavir plus efavirenz arm.

Carr and Amin (Abstract 782) presented a meta-analysis of all randomized control trials and prospective cohorts conducted for more than 28 weeks and published or presented after January, 1996. They extracted data from 143 studies on 23,067 patients and defined their primary endpoint as undetectable HIV RNA levels by intention-to-treat analysis. The mean intention-to-treat success, defined as percentage of people with HIV RNA levels below 50 copies/mL, was 59% at the mean follow-up time of 14.3 months. Factors independently associated with higher rates of undetectable HIV RNA levels were nonwhite race, antiretroviral regimens for which dosage was assigned regardless of food intake, third-drug class (most favorable were ritonavir-boosted PI regimens), and nRTI backbone (most favorable were didanosine/lamivudine or didanosine/emtricitabine). The authors noted that these findings differ from results of some other large studies, in that success was correlated with older age and lower CD4+ cell count, and that prior injection drug use or AIDS diagnosis were not inversely associated with success.

A similar tactic was used by investigators from the ACTG and Antiretroviral Therapy Cohort Collaboration (ART-CC), who compared the outcomes of abacavir- and efavirenz-based antiretroviral therapy in the A5095 trial with those seen in ART-CC patients (Abstract 783). Efavirenz was used more commonly in men, and median CD4+ counts were lower for patients initiating efavirenz versus abacavir (209 vs 251 cells/μL, respectively). The authors used findings from A5095 as a surrogate for efficacy and from the ART-CC as surrogate for effectiveness. As such, they determined that efficacy and effectiveness of efavirenz at 24 weeks was similar in the 2 groups (OR, 0.78 for A5095 vs ART-CC; 95% CI, 0.54-1.13), but effectiveness was significantly lower for abacavir (OR, 0.45 for A5095 vs ART-CC; 95% CI, 0.32-0.64). The percentage of participants reaching a 48-week AIDS or death endpoint also differed significantly: 3.1% in A5095 and 6.9% in the ART-CC (P < .01).

Lau and colleagues (Abstract 785) compiled data from the Johns Hopkins HIV Clinical Cohort to develop a prediction model for AIDS-defining illnesses or death after initiation of antiretroviral therapy. Their analysis included data from 2961 participants in the cohort who initiated antiretroviral therapy between 1996 and 2004, among which there were 772 AIDS-defining illnesses and 463 deaths over 10,728 person-years of follow-up. Variables predictive of shorter time to AIDS-defining illness or death were age, history of injection drug use, cocaine use, anxiety, depression, Pneumocystis jirovecii pneumonia prophylaxis, prior AIDS-defining illness, CD4+ count, HIV RNA level, total lymphocyte count, hemoglobin level, and albumin level. The model was compared with a published model derived from the EuroSIDA cohort and was found to have slightly better discrimination at 6 months (0.73 area-under-the-receiver-operator curve compared with 0.65 for EuroSIDA).

Predictors of Response to Second-line Antiretroviral Therapy

Moore presented an analysis of response to second-line therapy from the North American AIDS Cohort Collaboration on Research and Design (NA-ACCORD), which includes data from 22 cohorts from the United States and
Canada (Abstract 41). The authors included data from 5057 cohort participants who had initiated antiretroviral therapy between 1996 and 2005, had virologic failure of their first regimen, changed antiretroviral regimens, and had documented virologic failure of their second regimen. They defined virologic failure as having an HIV RNA level above 1000 copies/mL 6 months after initiating a second-line regimen or any time after they had obtained a level below 400 copies/mL on the second-line regimen.

The authors found a steady decrease in both the incidence and the adjusted relative risk of second-line failure over time, with an incidence of 113.6 failures per 100 person-years between 1996 and 1997, decreasing to 15.1 per 100 person-years between 2004 and 2005. Median survival post-virologic failure of the second-line regimen was 7.1 years (95% CI, 6.5-7.8), and CD4 cell count, HIV RNA level, and a history of AIDS at initiation of second-line treatment were all significantly associated with mortality. These 3 factors were predictive of mortality in an analysis limited to the 1276 patients who were antiretroviral-naive at the start of their first potent antiretroviral regimen.

Cozzi-Lepri and colleagues (Abstract 797) undertook a similar analysis of participants for whom second-line therapy failed in the EuroSIDA Study, which began enrolling in 1994 and now has 72 participating sites throughout Europe. Forty-five percent of patients who initiated second-line therapy experienced virologic failure, with a definition similar to the NA-ACCORD study; median time from start of the second regimen to virologic failure was 59 months. Factors associated with a relative hazard of virologic failure of second-line antiretroviral therapy were viral load at the start of the second regimen (adjusted relative hazard [aRH], 1.20 per log_{50} copies/mL higher; 95% CI, 1.04-1.40) and the use of nevirapine (aRH, 2.19; 95% CI, 1.38-3.50) or nelfinavir (aRH, 1.80; 95% CI, 1.13-2.87) as opposed to efavirenz in the second-line regimen. A substantial limitation to this study was that patients who changed antiretroviral therapy for reasons other than failure, like medication-associated toxicity or temporary suspension of treatment, were not excluded from the analysis.

Data from 982 participants in the Johns Hopkins and University of North Carolina prospective cohorts with virologic failure on their initial antiretroviral regimens were combined to determine the consequences of delay in antiretroviral regimen modification after confirmed virologic failure (Abstract 798). Delay in modification of the first antiretroviral regimen was associated with different HRs for death by regimen type: failing regimens containing PIs had an HR of 0.93 (95% CI, 0.87-0.99; P < .03) for each additional delay of 3 months (ie, patients who had a delay in switching antiretroviral therapy had a lower risk of death than those who switched immediately). However, patients experiencing failure of non-PI regimens, most of which contained NNRTIs, had an HR of 1.23 (95% CI, 1.08-1.40; P = .002) for each additional delay of 3 months compared with switching immediately. Delay in modification of first-line therapy was also associated with an increased HR for the combined endpoint of immunologic failure or death for those on non-PI regimens but not for subjects experiencing failure of a PI-based regimen or of second-line treatment regardless of regimen. Globally, a majority of patients initiate antiretroviral therapy with an NNRTI-based regimen, and efforts should be made to minimize the length of time spent on a virologically failing NNRTI regimen.

