Management of Antiretroviral Therapy

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As in previous years, the 9th Conference on Retroviruses and Opportunistic Infections provided a forum for a state-of-the-art update in antiretroviral therapy. Highlights included the status of new antiretroviral agents from both existing and new drug classes; presentation of trials in antiretroviral-naive and antiretroviral-experienced persons; updates on strategic approaches to therapy, including when to start therapy, treatment interruptions, and immune-based therapies; mechanisms and evolution of viral drug resistance; clinical applications of drug resistance testing; and therapeutic drug-level monitoring.

Antiretroviral Chemotherapy: New Investigational Agents

The advent of currently available antiretroviral medications has substantially reduced HIV-1-related morbidity and mortality. However, the increasing emergence of drug-resistant HIV-1 variants as well as short-term and long-term toxic effects of these agents limit their overall effectiveness. Several presentations at the conference addressed new antiretroviral agents, including new agents in existing classes with more favorable resistance or toxicity profiles, as well as agents in new classes with non-overlapping resistance mechanisms compared with currently available classes.

Entry Inhibitors

The chemokine receptors CCR5 and CXCR4 are coreceptors used by many strains of HIV-1 in addition to CD4 to enter cells. Attempts are under way to develop antiretroviral agents that inhibit HIV-1 entry by blocking these requisite coreceptors.

CCRX4 Receptor Blockers. AMD-3100 is a small-molecule CXCR4 receptor blocker with potent in vitro anti-HIV activity. Results of an open-label dose-escalation study to test the safety, pharmacokinetics, and antiviral effect of AMD-3100 were presented (Abstract 391-T). Forty HIV-infected volunteers with plasma HIV-1 RNA levels above 5000 copies/mL, on no or stable antiretroviral regimens, were enrolled and received 10 days of continuous intravenous infusion of AMD-3100 at a dose escalating from 2.5 µg/kg/hr up to 160 µg/kg/hr. Presence of the syncytium-inducing (SI) phenotype (one method for determining presence of CXCR4-using variants) was not part of the inclusion criteria, and only 28% of volunteers harbored SI variants.

The study was discontinued early because of adverse events and lack of antiviral effect. Adverse experiences, particularly gastrointestinal in nature, were generally common. Two patients experienced unexpected adverse events of premature ventricle contractions, and some patients in each dose group had atrial tachycardia. Three volunteers discontinued the study drug because of adverse events. No volunteer harboring SI virus showed a 1-log10 or higher drop in plasma HIV-1 RNA, but 1 patient harboring SI virus had a 0.9-log10 drop at day 10 of the highest dose. Of note however, through use of an entry assay that can identify HIV-1 isolates that are X4-, X5-, or dual-tropic, investigators observed that 9 of 19 patients with dual (X4/R5) or mixed (X4 and R5) virus at baseline exhibited a complete loss of X4 virus by day 11 of treatment. This result suggested the ability of the drug to eliminate X4 variants (Abstract 2). The drug is not currently going forward in clinical development, but proof of principle appears to have been established.

CCR5 Receptor Blockers. Laughlin presented the results for the first 12 HIV-infected volunteers treated with SCH-C, an orally bioavailable CCR5 receptor antagonist with potent in vitro antiviral activity against a broad range of primary HIV-1 isolates (Abstract 1). In this ongoing, sequential rising-dose trial, in which there will be 12 subjects per group, HIV-infected volunteers receive 10 days of SCH-C monotherapy with total daily doses of 50, 100, and 200 mg. To date, 12 HIV-infected adults, with CD4+ cell counts above 250/µL, currently not receiving antiretroviral therapy and with a non-SI phenotype, have received SCH-C 25 mg orally every 12 hours for 10 days and have undergone intensive pharmacokinetic and plasma HIV-1 RNA monitoring.

SCH-C was well tolerated, although in electrocardiogram testing, subtle prolongation of the mean QTc interval was seen over 10 days of the lowest dose. Ten of 12 volunteers experienced at least a 0.5-log10 reduction in plasma HIV-1 RNA level from baseline during dosing, and 4 subjects experienced a 1-log10 or greater drop in plasma HIV-1 RNA level from baseline. Thus these preliminary proof-of-principle data for SCH-C support further exploration of the CCR5 receptor as a target for antiretroviral therapy. The clinical future of SCH-C will depend in part on electrocardiographic findings at the higher doses.

One of the concerns of targeting the CCR5 coreceptor is that doing so could select for X4-using strains of HIV-1 that have been associated with more rapid CD4+ T-cell count decline and clinical progression. HIV-1 variants resistant to SCH-C were generated by in vitro pas- sage of HIV-1 strains in peripheral blood mononuclear cells (PBMCs) in the presence of increasing concentrations of SCH-C (Abstract 397-T). Characterization...
of the emerging variants with reduced sensitivity to SCH-C showed no switch to other chemokine receptors including CXCR4. However, it has not been determined whether this switch occurs in vivo. Similar findings in terms of continued CCR5 coreceptor use by resistant virus were reported from in vitro serial passaging experiments in the presence of SCH-D, another potent small-molecule antagonist of CCR5 in preclinical development (Abstract 396-T).

PRO 140 is an anti-CCR5 monoclonal antibody that potently inhibits HIV-1 entry in vitro. Results of a study evaluating the antiviral activity of PRO 140 in vivo in the hu-PBL-SCID mouse model of HIV-1 infection were presented (Abstract 403-T). The mice were infected with the R5 isolate HIV-1 JR-CSF and then treated intraperitoneally with PRO 140 or a control antibody. Both single-dose (1 mg) and multiple-dose (0.1-1.0 mg every 3 days for 3 weeks) PRO 140 reduced plasma HIV-1 RNA to levels below detection in all treated animals, with the highest plasma HIV-1 RNA level reduction being 1.8 log10 copies/mL. Dose-dependent differences were observed in the kinetics of the antiviral response. Further studies of this compound in HIV-infected volunteers are planned.

**Novel Entry Inhibitors.** Colonno described the identification and characterization of a novel small-molecule inhibitor of HIV-1 entry, BMS-806, which was identified using a cell-based screen and is believed to target the HIV-1 envelope protein (Abstracts 9 and 10). In vitro assays have demonstrated that the compound competitively inhibits the binding of gp120 to CD4 and that the radiolabeled inhibitor binds selectively to purified gp120 protein. The compound potently inhibits HIV-1 clinical isolates and laboratory strains (R5-, X4-, and dual-tropic variants) with a median effective concentration (EC50) of 62 nM in culture assays with subtype-B isolates, and is inactive against HIV-2 and simian immunodeficiency virus (SIV). BMS-806 has low cytotoxicity and is orally bioavailable in rats, dogs, and monkeys. Preliminary animal toxicology studies have revealed no safety concerns as of yet. In vitro passaging of HIV-1 strains in the presence of the compound selected for resistant strains, with mutations located within either gp41 or the CD4 binding site of gp120.

A cautionary note was sounded regarding the targeting of the very heterogeneous HIV-1 envelope protein: although 20 of 24 subtype-B isolates were inhibited by BMS-806 with an EC50 below 100 nM, 4 outliers had an EC50 as high as 10,000 nM. Future studies with this promising compound will elucidate the mechanism of this diminished susceptibility and the potential of this agent to inhibit a wide variety of HIV-1 strains.

**Integrase Inhibitors**

In vitro data for a new HIV-1 integrase inhibitor in clinical development were presented by Fujiwara and colleagues (Abstract 8). S-1360 is an orally available small-molecule inhibitor of HIV-1 integrase, the enzyme essential for the integration of HIV-1 proviral DNA into host-cell chromosomes. The compound is an integrase inhibitor with an EC50 of 28 to 74 ng/mL in vitro against clinical isolates, and has demonstrated anti-HIV activity in a mouse-MT4 in vivo assay. HIV-1 variants resistant to S-1360 have been isolated in vitro and the amino acid substitutions responsible for drug resistance have been shown to be in close proximity to the integrase active site (eg, T66I). This compound is currently being investigated in a phase 1/2 study of HIV-infected volunteers.

**Nucleoside and Nucleotide Reverse Transcriptase Inhibitors**

DPC 817 (Abstract 385-T) is a cytidine nucleoside reverse transcriptase inhibitor (nRTI) with activity against many lamivudine- and zidovudine-resistant HIV-1 isolates. It is rapidly converted to the active triphosphate form, which has an intracellular half-life of 13 to 17 hours. DPC 817 inhibits wild-type laboratory and clinical isolates of HIV-1 with a mean 90% inhibitory concentration value of 855 nM, and shows less than 5-fold reduction in activity against recombinant viruses containing as many as 10 mutations, including M41L, M184V, D67N, L74V, K70R, T215Y, or K219Q. Thus DPC 817 may be effective in individuals with resistance to other nRTIs and is currently under investigation in a phase 1/2 clinical trial.

**Nonnucleoside Reverse Transcriptase Inhibitors**

TMC125 is a novel, second-generation investigational nonnucleoside reverse transcriptase inhibitor (NNRTI) with equally potent in vitro activity against wild-type HIV-1 and NNRTI-resistant HIV-1 bearing the L100I, K103N, Y181C, Y188L, or G190A/S mutations. Gazzard (Abstract 4) presented results of a trial evaluating the antiviral activity of TMC125 in patients on failing NNRTI-containing regimens. Sixteen male volunteers with documented resistance to efavirenz (>10-fold decrease in susceptibility by VirtualPhenotype and/or Anti- virogram [Tibotec-Virco, Mechelen, Belgium], in whom an efavirenz- or nevirapine-containing regimen was failing, were enrolled. They received 900 mg of TMC125 orally twice daily for 7 days in place of the failing NNRTI, and continued to take their nRTIs unchanged. One patient was withdrawn because of non-adherence. Median baseline plasma HIV-1 RNA level was 10,753 copies/mL and median baseline CD4+ cell count was 389/µL. Median fold-change in EC50 to efavirenz at screening was 111 (range, 16-659), and all patients had greater than 35-fold decreased sensitivity to nevirapine.

