Advances in Antiretroviral Therapy

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As witnessed in previous years, antiretroviral therapy was a dominant theme of the 10th Conference on Retroviruses and Opportunistic Infections, with important information for clinicians presented in the areas of new antiretroviral agents, management of treatment-naive and -experienced patients, treatment strategies (particularly treatment interruptions), and drug resistance. This review will highlight the major findings presented at the conference from studies performed in the developed world. One important new aspect of this year's meeting, however, was the reporting of experiences with antiretroviral agents in the developing world. These reports will not be summarized here, but readers may visit the conference Web site for more information concerning these sessions (www.retroconference.org).

Investigational Antiretroviral Agents

Results of select studies on investigational antiretroviral agents are summarized in Table 1.

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Entry Inhibitors

CCR5 Antagonists. AK-602 is a CCR5 inhibitor in preclinical development. In vitro studies suggest that it preferentially blocks the HIV-CCR5 interaction and has less effect on the interaction of CCR5 and chemokines such as RANTES and MIP-1β (Abstracts 10 and 564a). It suppresses HIV replication and is orally bioavailable in the SCID-Hu mouse model. Although CCR5 Δ32 homozygosity appears to have no untoward effects in humans, CCR5 inhibitors, such as SCH-C and TAK-779, that affect chemokine-CCR5 interactions are, in fact, being studied in organ transplant recipients as possible immune modulators. This immune modulation is probably not a desirable quality when treating HIV infection, suggesting that CCR5 inhibitors that do not affect chemokine-CCR5 binding may be preferable to those that do. AK-602 has potent activity against a wide panel of primary R5 and multidrug-resistant isolates (50% inhibitory concentration [IC_{50}] 0.2-0.6 nM).

TAK-220 is a CCR5 inhibitor that is orally bioavailable, unlike manufacturer Takeda Chemical Industries' previous CCR5 inhibitor, TAK-779 (Abstracts 11 and 562). The authors did not present the structure of the new compound but did say that it was not similar to TAK-779. TAK-220 appears to bind specifically to CCR5 (not CCR1, CCR3, or other chemokine receptors). It is active in vitro against primary R5 viruses, including those resistant to other available drugs (50% effective concentration [EC_{50}] 1.1 nM and 90% effective concentration [EC_{90}] 13 nM), and appears synergistic with other antiretrovirals against wild-type R5 virus.

UK-427,857 is a CCR5 inhibitor that has entered phase 1 studies. Studies suggest that it is specific for CCR5-virus interactions and, consistent with the mechanism, is not active against X4 viruses (Abstracts 12, 546a, and 547). It is active against a broad range of viral isolates in vitro, including non-B subtypes. Phase 1 safety studies in HIV-seronegative individuals showed no obvious toxicities (including QTc interval prolongation) and that it was well-tolerated at a range of doses given for up to 12 days. The IC_{50} for HIV replication is 0.2 nM, and the IC_{50} for binding of MIP-1β is 3 to 7 nM. Pharmacokinetic studies in humans showed good absorption, with a terminal half-life of 17 hours with repeated doses.

CXCR4 Antagonist. AMD070 is an orally bioavailable CXCR4 inhibitor active in vitro against a wide variety of X4 viruses and R5/X4 dual tropic viruses (EC_{50} 1-10 nM), but not R5 viruses (Abstract 563). It is being developed by Anormed, whose development of AMD-3100 was stopped because of suboptimal efficacy but did establish proof of concept for targeting CXCR4. AMD070 appears to be either additive to or synergistic with other antiretrovirals and does not interact with any other chemokine receptor tested. Phase 1 studies are planned.

Monoclonal Antibody to CD4. TNX-355 is a human monoclonal antibody (IgG4) to CD4 formerly known as Hu5A8 (Abstract 13). It does not prevent attachment of HIV to CD4 but does prevent subsequent interactions. No immunosuppressive effects were noted in previous studies with peripheral blood lymphocytes or rhesus macaques. In this study, HIV-infected individuals on stable antiretroviral therapy or no antiretroviral therapy, and with plasma HIV-1 RNA levels of greater than 5000 copies/mL and CD4+ counts of greater than 100 cells/μL, were given a single dose of the agent at increasing amounts with successive cohorts. The mean baseline CD4+ count and plasma HIV-1 RNA levels were 354 cells/μL and 4.78 $\log_{10}$ copies/mL, respectively. Mean drops in plasma HIV-1 RNA of 1.48 $\log_{10}$ and 1.09 $\log_{10}$ were achieved at the 2 highest doses (10 mg/kg and 25 mg/kg), respec-

Table **1.** New Antiretroviral Agents

Drug Name	Abstract Nos.	Mechanism	Development Stage	Results
AK-602	10, 564a	Entry inhibitor (CCR5)	Preclinical	IC_{50} 0.2-0.6 nM
TAK-220	11, 562	Entry inhibitor (CCR5)	Preclinical	EC_{50} 1.1 nM
UK-427,857	12, 546a, 547	Entry inhibitor (CCR5)	Preclinical; phase 1 studies in HIV-seronegative subjects	IC_{50} 0.2 nM
AMD070	563	Entry inhibitor (CXCR4)	Preclinical	EC_{50} 1-10 nM
TNX-355	13	Fusion inhibitor (human monoclonal antibody)	Phase 1 studies in HIV-infected subjects	1.09-1.5 $\log_{10}$ copies/mL drop in plasma HIV-1 RNA levels after single dose
T-1249	14lb	Fusion inhibitor	Phase 2 studies in HIV-infected subjects	1.1 $\log_{10}$ copies/mL drop in plasma HIV-1 RNA levels after 11 days as functional monotherapy[1]
Racivir	552	Nucleoside reverse transcriptase inhibitor	Phase 2 studies in HIV-infected subjects	2.1-2.6 $\log_{10}$ copies/mL drop in plasma HIV-1 RNA levels after 28 days (given with stavudine/efavirenz)
V-165	9, 556	Integrase inhibitor (inhibits initial interaction of integrase and DNA)	Preclinical	EC_{50} 8.9 μM
PA-457	14	Gag processing inhibitor (inhibits processing of p24 capsid protein)	Preclinical	Not available
RO-033-4649	7	Protease inhibitor	Preclinical	IC_{50} 17 nM for wild-type viruses; IC_{50} 100 nM for highly PI-resistant viruses
TMC114	8, 549, 553	Protease inhibitor boosted with low-dose ritonavir	Phase 2 studies in HIV-infected subjects	1.1-1.5 $\log_{10}$ copies/mL reduction in plasma HIV-1 RNA levels after 14 days as functional monotherapy[2]

[1]This study substituted T-1249 for enfuvirtide (T-20) as the sole change in a failing antiretroviral regimen. Better efficacy was seen with a shorter time on the failing regimen containing enfuvirtide. [2]Participants were multiple-PI-experienced, and their PI-containing regimen was failing; the median baseline plasma HIV-1 RNA was 4.3 $\log_{10}$ copies/mL. TMC114/ritonavir was substituted for the failing PI or PIs as the sole change in antiretroviral therapy for 14 days.

IC_{50} indicates 50% inhibitory concentration; EC_{50}, 50% effective concentration.

tively. The nadir plasma HIV-1 RNA level was achieved at days 14 and 21, respectively. These days coincided with the duration of antibody coating of CD4, giving further support for the proposed mechanism of action. No CD4+ cell depletion was noted; in fact, CD4+ cell count increases were seen for the 3 highest dose groups (3, 10, and 25 mg/kg). No resistance has been created to date.

Fusion Inhibitor. Miralles and colleagues presented interim results of a study evaluating T-1249 in patients in whom a regimen containing enfuvirtide (T-20) was failing (Abstract 14lb). T-1249 is a fusion inhibitor similar to enfuvirtide given by subcutaneous injection once daily. It was substituted for enfuvirtide for 10 days as the sole change in the antiretroviral regimen. The endpoint was change in plasma HIV-1 RNA level at day 11. Participants were eligible if they were in a phase 2 or 3 enfuvirtide trial and their enfuvirtide regimen was failing, with a plasma HIV-1 RNA level of between 5000 and 500,000 copies/mL. The baseline plasma HIV-1 RNA level was 5 $\log_{10}$ copies/mL and the median duration of enfuvirtide use was 70 weeks. Overall, the median drop in plasma HIV-1 RNA was 1.12 $\log_{10}$ copies/mL. The drop in plasma HIV-1 RNA levels after substitution with T-1249 was related to the time on a failing regimen containing enfuvirtide: 7 of 7 patients in whom enfuvirtide failed for 24 to 48 weeks achieved greater than 1 $\log_{10}$ drop in plasma HIV-1 RNA, compared with 8 of 17 in whom the drug failed for more than 48 weeks. Presumably, this difference was due to the accumulation of more enfuvirtide-associated resistance mutations with longer exposure to the drug.

Integrase Inhibitors

V-165. V-165 is a new type of integrase inhibitor from the pyranodipyrimidine class that inhibits the binding of DNA to integrase (Abstracts 9 and 556). It is structurally different from the 2 integrase inhibitors currently in phase 1 trials—S-1360 from Shinogi and L-870,810 from Merck. S-1360 and L-870,810 are diketoacid and naphthyridine compounds, respectively, but they overlap in their resistance profiles (Abstract 140). V-165 has a different resistance pattern than these agents and is active against isolates resistant to the diketoacids. It is also active against nonnucleoside reverse transcriptase inhibitor (NNRTI)-, nucleoside reverse transcriptase inhibitor (nRTI)-, and fusion inhibitor-resistant viruses and is synergistic with zidovudine and nelfinavir versus wild-type virus. The in vitro potency (EC_{50} 8.9 µM) is comparable to that for the Merck integrase inhibitor, L-870,810.

Gag Processing Inhibitor

PA-457. PA-457 appears to target a new point in the HIV-1 life cycle: Gag processing, or specifically, the conversion of capsid protein p25 to p24 (Abstract 14). Martin and colleagues presented data supporting this mechanism of action, including electron micrographs showing morphologically defective HIV virions similar to those known to have a defect in the processing of p25 to p24. PA-457 does not act at other points in the HIV life cycle, such as fusion, reverse transcriptase, integrase, or protease. The inhibitor's specific molecular target, however, is unknown. Previous work has shown that it is orally bioavailable in rats. PA-457 is effective in vitro at low nM concentrations against a wide panel of isolates, including wild-type and resistant viruses, and is synergistic with other classes of antiretrovirals.

Reverse Transcriptase Inhibitors

Emtricitabine. Emtricitabine (FTC) is a cytosine analogue that has demonstrated potent activity against HIV-1. Wakeford and colleagues presented long-term results from the combined FTC 303 and FTC 350 trials, which evaluated the efficacy and safety of emtricitabine in HIV-infected subjects who switched from a lamivudine-containing regimen (Abstract 550). The parent study, emtricitabine 303, was a randomized, open-label, 48-week trial comparing emtricitabine 200 mg once daily with lamivudine 150 mg twice daily in 440 HIV-infected subjects who had achieved plasma HIV-1 RNA suppression of less than 400 copies/mL on a lamivudine-containing triple-drug regimen for at least 12 weeks prior to study entry. Subjects were randomized either to continue lamivudine therapy (n = 146) or to switch to emtricitabine (n = 294) within their current antiretroviral drug regimen. Subjects who maintained plasma HIV-1 RNA suppression of less than 400 copies/mL at week 48 of the FTC 303 study were then offered the option of participating in a rollover extension study, FTC 350, which evaluated the use of emtricitabine 200 mg once daily. The baseline median plasma HIV-1 RNA level and CD4+ cell count were 1.7 $\log_{10}$ copies/mL and 484 cells/µL, respectively.

At week 48, 77% of the subjects (n = 227) randomized to emtricitabine therapy achieved suppression of plasma HIV-1 RNA to less than 400 copies/mL. Of these 227 patients, 215 chose to continue emtricitabine therapy in the emtricitabine 350 study. After a median time of 140 weeks of emtricitabine treatment, 164 (56%) of 294 subjects in FTC 303 had discontinued emtricitabine therapy or had chosen not to enroll in emtricitabine 350. The majority of the subjects in FTC 350 (79%) received a protease inhibitor (PI)-containing highly active antiretroviral therapy (HAART) regimen; the remaining 21% of subjects received an NNRTI-based antiretroviral therapy regimen. With the Kaplan-Meier method, the probability of experiencing virologic failure (defined as plasma HIV-1 RNA level of at least 400 copies/mL on 2 consecutive visits) at 4 years was estimated at 11%.

Amdoxovir. Amdoxovir (DAPD; -b-D-2,6-diaminopurine dioxolane), a dioxalane guanosine analogue, is a novel nRTI inhibitor of HIV-1 replication in vitro. Amdoxovir is deaminated by adenosine deaminase to produce (-)–b-D-dioxolane guanine (DXG), which is the active moiety that is the substrate for HIV reverse transcriptase. In vitro, DXG has antiviral activity against zidovudine/lamivudine- and stavudine/lamivudine-resistant strains of HIV and those with a mutation at the codon 69 insert multidrug-resistance locus. After multiple passages of the virus in the presence of amdoxovir, 2 mutations in the reverse transcriptase gene have emerged: K65R and L74V.

Thompson and colleagues presented

the preliminary results from the DAPD-150 trial, a 96-week, open-label, 2-arm, phase 1/2 clinical study. The study evaluated the efficacy and safety of amdoxovir at 2 different doses in combination with background antiretroviral therapy in heavily treatment-experienced subjects (Abstract 554). Patients with a screening plasma HIV-1 RNA level between 5000 and 250,000 copies/mL and a CD4+ count of at least 50 cells/μL, and who had virologic failure of a prior zidovudine/lamivudine- or stavudine/lamivudine-containing antiretroviral therapy regimen, were eligible. A total of 18 HIV-infected subjects (94% male) with a mean age of 40 years, a median duration of 8 years of prior exposure to a median of 10 antiretroviral therapy drugs, and a median number of 3 nRTI mutations were enrolled. Median baseline plasma HIV-1 RNA level and CD4+ count were 4.41 $\log_{10}$ copies/mL and 326 cells/μL, respectively. Subjects were randomized to receive amdoxovir 300 mg twice daily (n = 8) or amdoxovir 500 mg twice daily (n = 10) in combination with optimized background antiretroviral therapy.

Of the 18 patients enrolled in this study, 11 discontinued the study for the following reasons: lens opacity (5), virologic failure (4), and voluntary withdrawal/noncompliance (2). The 300 mg arm achieved a median decrease from baseline in plasma HIV-1 RNA of 1.53 $\log_{10}$ copies/mL, compared with a 0.75 $\log_{10}$ copies/mL decline in plasma HIV-1 RNA levels in the 500 mg arm. These decreases were maintained through week 24. A median rise in CD4+ count from baseline to week 12 of 55 cells/μL was observed in both study arms. There were no serious adverse events reported in either study arm, and amdoxovir was well-tolerated at both doses. In animal toxicology studies, high doses of amdoxovir were associated with obstructive uropathy in monkeys and rats and with the development of elevated serum glucose levels and cataract formation in some monkeys. As a result, the DAPD-150 protocol was amended to require complete ophthalmologic assessments, with slit-lamp examinations at baseline in newly enrolled subjects and on a bimonthly basis to identify lens opacities in patients receiving amdoxovir. Five patients were documented to have lens opacities on formal ophthalmologic exam and were discontinued from study treatment. Since none of these 5 patients had ophthalmologic exams performed at baseline, it was unclear whether the lens opacities in these subjects were related to amdoxovir exposure.

Racivir. Racivir ([±]-2-hydroxymethyl–5 [5-fluorocytosine-1-yl]-1,3-oxathiolane) is an investigational nRTI that exhibits potent, highly selective activity against HIV-1 and hepatitis B virus in cell cultures and in animal models. This drug is composed of a mixture of emtricitabine with its positive enantiomer. This drug has been well-tolerated in preclinical safety studies conducted in dogs and rats and possesses an excellent oral bioavailability profile in animals and humans, which makes once-daily dosing feasible. Otto and colleagues presented the results of a dose-ranging phase 1b/2a study (Abstract 552) evaluating the antiviral activity and safety of racivir used at 3 different doses in combination with stavudine and efavirenz in HIV-infected, treatment-naive men. Subjects with plasma HIV-1 RNA levels greater than 5000 copies/mL and CD4+ counts greater than 50 cells/μL received racivir at a dose of 200 mg, 400 mg, or 600 mg once daily plus stavudine 40 mg twice daily and efavirenz 600 mg once daily for 14 days. Patients in all 3 racivir dosing arms achieved an initial rapid decline in plasma HIV-1 RNA levels and sustained a mean reduction in those levels ranging from 1.13 to 1.42 $\log_{10}$ copies/mL by day 4. Mean reductions in plasma HIV-1 RNA level ranging from 2.02 to 2.43 $\log_{10}$ copies/mL were seen by day 14. After stopping antiretroviral drugs on day 15, all 3 racivir dose groups maintained suppression of plasma HIV-1 RNA for more than 2 weeks; mean plasma HIV-1 RNA declines ranged from 2.1 to 2.6 $\log_{10}$ below baseline though day 28. At day 35, plasma HIV-1 RNA levels remained more than 1.0 $\log_{10}$ copies/mL below baseline values. All 3 doses of racivir were well-tolerated.

PIs

GW433908. GW433908, the prodrug formulation of amprenavir, is an investigational PI with a distinct resistance profile and no food restrictions for dosing. Nadler and colleagues presented the results of the NEAT study, an open-label, randomized trial (Abstract 177) that compared the efficacy and safety of GW433908 with that of nelfinavir over 48 weeks in antiretroviral therapy-naive HIV-infected subjects. A total of 251 subjects with plasma HIV-1 RNA levels greater than 5000 copies/mL and no CD4+ entry criteria were randomized in a 1:2 fashion to GW433908 1400 mg twice daily or nelfinavir 1250 mg twice daily. All patients also received abacavir and lamivudine twice daily. The primary endpoint was suppression of HIV-1 RNA to less than 400 copies/mL. At baseline, median plasma HIV-1 RNA levels were 4.82 and 4.85 $\log_{10}$ copies/mL in the GW433908 and nelfinavir arms, respectively; 44% and 48% of subjects had plasma HIV-1 RNA levels greater than 100,000 copies/mL. The median baseline CD4+ counts were 214 and 212 cells/μL in the GW433908 and nelfinavir arms, respectively.

At week 48, 66% of subjects in the GW433908 arm had achieved suppression of HIV-1 RNA to less than 400 copies/mL compared with 51% of subjects in the nelfinavir arm, and 55% and 41%, respectively, had achieved suppression to less than 50 copies/mL (intent-to-treat [ITT] analysis, rebound = failure). Sixty-seven percent of subjects in the GW433908 arm with HIV-1 RNA greater than 100,000 copies/mL at study entry achieved plasma HIV-1 RNA suppression to less than 400 copies/mL, compared with 35% of subjects in the nelfinavir arm. A median CD4+ count increase of 201 cells/μL from baseline at week 48 was seen in the GW433908 arm, compared with an increase of 216 cells/μL in the nelfinavir arm.

