UPDATE ON DEVELOPMENTS IN ANTIRETROVIRAL THERAPY

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Advances in antiretroviral chemotherapeutics were a dominant focus at the Conference. Within this rapidly expanding area, a number of major subtexts were highlighted at this year's meeting. These included (1) clinical trial results that described new options for initial therapy emphasizing protease inhibitor-sparing regimens; (2) new antiretroviral agents; (3) descriptions of the efficacy of a wide variety of combinations drawn from existing drug classes in antiretroviral-naive and -experienced individuals; (4) strategies of therapy including drug substitution and intensification; (5) new insights into viral resistance and its relevance for patient management; (6) drug activity in body compartments; (7) the utility of adjunctive agents such as interleukin-2 and hydroxyurea; and (8) immune reconstitution as a response to antiretroviral therapy. This review will summarize the major presentations in these areas.

OPTIONS FOR INITIAL THERAPY

Early trials of antiretroviral combination therapy confirmed the potency of triple-drug regimens consisting of a protease inhibitor with 2 nucleoside analogue reverse transcriptase inhibitors (nRTIs) and rapidly established them as reasonable options for initial therapy. However, the demonstration of extensive cross-resistance between protease inhibitors and adverse effects such as lipodystrophy has led to concerns over the use of these drugs in initial therapy and a search for alternative initial regimens. Reflective of these concerns are the studies presented at the Conference that examined the efficacy and tolerability of alternative initial regimens containing a nonnucleoside reverse transcriptase inhibitor (NNRTI) with nRTIs and triple-nRTI combinations relative to a single protease inhibitor plus 2 nRTI triple-drug regimen.

NNRTI/2 nRTI Versus Protease Inhibitor/2 nRTI Regimens

DMP 266-006 study.– The potential for an NNRTI-based initial regimen to be a viable alternative to a protease inhibitor-based regimen as initial antitretroviral therapy, even at high plasma HIV-1 RNA levels, was suggested in a late-breaker presentation of the 48-week data from the DMP 266-006 study (Table 1) **(Abstract LB-16)**. In this Phase III, multi-center, open-label trial, protease inhibitor-, NNRTI-, lamivudine naive subjects (85% antiretroviral naive) were randomized to efavirenz/zidovudine/lamivudine; indinavir/zido-vudine/lamivudine; or efavirenz/indinavir. The efavirenz/zidovudine/lamivudine group had a statistically greater number of subjects (65%) in whom plasma viral RNA levels decreased to below the level of detection (<50 copies/mL) than the other 2 groups (44% and 47%, respectively, by intent-to-treat [ITT] analysis, non-completion equals failure [NC=F]). The virologic efficacy analysis was further stratified by baseline plasma HIV-1 RNA quartiles: <50,000; 50,000-100,000; 100,000-300,000; and >300,000 copies/mL. In an ITT analysis (NC=F) of the 48-week virologic data, the efavirenz/zidovudine/lamivudine group had a statistically significant increase in the percentage of patients in the highest and lowest quartiles in achieving plasma viral reductions to <400 copies/mL versus indinavir/zidovudine/lamivudine (P=0.01 and P=0.003, respectively) and overall was better tolerated **(Abstracts 382, 383)**. Because indinavir/efavirenz were not placebo-controlled, some of the "benefit" seen with the efavirenz-containing regimen in an ITT analysis might be attributed to a higher drop-out rate of patients in the indinavir-containing arms.

The Atlantic study.– Katlama et al reported the 24-week data from the Atlantic study (Table 1), a randomized, multicenter, open-label trial comparing indinavir/stavudine/didanosine with nevirapine/stavudine/didanosine or a triple-nRTI regimen, lamivudine/stavudine/didanosine **(Abstract 18)**. Participants were antiretroviral naive and had mean baseline plasma HIV-1 RNA level and CD4+ cell count of 4.22 $\log_{10}$ and 418/μL, respectively. In an ITT analysis (the corresponding "as treated" analysis data are noted in parentheses) after 24 weeks of therapy, 78% (83%) of the subjects in the indinavir-containing arm versus 67% (85%) of the nevirapine-containing arm and 56% (64%) of the triple-nRTI group had reductions in plasma HIV-1 RNA levels below 50 copies/mL. Furthermore, no significant differences in the initial HIV-1 clearance rates and lag-time were noted among the 3 study groups **(Abstract 634)**.

Triple-nRTI Versus Protease Inhibitor/2 nRTI Regimens

Abacavir-containing regimens.– Two studies were presented at the Conference that examined the efficacy and safety of a triple nRTI regimen con-

sisting of abacavir combined with zidovudine/lamivudine: CNA 3003 and 3005 (Table 1). The 48- week results from the CNA 3003 study were reported by Fischl et al **(Abstract 19)**. The safety and efficacy of abacavir/zidovudine/lamivudine were compared with zidovudine/lamivudine in 173 antiretroviral-naive patients with baseline median plasma HIV-1 RNA levels of 4.5 $\log_{10}$ and baseline CD4+ cell counts of 427-473/μL. Subjects were allowed to change to the open-label triple-drug combination at week 16 (70% of the original zidovudine/lamivudine recipients added other drugs). Of all patients receiving abacavir/zidovudine/lamivudine, plasma HIV-1 RNA levels were below 400 copies/mL in 61% and below 50 copies/mL in 56% at study's end. No difference was noted in virologic response between those individuals who initiated therapy with abacavir and those who added it subsequently. However, there was a negative correlation between a higher baseline viral load and the ability to attain a virologic response below the level of detection at 48 weeks. Similar to prior clinical trial experience, abacavir hypersensitivity was noted in about 2% of recipients.