TMC125 was well tolerated in this study, with 11 patients reporting grade 1 adverse events, the most common of which were diarrhea and headache. No lab abnormalities or electrocardiographic changes were observed. The median drop in plasma HIV-1 RNA level at day 8 was 0.89 log10 copies/mL (mean, 0.86
Log_{10} copies/mL. Thus, TMC125 is well tolerated and has significant antiviral potency against NNRTI-resistant HIV-1 in vivo.

One question raised by this presentation is why the plasma HIV-1 RNA decline was less than that seen in NNRTI-naive individuals treated with TMC125 in a separate study (Abstract 5), despite the in vitro activity profile of the drug against NNRTI-resistant isolates. The possibility of pharmacokinetic interactions with lingering efavirenz or nevirapine was given as one possible explanation, but this needs to be clarified in future studies.

In the study of TMC125 in 12 NNRTI-naive subjects (Abstract 5), the initial rate of decline of plasma HIV-1 RNA observed during 1 week of monotherapy with TMC125 900 mg twice daily was compared retrospectively with that obtained during the previously performed 13-patient ERA study of a 5-drug combination of zidovudine, lamivudine, abacavir, indinavir, and nevirapine. The median decline in plasma HIV-1 RNA level was comparable between the 2 groups: 1.92 log_{10} copies/mL for TMC125-treated patients and 1.55 log_{10} copies/mL for ERA patients (P=0.40). The 2 groups, however, did differ significantly in terms of age (mean, 25 years for the TMC125 group and 40 years for the ERA group), and there was a trend toward higher baseline CD4+ counts in the TMC125 group (458 vs 360 cells/µL). The authors concluded that TMC125 is a highly potent NNRTI.

DPC 083 is another investigational NNRTI with activity against NNRTI-resistant isolates. Preliminary 8-week results were presented of Study DPC 083-203, an ongoing study of the use of DPC 083 (either 100 mg or 200 mg once daily) and 2 nRTIs (selected based on treatment history and baseline genotype) in patients failing NNRTI-containing regimens (Abstract 6). Fifty-one patients were enrolled, with a mean baseline plasma HIV-1 RNA level of 3.85 log_{10} copies/mL and a mean baseline CD4+ cell count of 473/µL. Nevirapine had failed in 61% and efavirenz had failed in 39%. In 94% of patients, baseline mutations were consistent with virologic failure on an NNRTI regimen. The on-treatment response rate at week 8 (HIV-1 RNA level <400 copies/mL, pooled for the 100 mg and 200 mg doses, was 57% and varied according to the number of new nRTIs used: 4 of 10 (40%) for patients starting no new nRTIs, 13 of 18 (72%) for patients starting 1 new nRTI, and 10 of 15 (66.7%) for patients starting 2 new nRTIs. Thus, data at 8 weeks suggest that DPC 083 has activity in patients in whom currently available NNRTIs are failing, but that the response rate improves when DPC 083 is used in combination with at least 1 new nRTI. However, almost 30% of patients enrolled were discontinued from the study, mostly because of protocol violations.

The 24-week results of a phase 2, double-blind, dose-ranging study (Study DPC 083-201) of DPC 083 (50, 100, and 200 mg once daily) versus efavirenz in combination with fixed-dose lamivudine/zidovudine in antiretroviral-naive patients were also presented (Abstract 7). As a result of this study, the 100-mg dose of DPC 083 was selected for a phase 3 study in NNRTI-naive patients. At this lower dose, DPC 083 was associated with less dizziness and the same frequency of rash as efavirenz.

**Protease Inhibitors**

Atazanavir is a once-daily protease inhibitor in development that has been shown not to increase total cholesterol, low-density lipoprotein (LDL), or triglyceride levels in antiretroviral-naive individuals. Haas presented the results of a randomized, active-controlled, blinded study that evaluated the safety, tolerability, and efficacy of atazanavir (400 or 600 mg qd)/saquinavir (1200 mg qd) and 2 nRTIs versus ritonavir (400 mg bid)/saquinavir (400 mg bid) and 2 nRTIs (Abstract 42). Study subjects were volunteers in whom a prior regimen was virologically failing. Efficacy and lipid results at week 48 were presented for 85 subjects having a plasma HIV-1 RNA level of 1000 to 100,000 copies/mL and CD4+ cell counts of at least 100/µL. There were fewer treatment discontinuations due to adverse effects in the atazanavir arm than in the ritonavir arm (9% vs 30%). The mean decrease in plasma HIV-1 RNA levels at week 48 was 1.44 log_{10} copies/mL in the 400-mg atazanavir arm, 1.19 log_{10} copies/mL in the 600-mg atazanavir arm, and 1.66 log_{10} copies/mL in the ritonavir arm.

Subjects receiving the atazanavir-containing regimen experienced decreases in cholesterol, LDL, and triglyceride levels with mean percent change from baseline of 1, −5, and −7, respectively, for the 400-mg dose of atazanavir; and −5, −7, and −27, respectively, for the 600-mg dose of atazanavir. In contrast, subjects in the ritonavir-containing arm experienced sustained increases in total cholesterol, LDL, and triglyceride levels, with mean percent change from baseline of +11, +23, and +93, respectively. A new protease inhibitor without adverse effects on lipids would be a welcome addition to the antiretroviral armamentarium.

**Antiretroviral Chemotherapy in Antiretroviral-Naive Subjects**

**Timing of Initial Antiretroviral Therapy**

Optimal timing of antiretroviral therapy initiation for HIV-infected patients remains unclear. Chaisson addressed this topic during the “Controversies in Antiretroviral Therapy” symposium (Abstract S17). He discussed whether data exist to justify the following rationales for early treatment:

1. Will early treatment lead to eradication? No, not with current therapy.
2. Does early therapy lead to better virologic response? Probably not; in studies that have shown a worse virologic response when treatment is initiated with CD4+ cell counts below 200/µL, the results may have been confounded by poorer adherence in the delayed initiators.
3. Do patients who are treated later experience more drug-related toxicity? Perhaps in the short-term, but some long-term toxicities such as new-onset hyperglycemia are common to all.

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Thus the remaining question is whether early treatment improves clinical outcome. The answer to this question remains elusive in part because of the difficulty in performing a randomized clinical trial to address the question. Chaisson discussed a previously published observational cohort study from the Johns Hopkins HIV program that followed 2 groups of patients who entered the clinic after July 1, 1996 (Sterling et al., AIDS, 2001). The first group initiated antiretroviral therapy for at least 90 days, and the second group did not initiate antiretroviral therapy. Patients who initiated antiretroviral therapy were more likely to be men, less likely to be African American or injection-drug users, and had lower baseline CD4+ cell counts and higher baseline plasma HIV-1 RNA levels than the group that did not initiate antiretroviral therapy.

Among persons with CD4+ cell counts below 200 µL at entry, patients who initiated antiretroviral therapy experienced a lower rate of progression to AIDS or death. Patients with CD4+ cell counts from 201 to 350 µL or higher experienced no change in clinical disease progression whether or not therapy was initiated. By multivariate analysis of persons on antiretroviral therapy, low CD4+ cell count (<200 µL) at the time of initiation predicted progression to AIDS, but the plasma HIV-1 RNA level was not as predictive.

Chaisson thus concluded that patients who initiate antiretroviral therapy at CD4+ cell counts above 350 µL have not been shown to benefit clinically and that the optimal time to initiate antiretroviral therapy for patients with CD4+ cell counts from 200 µL to 350 µL has not been determined. Patients with CD4+ cell counts below 200 µL should initiate treatment. He also concluded that a high plasma HIV-1 RNA level by itself should not be an indication for treatment, but might suggest more frequent monitoring. He acknowledged the following caveats to these conclusions: observational cohorts are subject to measurable and unmeasurable confounding and cannot replace randomized controlled trials; variability between cohorts is problematic; and follow-up is limited—we do not as yet know whether 5 or 10 years of follow-up will show that either early or delayed initiation is more beneficial. Survival data have been based on 2- or 3-year follow-up.

Paletta presented data from the HIV Outpatient Study (HOPS), which suggested that patients who initiate antiretroviral therapy at higher CD4+ cell counts experience lower mortality (Abstract 13). They grouped patients observed at 8 US clinics participating in the HOPS from January 1996 to March 2001 into 1 of 3 pretreatment CD4+ cell count strata: 501 to 750 cells/µL (n=126), 351 to 500 cells/µL (n=315), and 201 to 350 cells/µL (n=377). In a prospective analysis, they looked at mortality rates in each pretreatment therapy CD4+ cell count stratum, comparing patients who initiated antiretroviral therapy while in that pretherapy stratum with patients who delayed antiretroviral therapy until they reached a lower stratum.

For patients with CD4+ counts of 201 to 350 cells/µL, 20.8 deaths per 1000 person-years of observation occurred in 325 “initiators” and 70.6 deaths per 1000 person-years of observation occurred in 52 “delayers” (rate ratio [RR]=0.29, P<0.001; median years of follow-up, 3.0 for initiators and 3.3 for delayers, P>0.3). For patients with CD4+ counts between 351 and 500 cells/µL, 10.7 deaths per 1000 person-years of observation occurred in 229 initiators and 18.2 deaths per 1000 person-years of observation occurred in 86 delayers (RR=0.59, P>0.3; 95% confidence interval [CI], 0.21, 1.65; median years of follow-up, 3.7 for initiators and 3.4 for delayers, P>0.3). For patients with CD4+ counts of 501 to 750 cells/µL, 7.5 deaths per 1000 person-years of observation occurred in 54 initiators and 3.0 per 1000 person-years occurred in 72 delayers (RR=2.25, P<0.4), but only 3 deaths occurred in this stratum, none apparently HIV-related (median years of follow-up, 5.9 for initiators and 5.3 for delayers, P>0.3).