The GW433908 arm sustained increases in mean total cholesterol (from 152 to 197 mg/dL) and low-density lipoprotein (LDL) cholesterol levels (86 to 119 mg/dL) from baseline to 48 weeks that were similar to those observed in the nelfinavir arm (total cholesterol, 153 to 202 mg/dL; LDL cholesterol, 89 to 122 mg/dL). The nelfinavir arm, however, sustained an increase in mean triglyceride levels (154 to 200 mg/dL) by week 48. The nelfi-

navir arm had a higher incidence of diarrhea than did the GW433908 arm (18% vs 5%; $P < .002$), whereas rash was observed more frequently in the GW433908 arm (7%) than in the nelfinavir arm (2%). In this study population of treatment-naive subjects with moderately advanced HIV disease, therefore, GW433908 therapy was well-tolerated and conferred superior plasma HIV-1 RNA suppression at week 48 than did nelfinavir.

DeJesus and colleagues presented the week 24 results of the multicenter, randomized, open-label CONTEXT study (Abstract 178), which compared the efficacy and safety of GW433908/ritonavir, dosed once daily or twice daily, with lopinavir 400 mg/ritonavir 100 mg twice daily in PI-experienced subjects over 48 weeks. Antiretroviral therapy-experienced subjects with prior exposure to 1 or 2 PIs who were NNRTI-naive or -experienced, had a screening HIV-1 RNA level of at least 1000 copies/mL, and had any CD4+ cell count were eligible for study participation.

A total of 320 patients with median baseline plasma HIV-1 RNA level and CD4+ cell count of 4.14 $\log_{10}$ copies/mL and 263 cells/µL, respectively, were randomized in 1:1:1 manner to GW433908 1400 mg/ritonavir 200 mg once daily (n = 105), GW433908 700 mg/ritonavir 100 mg twice daily (n = 107), or lopinavir 400 mg/ritonavir 100 mg twice daily (n = 103). Each regimen included 2 active nRTI agents selected on the basis of genotypic testing. The study population was extensively NNRTI-experienced, with 52%, 60%, and 60% of subjects in the GW433908/ritonavir once daily, GW433908/ritonavir twice daily, and lopinavir/ritonavir twice daily arms, respectively, having received an NNRTI prior to study entry. The study population also had extensive prior use of nRTIs.

Using the primary endpoint of plasma HIV-1 RNA reduction as measured by the mean time-averaged change from baseline, the week 24 plasma HIV-1 RNA decreases were as follows: 1.48 $\log_{10}$ in the GW433908 once daily arm, 1.50 $\log_{10}$ in the GW433908 twice daily arm, and 1.66 $\log_{10}$ in the lopinavir/ritonavir twice daily arm. At week 24, 58% [40%], 60% [42%], and 69% [48%], respectively, of subjects achieved plasma HIV-1 RNA of less than 400 [less than 50] copies/mL. The lopinavir/ritonavir arm experienced fewer virologic failures than the GW433908 study arms (34%, 27%, and 21% in the GW433908/ritonavir once daily, GW433908/ritonavir twice daily, and lopinavir/ritonavir twice daily arms, respectively.) Nonvirologic treatment failures (8%, 10%, and 9%, respectively) were similar in all 3 arms, however. The median increase from baseline in CD4+ count ranged from 62 to 72 cells/µL at week 24 in the 3 arms. The study drug regimens were generally well-tolerated.

Atazanavir. Atazanavir is an azapeptide investigational PI administered on a once-daily dosing schedule that does not result in elevations in serum lipids. Murphy and colleagues presented the long-term results of the rollover/switch BMS 044 study (Abstract 555). The study evaluated the efficacy and safety of extended-use atazanavir in combination with stavudine and lamivudine in HIV-infected patients who were originally treated with atazanavir in the BMS 008 study or who switched from a nelfinavir-containing regimen to atazanavir. A total of 346 patients with plasma HIV-1 RNA levels of less than 10,000 copies/mL who had completed the BMS 008 study were randomized to continue atazanavir treatment at 400 mg once daily (n = 139) or at 600 mg once daily (n = 144), or to switch from nelfinavir to atazanavir at 400 mg once daily (n = 63). At baseline, median plasma HIV-1 RNA level and CD4+ count were 1.73 $\log_{10}$ copies/mL and 495 cells/µL, respectively, and 75% of patients had plasma HIV-1 RNA levels of less than 400 copies/mL.

At week 24, the proportion of subjects who achieved HIV-1 RNA levels less than 400 copies/mL [50 copies/mL] were as follows in the 3 study arms: 80% [58%] in the continued atazanavir 400 mg arm; 82% [54%] in the continued atazanavir 600 mg arm; and 86% [59%] in the switch arm. The median increases in CD4+ count at week 24 were 39, 34, and 33 cells/µL, respectively. For the nelfinavir-to-atazanavir switch arm, there were significant changes in total cholesterol (-16%), high-density lipoprotein (HDL) cholesterol (+5%), fasting LDL cholesterol (-20%), and fasting triglyceride levels (-25%). A switch from nelfinavir to atazanavir was associated with a low incidence (2%) of diarrhea. Elevations in total bilirubin (predominantly unconjugated) were the most frequent laboratory abnormality, with 26%, 44%, and 13% of patients in the continued atazanavir 400 mg, continued atazanavir 600 mg, and switch arms, respectively, experiencing grade 3 or 4 elevations in serum bilirubin. The investigators concluded that extended use of atazanavir/stavudine/lamivudine in treatment-naive HIV-infected patients results in sustained virologic suppression and continued increases in CD4+ cell counts with minimal changes in cholesterol, fasting LDL, and fasting triglyceride levels.

Tipranavir. Tipranavir, a novel nonpeptidic PI, exhibits a unique resistance profile and has demonstrated potent antiviral activity against multiple-PI-resistant isolates in vitro. Gathe and colleagues presented the results of the BI 1182.52 trial (Abstracts 179 and 528), a multicenter, randomized, blinded, phase 2 dose-finding study that evaluated 3 different tipranavir/ritonavir doses in highly treatment-experienced HIV-infected subjects. Entry criteria required subjects to have HIV-1 RNA levels greater than 1000 copies/mL, any CD4+ cell count, prior exposure to all 3 initial antiretroviral therapy classes, virologic failure of at least 2 PI-based regimens, and the presence of at least one or more major mutations in the protease gene (D30N, M46I/L, G48V, I50V, V82A/F/L/T, I84V, or L90M) but not more than one of V82L/T, I84V, or L90M. Three doses of tipranavir/ritonavir were evaluated: 500 mg/100 mg; 500 mg/200 mg; and 750 mg/200 mg. At study entry, subjects' current PI therapy was replaced with tipranavir/ritonavir, which was continued for 2 weeks prior to optimizing background therapy. A total of 216 patients with baseline median plasma HIV-1 RNA level and CD4+ count of 4.53 $\log_{10}$ copies/mL and 153 cells/µL, respectively, were randomized. Baseline genotypic and phenotypic resistance testing were conduct-

ed, which confirmed that the viral isolates within this study population had extensive resistance to currently available PIs.

At day 14, plasma HIV-1 RNA responses were as follows: the 500 mg/100 mg arm achieved a reduction in plasma HIV-1 RNA of 0.87 $\log_{10}$ copies/mL; the 500 mg/200 mg arm, a reduction of 0.97 $\log_{10}$ copies/mL; and the 750 mg/200 mg arm, a reduction of 1.18 $\log_{10}$ copies/mL. At day 14, 20% of participants had no changes made to their antiretroviral therapy background regimen due to lack of available active agents. All study arms maintained at least a 1.0 $\log_{10}$ decrease in plasma HIV-1 RNA from baseline through day 56. All patients had at least 5 PI mutations at study entry. Patients were subsequently grouped according to the number of mutations: 6 to 10 mutations; 11 to 15 mutations; 15 to 20 mutations; or more than 20 mutations. The reductions in plasma HIV-1 RNA from baseline were at least 0.8 $\log_{10}$ copies/mL regardless of the number of baseline PI mutations and, in the 500 mg/200 mg and 750 mg/200 mg dosing arms, ranged to 1.2 $\log_{10}$ copies/mL. Patients in the 500 mg/100 mg dosing arm with more than 20 mutations, however, did not achieve substantial reductions in plasma HIV-1 RNA level, with an average decline of 0.2 $\log_{10}$ copies/mL.

The 3 study drug regimens were generally well-tolerated. However, the 750 mg/200 mg study dosing arm had the highest proportion of participants who discontinued the study due to adverse events. Based on the similar antiviral activity demonstrated by the 500 mg/200 mg and 750 mg/200 mg dosing arms in this study and the lower frequency of grade 3 or 4 adverse events reported in the lower-dose arm compared to the 750 mg/200 mg arm, the dose selected for use in phase 3 development was tipranavir 500 mg/ritonavir 200 mg.

RO-033-4649. RO-033-4649 is a PI developed through structure-activity analysis of HIV-1 protease containing 1-5 site-directed mutations (Abstract 7). The in vitro results show potent activity against a panel of 50 viral strains, each with 10-fold or greater resistance in a phenotypic drug resistance assay to 4 of 5 marketed PIs (median IC_{50} 100 nM) as well as wild-type viruses (median IC_{50} 17 nM). Previous work showed favorable pharmacokinetic profiles in 3 animal species. Phase 1 studies are beginning.

TMC114. Arasteh and colleagues presented the phase 2a data on TMC114 coadministered with ritonavir in multiple PI-experienced patients (Abstracts 8, 549, and 553). Patients with CD4+ counts greater than 50 cells/µL, plasma HIV-1 RNA greater than 2000 copies/mL, previous treatment with 2 to 4 PIs for more than 2 months each, virologic failure on the current regimen, and no NNRTI use in the baseline failing regimen were eligible for study participation. Fifty subjects were randomized to continue their background antiretroviral therapy regimen plus TMC114 300 mg/ritonavir 100 mg twice daily (n = 13); to receive TMC114 600 mg/ritonavir 100 mg twice daily (n = 12); to receive TMC114 900 mg/ritonavir 100 mg once daily (n = 13); or to continue their current PI-based regimen (control arm; n = 12). Median baseline plasma HIV-1 RNA and CD4+ cell count were 4.3 $\log_{10}$ copies/mL and 305 cells/µL, respectively. After 2 weeks, TMC114 was stopped and the antiretroviral regimen changed according to the practitioner's wishes. At day 14, according to an ITT analysis, the median change in plasma HIV RNA from baseline was -1.24 $\log_{10}$ copies/mL in the 300 mg/100 mg arm; -1.13 $\log_{10}$ copies/mL in the 600 mg/100 mg arm; -1.50 $\log_{10}$ copies/mL in the 900 mg/100 mg arm; and +0.02 $\log_{10}$ copies/mL in the control arm. The median plasma HIV-1 RNA change from baseline to day 14 for the 3 TMC114 study arms was significantly greater than for the control arm ($P < .001$). The proportion of subjects who achieved plasma HIV-1 RNA suppression to less than 400 copies/mL at day 14 was 46% in the 300 mg/100 mg arm; 31% in the 600 mg/100 mg arm; 43% in the 900 mg/100 mg arm; and 8% in the control arm. Treatment with TMC114 at all 3 doses was generally well-tolerated; most side effects were gastrointestinal, with 32% of subjects experiencing diarrhea. Headache and dizziness occurred in 16% and 11% of TMC114-treated patients, respectively. There was 1 grade 4 rash (eczema) that occurred in the 300 mg/100 mg arm, which was deemed to be possibly related to study drug. All other rashes in the remaining TMC114 study arms were judged to be grade 2 or less in severity. One serious adverse event of hepatotoxicity in the 600 mg/100 mg dose arm was reported.

Treatment of Antiretroviral-Naive Patients

Results of select studies in antiretroviral-naive patients are summarized in Table 2.

Gilead 903 Study

The Gilead 903 Study, presented by Staszewski and colleagues (Abstract 564b), compared the efficacy and safety of the nucleotide reverse transcriptase inhibitor (ntRTI) tenofovir disoproxil fumarate 300 mg once daily with the nRTI stavudine 40 mg twice daily, each used in combination with a background of efavirenz 600 mg twice daily and lamivudine 50 mg twice daily in antiretroviral therapy-naive patients over 144 weeks. This phase 3, multicenter, randomized, double-blind, active-controlled trial enrolled 600 subjects with plasma HIV-1 RNA levels greater than 5000 copies/mL and no CD4+ cell count criteria. At baseline, the mean plasma HIV-1 RNA levels were 81,300 copies/mL each in the tenofovir (n = 299) and stavudine (n = 301) study arms; 46% and 43% of subjects, respectively, had plasma HIV-1 RNA levels greater than 100,000 copies/mL at study entry. Mean CD4+ counts at study entry in the tenofovir and stavudine arms were 276 and 283 cells/µL, respectively.

Through week 96, 82% of subjects in the tenofovir arm achieved plasma HIV-1 RNA levels of less than 400 copies/mL compared with 78% in the stavudine arm; 78% and 74% of subjects, respectively, had suppressed plasma HIV-1 RNA levels less than 50 copies/mL. The mean increase in CD4+ count at week 96 was 261 cells/µL in the tenofovir arm and 266 cells/µL in the stavudine arm. The incidence of grade 3 or 4 clinical adverse events was similar in both study arms. The tenofovir arm sustained significantly lower lipid elevations (triglyceride, total cholesterol, and LDL cholesterol levels)

Table 2. Trials in Antiretroviral-Naive Subjects

Study (Abstract No.), Description	Regimen/Study Arm (No. Patients)	Baseline Values HIV-1 RNA (copies/mL)	Baseline Values CD4+ (cells/µL)	Changes in Values HIV-1 RNA (copies/mL)	Changes in Values CD4+ (cells/µL)
903 Study (564b) 96-wk, phase 2, randomized, double-blind, active-controlled comparative trial of tenofovir and stavudine.	Tenofovir/efavirenz/ lamivudine (299)	81,300 (mean) 46% >100,000	276 (mean)	82% <400 78% <50 (ITT analysis; M=F)	+261 (mean)
	Stavudine/efavirenz/ lamivudine (301)	81,300 (mean) 43% >100,000	283 (mean)	78% <400 74% <50	+266 (mean)
Comment: Grade 3 and 4 adverse events were similar in both arms. The tenofovir arm sustained lower mean increases in triglyceride and fasting LDL cholesterol levels than did the stavudine arm (*P* <.001; *P* <.001). Time to use of a first lipid-lowering agent was longer in the tenofovir arm than in the stavudine arm (*P* <.001).					
2NN Study (176) 48-wk, multicenter, open-label, randomized comparative trial. *All patients also received stavudine/lamivudine	Nevirapine 400 mg/ efavirenz 800 mg qd (209)*			62% virologic success (combined endpoint) 63% <50 (ITT analysis; M=F)	+150 (median)
	Efavirenz 600 mg qd (400)*	4.7 $\log_{10}$ (overall median)	190 (overall median)	68% virologic success (combined endpoint) 70% <50	+160
	Nevirapine 400 mg qd (220)*			65% virologic success (combined endpoint) 70% <50	+170
	Nevirapine 200 mg bid (387)*			64% virologic success (combined endpoint) 65% <50	+160
Comment: The nevirapine/efavirenz arm had a higher discontinuation rate (29%) than did the other arms (16%, 24%, and 21% in the efavirenz, nevirapine qd, and nevirapine bid arms, respectively) due to toxicity. Grade 3 and 4 hepatobiliary adverse events were as follows: nevirapine qd vs efavirenz, *P* <.001; efavirenz vs nevirapine/efavirenz, *P* <.04.					
NEAT Study (177) 48-wk, multicenter, open-label, randomized comparative trial.	GW433908[1] 1400 mg bid/ abacavir/lamivudine (166)	4.82 $\log_{10}$ (median)	214 (median)	66% <400 55% <50 (ITT analysis; rebound=failure)	201 (median)
	Nelfinavir 1250 mg bid/ abacavir/lamivudine (83)	4.85 $\log_{10}$	212	51% <400 41% <50	216
Comment: For patients with baseline plasma HIV-1 RNA >100,000 copies/mL, 67% in the GW433908 arm achieved plasma HIV-1 RNA levels <400 copies/mL vs 35% in the nelfinavir arm. In the GW433908 arm, 14% experienced virologic failure compared with 28% in the nelfinavir arm.					
BMS 008/044 Study (555) Rollover/switch study to assess the long-term safety/ efficacy of atazanavir[1]. Rollover phase, 24 wks; total study duration, 72 wks. *All patients also received stavudine/lamivudine	Continue atazanavir 400 mg qd (139)*	1.73 $\log_{10}$ (overall median) 75% <400	495 (overall median)	80% <400 58% <50 (ITT analysis; observed data)	+39 (median)
	Continue atazanavir 600 mg qd (144)*			82% <400 54% <50	+34
	Switch from nelfinavir to atazanavir 400 mg qd (63)*			86% <400 59% <50	+33
Comment: Grade 3 and 4 bilirubin elevations (indirect) were more frequent in the atazanavir 600 mg arm (44%) than in the atazanavir 400 mg (26%) and switch (13%) arms. The switch arm sustained mean reductions in total cholesterol (16%; *P* <.001) and LDL cholesterol (21%; *P* <.001) levels.					

Table **2.** Trials in Antiretroviral-Naive Subjects, Continued

Study (Abstract No.), Description	Regimen/Study Arm (No. Patients)	Baseline Values		Changes in Values	
		HIV-1 RNA (copies/mL)	CD4+ (cells/μL)	HIV-1 RNA (copies/mL)	CD4+ (cells/μL)
Racivir (552) 2-wk, dose-ranging, phase 1b/2a study of racivir[1].	6 men at each dose received racivir 200 mg qd, racivir 400 mg qd, or racivir 600 mg qd. All patients also received efavirenz/ stavudine (18).	>5000	>50	2.02–2.43 $\log_{10}$ (overall mean reduction)	Not available
Comment: After stopping antiretroviral drugs on day 15, all 3 arms maintained suppression of plasma HIV-1 RNA levels for >2 wks. Mean plasma HIV-1 RNA reductions at day 28 ranged from 2.1 to 2.6 $\log_{10}$ copies/mL in patients who stopped antiretroviral therapy at day 14. All 3 doses of racivir were well-tolerated. Based on potency and oral bioavailability, racivir is targeted for once-daily combination therapy.					
QUEST (520) 48-wk study to evaluate virologic and immunologic outcomes of HAART initiation in primary HIV-1 infection.	Fixed-dose lamivudine/zidovudine plus abacavir/amprenavir for 18 months, then randomization to continue HAART ± vaccine prior to stopping HAART (148; 90% male)	5.4 $\log_{10}$ (median)	517 (median)	64% <50 47% <10 34% <3 (ITT analysis; M=F)	+157 (median)
Comment: In patients remaining on HAART, messenger RNA and DNA were <3 copies/10^6 peripheral blood mononuclear cells in 37% and 12%, respectively. In predicting plasma HIV-1 RNA levels <3 copies/mL, CD8/38+ count (HR, 2.2; 95% CI [1.3, 3.9]) and messenger RNA levels (HR, 1.4; 95% CI [1.1, 1.8]) were strongly associated with plasma HIV-1 RNA decline.					

