Advances in Antiretroviral Therapy

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2006 is the 25th anniversary of the AIDS epidemic and the 10th anniversary of the potent antiretroviral therapy era. During this period, the annual Conference on Retroviruses and Opportunistic Infections (CROI) has grown to represent one of the most important meetings of the year with respect to providing a forum for investigators to present the latest information on developments in the antiretroviral therapeutic arena. This year's conference maintained this tradition and was most notable for the presentations on new antiretroviral agents, therapeutic strategies including major results of treatment interruption studies, viral resistance, and encouraging results of antiretroviral rollout programs in the developing world which have brought us to the threshold of a new era in treatment and clinical investigation.

Investigational and New Antiretroviral Agents

Entry Inhibitors

TNX-355. Duensing and colleagues presented data on TNX-355, a humanized monoclonal antibody to CD4 (Abstract 158LB). They analyzed baseline samples from an ongoing phase II trial of TNX-355 in treatment-experienced subjects. All isolates were relatively sensitive to TNX-355 and sensitivity did not vary according to coreceptor tropism. They also examined paired samples from a phase I trial collected prior to treatment with TNX-355 and after 9 weeks of monotherapy. Resistance to TNX-355 was associated with a reduction in the maximal suppression achieved with TNX-355 rather than a shift of the inhibitory curve. TNX-355–resistant viruses became more sensitive to soluble CD4.

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Peptide Fusion Inhibitors. Delmedico and colleagues presented data on candidate peptide fusion inhibitors (Abstract 48). The goal of their development was to match or improve on the efficacy of enfuvirtide and to improve patient convenience. They presented data on 2 peptides. Enfuvirtide and the candidate fusion inhibitors block the binding of the heptad repeat (HR) 2 domain to the HR1 domain of gp41 in the "coil-coil interaction" prior to HIV fusion. The authors started with what they considered the optimized "slice" of the HR2 domain of gp41 (ie, the region of HR2 most important for this interaction). By itself, this peptide was very potent in vitro but had poor pharmacokinetic properties. They determined which amino acid residues of this peptide sequence were crucial for binding, and then set out to modify the peptide sequence while maintaining the crucial residues. The first strategy was to add helix stabilization motifs to the noncrucial residues, which yielded the peptide TRI-1144. The second strategy was to covalently add a fatty acid residue to the peptide yielding TRI-999. This peptide is stable in the presence of serum proteases. The pharmacokinetic profiles of these peptides were much improved compared with both the unmodified optimized "slice" of gp41 and enfuvirtide. Subcutaneous administration of these peptides to monkeys supported once-weekly administration. These peptides were potent in vitro and retained activity against enfuvirtide-resistant isolates.

CXCR4 Antagonists: KRH-3955 and KRH-3140. HIV entry requires binding of gp120 to a chemokine coreceptor (either CCR5 or CXCR4) after binding CD4. Utilization of the CXCR4 coreceptor becomes more common in treatment-experienced subjects and subjects with lower CD4+ cell counts. Tanaka and colleagues presented data on 2 candidate CXCR4 inhibitors (Abstract 49LB). They showed that these compounds bound CXCR4 but did not bind other chemokine receptors. They did not appear to cause any significant toxicity in rats and the compounds were orally bioavailable. These compounds seemed to be effective against CXCR4-tropic HIV in a severe combined immunodeficiency disease (SCID) mouse model.

PRO 140. Olson and colleagues presented data on PRO 140, a humanized IgG4 CCR5 monoclonal antibody (Abstract 515). They tested a single intravenous infusion of 0.1 to 5.0 mg/kg in healthy male subjects. The infusions were generally well tolerated and no significant toxicity was observed. The serum half-life was approximately 2 weeks. At the highest dose, the CCR5 receptors on lymphocytes remained coated with the antibodies through 60 days. No anti-PRO 140 antibodies developed in these patients and plasma levels of RANTES, one of the native chemokines that binds to CCR5, were unchanged.

Zinc Finger Protein Nucleases. Zinc finger proteins can be constructed to bind to specific DNA sequences of 9, 12, or 18 basepairs. Two zinc fingers coupled with FokI nucleases can pinpoint specific DNA sequences and introduce a targeted double-stranded break in the genome. Subsequent

repair can render the gene nonfunctional. Jouvenot and colleagues presented data using zinc finger nucleases to target the ***CCR5*** gene (Abstract 51). The CCR5 coreceptor is required for entry of CCR5-tropic HIV into CD4+ cells. They showed that CCR5 could be disrupted in 2 different cell lines, and these cells were protected against infection with CCR5-tropic HIV. The practical introduction of the zinc finger nucleases into CD4+ cells for possible clinical use still needs to be optimized.

Aprepitant. Wang and colleagues presented in vitro data on aprepitant (Abstract 511). This drug has been approved by the US Food and Drug Administration (FDA) for the treatment of chemotherapy-related nausea. It is a neurokinin-1 receptor antagonist. In vitro studies suggest that it downregulates CCR5 expression. The authors tested the antiretroviral activity of aprepitant in an in vitro cell culture system. Consistent with the mechanism of action, they found that aprepitant inhibited HIV infection with CCR5-tropic (but zidovudine-resistant) HIV, and was additive or synergistic with other currently approved antiretrovirals. It had no activity against a CXCR4-tropic strain.

Vicriviroc. Greaves and colleagues presented data from a treatment-naive study comparing the CCR5 antagonist, vicriviroc, with efavirenz—each given with fixed-dose zidovudine/lamivudine (Abstract 161LB). All subjects received 2 weeks of monotherapy with 1 of 3 doses of vicriviroc or placebo. Then all subjects received open-label zidovudine/lamivudine and subjects receiving placebo were changed to open-label efavirenz. The median CD4+ cell count at baseline was 290/µL and the mean plasma HIV-1 RNA level was 4.8 $\log_{10}$ copies/mL. After 14 days of monotherapy, all 3 doses of vicriviroc (25, 50, and 75 mg) were associated with a significantly greater decline in plasma HIV-1 RNA (0.8, 1.2, and 1.3) than with placebo (0.1; $P < .001$). The study was stopped early by the Data and Safety Monitoring Board because of increased virologic breakthrough in the vicriviroc arms. At the time the study was stopped, 56%, 41%, and 17% of subjects in the 3 vicriviroc arms experienced virologic breakthrough compared with 4% in the efavirenz arm. Subjects taking regimens that failed generally developed the M184V mutation (associated with lamivudine resistance). The authors did not present data on resistance to vicriviroc. Coreceptor tropism shifts were generally infrequent and occurred in both the vicriviroc and placebo arms. There were no significant safety concerns reported.

Reverse Transcriptase Inhibitors

GS9148. Cihlar and colleagues presented data on an adenosine-analogue nucleotide reverse transcriptase inhibitor (RTI), GS9148, and its prodrug (Abstract 45). These compounds have low cytotoxicity, low potential for mitochondrial toxicity, and achieve good intracellular levels in peripheral blood mononuclear cells (PBMCs). The median effective concentrations (EC_{50}) for these compounds are 3.5 and 0.09 µM, respectively. They are active in vitro against many different subtypes of HIV. GS9148 retained antiretroviral activity against clinical isolates with 4 to 5 thymidine analogue-associated mutations (TAMs; with and without M184V), K65R, and the T69 insert. A clinical isolate with Q151M was associated with a 3-fold change in susceptibility to GS9148. A serial passage experiment generated resistant isolates in vitro with the K70E mutation. The prodrug had good bioavailability in a dog model which favored once-daily dosing (Abstract 498).

1-(ß-D-Dioxolane) Thymine. This compound is a substrate for thymidine kinase. Prior studies have shown that 1-(ß-D-Dioxolane) Thymine (DOT) has low cytotoxicity, low potential for mitochondrial toxicity, and is orally bioavailable in monkeys (>95%). Lennerstrand and colleagues presented data on the in vitro activity of DOT against a panel of site-directed HIV drug-resistant mutants (Abstract 46). The EC_{50} was not significantly changed from that of wild-type by the presence of M184V or 4 to 5 TAMs. Low-level resistance was seen with K65R. However, significant resistance was observed in the presence of Q151M.

ß-D-2,6-Diaminopurine Dioxolane. Margolis and colleagues presented the results of AIDS Clinical Trials Group (ACTG) 5165, a phase I/II study of β-D-2,6-diaminopurine dioxolane (DAPD) with mycophenolate mofetil (MMF) or placebo in addition to optimized antiretroviral background (Abstract 517) in treatment-experienced persons. The primary endpoint was viral load change from baseline after a 2-week period of functional monotherapy. MMF did not enhance the activity of DAPD. After combining both groups, DAPD was associated with a 0.29-$\log_{10}$ reduction in plasma HIV-1 RNA after 2 weeks. Three of 40 (8%) subjects maintained at least a 0.5-$\log_{10}$ reduction in plasma HIV-1 RNA after 24 weeks of treatment with DAPD. DAPD appeared safe and well tolerated.

Dexelvucitabine. Erickson-Viitanen and colleagues presented the correlation of genotypic and phenotypic resistance with virologic efficacy in a study of dexelvucitabine (formerly DPC-817 or DFC; Abstract 632). The main results of study RVT-203 have been presented previously (Cohen, IAS, 2005). The study participants were treatment experienced and 58% had either 3 or 4 TAMs at baseline. The only mutation associated with baseline phenotypic resistance to dexelvucitabine and poorer virologic efficacy was the Q151M mutation. No specific mutations emerged in the subjects in whom dexelvucitabine was failing.

Nucleoside Competing Reverse Transcriptase Inhibitors. Nucleotide competing reverse transcriptase inhibitors (NcRTIs) bind to the active site of reverse transcriptase, but unlike nucleoside (or nucleotide) analogue reverse transcriptase inhibitors (nRTIs) they are not incorporated into the DNA chain and their structure is not similar to nucleotides. Prior data have shown

in vitro activity of the prototype compound NcRTI-1. Ehteshami and colleagues provided more detailed information about the mechanism of action of this agent (Abstract 47). NcRTI-1 traps reverse transcriptase in the post-translocation state (ie, after reverse transcriptase translocates by 1 base pair prior to binding a new nucleotide). This binding forms a stable dead-end complex. NcRTI-1 binds preferentially after the incorporation of a pyrimidine, but the nature of the template base pair does not appear to matter. Jochmans and colleagues reported on the in vitro activity of NcRTI-1 against a wide panel of HIV-1 isolates (n = 6000; Abstract 500). The antiretroviral activity of NcRTI-1 was diminished in the presence of the combination of M184V and Y115F. Hypersusceptibility was observed in the presence of K65R.

Maturation Inhibitors

UK-201844. Blair and colleagues presented data on a new maturation inhibitor. It prevents cleavage of gp160 and renders the virion noninfectious (Abstract 50LB). However, the in vitro antiviral activity is limited and it is not active against most clinical isolates. This compound, however, provides evidence of a potential new mechanism to inhibit maturation of HIV-1.

PA-457. PA-457 is a maturation inhibitor that blocks cleavage of the CA-SP1. Smith and colleagues presented pharmacokinetic and pharmacodynamic data from a 10-day monotherapy study in humans (Abstract 52). The primary results have been presented previously. The highest dose resulted in a median drop in plasma HIV RNA of 1.1 $\log_{10}$ copies/mL at day 10; however, several study subjects did not respond despite the presence of comparable drug levels in their plasma. The basis for variable responses among the study subjects remains to be explained. The pharmacokinetic data showed that the half-life was about 70 hours. Drug exposure (24-hour area under the curve, or AUC_{24}) accounted for 88% of the variability of antiviral response. The authors noted that the maximal antiviral response was not achieved with the highest dose studied suggesting that higher doses should be considered. Adamson and colleagues presented data on the generation of resistance to PA-457 in vitro (Abstract 156). Serial passage experiments selected mutations at the CA-SP1 cleavage site consistent with the purported mechanism of action. Further in vitro studies suggest that PA-457 is either additive or synergistic with other antiretrovirals (Abstract 509).

Integrase Inhibitors

MK-0518. Grinsztejn and colleagues presented data from a phase II study of MK-0518, an HIV-1 integrase inhibitor, in treatment-experienced subjects (Abstract 159LB). This study compared 3 doses of MK-0518 (200, 400, or 600 mg bid) or placebo given with an optimized background regimen. Subjects were required to have genotypic or phenotypic resistance to at least 1 drug from each of 3 classes. The mean baseline CD4+ counts were between 220 and 283 cells/μL in the 4 groups, and the mean baseline plasma HIV-1 RNA level was 4.6 to 4.8 $\log_{10}$ copies/mL. Forty to fifty percent of each group was phenotypically resistant to all antiretroviral drugs in the optimized background regimen. All 3 MK-0518 doses were significantly more likely than placebo to achieve an HIV-1 RNA level below 50 copies/mL at week 16 (56% to 72% for MK-0518 compared with 20% for placebo). Most side effects were mild to moderate and none appeared to be associated with MK-0518 compared with placebo.

GS-9137. DeJesus and colleagues presented phase I data on GS-9137, an HIV-1 integrase inhibitor (Abstract 160LB), given for 10 days as monotherapy. GS-9137 inhibits the strand-transfer step in the HIV integration process. The levels of GS-9137 are increased 20-fold when coadministered with 100 mg of ritonavir. The study included 40 subjects: 25 were treatment experienced and 15 were treatment naive. Subjects were randomized to 1 of 5 doses or placebo. The baseline plasma HIV-1 level was 4.75 $\log_{10}$ copies/mL, and the mean CD4+ count was 442 cells/μL. All subjects completed the study and there were no drug discontinuations. The pharmacokinetic analysis supported once-daily dosing when administered with ritonavir, and twice-daily dosing without ritonavir. The mean change in plasma HIV-1 RNA level was greatest for the 400 mg twice daily (–1.98 $\log_{10}$ copies/mL), 800 mg twice daily (–1.78 $\log_{10}$ copies/mL), and 50 mg with ritonavir 100 mg once daily (–2.03 $\log_{10}$ copies/mL) groups. All doses achieved a significantly greater decline in HIV-1 RNA than placebo ($P < .01$). There were no serious adverse events, and no adverse events appeared to be more common with GS-9137. The most common events reported were headache, nausea, and diarrhea.

Protease Inhibitors

SPI-256. Gulnik and colleagues presented data on a new protease inhibitor (PI), SPI-256 (Abstract 501). The in vitro activity of this PI was evaluated against a variety of clinical isolates using phenotypic analysis. The median inhibitory concentration (IC_{50}) for SPI-256 was 0.3 nM against wild-type and 3.9 nM against PI-resistant viruses. SPI-256 was 4 to 50 times more potent than currently available PIs (tipranavir was not tested) against highly PI-resistant HIV.

Trials with Current Antiretroviral Agents

Treatment of Antiretroviral-Naive Patients

Malan and colleagues (Abstract 107LB) presented the 48-week results of a 96-week, open-label trial comparing the efficacy of atazanavir 300 mg/ritonavir 100 mg (n = 95) with atazanavir 400 mg (n = 105) in combination with lamivudine/stavudine in antiretroviral-naive HIV-1–infected subjects. At baseline, mean CD4+ count and plasma HIV-1 RNA level were 235 cells/μL and 4.95 $\log_{10}$ copies/mL, respectively, and were not statistically significantly dif-

ferent between the groups. In the intent-to-treat (ITT) analysis, 75% of individuals in the ritonavir-boosted (/r) atazanavir arm versus 70% in the atazanavir arm reached plasma HIV-1 RNA below 50 copies/mL (***P***, not significant). Adverse event-related discontinuations occurred more commonly in the atazanavir/r group (8%) than in the atazanavir group (1%), most commonly due to hyperbilirubinemia. Three patients in the atazanavir/r group and 10 in the atazanavir group experienced virologic failure, defined as a plasma HIV-1 RNA level above 400 copies/mL. Resistance testing showed no major PI mutations and 1 nRTI mutation (to lamivudine) in the atazanavir/r group. In the atazanavir group there was 1 major PI mutation and 7 lamivudine-associated mutations.