The authors concluded that these preliminary data suggest that initiation of antiretroviral therapy for patients with CD4+ counts of 201 to 350 cells/µL, and possibly for patients with CD4+ counts of 351 to 500 cells/µL, is associated with a reduction in mortality in comparison with those who delay therapy.
logic response.

**CHARM Study.** The CHARM study was a phase 3, open-label, randomized, multicenter study to evaluate the efficacy and tolerability of adding nevirapine and/or hydroxyurea to a triple-nRTI regimen in treatment-naive HIV-1-infected subjects (Abstract 410-W). Volunteers with plasma HIV-1 RNA levels above 5000 copies/mL were randomized using a factorial design to add nevirapine and/or hydroxyurea to the combination of zidovudine, lamivudine, and abacavir. The primary endpoint was treatment failure defined as plasma HIV-1 RNA level above 50 copies/mL at or after week 24, or discontinuation of or change in randomized treatment. A total of 229 volunteers were enrolled, with baseline CD4+ cell count of 269/µL and baseline plasma HIV-1 RNA level of 4.6 $\log_{10}$ copies/mL.

By intent-to-treatment analysis at week 48, treatment failure had occurred in 60% of volunteers receiving nevirapine, compared with 62.3% of patients not receiving nevirapine ($P=.826$). The as-treated failure rates were 21.1% and 27.1%, respectively ($P=.445$). By intent-to-treatment analysis at week 48, treatment failure had occurred in 69.3% of volunteers receiving hydroxyurea, compared with 53.9% of patients not receiving hydroxyurea ($P=.017$). The as-treated failure rates were 23.9% and 24.3%, respectively ($P=.963$). The odds ratio of experiencing treatment failure at week 48 was 1.71 (95% CI, 1.11, 2.62) for hydroxyurea use.

Treatment-limiting adverse events occurred more frequently in subjects taking hydroxyurea (51.8%) than in those not taking hydroxyurea (26%; $P<.001$); adverse events also occurred more frequently in subjects taking nevirapine (46.1%) than in those not taking nevirapine (31.6%; $P=.024$). In the intent-to-treat analysis, a slower increase in mean CD4+ cell count was seen in subjects receiving hydroxyurea than in subjects not receiving hydroxyurea. Thus, neither the addition of hydroxyurea nor the addition of nevirapine to the triple-nRTI regimen decreased the primary endpoint of treatment failure, and addition of either hydroxyurea or nevirapine increased the incidence of adverse events.

**Study M99-056.** Eron presented the 48-week results of study M99-056 comparing once-daily and twice-daily dosing of...
The efavirenz/indinavir group had superior virologic response: 39 virologic failures vs 52 in indinavir arm (P=0.04). The nelfinavir/indinavir group had inferior virologic response: 81 virologic failures vs 52 in indinavir arm (P=.006).

Adverse events and adherence were similar in the 2 groups. The qd group had lower lopinavir trough levels.

36 patients (33%) discontinued therapy because of adverse events: 10, efavirenz-related rash or central nervous system symptoms; 6, neuropathy; 3, nausea; 2, leukopenia or anemia; 1, lipodystrophy; 1, asthenia; 2, emergence of resistance; and 11, reasons not related to therapy. Overall cholesterol levels increased by 28% from baseline.

Efavirenz. Domula presented the results of a study evaluating the safety and efficacy of efavirenz in combination with 3 different dual nRTI combinations in antiretroviral-naive HIV-1-infected patients (Abstract 408-W). Patients received efavirenz in combination with zidovudine/lamivudine (n=35), lamivudine/stavudine (n=35), or didanosine/stavudine (n=38). Median baseline plasma HIV-1 RNA level was 4.9 log₁₀ copies/mL and CD4+ cell count was 174/µL. By intent-to-treat analysis at 48 weeks, the percentage of patients with plasma HIV-1 RNA level below 50 copies/mL was 37% in the zidovudine/lamivudine group, 40% in the lamivudine/stavudine group, and 37% in the didanosine/stavudine group. (By on-treatment analysis, the percentages were 81%, 82%, and 74%, respectively.) There were no statistically significant differences in virologic response among the 3 groups.

Over 48 weeks, 36 patients (33%) discontinued therapy because of adverse events, although in 11, these were not related to therapy: 10 stopped because of efavirenz-related effects (rash and central nervous system effects), 6 because of didanosine/stavudine-related neuropathy, 3 because of nausea, 2 because of anemia or leukopenia, 1 because of lipodystrophy, 1 because of asthenia, and 2 because of development of resistance. Overall, cholesterol levels increased by 28% from baseline to week 48 (P=.0001), with a preponderance of cholesterol elevations in the didanosine/stavudine arm, and triglyceride levels increased by 38% from baseline (P=.004). The authors conclude that efavirenz in combination with any of the 3 different nRTI pairs is an effective initial antiretroviral regimen. However, 33% of volunteers terminated therapy early because of adverse events, of which approximately two-thirds were therapy related, and these protease inhibitor-sparing regimens were not immune to adverse effects on lipids.

Coformulated lopinavir/ritonavir in combination with stavudine and didanosine (Abstract 409-W). Thirty-eight antiretroviral-naive patients with median baseline plasma HIV-1 RNA level of 4.7 log₁₀ copies/mL and CD4+ cell count of 264/µL were randomized to receive lopinavir/ritonavir 800/200 mg once daily or lopinavir/ritonavir 400/100 mg twice daily in addition to the standard doses of stavudine and lamivudine. Lopinavir area-under-the-curve and maximum concentration (C_max) values were similar for the daily and twice-daily regimens, but overall median lopinavir trough concentration/IC₅₀ was lower in the daily than the twice-daily regimen (40 vs 84). Pharmacokinetic data from this study were also given in an oral presentation by Bertz (Abstract 126).

By intent-to-treat analysis in which missing data equaled failure, 74% and 79% of patients in the daily and twice-daily groups, respectively, had plasma HIV-1 RNA levels below 50 copies/mL at week 48. The mean CD4+ cell count increases from baseline to week 48 were 238/µL and 248/µL for the daily and twice-daily groups, respectively. Adherence was similar between the treatment groups as measured by medication event monitoring system (MEMS cap) analysis. The frequency of adverse events (nausea, diarrhea, lipid abnormalities) was comparable across the 2 groups.

Up to 20% of a study evaluating the safety and efficacy of efavirenz in combination with 3 different dual nRTI combinations in antiretroviral-naive HIV-1-infected patients (Abstract 408-W). Patients received efavirenz in combination with zidovudine/lamivudine (n=35), lamivudine/stavudine (n=35), or didanosine/stavudine (n=38). Median baseline plasma HIV-1 RNA level was 4.9 log₁₀ copies/mL and CD4+ cell count was 174/µL. By intent-to-treat analysis at 48 weeks, the percentage of patients with plasma HIV-1 RNA level below 50 copies/mL was 37% in the zidovudine/lamivudine group, 40% in the lamivudine/stavudine group, and 37% in the didanosine/stavudine group. (By on-treatment analysis, the percentages were 81%, 82%, and 74%, respectively.) There were no statistically significant differences in virologic response among the 3 groups.

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combined was not significantly different than the placebo arm at 48 weeks (77% vs 82%, respectively; P=.17).

Mellors presented an extensive analysis of the predictors of virologic failure. In a multivariate analysis, baseline phenotypic susceptibility to efavirenz was the most important predictor of virologic failure. Other important predictors were oral efavirenz clearance, NNRTI experience, medication adherence as measured by MEMS cap monitoring, and specific adherence to efavirenz. NNRTI-naive patients with a 0.4-fold or less change in baseline phenotypic resistance to efavirenz (ie, IC50 60% lower than laboratory strain), also known as “hypersusceptibility,” had less

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<tr>
<th>Authors, Study (Abstract No.), and Regimen (s)</th>
<th>N</th>
<th>Follow-up (weeks)</th>
<th>Baseline Values</th>
<th>Change in Values</th>
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<td>HIV-1 RNA (copies/mL)</td>
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<td>Haas et al, AI424-009 (42)</td>
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<tr>
<td>1. atazanavir 400 mg/saquinavir sgc 1200 mg qd/2 nRTIs</td>
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<td>Squires et al, Study 907 (413 W)</td>
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<td>Mellors et al, ACTG 398 (45)</td>
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<td>1. amprenavir/abacavir/efavirenz/adefovir/saquinavir sgc 1600 mg or indinavir 1200 mg or nelfinavir 1250 mg bid</td>
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ACTG indicates AIDS Clinical Trials Group; NNRTI, nonnucleoside reverse transcriptase inhibitor; nRTI, nucleoside reverse transcriptase inhibitor; sgc, soft-gel capsule; tenofovir, tenofovir disoproxil fumarate.
Atazanavir arms had fewer discontinuations due to adverse effects (10% vs 30%) and had a more favorable lipid profile.

Outcome was a time-weighted average decline of log_{10} plasma HIV-1 RNA level. Tenofovir had a significantly greater decline in plasma HIV-1 RNA levels than placebo (P<.0001). The subjects were highly antiretroviral-experienced: 48% had baseline NNRTI mutations, 58% had baseline protease inhibitor mutators, and 94% had nRTI mutations. The mean length of antiretroviral use was 5.4 years. Grade 3 or 4 abnormalities were <2% in all groups. Serum creatinine did not rise above 2.0 mg/dL in any patients. A change of >.5 mg/dL was seen in 12 (3%) participants receiving tenofovir for 48 weeks compared with 2 (1%) receiving placebo for 24 weeks. No one discontinued study drug because of change in creatinine or hypophosphatemia.