[1]Investigational drug; not approved by the US Food and Drug Administration.

ART indicates antiretroviral therapy; bid, twice daily; CI, confidence interval; HAART, highly active antiretroviral therapy; HR, hazard ratio; ITT, intent-to-treat analysis; LDL, low-density lipoprotein; M=F, missing data equals failure; qd, once daily.

at week 96 than did the stavudine arm. The tenofovir arm also experienced fewer toxicities associated with mitochondrial dysfunction (peripheral neuropathy and lactic acidosis) than did the stavudine arm at week 96: 4% (n = 11) versus 20% (n = 61; $P < .001$). In a subset of subjects evaluated for changes in body fat distribution by dual-energy x-ray absortiometry (DEXA) scan, those in the tenofovir arm had more preserved total limb fat ($P < .001$) and weight gain ($P = .002$) than did those in the stavudine arm at week 96.

2NN Study

Lange and colleagues presented the week-48 results from the 2NN clinical trial (Abstract 176). This was a multicenter, open-label, randomized trial that compared the antiviral activity of nevirapine, efavirenz, and the combination of nevirapine/efavirenz in treatment-naive HIV-infected patients. A total of 1216 subjects with screening plasma HIV-1 RNA levels greater than 5000 copies/mL and any CD4+ cell count, and at any stage of Centers for Disease Control and Prevention (CDC) classification of HIV/AIDS, were randomized to receive nevirapine 400 mg once daily (n = 220); nevirapine 200 mg twice daily (n = 387); efavirenz 600 mg once daily (n = 400); or nevirapine 400 mg/efavirenz 800 mg once daily (n = 209). All subjects received a nRTI backbone of stavudine/lamivudine. The median baseline plasma HIV-1 RNA level was 4.7 $\log_{10}$ copies/mL and median CD4+ count was 190 cells/μL.

At week 48, treatment success (a combined endpoint) achieved in each arm was as follows: nevirapine once daily, 56.4%; nevirapine twice daily, 56.3%; efavirenz once daily, 62.3%; and nevirapine/efavirenz, 46.9%. The only statistically significant difference was observed between the efavirenz and nevirapine/efavirenz arms ($P < .001$). The proportions of subjects in each arm who achieved plasma HIV-1 RNA suppression to less than 50 copies/mL at week 48 were as follows: nevirapine once daily, 70%; nevirapine twice daily, 65.4%; efavirenz once daily, 70%; and nevirapine/efavirenz once daily, 62.7%. No statistically significant differences were observed among the study arms with respect to the CD4+ cell count changes seen at week 48.

At week 48, the proportion of subjects in each study arm who experienced a grade 3 or 4 adverse clinical event was as follows: nevirapine once daily, 15%; nevirapine twice daily, 20.4%; efavirenz once daily, 18%;

and nevirapine/efavirenz once daily, 24.4%. The difference between the efavirenz and nevirapine/efavirenz arms was statistically significant ($P < .001$). Grade 3 or 4 clinical hepatotoxicity and laboratory hepatobiliary toxicity (elevation of transaminase levels) were noted, respectively, in each arm at week 48 as follows: nevirapine once daily, 1.4% and 13.2%; nevirapine twice daily, 2.1% and 7.8%; efavirenz once daily, 0.3% and 4.5%; and nevirapine/efavirenz once daily, 1.0% and 8.6%. Central nervous system toxicity and rash occurred, respectively, in each study arm as follows: nevirapine once daily, 1.4% and 4.1%; nevirapine twice daily, 3.5% and 3.1%; efavirenz once daily, 5.5% and 1.8%; and nevirapine/efavirenz once daily, 7.7% and 3.8%.

The proportion of subjects who discontinued the study in each arm over 48 weeks was nevirapine once daily, 24.1%; nevirapine twice daily, 21.2%; efavirenz once daily, 15.5%; and nevirapine/efavirenz once daily, 29%. There were 25 deaths during the study, and 2 were attributed to nevirapine: 1 female subject with no documented coinfection with hepatitis B or C virus developed toxic hepatitis, and 1 patient developed Stevens-Johnson syndrome complicated by sepsis. Both nevirapine regimens demonstrated similar potency to that of the efavirenz-based therapy at 48 weeks, and the nevirapine once-daily regimen had similar efficacy to that of the nevirapine twice-daily regimen. The use of dual-NNRTI therapy (nevirapine/efavirenz), however, resulted in substantial toxicity requiring treatment discontinuation and higher treatment failure rates.

Predictors of Response to Initial Antiretroviral Therapy

Defining immunologic, virologic, and host-cell factors that influence long-term outcomes of antiretroviral therapy is critical to providing effective individualized therapy for HIV-infected patients. Benson and colleagues analyzed baseline factors associated with treatment response at week 96 in treatment-naive HIV-infected patients enrolled in the A5001 (Adult AIDS Clinical Trials Group [AACTG] Longitudinal Linked Randomized Trials [ALLRT]) trial (Abstract 572). ALLRT is a prospective, planned series of meta- and cross-protocol analyses of patients enrolled in AACTG trials. This analysis was conducted in the 785 treatment-naive patients who were randomized to receive potent antiretroviral therapy (nRTIs plus a PI, an NNRTI, or both) in 3 clinical trials between 1998 and 2002.

At baseline, the median age of patients was 36 years; 83% were male; and 47% were white, 27% black, and 23% Hispanic. The median baseline CD4+ count and plasma HIV-1 RNA level were 222 cells/μL and 143,000 copies/mL, respectively. Forty-eight percent of patients had baseline CD4+ counts less than 200 cells/μL; 21% and 31% of patients, respectively, had baseline CD4+ counts between 200 and 350 and greater than 350 cells/μL. Fifty-seven percent of patients had baseline plasma HIV-1 levels greater than 100,000 copies/mL.

By week 96, 96% of patients achieved plasma HIV-1 RNA suppression to less than 50 copies/mL at least once. Higher baseline plasma HIV-1 RNA levels and younger age were associated with failure to achieve plasma HIV-1 RNA suppression. In regression models including baseline plasma HIV-1 RNA level and age, higher baseline hemoglobin level was associated with a greater probability of viral suppression, but sex was not.

The median rise in CD4+ count from baseline to week 96 was 237 cells/μL. Lower baseline plasma HIV-1 RNA level, older age, and male sex were each associated with smaller rises in CD4+ cell count at week 96. In regression models with baseline plasma HIV-1 RNA level, lower CD4+ cell count and higher percent of naive CD4+ cells were each significantly associated with greater increases in CD4+ cell count at week 96. Age and sex were not additionally predictive of CD4+ cell increases.

Treatment of Antiretroviral-Experienced Patients

Results of select studies in antiretroviral-experienced patients are summarized in Table 3.

HIV-NAT 009

The optimal antiretroviral therapy combination regimen for patients who experience virologic failure on nRTI therapy has not been defined. Boyd and colleagues presented the 48-week results from the HIV-NAT 009 trial (Abstract 566), a single-arm, open-label study that evaluated the use of an RTI-sparing regimen using ritonavir-boosted indinavir plus efavirenz for patients in whom nRTI-based therapy was failing. A total of 61 patients (38 men) with a mean duration of prior nRTI combination therapy of 4.1 years received indinavir 800 mg/ritonavir 100 mg twice daily plus efavirenz 600 mg once daily. At baseline, the median plasma HIV-1 RNA level and CD4+ count were 4.09 $\log_{10}$ copies/mL and 169 cells/μL, respectively. At week 48, the mean reduction in plasma HIV-1 RNA from baseline was 2.29 $\log_{10}$ copies/mL, and 53 (87%) of subjects achieved plasma HIV-1 RNA suppression to less than 50 copies/mL. The median increase in CD4+ count from baseline at week 48 was 116 (range, 47.5-179) cells/μL. The dual indinavir/ritonavir regimen in combination with efavirenz thus provided potent viral suppression and conferred robust immune responses in subjects with prior virologic failure of an nRTI-based therapy.

Primary HIV Infection

Response to Treatment

Vanhems and colleagues (Abstract 514) presented results from a prospective observational cohort of 99 patients starting antiretroviral therapy while either symptomatic from primary HIV infection, less than 6 months after primary HIV infection, or between 6 and 12 months after primary HIV infection. Those individuals starting antiretroviral therapy during true primary HIV infection reached a plasma HIV-1 RNA level below the limits of detection more often and had a higher CD4+ cell count 12 months after primary HIV infection than did the other groups. A similar study was performed by investigators from Boston, Massachusetts, and Sydney, Australia (Abstract 516). They evaluated

222 patients starting antiretroviral therapy during primary HIV infection (60%) or within 6 months of HIV seroconversion (40%). Seventy percent of participants reached a plasma HIV-1 RNA level below the limits of detection within the first year of infection. There was a greater likelihood of reaching a plasma HIV-1 RNA level below the limits of detection for those treated during primary HIV infection (hazard ratio, 0.73; $P = .057$) than for those in the other group.

QUEST Study

Kinloch and colleagues presented the week-48 preliminary results of the QUEST trial (Abstract 520), which evaluated the virologic and immunologic outcomes of patients with primary HIV-1 infection who initiated HAART for more than 18 months, followed by randomization to 6 months of continued HAART with or without vaccines before stopping antiretroviral therapy. Subjects with 3 or fewer bands on Western blot and with HIV viremia initiated fixed-combination zidovudine/lamivudine, abacavir, and amprenavir. The study enrolled 148 subjects (90% male) with a mean age of 33.9 years; median baseline plasma HIV-1 RNA level and CD4+ count were 5.4 $\log_{10}$ copies/mL and 517 cells/μL, respectively. At week 48, 28% of patients had stopped treatment and 59% had revised their initial HAART regimen. A median decrease in plasma HIV-1 RNA level from baseline to week 48 of 5.3 $\log_{10}$ copies/mL (range, 3.8 to 6.4 $\log_{10}$ copies/mL; $P < .001$) was sustained in this cohort and a median increase in CD4+ count from baseline to week 48 of 157 cells/μL (range, 0 to 290 cells/μL; $P < .001$) was observed. At 48 weeks, 83%, 61%, and 44% of subjects in this cohort with continued follow-up (n = 114) achieved suppression of plasma HIV-1 RNA levels to less than 50 copies/mL, less than 10 copies/mL, and less than 3 copies/mL, respectively. Using an ITT approach (missing data equals failure [M = F]), 64%, 47%, and 34% of subjects (n = 148) achieved suppression of plasma HIV-1 RNA levels to less than 50 copies/mL, less than 10 copies/mL, and less than 3 copies/mL, respectively. During follow-up, lower levels of CD8/38+ cells (activated CD8+ T lymphocytes), cellular messenger RNA (mRNA), and proviral DNA were associated with plasma HIV-1 RNA suppression. The patients with primary HIV-1 infection who were treated with HAART thus achieved a high rate of viral control as demonstrated by plasma HIV-1 RNA levels, mRNA, DNA, and CD8/38+ at week 48.

Interleukin-2 Plus Antiretroviral Therapy in Early HIV Infection

Hecht and colleagues examined virologic and immunologic outcomes in subjects with early HIV-1 infection who initiated HAART, had achieved suppression of plasma HIV-1 RNA to less than 500 copies/mL, and subsequently added interleukin-2 (IL-2) in an immediate versus delayed fashion (Abstract 649). The study enrolled 62 subjects who initiated fixed-combination zidovudine/lamivudine plus nelfinavir or other HAART regimens within 12 months of HIV infection. After achieving suppression of plasma HIV-1 RNA levels to less than 500 copies/mL, subjects were randomized to add IL-2 either immediately or after a delayed interval of 48 weeks. IL-2 was administered as 7.5 million units subcutaneous twice daily for 5 days every 8 weeks for 6 cycles. Of the 62 subjects, 29 were randomized to early IL-2 and 33 to the delayed group; 31 subjects had completed all 6 cycles of IL-2 (19 in the early IL-2 group and 12 in the delayed IL-2 group). From randomization to week 48, median CD4+ activation (CD38+) declined from 38.9 mean fluorescent intensity units to 5.5 in the early IL-2 group and from 115 to 3.7 in the delayed IL-2 group (difference between groups, $P = .12$). At week 12 of IL-2 therapy, the mean increases in percentage of naive and memory CD4+ cells were 2.1% and 0.8%, respectively. At 48 weeks after initiating IL-2 therapy, the median CD4+ count increased from 645 cells/μL to 1326 cells/μL in the early IL-2 group and from 629 to 1431 cells/μL in the delayed IL-2 group (difference between groups, $P = .81$).

Plasma HIV-1 RNA levels were suppressed to less than 50 copies/mL in 79% and 92% of the subjects randomized to the early and delayed IL-2 groups, respectively ($P = .62$). There were similar rises in CD4+ cell count when IL-2 was added to HAART in early HIV infection following suppression of plasma HIV-1 RNA levels to less than 500 copies/mL whether IL-2 was administered immediately or delayed by 48 weeks. Naive and memory CD4+ cells increased in equal proportion after IL-2 administration. CD4+/CD8+ activation declined on HAART with or without concurrent IL-2 administration. Unfortunately, no toxicity data were presented, which is important for this drug.

Treatment Interruptions

Hoen and colleagues (Abstract 512) presented interim results of the PRIMSTOP Pilot Trial from France. The 29 enrollees received a regimen of stavudine/didanosine/nelfinavir/hydroxyurea for 34 weeks, followed by a 50-week period of structured treatment interruptions (STIs), discontinuation of antiretroviral therapy at week 84, and follow-up to week 104. Of the 8 patients who completed the study, 2 maintained a plasma HIV-1 RNA level of less than 400 copies/mL and none reinitiated therapy. Of note, the use of stavudine and didanosine in initial therapy should be avoided due to higher rates of neuropathy and lactic acidosis, and combining these agents with hydroxyurea is associated with an unacceptably high rate of pancreatitis.

Lafeuillade and colleagues (Abstract 513) presented results of 30 patients treated with antiretroviral therapy during primary HIV infection: 15 with 3 nRTIs and 15 with stavudine, didanosine, nelfinavir, saquinavir, hydroxyurea, and 3 courses of IL-2. After 24 months, patients underwent 1 to 3 cycles of STI. Therapy was reinitiated when the plasma HIV-1 RNA level was consistently greater than 5000 copies/mL. Only 2 of 15 participants taking 3 nRTIs were able to maintain plasma HIV-1 RNA levels of less than 5000 copies/mL, compared with 12 of 15 on the dual-PI regimen. On multivariate analysis, the strength of proliferative responses to p24 antigen (9-fold for responders and 2-fold for nonresponders) and the level of proviral DNA (1.3 log copies/10^6 cells for responders vs 1.9 log copies/10^6 cells for nonresponders, $P = .01$) were related to

Table **3.** Trials in Antiretroviral-Experienced Subjects

Study (Abstract No.), Description	Regimen/Study Arm (No. Patients)	Baseline Values HIV-1 RNA (copies/mL)	Baseline Values CD4+ (cells/μL)	Changes in Values HIV-1 RNA (copies/mL)	Changes in Values CD4+ (cells/μL)
FTC 303/FTC 350 (550) Rollover study to determine the long-term efficacy and safety of emtricitabine[1] replacing lamivudine. Patients in FTC 303 (48 wks) with HIV-1 RNA <400 copies/mL were offered emtricitabine in FTC 350 (140 wks median).	**FTC 303** Emtricitabine + ART (294) Lamivudine + ART (146)	1.7 $\log_{10}$ (median)	484 (median)	77% <400 Using Kaplan-Meier method, probability of virologic failure (plasma HIV-1 RNA >400) at 4 yrs was 11%	Not available
	FTC 350 Continue or switch to emtricitabine + ART (215)				Not available
Comment: Of FTC 303 participants, 164 (56%) discontinued emtricitabine or did not roll over into FTC 350. Reasons for premature discontinuation of emtricitabine were patient request (20%); virologic failure (10%; n=28); or adverse event (8%; n=24). Tolerability failure (death or adverse event leading to permanent emtricitabine discontinuation) at 4 yrs was estimated at 13%.					
Amdoxovir (554) 24-wk, open-label, phase 1/2, 2-arm study evaluating efficacy and safety of amdoxovir[1].	Amdoxovir 300 mg bid + ART (8)	4.55 $\log_{10}$ (median)	310 (median)	-1.53 $\log_{10}$ (median change at wk 12)	+30 (wk 12) +70 (wk 24)
	Amdoxovir 500 mg bid + ART (10)	4.41 $\log_{10}$	329	-0.75 $\log_{10}$	+50 (wk 12) +150 (wk 24)
Comment: No serious adverse events were seen in either arm. 11 patients discontinued the study for lens opacity (5), virologic failure (4), or withdrawal/noncompliance (2). No grade 3 or 4 lab toxicities (except triglyceride-level elevations) were seen in either arm.					
ALIZE-ANRS 99 (551) 48-wk, prospective, randomized, open-label trial (n=355) to evaluate virologic outcomes of switch from PI to NNRTI qd regimen.	Emtricitabine/didanosine/efavirenz qd	1.7 $\log_{10}$ (median)	540 (median)	89% had no virologic failure (plasma HIV-1 RNA=400) to wk 48 (ITT [M=F]) 95% <50	+21 (median)
	Continue PI-based regimen			88% had no virologic failure 87% <50	+13
Comment: More patients in the qd arm achieved plasma HIV-1 RNA levels <50 copies/mL at week 48 than in the continue arm (P <.01). The once-daily arm sustained a greater increase in fasting HDL cholesterol levels than did the continue arm: +0.2 vs 0.0 nmol/L (P <.0001).					
CONTEXT (178) 24-wk comparative study of GW433908[1] with lopinavir/ritonavir in PI-experienced patients. Primary endpoint was the time-averaged change in plasma HIV-1 RNA level.	GW433908/ritonavir qd/ 2nRTIs (105)	4.53 $\log_{10}$ (overall median)	263 (overall median)	-1.48 $\log_{10}$ 40% <50	+62-72% (overall median)
	GW433908/ritonavir bid/ 2 nRTIs (107)			-1.50 $\log_{10}$ 42% <50	
	Lopinavir/ritonavir/ 2 nRTIs (103)			-1.66 $\log_{10}$ 48% <50	
Comment: Fewer virologic failures were sustained in the lopinavir/ritonavir arm (21%) than in the GW433908 arms (qd 34%; bid 27%). Regimens were well-tolerated. Cholesterol increases were minimal; grade 3 or 4 triglyceride elevations were seen in 4%-8% of patients in the GW433908 arms and in 4% in the lopinavir/ritonavir arm.					