In ACTG 5095, 1147 treatment-naive patients were randomized to receive zidovudine/lamivudine/abacavir; zidovudine/lamivudine with efavirenz; or zidovudine/lamivudine/abacavir with efavirenz. The zidovudine/lamivudine/abacavir arm was stopped early due to virologic inferiority compared with efavirenz-based regimens (Gulick et al, ***NEJM***, 2004). Gulick and colleagues (Abstract 519) presented the results of an open-label rollover study of tenofovir or efavirenz intensification in 170 patients who received zidovudine/lamivudine/abacavir and had plasma HIV-1 RNA below 200 copies/mL. Baseline characteristics were similar between both groups: mean CD4+ cell count was 484/µL and 73% had plasma HIV-1 RNA below 50 copies/mL. Overall, treatment failure (2 successive plasma HIV-1 RNA levels >200 copies/µL) occurred in 19% of subjects; there was no statistically significant difference between the 2 arms. Rate and time to virologic failure, rate and time to treatment discontinuation, CD4+ cell count response, new grade 3 or 4 adverse events, self-report of adherence, and emergence of viral resistance at the time of virologic failure were not statistically significantly different between the 2 groups over a median of 1.5 years of follow-up.

Optimal CD4+ Cell Count at Which to Initiate Antiretroviral Therapy

The optimal CD4+ cell count at which to initiate antiretroviral therapy remains unclear and currently there are no randomized controlled clinical trials underway to address this issue. Using data from a number of large cohort datasets, Sterne and colleagues (Abstract 525) attempted to address this question as others have done (eg, Egger et al, ***Lancet***, 2002). The authors reviewed data from antiretroviral-naive individuals in the Antiretroviral Therapy Cohort Collaboration (ART-CC) and compared them with the pre-antiretroviral therapy data from the Multicenter AIDS Cohort Study (MACS). At initiation of antiretroviral therapy, CD4+ count was at or below 200 cells/µL, 201 to 350 cells/µL, and 351 to 500 cells/µL in 40%, 37%, and 23% of individuals, respectively. The median length of follow-up was 2.7 years. Individuals who initiated treatment with CD4+ count at or below 200 cells/µL had higher rates of progression to AIDS and death than those who initiated therapy between 201 and 350 cells/µL (hazard ratio [HR] for AIDS, 3.68; 95% confidence interval [CI], 3.01–4.51; HR for AIDS and death, 2.93; 95% CI, 2.41–3.57). Starting antiretroviral therapy with a CD4+ count between 351 and 500 cells/µL, compared with a CD4+ count between 201 and 350 cells/µL, correlated with an increased risk of AIDS in the latter group (HR, 1.52; 95% CI, 1.10–2.10). The authors concluded that rates of progression to AIDS were lower in individuals who initiated antiretroviral therapy at higher CD4+ cell counts. Additional data are needed before current guidelines for the initiation of therapy are changed but the field may be witnessing a pendulum shift to earlier initiation of therapy in the years ahead.

Differences between treatment regimens and the degree to which individuals must adhere to medications to maintain virologic suppression ("forgiveness") is poorly understood. Gross and colleagues (Abstract 533) evaluated the relative forgiveness of PI-, nonnucleoside analogue reverse transcriptase inhibitor (NNRTI)-, and PI/r-based regimens by analyzing the association between adherence to different regimens and viral suppression. In the highly active antiretroviral therapy (HAART) Observational Medical Evaluation and Research (HOMER) Cohort, 1634 treatment-naive patients with at least 2 plasma HIV-1 RNA levels below 500 copies/mL were studied. At baseline, 46% of individuals were on PI-, 38.6% on NNRTI-, and 15% on PI/r-based regimens. The median baseline CD4+ cell count was 200/µL and the median time of follow-up was 29 months. Six hundred and six patients (37.1%) had virologic breakthrough, which was defined as a plasma HIV-1 RNA level above 1000 copies/mL. Risk of virologic breakthrough was most strongly associated with less than 95% adherence in the PI group (HR, 1.78; 95% CI, 1.41–2.29) followed by the NNRTI group (HR, 1.47; 95% CI, 1.01–2.14). Adherence above 95% was not associated with virologic breakthrough in the PI/r group. The authors concluded that boosted PIs are more forgiving than unboosted PI- and NNRTI-based regimens with respect to adherence—an expected result.

Treatment of Antiretroviral-Experienced Patients

Results of select treatment-strategy studies in antiretroviral-experienced individuals are summarized in Table 1.

Etravirine. Vingerhoets and colleagues presented the genotypic and phenotypic predictors of response to etravirine (formerly TMC125) in the TMC125-C223 trial (see Table 1; Abstract 154). Etravirine is a novel investigational NNRTI with antiretroviral activity against HIV resistant to currently available NNRTIs. The primary results of TMC125-C223 have been presented previously (Grossman, ICAAC, 2005). The etravirine arms (400 mg or 800 mg bid) had a significantly greater reduction in plasma HIV-1 RNA levels at week

Table **1**. Selected Antiretroviral Studies in Treatment-Experienced Patients

Study Name (Abstract No.) Description	Regimen(s) (No. of Patients)	Population	Baseline CD4+ Count (cells/μl)	Plasma HIV RNA (log_{10} copies/mL)	Follow-up	Response	Comments
TMC125-C223 (Abstract 154) Analysis of baseline resistance in TMC125-C223	Best available PI plus nRTIs with or without enfuvirtide (n=40) versus etravirine 800 mg bid plus lopinavir/r plus nRTIs with or without enfuvirtide (n=79)	3 or more major PI mutations, NNRTI resistance at screening or by history	99 (median)	4.7 (median)	24 weeks	Plasma HIV RNA change –0.19 versus –1.18 log_{10} copies/mL ($P < .05$)	Virologic response was related to number of NNRTI mutations at entry: –1.82 log_{10} copies/mL with 0 mutations, –1.65 with 1, –1.0 with 2, –0.66 with 3 or more; all were significantly better than control group.
POWER 1 and POWER 2 (Abstract 157) Analysis of baseline resistance in the combined POWER 1 and 2 studies	Best available PI (n=112) versus darunavir 600 mg/r 100 mg twice daily plus nRTIs with or without enfuvirtide (n=112)	1 or more major PI mutation, 3-class experience	141 (median; Katlama, CROI, 2005)	4.6 (median)	24 weeks	47% had HIV RNA <50 copies/mL versus 25% of control subjects receiving a sensitive PI (n=31) versus 9% receiving a resistant PI (n=81; $P < .001$)	V32I, L33F, I47V, and I54M were identified as key mutations for darunavir when present with many other PI mutations. They were associated with resistance when present at baseline or they emerged with loss of virologic response.
Protocol 005 (Abstract 159LB) Phase II, randomized, placebo-controlled trial	MK-0518 200 mg (n=24), 400 mg (n=26), or 600 mg (n=24) twice daily versus placebo (n=25) with optimized background regimen	3-class experienced, HIV RNA >5,000 copies/mL	220 to 283 (mean)	4.6 to 4.8 (mean)	16 weeks	56% to 72% of the MK-0518 groups had HIV RNA <50 copies/mL versus 16% in the control group	Safety profile was similar between control group and the 3 MK-0518 groups.
ACTG 5165 (Abstract 517) Phase I/II, randomized, placebo-controlled study	DAPD plus placebo versus DAPD plus mycophenolate mofetil plus optimized background regimen	CD4+ count >50 cells/μL; HIV RNA >2000 copies/mL	184 (median)	4.5 (median)	2 weeks of functional monotherapy	0.35 versus 0.24 log_{10}-copies/mL decrease in HIV RNA; (P = NS)	Response to DAPD was diminished with K65R, Q151M complex, and having 5 or more nRTI resistance mutations at baseline.
Darunavir/r plus etravirine in treatment-experienced subjects (Abstract 575c) Single-arm, open-label pilot study	Darunavir/r, etravirine, nRTIs with or without enfuvirtide (n=11)	3-class resistance	75 (median)	4.6 (median)	6 weeks	HIV RNA: 5 of 10 subjects with <50 copies/mL, 8 of 10 with <400 copies/mL	Primary endpoint was pharmacokinetic interaction of darunavir and etravirine.

bid indicates twice daily; nRTI, nucleoside (or nucleotide) analogue reverse transcriptase inhibitor; NNRTI, nonnucleoside analogue reverse transcriptase inhibitor; NS, not significant; PI, protease inhibitor; /r, ritonavir-boosted.

24 than the control group (1.04 and 1.18 $\log_{10}$ copies/mL versus 0.19; $P < .05$). The authors discussed the relationship of baseline genotypic resistance to virologic outcomes. The number of NNRTI mutations predicted the phenotypic resistance to etravirine ranging from 0.6-fold change with no NNRTI mutations to 3.1-fold change with 3 or more mutations. Twelve percent of baseline isolates had a greater than 10-fold change to etravirine. The number of NNRTI mutations present at baseline predicted virologic response: 1.8- with zero, 1.7- with 1, 1.0- with 2, and 0.7-$\log_{10}$ copies/mL decrease in plasma HIV-1 RNA with 3 or more NNRTI mutations.

Darunavir. De Béthune and colleagues presented the relationship of baseline and treatment-emergent genotypic mutations in HIV protease to the antiretroviral efficacy of darunavir- (formerly TMC114) containing regimens (Abstract 157). Darunavir is available through an expanded access protocol. This analysis used data from the previously presented POWER 1 and POWER 2 studies as well the POWER 3 study, which has not been presented. Only subjects receiving 600 mg of darunavir twice daily were included. All 3 of these studies enrolled highly treatment-experienced subjects. The virologic response to a darunavir-containing regimen appeared diminished in those subjects with 10 or more PI-associated resistance mutations at baseline. The V32I, L33F, I47V, I54L, and L89V mutations appear to be associated with decreased virologic efficacy of darunavir when present at baseline and these mutations emerged during virologic failure. These mutations had to be present with many other mutations to be associated with resistance. Isolates that were susceptible to tipranavir at baseline remained sensitive at the time of virologic failure on darunavir.

Darunavir/Etravirine. Boffito and colleagues reported on the combination of darunavir and etravirine given with an optimized background regimen in 10 highly treatment-experienced subjects (Abstract 575c). The pharmacokinetic profile of each drug was assessed after 28 days and compared with historic controls. They found that the profile for darunavir was not significantly different from the historic control, and the levels of etravirine were reduced by about 30%. The authors did not feel that this was clinically relevant. At week 12, all subjects had plasma HIV-1 RNA levels below 400 copies/mL and 8 of 10 had less than 50 copies/mL.

Acute HIV Infection

Patterson and colleagues (Abstract 370) presented the results of an enhanced HIV testing strategy to detect acute and established HIV infection in pregnant women in North Carolina as part of the Screening and Tracing Active Transmission (STAT) Program. The authors reported that among 187,135 women, 16 were found to have acute infection. Of these women, 5 were pregnant at the time of the diagnosis; no infants were infected. During the study period (from 2002 through 2005), 3 of 6 HIV-1-infected infants born in North Carolina were born to women who had been screened and were seronegative early in the pregnancy. To reduce residual mother-to-child transmission (MTCT), the authors suggested early testing in pregnancy, repeat testing in the third trimester, and pooled HIV-1 RNA screening of all antibody-negative women.

Brenner and colleagues (Abstract 373) reported the results of a population-based surveillance of primary HIV-1 infections in Quebec between 1997 and 2005. Fifty percent (298 of 598) of subtype B HIV-1 infections were present in 71 transmission clusters (2 to 14 persons per cluster). Thirty percent of transmission clusters included individuals with more than 5 partners 3 months prior to diagnosis. Nonsubtype B HIV-1 infections represented 16% of recent and 9% of primary infection in Quebec. The prevalence of resistance mutations to a single drug class and 2 or more drug classes was 10.4% and 3.8%, respectively, in transmission clusters.

Mendoza and colleagues (Abstract 383) examined viral tropism among 240 individuals with recent HIV infection in Spain. Mean time of infection was 7 months; 16.3% of individuals were infected with X4-tropic virus, and the rate of primary drug resistance was 10.7%; 8.2% of individuals were infected with nonsubtype B HIV-1. There was no association between HIV coreceptor tropism and plasma HIV-1 RNA level, HIV subtype, or drug resistance mutations. Persons infected with HIV-1 through intravenous drug use had a higher proportion of X4-tropic viruses than those infected through sexual contact (54% versus 14.3%, respectively; $P < .01$). Individuals infected with X4-tropic virus tended to have higher HIV-1 RNA levels 1 year after exposure than individuals infected with R5-tropic virus.

Cachay and colleagues (Abstract 392) examined the effect of HSV-2 infection on the plasma HIV-1 RNA level during early and acute HIV-1 infection. Among 295 individuals with early infection, 41.7% were seropositive for HSV-2 virus. Baseline and 6-month plasma HIV-1 RNA levels did not differ significantly between HSV-2 seropositive and seronegative individuals.

Kassutto and colleagues (Abstract 391) presented data on the efficacy of antiretroviral therapy initiated during primary and early HIV-1 infection (≤12 months after seroconversion) among 102 subjects. Median time of follow-up was 40 months; 99 (97%) individuals reached plasma HIV-1 RNA below 50 copies/mL. In 91% and 86% of subjects, plasma HIV-1 RNA level was maintained below 50 copies/mL at months 12 and 36, respectively. There were no differences in response between subjects who initiated antiretroviral treatment before or after seroconversion or by treatment regimen (PI- or NNRTI-based). Median time to plasma HIV-1 RNA below 50 copies/mL was 11.1 weeks. Median CD4+ cell count at 12 months was 702/μL.

Chaix and colleagues (Abstract 397) compared the response to antiretroviral therapy between patients with B or

non-B subtype HIV-1 infection who initiated treatment during acute infection (≤1 month after diagnosis). Between 1996 and 2005, 584 subjects were enrolled in the French PRIMO Cohort Study. Among 312 individuals who initiated treatment, 71 (23%) were infected with nonsubstype B strains. Since 2001, the proportion of patients infected with nonsubtype B HIV-1 increased from 16% to 27%. Baseline CD4+ cell counts were lower in the nonsubtype B group (442/μL versus 490/μL; ***P*** = .020), and plasma HIV-1 RNA levels were similar between the 2 groups. Overall, 88% of individuals received PI-based and 12% received NNRTI-based therapy. After 12 months of therapy, the CD4+ cell counts did not differ significantly between the 2 groups and 73% of individuals with subtype B, compared with 82% of individuals with nonsubtype B virus, achieved plasma HIV-1 RNA levels below 400 copies/mL (***P*** = .04).

Streeck and colleagues (Abstract 398) presented the results of short-course antiretroviral treatment on immunologic and virologic parameters in a group of acutely infected individuals. Twelve individuals initiated 24 weeks of antiretroviral therapy (median time from infection to initiation of therapy was 25.3 days); 12 individuals remained off therapy. Baseline plasma HIV-1 RNA levels and CD4+ cell counts were similar in the 2 groups. Baseline HIV-1 specific interferon (IFN)-γ and CD8+ T-cell responses did not differ between the 2 groups. There was an overall increase in the HIV-1 specific IFN-γ and CD8+ T-cell responses over 48 weeks; the increase was greater in the treated subjects. At week 24, everyone in the treated group achieved a plasma HIV-1 RNA level below 50 copies/mL; at 48 weeks, CD4+ cell counts and HIV-1 RNA levels did not differ significantly between the 2 groups.

Treatment Strategies

Results of select treatment-strategy studies in antiretroviral-experienced individuals are summarized in Table 2.

NEFA Study

Martínez and colleagues (Abstract 521) presented results from a multicenter, randomized, open-label study of 460 participants on PI-based regimens with HIV-1 RNA below 200 copies/mL randomized to switch PI to: nevirapine (n=155); efavirenz (n=156); or abacavir (n=149). All patients continued therapy with 2 nRTIs. At baseline, the most common regimens were stavudine/lamivudine/indinavir; zidovudine/lamivudine/indinavir; and stavudine/lamivudine/nelfinavir. Baseline median CD4+ cell counts were 508/μL, 558/μL, and 544/μL in the nevirapine, efavirenz, and abacavir arms, respectively. At 3 years, according to the ITT analysis, more patients switching from PI to abacavir reached the primary endpoint of death, virologic failure, or progression to AIDS: 34 (23%) compared with 23 (15%) and 17 (11%) in the efavirenz and nevirapine arms, respectively (***P*** = .031). Among individuals receiving prior mono- or dual therapy with nRTIs, those in the abacavir arm had a significantly greater risk of virologic failure than those in the nevirapine or efavirenz arms: 36% versus 11% and 8%, respectively (***P*** < .001). Individuals without prior suboptimal nRTI therapy had similar rates of virologic failure in all 3 arms (2% to 5%). There were fewer discontinuations in the abacavir arm due to clinical and laboratory adverse events. The most common adverse event in the efavirenz arm was neuropsychiatric symptomatology. Individuals in the abacavir arm had significantly lower median cholesterol levels than those in the nevirapine or efavirenz arms at 12, 24, and 36 months. Stopping the PI was associated with a decrease in body fat in all 3 arms: prevalence of moderate to severe lipohypertrophy decreased among all patients from 20% at baseline to 12% at 36 months (***P*** = .017); moderate to severe lipoatrophy significantly increased among all individuals from 27% at baseline to 45% at 36 months; there were no significant difference between treatment arms.