In the CNA 3005 study, equivalent marker responses were demonstrated with a triple-nRTI regimen consisting of abacavir/zidovudine/lamivudine compared with indinavir/zidovudine/lamivudine in 562 antiretroviral-naive patients with baseline median-plasma HIV-1 RNA levels and CD4+ cell counts of 4.88 $\log_{10}$ and 360/μL **(Abstract 20)**. At week 24, each group had an approximate 2-$\log_{10}$ reduction in HIV-1 viremia and 65% had below 400 copies/mL (ITT analysis). Similar CD4+ cell responses were also noted at this time point (103/μL and 105/μL increases, respectively). To address the question whether a protease inhibitor-based regimen might be more effective at higher baseline viral loads, the data were analyzed for variation in virologic responses based on baseline plasma HIV-1 RNA levels of 10,000 to 100,000 and above 100,000 copies/mL. No significant differences were noted between the regimens at these 2 viral load strata except for a slight trend in favor of indinavir/zidovudine/lamivudine for up to 16 weeks. Abacavir hypersensitivity was reported in 5% of recipients.

New Investigational Agents

In addition to reports of the above-mentioned new combinations of more established antiretroviral drugs, data were presented on investigational compounds that continue to progress through more advanced stages of clinical testing or that show promising preclinical antiviral and pharmacokinetic properties.

Nucleoside Analogue Reverse Transcriptase Inhibitors

FTC.– Phase I/II FTC clinical trial data were presented by Delehanty et al **(Abstract 16)**. In this preliminary study of short-term 12-day virologic activity of this drug relative to lamivudine, 81 antiretroviral-naive patients were randomly assigned to either standard lamivudine dosing or FTC at 25, 100, or 200 mg administered once daily. Relative to the lamivudine study group, the FTC 200 mg group had significantly greater plasma HIV-1 RNA reductions from baseline levels of approximately 4.5 $\log_{10}$ by 1.45 and -1.70 $\log_{10}$, respectively (P=0.047). The rate of HIV-1 RNA reduction in this group was also significantly greater.

Other nRTIs.– Preclinical data from several other promising new nRTIs were presented including L-d4N analogues **(Abstracts 593, 597)**; BCH-10652 (dOTC), a cytidine analogue approximately 10-fold more potent than lamivudine and favorable pharmacokinetics **(Abstracts 595, 596)**; and a 5' hydrogen phosphonate zidovudine prodrug.

Nonnucleoside Reverse Transcriptase Inhibitors

Preclinical data were reported on several NNRTIs including AG1549 **(Abstract 12)**, DMP 961 and DMP 963 **(Abstract 13)**, GW420867X **(Abstracts 599, 600)**, and (-)calanolide B and (+)calanolide A **(Abstracts 602, 606)**. These compounds, in general, distinguish themselves from currently available NNRTIs with higher antiretroviral potency including, in some cases, activity versus strains with K103N as the key mutation and promising pharmacokinetic properties. AG1549, for example, is an NNRTI that exhibits low levels of protein binding and potent anti-HIV-1 activity (EC_{50} = 1.1 nM and EC_{90} = 3.4 nM) without substantial EC_{50}-fold increases to HIV-1 variants containing pivotal NNRTI-resistance mutations such as K103N, V106A, Y181C, Y188C, and P236L **(Abstract 12)**. High-level resistance, however, results from the presence of clusters of resistance mutations at positions 41, 62, 75, 77, 116, 151, 184, 103, and 181 (115-fold increase) and 41, 67, 69, 210, 215, 98, 181, and 190 (950-fold increase). Serial in vitro passage selects for 2 predominant genotypes: K103T/V106A/L234I and V106A/F227L.

Protease Inhibitors

ABT-378.– Marker efficacy data for the protease inhibitor ABT-378 pharmacokinetically enhanced by ritonavir (a potent inhibitor of ABT-378 metabolism) was presented by Murphy et al for the M97-720 Study Group (Table 1) **(Abstract 15)**. In this