Table **3.** Trials in Antiretroviral-Experienced Subjects, Continued

Study (Abstract No.), Description	Regimen/Study Arm (No. Patients)	Baseline Values		Changes in Values	
		HIV-1 RNA (copies/mL)	CD4+ (cells/µL)	HIV-1 RNA (copies/mL)	CD4+ (cells/µL)
BI 1182.52 (179) 2-wk, randomized, blinded, phase 2, dose-finding study (n=216) to evaluate 3 doses of tipranavir[1]/ritonavir. At entry, PIs were stopped and replaced with tipranavir/ritonavir for 2 weeks; ART was optimized at week 2.	Tipranavir 500 mg/ ritonavir 100 mg	4.53 $\log_{10}$ (overall median)	153 (overall median)	-0.87 $\log_{10}$ (ITT analysis; LOCF)	Not available
	Tipranavir 500 mg/ ritonavir 200 mg			-0.97 $\log_{10}$	
	Tipranavir 750 mg/ ritonavir 200 mg			-1.18 $\log_{10}$	
Comment: All study arms maintained a 1 $\log_{10}$ copies/mL decrease in HIV-1 RNA through day 56. 4 protease mutations (L33I/V/F, V82A, M184V, and L90M) were observed in the setting of PI cross-resistance. If 3 such mutations were present, the median HIV-1 RNA reductions were 0.19, 0.33, and 0.54 $\log_{10}$ copies/mL in the 500 mg/100 mg, 500 mg/200 mg, and 750 mg/200 mg dosing arms, respectively. The 750 mg/200 mg arm had the highest study discontinuation rate due to adverse events: 15% vs 5.6% in the 500 mg/200 mg arm and 2.7% in the 500 mg/100 mg arm.					
TMC114 (8) 2-wk, open-label, randomized, phase 2a study to evaluate the efficacy, safety, and pharmokinetic profile of TMC114[1] when given to PI-experienced patients at 3 different doses with ritonavir.	TMC114 300 mg/ ritonavir 100 mg bid (13)	4.3 $\log_{10}$ (overall median)	305 (overall median)	-1.24 $\log_{10}$ (median change) 46% <400 (ITT analysis)	Not available
	TMC114 600 mg/ ritonavir 100 mg bid (12)			-1.13 $\log_{10}$ 31% <400	
	TMC114 900 mg/ ritonavir 100 mg bid (13)			-1.50 $\log_{10}$ 43% <400	
	Continue current PI as control (12)			+0.02 $\log_{10}$ 8% <400	
Comment: No correlation was seen between baseline resistance to PIs and HIV-1 RNA response. Treatment with TMC114 at all 3 doses was well-tolerated. 32% of patients developed diarrhea. Central nervous system side effects included headache (16%) and dizziness (11%). 1 patient developed a grade 4 rash, and 1 patient had hepatotoxicity; liver function tests normalized with drug treatment interruption.					
HIV-NAT 009 (566) 48-wk, single-arm, open-label study that evaluated indinavir/ritonavir/efavirenz in patients in whom an nRTI-based regimen had failed. Mean duration of prior nRTI therapy was 4.1 yrs.	Indinavir 800 mg bid/ ritonavir 100 mg bid/ efavirenz 600 mg qd (61)	4.09 $\log_{10}$ (median)	169 (median)	-2.29 $\log_{10}$ (mean reduction) 53 (87%) <50	+116
Comment: Drug interruptions occurred in 16% of patients due to study drug-related events. The most frequent laboratory-related toxicity was elevated triglyceride levels in 9 (15%) patients. Rash occurred in 23 (38%) patients, but no patient interrupted drug therapy due to rash. 3 (5%) patients developed renal stones; 2 required study drug interruption and all 3 had recurrent stones/sludge.					

[1]Investigational drug; not approved by the US Food and Drug Administration.

ART indicates antiretroviral therapy; bid, twice daily; HDL, high-density lipoprotein; ITT, intent-to-treat analysis; LOCF, last observation carried forward; M=F, missing data equals failure; NNRTI, nonnucleoside reverse transcriptase inhibitor; nRTI, nucleoside reverse transcriptase inhibitor; PI, protease inhibitor; qd, once daily.

maintaining a plasma HIV-1 RNA level of less than 5000 copies/mL.

Hecht and colleagues presented data on behalf of the Acute Infection Early Disease Research Program (Abstract 519). They compared those who started antiretroviral therapy within 6 months of seroconversion and later underwent STI with those choosing to defer antiretroviral therapy. After adjusting for baseline plasma HIV-1 RNA level and estimated number of weeks since infection, subjects starting antiretroviral therapy had a lower plasma HIV-1 RNA level and a higher CD4+ cell count off antiretroviral therapy than did those deferring antiretroviral therapy. However, the unadjusted analysis did not show a clear benefit, and the authors suggested that a randomized trial is necessary to definitively assess the role of treatment in primary HIV infection.

Superinfection

Several studies concerned so-called superinfection with viral variants phylogenetically distinct from preceding HIV isolates. Wong and colleagues (Abstract 485) described 2 cases in which new clade B strains were retrospectively identified by phylogenetic analysis of *env* clones in female sexworkers who were also injection drug users. Allen and colleagues (Abstract 307) described a single individual who received HAART at primary infection and later went on to 4 cycles of STI. Phylogenetic analysis of *gag* sequences from 4 time points demonstrated emergence of a strain with 12% heterogeneity from the strain at seroconversion. This second strain persisted during the second and third STIs despite the presence of an immunodominant CD8+ T-cell epitope in p24 common to both viruses. Subbarao and colleagues (Abstract 486) described cell-free HIV RNA and proviral DNA levels using a real-time reverse transcriptase polymerase chain reaction method adapted to distinctly quantify subtypes B and CRF01_AE in a coinfected individual. Initially, the plasma virus was a subtype B strain. Subtype CRF01_AE was detected at 8 and 20 months in plasma and proviral DNA, respectively. The plasma HIV-1 RNA level for subtype B ranged from 7484 to 237,649 copies/mL over 44 months but for CRF01_AE was consistently lower, ranging from 3320 to 18,348 copies/mL over 33 months, respectively.

Treatment Strategies

Results of select studies of STIs in antiretroviral-experienced patients are summarized in Table 4.

STIs in Persons with Virologic Suppression

Ananworanich and colleagues presented the 48-week results of HIV-NAT 001.4 (Abstract 64), a prospective, open-label, randomized trial conducted in Thailand that evaluated HIV disease progression and safety of a STI undertaken in patients with chronic HIV infection. A total of 74 Thai patients who had received 1 year of dual nRTIs followed by PI-based therapy (saquinavir soft gel capsule 1600 mg/ritonavir 100 mg once daily) for 3 years were enrolled. The trial examined STIs based upon a CD4+ count decline versus 1 week on/1 week off antiretroviral therapy. When CD4+ count was greater than 350 cells/μL and plasma HIV-1 RNA was less than 50 copies/mL for at least 6 months, subjects were randomized to 1 of 3 study arms: continuous antiretroviral therapy (n = 25), CD4+ count-guided arm (n = 23), or 1 week on/1 week off arm (n = 26). The STI in the CD4+ count-guided arm was based on a CD4+ count of 350 cells/μL or less or a 30% drop or rise in CD4+ cell count. Treatment failure was defined as plasma HIV-1 RNA levels greater than 1000 copies/mL or CD4+ count of 350 cells/μL or less in the continuous and week on/week off study arms. Baseline characteristics were similar between arms with regard to sex (49% male), mean age (34 years), and mean CD4+ count (644 cells/μL). Preantiretroviral therapy and pre-HAART plasma HIV-1 RNA levels were higher in the CD4+ count-guided arm (4.8 and 3.2 $\log_{10}$ copies/mL, respectively) and in the week on/week off arm (4.9 and 3.4 $\log_{10}$ copies/mL, respectively) than in the continuous arm (4.3 and 2.6 $\log_{10}$ copies/mL, respectively; $P < .05$).

At week 48, no differences between study arms in HIV disease progression (AIDS or death), adverse events, serum lipid levels, or quality of life were demonstrated. One subject in the CD4+ count-guided arm developed an acute retroviral syndrome while off therapy. Median changes in CD4+ count from baseline to week 48 were an increase of 5 cells/μL in the continuous arm, a decline of 178 cells/μL in the CD4+ count-guided arm, and a decline of 6 cells/μL in the week on/week off arm ($P < .05$). All patients (25/25) in the continuous arm maintained CD4+ counts greater than 350 cells/μL through week 48. The proportion of patients who maintained CD4+ counts greater than 350 cells/μL through week 48 in the other 2 arms was 87% (20/23) in the CD4+ count-guided arm and 96% (25/26) in the week on/week off arm. Twelve of the 23 patients in the CD4+ count-guided arm were off antiretroviral therapy at study analysis. No treatment failures occurred in the continuous or CD4+ count-guided study arms through 48 weeks of follow-up. There were 8 treatment failures in the week on/week off study arm: 7 subjects had virologic failure with HIV-1 RNA levels greater than 1000 copies/mL and 1 patient sustained a decrease in CD4+ count to less than 350 cells/μL. Two additional patients were lost to follow-up. The median time to virologic failure in the week on/week off study arm was 16 weeks. Of 9 subjects in the week on/week off arm for whom genotypic testing results were available, 4 had resistance mutations (3 in the reverse transcriptase gene and 1 in the protease gene). At week 48, the proportion of subjects in each study arm who achieved suppression of plasma HIV-1 RNA to less than 500 [50] copies/mL was 100% [96%] in the continuous arm; 100% [83%] in the CD4+ count-guided arm; and 54% [35%] in the week on/week off study arm (HIV-1 RNA < 500 copies/mL, $P < .05$; HIV-1 RNA < 50 copies/mL, $P < .05$). All subjects who had virologic failure in the week on/week off study arm achieved plasma HIV-1 RNA suppression of less than 50 copies/mL within a median of 12 weeks after resuming the same PI-based antiretroviral therapy regimen. The CD4+ count-guided study arm provided the best cost-saving strategy and had simi-

lar virologic outcomes to the continuous therapy arm, whereas the week on/week off study arm had unacceptably high rates of virologic failure.

Ruiz and colleagues presented the 48-week results of a multicenter, controlled, open-label, randomized clinical trial (Abstract 65) that evaluated the strategy of continuous versus intermittent antiretroviral therapy guided by CD4+ cell counts and plasma HIV-1 RNA levels. The primary objective of this study was to compare the safety of continuous versus intermittent antiretroviral therapy in chronically HIV-infected patients who had maintained viral suppression on the current regimen. Virologic and immune responses were assessed. Patients with plasma HIV-1 RNA of less than 50 copies/mL for 1 year or greater, CD4+ count greater than 500 cells/μL for at least 6 months, and nadir CD4+ count greater than 100 cells/μL were eligible. A total of 120 patients were randomized to either interrupt therapy (n = 59) or continue the same prior antiretroviral therapy (n = 61). The criteria for resuming antiretroviral therapy in the interrupt study arm included CD4+ count decline below 350 cells/μL, plasma HIV-1 RNA increase to greater than 100,000 copies/mL, or an AIDS-defining event. Those patients who had resumed antiretroviral therapy would stop treatment again when CD4+ counts had risen to greater than 500 cells/μL and plasma HIV-1 RNA levels had suppressed to less than 50 copies/mL. The median baseline CD4+ count was 851 cells/μL in the interrupt arm and 800 cells/μL in the continue arm; nadir CD4+ counts were 416 and 379 cells/μL in the interrupt and continue study arms, respectively. The median pretreatment plasma HIV-1 RNA level was 4.5 $\log_{10}$ copies/mL.

No AIDS-defining events occurred in either study arm; no subject sustained a decline in CD4+ count to less than 200 cells/μL. One subject in the interrupt arm sustained a CD4+ count decrease to between 200 and 250 cells/μL. Four patients in the interrupt arm experienced a decrease in CD4+ count to between 250 and 350 cells/μL, compared with no patients in the continue arm ($P = .02$). Six (10%) patients in the interrupt arm developed an acute seroconversion illness; the plasma HIV-1 RNA level threshold off antiretroviral therapy was not correlated with the risk of developing an acute seroconversion syndrome. In those patients who remained off treatment for 48 weeks, a CD4+ count decrease of 335 cells/μL was observed at week 48 and a loss of 33 CD4+ cells/μL/month was incurred. Of these 33 patients, 23 (70%) experienced plasma HIV-1 RNA rebound to greater than 100,000 copies/mL at a median of 8 weeks after stopping treatment; 2 (6%) sustained a decline in CD4+ count to 350 cells/μL or below; and 8 (24%) met both plasma HIV-1 RNA rebound and CD4+ criteria to resume treatment. The median time off antiretroviral therapy was 32 weeks. Those patients in the interrupt arm who remained off treatment (n = 26) had a higher CD4+ count nadir of 454 cells/μL than did those subjects who resumed treatment (n = 33), who had a CD4+ count nadir of 363 cells/μL ($P = .06$). A higher CD4+ cell count was associated with remaining off antiretroviral therapy for a longer period of time. In a multivariate analysis, CD4+ cell count nadir and preantiretroviral therapy plasma HIV-1 RNA level were both strongly associated with risk for resuming treatment ($P = .004$ and $P = .009$, respectively).

Vella and colleagues presented the first results of the ISS-PART Trial, sponsored by the Italian HIV Clinical Research Program (Abstract 66). This study randomized 273 subjects with plasma HIV-1 RNA levels of less than 400 copies/mL and CD4+ counts greater than 350 cells/μL to continue their current PI- or NNRTI-based therapy or to interrupt their therapy on an increasing schedule of 3 months on treatment alternating with 1, 1, 2, 2, and 3 months off. The median baseline CD4+ counts were 699 and 673 cells/μL in the 2 arms, respectively. After a median follow-up of 56 weeks, there were more dropouts in the intermittent therapy arm than in the continuous therapy arm (25 vs 5, respectively), mainly due to physician or patient request. Of those completing 12 months of follow-up, 42 (89%) of 47 subjects in the continuous therapy arm remained virologically suppressed; in the intermittent therapy arm 35 (97%) of 37 followed to this time point resuppressed plasma HIV-1 RNA levels to less than 400 copies/mL after the third cycle. CD4+ cell counts were well-maintained in the latter group. Over the period spanning the first 3 interruptions, 33 (24.2%) of 136 subjects demonstrated a drug-resistance mutation, with M184V most frequently detected. Twenty-four of these 33 were studied further, and 14 (58%) of these 24 were found to have mutations in their baseline peripheral blood mononuclear cell or plasma samples. Plasma HIV-1 RNA and CD4+ cell changes during each interruption did not correlate with whether mutations were detected. Importantly, subjects with mutations suppressed plasma HIV-1 RNA levels with reinstitution of the same therapy at rates of 91%, 88%, and 92% after the first, second, and third interruption, respectively. The suppression rates for those with no detectable mutations were 96%, 92%, and 100%, respectively. It will be important to see how the mutational frequency and virologic failure rates compare in the 2 arms of this study with longer follow-up.

Dybul and colleagues reported the National Institute of Allergies and Infectious Diseases' trial results with cyclic antiretroviral therapy involving 8 weeks on and 4 weeks off (Abstract 68lb). Fifty-two patients with plasma HIV-1 RNA levels of less than 50 copies/mL and CD4+ counts greater than 300 cells/μL were randomized to continue therapy or to interrupt therapy as noted. Enrollment was halted early because in the intermittent therapy arm, 3 patients on efavirenz-based therapy developed lamivudine- or NNRTI-associated mutations, and 1 patient receiving a PI-based regimen developed lamivudine resistance. Toxicity markers were not significantly improved in the intermittent therapy arm compared with in the continued therapy arm. Thus, no clear benefit and a higher risk of viral resistance was seen in the intermittent therapy arm. These data are in contrast to the previously published work of Dybul and colleagues reporting the efficacy of short-cycle therapy (7 days on, 7 off).

STIs in Treatment-Experienced Patients

CPCRA 064. Lawrence and colleagues presented the results of the CPCRA 064 study, a randomized, prospective, clinical endpoint trial conducted in HIV-infected patients with virologic failure that evaluated the impact on HIV disease progression of initiating an STI strategy prior to a salvage antiretroviral therapy regimen (Abstract 67). This multicenter study enrolled HIV-infected patients with advanced disease who had experienced virologic failure and continued on stable antiretroviral therapy regimens with screening plasma HIV-1 RNA levels greater than 5000 copies/mL. Multidrug-resistant HIV was documented by genotypic testing. Baseline genotypic and phenotypic testing was performed to help guide the selection of active drugs in the new salvage regimen. The primary endpoint was progression of HIV disease or death. A total of 270 patients with mean baseline CD4+ count and plasma HIV-1 RNA of 180 cells/μL and 5.0 $\log_{10}$ copies/mL, respectively, were randomized 1:1 to a 4-month STI followed by a new salvage regimen or to an immediate change in antiretroviral therapy regimen. At baseline, 9% of subjects were female; 26% had CD4+ count of 50 cells/μL or below, with median CD4+ count nadir of 69 cells/μL; and 56% had developed a prior opportunistic infection. This study population was extensively treatment-experienced, with prior exposure to a mean of 5 nRTIs, 1.5 NNRTIs, and 4.2 PIs. At study entry, 48% of patients had resistance to all 3 drug classes on testing. The total number of antiretroviral [active] drugs provided to each of the study arms was 3.6 [2.7] in the STI arm and 3.8 [2.8] in the no-STI arm.

A total of 34 clinical endpoints (HIV disease progression or death) were reached: 22 endpoints in the STI arm and 12 in the no-STI arm (hazard ratio, 2.6; 95% confidence interval, 1.2-5.5; $P < .01$). The STI arm experienced 17 progression-of-disease events: 7 (41%) patients developed esophageal candidiasis; 4 (24%), *Pneumocystis carinii* pneumonia (PCP); 3 (18%), cryptosporidiosis; 2 (12%), lymphoma; and 1 (6%) cytomegalovirus disease. Eight deaths occurred in each study arm. The mean difference in CD4+ count favored the no-STI arm over the STI arm, with 85 cells/μL ($P < .001$) for months 1 through 4 (STI phase), 47 cells/μL ($P < .001$) for months 5 through 8, and 31 cells/μL ($P = .11$) for months 12 through 20. In the STI arm, 52% sustained a greater than 50% decrease in CD4+ cell count. The mean changes in plasma HIV-1 RNA in the STI arm were +0.31 $\log_{10}$ copies/mL and -0.76 $\log_{10}$ copies/mL at 4 months and 12 months, respectively, compared with -0.75 $\log_{10}$ copies/mL and -0.66 $\log_{10}$ copies/mL, respectively, in the no-STI arm. At month 4, 64% of patients in the STI group had wild-type virus on genotypic testing and sustained plasma HIV-1 RNA suppression of 0.7 $\log_{10}$ copies/mL at 20 months. The study was closed prior to full accrual based upon recommendations from a data and safety monitoring board. Given the persistently inferior CD4+ cell count responses and higher number of clinical events in the STI arm, there was no clinical or immunologic benefit conferred by STI as a salvage strategy in this group of patients with advanced HIV disease and multidrug-resistant HIV.