Nasta and colleagues (Abstract 523) presented results of a 48-week, open-label, randomized prospective study of individuals who were randomized to maintain current treatment (arm A, n=102) or add lopinavir/r (arm B, n=99). Subjects were lopinavir/r-naive, had a history of 2 or more failed regimens, and HIV-1 RNA level between 1000 and 20,000 copies/mL. Mean baseline CD4+ cell counts and plasma HIV-1 RNA levels were 422/μL and 3.6 $\log_{10}$ copies/mL, respectively. At week 48, mean plasma HIV-1 RNA decrease was 0.16 $\log_{10}$ copies/mL and 1.4 $\log_{10}$ copies/mL in arm A and B, respectively. Forty-nine percent of subjects in arm B reached a plasma HIV-1 RNA level below 50 copies/mL versus none in arm A. Eleven individuals (10%) in arm A versus 3 (3%) in arm B achieved plasma HIV-1 RNA levels above 30,000 copies/mL or CD4+ cell count above 200/μL (***P*** = .03). Sixty-nine percent of subjects in arm A were on a PI-sparing regimen. There was no change in the total number of mutations at week 48, and a small decrease in mean number of protease mutations (from 3.2 to 2.8; ***P*** = .006).

Katlama and colleagues (Abstract 520) presented the combined week-48 results of the RESIST-1 and RESIST-2 trials. This study compared tipranavir/r to comparator PIs (CPIs) with optimized background in subjects with 3-drug class experience. Patients had 1 or more major protease mutations (D30N, M46I/L, G48V, I50V, V82A/F/L/T, I84V, L90M) and fewer than 3 mutations at codons 33, 82, 84, and 90. At study entry, 746 individuals were randomized to the tipranavir/r arm and 737 to CPI/r arm. Baseline mean CD4+ cell counts were 196/μL and 195/μL, in the tipranavir/r and CPI/r arms, respectively; mean plasma HIV-1 RNA level was 4.73 $\log_{10}$ copies/mL in both arms. The CPIs included lopinavir/r, indinavir/r, saquinavir/r, and amprenavir/r.

The week-48 risk of not achieving a 1-$\log_{10}$ copies/mL or greater reduction in plasma HIV-1 RNA level was 39% lower in the tipranavir/r than in the CPI/r arm (HR, 0.63; ***P*** < .0001). The proportion of subjects who reached plasma HIV-1 RNA levels below 50 copies/mL was higher in the tipranavir/r

Table **2**. Treatment Strategies in Antiretroviral-Experienced Patients

Study Name (Abstract No.) Description	Study Arm (No. of Patients)	Baseline HIV-1 RNA (copies/mL)	Baseline CD4+ Count (cells/μL)	Plasma HIV-1 RNA Response (copies/mL)	CD4+ Count Change (cells/μL)	Comments
ACTG 5170 (Abstract 101) 96-week multicenter prospective study Patients had been on antiretroviral therapy for ≥6 months, had plasma HIV-1 RNA <55,000 copies/mL, and CD4+ count >350 cells/μL at baseline. Primary endpoint defined as time to CD4+ count <250 cells/μL, or AIDS-related event or death.	STI (n=167)	71% with <50	833 (median); 436 (median nadir)	+3 $\log_{10}$ (mean) in first 8 weeks; no change thereafter	–20/week (mean) in first 8 weeks; –1.7/week (mean) thereafter	Nadir CD4+ count <400 cells/μL and baseline plasma HIV RNA >400 copies/mL were associated with higher likelihood of reaching endpoint (HR=1.95 and 2.75, respectively). 46 patients restarted therapy. Of 5 deaths, 3 were coronary artery disease-related
STACCATO (Abstract 102) CD4+ count-guided STI compared with continuous therapy for a median of 21.9 months Patients had CD4+ count >350 cells/μL and plasma HIV RNA <50 copies/ml. Treatment restarted at CD4+ count <350 cells/μL in the STI arm. At study end all patients resumed continuous therapy.	STI (n=299)	4.72 $\log_{10}$ (median)	470 (median)	NA	374 (median) 60.5% with >350	After resuming therapy, 91% in STI and 92% in continuous therapy (P = .9) arms achieved plasma HIV-1 RNA <50 copies/mL. 85.9% in the STI and 96.9% in the continuous therapy arms reached CD4+ count >350 cells/μL. 17 patients (5.8%) in STI arm had acute retroviral syndrome. Of 2 deaths (1 in STI arm), none were AIDS-related.
	Continuous therapy (n=154)	4.76 $\log_{10}$ (median)	506 (median)	NA	601 (median); 96.2% with >350	
ISS PART (Abstract 103) Randomized comparison of STI versus continuous antiretroviral therapy in patients with viral suppression Primary endpoint was defined as the proportion of patients with CD4+ count >500 cells/μL at 24 months.	24-month continuous therapy (n=137)	<400	768 (mean)	92.3% with <400 at 24 months	+6 (median) 86.5% with >500 at 24 months	Only 56 patients in STI arm at end of study. In ITT analysis, cumulative risk of plasma HIV RNA >400 was 24% in continuous therapy and 26% in STI arms. Cumulative risk of resistance (≥1 mutation) at 24 months in STI arm was 30%. Unboosted PI and archived mutations in proviral DNA independently associated with higher risk of resistance during STI. Resistance associated with increased risk of failure (HR, 2.64).
	1- to 3-month STI (n=136)	<400	714 (mean)	91.1% with <400 at 24 months	–26 (median) 69.1% with >500 at 24 months	

Table **2**. Treatment Strategies in Antiretroviral-Experienced Patients (continued)

Study Name (Abstract No.) Description	Study Arm (No. of Patients)	Baseline HIV-1 RNA (copies/mL)	Baseline CD4+ Count (cells/μL)	Plasma HIV-1 RNA Response (copies/mL)	CD4+ Count Change (cells/μL)	Comments
ANRS 106 WINDOW (Abstract 104) A 96-week prospective randomized trial of IT in patients with CD4+ count >450 cells/μL and plasma HIV RNA <200 copies/mL.	8 weeks on, 8 weeks off IT (n=197)	<200	739 (median)	81% with <400 at 96 weeks	–155 (median)	3.6% and 1.5% in the IT and continuous arms, respectively, reached CD4+ count <300 cells/μL.
	Continuous therapy (n=194)	<200	748 (median)	90% with <400 at 96 weeks (P = .02)	-8 (median)	3 patients in the IT arm developed acute retroviral syndrome.
ANRS 1269 TRIVACAN (Abstract 105LB) 24-month- randomized comparison of CD4+ count-guided therapy with continuous therapy. Patients had CD4+ count >350 cells/μL and plasma HIV RNA <300 copies/mL. Initiation and interruption threshold of 250 to 350 cells/μL, respectively. The CD4+ count-guided therapy arm was stopped early due to increased morbidity.	Continuous therapy (n=110)	<300	461 (median)	NA	600 (mean)	Incidence of serious morbidity was 5.7% in continuous therapy versus 17.6% in CD4+ count-guided therapy arm (mainly due to invasive bacterial infections). The fixed treatment interruption arm (2 months off/4 months on treatment) is ongoing.
	CD4+ count-guided therapy (n=216)	<300	457 (median)	NA	300 to 350 (mean range)	
SMART (Abstract 106LB) Randomized comparison of episodic CD4+ count-guided therapy with continuous therapy Initiation and interruption threshold of 250 to 350 cells/μL, respectively, in the drug conservation arm.	Continuous therapy (n=2736)	70.8% with <400	599 (median)	NA	NA	33% versus 93% of follow-up time on therapy in the continuous versus drug conservation therapy arms. 3.1% versus 0.8% of follow-up time at CD4+ count <200 cells/μL. Relative risks of clinical disease progression or death, nonfatal cardiovascular disease, and nonfatal renal events in the drug conservation versus continuous therapy arms were 2.5, 1.5, and 2.5, respectively (P < .0001).
	Drug conservation (n=2736)	71.0% with <400	596 (median)	NA	NA	

HR indicates hazard ratio; IT, intermittent therapy; ITT, intent-to-treat analysis; NA, not available; STI, scheduled treatment interruption.

arm than in the CPI/r arm, regardless of the PI (23.9% in the tipranavir/r arm versus 16.8% in the lopinavir/r arm; 22.4% in the tipranavir/r arm versus 6.2% in the saquinavir/r arm), baseline CD4+ cell counts, or baseline plasma HIV-1 RNA levels. Individuals who initiated tipranavir/r with higher baseline CD4+ cell counts or lower baseline plasma HIV-1 RNA levels were more likely to achieve plasma HIV-1 RNA reduction than those with lower baseline CD4+ cell counts or higher plasma HIV-1 RNAs. Forty-two percent of subjects with baseline CD4+ cell count above 200/µL compared with 18% of individuals with baseline CD4+ cell counts below 50/µL achieved a 1-$\log_{10}$ copies/mL or greater reduction in plasma HIV-1 RNA level at week 48. Over 50% of individuals who started tipranavir/r with a baseline plasma HIV-1 RNA level below 10,000 copies/mL compared with 26% of individuals with a baseline plasma HIV-1 RNA level above 100,000 copies/mL achieved a 1-$\log_{10}$ copies/mL or greater reduction in plasma HIV-1 RNA level at week 48.

Swindells and colleagues (Abstract 108) presented the 24-week results from the ACTG 5201. This was a prospective open-label, single-arm study of simplified maintenance antiretroviral therapy with atazanavir/r in individuals with plasma HIV-1 RNA levels below 50 copies/mL on 48 or more weeks of a regimen of 2 nRTIs plus a PI. Thirty-six individuals switched therapy to atazanavir/r and 2 nRTIs for 6 weeks; nRTIs were stopped and individuals were followed up on atazanavir/r for 24 weeks. Primary endpoint (virologic failure) was defined as 2 plasma HIV-1 RNA measurements above 200 copies/mL by week 24. Median follow up was 194 days. Two individuals discontinued before the maintenance phase (1 icteric sclerae; 1 with HIV-1 RNA >50 copies/mL). Baseline median CD4+ cell count was 616/µL. At week 24, 91% of participants remained virologically suppressed below 50 copies/mL; there were no adverse events. Three individuals had virologic failure; of these, 2 had undetectable plasma atazanavir levels at 1 or more visits. Virologic failure was not associated with development of protease resistance mutations; it was associated with low or undetectable plasma atazanavir levels in 2 out of 3 participants.

Treatment Interruptions

ACTG 5170. Skiest and colleagues (Abstract 101) presented the results of ACTG 5170, a multicenter, prospective study that evaluated the safety of treatment interruption among subjects on stable antiretroviral therapy for 6 months or more. Primary endpoint was defined as time to CD4+ count at or above 250 cells/µL, AIDS-related event, or death. One hundred sixty-seven individuals with median CD4+ cell count of 833/µL, 71% of whom had plasma HIV-1 RNA below 50 copies/mL discontinued antiretroviral therapy for up to 96 weeks. At study entry, the median time of antiretroviral therapy was 4.5 years; 37% of subjects were on PI-based and 36% on NNRTI-based therapy. Median CD4+ cell-count decrease was 20/µL/week during the first 8 weeks of treatment interruption, and 1.7/µL/week thereafter. By week 96, 26 individuals reached the primary endpoint; there were 5 deaths and 3 were related to cardiovascular events. Forty-six participants restarted antiretroviral therapy; among them, 14 resumed the same regimen (64% reached plasma HIV-1 RNA levels <50 copies/mL), and 32 initiated a new regimen. Nadir CD4+ cell count below 400/µL and baseline plasma HIV-1 RNA level above 400 copies/mL were associated with increased risk of reaching the endpoint (HR, 1.95 and 2.75, respectively). Plasma HIV-1 RNA level prior to antiretroviral therapy was not predictive of reaching an endpoint.

STACCATO. Ananworanich and colleagues (Abstract 102) presented the results of a randomized, multicenter trial of CD4+ count-guided scheduled treatment interruptions compared with continuous antiretroviral therapy. Five hundred forty-eight individuals with CD4+ cell counts above 350/µL and plasma HIV-1 RNA levels below 50 copies/mL were randomized to the CD4+ count-guided treatment interruption arm (n=299) or continuous therapy (n=154). Individuals in the treatment interruption arm stopped antiretroviral therapy if the CD4+ count was above 350 cells/µL and resumed treatment if the CD4+ count was below 350 cells/µL; at study end all patients resumed continuous antiretroviral therapy for 12 to 24 weeks.

Baseline median CD4+ cell counts and plasma HIV-1 RNA levels were 470/µL and 4.72 $\log_{10}$ copies/mL versus 506/µL and 4.76 $\log_{10}$ copies/mL in the treatment interruption and continuous therapy arms, respectively. Median duration of prior antiretroviral therapy was 13.7 months in the treatment interruption and 15.6 months in the continuous therapy arm; 80% of individuals were on a saquinavir/r-based regimen. Participants were randomized for a median of 21.9 months. At the end of the study period, median CD4+ cell counts were 601/µL and 374/µL ($P < .002$) in the continuous therapy and treatment interruption arms, respectively. Adverse events related to HIV disease were more common in the treatment interruption than the continuous therapy arm and included oral candidiasis (3.5% versus 0%; $P = .04$), vaginal candidiasis (1.7% versus 0.6%; $P > .05$); diarrhea and neuropathy were reported more often in the continuous therapy arm (23.8% versus 15.7% and 4.6% versus 1.9%, respectively). Seventeen patients (5.8%) in the treatment interruption arm had acute retroviral syndromes. Total cholesterol was lower in the treatment interruption arm at the end of the study period: 179.4 mg/dL compared with 195 mg/dL ($P = .05$), as was self-reported lipodystrophy (7.9% versus 13.5%; $P = 0.05$); triglycerides did not differ between the arms. After resuming continuous antiretroviral therapy, 91% in the treatment interruption arm and 92% in continuous therapy arms ($P = .9$) achieved plasma HIV-1 RNA levels below 50 copies/mL; 85.9% in the treatment interruption and 96.9% in the continuous therapy arms maintained CD4+ counts above 350 cells/µL after 24 weeks of therapy.

In a separate presentation, Anan-

woranich and colleagues (Abstract 622b) reported data on the development of resistance mutations among 430 Staccato participants in the continuous therapy (n=146) or treatment interruption arms (n=284). A total of 79.1% of individuals received saquinavir/r in combination with 2 nRTIs (didanosine/stavudine or tenofovir/lamivudine). Genotyping was performed in individuals with plasma HIV-1 RNA levels above 500 copies/mL after 12 or more weeks of treatment (22 in continuous therapy arm and 10 in treatment interruption arm) or individuals with 2 or more treatment interruption cycles (n=111). There was no difference in the development of resistance between the arms (2%). The most prevalent mutation was M184V. The relative risk of resistance was 0.95 (95% CI, 0.11–7.91) for individuals on NNRTI-based regimens and 14.96 (95% CI, 3.02–74.08) for individuals on 3 nRTIs compared with those on saquinavir/r therapy.

ANRS 106 (WINDOW). Marchou and colleagues (Abstract 104) presented the results of a 96-week prospective randomized trial evaluating the safety of fixed-time scheduled treatment interruption. Participants were randomized to an 8-weeks on/8-weeks off arm (intermittent therapy, n=197) or continuous therapy arm (n=194). Baseline median CD4+ cell counts were 739/µL and 748/µL. Individuals had a median of 5.2 and 5.1 years of antiretroviral therapy in the intermittent therapy and continuous therapy arms, respectively. Twenty-seven (17%) and 16 (8%) individuals in the intermittent therapy and continuous therapy arms, respectively, discontinued study participation (***P*** = .09). At week 96, according to the ITT analysis, 3.6% in the intermittent therapy and 1.5% in the continuous therapy arm reached CD4+ counts below 300 cells/µL; 81% in the intermittent therapy versus 90% in the continuous therapy arm maintained plasma HIV-1 RNA levels below 400 copies/mL (***P*** = .02). There were 2 deaths in the intermittent therapy arm (liver failure and violence). Median changes in CD4+ cell counts were –155/µL and –8/µL in the intermittent therapy and continuous therapy arms, respectively (***P*** < .0001). Adverse events included acute retroviral syndrome (3 in intermittent therapy arm), mucosal candidiasis (10 in intermittent therapy versus 6 in continuous therapy arm), and lymphadenopathy (10 in intermittent therapy versus 3 in continuous therapy arm). Nine subjects in the intermittent therapy arm and 2 in the continuous therapy arm developed grade 3 or 4 thrombocytopenia. Thirty-one participants (17 in intermittent therapy and 14 in continuous therapy arm) had plasma HIV-1 RNA levels above 1,000 copies/mL for longer despite more than 6 weeks of therapy. Of these, 14 in the intermittent therapy arm and 10 in the continuous therapy arm underwent genotypic testing; there were no differences in the number of PI, NNRTI, or nRTI resistance mutations between the 2 arms.