Table 1. Trials in Antiretroviral-Naive Patients

Study Name (abstract number)	Regimen/Study Arm	Number of Patients	Duration of Therapy (weeks)	Baseline Plasma HIV-1 RNA (log_{10})	Baseline CD4+ (cells/μL)	Plasma HIV-1 RNA Change (log_{10}) or number (copies/mL)	CD4+ Change (cells/μL)	Comments
M97-720 **(15)**	ABT-378/ritonavir	101	24	4.8	399	93% and 95% of Group 1 and 2 with < 400copies/mL, respectively (observed)		ABT-378 administered at 200/100 mg or 400/100 mg bid (Group 1) or 400/100 mg or 400/200 mg bid (Group 2) Most common adverse effects: diarrhea, nausea; increased cholesterol in approximately 10%
CNA 3003 **(19)**	abacavir/zidovudine/ lamivudine	164	48	4.5	450	61% < 400 copies/mL 56% < 50 copies/mL	158	Baseline plasma HIV-1 RNA predicted 48 week virologic response
CNA 3005 **(20)**	abacavir/zidovudine/ lamivudine indinavir/zidovudine/ lamivudine	562	24	4.88	360	-2 -2		No difference in response between the abacavir- and indinavir-containing arms when baseline plasma HIV-1 RNA stratified to 10,000-100,000 and >100,000 copies/mL
HIV NAT 003 **(623)**	zidovudine/lamivudine/ didanosine zidovudine/lamivudine	106	48	3.83	340 (mean)	-1.23 -0.87	118 73	Significant difference between CD4+ cell changes (P<0.05)
Virgo I **(632)**	nevirapine (bid)/stavudine/ didanosine	60	52	4.51	415	-2.16	209 (+121 naive T-cells)	At 36 weeks, 76% <50 copies/mL; 5/6 patients with baseline plasma HIV-1 RNA >100,000 copies/mL with <50 copies/mL virologic response.
Virgo II **(632)**	nevirapine (qd)/stavudine/ didanosine	30	24	4.53	412	-2.53	140	At 24 weeks, 83% <50 copies/mL
M/3331/ 0013C **(624)**	delavirdine/zidovudine/ lamivudine zidovudine/lamivudine	152	54	5.33 5.27 (mean)	185 209	-1.9 -1.3	120 60	Rash seen in 36% of patients in the delavirdine arm
Ozcombo I **(633)**	indinavir/zidovudine/lamivudine indinavir/stavudine/lamivudine indinavir/stavudine/didanosine	109	52	5.08 (mean)	289 (mean)	-2.14 -2.59 -2.16	122 141 116	No difference between the virologic and immunologic responses of the 3 groups (P=0.11 and P=0.35, respectively)
DMP 266-003 **(383)**	efavirenz/indinavir	59	60	5.11 (mean)	282 (mean)	70% <50 copies/mL		Approximately 70% of patients decreased plasma HIV-1 RNA levels to <50 copies/mL from baseline plasma RNAs < and >100,000 copies/mL
DMP 266-020 **(383)**	efavirenz/2 nRTIs	92	48	4.32 (mean)	320 (mean)	36% <50 copies/mL		Approximately 36% of patients decreased plasma HIV-1 RNA levels to <50 copies/mL from baseline plasma RNAs <and> 100,000 copies/mL
DMP 266-006 **(LB-16)**	efavirenz/zidovudine/lamivudine indinavir/zidovudine/lamivudine efavirenz/indinavir	154* 148* 148*	48	4.77	348	65% <50 copies/mL 44% <50 copies/mL 47% <50 copies/mL		*Patients were protease inhibitor, NNRTI, lamivudine naive (85% were anti-retroviral naive). Intent-to-treat analysis (NC=F).CNS adverse effects observed in approximately 50% of efavirenz recipients. Efavirenz/zidovudine/lamivudine with significantly higher numbers of patients with week 48 HIV1RNA levels <400 copies/mL versus indinavir/zidovudine/lamivudine stratified by baseline viremia (<50,000 and >300,000 copies/mL) (P=0.01 and P=0.03, respectively).
Atlantic **(18)**	indinavir/stavudine/didanosine nevirapine/stavudine/didanosine lamivudine/stavudine/didanosine	300	24	4.22 (mean)	418 (mean)	71% <50 copies/mL 67% <50 copies/mL 56% <50 copies/mL		Intent-to-treat analysis
Atlantic **(631)**	ritonavir/indinavir/2nRTIs	67	24	5.32	227	67% <80 copies/mL		Adverse effects: mild diarrhea, nausea, and elevated triglycerides
IRIS **(630)**	ritonavir/saquinavir/ 1 nRTI indinavir/2 nRTIs	80 77	52	5 5.2 (mean)	213 243 (mean)	-2.4 -2.4	123 178	No significant differences in virologic or immunologic responses. Intent to-treat analysis
IRIS **(393)**	ritonavir/nelfinavir	20*	48	4.5	323	4/12 patients <20 copies/mL		*Half of patients nRTI protease inhibitor naive. Adverse effect: diarrhea. No consistent resistance genotype selected by ritonavir/nelfinavir.
SCAN **(628)**	nevirapine(qd)/stavudine/ didanosine nevirapine(bid)/stavudine/ didanosine	33 34	24	>5000	>500	-1.6 -1.7	148 102	No significant differences in virologic or immunologic responses (P=0.53 and P=0.60,respectively).
SCAN **(626)**	abacavir/amprenavir	11	72	4.42	756	72% <50 copies/mL 54% <5 copies/mL	175 naive T-cells	Most common adverse effect: nausea.
CNA 2004 **(625)**	abacavir/protease inhibitor (amprenavir, indinavir, nelfi-navir, ritonavir, or saquinavir)	82	48	4.78	349	44-60% <50 copies/mL		3% of patients with abacavir hypersensitivity. Of subjects with plasma HIV-1 RNA levels >400 copies/mL at week 16, 7 of 15 had protease mutations and 3 of 15 had an M184V abacavir mutation **(Abstract 115).**
Merck 035 **(388)**	indinavir/zidovudine/ lamivudine	33*	148	4.62	133	65% <50 copies/mL	>200	Intent-to-treat analysis. Adverse effects: nephrolithiasis and lipodystrophy in 38% and 19%, respectively.* Patients were zidovudine-experienced.
TRI-003 **(LB13)**	T-20 with a stable antiretroviral background	78	4	5.02	96			*Transient -1.5 log_{10} decrease in plasma HIV-1 RNA

clinical trial, approximately 100 antiretroviral-naive subjects were randomly assigned to 1 of 2 comparative dosing groups of: 200/100 mg bid or 400/100 mg bid combination of ABT-378/ritonavir (group 1) or a 400/100 versus 400/200 mg combination (group 2), respectively, in combination with stavudine/lamivudine in group 2. At baseline, participants had median plasma HIV-1 RNA levels of 4.8 $\log_{10}$ and CD4+ cell counts of 400/μL. By week 24, more than 90% of patients had plasma viral levels below 400 copies/mL in both treatment groups, and 89% of group 2 had reductions to below 50 copies/mL.

Data on other promising protease inhibitors in development were also presented including AG1776 **(Abstract 11)** and BMS-232632 **(Abstracts 603, 604)**.

Novel Agents

Fusion and cell entry inhibitors. In addition to advances in more established antiretroviral therapy that target the HIV-1 reverse transcriptase and protease, several groups at the Conference reported preclinical and clinical data characterizing the antiviral activity of compounds designed to disrupt other HIV-1 replicative functions, most prominently, HIV-1 cell fusion and entry **(Abstracts 608-618, LB13)**. In the late-breaker session, for example, Eron presented results from TRI-003, a multicenter, open-label Phase II clinical trial of T-20, a 36-amino-acid-peptide HIV gp-41-mediated fusion inhibitor (Table 1) **(Abstract LB13)**. Seventy-eight patients with either stable or no antiretroviral therapy (99% were antiretroviral experienced) and baseline plasma HIV-1 RNA levels and CD4+ cell counts of 5.02 $\log_{10}$ and 96/μL, respectively, were randomized to T-20 administered either by continuous or twice-daily subcutaneous injections. Over the 28-day study period, adequate trough levels were maintained with the twice-daily dosing schedule. Although viral rebound toward baseline was noted, within the first months of therapy, a transient 1.5-$\log_{10}$ reduction in viremia was observed. Genotypic analysis of these viral isolates showed mutations in the gp41 target site of T-20 at amino acid residues 36, 32, 38, and 39 **(Abstract 611)**. In general, the regimen was well tolerated.