ANRS 097. Katlama and colleagues presented the results of the GIGHAART ANRS 097 study, which evaluated the impact on virologic outcome of STI as a salvage strategy in patients with advanced HIV disease and multiple treatment failures (Abstract 68). This prospective, open-label, randomized trial enrolled 70 HIV-infected patients with screening plasma HIV-1 RNA greater than 50,000 copies/mL and CD4+ count of 200 cells/μL or below. Patients were randomized to an immediate therapy arm or to a deferred therapy arm initiated after an 8-week treatment interruption. The GIGHAART regimen consisted of 7 to 9 drugs: 3 or 4 nRTIs and 1 NNRTI with or without hydroxyurea 500 mg twice daily, in combination with ritonavir 400 mg twice daily and amprenavir 600 mg twice daily or lopinavir 400 mg/ritonavir 100 mg twice daily, and a third PI (indinavir 400 mg twice daily, saquinavir 600 mg twice daily, or nelfinavir 1250 mg twice daily). The primary endpoint was a decrease in plasma HIV-1 RNA levels of greater than 1 $\log_{10}$ copies/mL after 12 weeks of therapy. Sixty-eight of the 70 randomized patients initiated treatment; 63 were evaluated at weeks 12 and 24, and 64 at week 48. At baseline, median plasma HIV-1 RNA level and CD4+ count were 5.3 $\log_{10}$ copies/mL and 27 cells/μL, respectively. The median duration of prior antiretroviral therapy was 6.6 years with a median of 11 antiretroviral drugs. There was extensive 3-class antiretroviral therapy drug resistance present at baseline in this study population: 88% and 72% of subjects in the immediate and deferred arms, respectively, had more than 3 nRTI-associated mutations (NAMs), and 79% and 91% of subjects, respectively, had at least 1 major PI mutation. Genotypic reversion occurred in 48% of subjects following an 8-week treatment interruption.

The proportion of subjects who achieved a greater than 10-fold decrease in plasma HIV-1 RNA was 26% at week 12 and 24% at week 24 in the immediate arm, compared with 62% at week 12 and 50% at week 24 in the STI arm (week 12, $P = .007$; week 24, $P = .043$). The immediate arm sustained median decreases in plasma HIV-1 RNA from baseline of 0.37 $\log_{10}$ copies/mL at week 12; 0.29 $\log_{10}$ copies/mL at week 24; and 0.37 $\log_{10}$ copies/mL at week 48. By comparison, the STI arm sustained median plasma HIV-1 RNA decreases of 1.91 $\log_{10}$ copies/mL, 1.08 $\log_{10}$ copies/mL, and 0.79 $\log_{10}$ copies/mL, respectively. The proportion of subjects who achieved suppression of plasma HIV-1 RNA level to less than 400 copies/mL was 15% at week 12 and 12% at week 24 in the immediate arm versus 38% at week 12 and 32% at week 24 in the STI arm (week 12, $P = .053$; week 24, $P = .077$). The median increase in CD4+ count from baseline was 7 cells/μL at week 24 and 7 cells/μL at week 48 in the immediate arm versus 51 cells/μL and 69 cells/μL, respectively, in the STI arm. There were 2 deaths in each study arm. At week 48, 22% and 47% of subjects in the immediate and STI arms, respectively, remained on giga-HAART salvage therapy (more than 6 drugs). In a multivariate regression model evaluating baseline predictors of virologic success, 3 factors were associated with favorable

Table **4.** Structured Treatment Interruptions (STIs) in Antiretroviral-Experienced Patients

Study (Abstract No.), Description	Regimen/Study Arm (No. Patients)	Baseline Values: HIV-1 RNA (copies/mL)	Baseline Values: CD4+ (cells/μL)	Changes in Values: HIV-1 RNA (copies/mL)	Changes in Values: CD4+ (cells/μL)
HIV-NAT 001.4 (64) 48-wk, prospective, open-label, randomized trial conducted in Thailand that evaluated HIV progression and safety of STI in patients with HIV-1 RNA <50 copies/mL. Prior to entry, all patients had received at least 3 years PI-based therapy of saquinavir sgc 1600 mg/ritonavir 100 mg/2 nRTIs qd.	Continuous ART (25)	2.6 $\log_{10}$ (pre-HAART)	644 (overall mean)	96% <50	100% >350
	CD4+-guided STI (23)	3.2 $\log_{10}$		83% <50	87% >350
	1 wk on/1 wk off (26)	3.4 $\log_{10}$		35% <50	96% >350
Comment: No treatment failures occurred in the continuous arm vs 8 treatment failures in the wk on/wk off arm: 7 with HIV RNA >1000 copies/mL and 1 with CD4+ decrease <350. 2 patients were lost to follow-up. Median time to virologic failure in the wk on/wk off arm was 16 wks. One patient in the CD4+-guided arm had acute retroviral syndrome. The CD4+-guided arm had similar virologic outcomes as did the continuous arm. Time spent on ART was 33% in the CD4+-guided arm vs 59% in the wk on/wk off arm.					
Continuous vs Intermittent ART (65) 48-wk, multicenter, controlled, open-label, randomized trial that evaluated continuous vs intermittent HAART guided by CD4+ count and HIV-1 RNA levels in patients with HIV-1 RNA suppression <50 copies/mL. Criteria for resuming ART in the interrupt arm were CD4+ decrease to <350 cells/mL; a confirmed HIV-1 RNA increase to 100,000 copies/mL or greater or an AIDS-defining event.	Interrupt (59)	4.5 $\log_{10}$ (median)	851 (median)	4.1 $\log_{10}$ in patients remaining off ART; 33 (56%) resumed ART and of these, 23 (70%) had >100,000	96 (median decrease)
	Continue (61)	4.5 $\log_{10}$	800	97% <50	804 (median count)
Comment: 6 (10%) of patients in the interrupt arm developed acute seroconversion illness; HIV-1 RNA threshold was not correlated with risk of such illness. Median time off ART in the interrupt arm was 32 wks. Patients in the interrupt arm who remained off ART (n=26) had a higher nadir CD4+ count (454 cells/μL) than did those (n=26) who resumed ART (363 cells/μL). Of 33 patients in the interrupt arm with viral rebound, 2 (6%) had CD4+ cell counts <350; 8 (24%) met viral rebound and CD4+ criteria to resume ART. No AIDS-defining events occurred in either arm. CD4+ nadir (*P*=.004) and pre-ART HIV-1 RNA levels (*P*=.009) were associated with resuming ART.					
CPCRA 064 (67) Randomized, prospective, clinical endpoint trial in patients with virologic failure (n=270) that evaluated the impact on HIV disease progression of STI prior to devising salvage regimen. STI interval was 4 mos. Median wks of follow-up was 11.3 months; study closed prior to full accrual based on DSMB recommendation.	4-mo STI	5.0 $\log_{10}$ (mean)	180 (mean)	+0.31 $\log_{10}$ (4 mos) -0.76 $\log_{10}$ (12 mos)	Difference between no-STI and STI arms: 85 (1-4 mos) 47 (5-8 mos) 31 (12-20 mos)
	No STI			-0.75 $\log_{10}$ -0.66 $\log_{10}$	
Comment: At 4 mos, 64% of patients in the STI arm had wild-type virus and sustained HIV-1 RNA decrease of 0.7 $\log_{10}$ copies/mL at 20 months. 34 clinical endpoints (disease progression/death) were reached: 22 in the STI arm vs 12 in the no-STI arm (HR 2.6; 95% CI [1.2, 5.5]; *P* <.01). 8 deaths occurred in each arm. The STI arm had 17 disease events: 7 (41%) candidal esophagitis; 4 (24%) PCP; 32 (18%) cryptosporidiosis; 2 (12%) lymphoma; and 1 (6%) cytomegalovirus. In the STI arm, 52% of patients had a >50% decrease in CD4+ cell count.					

Table **4.** Structured Treatment Interruptions (STIs) in Antiretroviral-Experienced Patients, Continued

Study (Abstract No.), Description	Regimen/Study Arm (No. Patients)	Baseline Values		Changes in Values	
		HIV-1 RNA (copies/mL)	CD4+ (cells/μL)	HIV-1 RNA (copies/mL)	CD4+ (cells/μL)
GIGHAART ANRS 097 (68) 48-wk, prospective, open-label, randomized trial to evaluate the impact of STI vs immediate salvage therapy on virologic outcome in patients with multiple virologic failures (n=70). Primary endpoint was decrease in plasma HIV-1 RNA >1 $\log_{10}$ copies/mL after 12 weeks of salvage therapy.	Deferred therapy (8-week STI)	5.3 $\log_{10}$ (overall median)	27 (overall median)	Wk 12: -1.91 $\log_{10}$ 38% <400 (ITT analysis, M=F) Wk 24: -1.08 $\log_{10}$ 32% <400 Wk 48: -0.79 $\log_{10}$	Week 24: +51 Week 48: +69
	Immediate salvage: 3 or 4 nRTIs/1 NNRTI ± hydroxyurea 500 mg bid/ritonavir 400 mg bid/amprenavir 600 mg bid or lopinavir 400 mg/ritonavir 100 mg/third PI (saquinavir 600 mg bid, indinavir 400 mg bid, or nelfinavir 1250 mg bid)			Wk 12: -0.37 $\log_{10}$ 15% <400 Wk 24: -0.29 $\log_{10}$ 12% <400 Wk 48:-0.37 $\log_{10}$	Week 24: +7 Week 48: +7
Comment: On ITT analysis (M=F), 62% of patients in the deferred arm sustained a >1 $\log_{10}$ copies/mL decline in HIV-1 RNA levels at wk 12, compared with 26% in the immediate arm (*P*=.007). There were 2 deaths in each study arm. At wk 48, 22% and 47% of patients in the immediate and deferred arms, respectively, remained on mega-salvage therapy. In a multivariate regression model, 3 factors were predictive of favorable HIV-1 RNA response: reversion of resistance (RH, 12.4); adequate drug exposure (RH 5.6); and lopinavir use (RH 6.0).					
ISS-PART (66) 56-wk, prospective, multicenter, randomized trial of STI in subjects with chronic HIV infection and stable HIV replication (<400 copies/mL). Study endpoint was the proportion of patients with CD4+ count >500 cells/μL at 24 mos.	Continued ART (137)	<400	699	Not available	Not available
	5 STIs: 1, 1, 2, 2, and 3 months duration, each followed by 3 months on ART (136)	<400	673	After first STI: 88.9% <400 Second STI: 96.8% <400 Third STI: 100% <400	After first STI: -72 Second STI: -60 Third STI: -147
Comment: After ART was reinitiated, median CD4+ counts in the STI arm returned to baseline values. After the first STI, 33 (25%) of patients had no plasma HIV-1 RNA rebound, compared with 25 (27%) after the second STI and 3 (8.8%) after the third STI. Most patients achieved plasma HIV-1 RNA suppression <400 copies/mL with ART resumption after STI, but a trend of increased resistance mutations was noted with STI. Mutations were identified in 24% of STI patients; approximately 50% of these mutations were present at baseline (largely nRTI-associated mutations). M184V was the most frequently detected mutation. NNRTI- and PI-associated mutations were identified in 6% and 8% of patients, respectively, in the STI group.					

ART indicates antiretroviral therapy; bid, twice daily; CI, confidence interval; DSMB, Data and Safety Monitoring Board; HAART, highly active antiretroviral therapy; HR, hazard ratio; ITT, intent-to-treat analysis; M=F, missing data equals failure; NNRTI, nonnucleoside reverse transcriptase inhibitor; nRTI, nucleoside reverse transcriptase inhibitor; PCP, *Pneumocystis carinii* pneumonia; PI, protease inhibitor; RH, relative hazard; sgc, soft-gel capsule.

plasma HIV-1 RNA response: reversion of resistance, adequate drug exposure, and use of lopinavir/ritonavir.

The reasons for the apparently conflicting results of CPCRA 064 and ANRS 097 are not clear. The patients in the latter study, however, had more advanced HIV disease with a lower baseline CD4+ cell count than those in the former study, underwent a shorter length of treatment interruption, and were treated with a multidrug rescue therapy (mega- or giga-HAART).

Haubrich and colleagues presented a preliminary analysis of a California Collaborative Treatment Group (CCTG) 578 substudy (Abstract 565). This study evaluated the benefit of an STI in PI-experienced patients in whom HAART was failing. Subjects were treated with a lopinavir/ritonavir-inclusive regimen immediately (n = 16) or after an STI of more than 4 months (n = 20). The exploratory analyses did not demon-

strate differences in 6-week CD4+ counts, plasma HIV-1 RNA levels, or changes in CD4+ counts from baseline between the 2 arms.

Selective (Partial) Treatment Interruption

Deeks and colleagues evaluated the relative impacts of interrupting either the PI (n=15) or the nRTI (n=5) components of a stable HAART regimen while continuing the other antiretrovirals, a so-called partial treatment interruption (Abstract 640). The study population was a highly selected cohort of 20 antiretroviral-adherent individuals with stable on-treatment viremia and CD4+ counts but high levels of antiretroviral resistance. PI or nRTI therapy was interrupted based on patient-specific toxicity. In brief, there were immediate increases in plasma HIV-1 RNA levels with later reductions in CD4+ cell counts in the stop-nRTI/continue-PI group. Conversely, these values remained stable in the stop-PI/continue-nRTI group. In the latter group, the PI mutations persisted through week 24, and thus replication capacity remained reduced during this period. The implications of these findings for clinical management are not yet clear.

Switching/Simplification

Molina and colleagues presented the 48-week results from the ALIZE-ANRS 99 study, a prospective, randomized, open-label, multicenter, non-inferiority trial (Abstract 551). Investigators evaluated virologic outcomes in HIV-infected subjects with plasma HIV-1 RNA of less than 400 copies/mL on current PI-based therapy who either continued a PI-containing regimen or switched to a once-daily combination antiretroviral therapy regimen of the investigational drug emtricitabine/didanosine/efavirenz. Virologic failure was defined as a confirmed plasma HIV-1 RNA level of 400 copies/mL or greater.

A total of 355 patients with plasma HIV-1 RNA levels of less than 400 copies/mL were randomized; 86% were male, the median age was 41 years, and the median duration of PI therapy was 35 months. Baseline median CD4+ count was 540 cells/μL. The proportions of patients who achieved virologic success at week 48 using as-treated and ITT (M=F) analyses were 96% and 89%, respectively, in the once-daily study arm, compared with 93% and 88%, respectively, in the continued-PI therapy arm. At 48 weeks, 95% of patients in the once-daily arm had achieved suppression of plasma HIV-1 RNA to less than 50 copies/mL, compared with 87% of patients in the continued-PI therapy arm ($P < .01$). The median CD4+ count increase was similar at week 48 between the study arms (21 and 13 cells/μL in the once-daily and continued-PI therapy arms, respectively). A statistically significant increase in median fasting HDL cholesterol levels was observed in the once-daily arm compared with the continued-PI therapy arm: 0.2 vs 0.0 nmol/L, re-spectively ($P < .0001$). The substitution of a PI-based regimen with a once-daily NNRTI-based combination regimen of emtricitabine/didanosine/efavirenz thus demonstrated continued suppression of plasma HIV-1 RNA levels and conferred continued increases in CD4+ cell counts for 48 weeks.

Dalmau and colleagues described the 24-month outcomes in the NEFA study (Abstract 608). Subjects on at least 1 PI plus 2 nRTIs who had plasma HIV-1 RNA levels of less than 200 copies/mL for at least 6 months and who were randomly assigned to switch off the PI to either nevirapine (n=155), efavirenz (n=156), or abacavir (n=149) were evaluated. A history of mono- or dual-nRTI therapy was permitted in this study. Briefly, 11% of subjects had plasma HIV-1 RNA levels greater than 200 copies/mL at 24 months. In the nevirapine, efavirenz, and abacavir arms the failure rates were 15/155, 12/156, and 24/149, respectively. Genotypic testing demonstrated greater nRTI resistance in the abacavir arm than in the NNRTI arms. No differences in failure rates were observed between those with no prior nRTI exposures. These data support prior studies on the reduced potency of nRTI-only regimens in highly nRTI-experienced individuals.

Antiretroviral Drug Resistance and Replication Capacity

Results of select studies of antiretroviral drug resistance and replication capacity are summarized in the Appendix.

Treatment-Naive Patients

Little and colleagues presented data on behalf of the Acute HIV Infection and Early Disease Research Program (Abstract 152). They evaluated the relationship between virologic set point, drug susceptibility, and viral replication capacity in 194 subjects remaining treatment-naive after primary HIV infection (range, 5-24 months). No relationship was noted between the mean baseline replication capacity and the plasma HIV-1 RNA level or CD4+ cell count. The mean baseline CD4+ cell percent was higher in those with resistance to any drug compared with those with fully susceptible isolates, 34% and 28% ($P=.05$), respectively. The mean replication capacity for isolates with PI hypersusceptibility (<0.4-fold change to ≥1 PI) and for those with PI susceptibilities in the standard susceptibility range were 30% and 50%, respectively ($P < .0001$). PI hypersusceptibility was observed more commonly at primary infection than in established infection, 33% and 18%, respectively. The authors suggest that viruses with low replication capacities at primary infection may evolve to higher replication capacity in established infection. Among subjects with NNRTI resistance the mean plasma HIV-1 RNA set point was 0.6 $\log_{10}$ copies/mL higher than the mean set point in those without NNRTI resistance ($P=.005$).

Employing 188 isolates from this same data set, Leigh Brown (Abstract 594) analyzed the genotypic factors associated with variations in baseline PI susceptibility. Combinations of changes at codons in both protease codons 10, 13, 37, 57, 62, 63, and 73 and *gag* cleavage sites were identified that were associated with hypersusceptibility to ritonavir (n=22). A strong association was noted between increasing hypersusceptibility to ritonavir and replication capacities of 10%

or lower ($P < .0001$).

Grant and colleagues presented data from the Options Project, which follows HIV-serodiscordant couples (Abstract 505). Viral phylogenetic linkages were established in 35 partnerships. Investigators compared those individuals who transmitted virus to their partners (n = 33) with those who did not (n = 26). Transmitters were less likely to have PI mutations than were nontransmitters (9% vs 23%, $P = .09$), whereas the prevalence of nRTI and NNRTI mutations was similar in both, suggesting that PI mutations may be associated with decreased infectiousness. However, it is not clear whether the presence of PI mutations in the known HIV-seropositive partner was associated with a lower plasma HIV-1 RNA level leading to a decreased risk of transmission. Importantly, all transmitters with drug-resistant viremia (n = 9) transmitted drug-resistant virus to their partners, and all circulating mutations were transmitted in 7 of 9 cases. These data stand in contrast to the findings by other investigators of a low prevalence of drug-resistance mutations in newly infected individuals (Abstracts 502 and 504).