ANRS 1269 (TRIVACAN). Danel and colleagues (Abstract 105LB) presented preliminary results of a randomized study comparing 2 treatment interruption strategies with continuous therapy in sub-Saharan Africa. Individuals with plasma HIV-1 RNA levels below 300 copies/mL were randomized to 3 arms: continuous therapy arm (n=110); 2 months off/4 months on treatment-interruption arm (n=325); or CD4+ cell count-guided intermittent therapy arm (n=216). Participants in the CD4+ count-guided therapy arm stopped antiretroviral therapy when CD4+ cell counts were above 350µL and resumed when CD4+ cell counts declined below 250/µL. The CD4+ count-guided therapy arm was stopped early due to increased morbidity; the other treatment interruption arm is currently ongoing. Baseline median CD4+ cell counts were 457/µL and 461/µL in the CD4+ count-guided therapy and continuous therapy arms, respectively. At study entry, 89% of individuals in the CD4+ count-guided therapy and 83% in the continuous therapy arms received 6 months or more of zidovudine/lamivudine/efavirenz; 7% in the CD4+ count-guided therapy and 10% in the continuous therapy arms received 6 months or more of zidovudine/lamivudine/indinavir/r. Mean follow-up time was 19.4 months in the continuous therapy arm and 19.2 months in the CD4+ count-guided therapy arm.

The incidence of serious morbidity in the CD4+ count-guided therapy arm was 2.6-times higher than in the continuous therapy arm (17.6 per 100 person-years of observation in the CD4+ count-guided therapy arm compared with 6.7 per 100 person-years in the continuous therapy arm; incidence rate ratio [IRR], 2.6; 95% CI, 1.3–5.6; ***P*** = .001). These events included invasive bacterial infections (IRR, 15.9; 95% CI, 2.6–64.8); oropharyngeal candidiasis (IRR, 2.7; 95% CI, 0.9–11.0); and tuberculosis (IRR, 1.5; 95% CI, 0.5–6.5). ***Salmonella typhi*** and ***Streptococcus pneumoniae*** were the most commonly isolated bloodstream pathogens; 85% of bacterial infections were resistant to trimethoprim/sulfamethoxazole. The overall mortality rate was 0.6 per 100 person-years in the continuous therapy arm versus 1.2 per 100 person-years in the CD4+ count-guided therapy arm (***P*** = .57). The number of outpatient visits and days spent in the hospital were significantly higher in the CD4+ count-guided therapy than in the continuous therapy arm. Five percent of individuals in the continuous therapy arm compared with 11% in the CD4+ count-guided therapy arm, had virus strains emerge which were resistant to at least 1 drug.

SMART. El-Sadr and colleagues (Abstract 106LB) presented the results of the Community Program for Clinical Research on AIDS (CPCRA)-sponsored Strategies for Management of Antiretroviral Therapy (SMART) study. This was a prospective, randomized, multicenter study of 5472 individuals with CD4+ cell counts above 350/µL randomized to a continuous treatment virus suppression arm (n=2752) or drug conservation arm (n=2720). Individuals in the drug conservation arm stopped antiretroviral treatment when CD4+ cell counts reached above 350/µL and resumed treatment when

CD4+ cell counts declined below 250/μL. The Data Safety Monitoring Board recommended stopping enrollment in January 2006 because of an increased risk of death or HIV-1 disease progression in the drug conservation arm. At baseline, median CD4+ cell counts in the virus suppression arm and the drug conservation arm were 599/μL and 596/μL, respectively; only 4.7% of individuals were antiretroviral-treatment naive. Median duration of antiretroviral therapy was 6 years in both groups. Individuals in the drug conservation arm had a 2.5-fold greater risk of HIV disease progression or death than in the virus suppression arm (95% CI, 1.8–3.6; ***P*** < .0001). The rate of HIV disease progression or death was 3.7 per 100 person-years in the drug conservation arm versus 1.5 per 100 person-years in the virus suppression arm. The relative risk (RR) of death due to cardiovascular, liver, or renal disease was 1.4 (95% CI, 0.7–2.8) in the drug conservation arm compared with participants in the virus suppression arm; the RR of nonfatal cardiovascular events was 1.5 (95% CI, 1.0–2.5), of nonfatal renal events was 2.5 (95% CI, 0.5–13) in the drug conservation arm compared with the virus suppression arm. The RR of disease progression or death was higher in the drug conservation arm than in the virus suppression arm, but there was no difference in the RR by nadir CD4+ cell count stratum: RR of disease progression or death for the below 50/μL stratum was 2.9 (95% CI, 1.0–8.0) versus 2.5 (95% CI, 1.2–5.0) in the 300 to 399/μL stratum. Risk of disease progression or death in the drug conservation versus virus suppression arms was 3.8-times higher for subjects with baseline plasma HIV-1 RNA levels above 400 copies/mL than for those with baseline plasma HIV-1 RNA levels below 400 copies/mL. Individuals in the drug conservation and virus suppression arms spent 3.1% versus 0.8% of follow-up time at CD4+ cell counts below 200/μL, respectively. The authors concluded that episodic, CD4+ count-guided treatment interruption was inferior to the continuous therapy with respect to both HIV disease progression and major cardiac, renal, and hepatic adverse events. The increased rate of the latter events in the drug conservation arm was unexpected and will require more investigation to explain from a pathogenetic perspective.

PART. Palmisano and colleagues (Abstract 103) presented results of a randomized trial of structured treatment interruptions of increasing length compared with continuous antiretroviral treatment. Participants with plasma HIV-1 RNA below 400 copies/mL were randomized to continuous treatment (n = 137) or treatment interruption arm (n = 136). Individuals in the treatment interruption arm underwent interruptions of increasing duration (1 to 3 months) separated by 3 months of treatment.

Baseline mean CD4+ counts were 768 cells/μL and 714 cells/μL in the continuous treatment and treatment interruption arms, respectively. Over-all duration of prior antiretroviral therapy was 26 months. At 24 months, according to the on-treatment analysis, 86.5% in the continuous treatment arm compared with 69.1% in the treatment interruption arm maintained a CD4+ cell count above 500/μL. The study did not demonstrate noninferiority of the treatment interruption strategy. Male sex and nadir CD4+ cell count were independently associated with primary endpoint (defined as the proportion of patients with CD4+ count above 500 cells/μL at 24 months). In the ITT analysis, 92.3% in the continuous treatment arm and 91.1% in the treatment interruption arm achieved HIV-1 RNA levels below 400 copies/mL at 24 months. One individual in the treatment interruption arm had acute retroviral syndrome; 27 individuals in the continuous treatment and 12 in the treatment interruption arm developed grade 3 to 4 laboratory adverse events. Resistance mutations emerged in 38 of 136 individuals in the treatment interruption, corresponding to a cumulative 24-month risk of resistance of 30%.

The M184V/I mutations were detected in 17% of lamivudine-treated subjects; K103N was detected in 8% of NNRTI-treated individuals. Resistance mutations emerged in 50% of individuals on PI-based and 20% on NNRTI-based regimens. Baseline proviral DNA genotyping was performed in 82 subjects in the treatment interruption arm. Archived mutations were found in 9 of 27 individuals (33%) who subsequently developed resistance and in 1 of 55 subjects with wild-type virus. In a logistic regression model, mutations in proviral DNA and an (unboosted) PI-based regimen were associated with an increased risk of resistance during treatment interruption (***P*** = .002 and ***P*** = .048, respectively). Resistance was associated with an increased risk of not reaching the primary endpoint (HR, 2.64; 95% CI, 1.2–5.9).

Antiretroviral Drug Resistance and Replicative Capacity

The K70E mutation in the HIV-1 reverse transcriptase has become more prevalent since the introduction of tenofovir. In a recent study, K70E was selected in 10% of antiretroviral-naive subjects on tenofovir, abacavir, and lamivudine (Ross et al, ***Antivir Ther***, 2005). Sluis-Cremer and colleagues (Abstract 152) reported that the K70E mutation significantly impairs the reverse transcriptase's ability to excise zidovudine monophosphate from the proviral DNA chain suggesting that this mutation may be antagonistic toward TAMs. The authors suggested that inclusion of zidovudine in the nRTI component of an antiretroviral regimen may reduce the selection of K70E.

Variations in the ***env*** variable regions and N-glycosylation sites are known to influence susceptibility to attachment inhibitors. Toma and colleagues (Abstract 153) demonstrated that minor genetic changes in constant regions of ***env*** and the variable regions of gp120 and gp41 can result in large changes to phenotype. This may affect susceptibility to anti-CD4 antibodies, CD4 binding-site inhibitors, and monoclonal antibodies that target either gp120 or gp41. These observations are consistent with a structurally integrated model of the gp120-gp41 glycoprotein complex.

Drug Resistance Testing and Transmission of Drug-Resistant Virus

Palella and colleagues (Abstract 654) described the impact of HIV-1 genotypic and phenotypic susceptibility testing on the rate of survival among subjects in the HIV Outpatient Study (HOPS) between 1999 and 2005. Among 4186 individuals with plasma HIV-1 RNA levels above 1000 copies/mL, 25% underwent susceptibility testing. The median number of regimens before genotypic and phenotypic testing was 3. Subjects with 1 or more genotypic or phenotypic tests had a 59% improvement in survival (HR, 0.41; $P < .01$). Individuals most likely to undergo HIV susceptibility testing had lower CD4+ cell counts, higher plasma HIV-1 RNA levels, were white, and were younger than 40 years of age.

To evaluate transmission of drug-resistant virus, a real-time polymerase chain reaction (PCR) point-mutation assay was developed and used to detect low-frequency mutations among 277 antiretroviral-naive individuals infected with drug-resistant HIV-1 (Abstract 642). The authors identified previously undetected resistant HIV-1 viruses at frequencies between 0.2% and 14%. Use of the real-time PCR assay increased the detected prevalence of L90M from 8% to 10%, M41L from 16% to 26%, and M184V from 9% to 11%. Identification of additional mutations resulted in an additional 5% of the samples being classified as having resistance to another drug class; the frequency of HIV-1 resistance to 2 or more drug classes increased from 17% to 22%.

Pilon and colleagues (Abstract 646) described transmission of drug-resistant virus among 537 newly diagnosed HIV-1–infected individuals in Canada between January and December 2004. The prevalence of drug resistance ranged from 5.6% to 18.4% and varied by region. Resistance to any drug class was 9.7%, and has been constant over the last several years. The prevalence of nonsubtype B HIV-1 strains among subjects varied by region and ranged from 8.7% to 36%. The overall prevalence of nonsubtype B HIV-1 infections in Canada had increased since 2001. Gatanaga and colleagues (Abstract 647) reported a lower rate of transmission of drug-resistant virus in Japan. Among 575 newly diagnosed individuals between 2004 and 2005, 5% were resistant to at least 1 drug. Of these individuals, 3.5%, 1.2%, and 0.9% had evidence of nRTI, NNRTI, and PI resistance mutations, respectively.

Hypersusceptibility, Fitness, and Replication Capacity

Prior studies have demonstrated the importance of T215Y and H208Y in inducing efavirenz hypersusceptibility. Shulman and colleagues (Abstract 624) postulated that hypersusceptible viruses have a reduced replication capacity compared with wild-type virus. They evaluated the impact of T215Y and H208Y mutations on the replication capacity of HIV-1. Mutants analyzed included T215Y, H208Y, T215Y+H208Y, T215Y+H208Y+V118I, and H208Y +V118I. All mutants, with the exception of those containing T215Y alone, were hypersusceptible to efavirenz. The presence of the H208Y mutation alone reduced the replication capacity to 9.3%; this was restored to 70% when T215Y was present.

Kitchen and colleagues (Abstract 626) identified the following positions in the protease gene at which mutations resulted in decreased replication capacity: 30, 36, 63, 77, 82, and 90. The D30N mutation conferred the greatest defect in replication capacity. Paredes et al (Abstract 628) evaluated the effect of the M184V mutation on viral fitness using the sensitive allele-specific PCR assay in 6 subjects who stopped all RTIs and remained on PIs. Lamivudine was stopped in 5 of 6 subjects. M184V was detected in all subjects discontinuing lamivudine. The proportion of M184V mutants remained stable for 16 weeks. After week 16, M184V decayed rapidly. The authors concluded that in the absence of drug pressure, M184V decreases the fitness of HIV in vivo, consistent with previously reported in vitro data.

Bezemer and colleagues (Abstract 630) described the evolution of mutations in the reverse transcriptase and protease gene among 20 recently infected antiretroviral-naive individuals from the Concentrated Action on SeroConversion to AIDS and Death in Europe (CASCADE) cohort. Individuals had genotypic testing at the time of diagnosis and after a median follow-up time of 15 months. The following mutations in reverse transcriptase did not evolve: M41L, T215D, and T215S; whereas K70R, M184V, T215Y, and T215F evolved or reverted to alternative codons. Mutations in the protease gene remained stable over 15 months. Twelve individuals demonstrated evolving resistance mutations and this was associated with slower CD4+ cell decline following seroconversion compared with individuals infected with HIV-1 that did not revert. The authors concluded that T215Y/F, K70R, or M184V may confer reduced fitness over the short term.

Cong and colleagues (Abstract 627) evaluated the impact of mutational interactions on viral fitness in HXB2-derived mutants and transmitted drug-resistant isolates. The lowest fitness cost was seen in mutants with K70R, L210W, Y181C, or M41L (0.4-, 0.9-, 1.3-, and 4-fold, respectively); the highest cost was seen in viruses with K65R, M184V, or T215Y (26-, 14-, and 11.5-fold, respectively). The fitness cost of mutations varied with the presence of additional reverse transcriptase mutations. The low fitness cost of the K70R mutation was found to increase in HXB2 viruses with D67N/K219Q (4.6-fold) and in viruses with only D67N (6-fold). Similarly, the high fitness cost of M184V was reduced in HXB2 viruses carrying the D67N/K70R/K219Q or M41L/L210W/T215Y genotypes (2.3- and 8.9-fold, respectively) but remained high in viruses with M41L/L210W/T215Y/K103N or D67N/K70R/K219Q/T215F (23- and 16.1-fold, respectively). A similarly wide range of fitness costs of M184V (from 2- to 20-fold) was seen in transmitted isolates carrying M184V alone or in association with K70R, K103N, or M41L/T215Y. The authors concluded that modulation of fitness cost may

play a role in the rate of reversion and persistence of transmitted resistance mutations. The authors concluded that a more fit mutant has a greater persistence potential in vivo and a less fit mutant may predict rapid reversion of the mutation(s).

Resistance in Treatment-Experienced Patients

Enfuvirtide. Mutations associated with enfuvirtide develop at residues 36 to 45 of HIV-1 gp41 HR1 domain. Aquaro and colleagues (Abstract 596) compared gp41 mutations selected during long-term enfuvirtide treatment with gp41 sequences in enfuvirtide-naive individuals. Enfuvirtide was added to failing therapy in 54 individuals with a median plasma HIV-1 RNA level of 5.1 $\log_{10}$ copies/mL and a median CD4+ cell count of 48/µL. Individuals had a median number of 2 NNRTI mutations, 8 PI mutations, and 5 nRTI mutations. At week 8, median HIV-1 RNA level decreased from 5.1 $\log_{10}$ copies/mL to 4.2 $\log_{10}$ copies/mL. By week 24, however, HIV-1 RNA level increased to 4.8 $\log_{10}$ copies/mL. By week 36, median CD4+ cell count increased to 136/µL. Enfuvirtide resistance mutations developed in 45 of 54 subjects, 28% of whom developed V38A/E. At week 24, 9% developed a Q40H plus L45M. V38A/E mutations were associated with a 4.5-fold increase in CD4+ cell count at week 24 compared with wild-type gp41 (94 versus –25/µL; ***P*** = .004). At week 24, the median CD4+ cell count decreased by 45/µL in subjects with the Q40H+L45M combination versus 25/µL in those with wild-type gp41 (***P*** = .02). The N126K mutation was associated with a 2.1-fold increase in CD4+ cell count at 24 weeks. There was no association between enfuvirtide mutations and plasma HIV-1 RNA levels at week 24.