Of the participants, 44% were NNRTI-experienced. Virologic suppression was strongly predicted by efavirenz hypersusceptibility (<.4-fold resistance) having a 0.27 odds of virologic failure (P<.001). There was a high dropout rate due to toxicities (30% at 24 weeks and 42% at 48 weeks).

(table continued on next page)

**Strategies for Antiretroviral Therapy**

**Structured Treatment Interruptions**

Hirschel gave an overview of the controversies associated with structured treatment interruptions (STIs) during the “Controversies in Antiretroviral Therapy” symposium (Abstract S18). The main reasons he outlined for considering stopping therapy were to decrease cost, avoid adverse effects, and boost HIV-specific immunity. The 3 situations in which STI is currently being studied are (1) patients who began potent antiretroviral therapy prior to seroconversion and are chronically virologically suppressed, (2) patients who began potent antiretroviral therapy during the chronic phase of infection (ie, established infection) and who are virologically suppressed, and (3) prior to a salvage regimen in patients with highly drug-resistant virus, to induce resensitization of virus. He stressed that large studies are needed to compare STI to simply discontinuing therapy and to weigh the risks and benefits of STI. Abstracts from the conference examining STI in each of these situations will be discussed in the following sections.

**Primary Infection.** Miró and colleagues (Abstract 529-M) reported preliminary results from an ongoing study of 12 patients who began highly active antiretroviral therapy (HAART) during primary HIV infection at least 1 year prior to enrollment and who had sustained virologic suppression. These participants will undergo 4 cycles of STI: 2 months off followed by 2 to 4 months on therapy. Viral suppression to below 5000 plasma HIV-1 RNA copies/mL was achieved in 4 of 12 patients after the third STI. A strong CD8+ cytotoxic T lymphocyte (CTL) response developed in 7 of 9 participants after the third STI.

Yu and colleagues described the CTL response in a single patient treated with HAART during acute HIV infection (Abstract 537-M). They were able to document a broadening CTL response in this patient during 2 subsequent STIs using 505 overlapping peptides spanning the entire expressed HIV-1 sequence. Only 2 epitopes were targeted during acute infection compared with 25 at the end of the second STI. However, as of the end of the second STI, virologic control in this patient was not maintained off HAART.

**Chronic (Established) Infection.** Several presentations examined the outcomes associated with treatment interruptions in the setting of established infection. The largest of these studies came from the EuroSIDA group (Abstract 48) in
which 565 of 3610 assessable patients interrupted HAART. The median nadir CD4+ cell count prior to beginning HAART for those subsequently interrupting therapy was 130/µL and the median CD4+ cell count at time of interruption was 242/µL. Participants had to be followed up for at least 3 months after stopping to be included in this analysis. The risk of developing a new AIDS-defining event or death was 6 times higher among those stopping antiretroviral therapy than among those who did not. When controlling for the last-known CD4+ cell count and HIV-1 RNA level,

### Table 2. Trials in Treatment-Experienced Patients (continued from page 24)

<table>
<thead>
<tr>
<th>Authors, Study (Abstract No.), and Regimen (s)</th>
<th>N</th>
<th>Follow-up (weeks)</th>
<th>Baseline Values</th>
<th>Change in Values</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Lalezari et al, T20-206 (418-W)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1. Pentafuside (50, 75, or 100 mg) bid/abacavir/efavirenz/amprenavir/ritonavir bid</td>
<td>52</td>
<td>48</td>
<td>4.28 log₁₀</td>
<td>279</td>
</tr>
<tr>
<td>2. abacavir/efavirenz/amprenavir/ritonavir bid</td>
<td>19</td>
<td></td>
<td>4.25 log₁₀</td>
<td>201</td>
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<tr>
<td><strong>Boyd et al, HIV-NAT 005 (422-W)</strong></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1. zidovudine/lamivudine/indinavir 800 mg/ritonavir 100 mg bid</td>
<td>50</td>
<td>76</td>
<td>4.0 log₁₀</td>
<td>168</td>
</tr>
<tr>
<td>2. zidovudine/lamivudine/indinavir tid</td>
<td>54</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Baldini et al (423-W)</strong></td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Single arm: lopinavir/ritonavir 400 mg/100 mg bid/amprenavir 600 mg bid/and 2 nRTIs</td>
<td>22</td>
<td>24</td>
<td>4.8 log₁₀</td>
<td>177</td>
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<tr>
<td><strong>Albrecht et al, ACTG 364 (425-W)</strong></td>
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<td></td>
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<td></td>
</tr>
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<td>1. nelfinavir/placebo/2 nRTIs</td>
<td>195</td>
<td>144</td>
<td>3.9 log₁₀</td>
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<td>2. efavirenz/placebo/2 nRTIs</td>
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<td><strong>Lafeuillade et al, HYDILE (424-W)</strong></td>
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<tr>
<td>1. didanosine/stavudine/abacavir/efavirenz</td>
<td>24</td>
<td>48</td>
<td>4.2 log₁₀</td>
<td>386</td>
</tr>
<tr>
<td>2. didanosine/stavudine/abacavir/efavirenz/hydroxyurea</td>
<td>22</td>
<td></td>
<td>3.8 log₁₀</td>
<td>386</td>
</tr>
<tr>
<td>3. didanosine/stavudine/abacavir/efavirenz/hydroxyurea/interleukin-2</td>
<td>23</td>
<td></td>
<td>3.9 log₁₀</td>
<td>386</td>
</tr>
</tbody>
</table>

ACTG indicates AIDS Clinical Trials Group; NNRTI, nonnucleoside reverse transcriptase inhibitor; nRTI, nucleoside reverse transcriptase inhibitor; sgc, soft-gel capsule; tenofovir, tenofovir disoproxil fumarate.

International AIDS Society–USA  Topics in HIV Medicine
The most common adverse effect was local injection site reaction (in 69%), leading to discontinuation in 3 participants (8%). There were no other adverse effects clearly related to pentafluvir. This study was not powered to show efficacy.

All participants had at least 3 months of prior zidovudine use. Although not statistically significant, nephrolithiasis, hyperbilirubinemia, and hyperlipidemia were more common in the bid dose group. Drug interruptions or dose reduction was more common in the bid arm than in the tid arm (48% vs 30%, P=.05).

Pharmacokinetic data showed lopinavir levels were in the expected range but amprnavir levels were reduced by about 30%.

The efavirenz and efavirenz/nelfinavir arms were superior to the nelfinavir-only arm (P=.028 and P<.001, respectively). The nRTIs were open-label and based on prior regimens.

All patients were naive to NNRTIs and abacavir, but nearly all had received stavudine and didanosine. Plasma HIV-1 RNA level in the hydroxyurea arms was more likely to be suppressed (P=.008), but toxicities were more common in these groups, including 2 cases of lactic acidosis, 2 cases of peripheral neuropathy, and 1 case of grade 3 hepatitis.

the risk was still 2.4 times higher in those interrupting therapy (P=.0001). This implies that antiretroviral regimens having poor virologic and immunologic response are associated with a slower disease progression. The magnitude of this risk was strongly correlated with CD4+ cell count. The rate of AIDS-defining events or death was .48 per person-years of observation in those interrupting therapy at a CD4+ cell count below 200/µL, compared with .03 per person-years of observation in those interrupting therapy at a CD4+ cell count above 200/µL. As this is an observational cohort study, caution should be exercised in interpreting the implications of the findings for STIs in the setting of chronic HIV infection.

A note of caution was also made by investigators studying the dynamics of HIV in the cerebrospinal fluid (CSF) after treatment interruption (Abstract 49). Ellis and colleagues demonstrated a rapid rebound of HIV in the CSF among patients interrupting therapy, which lagged only several days behind the plasma HIV-1 RNA level. Four of 12 patients tested also developed a brisk pleocytosis (white blood cell count >10/µL), which followed viral rebound. The neurocognitive consequences of this viral rebound are a planned focus of future investigations.

Another theoretical concern about treatment interruption is that viral rebound can expand the size of the viral reservoir in latently infected T-cells that decay slowly on HAART. Blankson and colleagues (Abstract 491-M) closely followed 5 individuals during STI to characterize the latent reservoir in CD4+ T cells. They found that the frequency of latently infected CD4+ T cells rapidly increased to levels similar to those in primary HIV infection, but also decayed rapidly after reinstitution of HAART, leading the investigators to conclude that the size of the latent reservoir was not dramatically increased during STI.

The Swiss-Spanish Intermittent Treatment Trial is a prospective trial of treatment interruptions in patients beginning HAART in the chronic phase of infection. Hirschel presented data on behalf of the study team in both the previously mentioned symposium on controversies in the management of HIV and a poster session (Abstracts 528-M, S18). This is the largest study to date examining STI in this situation. They studied 133 individuals, 96% of whom began antiretroviral therapy during the chronic phase of their infection with a median CD4+ cell count of 740/µL. All participants underwent the same protocol of STI: 2 weeks off therapy followed by 8 weeks on therapy for 4 cycles, followed by discontinuation of all antiretroviral medications. The primary outcome was proportion with plasma HIV-1 RNA level below 5000 copies/mL (“responders”) at week 52 (12 weeks off therapy) and week 96 (56 weeks off therapy). The proportion of responders was 18% at week 52 and 11% at week 96. Response was predicted by a low pre-HAART plasma HIV-1 RNA level and lack of rebound during STI and was not correlated to HIV-specific immunity as measured. This led the investigators to conclude that this intervention would rarely be sufficient for the long-term management of patients and that the “autovaccination” hypothesis was problematic. The largest CD4+ cell drop occurred during the first 12 weeks off therapy followed by a slower decline thereafter. One person required salvage therapy because of the emergence of virologic resistance, and 2 patients developed symptoms consistent with the acute retroviral syndrome.