Barbour and colleagues evaluated the evolution of replication capacity and phenotypic drug susceptibility in 22 untreated HIV-infected adults within 6 months of seroconversion, who were followed up for a median of 1 year (Abstract 617). At baseline, the median replication capacity (percent control, not normalized), plasma HIV-1 RNA level, and CD4+ count were 47%, 3.79 $\log_{10}$ copies/mL, and 608 cells/µL, respectively. Eight of 22 (38%) isolates demonstrated PI hypersusceptibility (< 0.4-fold change to ≥1 PI) and 6 of 22 (27%) demonstrated resistance by phenotypic testing to more than 1 drug. The median replication capacity for the 6 drug-resistant isolates was lower than for the 16 wild-type isolates (21% and 61%, respectively; $P = .07$). In follow-up, modest but statistically significant decreases in replication capacity of 0.54% per month ($P = .02$) were observed.

Simon and colleagues (Abstract 504) compared viral resistance and phylogenetic profiles among HIV isolates derived from newly infected individuals over 3 time periods: 1995 to 1998 (n = 76), 1999 to 2000 (n = 71), and 2001 to 2002 (n = 102). Resistance to nRTIs was less frequent over time, and PI and NNRTI resistance was more common. Transmission of drug-resistant virus was observed in 3 clades representing 14.6% of all drug-resistant variants observed over the period from 1995 to 2002. The individual mutations observed were K70R and K103N in reverse transcriptase and L90M in protease.

Treatment-Experienced Patients

'Immune-Discordant' Patients. Linden and colleagues presented single-time-point observational data from a cohort of 50 subjects adherent to stable HAART regimens (Abstract 146). Twenty "immune discordant" subjects (10 on PIs, 10 on NNRTIs) had CD4+ counts of 200 cells/µL or greater, which were stable or increasing, and plasma HIV-1 RNA levels ranging from 500 to 10,000 copies/mL. Another group of 20 subjects (10 on PIs, 10 on NNRTIs) had plasma HIV-1 RNA levels of less than 50 copies/mL and CD4+ counts of above 200 cells/µL that were stable or increasing. A further 10 subjects in whom PI therapy was failing had increasing plasma HIV-1 RNA levels and falling CD4+ counts. Comparing the discordant and treatment failure groups, the following were observed more frequently in the discordant group: nonsyncytium-inducing virus (0/15 discordant and 7/9 treatment failure, respectively; $P < .007$), higher levels of HIV Gag-specific immune responses, and lower levels of CD38+ cells. Lower median replication capacities were observed among the discordant-on-PI group than among the discordant-on-NNRTI and PI-failing groups, at 12%, 27%, and 22%, respectively ($P = < .05$ for differences between discordant-on-PI and discordant-on-NNRTI). This study includes subjects with immunologic failure on HAART and enhances our understanding of immunologic failure in populations with stable virologic failure.

Lopinavir/ritonavir. Kempf and colleagues presented a resistance analysis of the 96-week data from M98-863 (Abstract 600). This study evaluated antiretroviral-naive subjects with virologic failure on either lopinavir/ritonavir or nelfinavir, each combined with stavudine/lamivudine. The findings demonstrated the absence of lopinavir resistance in those with extended periods of viremia on lopinavir/ritonavir. The study also described the lower incidence of lamivudine and stavudine resistance in those taking lopinavir/ ritonavir than in those taking nelfinavir. These results extend observations made by others of the lower frequency of viral resistance in antiretroviral-naive subjects on ritonavir-boosted PI regimens (eg, the SOLO study, discussed in Abstract 598).

Atazanavir. Colonno and colleagues described the prevalence of atazanavir resistance in 7 trials, including 3 studies of PI-naive subjects (Abstract 597). Atazanavir resistance was observed in 4% of all subjects and 14% of those with virologic failure. Data on 58 atazanavir-resistant isolates were presented. A unique protease mutation, I50L (typically occurring with A71V), was observed in 26 isolates (23 from PI-naive subjects). In 18 of 19 isolates with matched phenotypic data, I50L conferred a 4-fold or greater increase in atazanavir resistance from baseline but also conferred hypersusceptibility (fold change to 0.4-fold or lower) to at least one other PI. Thus, the I50L mutation appears to broadly enhance susceptibility to available PIs while conferring atazanavir resistance (as determined by phenotypic assay). In recombinant isolates bearing the I50L mutation, the A71V mutation increased the level of atazanavir resistance without an apparent effect on the broad enhancement of susceptibilities to other PIs. Conversely, in PI-experienced individuals, atazanavir resistance was associated with the presence of at least 5 of the following 14 specific mutations: L10I/V/F, K20/R/M/I, L24I, L33I/F/V, M36I/L/V, M46I/L, G48V, I54V/L, L63P, A71V/T/I, G73C/S/T/S, V82A/F/S/T, I84V, and L90M).

Tipranavir. Cooper and colleagues described the virologic response and baseline phenotypic susceptibilities to the investigational drug tipranavir and other PIs in isolates derived from 216 multiple PI-experienced individuals

entering BI 1182.52, a tipranavir/ritonavir dose-ranging study (Abstract 596). Genotypic screening was employed as part of the study entry criteria. Isolates at entry had at least 1 of the following protease mutations: D30N, M46I/L, G48V, I50V, V82A/F/L/T, I84V, and L90M. However, isolates did not have more than 1 of V82L/T, I84V, or L90M. At baseline, 41 of 216 (19%) subjects had isolates with genotypic changes associated with resistance to all available PIs, and 22% of individuals had isolates with 3 or more of the following mutations observed in the setting of cross-resistance among PIs: L33I/V/F, V82A/F/L/T, I84V, and/or L90M. At baseline, 42%, 27.4%, and 30.6% of isolates had a fold change of less than 1.0, between 1.0 and 2.0, and greater than 2.0, respectively. Presence of 3 PI cross-resistance mutations was associated with greater than 2-fold tipranavir resistance, which was in turn associated with diminished virologic response.

GW433908. MacManus and colleagues evaluated the relative frequency of drug resistance evolution in antiretroviral-naive subjects taking the investigational drug GW433908 (a prodrug of amprenavir) with or without low-dose ritonavir or taking nelfinavir twice daily. All subjects also received abacavir/lamivudine at standard doses (Abstract 598). Patients studied were enrolled in the SOLO or NEAT trials; details of the latter are reviewed earlier in this article (Abstract 177). Genotypic data were obtained from subjects with plasma HIV-1 RNA levels greater than 1000 copies/mL at 2 consecutive visits from 12 weeks. The NEAT study compared GW433908 1400 mg twice daily with nelfinavir 1250 mg twice daily, each with twice-daily abacavir/lamivudine. The SOLO study evaluated GW433908 1400 mg once daily/ritonavir 200 mg once daily versus nelfinavir 1250 mg twice daily, each with twice-daily abacavir/lamivudine. At virologic failure in the NEAT study, comparing the GW433908 and nelfinavir arms showed no statistically significant differences in the incidence of PI mutations (8/29 vs 8/26, respectively) or lamivudine mutations (16/29 vs 20/26, respectively). Conversely, in the SOLO study at virologic failure there were no PI mutations in the GW433908/ritonavir arm (0/32) compared with 27 of 54 developing PI mutations in the nelfinavir arm ($P < .001$). In the SOLO study the incidence of M184V was also significantly lower in the GW433908/ritonavir arm than in the nelfinavir arm (4/32 vs 30/54, $P < .001$). For subjects receiving unboosted GW433908, the following mutations associated with resistance to GW433908 were observed to emerge during treatment failure: I54L/M, V32I, I47V, and M46I. These observations extend prior studies describing the absence of PI evolution on ritonavir-boosted regimens after virologic failure.

Amprenavir. In ESS400006, Schooley and colleagues evaluated baseline susceptibility to amprenavir as a predictor of 24-week virologic outcomes in subjects who had 3 or more months of prior PI failure and who were treated with amprenavir/ritonavir salvage therapy (Abstract 143). At entry, subjects had plasma HIV-1 RNA levels greater than 1000 copies/mL, CD4+ counts greater than 50 cells/μL, 5-fold or lower change in IC_{50} for abacavir resistance, and 4-fold or lower change in IC_{50} for other nRTIs. Subjects received abacavir with 1 other active nRTI. NNRTI-naive subjects (n = 38) received efavirenz, and NNRTI-experienced subjects received tenofovir (n = 76; 90% with tenofovir fold change less than 2.5). Subjects were randomized to receive amprenavir/ritonavir at 900 mg/100 mg or 600 mg/100 mg twice daily. Among those receiving efavirenz, between 85% and 95% had plasma HIV-1 RNA levels of less than 200 copies/mL at 24 weeks. Among those on tenofovir, at baseline all isolates had less than 4-fold change in amprenavir IC_{50} and 84% had at least 1 mutation associated with drug resistance. Also, among those receiving tenofovir, multivariate analyses demonstrated that a baseline amprenavir fold change in IC_{50} of less than 0.66 ($P = .015$), the absolute amprenavir fold change ($P = .018$), and the baseline plasma HIV-1 RNA level ($P = .022$) were associated with increased odds of achieving a plasma HIV-1 RNA level of less than 200 copies/mL at 24 weeks.

***Gag-Pol* Mutations.** Lastere et al retrospectively evaluated the impact of alterations in the *gag-pol* cleavage sites CA-p2, p2-NC, p7-p1 (A431V), and p1-p6 (L499 and P453) on week-12 virologic response to amprenavir among 82 amprenavir-naive subjects in the NARVAL trial (ANRS 088; Abstract 599). Subjects were highly antiretroviral-experienced with prior exposure to a median of 5 nRTIs and 3 PIs but were amprenavir-naive. No association was observed between any mutation and week-12 plasma HIV-1 RNA level. The frequency of 1 or more cleavage site mutations was CA-p2, 12 of 82 (14.6%); p2-NC, 75 of 82 (91.5%); p7-p1 (A431V), 28 of 82 (34%); and p1-p6 (L499P/F), 16 of 82 (19.5%), and P453, 19 of 82 (23%). The following significant associations were noted: A431V (34%) with changes at protease codons 10, 30, 54, and 82 ($P < .05$) and P453L with changes at codons 20, 82, and 88 ($P < .05$). A variety of polymorphisms were seen in the $p6^{gag}$ region. Thirty-seven isolates had insertions at the PTAPP motif. Fourteen of these insertions were at position P459 and were associated with mutations at protease codon 82 ($P = .02$). The mean 12-week plasma HIV-1 RNA decreases in isolates with and without P459 insertions were 0.3 and 1.0 $\log_{10}$ copies/mL, respectively ($P = .006$).

Enfuvirtide. Delfraissy and colleagues presented pooled efficacy data from the TORO I and II trials, in which enfuvirtide was added to an optimized background regimen in an open-label, randomized (2:1) fashion (Abstract 568). In the TORO I (n = 661) and II (n = 334) arms, multiple regression analyses demonstrated the following as significant predictors of change in plasma HIV-1 RNA level at 24 weeks (ITT, last observation carried forward): entry CD4+ count ($P < .0001$); use of enfuvirtide ($P < .0001$); use of lopinavir/ritonavir in the optimized background ($P = .0037$); prior lopinavir/ritonavir use ($P < .0001$); and phenotypic sensitivity score per unit ($P < .0001$). Notably, there was a significantly greater incidence of bacterial pneumonia in the enfuvirtide plus optimized background arm than in the optimized background alone arm (4.5% and 0.3%, respectively; $P = .0094$).

Whitcomb and colleagues evaluated enfuvirtide susceptibilities in 612 baseline isolates derived from the subjects in the TORO I and II trials (Abstract 557). Isolates were found to use CCR5 or CXCR4 or to be dual tropic in 62%, 4%, and 34% of cases, respectively. X4 isolates had slightly higher IC_{50} values than did R5 isolates (2.8 and 1.2, respectively). Baseline gp41 substitutions in the 36 to 45 codon region were uncommon (2%). Among R5 viruses an N42S substitution (15%) was associated with modest but significantly greater enfuvirtide susceptibility than that seen in isolates that were wild-type at this codon ($P < .001$). In addition, Heil and colleagues described 5 patient-derived isolates for which resistance to enfuvirtide and the investigational agent T-1249 appeared to localize to the HR2 domain of gp41, distinct from changes at the HR1 domain typically associated with enfuvirtide resistance (Abstract 615).

The impact of baseline and on-treatment enfuvirtide susceptibilities on 24-week virologic outcomes in TORO I and II was described by Greenberg and colleagues (Abstract 141). They evaluated 612 baseline phenotypes and results for the 205 of 218 enfuvirtide failures for which complete resistance data were available. For all isolates the mean baseline enfuvirtide EC_{50} was 0.258 µg/mL (range 0.007-7.526 µg/mL [+2 standard deviations (SD) 1.956 µg/ml; n = 16, 2.6%]). The week-24 change in plasma HIV-1 RNA level was not predicted by the following baseline characteristics: enfuvirtide susceptibility (612 isolates); enfuvirtide susceptibility of isolates at +/-1 or +/-2 SD from mean; HIV subtype; or coreceptor tropism. Among the enfuvirtide failures, the mean EC_{50} was 5.67 µg/mL (21-fold increase from baseline [range, <1- to 422-fold]). Mutations at codons 36 to 45 were seen in 185 of 187 (99%) patients with 4-fold or greater enfurvirtide resistance, including changes at codons V38 (n = 27, 42-fold change) and N43 (n = 19, 29-fold change).

Reverse Transcriptase Inhibitors. Lanier and colleagues described the median phenotypic reverse transcriptase inhibitor susceptibilities of distinct reverse transcriptase mutation clusters within a commercial database (Abstract 586). The mean fold changes for zidovudine of M184V plus M41L-L210W-T215Y/F (n = 108) and M184V plus D67N-K70R-K219Q/E/N/R (n = 130) were 15.6 and 3.7; for stavudine, 2.0 and 1.3; for abacavir, 6.5 and 4.0; for didanosine, 1.8 and 1.5; and for tenofovir, 1.4 and 1.0. This study also described the median nRTI fold changes in IC_{50} of the mutations K65R, K65R-M184V, and L74V/I-M184V as follows: zidovudine (0.5, 0.4, and 0.3), stavudine (1.4, 0.9, and 0.8), didanosine (2.1, 2.9, and 2.2), abacavir (2.7, 6.7, and 6.8), and tenofovir (1.9, 1.4, and 0.4). Therefore, zidovudine/stavudine resistance was not conferred by these non-NAM mutations.

Other Factors

Subtypes and Resistance. There were a number of presentations describing HIV infection with nonsubtype B strains (Abstracts 623, 624, 625, 628, and 629). Grossman and colleagues described differences in NNRTI genotypic resistance profiles in 279 patient-derived subtype C isolates (73 drug-naive, 224 experienced), 141 subtype B isolates (28 drug-naive, 113 experienced), and 476 subtype B isolate sequences in the Stanford database (Abstract 624). In the clinical cohort no statistically significant differences in mean nRTI and NNRTI exposure times were observed. Compared with the Stanford database, 3 mutations were significantly more frequent in subtype C than B isolates after NNRTI exposure: A98G/S postefavirenz (C = 35%, B = 8%; $P < .0001$), 98G/S postnevirapine (C = 46%, B = 13%; $P < .0001$), V106M postefavirenz (C = 19%, B = 1%; $P < .0001$), and Y188H/L postnevirapine (C = 11%, B = 2%; $P = 0.039$).

Kantor and colleagues presented preliminary comparative genotypic analyses of non-B HIV subtypes derived from numerous patients worldwide (Abstract 623). The 2267 isolates were from 836 treated and 1431 drug-naive subjects and included subtypes A, C, D, F, G, H, J, and K. Among drug-naive individuals, subtype-specific polymorphisms included, in reverse transcriptase, G190A/R in 2% of A isolates, and in protease, M46I/L in 3% of G isolates and V82I in 5% of C isolates and 85% of G isolates. Among treated individuals, L90M (33/73) was more frequent than D30N (2/73) after nelfinavir failure in subtypes A, C, or G ($P = .0001$). Protease mutation I54V was more common at first protease failure in subtypes F (11/19) and G (20/66) than in B (60/456, $P = .001$). The authors note that, in general, functionally important drug-resistant mutations were preserved across subtypes.

Colson and colleagues evaluated the protease sequences in 32 HIV-2 infected subjects from Marseilles, France (Abstract 628). Natural polymorphisms were observed at codons 14, 40, 43, 46, 65, and 70. Among PI-naive subjects, mutations L10V, V32I, M36I, M46I, I47V, A71V, and G73A were observed. Among PI-treated subjects, changes at codons K7R, V62T/A, and L99F were observed. These data highlight the importance of understanding the resistance profiles in HIV-2 and non-B subtype HIV-1 isolates.

NAMs and Replication Capacity. Miller and colleagues compared the median normalized replication capacities of selected isolates without associated PI mutations from a commercial database (Abstract 616). The mutations studied (number, percent replication capacity) were as follows: M184V (n = 57, 75%), K65R (n = 8, 56%) K65R-M184V (n = 3, 29%), Q151M-M184V (n = 2, 30%), and T69 insertion-M184V (n = 3, 29%). The replication capacity analyses for NAM-bearing isolates (number, percent replication capacity without M184V; number, percent replication capacity with M184V) are as follows: 1 or 2 NAMs (n = 60, 80%; n = 61, 66%), 3 or 4 NAMs (n = 36, 73%; n = 68, 55%), and more than 4 NAMS (n = 9, 82%; n = 21, 47%).

Long-Term Nonprogressors and Replication Capacity. Rodes and colleagues described the replication capacities and other characteristics in a cohort of 19 untreated long-term nonprogressors with a median estimated duration of infection of 14 years (Abstract 469). The median CD4+ count was 891 cells/µL. Subjects were described as slow progressors if they had net CD4+ count declines (n = 7) and nonprogressors if they had stable or increasing CD4+

counts (n = 12). Comparing slow progressors and nonprogressors, the median plasma HIV-1 RNA levels were 1118 copies/mL and 85 copies/mL, respectively ($P \leq .007$). In 10 of 12 nonprogressors the plasma HIV-1 RNA level was consistently less than 50 copies/mL. Comparing slow progressors and nonprogressors, 3 of 7 and 0 of 12, respectively, were heterozygous for the Δ32 CCR5 genotype ($P = .036$); coreceptor use was by CCR5 in 5 of 5 and 2 of 2, respectively. Replication capacity values in 6 isolates (2 nonprogressors and 4 slow progressors) were low, ranging from 3% to 45%.