Atazanavir. Coakley and colleagues (Abstract 634) validated the phenotypic clinical cutoff for atazanavir/r based on data from the BMS 045 study. BMS 045 was a randomized, open-label study of patients randomized to tenofovir and 1 nRTI and either atazanavir/r 300/100 mg; lopinavir/r 400/100 mg; or atazanavir/saquinavir 400/1200 mg. Baseline fold change below 5.2 correlated with best response to atazanavir/r: at week 2, 89% of subjects with fold change below 5.2 reached at least 1.0-$\log_{10}$ copies/mL decrease in plasma HIV-1 RNA level versus 26% of patients with a fold change of at least 5.2. This phenotypic cutoff was associated with virologic response regardless of the presence of baseline protease mutations.

nRTI-associated K65R mutation. Previous studies have shown reduced HIV-1 RNA responses to tenofovir in individuals with multiple TAMs, including either the M41L or L210W mutation (Miller et al, ***J Infect Dis,*** 2004). The L74V mutation has been associated with a reduced tenofovir response and development of the K65R mutation (Bae et al, ***Antivir Ther***, 2004).

Waters and colleagues (Abstract 633) evaluated the impact of TAMs and K65R on the response to tenofovir among individuals enrolled in the Gilead 907 and 902 trials. These were studies of individuals on stable antiretroviral regimens with plasma HIV RNA levels above 400 copies/mL randomized to the addition of either tenofovir or placebo. The previous baseline resistance analysis included 333 patients (222 assigned to tenofovir, 111 to placebo); the current analysis included 233 additional patients (158 to tenofovir and 75 to placebo), of whom 94% had baseline nRTI mutations. At week 24, individuals on tenofovir achieved a 0.6-$\log_{10}$ copies/mL decrease in plasma HIV-1 RNA level. The authors confirmed that the presence of 3 or more TAMs or the L74V mutation was associated with a reduced response to tenofovir (defined as a smaller reduction in plasma HIV-1 RNA level). The L74V mutation was also associated with multiple TAMs and with the development of K65R; 2.8% of subjects had the K65R mutation which predicted poor response to tenofovir. M184V was associated with a better plasma HIV-1 RNA response to tenofovir (0.13-$\log_{10}$ copies/mL reduction in HIV-1 RNA level; ***P*** = .0026).

The emergence of viruses containing both K65R and L74V appears to be relatively infrequent. To better characterize tenofovir resistance, Frankel and colleagues (Abstract 608) studied purified reverse transcriptase sequences containing K65R, L74V, or both. They reported that the co-occurrence of K65R and L74V may potentiate resistance to tenofovir. Addition of M184V resulted in resensitization to tenofovir but not to dideoxynucleoside adenosine triphosphate (ddATP). Antinori and colleagues (Abstract 636) evaluated the impact of the K65R mutation on response to salvage therapy among 145 individuals from 6 Italian centers. Subjects switched antiretroviral regimens after genotypic resistance testing. The median baseline plasma HIV-1 RNA level and CD4+ cell count were 4.17 $\log_{10}$ copies/mL and 312/µL, respectively; 56.5% of individuals were on tenofovir, 56.5% on lamivudine, and 55.7% on didanosine. Among these individuals, 44.8% had M184V; 15.2% and 22.8% had mutations from TAM-1 (M41L, L210W, and T215Y) and TAM-2 (D67N, K70R, and K219Q/E) pathways, respectively. After genotypic resistance testing, individuals changed therapy to lamivudine (59.7%), zidovudine (29%), stavudine (27.4%). The best predictor of achieving a treatment response (defined as a plasma HIV-1 RNA level below 50 copies/mL at 12 months), was associated with the presence of the M184V mutation (HR, 1.97; 95% CI, 1.0–3.86; ***P*** = .05); and the addition of a thymidine analogue to the salvage regimen (HR, 2.55; 95% CI, 1.25–5.19; ***P*** = .01). Inclusion of zidovudine rather than stavudine was associated with a better outcome (HR, 2.66; ***P***=04). The authors concluded that development of K65R may not limit the effectiveness of salvage therapy.

Evolution and Persistence of Resistance

Wind-Rotolo and colleagues (Abstract 616) evaluated the persistence of

NNRTI resistance mutations in resting CD4 + T cells in 6 individuals with previously documented resistance. Samples were obtained 36 to 64 months after stopping NNRTIs. HIV-1 clones with K103N or Y181C were found in the resting CD4 + T cells but not in the plasma in 3 of 5 individuals. NNRTI resistance mutations were present in proviral DNA sequences in 3 of 3 subjects with plasma HIV-1 RNA levels below 50 copies/mL.

Easterbrook and colleagues (Abstract 620) evaluated the prevalence of protease mutations in PI-naive and PI-experienced individuals infected with nonsubtype B virus. The United Kingdom HIV Drug Resistance Database collected 15,624 samples between 1996 and 2002, which were then reviewed. Of these, 11,692 samples were subtype B HIV-1. The most common non-B subtypes were subtypes C (n = 2043), A (n = 815), and D (n = 428). The authors found differences in the amino acid sequences between PI-naive and PI-exposed individuals in non-B subtypes at the positions known to be associated with drug resistance in subtype B viruses: specifically, at codons 10, 20, 30, 46, 63, 71, 82, and 90. New protease mutations in non-B subtypes were rare (at codons 13, 6, 33, 37, 41, 57, 65, 72, 74, and 89). Significant association with PI exposure was found for more than 1 non-B subtype only at position M89I/V.

Resistance to Entry Inhibitors

Maraviroc. (UK-427,857) is a CCR5 antagonist currently in phase IIb/III clinical trials. The compound binds within the transmembrane region of the receptor while gp120 interacts with the N-terminus and extracellular loop of CCR5. Mosley and colleagues (Abstract 598) characterized phenotypic and genotypic determinants of maraviroc resistance. The emergence of maraviroc resistance was associated with A316T and I323V mutations in the V3 region of gp120. Both mutations were necessary and sufficient for the fully resistant phenotype. Resitance to maraviroc was not associated with cross-resistance to aplaviroc or enfuvirtide.

Resistance Associations by Genotypic Database Analyses

Ross and colleagues (Abstract 602) evaluated differences in susceptibility between lamivudine and emtricitabine. Samples from a commercial database that had susceptibility to both drugs did not have the M184I/V mutation, but did contain: K65R, L74I/V, Q151M, T69 insertions, 2 or 3 TAMs from those at positions 41, 210, or 215, 2 or 3 TAMs from positions 67, 70, or 219, any 3 or 4 TAMs, any 5 or 6 TAMs (with and without E44D/V118I), or K65R + Q151M were identified. In the presence of K65R, L74I/V, or Q151M without TAMs, there were no differences in the mean fold change in resistance between lamivudine and emtricitabine. In samples containing 2 or more TAMs, the mean fold change in resistance was higher for emtricitabine than for lamivudine ($P < .001$).

A tipranavir mutation score was derived from analysis of a limited number of samples from phase II and III clinical trials and took into account the following mutations in the protease: L10V, I13V, K20M/R/V, L33F, E35G, M36I, K43T, M46L, I47V, I54A/M/V, Q58E, H69K, T74P, V82L/T, N83D, and I84V. Each mutation is scored equally.

Parkin and colleagues (Abstract 637) used samples from a commercial database to evaluate the accuracy of the tipranavir mutation score in predicting phenotypic susceptibility. Tipranavir fold change significantly correlated with the tipranavir mutation score ($P < .0001$). Several new mutations were significantly associated with higher-than-expected tipranavir fold change: A71L, V11L, G73T, L89V, I84V, V32I, M36L, I66, D60E, K55R, L90M, M46I, and L10I. Additional mutations were significantly associated with lower-than-expected tipranavir fold change: I50V, D30N, L76V, L24I, V82I, I50L, I54L, N88D, and L10F. The authors proposed a revised tipranavir mutation score that incorporated new mutations and had greater correlation with measured phenotype, and lower phenotypic and genotypic discordance than the current mutation score.

Pharmacology and Therapeutic Drug Monitoring

Selected Drug-Drug Interactions

P-glycoprotein. P-glycoprotein is a cellular efflux transporter that can affect absorption, tissue penetration, and intracellular concentrations of certain antiretroviral agents. Although it is expressed in T lymphocytes, its relevance to antiretroviral effectiveness is unclear. Cyclosporine A is an inhibitor of P-glycoprotein in vitro. Hulgan and colleagues presented data on the inhibition of P-glycoprotein in vivo from a substudy of ACTG 5138, a randomized open-label trial of antiretroviral therapy with or without cyclosporine A (Abstract 564). Subjects initiated antiretroviral therapy with fixed-dose abacavir/lamivudine/zidovudine for 14 days after which efavirenz was added. Nine subjects received cyclosporine A in addition to antiretroviral therapy and 7 subjects received antiretroviral therapy alone. P-glycoprotein activity was measured at baseline, day 14, and week 4. Cyclosporine A plus 3 nRTIs was associated with an 8% decrease in P-glycoprotein activity compared with baseline ($P = .03$) and was positively associated with cyclosporine A trough levels. No difference was found in those not receiving cyclosporine A. At week 4 (2 weeks after efavirenz was added), P-glycoprotein activity was not different from baseline in either group. This study shows that targeted inhibition of P-glycoprotein activity is feasible. The relevance to antiretroviral activity remains to be shown.

Marzolini and colleagues investigated the effect of P-glycoprotein and other drug transporters on the distribution of efavirenz (Abstract 565). They administered radiolabeled efavirenz to mice that did or did not express P-glycoprotein. They found that tissue levels in the brain, liver, kidney, testes, and plasma were not

statistically significantly different. They also looked at cell cultures with varying expression of other transporters and did not find an effect on efavirenz transport. The authors concluded that pharmacologic alteration of drug transporters was unlikely to affect efavirenz disposition in vivo.

Dupuis and colleagues tested the interaction of diketo acid integrase inhibitors and P-glycoprotein (Abstract 566). They found that integrase inhibtors competed with other P-glycoprotein substrates for cellular efflux. Also, prolonged treatment of cell cultures that had a low expression of P-glycoprotein with integrase inhibitors resulted in increased P-glycoprotein expression and activity. This may have implications for modulation of the absorption of integrase inhibitors and their ability to penetrate the central nervous system and genital compartments over time.

Tenofovir. Kiser and colleagues hypothesized that ritonavir may decrease the renal clearance of tenofovir by affecting proximal renal tubular cells (Abstract 570). They compared 15 subjects receiving tenofovir and lopinavir/r with age-, race-, and sex-matched controls that were receiving tenofovir and nRTIs or an NNRTI. They found that the clearance of tenofovir was greater in those subjects not receiving ritonavir and that the clearance of tenofovir and glomerular filtration rate were associated with intracellular PBMC tenofovir diphosphate levels. However, no difference in intracellular levels was seen between groups. The authors concluded that the mechanism of this interaction merits further study.

Efavirenz. Prior data from ACTG 5095 implicated genetic polymorphisms in the CYP2B6 gene (the enzyme mainly responsible for metabolizing efavirenz) with efavirenz plasma levels and toxicities, which was confirmed with data from a second efavirenz-containing study, ACTG 384 (Haas et al, ***AIDS***, 2004; Haas et al, ***J Infect Dis***, 2005). Polymorphisms in the ***mdr1*** gene, which encodes P-glycoprotein, were shown to be related to decreased virologic failure on an efavirenz-based regimen but not to plasma levels. Motsinger and colleagues presented further data on interactions between these polymorphisms and their relationship to plasma levels, toxicity, and virologic failure among subjects receiving efavirenz in ACTG 384 (Abstract 571). They were better able to predict higher plasma levels and AUC of efavirenz, efavirenz toxicity, and virologic failures by considering 2-gene interactions. However, the accuracy of these predictions and the specific polymorphisms involved varied according to race.

Gupta and colleagues presented data on the pharmacokinetics of lopinavir/r or efavirenz in subjects on hemodialysis compared with historic controls (Abstract 573). They found that the average AUC (90% CI) of efavirenz for subjects on hemodialysis was 135% (89%–170%) that of historic controls. The AUC of lopinavir and ritonavir were 77% (65%–91%) and 91% (73%–115%), respectively. Although the lopinavir AUC was reduced compared with controls, the lopinavir inhibitory quotient for wild-type HIV remained high. These data suggest that dose adjustment of these drugs may not be necessary for subjects on hemodialysis.

Rifampin. Pujari and colleagues investigated the effect of rifampin on the pharmacokinetics of nevirapine in non-HIV–infected subjects from India (Abstract 574). Consistent with studies in other populations, rifampin markedly reduced the AUC of nevirapine by 80% ($P < .0001$), suggesting that concomitant administration of these drugs is problematic. Both carbamazepine and efavirenz are substrates and inducers of CYP3A4 and CYP2B6. Kaul and colleagues examined the pharmacokinetic interactions of these drugs given in combination in 36 non-HIV–infected subjects in a crossover design (Abstract 575a). They found that the AUC of efavirenz was reduced by 34% when coadministered with carbamazepine (90% CI; 32%–40%). Similarly, the AUC of carbamazepine was reduced by 27% (20%–33%). This 2-way drug interaction suggests that coadministration of these drugs may compromise antiretroviral or anticonvulsant efficacy.

Etravirine. As noted earlier, etravirine is a novel investigational NNRTI that is active against HIV resistant to currently available NNRTIs, making it a potential option for treatment-experienced patients. Harris and colleagues examined the interactions between etravirine and 3 PIs: lopinavir, ritonavir, and saquinavir (Abstract 575b). They studied 15 HIV-seropositive subjects who were receiving lopinavir/r, saquinavir, and 2 nRTIs with plasma HIV RNA levels below 50 copies/mL. They assessed the pharmacokinetics of the PIs at baseline and after 2 weeks of coadministration with etravirine. The 12-hour AUCs for lopinavir, ritonavir, and saquinavir were reduced by 18%, 13%, and 13%, respectively. Only the change in lopinavir 12-hour AUC was statistically significant ($P = .04$). The HIV-1 RNA level remained below 50 copies/mL for all subjects.

Schöller and colleagues evaluated the interaction of tipranavir/r and etravirine in 24 subjects utilizing a crossover design (Abstract 583). They found that the AUC of tipranavir was increased by 18% after coadministration with etravirine compared with tipranavir alone and the AUC of ritonavir was increased by 23%. However, the AUC of etravirine was reduced by 76% (90% CI; 67%–82%) precluding coadministration of these drugs.

Atazanavir. Best and colleagues presented data on behalf of the Central Nervous System HIV Antiretroviral Therapy Effects Research (CHARTER) study (Abstract 576). They collected concomitant cerebrospinal fluid and plasma samples in 26 subjects who were receiving atazanavir/r. They found that the ratio of cerebrospinal fluid to plasma levels was 0.0098. The cerebrospinal fluid levels were often below the IC_{50} for wild-type virus. The mean plasma HIV RNA level was 2.7 $\log_{10}$ copies/mL and the mean cerebrospinal fluid HIV-1 RNA level was

1.9 $\log_{10}$ copies/mL. The authors suggested that the observed cerebrospinal fluid levels may not be sufficient to control HIV replication in the central nervous system compartment.

Gastric acid suppression has been associated with reduced levels of atazanavir, but data on other PIs have been incomplete. Klein and colleagues investigated the pharmacokinetics of lopinavir/r with and without omeprazole and ranitidine (Abstract 578). They did not find a significant alteration with coadministration of either acid-reducing agent with lopinavir/r given once daily or twice daily.

Vicriviroc. The levels of vicriviroc, an investigational CCR5 antagonist, are markedly enhanced by coadministration with ritonavir. Sansone and colleagues studied HIV-seronegative subjects who received 14 days of vicriviroc and 100 mg of ritonavir once or twice daily depending on assigned PI cohort (Abstract 582). After this, they received indinavir, fosamprenavir, nelfinavir, or saquinavir soft gel capsules for 2 weeks or atazanavir for 1 week. The pharmacokinetic profile of vicriviroc was not altered after the addition of the second PI for any of the 5 cohorts.