Combination Regimens

Numerous clinical trials were reported that studied the virologic and immunologic profiles of rapidly increasing permutations of potent antiretroviral combinations, compared streamlined dosing schedules to standard regimens, and examined marker efficacy of combination regimens in specific clinical scenarios (Table 1).

Primary HIV-1 Infection

Prompted by recent immunologic studies that suggest that without antiretroviral therapy initiation early in HIV-1 infection there may be a loss of HIV-1 specific immune response, studies were presented that examined the efficacy of potent combination therapy started during primary HIV-1 infection.

One such study was reported by Markowitz et al **(Abstract 636)**. This was a 3-year follow-up of 38 newly infected patients who took protease inhibitor-containing combination therapy (ritonavir, indinavir, or ritonavir/saquinavir with 2 nRTIs) **(Abstract 636)**. All of these subjects had HIV-1 viremia reduced to below 500 copies/mL by 4.5 weeks and to below 400 copies/mL by 7.1 weeks. Of the 27 subjects remaining on study, 20 continued to have plasma HIV-1 RNA levels below 50 copies/mL and 7 had intermittently detectable viremia from a baseline mean of 309,832 copies/mL. Of 9 individuals with maximally suppressed HIV RNA, 7 had no detectable follicular dendritic cell-associated virus.

Soravia-Dunand et al also reported a primary HIV-1 infection therapeutic trial, in which indinavir/zidovudine/lamivudine was used in a multicenter, open-label observational fashion in patients presenting with acute HIV-1 infection (mean time from onset of symptoms to treatment was 29 days) **(Abstract 637)**. Subjects had a baseline mean plasma HIV-1 RNA level of 5.2 $\log_{10}$ and CD4+ cell count of 565/μL. At 24 months, the mean reduction in plasma viral levels was 2.1 $\log_{10}$ and mean CD4+ cell count was approximately 750/μL.

A third trial described by Kost et al employed a combination regimen of amprenavir/abacavir/zidovudine/lamivudine in recently (<90 days) infected HIV-1 patients **(Abstract 639)**. At 1 year, 7 of 9 patients had sustained plasma HIV-1 RNA levels below 50 copies/mL from a baseline mean of 156,725 copies/mL. Coincident mean CD4+ cell increases were 197/μL from a baseline of 610/μL. At week 26, naive CD4+ cells increased by a mean of 81/μL.

Therapy in Antiretroviral-Naive Patients: Protease Inhibitor-Containing Regimens

Indinavir/2 nRTI regimens.– The purpose of the Ozcombo I Study, reported by Carr et al, was to assess potential differences in marker efficacy between regimens containing indinavir paired with 3 different dual nRTI combinations including zidovudine/lamivudine, stavudine/lamivudine, and stavudine/didanosine **(Abstract 633)**. In this clinical trial, 109 antiretroviral-naive subjects with

mean baseline CD4+ and plasma HIV-1 RNA levels of 289/μL and 5.08 $\log_{10}$, respectively, were randomized to 1 of the 3 treatment groups. After 52 weeks of therapy, there were no statistically significant differences in virologic or immunologic response or in serious adverse effects among the study arms (Table 1).

Ritonavir/nelfinavir.– Gallant et al presented a 20-patient Phase II study evaluation of the marker efficacy and safety of a dual protease inhibitor (ritonavir/nelfinavir) (Table 1) **(Abstract 393)**. This open-label, multiple-dose trial enrolled protease inhibitor-naive patients (with a median baseline plasma HIV-1 RNA and CD4+ cell count of 4.5 $\log_{10}$ copies/mL and 323/μL, respectively. Ritonavir, 400 mg every 12 hours, was combined with either nelfinavir 500 mg (cohort I) or 750 mg (cohort II) every 12 hours, utilizing ritonavir's ability to enhance the pharmacokinetics of both nelfinavir and its metabolite, M8. After 48 weeks of therapy, the respective mean plasma HIV-1 RNA reductions and CD4+ cell increases in cohorts I and II were 2.82 and 2.21 $\log_{10}$ and 236 and 120/μL, respectively. Of the 12 patients completing this treatment duration, 4 had viral load levels below 20 copies/mL. Diarrhea was the most common adverse effect.

Ritonavir/indinavir.– In a study presented by Rockstroh on behalf of the German Ritonavir/Indinavir Study Group, 67 antiretroviral-naive recipients of these protease inhibitors combined with 2 nRTIs (predominantly zidovudine/lamivudine)resulted in the diminution of median baseline HIV-1 RNA levels from 5.32 to 1.90 $\log_{10}$ by week 24 (Table 1) **(Abstract 631)**. Of the patients analyzed at that time, 67% decreased plasma viral levels to below 80 copies/mL. In the same period, CD4+ cell counts increased from a baseline median of 227 to 424/μL. Ritonavir combined with indinavir, akin to ritonavir administered with nelfinavir, results in favorable pharmacokinetic interactions and allows for a twice-a-day dosing schedule and administration with food **(Abstracts 362, 363)**.

Protease Inhibitor/ Abacavir Combinations

Amprenavir/abacavir.– The recently approved 2' deoxyguanosine analogue reverse transcriptase inhibitor, abacavir, has been studied in combination that several protease inhibitors. Mellors et al presented updated data from the CNA 2004 study that examined the activity of abacavir administered with the 4 approved protease inhibitors as well as amprenavir in 82 antiretroviral-naive subjects with a baseline plasma HIV-1 RNA level of 4.78 $\log_{10}$ and CD4+ cell count of 349/μL **(Abstract 625)** (Table 1). At 48 weeks, between 44% and 60% of subjects (ITT analysis) had plasma HIV-1 levels below 50 copies/mL. As with previously reported results from this study, there were no statistically significant differences in marker efficacy between the abacavir/protease inhibitor dual regimens.