Wilkin and colleagues, reported findings from a meta-analysis of recent clinical trials involving CCR5 inhibitors (Abstract 800). They included 16 clinical trials with 37 total treatment arms and found that factors associated with CD4+ count gain were virologic suppression (estimated 12-cell/µL increase per 10% higher proportion of HIV RNA level below 50 copies/mL; P < .0001), baseline HIV RNA level (45-cell/µL increase per log_{50} copies/mL increase; P = .005), and use of a CCR5 inhibitor (32-cell/µL increase; P < .0001). The fact that the use of a CCR5 inhibitor was associated with CD4+ count increases, even after controlling for degree of virologic suppression, warrants further exploration of the role of CCR5 inhibitors in enhancement of the immune response.

**Pharmacokinetic Considerations**

**CCR5 Antagonists**

Maraviroc in the genital tract. Dumdum and colleagues presented data on the levels of maraviroc, a CCR5 antagonist, in the female genital tract (Abstract 135LB). Cervicovaginal levels of maraviroc exceeded that of plasma throughout the dosing cycle. The AUC was approximately 4 times higher in the genital tract than in the plasma. The authors also performed vaginal biopsies and found levels that were generally higher than that found in the plasma, suggesting that maraviroc may be a useful agent for preexposure prophylaxis.

**Nucleoside Analogue Reverse Transcriptase Inhibitors**

Tenofovir concentration in cerebrospinal fluid. Best and colleagues presented data on the concentration of tenofovir in cerebrospinal fluid (CSF) (Abstract 131). They analyzed paired plasma and CSF samples from 63 subjects and found that tenofovir levels in the CSF were 4% of those in plasma. The CSF levels were below the IC_{50} for wild-type HIV. The authors asserted that this would put subjects at risk for viral replication in the central nervous system, but clinical confirmation of this concern is needed.

**Nonnucleoside Analogue Reverse Transcriptase Inhibitors**

Pharmacodynamics of etravirine. Kakuda and colleagues presented combined data from 2 phase III studies of etravirine (Abstract 762). They did not find a relationship between the AUC or C_{min} and the probability of achieving a plasma HIV RNA level below 50 copies/mL. They did not find any subgroups that required dosing adjustment to improve outcomes.
Protease Inhibitors

Lopinavir/ritonavir formulations. Best and colleagues compared the pharmacokinetics of once-daily administration of lopinavir in liquid, soft-gel, and tablet formulations (Abstract 766a). The tablet formulation resulted in significantly higher trough concentrations than did the liquid or soft-gel formulations (3.7 μg/mL vs 1.1 and 1.6, respectively; P < .05).

Antimalarial drugs and lopinavir/ritonavir. Artemisinin-based regimens are being used increasingly for treatment of malaria throughout the world. German and colleagues investigated the interactions of lopinavir/ritonavir (inhibitor of CYP3A4) with fixed-dose combination of artemisinin/lumefantrine (substrate of CYP3A4) (Abstract 132). The addition of lopinavir/ritonavir significantly increased the levels of lumefantrine. The AUC increased 298%, and the maximum plasma concentration (Cmax) increased 82%. The changes were highly variable among subjects. The levels of lopinavir and ritonavir were not affected significantly. The authors concluded that these drugs could be coadministered despite the interaction based on the excellent safety record for lumefantrine.

Rifampin and atazanavir/ritonavir. Haas and colleagues have previously presented data on the interaction of rifampin and atazanavir/ritonavir. They updated this trial with information from 3 subjects out of a planned sample size of 14 who received atazanavir 300 mg and riftonavir 100 mg twice daily in addition to rifampin 600 mg daily started 7 days before the atazanavir/ritonavir (Abstract 766b). All 3 participants experienced nausea and vomiting and had increased levels of hepatic transaminase. This prompted discontinuation of the study. The authors theorized that preinduction of CYP3A4 by rifampin led to creation of a toxic metabolite of ritonavir or that inhibition of CYP3A4 by ritonavir blocked clearance of a rifampin metabolite, leading to toxicity.

Switch from atazanavir/ritonavir to unboosted atazanavir. Rodriguez-Novoa and colleagues presented data from a single-arm, open-label trial of 56 patients who changed from atazanavir/ritonavir to unboosted atazanavir after having adverse events from atazanavir/ritonavir such as jaundice or gastrointestinal distress. The average Cmax value dropped from 880 ng/mL to 283 ng/mL after switching to unboosted atazanavir. Four subjects (7%) had a Cmax value below the desired trough concentration of 150 ng/mL, 3 of whom were receiving tenofovir. The proportion of subjects with grade 3 or 4 bilirubin dropped from 29 (52%) to 7 (12%) after the switch. Virologic failure developed in 1 subject after a mean follow-up time of 10 months.

Conclusion

The 15th Conference on Retroviruses and Opportunistic Infections in Boston maintained the tradition of being the preeminent conference for the presentation of the latest data on antiretroviral therapeutics. This year’s meeting was characterized by a balance of new discoveries and consolidation of existing knowledge. The field remains dynamic and, although progress in both the developed and developing worlds has been impressive, major challenges remain if we are to deliver and sustain the benefits of antiretroviral therapy to the global population in need.

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Additional References