Two studies examined the pharmacokinetic effect of atazanavir on other PIs without using ritonavir. King and colleagues compared saquinavir hard gel capsules and atazanavir (1000 mg/200 mg twice daily and 1500 mg/200 mg twice daily) with saquinavir/r (1000 mg/100 mg twice daily) in a crossover design in which each participant received all 3 regimens (Abstract 586). They found that the saquinavir pharmacokinetic profile (maximum concentration [C_{max}], minimum concentration [C_{min}], and 12-hr AUC) was markedly reduced compared with saquinavir/r. The atazanavir levels were comparable to levels reported for atazanavir 400 mg daily. They also noted that female subjects had higher drug levels than men even after controlling for differences in weight. Clay and colleagues performed a similar study of 21 subjects who first received fosamprenavir alone followed by atazanavir alone, followed by a combination of the 2 drugs (Abstract 587). The AUC and C_{min} of fosamprenavir were increased by 78% and 283% respectively when coadministered with atazanavir, but the AUC and C_{min} of atazanavir were reduced by 33% and 57%, respectively.

Therapeutic Drug Monitoring

Best and colleagues reported the results of California Collaborative Treatment Group 578 Study (Abstract 589). This involved both adherence interventions and therapeutic drug monitoring (TDM). Only the results of the TDM intervention were reported. Eligible subjects were receiving either an NNRTI- or PI-based regimen. One hundred ninety-nine subjects were randomized to standard dosing or to dose modifications by an expert panel based on drug levels and patient history; 137 subjects completed the study. At baseline, 81% were men and 29% were treatment naive. The median CD4+ count and plasma HIV-1 RNA level were 190 cells/μL and 5.2 $\log_{10}$ copies/mL, respectively. Of 647 TDM evaluations, 225 suggested a change in PI or NNRTI dose. In the TDM arm, 77% of recommendations were followed by the providers, and 60% of these subjects achieved the targeted drug levels compared with only 35% of subjects in the standard-of-care arm. This study showed that one third of patients receiving a PI- or NNRTI-based regimen have suboptimal drug levels, and that TDM followed by dose modification was able to achieve targeted drug levels twice as often as no dose modification.

Podsadecki and colleagues examined patterns of adherence among subjects in a study comparing once- with twice-daily dosing of lopinavir/r soft gel capsules (Abstract 590). They measured adherence with self-report, lopinavir levels, and electronically captured dosing events (MEMS caps). They noted a phenomenon termed "white coat compliance." It is described as excellent adherence for several days before a study visit coupled with suboptimal adherence at other times. The lopinavir levels in these individuals were generally within the therapeutic range. This occurred at 31% of visits and occurred at least once in 66% of patients. The opposite pattern, suboptimal adherence just before a visit coupled with excellent adherence at other times, was rare (1% of study visits).

Gandhi and colleagues examined a wide variety of factors affecting drug levels of nevirapine, efavirenz, or lopinavir/r among women in the Women's Interagency HIV Study (WIHS) cohort (Abstract 592). They found that women coinfected with hepatitis C virus (HCV) had a nevirapine AUC 1.23-times higher than women without HCV. The AUCs of both nevirapine and efavirenz were greater with higher levels of hepatic transaminases. For all 3 drugs, an increase in lean body mass was associated with a reduced AUC.

Mother-To-Child Transmission of HIV

MTCT of HIV remains a significant problem in resource-limited settings. At this year's conference, several areas of research regarding prevention of MTCT (pMTCT) were highlighted including implications of single-dose nevirapine for future pMTCT and development of resistance; results of combination PI- and NNRTI-based maternal prophylaxis; and prevention of breast milk-associated MTCT of HIV.

The HIV Network for Prevention Trials (HIVNET) 012 study demonstrated that single-dose nevirapine was efficacious in pMTCT but increased the risk of NNRTI resistance (Guay et al, ***Lancet***, 1999; Eshleman et al, ***J Acquir Immune Defic Syndr***, 2004). In resource-limited settings where the availability of combination antiretroviral therapy is limited, the implications of these findings are unclear as rates of resistance appear to decline and long-term resistance patterns and response to treatment in women and infants exposed to single-dose nevirapine are unknown (Coovadia, ***N Engl J Med***, 2004). Two abstracts at this year's conference (Abstracts 125 and 722) evaluated the effectiveness of single-dose

nevirapine in preventing HIV transmission in consecutive pregnancies.

Eure and colleagues (Abstract 125) retrospectively identified Ugandan women who had received single-dose nevirapine (n = 59) or short-course zidovudine (n = 41) through HIVNET 012 and received single-dose nevirapine for pMTCT during a subsequent pregnancy. A parallel, prospective study identified women who had received single-dose nevirapine through HIVNET 012 or other protocols (n = 38) and women who had not received single-dose nevirapine in prior pregnancies (n = 63) and monitored the effects of single-dose nevirapine on rates of HIV-1 transmission during subsequent pregnancies. In each study, rates of MTCT were compared between the single-dose nevirapine-naive and -experienced women during the second pregnancy. In the prospective group, there were no statistically significant differences in baseline median CD4+ counts (463–486 cells/μL) or plasma HIV-1 RNA levels (19,900–22,950 copies/mL) between nevirapine-experienced and nevirapine-naive women. Time between pregnancies for the majority of women (97%) was 12 months or more. In the retrospective and prospective groups, 6- to 9-month transmission rates among single-dose nevirapine-experienced versus single-dose nevirapine-naive women were not statistically different: 11.8% versus 17%, respectively, in the retrospective group and 18.4% versus 17.5%, respectively, in the prospective group. The authors concluded that single-dose nevirapine is an effective option for sequential pregnancies for pMTCT in resource-limited settings where more complex options are not yet feasible.

Martinson and colleagues (Abstract 722) conducted a similar study to evaluate the effectiveness of single-dose nevirapine in consecutive pregnancies in Soweto, South Africa, and Abidjan, Côte d'Ivoire. In Soweto (n = 122), women who participated in HIVNET 012, had not breast fed their first infant, and had received single-dose nevirapine during both pregnancies were enrolled. In Abidjan (n = 41), women from the MTCT-plus or DITRAME-plus programs were enrolled during their first pregnancies; all women received single-dose nevirapine with either zidovudine or zidovudine/lamivudine in both pregnancies. The median interdelivery time between pregnancy and CD4+ count during second pregnancy in the Soweto group were 21 months and 400 cells/μL versus 26 months and 462 cells/μL in the Abidjan group. The rate of cesarean deliveries during both births was greater in Soweto than Abidjan at 21% and 2% to 3%, respectively. The reported rates of HIV transmission for the first and second pregnancies were 10.9% (10 of 92) and 13.6% (14 of 103), respectively, in Soweto and 13.2% (5 of 38) and 5.49% (2 of 37), respectively, in Abidjan. Of note, infant HIV status was not known for all of the women for both pregnancies at the time of the presentation. Furthermore, infants were tested for HIV a median of 87 weeks (Soweto) and 74 weeks (Abidjan) earlier in the second pregnancies than in the first pregnancies. Rates of transmission in women with an interdelivery time of less than 12 months was 27% versus 7.7% in women with an interdelivery time of 12 months or more ($P = .032$). The authors concluded that rates of transmission were similar to those in the first pregnancy at both sites. Additionally, they noted that increased interdelivery time might be protective against transmission in the setting of single-dose nevirapine, possibly because of reversion to wild-type virus in the absence of sustained nevirapine pressure.

Hanlon and colleagues (Abstract 721) presented an open-label, prospective study evaluating the efficacy and safety of a ritonavir-boosted, saquinavir-based versus a nelfinavir-based regimen with a zidovudine/lamivudine backbone for pMTCT. Sixty-six antiretroviral-naive pregnant women were enrolled from sites around the world (Ireland, sub-Saharan Africa, Eastern Europe) and initiated therapy during the third trimester for a minimum of 6 weeks prior to delivery. Women were randomized to receive an 8-tablet-per-day regimen of zidovudine/lamivudine/saquinavir/r (n = 19), a 6-tablet-per-day regimen of zidovudine/lamivudine/nelfinavir (n = 6), or a 12-tablet-per-day regimen of zidovudine/lamivudine/nelfinavir (n = 42). Ninety-four percent of women in the saquinavir group (14 of 16) and 84% in the nelfinavir group (42 of 48) received intrapartum zidovudine. Mode of delivery in the saquinavir group was 56.3% spontaneous vaginal delivery, 6.2% elective caesarian delivery, and 37.5% emergency caesarian delivery. In the nelfinavir group, the above modes of delivery were 56.3%, 31.2%, and 12.5%, respectively. At 36 weeks, 87.5% of women in the saquinavir arm versus 56.3% in the nelfinavir arm reached plasma HIV-1 RNA levels below 50 copies/mL. One infant in the nelfinavir group seroconverted in the setting of maternal delivery at 36 weeks with ruptured membranes for more than 24 hours and maternal HIV RNA below 50 copies/mL. No infants in the saquinavir group seroconverted. At 6 weeks postpartum, genotypic testing was performed in both groups and no major PI resistance mutations were reported. Saquinavir peak and trough levels were evaluated in 4 patients, all of whom had adequate levels. The authors concluded that treatment with zidovudine/lamivudine/saquinavir/r achieved better virologic suppression than zidovudine/lamivudine/nelfinavir ($P < .01$). The absence of PI mutations in either group post-treatment suggests that short-term PI administration has no detrimental effect on future antiretroviral therapy options.

Previous studies have noted that in the setting of single-dose nevirapine, a greater proportion of nevirapine resistance is found in subtype C virus than A or D and that the K103N mutation is the most common nevirapine resistance mutation (Eshleman, CROI, 2005). Flys and colleagues (Abstract 726) reported the prevalence of K103N mutations among subtypes A, C, and D in women who had previously received single-dose nevirapine for pMTCT. A sensitive and quantitative point-mutation assay was conducted in samples from women collected 6 to 8 weeks after receiving single-dose nevirapine through the HIVNET 012 and the Nevirapine and Zidovudine

(NVAZ) protocols in Uganda and Malawi, respectively. Samples from 238 Ugandan women (144 subtype A and 94 subtype D) and 63 Malawian women (all subtype C) were analyzed. K103N variants were found more commonly in subtype C (69.8%) than subtype A virus (41.7%). In multivariate analysis, K103N variants were associated with increased plasma HIV-1 RNA levels at delivery, and HIV-1 subtype (subtype C more so than A; odds ratio [OR], 2.48). HIV-1 subtype C versus D, D versus A, parity, and number of days since nevirapine dose did not significantly correlate with presence of the K103N mutation.

Emergence of NNRTI resistance has been shown to be less frequent if nevirapine is administered with a short course of zidovudine and lamivudine (Chaix et al, CROI, 2005). Perez and colleagues (Abstract 725) evaluated 25 plasma samples from 20 pregnant women in whom zidovudine/lamivudine/nevirapine was initiated during their second or third trimester and continued until delivery. Prepregnancy, all women were either antiretroviral therapy naive or had received only zidovudine during a previous pregnancy. Eighty percent were infected with subtype B/F and 20% with subtype B HIV-1. Median plasma HIV-1 RNA level at labor was below 50 copies/mL (range, <50–108 copies/mL). Plasma samples were collected up to 15 months after discontinuation of therapy. Using standard bulk sequencing, there were no mutations associated with resistance to PIs or RTIs except for 1 M41L mutant. One sample was not amplified and there were no episodes of MTCT. The authors concluded that in this sample of women, zidovudine/lamivudine/nevirapine was highly effective in preventing MTCT and the risk of selection for NNRTI-resistant virus was low.

Karchava and colleagues from the New York State Department of Health (Abstract 724) presented rates of resistance in 51 perinatally infected infants diagnosed between 2001 and 2002. Of them, 42 had samples available for resistance testing. Eight (19%) had at least 1 drug resistance mutation of which 7.1% conferred nRTI resistance, 11.9% NNRTI resistance, and 2.4% PI resistance. Compared with a prevalence study from 1998 to 1999, rates of overall resistance increased from 12.1%, NNRTI resistance increased from 3.3%, and nRTI and PI resistance rates remained relatively stable. Four of 8 infants with resistance mutations had perinatal antiretroviral therapy exposure; of these, 1 was resistant to the drug administered. Phylogenetic analysis revealed 7 (17%) infants were infected with nonsubtype B virus (2 [4.8%] had subtype C and 5 [11.9%] had circulating recombinant form [CRFO2]).

Eshleman and colleagues (Abstract 719) evaluated the association between HIV replication capacity and MTCT. In a random subset of women from the NVAZ late-presenter trial in Malawi, replication capacity in 52 transmitters (women whose infants were HIV-seropositive at birth or 6 to 8 weeks postpartum) was compared with replication capacity in 48 nontransmitters (women whose infants were uninfected at 6 to 8 weeks postpartum). Fifty-four percent of infants had received single-dose nevirapine only and 46% received single-dose nevirapine followed by 1 week of zidovudine; mothers presented too late to receive antiretroviral therapy prophylaxis. All women had subtype C HIV and there were no cesarean deliveries or twins. All but one infant was breast fed at 6 to 8 weeks postpartum. Replication capacity was evaluated in maternal plasma samples obtained at delivery via a phenotypic assay. Mean replication capacity and maternal plasma HIV-1 RNA level at delivery were higher in transmitters than in nontransmitters: 35% versus 27.4% ($P = .02$) and 5.1 versus 4.6 $\log_{10}$ RNA copies/mL ($P = .001$), respectively. Maternal age, infant antiretroviral therapy regimen, and parity were not statistically significantly different. Adjusting for maternal viral load at delivery, maternal age, and infant regimen, replication capacity was significantly associated with transmission (OR, 6.60; 95% CI, 1.23–35.31). The authors concluded that replication capacity appears to be related to MTCT and should be further evaluated in different HIV-1 subtypes, clinical settings, and modes of transmission.

Handelsman and colleagues (Abstract 718) presented results from a matched, case-control study comparing rates of GB virus C (GBV-C) viremia among HIV-seropositive women in the Women and Infants Transmission Study (WITS) who had (n = 133) and had not (n = 266) transmitted HIV to their infants. GBV-C viremia has been associated with improved survival, nonprogression, and response to antiretroviral therapy in HIV-infected persons (Williams et al, ***N Engl J Med***, 2004; Souza et al, ***HIV Med***, 2006). Of 397 women, 11% had evidence of active GBV-C and 36% had past infection. There was a trend toward protection against MTCT in women with active GBV-C (OR, 0.79; 95% CI, 0.52–1.2). Women with GBV-C viremia had lower plasma HIV-1 RNA levels and higher CD4+ cell counts than women without GBV-C infection. As noted in other studies, low birth weight, lack of antiretroviral therapy, and maternal HIV-1 RNA level during pregnancy were associated with MTCT. The authors conclude that the association between GBV-C viremia and lower HIV viral load and higher CD4+ cells counts, rather than the presence of GBV-C viremia itself, may explain the association with decreased MTCT that has been reported in other studies. Although there was a trend toward an independent correlation between GBV-C viremia and decreased MTCT, this trend was not statistically significant. More and larger cohorts are necessary to further evaluate the relationship between GBV-C viremia and MTCT.

Kissin and colleagues (Abstract 127) analyzed a point-of-care rapid HIV testing program in St. Petersburg, Russia. The program was initiated in April, 2004 in 2 maternity hospitals where women in St. Petersburg with unknown HIV status (had either never been tested or had their last test before 34 weeks gestation) are referred for labor and delivery.

All women with unknown HIV status are offered opt-out testing with a

rapid, HIV-1/HIV-2 test that has 100% sensitivity and 99.9% specificity. Standard enzyme immunoassay (EIA) and Western blot (WB) HIV testing is done in parallel with the rapid test. HIV-seropositive mothers and their infants receive single-dose nevirapine and infants receive replacement feeding. From April 2004 to April 2005, 4353 pregnant women presented to these hospitals and were eligible for rapid testing: 1408 women had never had an HIV test and 2945 had their last HIV test at before 34 weeks gestation; 2.3% of the women never tested and 22% of women whose last test was before 34 weeks gestation did not receive rapid testing. Results were not available at the time of delivery in 18.7% of the women who had never been tested and 4.1% of women whose last test was before 34 weeks gestation. Maternal seroprevalence was 6.6% (90 of 1375) in the never-before tested group and 0.4% (10 of 2296) in the group whose last test was before 34 weeks gestation. Seventy-six percent of seropositive women and 97.9% of their infants received HIV prophylaxis. By 18 months of age, infant HIV status had been determined in only 52.1% of infants born to seropositive mothers (49 of 94). Of the 49 with known HIV status, 10.2% were definitively or presumed to be HIV-seropositive and 89.8% were definitively or presumed to be HIV-seronegative. The authors concluded that the rapid HIV testing program is clinically successful; 22% of all maternal HIV diagnoses in St. Petersburg during the evaluation year were identified through this program.