Plana and colleagues evaluated STI with and without hydroxyurea (Abstract 535-M). Twenty patients who began HAART in chronic infection with a baseline plasma HIV-1 RNA level above 5000 copies/mL and CD4+ cell count above 500/µL who had achieved virologic suppression for more than 32 weeks were enrolled in this study. The antiretroviral regimens were changed to stavudine/didanosine/nelfinavir with or without hydroxyurea for 24 weeks. The patients then underwent 5 treatment interruptions separated by 2 months using the same HAART regimen. Hydroxyurea was continued after the third interruption without subsequent discontinuation. They found that 8 of 9 hydroxyurea recipients maintained a plasma HIV-1 RNA level below 5000 copies/mL compared with 4 of 10 without hydroxyurea, (P=.02). The HIV-specific CTL did not differ between arms. It is not possible to distinguish whether STI had an effect in addition to the antiretroviral activity of hydroxyurea in this study.

Prior to Salvage Therapy. Ruiz and colleagues evaluated the utility of an STI prior to a salvage regimen in 46 patients
in whom a third HAART regimen was failing and who had resistance mutations in all 3 drug classes (Abstract 421-W). Patients eventually received a “mega-HAART” regimen consisting of didanosine, abacavir, lamivudine, saquinavir soft-gel capsule, and lopinavir/ritonavir. They were randomized to an immediate switch to this regimen or to starting after discontinuing their previous antiretroviral medications for 3 months. There was a high prevalence of genotypic mutations that subsequently faded in those randomized to treatment interruption. The plasma HIV-1 RNA level increased by 0.9 log10 copies/mL and the CD4+ cell count decreased by 131/μL in those off therapy. In 47% of patients receiving the STI, plasma HIV-1 RNA level declined below 80 copies/mL compared with 36% of those not receiving the STI (P=not significant). This study had limited power to detect subtle treatment effects. No adverse events were noticed, but participants started with a high median CD4+ cell count, 392/μL and 322/μL in the STI and immediate switch arms, respectively.

**Switch Studies and Simplification**

NEFA is a multicenter, randomized, open-label trial examining the virologic response and adverse effect profiles of changing either a single or dual protease inhibitor to one of 3 drugs: nevirapine, efavirenz, or abacavir (Abstract LB17). Four hundred sixty participants were enrolled and the primary outcome was proportion with undetectable plasma HIV-1 RNA after 12 months. The intent-to-treat analysis showed 78%, 74%, and 77% of individuals had plasma HIV-1 RNA levels below 200 copies/mL at 12 months in the nevirapine, efavirenz, and abacavir arms, respectively (P=.7). The on-treatment analysis showed 94%, 94%, and 87% had plasma HIV-1 RNA levels below 200 copies/mL in the 3 arms respectively (P=.06). More treatment discontinuations due to adverse effects were seen in the efavirenz (17%) and nevirapine (16%) arms than in the abacavir arm (7%), but abacavir was associated with a higher rate of virologic failure. Twenty-three of 28 participants from all 3 arms who developed virologic failure had received single or dual nRTI therapy prior to beginning HAART.

Hydroxyurea combined with didanosine was studied as an attempt to simplify the antiretroviral therapy regimens of patients with virologic suppression on HAART for more than 1 year (Abstract 533-M). Patients were randomized to continuing HAART or changing to hydroxyurea/didanosine. In an intent-to-treat analysis, 41 (38%) of 107 patients in the continuing HAART arm maintained virologic suppression at 48 weeks compared with 45 (39%) of 116 patients in the hydroxyurea arm. Success on the hydroxyurea/didanosine regimen was correlated with lower baseline plasma HIV-1 RNA level, lack of didanosine experience, higher nadir CD4+ cell count, and shorter time on HAART. Patients continuing on HAART had an increased number of adverse reactions compared with patients in the hydroxyurea arm.

**Therapeutic Vaccines**

Autran reviewed immune reconstitution and the state of therapeutic vaccine trials (Abstract L3). Patients in the chronic phase of HIV infection commonly have HIV-specific T-cell responses as determined by more sensitive assays such as the interferon-gamma enzyme-linked immunospot (ELISPOT). However, the strength of these responses is diminished compared with those in individuals treated during primary infection. The HIV-specific CD8+ T cells decrease proportionately with the decline in plasma HIV-1 RNA level associated with HAART. This led researchers to explore reconstitution of HIV-specific T-cell responses using HIV itself through STI. Preeexisting immunodominant HIV-specific CD8 T cells have been found to rebound with STI, but this rebound is directly related to plasma HIV-1 RNA level, and control of viremia in the absence of HAART has not been predictably or routinely achieved.

Autran then discussed the work of her laboratory and others in the search for immune, viral, and genetic correlates of protection against HIV by studying long-term nonprogressors. She was able to rule out any viral factors being responsible in the patients studied. There did seem to be genetic factors such as CCR5-∆32 heterozygosity and various human leukocyte antigen alleles that were associated with virologic control. Both the intensity and breadth of the CD4+ T-helper response was increased among the long-term nonprogressors and negatively correlated with HIV-1 RNA level and viral DNA. In addition, the antibody response was also negatively correlated with HIV-1 RNA level, in particular the IgG2 response. The combination of IgG2 response and T-helper response as measured by interferon-gamma ELISPOT was the best predictor of the maintenance of the long-term nonprogressor status in a multivariate model.

The immunologic goals of a therapeutic vaccine, as outlined by Autran, are to produce a strong and durable T-helper response and a more intense and broader CTL response. This vaccine would be given during HAART prior to a treatment interruption. The clinical goal would be to lower the viral set point and prolong the time off antiretroviral therapy. Several trials constructed in this manner are currently under way using viral vectors (canarypox and replication-defective adenovirus) that express portions of the HIV genome, some in combination with interleukin-2 (IL-2) or a DNA prime. Although no results are available, these vaccines were able to induce T1 responses, and the measurement of the CD8+ cell response is in progress. She ended with the promise of new trials involving improved vaccines in the context of a large international effort.

Several poster presentations discussed therapeutic vaccines in both animal models and human subjects (Abstract 312-W). DermaVir (George-town University Research Institute for Genetic and Human Therapy, Washington, DC) is a novel topical immunization composed of plasmid DNA combined with polyethylamine-mannose (PEIm). The PEIm allows the plasmid to enter the dendritic cells and avoid degradation by the endosome. The dendritic cells then present the DNA-based antigens to naïve T cells. The investigators studied 10 SIV-infected macaques with late-stage AIDS that were randomized to HAART alone or STI/HAART for 6 cycles followed by DermaVir (using SIV DNA) and 4 additional cycles of STI/HAART. All of the continuous HAART macaques died, but only 1 STI macaque died. The macaques had consistent viral rebounds during the first 6 cycles, but these rebounds declined sharply after
DermaVir and the median viral load after the last STI was below 200 copies/mL. Virologic control was associated with a strong SIV-specific T-cell response. The authors note that the pattern of progressive virologic control in association with DermaVir was similar to macaques treated early after infection with STI/HAART, and was remarkable considering the macaques' advanced stage of disease when starting this treatment.

Tryniszewska and colleagues studied 2 highly attenuated poxvirus vectors expressing different SIV proteins (NYVAC-SIV-gpe and NYVAC-SIV-rtn) with and without IL-2 in SIV251-infected rhesus macaques receiving HAART compared with controls for 8 months (Abstract 313-W). They were able to demonstrate CD8+ T-cell response to the immunodominant Gag epitope in vaccinated macaques. The vaccinated monkeys had a significantly lower viral rebound after discontinuing HAART. The authors argue that this provides proof-of-concept for therapeutic vaccines in the model that best predicts HIV infection.

There were several studies using REMUNE (Immune Response Corporation, Carlsbad, Calif), an envelope-depleted, inactivated Zairian isolate given with incomplete Freund's adjuvant. Bucy and colleagues studied REMUNE compared with the adjuvant in 28 human subjects who underwent treatment interruption (Abstract 314-W). They found a non-significant decrease in the peak and post-peak viral loads off therapy. Robbins and colleagues were able to demonstrate an augmentation of HIV-specific helper T-cell responses in 5 of 5 REMUNE-vaccinated individuals compared with 0 of 4 controls (Abstract 315-W). All patients remained on therapy and did not undergo a treatment interruption.

Fernandez-Cruz and colleagues presented data from the STR-2102 trial that studied time to virologic failure for patients receiving zidovudine/didanosine or stavudine/lamivudine/indinavir with and without REMUNE every 3 months (Abstract 318-W). They found that REMUNE was associated with more durable virologic suppression (plasma HIV-1 RNA <5000 copies/mL) than antiretroviral therapy alone. They did not stratify time to virologic failure by the use of dual or triple antiretroviral therapy.

**Immunotherapy**

Levy and colleagues presented the final analysis of the ANRS 079 trial, which studied the efficacy of IL-2 therapy in HIV infection (Abstract 514-M). Patients naive to antiretrovirals or protease inhibitors were randomized to start HAART (stavudine, lamivudine, and indinavir) or HAART plus 10 cycles of IL-2 given over 74 weeks. The median length of follow-up of the 118 patients randomized was 35 months. The study had some protocol deviations, with participants in both arms receiving cycles of IL-2 after week 74. The IL-2 arm had a significantly higher and faster CD4+ cell count rise through week 74 than the HAART-only arm (835/µL vs 262/µL, P<0.001). The CD4+ cell count rise remained significantly higher in the IL-2 arm than in the HAART-only arm at the last analysis (604/µL vs 365/µL, P=0.002). The proportion of participants with a plasma HIV-1 RNA level below 50 copies/mL was similar in both groups (76% vs 78%).

In a substudy of ANRS 079, investigators examined the change in HIV proviral DNA in PBMCs over time (Abstract 515-M). The decay in log DNA/10^6 PBMCs was similar in the HAART-only and IL-2 arms, suggesting that IL-2 did not enhance the effect of HAART on the reservoir of proviral DNA in PBMCs nor did it expand the pool of latently infected T cells.