Updated data on the efficacy of amprenavir/abacavir were reported by Bart et al **(Abstract 626)** (Table 1). Of the 11 patients followed up for 72 weeks, 77% and 54% (ITT analysis) had plasma HIV-1 RNA levels reduced to below 50 and 5 copies/mL, respectively, from a baseline mean value of 4.42 $\log_{10}$. CD4+ cell counts increased to a mean of 974/μL from a baseline of 756/μL. A more detailed immunologic week-72 examination revealed an average increase of naive memory cells of greater than 150/μL and a statistically insignificant difference in CD4+:CD8+ lymphocyte ratios in lymph nodes between week 72-treated patients and HIV-1 seronegative controls.

NNRTI-Containing Regimens

Efavirenz-containing regimens.– In addition to the DMP 266-006 study discussed above, other studies were presented that examined the efficacy of efavirenz-containing combinations as initial antiretroviral therapy. Manion et al reported the results of post-hoc subgroup analyses on data from the DMP 266-003, -006, and -020 trials in order to determine the efficacy of these regimens in HIV-infected individuals with high baseline viral loads (ie, >5 $\log_{10}$ copies/mL) **(Abstract 383)** (Table 1). In the week 60 evaluation of the DMP 266-003 study, antiretroviral-naive recipients of efavirenz/indinavir with baseline plasma HIV-1 RNA levels above and below 5 $\log_{10}$ had comparable (approximately 70%) percentages of subjects in whom their viral loads were decreased to below 50 copies/mL (ITT, analysis NC=F). Similarly, in DMP 266-020, at week 48, approximately 36% of subjects from both baseline viral load strata had below <50 copies HIV RNA/mL plasma of detection on efavirenz/indinavir/nRTI (ITT, analysis NC=F).

Nevirapine/2 nRTI regimens.– Among the several clinical trials presented at the Conference that employed nevirapine plus 2 nRTIs as initial antiretroviral therapy was the Virgo Trial, which examined stavudine/didanosine once daily/nevirapine once or twice daily in 60 antiretroviral-naive subjects with median plasma HIV-1 RNA levels of 4.51 $\log_{10}$ and CD4+ cell count of 415/μL (Table 1) **(Abstract 632)**. In an ITT analysis at week 52 of stavudine/didanosine/nevirapine twice-daily therapy (Virgo I), 79% had plasma viral levels reduced to

Table 2. Trials in Antiretroviral-Experienced Patients

Study	Abstract Number	Prior Experience	Regimen/Study Arm	Number of Patients	Baseline HIV-1 RNA (median $\log_{10}$ copies/mL)	$CD4_+$ Count (cells/μL)
ACTG 370	488	(stavudine or didanosine)/ lamivudine	zidovudine/lamivudine/indinavir zidovudine/delavirdine/indinavir	33 30	3.6 3.5	90 80
Merck 035	388	zidovudine	indinavir/zidovudine/lamivudine	30	4.6	133
TIDBID	390	nRTIs	saquinavir (tid)/2nRTIs saquinavir (bid)/2nRTIs saquinavir(bid)/nelfinavir(bid)/ 1nRTI	47 39 47	*4.7 *4.7 *4.7	*312 *359 *334
SPICE	389	nRTIs	saquinavir (tid)/2 nRTIs nelfinavir (tid)/2 nRTIs saquinavir (tid)/nelfinavir (tid)/ 2 nRTIs saquinavir (tid)/nelfinavir (tid)	12 12 24 24	4.7 – 7.8	300 – 334
ACTG 364	489	nRTIs	nelfinavir/nRTIs efavirenz/nRTIs nelfinavir/efavirenz/nRTIs	66 65 64	3.9 3.9 3.8	384 385 397
ACTG 372B	490	nRTI/indinavir Salvage	adefovir/efavirenz/abacavir/nelfinavir adefovir/efavirenz/abacavir/nelfinavir placebo adefovir/efavirenz/nRTIs/nelfinavir adefovir/efavirenz/nRTIs/nelfinavir plc.	24 26 21 23	4.2 4.6 4.7 4.5	182 194 164 233
AG 1343-511/506	392	nRTI/nelfinavir Salvage	stavudine/lamivudine/ritonavir/ saquinavir	26	4.7	222
CNA 2007	133	nRTI/NNRTI/ protease inhibitor Salvage	abacavir/efavirenz/amprenavir	101		
Salvage	140	nRTI/protease inhibitor (minimal NNRTI) Salvage	nelfinavir/saquinavir/nRTIs nelfinavir/nRTIs nelfinavir/nRTIs/NNRTI	62	5.16	133

* Median CD4 and $\log_{10}$ HIV RNA values represent those for the study as a whole