HIV-1 Transmission in Breast Milk

It is estimated that breast milk transmission of HIV-1 accounts for nearly one half of all pediatric HIV-1 infections thereby significantly reducing the effects of prenatal and perinatal pMTCT (John et al, ***E Afr Med J***, 2001). The following studies evaluated factors associated with breast milk transmission of HIV in resource-limited settings where formula feeding is often associated with social stigma and other health risks (such as enteric infections due to contaminated water), and is frequently inaccessible due to cost.

Hoffman and colleagues (Abstract 730) presented results from a substudy of infants from HIV Prevention Trials Network (HPTN) 024. HPTN 024 was a multicenter, randomized, double-blind, placebo-controlled trial of antibiotics to prevent choriamnionitis-associated perinatal transmission. There were 2128 pregnant women from 4 sub-Saharan African sites (Blantyre and Lilongwe, Malawi; Dar es Salaam, Tanzania; and Lusaka, Zambia) enrolled. All received single-dose nevirapine according to the HIVNET 012 regimen and no difference in rates of transmission was found either at birth or at 4 to 6 weeks in the antibiotic versus placebo groups. Inclusion criteria for the substudy were infants from HPTN 024 who were HIV-seronegative as of 4 to 6 weeks but were subsequently HIV-seropositive (presumably via breast milk transmission if breast fed) in whom follow-up information was available (n = 1538). The cumulative incidence of HIV infection in the substudy group was 6.81 per 100 person-years of observation. Specific maternal socioeconomic factors (ie, literacy, parity, electricity in the house, body mass index [BMI]) and presence of breast infection were not associated with transmission. Higher levels of maternal hemoglobin and CD4 + cell count correlated with protection against transmission and higher plasma HIV-1 RNA levels and cervicovaginal HIV-1 RNA level were associated with risk for transmission in univariate analysis. In multivariate analysis, high plasma viral load and low CD4 + cell count remained statistically significantly associated with transmission. Infant factors including Apgar score, birth weight, presence of oral thrush, and sex did not correlate with transmission. Incidence of transmission after 4 to 6 weeks varied significantly among study sites with Dar es Salaam having the lowest incidence (3.5%) and Lusaka having the highest (10.5%). Biologic factors did not account for this difference in rates and the authors hypothesized that length and intensity of breast feeding may have accounted for regional differences. At Dar es Salaam, 98% of infants are weaned at 6 months and at the other sites, a majority of infants continued to be breast fed at 12 months.

Four abstracts at this year's conference (Abstracts 727, 728, 729, 730) evaluated the association between maternal factors and HIV-1 RNA level in breast milk.

Giuliano and colleagues from the Drug Resource Enhancement against AIDS and Malnutrition (DREAM) program (Abstract 727) in Mozambique conducted an observational study comparing levels of HIV-1 RNA in the breast milk of women who had or had not received prophylactic antiretroviral therapy for pMTCT. Through the DREAM program, pregnant, HIV-seropositive women received antiretroviral prophylaxis (zidovudine/lamivudine/nevirapine or stavudine/lamivudine/nevirapine) at 28 weeks gestation through 6 months postpartum and infants receive single-dose nevirapine within 72 hours of delivery. Levels of HIV-1 RNA in breast milk of 40 women enrolled in DREAM prepartum were compared with breast milk from 40 women diagnosed with HIV infection at delivery (who had therefore not received prophylaxis with potent antiretroviral therapy). Pretherapy median CD4 + count, HIV-1 RNA level, and time of therapy use in the treatment group was 538 cells/μL, 4.2 $\log_{10}$ copies/mL, and 83 days, respectively. At delivery and 7 days postpartum, HIV-1 RNA in breast milk of women who received antiretrovirals was lower than in women who did not: the median level was 2.3 $\log_{10}$ copies/ mL in the antiretroviral therapy group versus 3.4 $\log_{10}$ copies/mL in the nontherapy group at delivery and 1.9 $\log_{10}$ copies/mL versus 3.6 $\log_{10}$ copies/mL 7 days postpartum ($P \leq .001$ for both). The proportion of women with HIV-1 RNA level below 400 copies/mL in breast milk was also higher among therapy-treated women at delivery and 7 days postpartum: 46% treated versus 15% not treated at both time points ($P = .01$). Use of antiretrovirals was the strongest predictor of an HIV-1

RNA level below 400 copies/mL in breast milk. The authors concluded that these data support the role of maternal antiretroviral prophylaxis in prevention of breast-feeding associated HIV-1 transmission. Further studies are needed to determine if the observed decrease in breast milk viral load translates to a significant reduction in postnatal HIV-1 transmission.

Gantt and colleagues (Abstract 728) presented results from a prospective cross-sectional study of postpartum HIV-1–infected women in Zimbabwe to determine if infectious clinical and subclinical mastitis was associated with the level of detectable HIV-1 RNA in breast milk. Two hundred seventeen women were enrolled 1.5 to 7 months postpartum. Breast milk was aseptically collected, cultured for bacteria and fungi, and analyzed for HIV-1 RNA levels and absolute and differential white blood cell (WBC) counts. Seventeen of 217 (8%) women had symptoms consistent with clinical mastitis. Fifty of 428 samples of breast milk (12%) were culture positive for a bacterial or fungal pathogen, the most common pathogen being ***Staphylococcus aureus***. Subclinical mastitis (defined as total WBC count $>10^6$/mL breast milk) occurred in 60 of 217 women (28%). Positive culture was not associated with rate of detectable HIV-1 RNA, level of HIV-1 RNA, or clinical or subclinical mastitis. Presence of subclinical mastitis was not associated with symptoms. Absolute neutrophil count (ANC) was associated with detectable HIV-1 RNA in breast milk—the highest quartile of ANC (102 of 409 samples) had an OR of 3.64 for detectable HIV-1 RNA. The authors concluded that this elevated ANC, and therefore detectable level of HIV-1 RNA, could be associated with other infectious agents such as viruses, mycobacteria, or mycoplasma that were not looked for in this study.

Antiretroviral Therapy in Resource-Limited Settings

Results of selected studies are presented in Table 3. Etard and colleagues representing the Agence Nationale de Recherches sur la Sida (ANRS; Abstract 63) presented results of a prospective cohort study of patients treated through the Senegalese antiretroviral drug-access initiative program, the first government-sponsored treatment program in Africa. Four hundred four patients were observed for a median of 46 months. At study entry, 5% were antiretroviral therapy-experienced, and 55% had Center for Disease Control and Prevention (CDC) Stage C disease. Baseline median CD4+ cell count and plasma HIV-1 RNA were 128/μL and 5.2 $\log_{10}$ copies/mL, respectively. At treatment initiation, 41% received therapy free of charge, 42% started a PI-based regimen, and 79% were started on cotrimoxazole prophylaxis. At 60 months, the median CD4+ cell count increased by 300/μL, the median plasma HIV-1 RNA level decreased by 3 $\log_{10}$ copies/mL, and 60% had HIV-1 RNA below the limits of detection. During the follow-up period, 93 patients died, a majority (n=47) within the first year of antiretroviral initiation. The overall rate of death was 6.2 per 100 person-years (95% CI, 5.0–7.6). The death rate decreased over time with the cumulative probability of dying being 11.7% (95% CI; 8.5%–15.3%) during the first year and 25.7% (95% CI; 21.1%–31.0%) in year 6. Adjusting for baseline characteristics, independent predictors of survival were BMI at or above 19 kg/m^2 (HR for death, 0.54; 95% CI, 0.35–0.82); hemoglobin level at or above 10 g/dL (HR, 0.56; 95% CI, 0.37–0.85); and CD4+ count of 200 cells/μL or higher (HR, 0.43; 95% CI, 0.24–0.77). Age, sex, PI-containing regimen, financial participation, cotrimoxazole prophylaxis, and HCV or hepatitis B virus (HBV) carrier status were not statistically significant predictors of survival. Cause of death was ascertained in 76 instances through hospital records or postmortem interviews. Mycobacterial infections (n=17), neurologic disorders (n=16), and septicemia (n=10) were the most frequent causes of death.

Sinkala and colleagues (Oral Abstract 64) presented 1-year clinical and immunologic outcomes from a rapid scale-up of antiretroviral treatment programs in 18 public and private clinical sites across 3 provinces in Zambia. This government-sponsored treatment program, which provides antiretrovirals at no cost, started in May of 2004 and as of December 2005, 36,566 HIV-seropositive adults and children had been enrolled in the program and 22,121 patients had been started on antiretroviral therapy. A cohort of 18,075 adults enrolled from April 2004 to August 2005 of whom 11,074 (61%) started antiretroviral therapy. Among individuals who initiated antiretroviral therapy, 61% were women, and the median age and mean CD4+ count were 35 years and 131 cells/μL, respectively. Ten percent had hemoglobin below 8.0 g/dL and 73% were at World Health Organization (WHO) stage III or IV. Forty-seven percent started zidovudine/lamivudine/nevirapine, 45% stavudine/lamivudine/nevirapine, 4% zidovudine/lamivudine/efavirenz, and 4% stavudine/lamivudine/efavirenz. Over 81,248 patient-months, 1269 patients died (crude death rate 0.016 deaths per patient-month). Forty-three percent of deaths occurred in patients with entry CD4+ counts at or below 50 cells/μL and 53% of deaths occurred within 60 days of enrollment. Adjusted for baseline characteristics, risk of death was associated with CD4+ count between 50 and 200 cells/μL (HR, 1.5; 95% CI, 1.1–2.0); CD4+ count at or below 50 cells/μL (HR, 2.1; 95% CI, 1.5–3.0); WHO stage III (HR, 2.0; 95% CI, 1.4–2.7); WHO stage IV (HR, 3.3; 95% CI, 2.3–4.9); BMI below 16 kg/m^2 (HR, 2.3; 95% CI, 1.8–3.0); hemoglobin below 8.0 g/dL (HR, 3.1; 95% CI, 2.4–4.0); and nonadherence (90th percentile; HR, 3.1; 95% CI, 2.1–4.5). CD4+ cell count at 6 months was available for 11,854 individuals, 8284 of whom had started antiretroviral therapy. Individuals on antiretroviral therapy had a greater mean increase in CD4+ count at 6 months (61 versus 5 cells/μL; $P < .0001$) and at 12 months (85 versus –23 cells/μL; $P < .0001$) than those not on therapy.

Semitala and colleagues with the Academic Alliance for AIDS Care and Prevention in Africa (Abstract 555) presented the 6-month results of a treat-

Table **3**. Selected Studies from Resource-Limited Settings

Abstract Name (Abstract No.)	**Country, Treatment Program Type, Years of Enrollment**	**Baseline Treatment Regimen (No. of Patients)**	**Baseline Age (years), Sex, Clinical Stage, Treatment Experience**	**Baseline CD4+ Count (cells/μL), Plasma HIV RNA (log_{10} copies/mL)**	**CD4+ Count (cells/μL) Response**	**Plasma HIV RNA (log_{10} copies/mL) Response**	**Mortality**	**Comments**
Mortality and Causes of Death in Adults Receiving HAART in Senegal: A 7-Year Cohort Study (Abstract 63) Median follow-up of 46 months	Senegal Government–sponsored with ANRS 41% of subjects received antiretrovirals at no cost at enrollment (100% of participants received antiretrovirals at no cost by 2003) August 1998 to April 2002	First-line nRTI plus an NNRTI or PI 42% PI-based at initiation (n=404)	37 (median) 55% female 55% CDC class C 5% antiretroviral therapy-experienced	128 (median) 5.2 (median)	At month 60: +300 (median)	At month 60: –3 (median) 60% with <400	93 documented deaths, 51% in first year of antiretroviral therapy Death rate 6.2/100 person-years and decreased over time	Leading causes of death: mycobacterial infections, neurologic conditions, or septicemia or other infectious disease. Baseline BMI ≥19 kg/m^2, hemoglobin level ≥10 g/dL, and CD4+ count ≥200 cells/μL were predictors of survival.
Rapid Scale-up of Antiretroviral Services in Zambia: 1-year Clinical and Immunologic Outcomes (Abstract 64) Median follow-up was 165 days (range: 1 to 562 days)	Zambia Government-sponsored 100% of cohort received antiretrovirals at no cost April 2004 to August 2005	Zidovudine/lamivudine/nevirapine (47%) Stavudine/lamivudine/nevirapine (45%) Zidovudine/lamivudine/efavirenz (4%) Stavudine/lamivudine/efavirenz (4%; n=11,074)	35 (median) 61% female 73% WHO stage III or IV Antiretroviral therapy experience not reported	131 (mean) HIV RNA not available	At 6 months: +61 (mean); at 12 months: +85 (mean) At 12 months: +85 (mean) (n=8284)		1269 documented deaths, 53% within 60 days, 43% CD4+ count ≤50 cells/μL Crude death rate: 0.016 deaths/patient-month of observation	Risk of death associated with CD4+ count <200 cells/μL, WHO stage III or IV, hemoglobin <8.0 g/dL, and nonadherence (90th percentile) at baseline.

(continued next page)

Table **3**. Selected Studies from Resource-Limited Settings (continued)

Abstract Name (Abstract No.)	**Country, Treatment Program Type, Years of Enrollment**	**Baseline Treatment Regimen (No. of Patients)**	**Baseline Age (years), Sex, Clinical Stage, Treatment Experience**	**Baseline CD4+ Count (cells/μL), Plasma HIV RNA (log_{10} copies/mL)**	**CD4+ Count (cells/μL) Response**	**Plasma HIV RNA (log_{10} copies/mL) Response**	**Mortality**	**Comments**
Early Success of Antiretroviral Therapy in a Sub-Saharan African Cohort (Abstract 555) Follow-up of 6 months	Uganda Infectious Diseases Institute of Makerere University 100% of cohort received antiretrovirals at no cost	Stavudine/ lamivudine/ nevirapine (fixed-dose combination) Atazanavir/ lamivudine (fixed-dose combination) plus efavirenz stavudine/ lamivudine/ efavirenz (n=582)	37 (mean) 69% female 90% WHO stage III or IV 100% antiretroviral therapy-naive	100 (median) 5.8 (median; n=448)	221 (median; n=365)	85% <400 (n=448, not ITT)	58 documented deaths	No losses to follow-up or transfers. No statistically significant differences in baseline characteristics of HIV RNA level <400 copies/mL and ≥400 copies/mL. Baseline Karnofsky score, CD4+ cell count, and hemoglobin were predictors of survival.
Implementation of an Antiretroviral Therapy Access Program for HIV-Infected Individuals in Resource-limited Settings: Clinical Trial Results from 4 African Countries (Abstract 558) Follow-up of 24 months	Senegal, Côte d'Ivoire, Uganda, Kenya Supported by PharmAccess International and industry partner 100% of subjects received antiretrovirals at no cost February 2002 to December 2002	206 subjects enrolled; 192 received treatment Saquinavir/ ritonaivr (fixed-dose combination)plus lamivudine plus zidovudine	36 (median) 62% female 78% CDC class B or C (n=206)	119 (median) 5.5 (median)	+198 (median)	<400 (OT/ITT) across sites: 65%/52%; Kenya, 51%/40%; Senegal, 56%/46%; Côte d'Ivoire, 69%/54%; Uganda, 83%/69%.	16 deaths (7.8%)	6.3% lost to follow-up 5.3% withdrew (patient decision or inability to pick up medication). Exclusion criteria: investigator's opinion that subject unlikely to complete cohort or adhere to medications, severe HIV-related illness or opportunistic infection at time of enrollment, and hemoglobin <8 g/dL.