The ESPRIT trial is an open-label, randomized, controlled trial assessing HAART versus HAART plus IL-2 in terms of clinical outcome (Abstract 517-M). This ambitious effort will study 4000 participants for 5 years. Labriola and colleagues presented preliminary data on the predictors of CD4+ cell count rise associated with IL-2. The CD4+ cell count response among patients receiving IL-2 was greater among those with a higher nadir CD4+ cell count and was inversely related to length of time on antiretroviral therapy.

Hecht and colleagues presented preliminary results of a randomized study comparing HAART alone and HAART with IL-2 in the treatment of early HIV infection (<12 months post-seroconversion). Data were presented on the first 43 subjects (Abstract 527-M). At 48 weeks, the mean CD4+ cell count was higher in the IL-2 group (1669/µL vs 686/µL, P<0.001), with 87% having an HIV-1 RNA level below 50 copies/mL compared with 70% of controls (P=not significant). Three of 5 participants tested in the IL-2 arm developed CTL responses to new epitopes compared with 1 of 7 controls. By protocol, all subjects were to remain on HAART, but the 1 responding participant in the HAART-only arm and 1 of the 3 responding patients in the IL-2 arm had a treatment interruption that can increase the CTL response. The authors found the 2 additional CTL responses in the IL-2 arm encouraging but say that they may have been due to undetected "blips" associated with IL-2 injections. These data are too preliminary to draw any conclusions at this time.

Lu and colleagues reviewed the gene therapy studies of the National Institutes of Health/National Institute of Allergy and Infectious Diseases involving serodiscordant monoyzotic twins (Abstract 525-M). The 2 studies involved syngeneic lymphocytes virally transduced with the chimeric receptor gene (CD4/CD3-zeta) or the neomycin phosphotransferase gene. Genetically modified CD4+ T cells persisted for a mean of 3.3 and 5.2 years, respectively, and this persistence was enhanced by IL-2 administration. They argue that these results provide a basis for pursuing genetic strategies for the treatment of HIV infection.

Pomerantz and colleagues presented results from the Residual HIV-1 Disease Eradication Trial, an attempt to eradi cate the latent reservoir of HIV in 3 patients (Abstract 405-T). These patients were on potent antiretroviral therapy with HIV-1 RNA levels below 50 copies/mL for 1 year prior to enrollment. Their regimens were intensified for at least 1 month with hydroxyurea and didanosine. After receiving anti-CD3 antibodies and IL-2, they continued the same antiretroviral regimen for an additional 5 to 6 months. Tonsillar biopsies showed no HIV-1 RNA by in situ hybridization in either follicular dendritic cells or lymphocytes. Unfortunately, the plasma HIV-1 RNA level eventually rebounded in all 3 participants.
Blips

Blips in viral load are defined as single measurements of HIV-1 RNA level above 50 copies/mL with subsequent measurements below 50 copies/mL. Previous reports indicate that these blips are not associated with subsequent virologic failure. Havlir and colleagues presented data on blips occurring during salvage therapy of heavily treatment-experienced patients (Abstract 15). These data came from participants enrolled in ACTG 398—a study of protease inhibitor- and NNRTI-experienced patients randomized to efavirenz, abacavir, adefovir, and amprenavir, with or without a second protease inhibitor—and ACTG 359, in which indinavir- and nRTI-experienced patients were randomized to nelfinavir/saquinavir or ritonavir/ saquinavir with either delavirdine, adefovir, or both. They found that these blips did not predict subsequent virologic failure (RR, 1.13; 95% CI, 4.2-3.05).

Di Mascio and colleagues examined whether the frequency of blips in viral load varied with time. They found that 77.5% of 123 patients on their first HAART regimen exhibited blips at a mean frequency of .09 per sample with a mean amplitude of 165 plasma HIV-1 RNA copies/mL. They concluded that viral blips appeared randomly, and that neither blip frequency nor amplitude increased with time.

Postexposure Prophylaxis

A concern that has been expressed about offering postexposure prophylaxis (PEP) after high-risk sexual encounters is that sexual behavior may be disinhibited, leading to an increased frequency of high-risk behavior. To address this question, Schechter and colleagues prospectively studied 202 HIV-seronegative homosexual men in a trial of the acceptability and behavioral impact of PEP (Abstract 15). All participants received counseling on high-risk sexual behavior at baseline and were provided with a 4-day supply of zidovudine/lamivudine. During the 2-year follow-up period, participants began antiretrovirals after any sexual encounter they deemed to be high risk. They were instructed to present to the study site for evaluation within 4 days of beginning medications. Sexual behavior and HIV serostatus were assessed at baseline and every 6 months for 2 years.

The investigators found that high-risk sexual behavior actually decreased after beginning the study. Seventy-three participants began PEP 110 times, and 101 (91.8%) of the sexual acts that preceded PEP initiation met criteria for high-risk behavior, prompting investigators to prescribe a 28-day course of zidovudine/lamivudine. Eleven seroconversions occurred during the study, 10 among participants who did not start PEP after high-risk encounters and 1 who did. The viral genotype from this person showed the M184V mutation.

Viral Resistance

A number of presentations focused on resistance to antiretroviral therapies and the mechanisms thought to underlie resistance.

Resistance to Lamivudine

In an overview of the major resistance mechanism for lamivudine (and other “L-nRTIs,” including emtricitabine, L-d4FC, and dOTC), Mellors (Abstract L6) described the mechanism of action of the M184V mutation, which confers 50-to 100-fold resistance to these drugs. Studies have shown that M184V does not affect lamivudine’s binding to the active site of reverse transcriptase but does markedly decrease its incorporation into the growing DNA chain. This is thought to occur because of steric hindrance. In the 3-dimensional view, the ring structure of L-nRTIs points up whereas the ring structures of endogenous deoxynucleotide triphosphates (dNTPs) point down. When the methionine at position 184 mutates to a valine, steric hindrance between the relatively bulky valine molecule and the lamivudine ring occurs, malpositioning lamivudine and preventing its incorporation into the growing DNA chain.

Eron and colleagues (Abstract 570-T) evaluated 119 subjects with plasma HIV-1 RNA levels below 120 copies/mL who were enrolled in the NZTA4002 study, an open-label trial of zidovudine/lamivudine/abacavir/amprenavir versus zidovudine/lamivudine/nelfinavir. Their objective was to determine if emergence of the M184V mutation during virologic suppression was predictive of virologic failure. Of 26 patients having M184V at 24 weeks, 12 (46%) eventually had treatment failure compared with 28 of 93 subjects (30%) without M184V. These differences were not statistically significant and the authors concluded that emergence of M184V during virologic suppression was not predictive of treatment failure.
that the choice of dual-nRTI therapy may influence the development of NAMs.

Garcia-Lerma and colleagues (Abstract 571-T) have previously shown that viruses with T215D/C, a naturally occurring polymorphism that may be due to revertant T215Y mutants, are more likely than wild-type viruses to select for T215Y in the presence of zidovudine. In this presentation they showed that 4 of 6 viruses with T215D/C selected for T215Y in the presence of stavudine in vitro, compared with 0 of 3 wild-type viruses. They suggest that patients infected with T215D/C viruses and treated with zidovudine or stavudine may be at increased risk of quickly developing T215Y mutants.

Whitcomb and colleagues (Abstract 569-T) looked at nRTI susceptibilities from 2500 samples with matched phenotypic and genotypic measurements and saw that increasing numbers of NAMs correlated with decreased susceptibilities to all nRTIs. M184V modulates this cross-resistance, decreasing susceptibility to didanosine, zalcitabine, abacavir, and lamivudine and increasing susceptibility to zidovudine, stavudine, and adefovir.

**Resistance to Tenofovir**

Miller and colleagues reported on the effect of baseline nRTI mutations in response to tenofovir therapy (Abstract 43). Based on pooled data from 2 studies, they noted that the type and number of NAMs at baseline had significant effects on tenofovir response. Patients with no NAMs at baseline had a 0.8-log10 copies/mL drop in HIV-1 RNA on tenofovir, and those with 1 to 2 NAMs had a 0.7-log10 copies/mL drop. Patients with 3 or more NAMs including either M41L, L210W, or T215Y/F had only a 0.2-log10 copies/mL decline in HIV-1 RNA on tenofovir. Patients with 3 or more NAMs but without M41L, L210W, or T215Y/F had a 0.7-log10 copies/mL decline. Furthermore, the presence of L210W was diagnostic of 3 or more NAMs and was the strongest single marker of lack of response to tenofovir. Resistance to tenofovir now appears to be mediated by K65R (a rarely occurring mutation with tenofovir therapy), the T69S insertion, and multiple NAMs (>3.8 by statistical analysis). Phenotypically, a 4-fold decrease in susceptibility correlates with a diminished response to tenofovir.

Tuske and colleagues (Abstract 44) solved the crystal structure of tenofovir complexed with reverse transcriptase and suggest that the acyclic nature of tenofovir allows it to avoid steric hindrance, as occurs with lamivudine and M184V. Additionally, the flexible nature of tenofovir allows it to assume multiple conformations at the reverse transcriptase active site, making it a poor substrate for excision by phosphorylase as is seen with zidovudine. They concluded that the structure of tenofovir could account for its slow development of resistance.