Follow Up (weeks)	Plasma HIV-1 Change of % of Patients below Detection	CD4+ Change (median cells/μL)	Comments
20 – 24	42% <50 copies/mL 67% <50 copies/mL	80 – 100 80 – 100	Differences in outcomes did not reach statistical significance. Statistically significant incidence of hyperbilirubunemia in indinavir/delaviridine arms. Indinavir dosed at 600 mg q8h in indinavir/delaviridine-containing arms
148	66% <50 copies/mL	198	8/9 virologic failures had multiple RT + protease mutations 1/9 failed at 16 weeks with only M184V (RT) and L63P (protease) 13 (39%) subjects had 1 or more episodes of nephrolithiasis 4/21 met the clinical definition of lipodystrophy
32	32% ITT, (60%, OT) <50 copies/mL 20% ITT, (35%, OT) <50 copies/mL 35% ITT, (65%, OT) <50 copies/mL	175 150 160	For the study as a whole diarrhea was more frequent in the 2 protease inhibitor-containing arms (14% vs 8-9%)
72	33% <50 copies/mL (ITT, M=F) 25% <50 copies/mL 46% <50 copies/mL 21% <50 copies/mL	*200 – 300	The incidence of diarrhea was greatest in the 2 protease inhibitor arms
40 – 48	35% <500 copies/mL 60% <500 copies/mL 74% <500 copies/mL	94 94 94	3-way *P* value=0.001 for virologic outcome RT genotyping (n=146) revealed a median of 3 mutations/isolate. Virologic failure was significantly associated with prior lamivudine experience (OR, 5.2), baseline HIV-1 RNA level (OR, 2.4/log) and the number of RT mutations (OR, 1.3/mutation)
16	45% and 24% <500 copies/mL for NLV versus nelfinavir placebo, respectively (*P*=0.046) 37% and 32%,<500 copies/mL for abacavir versus nRTIs, respectively, (*P*=0.62)	60 14 36 36	CNS symptoms, rash and grade 2+ proteinuria were observed in 18%, 6%, and 17% of all subjects, respectively.
60	58% (LOCF)	120 (48 weeks)	21/26 subjects were multiply nucleoside experienced. Baseline viral load >30,000 copies/mL associated with virologic failure (*P*=0.03). Mutations at protease codons 48, 54, 82 and 84 not present at baseline. At baseline the presence of mutations D30N, L90M, M36I, or N88D was not correlated with virologic outcome at 48 weeks.
16	Of the 1st 65 subjects to reach 16 weeks, 34% had 1 $\log_{10}$ or greater decline in plasma RNA or <400 copies/mL RNA in plasma		Baseline factors associated with virologic failure included higher baseline viral loads, (*P*=0.0005), phenotypic resistance to efavirenz (*P*=0.006) or to abacavir (*P*=0.006), and the following RT mutations >2 zidovudine-associated mutations, T69D, Q151M complex, 68-69 insertion variants and NNRTI mutations Protease genotype at baseline was not predictive of virologic outcome
12	3% <400 copies/mL		At baseline the total number of protease inhibitor + RT mutations was the only factor significantly predictive of failure

below 500 copies/mL and CD4+ cell counts increased by 209/μL. Using the same regimen except with nevirapine dosed once a day (Virgo II), plasma HIV-1 RNA levels were reduced to below 500 copies/mL in 79% of cases by week 24. Coincident total CD4+ cell count increases were approximately 140/μL. Similarly, the Spanish Scan study, reported by Garcia et al, examined the virologic utility of stavudine/didanosine combined with either nevirapine dosed twice daily or once daily in antiretroviral-naive patients and found no statistically significant differences among the plasma HIV-1 RNA, CD4+ cell count, or tolerability between the 2 nevirapine dosing study groups (Table 1) **(Abstract 628)**.

Delavirdine/2 nRTI regimens.– Wood et al reported the results of M/3331/0013C, a placebo-controlled clinical trial comparing delavirdine/zidovudine/lamivudine and zidovudine/lamivudine in antiretroviral-naive subjects with mean baseline marker levels depicted in Table 1 **(Abstract 624)**. In on-treatment analyses, both virologic and immunologic responses at week 54 in the delavirdine/zidovudine/lamivudine group were significantly improved over the dual nRTI arm with mean CD4+ cell counts increasing by 120/μL (versus 60/μL) and plasma HIV-1 RNA levels reduced by 1.9 $\log_{10}$ (versus 1.3 $\log_{10}$). In a 24-week ITT analysis of virologic response according to baseline plasma HIV-1 RNA levels (<100,000 or >100,000 copies/mL), 68% of delavirdine/zidovudine/lamivudine recipients had <400 copies HIV RNA/mL plasma in the former group and 52% in the latter higher viral load group.

Clinical Trials in Antiretroviral-Experienced Patients

nRTI-Experienced subjects

Indinavir/2 nRTIs.– The 148-week follow-up of the Merck 035 study was presented in which 33 highly zidovudine-experienced subjects were treated with standard doses of indinavir, lamivudine, and zidovudine (Table 2) **(Abstract 388)**. The median baseline HIV-1 RNA level and CD4+ cell count were 4.6 log10 copies/mL and 133/μL, respectively. Prior to week 148, 11 subjects withdrew from the study; 7 because of viral rebound and 3 because of nephrolithiasis. At week 148, by ITT analysis with last observations carried forward (LOCF), 20 of 30 (66%) evaluable subjects had plasma HIV-1 RNA values <50 copies/mL with a median increase in CD4+ cells of 198/μL from baseline in these 30 subjects.

Saquinavir/nRTIs (+/-nelfinavir).– In this multicenter, randomized, open-label trial, saquinavir soft gelatin capsule (saquinavir-SGC) was administered at 1200 mg tid with 2 nRTIs (arm I); at 1600 mg bid with 2 nRTIs (arm II); or at 1200 mg bid with nelfinavir 1250 mg bid and 1 nRTI (arm III) (Table 2) **(Abstract 390)**. At baseline, the mean plasma HIV-1 RNA level was 4.7 $\log_{10}$ copies/mL and the mean CD4+ cell counts ranged from 312-359/μL in the 3 arms. This study included 47, 39, and 47 nRTI-experienced subjects in arms I, II, and III, respectively. At 32 weeks' follow-up, there were 32%, 20%, and 35% (ITT) and 60%, 35%, and 65% (OT) of experienced subjects with <50 copies HIV-1 RNA/mL of plasma.

Saquinavir-SGC and/or nelfinavir and/or nRTIs.– The 72-week follow-up data of the SPICE study were presented (Table 2) **(Abstract 389)**. In this trial 157 subjects (approximately 50% being nRTI experienced) were randomized to 1 of 4 arms: saquinavir-SGC 1200 mg tid/2 nRTIs (arm A); nelfinavir 750 mg tid/2 nRTIs (arm B); saquinavir-SGC 800 mg tid/nelfinavir 750 mg tid/2 nRTIs (arm C); saquinavir-SGC 800 mg tid/nelfinavir 750 mg tid (arm D). The mean baseline plasma HIV-1 RNA values and CD4+ cell counts ranged from 4.7-4.8 $\log_{10}$ copies/mL and 300-334/μL. The numbers of experienced subjects in arms A through D were 12, 12, 24, and 24, respectively. At 72 weeks, by ITT analysis and defining missing data equal to failure, the percentages of nRTI-experienced subjects with below 50 copies HIV-1 RNA/mL were 33%, 25%, 46%, and 21% in arms A, B, C, and D, respectively. Overall, the 4-drug regimen appeared to be superior to the other 3 arms in terms of suppression of plasma HIV-1 RNA levels and time to virologic failure.