ANRS indicates Agence nationale de recherches sur le Sida; BMI, body mass index; CDC, Centers for Disease Control and Prevention; HAART, highly active antiretroviral therapy; ITT, intent-to-treat; nRTI, nucleoside (or nucleotide) analogue reverse transcriptase inhibitor; NNRTI, non-nucleoside analogue reverse transcriptase inhibitor; OT, on-treatment; PI, protease inhibitor; WHO, World Health Organization.

ment program in Uganda where antiretroviral therapy is available at no cost to patients. Between January 2004 and June 2005, 647 HIV-infected, antiretroviral therapy-naive adults were consecutively enrolled into an observational cohort at the Infectious Diseases Institute at Makerere University, Kampala, Uganda. Antiretroviral therapy was initiated shortly after enrollment in 582 patients and deferred in the rest. At baseline, 90% of individuals met the criteria for WHO clinical stage III or IV of disease. The initial regimen was stavudine/lamivudine/nevirapine (fixed-dose combination), zidovudine/lamivudine (fixed-dose combination)/efavirenz, or stavudine/lamivudine/efavirenz. By 6 months, 58 had died, 378 had plasma HIV-1 RNA levels at or below 400 copies/mL, 68 had plasma HIV-1 RNA levels above 400 copies/mL, and 78 were confirmed to be alive but had not completed the 6-month visit. There were no losses to follow-up and no transfers. Adjusting for baseline characteristics, predictors of plasma HIV-1 RNA level at or below 400 copies/mL were female sex (OR, 1.9; 95% CI, 1.10–3.30), Karnofsky score (OR, 0.97; 95% CI, 0.94–0.99), and stavudine dose (40 mg versus 30 mg: OR, 0.44; 95% CI, 0.22–0.88). Karnofsky score (OR for death, 0.97; 95% CI, 0.91–0.97), baseline CD4+ cell count (OR, 0.99; 95% CI, 0.99–0.999), and baseline hemoglobin (OR, 0.81; 95% CI, 0.68–0.95) were predictors of survival.

Results from an open-label treatment program conducted in 4 urban clinics in Senegal (Dakar), Côte d'Ivoire (Abidjan), Uganda (Kampala), and Kenya (Nairobi) were presented by Sow and colleagues (Abstract 558). Antiretrovirals were provided at no cost to patients and after participation in the study, patients were enrolled in government-sponsored antiretroviral provision programs; 206 individuals initiated therapy in 2002. Baseline characteristics were as follows: 78% CDC clinical category B or C, median CD4+ count 119 cells/μL, and median plasma HIV-1 RNA level 5.5 $\log_{10}$ copies/mL. At week 96, according to the ITT analysis, 52% of patients had plasma HIV-1 RNA levels below 400 copies/mL. Rates of viral load suppression varied by site: 40% in Nairobi, 46% in Dakar, 54% in Abidjan, and 69% in Kampala. The median increase in CD4+ count from baseline was 198 cells/μL (range 191 to 292 cells/μL) and did not differ significantly among sites. Of the 206 individuals who initiated therapy, 16 died (8%), 13 were lost to follow-up (6%), 11 discontinued due to patient decision, inability to pick up medications, or for unknown reasons (5%), and 166 (81%) are continuing treatment. Non-HIV–related serious adverse events were reported in 55 patients (27%); anemia and neutropenia were the most frequently reported (13 and 7 patients respectively). Thirty-five patients (17%) changed treatment due to toxicities.

Dillingham and colleagues (Abstract 556) conducted a retrospective analysis of 622 patients from Haiti who initiated antiretroviral therapy at the Groupe Haïtien d'Etude du Sarcome de Kaposi et des Infections Opportunistes (GHESKIO) Centers between March 2003 and June 2005. Baseline characteristics were mean weight for women was 112.5 lb, mean weight for men was 126.1 lb, mean CD4+ cell count 129/μL, and mean hemoglobin 10.5 g/dL. During follow-up, 69 (11%) patients died, 51 (74%) within the first 6 months. One-year survival was 86%. In a univariate analysis, the presence of diarrhea at initiation of antiretroviral therapy, the presence of wasting (weight < 25th percentile for sex), hemoglobin below 9.5 g/dL, and CD4+ cell count correlated with 1-year mortality. Sex, age, and tuberculosis at presentation were not significant predictors of survival. Adjusting for baseline characteristics, wasting (OR, 2.4; 95% CI, 1.4–3.9; $P = .001$) and hemoglobin below 9.5 g/dL (OR, 2.1; 95% CI, 1.3–3.5; $P = .003$) were the only independent risk factors for death in the first year. The authors concluded that intensive nutritional rehabilitation, micronutrient supplementation, and treatment of anemia could improve survival in resource-limited settings. It is also possible that low hemoglobin and presence of wasting are indicators of an undiagnosed underlying condition such as an opportunistic infection. The cause of death in this cohort was not assessed.

Adherence

Ensuring adherence to medications and clinic visits is essential to any successful antiretroviral treatment program. Several studies evaluated rates and predictors of adherence and tools to measure adherence in various resource-limited settings.

Marazzi and colleagues (Abstract 551) presented adherence results from the DREAM program in Matola, Mozambique. The DREAM program began in January 2002 and addresses specific psychosocial factors that interfere with adherence through the use of interventions such as health education and counseling for patients and staff, free antiretroviral treatment and laboratory tests (including CD4+ cell counts and viral load), nutritional support, and involvement of family and peer health educators in patient care. Therapy was initiated in 569 adult patients. At baseline, 3.7%, 19.5%, 35.1%, and 41.7% had been on antiretroviral therapy for more than 3 years, 2 to 3 years, 1 to 2 years, and 0 to 1 year, respectively. During the follow-up period, 28 patients (4.9%) died, 34 (6.0%) transferred to other clinics, and 20 (3.5%) abandoned the program, leaving 487 patients (85.6%) on treatment. Of those remaining on treatment, the last viral load was below 400 copies/mL in 359 (73.7%). Of the 128 with plasma HIV-1 RNA levels above 400 copies/mL, 100 (78.1%) kept 96.2% of their appointments (including visits for medical checkups, medication pickup, and laboratory tests) and were considered to have unsuppressed viral load due to problems unrelated to adherence. The other 28 with a detectable viral load (21.9%) kept fewer than 90% of their appointments, and were considered to be unsuppressed due to nonadherence. Using the definition of adherence as keeping more than 90% of all appointments (visits for medical checkups, medication pickup, and laboratory

tests) overall, 90.5% of patients were adherent and 9.5% nonadherent. This study illustrates that with a multidisciplinary approach, high levels of adherence, and minimal loss to follow-up can be maintained in resource-limited settings.

Ramadhani and colleagues (Abstract 553) evaluated predictors of nonadherence among patients at the Kilimanjaro Christian Medical Center Adult HIV Clinic in northern Tanzania. One hundred fifty consecutive adult patients on stavudine/lamivudine/nevirapine for 6 months or longer enrolled in the study. A structured questionnaire regarding adherence to antiretroviral therapy, sociodemographics, economic conditions, knowledge, beliefs, disclosure relating to HIV and antiretroviral therapy, access to care, and mental health was administered. Of the 150 patients, 16% were nonadherent (defined as self-reported adherence of less than 100%), 57% had no formal education or had primary education only, and 73% had started antiretroviral therapy before it was available for free. Poor adherence was associated with sacrificing healthcare to pay for food, education, or housing; self-pay for antiretroviral therapy; having to walk more than 19 minutes to the clinic; and paying more than US $3.60 per month for medicines. Free antiretroviral therapy and discussion of antiretroviral therapy side effects with healthcare worker at initiation of treatment was protective against poor adherence. Adjusting for baseline characteristics, sacrificing healthcare to pay for food, education, or housing remained a risk factor for nonadherence (OR, 59.9; 95% CI, 7.6–46.2) as did needing to walk more than 19 minutes to the clinic (OR, 7.3; 95% CI, 1.9–27.7). Discussion of antiretroviral therapy side effects with a healthcare worker at initiation of treatment (OR, 0.15; 95% CI, 0.04–0.60) and disclosure of HIV status to persons other than healthcare workers (OR, 0.10; 95% CI, 0.02–0.06) protected against nonadherence.

Muhindo and colleagues (Abstract 557) conducted a retrospective chart review of the first 500 antiretroviral therapy-naive patients initiating a self-pay, fixed-dose combination stavudine/lamivudine/nevirapine. At baseline, 16% had a prior history of tuberculosis; mean weight was 57 kg and mean CD4+ cell count (available for 81% of patients) was 98/μL. The median follow-up time was 21.5 months and the median treatment time was 18 months. At 12 months, 63% were on the initial regimen, 3.8% changed regimens, 5.0% had documented discontinuation of regimen, 20.8% were lost to follow-up, and 6.4% had documented death. During the entire follow-up period, 6.2% (n=31) had discontinued their regimen, 45% due to treatment of tuberculosis and 42% due to cost. Predictors of treatment discontinuation (adjusted for baseline characteristics) were baseline weight (HR, 0.98 per kg; 95% CI, 0.95–1.0), chronic diarrhea (HR, 2.80; 95% CI, 1.32–5.91) and having children (HR, 0.48; 95% CI, 0.24–0.99). This study highlights the fact that self-pay for antiretroviral therapy plays an important role in the ability to maintain antiretroviral therapy and follow-up for care.

Prior studies have shown that pharmacy data are a simple and useful way to evaluate adherence (Grossberg et al, ***J Clin Epidemiol***, 2004), which has been associated with survival (Nachega et al, CROI, 2005; Garcia de Olalla et al, ***J Acquir Immune Defic Syndr***, 2002). Nachega and colleagues (Abstract 62) presented a study evaluating the correlation between pharmacy refill data and plasma HIV-1 RNA level below 400 copies/mL. Among 3325 South African antiretroviral therapy-naive individuals who had initiated NNRTI-based regimens, the median CD4+ count was 151 cells/μL and the median plasma HIV-1 RNA level was 5.1 $\log_{10}$ copies/mL. The median follow-up time was 2.4 years. Adherence to antiretroviral therapy was calculated as a percentage: number of months patients submitted claims divided by number of months since antiretroviral therapy initiation. A significant dose-response relationship was seen between viral load suppression and adherence across strata with viral suppression achieved in 22% of patients with less than 70% adherence, 56% with 70% to 79% adherence, 69% with 80% to 89% adherence, 76% with 90% to 94% adherence, and 80% with 95% or better adherence (***P*** for trend < .001). Adjusting for baseline characteristics, high antiretroviral therapy adherence (≥95% versus <70%: OR, 15.6; 95% CI, 12.4–19.5), high baseline CD4+ cell count (>200/μL versus ≤50/μL: OR, 1.4; 95% CI, 1.1–1.7) and low baseline viral load (≤10^5 $\log_{10}$ copies/mL versus >10^5 $\log_{10}$ copies/mL: OR, 1.3; 95% CI, 1.1–1.5) were significantly associated with viral suppression. The authors concluded that pharmacy records are a simple and valid tool to monitor adherence at the program level.

Evaluating Response to Therapy in Resource-Limited Settings

Plasma HIV-1 RNA levels are crucial to accurately assess response to antiretroviral therapy but are much more expensive and therefore even more difficult to obtain than CD4+ cell counts in resource-limited settings. More cost-effective and accessible viral load methodologies are under development. Several presentations evaluated the utility of changes in CD4+ cell counts to approximate changes in viral load and responses to antiretroviral treatment.

Schechter and colleagues from the Antiretroviral Treatment in Lower-Income Countries (ART-LINC) Collaboration (Abstract 559) analyzed discordant immunologic and virologic responses to antiretroviral therapy among treatment-naive adults initiating antiretroviral therapy in resource-constrained settings. The ART-LINC Collaboration is a multinational network of HIV treatment programs in Africa, Brazil, and Asia. Eligibility criteria were previously being treatment naive, being older than 16 years, initiating treatment with 3 or more antiretroviral drugs, and availability of CD4+ cell counts and HIV-1 RNA results at 6 months (±1.5 months). In total, 1916 patients from 15 centers were eligible. Complete responders

were defined as individuals with an increase in CD4+ count of 50 or more cells/μL and a plasma HIV-1 RNA level below 500 copies/mL at 6 months. Discordant responders had increases in CD4+ counts of 50 or more cells/μL but plasma HIV-1 RNA levels above 500 copies/mL (CD4+/RNA-) or plasma HIV-1 RNA levels below 500 copies/mL but an increase in CD4+ count of 50 or less cells/μL (RNA+/CD4-). One thousand ninety-four individuals (57%) were complete responders, 365 (19%) were CD4+/RNA- discordant, 269 (14%) were RNA+/CD4- discordant, and 188 (10%) had no CD4+ cell count or viral load response and were excluded from the analysis. Older patients and those with higher baseline CD4+ cell counts were more likely to be CD4+/RNA- discordant. Younger patients, those with lower baseline CD4+ cell counts or higher baseline plasma HIV-1 RNA levels, and those who initiated a regimen that was not NNRTI-based were more likely to be RNA+/CD4- discordant.

Bisson and colleagues (Abstract 548) evaluated 384 treatment-naive patients at 2 clinics in Gaborone, Botswana to determine the accuracy of CD4+ cell count response in predicting plasma HIV-1 RNA levels at or below 400 copies/mL 6 months after initiation of antiretroviral therapy. Sixty-two percent were women and baseline median CD4+ count and plasma HIV-1 RNA level were 101 cells/μL and 5.5 $\log_{10}$ copies/mL, respectively. Eighty-three percent had HIV-1 RNA below the limits of detection at the 400 - copies/mL level at follow-up. Median increase in CD4+ cell count in those who became undetectable was 128/μL compared with 49/μL in those who were not undetectable ($P < .0001$). The discriminative ability of increases in CD4+ cell count from baseline to predict undetectable viral load at 6 months was determined by calculating the sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) for each cutoff point and further evaluated using receiver-operator characteristic (ROC) curves. A CD4+ count increase of 50 or more cells/μL from baseline in individuals with a baseline CD4+ count above 100 cells/μL (n=194) resulted in sensitivity, specificity, PPV, and NPV that predicted undetectable viral load of 73.1%, 41.2%, 85.4%, and 24.6%, respectively. These performance characteristics improved in individuals with a baseline CD4+ count of 100 or fewer cells/μL (n=190) with sensitivity, specificity, PPV, and NPV of 93.1%, 91.3%, 92.5%, and 63.3%, respectively. In the cohort of individuals with a baseline CD4+ count of 100 or fewer cells/μL, restricting viral load tests to individuals with an increase in CD4+ count of fewer than 50 cells/μL would lead to a decrease in confirmatory testing of 93% of individuals with undetectable viral loads and would detect 61% of failures. If the cutoff in this same cohort were changed to an increase in CD4+ count of 150 cells/μL, confirmatory HIV-1 RNA would be avoided in 48% of individuals with a detection of 90% of failures. The authors concluded that using changes in CD4+ cell counts to prioritize the use of viral load tests in resource-limited settings should be considered. Ultimately, having universal access to cost-effective viral load testing should be the goal for resource-limited settings.

Moore and colleagues (Abstract 547) performed similar analyses in 1125 antiretroviral therapy-naive individuals in British Columbia. The median baseline CD4+ count was 90 cells/μL. Suppressed viral load was defined as plasma HIV-1 RNA at or below 500 copies/mL at 2 time points within the first year of primary initiation of antiretroviral therapy. At 6 months, median CD4+ count was 180 cells/μL reflecting a median increase of 100 cells/μL. Sixty percent (n=674) had suppressed plasma HIV-1 RNA levels. Median time to viral load suppression was 2.4 months. Using criteria of no increase in CD4+ cell count by 6 months, sensitivity, specificity, PPV, and NPV to predict suppressed viral load were 34%, 94%, 75%, and 71%, respectively. Changing the threshold to no increase in CD4+ cell count by 12 months slightly improved these performance characteristics to 35%, 95%, 79%, and 73%, respectively. Using no increase in CD4+ cell count from baseline at 6 and 12 months, 21% and 25%, respectively would be incorrectly classified as failing treatment and only 34% to 35% of true treatment failures would be identified through these criteria.

Each of these studies highlights the significant discordance between CD4+ cell count and viral load responses to treatment and the effect that various patient characteristics have on the degree and direction of the discordance. In resource-constrained settings, there may be a role for CD4+ cell count in predicting virologic failure; however, more studies with larger cohorts are needed to further evaluate this relationship.

Conclusions

This year's conference proved itself to be the premier meeting of the year with respect to updating the field on the state-of-the-art of antiretroviral therapy. The new antiretroviral agent pipeline remains robust and promising; the results of treatment interruption trials have immediate implications for clinical practice; and the data presented from resource-limited settings are encouraging as reflections of the reality of antiretroviral rollout programs and the importance of reporting clinical and translational research results from the areas of the world that carry more than 90% of the global HIV-1 disease burden. As we mark the 25th anniversary of the AIDS epidemic and the 10th anniversary of the potent antiretroviral therapy era, the opening of a new era of life-saving therapy in the developing world is welcome and overdue.

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A list of all cited abstracts appears on pages 63 to 70.

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