**NNRTI Hypersusceptibility**

Several sessions touched on NNRTI hypersusceptibility, which has been described in the presence of nRTI mutations. Swanstrom and colleagues looked at the development of resistance to delavirdine in the presence of nRTI-associated mutations conferring NNRTI hypersusceptibility (Abstract 567-T). In the subset of patients who had NNRTI hypersusceptibility at baseline and who developed delavirdine resistance (K103N), nRTI-associated mutations conferring NNRTI hypersusceptibility were retained. Additionally, the presence of NNRTI hypersusceptibility did not improve treatment outcome in this study although it was associated with 0.54-log10 copies/mL lower baseline plasma HIV-1 RNA level. Mellors and colleagues reported on the positive effect of NNRTI hypersusceptibility on the virologic response to an efavirenz-containing salvage regimen in ACTG 398 (Abstract 45; please see the "Trials in Treatment-Experienced Patients" section).

**Protease Inhibitor Resistance**

Obry and colleagues reported on hypersusceptibility to protease inhibitors using resistance phenotypes obtained from participants in the ANRS 088 (NARVAL) trial of the effect of resistance testing on outcome (Abstract 557-T). They reported that mutations at codons 30 and 88 in protease are associated with significant cross-protease inhibitor resistance, but they confer hypersusceptibility to amprenavir and ritonavir. They further noted that N88S/T was associated with hypersusceptibility to amprenavir and D30N confers hypersusceptibility to ritonavir.

Isaacson and colleagues used data from the lopinavir/ritonavir expanded access database comprising 792 antiretroviral-experienced patients who started on combination regimens including lopinavir/ritonavir to determine the genotypic predictors of lopinavir/ritonavir failure (Abstract 559-T). They determined that the presence of mutations at positions 10, 20, 33, 36, 54, and 82 in the presence of multiple other mutations was statistically significantly associated with virologic failure. Mutations at 24, 47, 48, and 84 also seemed to influence virologic failure, but the association was not statistically significant. They suggested that a weighted algorithm based on these findings may be a better predictor of response to lopinavir/ritonavir than the current mutation score. Conversely, Loutfy and colleagues looked at 167 patients on lopinavir/ritonavir therapy and found that the current mutation score had a linear relationship to virologic failure (Abstract 560-T). They further found that the presence of L90M was highly predictive of failure.

Schwartz and colleagues (Abstract 562-T) followed 41 patients on the investigational drug tipranavir for 1 year looking for reduced susceptibility. Commonly seen protease inhibitor cross-resistance mutations including 46, 82, 84, and 90 did not confer tipranavir resistance. The V82T mutation in combination with an L33I/F/V was associated with decreased susceptibility in 4 of 6 patients.

A molecular mechanism for amprenavir resistance was suggested by Xu and colleagues (Abstract 563-T). Amprenavir resistance is primarily mediated through 150V, although multiple other mutations are required for high-level resistance. It is known that the presence of 150V decreases the affinity of protease for amprenavir, but the molecular correlates of this finding are not known. The authors suggest that the loss of a methyl group when valine (V) replaces isoleucine (I) results in loss of hydrophobic contacts, creation of space, and loss of the close contact of protease with amprenavir needed for the drug to inhibit enzymatic activity.
Other Agents

True diketoacid integrase inhibitors have now been identified and resistance has been induced in vitro by numerous passages of virus in the presence of these agents. Witvrouwen and colleagues (Abstract 573-T) identified new integrase inhibitor resistance mutations selected for by L-708,906, a novel investigational integrase inhibitor, in vitro. As had been shown previously by Hazuda and colleagues, the T66I mutation appeared early. With further passages, L74M and S230R mutations were also detected. This virus was highly resistant to L-708,906 but retained full susceptibility to entry inhibitors, nRTIs, and NNRTIs, and protease inhibitors.

Resistance in Non-B Subtypes

Several abstracts addressed potential differences in treatment and resistance of non-B subtypes. Agwale and colleagues phenotypically analyzed 14 subtype-G and 4 subtype-A/G recombinants from patients in Nigeria prior to starting antiretroviral therapy and found that all but 1 exhibited full susceptibility to all antiretroviral medications, with the remaining sample having a 3.4-fold change to nelfinavir and ritonavir (Abstract 461-W). Portugal has an increasing prevalence of subtype-G infections, leading Gomes and colleagues to review the patterns of resistance for individuals in whom a nelfinavir-based antiretroviral regimen is failing (Abstract 46). They found that a nelfinavir-based regimen was 3 times more likely to fail in subtype-G patients than in subtype-B patients. Moreover, none of the 10 subtype-G patients in whom a nelfinavir-based regimen had failed developed the D30N mutation compared with 6 of 11 patients with subtype-B (P<.01). The subtype-G patients exhibited either the L90M pathway or other mutations on genotypic analysis.

Pillay and colleagues reviewed 113 pediatric patients from the Penta 5 trial, 67 (59%) of whom had non-B subtypes (Abstract 813-W). They did not find a difference in treatment outcomes or resistance patterns with respect to subtype, but the number of each of the 7 non-B subtypes or recombinants was small.

Grossman and colleagues compared 41 subtype-C patients and 67 subtype-B patients in whom antiretroviral therapy had failed (Abstract 565-T). They found a mutation pattern that was generally similar in both groups.

Additional information regarding treatment and resistance of non-B subtypes should be forthcoming as antiretroviral treatment programs in Africa and Asia expand. Non-B subtypes continue to spread through Europe, as evidenced by J/A recombinants in newly seroconverting injection drug users in Lausanne, Switzerland (Abstract 17), and by the diverse subtype-G recombinants spreading through Southern Europe (Abstract 759-W).

Resistance and Fitness

There has been considerable interest in the issue of viral fitness in patients with multiply resistant viruses. Barbour and colleagues evaluated specimens from 20 patients who were experiencing virologic failure on protease inhibitor-based regimens but who had plasma HIV-1 RNA levels lower than their baseline levels (Abstract 575-T). Early virologic failure (ie, <6 months) in these patients was associated with reduced viral replicative capacity. The degree of reduction in replicative capacity was directly associated with the decrease in plasma HIV-1 RNA level relative to pretherapy level. However, with long-term failure, plasma HIV-1 RNA levels did increase and this was associated directly with protease inhibitor resistance.

Weber and colleagues evaluated samples from 2 patients participating in ACTG 315 (zidovudine/lamivudine/ritonavir recipients) to determine if the baseline genetic background of the virus correlated with viral fitness (Abstract 576-T). Two patients retained wild-type virus and 2 patients developed resistant virus. The resistant viruses had lower replicative capacities than wild-type virus. One of the 2 patients had baseline natural compensatory mutations, and this patient’s virus had an increase in viral fitness over time. The authors suggest that the presence of background compensatory mutations may allow for more rapid recovery of replicative capacity.

Soderberg and colleagues looked at the accumulation of NNRTI mutations in relation to viral fitness (Abstract 577-T). They determined that, although substantial variability in fitness exists, in general, viral fitness decreases as the number of NNRTI mutations increases. The M184V lamivudine-associated mutation has been shown to result in decreased viral fitness. Wei and colleagues analyzed a number of M184V mutant viruses to determine the biochemical explanation for this finding (Abstract 578-T). They presented data suggesting that reverse transcriptase containing the M184V mutation does not recognize the initiation complex for synthesis of viral DNA as well as wild-type enzyme, and they postulated that this may account for decreased viral fitness in these viruses.

Resistance Testing

The utility of genotypic or phenotypic testing in managing HIV infection has been controversial. Several studies addressing the issue were presented. Torre and colleagues presented the results of a meta-analysis of 6 randomized controlled trials designed to determine the impact of resistance-guided antiretroviral therapy on virologic outcome (Abstract 584-T). At 6 months, 38.8% of patients who received genotypic resistance testing had undetectable plasma HIV-1 RNA levels versus 28.7% of patients receiving standard of care. Expert interpretation offered in conjunction with genotypic testing increased the rate of viral suppression (50.7% vs 35.8%). Phenotypic testing did not seem to offer an advantage over standard of care in this small meta-analysis.

Perez-Elias and colleagues presented the results of a prospective study of 276 patients in whom antiretroviral therapy was failing who were randomized to receive either actual phenotype or virtual phenotype testing (Realvirfen study, Abstract 586-T). In a multivariate linear regression analysis, patients in the virtual phenotype arm had a significantly greater decrease in plasma HIV-1 RNA level than those in the actual phenotype group (P=.01). Mazzotta and colleagues presented the results of the GenPherex trial comparing virtual and real phenotypes in 173 patients in whom antiretroviral therapy was failing (Abstract 589-T). Virologic outcome did not differ
between the 2 groups and CD4+ cell counts rose in both groups, with a trend toward a greater increase in the virtual phenotype group. The authors conclude that virtual phenotype is as reliable as standard phenotype.

Workman and colleagues presented the results of CREST, a multicenter randomized comparison of the effect of genotype and virtual phenotype testing on antiretroviral therapy-prescribing patterns (Abstract 587-T). The study included 330 patients in whom antiretroviral therapy was failing. No difference was seen between the genotype and virtual phenotype groups in the numbers of changes made to planned regimens after resistance-testing results were available. It was noted that the virtual phenotype arm had significantly less resistance reported than did the genotype arm; however, the clinical significance of this finding is not known. This, however, is to be expected, because for a number of drugs, multiple mutations are needed before a significant change in susceptibility can be detected.

**Pharmacology**

**Therapeutic Drug Monitoring**

The clinical utility of therapeutic drug monitoring (TDM) is currently being debated. In a plenary talk, Back explored the pros and cons of TDM and reviewed a number of trials (Abstract S20). In favor of TDM are the well-defined relationship between drug exposure and efficacy, the large interpatient variability in drug levels, and the narrow therapeutic window. Against the use of TDM are high intrapatient variability, unclear concepts of the role of protein binding, logistics (more blood draws, scheduling, etc), lack of expert interpretation, and the lack of randomized controlled trials showing efficacy. Only a few randomized controlled trials of TDM have been carried out to date. The ATHENA trial looked at the role of TDM in 92 antiretroviral therapy-naive patients starting on a nelfinavir-based regimen. At 12 months, those patients receiving TDM had a significantly lower plasma HIV-1 RNA level than those without TDM. In a separate arm, 55 patients starting on indinavir were randomized to receive TDM or standard of care. Those in the TDM arm had significantly lower toxicity than those in the standard-of-care arm.