nRTIs in combination with nelfinavir and/or efavirenz.– Albrecht et al presented updated 16-week data from ACTG 364, which was a randomized Phase II, roll-over trial (from ACTG 175, 302, and 303) of 195 highly nRTI-experienced subjects on stable nRTI therapy but who were protease inhibitor and NNRTI naive (Table 2) **(Abstracts 489, 138)**. The median baseline plasma HIV-1 RNA level and CD4+ cell count were 3.9 $\log_{10}$ copies/mL and 389/μL, respectively. Subjects were randomized to 1 of 3 arms containing 1 or 2 new nRTIs with either nelfinavir (arm I); or efavirenz (arm II); or nelfinavir/efavirenz (arm III). At 48 weeks of follow-up in arms I, II, and III, the proportion of subjects with <500 copies/mL HIV-1 RNA in plasma were 35%, 60%, and 74%, respectively (3-way P=0.001). Across the 3 arms the median increase in CD4+ cell counts was 94/μL at 40 to 48

weeks. Virologic failure was significantly associated with prior lamivudine experience (odds ratio [OR], 5.2), baseline HIV-1 RNA level (OR, 2.4 per log increase), and the number of reverse transcriptase mutations (OR, 1.3 per mutation). Overall, in this study a highly significant difference in virologic suppression was noted among the 3 treatment arms favoring the efavirenz/nRTI and efavirenz/nelfinavir/nRTI arms over the nelfinavir/nRTI arm.

Salvage Therapies for nRTI- and Protease Inhibitor-Experienced Subjects:

Adefovir/efavirenz/abacavir/nelfinavir in nRTI/indinavir failure. – Hammer et al (ACTG 372B) investigated a variety of salvage regimens in 94 NNRTI naive, highly nRTI-experienced subjects in whom a stable regimen of zidovudine (or stavudine)/lamivudine/indinavir failed (Table 2) **(Abstract 490)**. Median baseline HIV-1 RNA levels and CD4+ cell counts were 4.59 $\log_{10}$ copies/mL and 196/μL. Subjects were randomized to 1 of 4 arms, comprising an adefovir/efavirenz backbone in combination with (abacavir or 1 or 2 nRTIs) plus (nelfinavir or nelfinavir-placebo), see Table 2. The percentages of subjects at 16 weeks with plasma viral RNA levels <500 copies/mL in the nelfinavir versus placebo-nelfinavir arms were 45% versus 24%, respectively (P=0.046). The mean increases in CD4+ cells from baseline in the nelfinavir and nelfinavir-placebo arms were 60/μL and 14/μL. At week 16, the percentages of subjects with plasma HIV-1 viral loads <500 copies/mL in the abacavir and nRTI-containing arms were 37% and 32%, respectively (P= 0.623), and the mean increases in CD4+ cells from baseline were similar in each arm, approximately 36/μL. Although there was under accrual within this study, in this indinavir-failure population, efavirenz in combination with adefovir, nelfinavir, and nRTI therapy provided superior suppression of plasma HIV-1 RNA at 16 weeks of follow-up compared with regimens without nelfinavir.

Ritonavir/saquinavir/nRTIs in nelfinavir/nRTI failure.– Tebas et al presented the 60-week follow-up of 26 subjects in whom a nelfinavir/nRTI-based regimen failed **(Abstract 392)**. At entry subjects had a median viral load of 4.7 $\log_{10}$ copies/mL, a median CD4+ cell count of 222/μL, and a median of 55 weeks of nelfinavir experience. Subjects received stavudine/lamivudine/ritonavir/saquinavir-SGC. At week 60, 24 of 26 remained in the study, 58% (LOCF analysis) having plasma HIV RNA <500 copies/mL. Mean gains in CD4+ counts of 120/μL were maintained at 48 weeks. Baseline protease genotype was not predictive of virologic outcome at 48 weeks. However, a baseline viral load of >30,000 copies/mL was associated with a greater risk of virologic failure at the same time point (P=0.03; relative risk [RR], 2.5).

NRTI-, NNRTI-, and Protease Inhibitor-Experienced Subjects

Data were presented from CNA 2007, an ongoing open-label study evaluating salvage therapy with abacavir/efavirenz/amprenavir in 101 subjects in whom a stable protease inhibitor-based regimen failed. Prior nRTI (with the exception of abacavir), NNRTI, and protease inhibitor exposure was allowed.

Baseline genotypic analysis revealed that 71% of isolates had 5 or more reverse transcriptase-associated mutations (nRTI + NNRTI). NNRTI-associated mutations were observed in 38% of isolates and a majority of isolates had 5 or more protease-associated mutations (83% of the 65 virology substudy subjects). Baseline phenotypic analysis demonstrated that 57%, 25%, and 45% of baseline isolates were phenotypically resistant to abacavir, efavirenz, and amprenavir, respectively. The levels of phenotypic cross-resistance within the nRTI, NNRTI, and the protease inhibitor classes were also high, 19% to 90%, 25% to 40%, and 45% to 84%, respectively.

Of the first 65 subjects reaching 16 weeks, only 34% had viral load reduced to below 400 copies/mL or a (1 $\log_{10}$ decline in plasma RNA level. At 16 weeks the highest proportion of subjects with HIV-1 RNA values <400 copies/mL (53%) was observed in NNRTI-naive subjects with baseline plasma HIV-1 RNA values <4.6 $\log_{10}$ copies/mL. The presence of several specific mutations or groups of mutations was associated with a poorer virologic outcome (Table 2).

Significant predictors of failure of suppression of plasma viral load (1 $\log_{10}$ or to <400 copies/mL were: (1) higher baseline viral loads (P=0.0005) and (2) phenotypic resistance to efavirenz (P=0.006) or to abacavir (P=0.006). Suppression of viral load to <400 copies/mL was observed in 5 of 9 (56%) subjects with baseline isolates susceptible to all 3 drugs and only 4 of 21 (19%) of subjects with baseline isolates susceptible to 1 or no drugs. These data demonstrate the utility of genotypic and phenotypic assay results in predicting virologic failure (and to a lesser extent response) of salvage regimens **(Abstract 133)**.