Low-Level Viremia and Viral Persistence

A number of studies highlighted ongoing viral replication in the setting of HAART, the natural history of viremia at the lowest levels, and associated viral resistance. These observations will be of growing importance as plasma HIV-1 RNA levels and resistance tests with increasing sensitivity become incorporated into clinical care (Abstracts 183, 465, 466, 494, 576, and 609). Maldarelli and colleagues described a novel plasma HIV-1 RNA quantitation assay employing 7.0 mL of plasma, which has a lower limit of quantification than has previously existed—as low as 1 copy/mL (Abstract 466). The plasma HIV-1 RNA level was quantified by bDNA assay (version 3.0) in 22 subjects with on-treatment plasma HIV-1 RNA levels sustained at 75 copies/mL or lower for at least 4 months. Of these, 7 of 22 had plasma HIV-1 RNA levels of 1 copy/mL or lower, 6 of 22 had between 1 and 5 copies/mL, and 9 had consistently quantifiable plasma HIV-1 RNA below 75 copies/mL for follow-up times ranging from 7 to 12 months.

The persistence of HIV replication in lymphoid tissue of patients on antiretroviral therapy was evaluated by Alós and colleagues (Abstract 465) and van Lunzen and colleagues (Abstract 183). Alós and colleagues compared tonsillar lymphoid tissue at baseline and after 1 year on HAART in subjects with plasma HIV-1 RNA levels of less than 20 copies/mL. Tissue samples were graded by architecture, p24 antigen staining, tissue CD4+ cells/CD8+ cells/cytotoxic T lymphocytes (CTLs), and lymphoid tissue HIV-1 RNA level. At baseline, 8 of 14 samples had an absence of lymphoid follicles and 12 of 14 had extensive and intense p24 staining cells. The mean lymphoid tissue HIV-1 RNA level at baseline and at 1 year were significantly different: 5.85 and 3.15 $\log_{10}$ copies/mg tissue, respectively ($P < .001$). At 1 year, 14 of 14 samples had lymphoid follicles and 0 of 8 samples positive for p24 had extensive and intense staining. Also at 1 year, inverse relationships were noted between the mean lymphoid tissue HIV-1 RNA level and the severity of histologic grading ($P = .03$) and the mean number and mean size of follicular centers ($P = .028$ and $P = .019$, respectively). Similar correlations were noted for p24 staining. Significant reductions in lymphoid CD8+ cells and CTLs and increases in CD4+ cells were also observed compared with baseline ($P < .001$), but these were significantly lower than cell counts in HIV-seronegative samples ($P < .001$). The authors suggest that although subjects had plasma HIV-1 RNA levels sustained below 20 copies/mL, ongoing local HIV replication was present and correlated with the degree of abnormal tissue histology.

Van Lunzen and colleagues evaluated axillary lymphoid tissue samples from 32 subjects with plasma HIV-1 levels suppressed to less than 25 copies/mL for a mean of 18 months on antiretroviral therapy. Treatment regimens comprised 2 or 3 nRTIs only (n = 7), 2 nRTIs plus a PI (n = 14), and 2 nRTIs plus an NNRTI (n = 11). In the nRTI, PI, and NNRTI groups, the proportions of samples with follicular virions trapped in dendritic cells were 3 of 6, 1 of 14, and 0 of 8, respectively; with detectable plasma HIV-1 RNA at germinal centers, 5 of 6, 6 of 12, and 5 of 8; and with staining for HIV at extrafollicular tissue, 3 of 6, 10 of 11, and 8 of 9. Coculture of HIV from lymph node was positive in 4 subjects, 3 of whom were on nRTIs only; viruses from these subjects variously demonstrated the M41L, M184V, and/or T215Y reverse transcriptase mutations. Lymphoid tissue from 1 subject on abacavir/zidovudine/lamivudine with transient viremic episodes or "blips" in plasma HIV-1 RNA levels yielded virus with the M184V mutation. These data extend prior observations on the potential for ongoing lymphoid viral replication while on antiretroviral therapy, especially among those on nRTI-only regimens.

Persaud and colleagues presented data derived from 12 children with plasma HIV-1 RNA levels below the limit of detection (ie, less than 50 or less than 20 copies/mL) for 1 to 6 years on a PI-inclusive regimen (Abstract 619). Three of 21 samples were taken during blips in plasma HIV-1 RNA level to less than 200 copies/mL. A highly sensitive plasma HIV-1 RNA assay (lower limit of detection, 2.5 copies/mL) demonstrated quantifiable plasma HIV-1 RNA in 11 of 12 subjects. In only 2 subjects on nelfinavir therapy, 199 clones from 54 positive amplifications of HIV protease demonstrated major protease mutations: 1 V32I in 2 of 6 clones during a blip to 241 copies/mL and 1 N88S in 1 of 6 clones in a subject with a plasma HIV-1 RNA level below 20 copies/mL. The authors note that viral replication appears to continue on effective antiretroviral therapy but is maintained largely by archival virus rather than by virus with ongoing evolution of resistance.

Di Mascio (Abstract 521) evaluated blips in 76 subjects treated within 6 months of primary infection with PI-inclusive HAART. Subjects had overall sustained suppression of HIV-1 RNA level to less than 50 copies/mL or below over the period of observation (mean 719 days), with plasma HIV-1 RNA testing every 23 days (mean). The mean and median frequencies of viral blips were 0.07 and 0.04 per sample, respectively. Only 32 patients (45%) did not show a viral blip during the entire period of plasma HIV-1 RNA suppression. The mean and median amplitudes of blips were 176 and 119 copies/mL, respectively. Pretherapy drug-resistance genotypic testing demonstrated mutations in 7 of 76 patients (9.2%). However, in only 3 cases did mutations confer resistance to drugs in the current regimen. No association was found between blip frequency and baseline drug resistance. However, blip frequency correlated with plasma HIV-1 RNA level at pretherapy setpoint ($P = .0009$).

Compartments

Several studies evaluated the plasma HIV-1 RNA levels and resistance profiles in different body compartments or fluids, including semen and prostate (Abstracts 454 and 459), female genital secretions collected by cervico-vaginal lavage (Abstracts 620 and 621), and breast milk (Abstract 96). Taylor and colleagues evaluated blood and semen samples from 72 HIV-seropositive men with detectable plasma HIV-1 RNA levels (Abstract 454). A significant correlation was noted between HIV-1 RNA levels in blood plasma and semen plasma (Spearman R = 0.53, $P < .0001$). Thirty percent of semen plasma HIV-1 RNA levels were less than 400 copies/mL. Median blood plasma HIV-1 RNA levels were significantly higher than corresponding semen plasma values: 4.70 $\log_{10}$ copies/mL and 3.56 $\log_{10}$ copies/mL, respectively ($P < .0001$). Nine subjects were identified with plasma HIV-1 RNA levels greater in semen than in blood. Urethritis was diagnosed in 3 of these 9 subjects (33%), compared with 3 of the 63 remaining subjects (4.8%; $P = .02$). Smith and colleagues evaluated HIV-1 RNA levels in weekly semen samples from 9 subjects (Abstract 459a). Subjects underwent prostate massage at weeks 5 to 10 prior to sample submission. HIV-1 RNA levels were more frequently detectable in semen samples obtained after prostate massage than without massage ($P = .035$).

Conley and colleagues compared the HIV genotypic profiles of concurrent plasma and cervico-vaginal lavage isolates from 22 women with stable or rebounding plasma HIV-1 RNA levels after an initial response to therapy (Abstract 620). Subjects were followed up for a median of 20 months and had a median of 3.5 samples taken. Resistance was present at baseline in 4 of the 22 women and emerged later in 10 of the 18 remaining women. Of these 10, only 5 had matching samples in both plasma and cervico-vaginal lavage, and in 4 of those 5 the resistance patterns were the same. Complete data were available on 13 women in whom resistance was observed to emerge over 29 visits. Resistance evolved over 9 of the 29 (31%) visits, but the resistance profiles were different in the 2 compartments at only 1 of the 9 (11%) visits. The authors suggest that in most women the resistance profiles in plasma and vaginal secretions are closely matched.

Pharmacology

Once-Daily Dosing

Didanosine with enteric coating (EC) and tenofovir are used together in once-daily antiretroviral therapy regimens. However, didanosine levels are elevated when administered with tenofovir, which prompted consideration of reducing the didanosine EC dose to 250 mg once daily. Kearney and colleagues presented pharmacokinetic data from healthy volunteers who were first given a single dose of didanosine EC 400 mg alone as a reference treatment. Subjects then received tenofovir 300 mg and a reduced dose of didanosine EC 250 mg in 3 different manners: staggered, with didanosine EC given in a fasted state 2 hours after tenofovir; simultaneously after a light meal (373 kcal, 20% fat); or simultaneously in a fasted state (Abstract 533). The tenofovir 300 mg/didanosine EC 250 mg 24-hour area under the curve (AUC_{24}) for all 3 groups was similar to the AUC_{24} of the single dose of didanosine EC 400 mg, with the former AUC_{24} nearly identical to the latter AUC_{24} for the staggered group, 11% lower for the light-meal group, and 14% higher for the fasted group. This finding suggests that staggering the doses results in acceptable drug levels but that other options exist for the 2 drugs to be taken simultaneously in a true once-daily regimen.

Kaul and colleagues also presented data on possible interactions between tenofovir and stavudine in extended-release format (XR) (Abstract 534). There were no differences seen in the value of maximum concentration (C_{max}), AUC_{24}, or median time of maximum concentration (T_{max}) of stavudine XR when given at 100 mg alone or with tenofovir 300 mg after a light meal (373 kcal). This result provides additional pharmacokinetic support for coadministering stavudine XR and tenofovir in once-daily regimens.

Drug-Drug Interactions

Efavirenz/Nelfinavir. Smith and colleagues evaluated the effect of efavirenz on the pharmacokinetics of nelfinavir (Abstract 148). Previous studies in healthy volunteers suggested that nelfinavir levels are increased by coadministration of efavirenz. This substudy of ACTG 384, however, found a trend in HIV-seropositive patients toward lower nelfinavir levels when the drug was coadministered with efavirenz at week 32 (ΔC_{max} $P = .08$, change in value of minimim concentration [ΔC_{min}] $P = .04$, ΔAUC_{12} $P = .07$). Although the combination of efavirenz and nelfinavir is rarely used in clinical practice, this study suggests that short-term pharmacokinetic data from healthy volunteers do not necessarily generalize to HIV-infected individuals.

Tenofovir/Ritonavir/Atazanavir. Taburet and colleagues presented data on a possible interaction between tenofovir and ritonavir/atazanavir (Abstract 537). They compared several pharmacokinetic parameters of ritonavir and atazanavir before and after addition of tenofovir. Although not all changes reached statistical significance, atazanavir and ritonavir levels were both reduced when the drugs were administered with tenofovir. The investigators felt that the reduced levels of atazanavir were likely due to reduced levels of ritonavir, the mechanism of which is unknown. Similar studies of tenofovir and atazanavir given without ritonavir are highly anticipated, as these 2 drugs will be an attractive combination for once-daily dosing.

Atazanavir/Efavirenz. Tackett and colleagues presented data on the interaction of atazanavir and efavirenz (Abstract 543). The investigators tested 2 strategies to overcome the reduction of atazanavir levels when the drug is coadministered with efavirenz. They compared pharmacokinetic parameters between atazanavir 400 mg once daily without efavirenz (standard dosing) and either atazanavir 300 mg/ritonavir 100 mg or atazanavir 600 mg, both with efavirenz 600 mg once daily. They found that the atazanavir AUC was increased by 39% when giving

atazanavir 300 mg/ritonavir 100 mg/efavirenz 600 mg and decreased by 21% when giving atazanavir 600 mg/efavirenz 600 mg. Further data are needed before firm recommendations can be made regarding coadministration of atazanavir and efavirenz.

Lopinavir/Ritonavir/Indinavir. Dual- and triple-PI combination regimens are used with increased frequency when devising salvage therapy in PI-experienced individuals with virologic failure. Pharmacokinetic drug interactions, however, have been challenging to overcome with regard to potential toxicities and subtherapeutic PI drug concentrations resulting from such drug combinations. Isaac and colleagues presented the results of the Protect Study of pharmacokinetic interactions, which evaluated the feasibility of combining lopinavir/ritonavir with indinavir (Abstract 531). Plasma drug concentrations of both drugs and determinations of cerebrospinal fluid (CSF) and seminal plasma concentrations were examined when these drugs were coadministered. Ten HIV-infected male subjects taking lopinavir 400 mg/ritonavir 100 mg twice daily in combination with at least one nRTI (with 3 subjects also taking nevirapine) were enrolled. Indinavir 400 mg twice daily was added to stable background therapy, and pharmacokinetic sampling was performed prior to and 2 weeks after adding indinavir therapy.

No significant differences in lopinavir pharmacokinetic parameters were demonstrated when lopinavir/ritonavir was coadministered with indinavir 400 mg twice daily, although marked interpatient variability was noted. Median lopinavir C_{max}, C_{min}, and AUC_{12} increased by 9%, 46%, and 20%, respectively, after the addition of indinavir ($P < .30$; $P < .33$; and $P < .06$; Wilcoxon test). Lopinavir trough concentrations in seminal plasma and CSF were low and comparable with published data. All lopinavir was below detection limits in all CSF samples before the addition of indinavir; following indinavir, 2 of 4 samples were above the nonprotein-bound IC_{50} for lopinavir of 11 ng/mL. Seminal plasma concentrations were significantly lower than blood concentrations, and only 2 of 5 semen samples had lopinavir concentrations in excess of the protein-corrected minimum effective concentration (MEC) for lopinavir of 700 ng/mL. Trough blood plasma indinavir concentrations were above the protein-corrected MEC for wild-type virus of 80 to 100 ng/mL in 7 (88%) of 8 patients. Indinavir seminal concentrations were above the plasma MEC of all samples and indinavir CSF concentrations were in excess of the nonprotein-corrected IC_{95} for indinavir (21 ng/mL) in all samples.

The lopinavir/ritonavir/indinavir PI combination regimen was well-tolerated. The addition of indinavir 400 mg twice daily to the lopinavir/ritonavir regimen did not significantly alter the median lopinavir pharmacokinetic parameters. Blood lopinavir plasma concentrations were therapeutic in all patients both before and after the addition of indinavir; CSF and seminal concentrations, however, were subtherapeutic in the majority of samples tested before and after coadministration of indinavir. In contrast, the indinavir concentrations in blood plasma (C_{min}), CSF, and seminal plasma were above the target concentrations in 7 of 8 plasma samples tested and in all CSF and seminal plasma samples collected.

Food Interactions

Petersen and colleagues examined how to optimize nelfinavir pharmacokinetics with food (Abstract 544). They found a dramatic variation in the C_{max} and AUC of nelfinavir according to different meals. The AUC_{12} and C_{max} were 4.3 and 3.3 times higher, respectively, when subjects took nelfinavir with a 100 kcal/50% fat meal than when they were fasting. In addition, the AUC_{12} and C_{max} levels of nelfinavir were 1.5 and 1.4 times higher, respectively, for a 1000 kcal/50% fat meal than for a 500 kcal/20% fat meal. More data are needed to understand the relative importance of total calories and fat content on nelfinavir pharmacokinetics.

Hepatitis B and C Virus Interactions

Bossi and colleagues presented interesting data from a GENOPHAR substudy evaluating indinavir pharmacokinetics in participants with either chronic hepatitis B virus or chronic hepatitis C virus infection (Abstract 546). Five of 6 patients with chronic hepatitis B or C virus had a C_{min} of indinavir (given at 400 mg with ritonavir 100 mg twice daily) above the therapeutic range, compared with 3 of 16 patients without either of these conditions. Normal drug levels were achieved in all patients with supratherapeutic levels by reducing the dose to indinavir 200 mg/ritonavir 100 mg twice daily. Given the high prevalence of chronic hepatitis in HIV-infected individuals, further pharmacokinetic studies in coinfected patients are warranted.

Conclusions

The conference once again demonstrated that it is the premier meeting of the year during which new developments in antiretroviral therapy are presented. Covering such topics as the promise of new drugs, the reality of simplified regimens, important data from randomized trials of treatment interruptions, and the increasing complexity of drug resistance, the meeting was again notable for moving the field forward in incremental but substantial ways. The conference embodies the nexus between clinical research and clinical practice in this rapidly moving field.

Written by Drs Albrecht, Wilkin, Coakley, and Hammer in March 2003.

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Appendix. Antiretroviral Drug Resistance and Replication Capacity

Authors (Abstract), Description	Results and Comments
Greenberg et al (141) Impact of baseline enfuvirtide susceptibilities on virologic outcomes to 24 wks in TORO I and II, using 612 baseline phenotypes and results from 205/218 enfuvirtide failures with complete resistance data.	**Enfuvirtide baseline EC_{50}** • Range: 0.007-7.526 µg/mL • Mean: 0.258 µg/mL • 2 SD: 1.956 µg/mL (n=16, 2.6%) **Wk-24 change in HIV-1 RNA levels not predicted by:** • Baseline enfuvirtide susceptibility (612 isolates) • Baseline enfuvirtide susceptibility of isolates at 1 or 2 SD from mean • Clade • CCR5/CXCR5 tropism **Enfuvirtide resistance** • Mean enfuvirtide EC_{50} = 5.67 µg/mL • 21-fold increase from baseline (<1-422-fold) • 185/187 (99%) with ≥4-fold enfuvirtide resistance had mutations at gp41 codons 36-45, including V38 (n=27, mean 42-fold change) and N43 (n=19, mean 29-fold change) **Comment:** There is a broad natural range of enfuvirtide susceptibilities, which in this analysis was not predictive of virologic response. Enfuvirtide resistance is closely linked to mutations at gp41 codons 36-45.
Schooley et al (143) ESS40006 study of baseline amprenavir susceptibility as a predictor of 24-wk virologic outcome in subjects receiving salvage therapy. Subjects received abacavir + 1 other nRTI with amprenavir/ritonavir 100 mg/900 mg bid or 100 mg/600 mg bid. NNRTI-naive subjects (n=38) received efavirenz; NNRTI-experienced subjects (n=76) received tenofovir (90% <2.5-fold change to tenofovir).	**Baseline Data** • HIV-1 RNA level ≥1000 copies/mL • CD4+ count >50 cells/µL • Resistance ≤5-fold resistance to abacavir ≤4-fold resistance to other NNRTIs **Wk 24** • HIV-1 RNA levels <200 copies/mL (%) (ITT observed) On efavirenz: 27/31 (87%) On tenofovir: 38/59 (64%) • For those on tenofovir, mean prior PI experience was 3.3 years; all isolates had <4-fold change to amprenavir • In multivariate analyses, the following were associated with increased odds of an HIV-1 RNA level <200 copies/mL: Baseline amprenavir fold change <0.66 (OR, 7.24; *P*=.015) Baseline HIV-1 RNA level (OR, 0.35, *P*=.022) **Comment:** The potency of NNRTIs in salvage is highlighted. Amprenavir hypersusceptibility was predictive of outcomes on pharmacokinetically boosted amprenavir regimens.
Miller et al (616) Evaluated median normalized RCs of isolates in a commercial database with specific RT mutations and without PI resistance.	**RT mutations: RC (no. patients)** • M184V: 57% (130) • K65R: 56% (8) • K65R + M184V: 29% (3) • Q151M + 184V: 30% (2) • T69insertion + M184V: 29% (3) • 1-2 NAMS [+ M184V]: 80% (61) [66% (60)] • 3-4 NAMS [+ M184V]: 73% (36) [55% (68)] • >4 NAMS [+ M184V]: 82% (9) [47% (21)] **Comment:** K65R and K65R + M184V were associated with large reductions in RC. The mean RC of representative wild-types viruses was 94%.