Castagna and colleagues looked at the predictive value of the normalized inhibitory quotient (NIQ) in determining response to lopinavir in combination with ritonavir (Abstract 128). An NIQ was defined as the ratio of the patient’s trough drug concentration to the fold change in IC50 of the patient’s virus (inhibitory quotient [IQ]) divided by the ratio of the median population trough drug concentration to the population cutoff fold change in IC50. This NIQ obviates the need for correcting for protein binding. In the study, 52 antiretroviral therapy-experienced patients were given lopinavir/ritonavir in combination with other antiretroviral therapy chosen by their health care providers. Although NIQ was not predictive of initial response, it was highly predictive of response from week 12 onward, and at 48 weeks was more predictive than resistance testing. Also, although 100% of patients with the highest NIQs had plasma HIV-1 RNA levels below detection limits, only 15% of those with the lowest NIQ responded to therapy.

Fletcher presented the results of the predictive value of IQs in patients on saquinavir plus either ritonavir or nelfinavir as part of ACTG 359 (Abstract 129). They found that IQ predicted response at weeks 4, 8, and 12 but not at week 16; and had decreasing correlation with outcome after week 4.

Phillips and colleagues reported on a study of virtual inhibitory quotients (VIQs) in antiretroviral therapy-experienced patients taking amprenavir and lopinavir/ritonavir in combination (Abstract 130). A VIQ was defined as the patient’s trough drug concentration divided by the virtual phenotype and the protein-adjusted IC50. The VIQ of amprenavir was highly predictive of suppression and there was a trend toward this with lopinavir. Eighty percent of patients with a lopinavir VIQ greater than 15 and an amprenavir VIQ greater than 1.3 had plasma HIV-1 RNA levels less than 50 copies/mL.

The protein binding of antiretroviral drugs, especially the protease inhibitors, is thought to limit the usefulness of IQs. A presentation by de Béthune and colleagues suggested that the effect of plasma protein binding to the protease inhibitors may be overestimated and may not need to be included in IQ calculations (Abstract 449-W). They reached this conclusion by looking at the effect of plasma protein binding on physiologic doses of saquinavir, ritonavir, nelfinavir, amiprenavir, and the investigational protease inhibitor TMC 114. There was a less than 5-fold decrease in potency in the presence of the major protease inhibitor binding protein alpha-1-acid glycoprotein.

TDM has been thought to be difficult to implement for nRTIs because it is the concentration of the intracellular drug triphosphates that is important in their efficacy. Becher and colleagues (Abstract 452-W) developed a direct liquid chromatography/tandem mass spectrometry assay to measure the active intracellular triphosphorylated anabolites of stavudine and didanosine in peripheral blood mononuclear cells. They were able to quantify median intracellular concentration (ICC) in 22 patients with plasma HIV-1 RNA levels below detection limits for both stavudine and didanosine and suggest that further studies of ICCs of nRTIs may be useful.

The effect of intracellular triphosphate anabolite concentrations was also studied by Hoggard and colleagues (Abstract 455-W). They looked at levels of intracellular lamivudine triphosphate (lamivudine-TP) and the ratio of lamivudine-TP to endogenous deoxycytidine triphosphate (dCTP) in patients responding to therapy and those in whom therapy had failed. They determined that ICCs of lamivudine-TP and lamivudine-TP/dCTP were lower in nonresponders than in those responding to therapy despite no differences in levels of endogenous dCTP between the groups.

**Pharmacokinetics of Antiviral Drugs**

Lopinavir/ritonavir Daily Versus Twice Daily. A great deal of interest is currently being shown in once-daily preparations of antiviral agents. M99-056, a study of once-daily versus standard twice-daily dosing of lopinavir/ritonavir was presented by Bertz and colleagues (Abstract 126). Lopinavir/ritonavir was given as a single 800 mg/200 mg dose
daily or as 400 mg/100 mg twice daily in a prospective trial. At 38 weeks, no significant difference was seen between the groups in the numbers of patients who achieved plasma HIV-1 RNA levels below detection limits. However, it was noted that the median IQ was lower in patients receiving the once-a-day dose compared with those on standard dosing (40 vs 84) and that the 24-hour trough concentration was lower in patients receiving once-daily dosing. These findings suggested that once-daily dosing may have a narrower therapeutic window than standard dosing, and the conclusion was reached that twice-daily dosing is still the optimal way to dose lopinavir/ritonavir.

**Stavudine Extended Release.** Kaul and colleagues studied the pharmacokinetics of once-daily versus twice-daily stavudine in 2 studies. The first was a multiple-dose study (Abstract 429-W). Fifteen HIV-infected volunteers received either stavudine extended release 100 mg daily or the standard 40 mg twice daily dosing over a 9-day period. The once-daily dosing formulation achieved higher maximal concentrations and 24-hour area-under-the-curve values than standard dosing. No accumulation of drug was seen, and interpatient and intrapatient variability was low. It was believed that the pharmacokinetic profile supported once-daily dosing.

The second study was a 48-week phase 2 trial of stavudine extended release versus standard stavudine in combination with lamivudine and efavirenz (Abstract 430-W). Intensive pharmacokinetic studies on a subset of patients were performed during the first 2 weeks of the trial. For both preparations, pharmacokinetic parameters were similar on days 1 and 14. The geometric mean maximum concentration of the once-daily preparation was approximately 50% lower than the standard preparation. However, the geometric minimum concentration was 5.5 times higher for the once-daily preparation. These authors again concluded that the pharmacokinetic studies supported the use of once-daily stavudine preparations.

**Drug-Drug Interactions.** Several presentations focused on the pharmacokinetic interactions among antiretroviral agents. Wire and colleagues studied the pharmacokinetics of amprenavir, given as the prodrug GW433908, when given in combination with ritonavir (100 or 200 mg) and efavirenz (Abstract 431-W). In the 26 patients completing pharmacokinetic analysis, the addition of efavirenz to amprenavir and ritonavir had no effect on plasma concentrations of amprenavir. Additionally, giving 200 mg of ritonavir instead of 100 mg did not significantly increase plasma amprenavir levels.

Solas and colleagues (Abstract 440-W) looked at the effect of coadministration of lopinavir/ritonavir with amprenavir. Plasma trough concentrations of amprenavir and lopinavir were measured in 46 patients on 2 different doses of amprenavir (600 mg vs 750 mg bid) in combination with lopinavir/ritonavir (400 mg/100 mg). Decreases of 51% in the 600-mg dose group and 33% in the 750-mg dose group were noted for patients taking amprenavir in combination with lopinavir/ritonavir when compared with those taking amprenavir/ritonavir. It was noted that 85% of these patients still had median minimum concentration values up to 3-fold higher than standard, non-boosted amprenavir dosing. Lopinavir levels were not affected by coadministration with amprenavir. It was suggested that TDM may play a role in amprenavir/lopinavir/ritonavir combination regimens.

Preston and colleagues evaluated the pharmacokinetics of atazanavir in combination with efavirenz (Abstract 443-W). Coadministration of these agents resulted in atazanavir levels that were significantly lower than atazanavir alone, leading the authors to suggest that atazanavir dosing should be adjusted if used in combination with efavirenz. O’Mara and colleagues looked at the effect of adding low-dose ritonavir to atazanavir plus efavirenz (Abstract 444-W). Adding 200 mg of ritonavir to the regimen increased atazanavir levels 3-fold over atazanavir alone.

Other studies looked at the effect of other agents on antiretroviral pharmacokinetics. Agarwala and colleagues evaluated the effect of rifabutin on atazanavir with or without ritonavir boosting (Abstract 445-W). They concluded that rifabutin may be coadministered with atazanavir without dose modification of atazanavir but suggested that rifabutin dose modification may be necessary. Moyle and colleagues looked at the effect of pravastatin on protease inhibitors in patients suppressed on protease inhibitor therapy (Abstract 446-W). No impact of pravastatin was seen on protease inhibitor trough concentrations and the authors concluded that the efficiency and lack of interactions with this agent make it a good choice for therapy in patients with hypercholesterolemia on antiretroviral therapy. Cardiello and colleagues studied the effect of itraconazole on saquinavir soft-gel formulation (Abstract 447-W). They determined that lower doses of saquinavir (800 or 1200 mg vs standard 1400 mg bid) resulted in adequate pharmacokinetic values when combined with 100 mg of itraconazole.

**Compartmental Penetration.** The distribution of antiretroviral agents into the cerebrospinal fluid and genital tract was the subject of several presentations. Haas and colleagues looked at the effect of ritonavir boosting on indinavir levels in the cerebrospinal fluid (Abstract 437-W) and found that low-dose ritonavir increased indinavir levels 3-fold primarily by increasing plasma levels. Sankasing and colleagues looked at seminal plasma levels of lopinavir in HIV-infected men on lopinavir-containing regimens for more than 4 weeks (Abstract 439-W) and found that seminal plasma levels were significantly lower than plasma levels. They concluded that lopinavir has poor penetration into the seminal plasma and are currently investigating whether this will lead to suboptimal viral suppression and resistance in this compartment.

**Conclusion.** The 9th Conference on Retroviruses and Opportunistic Infections once again revealed itself to be a premier scientific meeting devoted to bringing together advances in basic and clinical HIV research in 1 forum. Antiretroviral therapy remained a dominant component of the meeting and although no major breakthroughs were evident, substantial advances were reported with respect to new antiretroviral agents, strategies of therapy, and the applications of drug...
resistance testing and therapeutic drug level monitoring. In parallel, the many unanswered questions in the field that were highlighted will no doubt form the focus of many of next year’s presentations.

Additional Suggested Reading

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