Appendix. Antiretroviral Drug Resistance and Replication Capacity, Continued

Authors (Abstract), Description	Results and Comments
Little et al (152) Evaluated the relationship between set point viremia, drug susceptibility, and RC in 194 treatment-naive subjects 5-24 months after primary infection. The mean baseline HIV-1 RNA level, CD4+ count, RC, and time from infection to evaluation were 4.5 $\log_{10}$ copies/mL, 531 cells/µL, 43%, and 123 days, respectively.	**Resistance data** • Prevalence of resistance nRTI (>4-fold): 4% NNRTI (>10-fold): 7% PI (>10-fold): 4% • Mean % CD4+ for baseline isolates Drug-resistant: 34% Drug-susceptible: 28% (*P*=.05) No difference in mean HIV-1 RNA levels between resistant and susceptible baseline isolates **RC data** • No differences in baseline HIV-1 RNA levels or CD4+ counts by baseline RC • Mean RCs PI-hypersusceptible[1] isolates: 50% PI-susceptible isolates: 30% (*P* <.0001) • PI hypersusceptibility among subjects infected with drug sensitive-virus Primary infection: 33% Established infection: 18% • Viremia set point 0.6 $\log_{10}$ copies/mL higher with NNRTI resistance than without (*P* =.005); no difference noted with other drugs **Comment:** No relationship was observed between RC and HIV-1 RNA levels. The authors suggest that low-RC virus at primary infection may evolve to higher-RC virus over time.
Simon et al (504) Surveillance study of 102 newly infected individuals. Resistance and phylogenetic analyses of isolates from 1995-1998 (n=76), 1999-2000 (n=71), and 2001-2002 (n=102) were conducted.	• Resistance was observed more frequently to nRTIs and less frequently to PIs and NNRTIs over time. • Phylogenetic clustering was seen in 54/241 (21%) patients. • Transmission of drug-resistant virus was seen in 3 clades (14.6%) of all resistant isolates. **Comment:** The reduced incidence of PI and nRTI resistance is notable. The transmission of drug-resistant virus is also highlighted.
Haubrich et al (565) CCTG 578 substudy of PI-experienced patients who either switched immediately to lopinavir/ritonavir or underwent a >4-month STI prior to starting lopinavir/ritonavir.	**Immediate change group (n=16)/treatment interruption group (n=14)** • Prior use of ≥2 PIs: 25%/38% • HIV-1 RNA levels (copies/mL): 4.5 $\log_{10}$/5.2 $\log_{10}$ (*P* <.05) • CD4+ cells/µL: 190/172 • Sensitive to ≥2 drugs: 73%/100% • Lopinavir C_{12}/IC_{50}: 17/26 **Wk 6** • HIV-1 RNA levels, CD4+ counts, and changes in CD4+ count from baseline not significantly different between arms. **Comment:** Exploratory analyses did not demonstrate a definitive benefit for STI.
Lanier et al (635) Queried a commercial HIV data warehouse for changes in resistance patterns on genotypic tests for the period 1/99-7/02.	• Wild-type: 29%⇒37% • K65R: 0.64%⇒1.69%* • Y115F: 0.59%⇒1.42%* • L74V: 9.77%⇒7.85% • T215Y: 32%⇒23% • D67N/K70R/K219Q/E: 13%⇒8%* • M41L/L210W/T215Y: 17%⇒11%* • K103N: 29%⇒30% • Y181C: 19%⇒12%* **Comment:** A relative reduction in nRTI resistance was noted. **P* <.0001

Appendix. Antiretroviral Drug Resistance and Replication Capacity, Continued

Authors (Abstract), Description	Results and Comments
Delfraissy et al (568) Pooled efficacy data from TORO I and II: open-label, randomized trials of OB alone vs OB + enfuvirtide.	**Baseline values: Enfuvirtide + OB (n=661) vs OB (n=334)** • Median HIV-1 RNA (log_{10} copies/mL): 5.2/5.1 • Median CD4+ cells/μL: 88/97 • Mean genotypic susceptibility score: 1.7/1.8 • Mean phenotypic susceptibility score: 1.6/1.6 **Outcomes: Enfuvirtide + OB vs OB** • % HIV-1 RNA <50 copies/mL: 15.9/6.3 (*P* <.0001) • % HIV-1 RNA <400 copies/mL: 32.7/15.0 (*P* <.0001) • Difference in HIV-1 RNA reduction (Enfuvirtide + OB) - OB: -0.846 log_{10} copies/mL • Difference in CD4+ count increase (Enfuvirtide + OB) - OB: 36.6 cells/μL **Regression analyses for change in HIV-1 RNA levels at 24 wks** • Use of enfuvirtide: -0.89* • Lopinavir/ritonavir in OB: -0.22* • History of lopinavir/ritonavir use: +0.83* • Phenotypic susceptibility score: -0.26* **P* values: .0037-<.0001 **Comment:** Bacterial pneumonia was more frequent in the enfuvirtide + OB arm (4.5%) than in the OB-only arm (0.3%), (*P*=.0094).
Parkin et al (585) HIV phenotypic assay sensitivity and reproducibility in 2000 wild-type viruses and 10 resistant clones derived from a commercial database.	**Median IC_{50}s of wild-type viruses** • Tenofovir: 0.86 • Zidovudine: 0.89 • Abacavir: 0.90 • Stavudine: 0.95 • Didanosine: 0.95 • Lamivudine: 1.01 • Nevirapine: 0.89 • Delavirdine: 1.25 • Efavirenz: 0.86 • Lopinavir: 0.69 • Amprenavir: 0.70 • Atazanavir[2]: 0.70 • Saquinavir: 0.70 • Indinavir: 0.78 • Ritonavir: 0.82 • Nelfinavir: 1.04 **Mean coefficients of variation of IC_{50}s for resistant isolates** • 10 resistant clonal isolates were phenotyped multiple times and coefficients of variation calculated: Zidovudine: 32% Other nRTIs: 12%-18% NNRTIs: 12%-15% PIs: 14%-17% **Comment:** In wild-type viruses, nelfinavir fold change >2.0 was associated with the following mutations: L10V/I, G16A, D60E, Q61N or A71V/T (OR=2.2-4.5, P <.0001- .0054). The median susceptibility for most wild-type isolates was <1.0.
Scott el al (631) Noted changes in the prevalence of antiretroviral resistance from 1998-2000 in clinics throughout Britain. Samples were taken from 1 calendar month for each year.	• Comparing 1998 with 2000, reductions in resistance to nRTIs (OR=0.17, *P* =.001) and PIs (OR=0.23, *P* =.02) were observed • Prevalence of the K103N mutation increased (OR=3.53, *P*=.005) concurrent with widespread use of NNRTIs **Comment:** A relative reduction in nRTI resistance was noted.

Appendix. Antiretroviral Drug Resistance and Replication Capacity, Continued

Authors (Abstract), Description	Results and Comments

Lanier et al (586)

Measured median nRTI susceptibilities of specific mutation clusters in a commercial database (susceptible isolates in italics).

Mutations	Zidovudine/stavudine fold changes	Didanosine/abacavir/ tenofovir fold changes
M184V + M41L-L210W-215Y/F (n=108)	15.6 / 2.0	1.8 / 6.5 / 1.4
M184V + D67N-K70R-K219Q/E/N/R (130)	3.7 / *1.3*	*1.5* / *4.0* / *1.0*
K65R (22)	*0.5* / *1.4*	2.1 / *2.7* / 1.9
K65R-M184V (7)	*0.4* / *0.9*	2.9 / 6.7 / 1.4
L74V/I-M184V (68)	*0.3* / *0.8*	2.2 / 6.8 / *0.4*

Comment: The M184V + M41L/L210W/215Y/F cluster conferred greater cross-resistance than did other clusters. Non-NAMs did not confer zidovudine/stavudine resistance.

Leigh Brown et al (594)

Analyzed genotypic profiles associated with ritonavir hypersusceptibility in 188 antiretroviral-naive individuals.

- Combinations of changes at protease codons 10/13/37/57/62/63/73 and *gag* cleavage sites were identified that were associated with ritonavir hypersusceptibility (n=22).
- A strong association was noted between increasing ritonavir hypersusceptibility and RCs ≤10% (Pearson correlation, 0.51; $P < 10^{-10}$).

Comment: Lower RC was closely associated with PI hypersusceptibility in antiretroviral-naive subjects.

Cooper et al (596)

BI 11823.52: A double-blind, randomized study of tipranavir[2]/ritonavir in highly PI-experienced subjects at the following doses: OB + tipranavir/ritonavir 500 mg/100 mg bid, 500 mg/200 mg bid, or 750 mg/200 mg bid.

Resistance at baseline

- Genotypic screening at baseline allowed isolates with ≥1 of the following PI mutations: D30N, M46I/L, G48V, I50V, V82A/F/L/T, I84V, and L90M; however, it did not allow ≥1 of V82L/T, I84V, or L90M
- 41/216 (19%) of baseline isolates had genotypic resistance to all available PIs
- 22% had ≥3 of the following PI cross-resistance mutations: L33I/V/F, V82A/F/L/T, I84V, and/or L90M

Median IC_{50}s of baseline isolates and those with 3 PI cross-resistance mutations (measured by commercial assay)

- All isolates, isolates with 3 PI cross-resistance mutations

Tipranavir:	1.1, 2.2
Lopinavir:	76.5, 102.8
Amprenavir:	8.7, 22.1
Saquinavir:	7.0, 32.9
Indinavir:	12.2, 17.1
Nelfinavir:	36.8, 43.4
Ritonavir:	94.2, 422.0

Overall median day 14 change in HIV-1 RNA by baseline tipranavir susceptibility

- Fold change: Change in HIV-1 RNA (log_{10} copies/mL)

<1.0:	-1.23
1.0-2.0:	-1.24
2.0-4.0:	-0.20
>4.0:	-0.19
>4.0:	0.0 in tipranavir/ritonavir dose arm 500 mg/100 mg
>4.0:	-0.58 in tipranavir/ritonavir dose arm 750 mg/200 mg

Comment: Three PI cross-resistance mutations were associated with >2-fold change to tipranavir, which in turn was associated with diminished virologic response.

Appendix. Antiretroviral Drug Resistance and Replication Capacity, Continued

Authors (Abstract), Description	Results and Comments
Colonno et al (597) Measured atazanavir resistance in 3 trials of PI-naive subjects and 4 of PI-experienced subjects.	• Unique protease mutation I50L (±A71V) seen in 26 isolates (23 from PI-naive subjects) • 18/19 I50L isolates with matched phenotypic data from baseline had a ≥4-fold change in atazanavir resistance and also had hypersusceptibility (≤0.4-fold change) to at least 1 PI • In I50L recombinants, the A71V mutation increased resistance to atazanavir without apparent effect on observed hypersusceptibility conferred to other PIs, including nelfinavir and amprenavir • In PI-experienced individuals, atazanavir resistance was associated with 5/14 mutations: L10I/V/F, K20/R/M/I, L24I, L33I/F/V, M36I/L/V, M46I/L, G48V, I54V/L, L63P, A71V/T/I, G73C/S/T/S, V82A/F/S/T, I84V, and L90M **Comment:** Protease mutation I50L (±A71V) appears to confer modest atazanavir resistance while broadly enhancing susceptibilities of available PIs.
Macmanus et al (598) NEAT and SOLO studies of resistance data for GW433908[2] vs nelfinavir. Subjects had HIV-1 RNA levels >1000 copies/mL at 2 consecutive visits after study wk 12.	**Regimens** • NEAT: GW433908 1400 mg bid + abacavir/lamivudine bid vs nelfinavir 1250 mg bid + abacavir/lamivudine bid • SOLO: GW433908 1400 mg/ritonavir 200 mg qd + abacavir/lamivudine bid vs nelfinavir 1250 mg bid + abacavir/lamivudine bid **Primary or secondary PI mutations at virologic failure** • NEAT GW433908: 8/29 Nelfinavir: 8/26 (*P*=NS) • SOLO GW433908: 0/32 Nelfinavir: 27/54 (*P* <.001) **M184V mutation at virologic failure** • NEAT GW433908: 16/29 Nelfinavir: 20/26 (*P*=NS) • SOLO GW433908: 4/32 Nelfinavir: 30/54 (*P* <.001) **Comment:** The absence of PI resistance in pharmacokinetically boosted GW433908 compliments the M98-863 study findings (Abstract 600; see below). D30N or L90M emerged in 28/80 (35%) in whom nelfinavir was failing. On "unboosted" GW433908, at codons I54L/M, V32I, I47V, and M46I emerged.
Lastere et al (599) Studied the impact of *gag/pol* cleavage site changes on week 12 HIV-1 RNA levels among 82 amprenavir-naive subjects treated with amprenavir in the NARVAL trial (ANRS 088).	• Cleavage site mutation frequencies CA-p2: 12/82 (14.6%) p2-NC: 75/82 (91.5%) p7-p1 A431V: 28/82 (34%) p1-p6 L499P/F/V 16/82 (19.5%); P453L 19/82 (23%) • No association observed between any mutation and wk 12 HIV-1 RNA changes A431V associated with changes at codons 10, 30, 54, and 82 (*P* <.05) P453L associated with PI mutations at codons 20, 30, 82, and 88 (*P* <.05) • 37 isolates had cleavage site insertions at the PTAPP motif; 14/37 were at position P459 • Mean wk-12 HIV-1 RNA change With P459 insertions: -0.3 $\log_{10}$ copies/mL Without insertions: -1.0 $\log_{10}$ copies/mL (*P*=.006) **Comment:** Insertions at position P459 may negatively impact PI activity in salvage regimens.

Appendix. Antiretroviral Drug Resistance and Replication Capacity, Continued

Authors (Abstract), Description	Results and Comments
Kempf et al (600) M98-863 study: 96-wk comparison of virologic failure (>400 copies/mL HIV-1 RNA) with lopinavir/ritonavir vs nelfinavir. The proportions of patients with virologic failure (with available genotypic test results) were 51/326 (15.6%) in the lopinavir/ritonavir arm and 96/327 (29%) in the nelfinavir arm.	**PI resistance** • Lopinavir/ritonavir + stavudine/lamivudine: 0/51 (0%) • Nelfinavir + stavudine/lamivudine: 46/96 (48%) (*P* <.001) **Lamivudine resistance** • Lopinavir/ritonavir arm: 19/51 (37%) • Nelfinavir arm: 79/96 (82%) (*P* <.001) **Risk of resistance in nelfinavir arm for those with 1 yr virologic failure after initial suppression** • Lamivudine: 100% • Nelfinavir: 74% • Stavudine: 15% **Comment:** In the lopinavir/ritonavir arm, 7/51 had mutations at codons 36, 10, or 71 but without change in lopinavir susceptibility. These findings compliment SOLO study resistance data (Abstract 598; see above).
Dalmau et al (608) NEFA trial: Examined the comparative 24-mo outcomes of 3 "switch-off" strategies in 460 subjects on 1 PI/2 nRTIs with HIV-1 RNA levels <200 copies/mL for ≥6 mos.	**Baseline** • Subjects switched off PI and randomized to start efavirenz (n=156), nevirapine (155), or abacavir (149). • History of mono- or bi-nRTI use permitted • Median mos on HAART (percent with prior nRTI-only therapy) Nevirapine arm: 29 (50%) Efavirenz arm: 31 (58%) Abacavir arm: 30 (46%) **At 24 mos** • 11% had HIV-1 RNA levels >200 copies/mL • Rates of failure Nevirapine: 15/155 Efavirenz: 12/156 Abacavir: 24/149 • No differences observed in failure rates among those with no prior nRTI exposure • Genotypic NRTI resistance was more frequent in those failing in the abacavir arm than in the other 2 arms **Comment:** Greater numbers in the abacavir arm had virologic failure. These data extend prior observations on the reduced potency of nRTI-only regimens in nRTI-experienced subjects.
Deeks et al (640) 16-wk outcomes of partial treatment interruption of either PI (n=15) or nRTI (n=5) therapy and continuation of other antiretroviral drugs in a highly selected cohort of subjects with ongoing viremia on a stable HAART regimen.	**Median baseline characteristics (n=20)** • CD4+ count: 336 cells/μL; change from pretherapy baseline: +245 cells/μL • HIV-1 RNA level: 3.9 $\log_{10}$ copies/mL; change from pretherapy: -1.2 $\log_{10}$ copies/mL • Abacavir fold change: 5.2; ritonavir fold change: 31.0 **Outcomes to wk 16: Stop PI (n=15)/stop nRTI (n=5)** • Mean HIV-1 RNA change ($\log_{10}$ copies/mL): 0.005/0.03 (*P* <.001*) • Mean change in CD4+ count (cells/μL/wk): 0.0/-3.5 (*P*=.006*) • No. with sustained HIV-1 RNA increase >0.5 $\log_{10}$ copies/mL: 2 of 15/5 of 5 **P* values reflect change in outcome vs change=0 **Comment:** The stop-PI group had greater HIV-1 RNA changes at wk 2 (*P* =.001) and significant reductions in wk 4 fasting lipids. Little short-term alteration in drug susceptibilities was noted in most subjects.

Appendix. Antiretroviral Drug Resistance and Replication Capacity, Continued

Authors (Abstract), Description	Results and Comments
Barbour et al (617) Measured evolution of RC (nonnormalized) and drug susceptibilities in 22 untreated subjects with early HIV infection followed up for median of 1 yr.	**Median baseline values** • HIV-1 RNA: 3.79 $\log_{10}$ copies/mL • CD4+ count: 608 cells/μL • PI hypersusceptibility (fold change ≤0.4 to ≥1 PI): 7/21 (33%) • Resistance to ≥1 drug: 6/22 (27%) • RC, all isolates (n=22): 47% • RC, wild-type isolates (n=16): 61% • RC, drug-resistant isolates (n=6): 21% (*P* =.07 vs wild-type RC) **Comment:** Modest but significant decreases in RC of 0.54% per month (*P* =.02) were observed in follow-up.

[1]PI hypersusceptibility is a fold change ≤ 0.4 to at least 1 PI.

[2]Investigational drug; not approved by the US Food and Drug Administration.

bid indicates twice daily; C_{12}, plasma concentration at 12 hours; EC_{50}, 50% effective concentration; HAART, highly active antiretroviral therapy; IC_{50}, 50% inhibitory concentration; NAM, nRTI-associated mutation; NNRTI, nonnucleoside reverse transcriptase inhibitor; nRTI, nucleoside reverse transcriptase inhibitor; OB, optimized background; OR, odds ratio; PI, protease inhibitor; RC, replication capacity; SD, standard deviation; STI, structured treatment interruption.

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