STRATEGIES FOR THERAPY

Antiretroviral Drug Substitution in Stably Suppressed Individuals

The relative merits of substituting an NNRTI for a protease inhibitor in individuals on stable therapy was

addressed in 2 studies. Ruiz et al described a study in which 60 subjects on stable protease inhibitor-containing regimens for 9 months or longer and with plasma HIV-1 RNA levels below 400 copies/mL for 6 months were randomized to stavudine/lamivudine/protease inhibitor or to stavudine/didanosine/nevirapine **(Abstract LB14)**. Follow-up data at 3 months were available for 14 and 15 subjects in the protease inhibitor and NNRTI arms, respectively. In both groups there were no significant changes in CD4+ cell counts from baseline, and plasma HIV-RNA levels remained <50 copies/mL. There was a statistically significant decrease in triglyceride and cholesterol levels from baseline in the NNRTI arm. The switch to nevirapine, empirically covered with antihistamines, was well tolerated with no recorded rash. Although the follow-up time in these studies is relatively short, these data suggest that NNRTI substitution might be a viable alternative in protease inhibitor-intolerant patients.

These findings were echoed by those of Raffi et al in a similarly constructed study in which subjects on stable protease inhibitor-based therapy switched to nevirapine (n=16) or efavirenz (n=2) **(Abstract 381)**. After a median follow-up time of 17 weeks, 16 of 18 had plasma HIV-1 RNA levels below assay detection limits. The switch was generally well tolerated with nevirapine-associated rash developing in only 1 of 16 subjects.

Intensification

Abacavir added to zidovudine/lamivudine.– Rozenbaum et al presented the 48-week follow-up of CNA 3009, an open-label multicenter trial in 52 subjects, in which abacavir was added to the dual nRTI regimen of zidovudine/lamivudine of more than 12 weeks' duration **(Abstract 377)**. The median baseline CD4+ cell count and HIV-1 RNA level were 543/μL and 2.88 log10 copies/mL, respectively. The regimen was well tolerated for up to 48 weeks when, by on-treatment analysis, 46% of subjects had a plasma viral load <20 copies/mL (ITT analysis). The median increase in CD4+ cell count at 48 weeks was 114/μL.

Abacavir added to a stable antiretroviral background therapy.–Ait-Khald et al presented 16-week follow-up data from a randomized, double-blind, placebo-controlled trial in which abacavir or placebo was added to stable background therapy (CNA 3002) **(Abstract 114)**. In the abacavir and placebo arms, 92 and 93 subjects were enrolled, respectively. The median CD4+ cell counts and plasma HIV-1 RNA levels in the abacavir and placebo groups were 408 and 411/μL and 3.68 and 3.52 $\log_{10}$ copies/mL, respectively. The background therapy was similar in both groups, ie, dual nRTI in 81% and 78% in abacavir and placebo arms, respectively. At 16 weeks, 39% and 8% of the abacavir and placebo recipients, respectively, had plasma HIV-1 RNA levels <400 copies/mL (ITT, P<0.001). These differences remained significant for lamivudine-experienced and -naive subjects. At 16 weeks of follow-up the median CD4+ cell count was modestly increased in the abacavir arm (by 19/μL) but declined in the placebo arm (by 3/μL) (P=0.09). The presence of the 184V mutation did not appear to diminish the efficacy of abacavir-containing regimens **(Abstracts 378, 114)**.

RESISTANCE

Resistance Prevalence in Primary Infection

Wegner et al **(Abstract LB9)** presented genotypic and phenotypic analyses of 95 and 91 isolates, respectively, derived from 114 drug-naive subjects in North America who had documented seroconversion within the last 3 years. Isolates were tested against currently available NNRTIs, nRTIs, and protease inhibitors using a recombinant virus assay (Virco). Phenotypically, isolates were defined as resistant, intermediate, or susceptible (>10-, 5 to 10-, and <5-fold relative decreases in susceptibility, respectively). Overall, 6% of isolates expressed high-level phenotypic and genotypic resistance to 1 drug class. Intermediate levels of phenotypic and genotypic resistance were observed in 21% and 17% of isolates. Resistance to NNRTIs accounted for most of the observed resistance. Genotypic evidence of resistance to nRTIs, NNRTIs, and protease inhibitors was observed in 4%, 15%, and 10% of isolates, respectively; phenotypic resistance was observed in 7%, 27%, and 1% of isolates, respectively.

One multidrug-resistant isolate was observed demonstrating mutations at codons 10, 73, 77, and 90 in the protease and codons 67, 70, 100, and 184 in the reverse transcriptase. This isolate demonstrated high-level phenotypic resistance to nelfinavir (intermediate-level resistance to the other protease inhibitors) and high-level resistance to lamivudine (intermediate-level resistance to zidovudine, nevirapine, and efavirenz).

A similar study by Little et al **(Abstract LB10)** evaluated phenotypic susceptibilities in isolates derived from 69 subjects in North America who were less than 12 months from documented seroconversion and who had 7 or less days of prior antiretroviral therapy. The drug susceptibility assay employed was the recombinant virus assay ViroLogic, Inc with relative fold differences in susceptibilities of <2.5, 2.5-10, and >10 being used to define susceptible, intermediate, or resistant. High-level resistance was

observed in 3%, 1%, and 3% of isolates to nRTIs, NNRTIs, and protease inhibitors. Overall, 3% of isolates were resistant to 2 or more drug classes and 1% were resistant to 3 drug classes. These studies suggest that in the recent past within the United States, the prevalence of high-level multidrug resistance appears to be relatively low. However, the prevalence of viral resistance overall appears to be increasing and is a worrisome trend.

The Clinical Utility of Resistance Testing

The impact on response to therapy of a mutation at codon 215 of reverse transcriptase.– Mayers et al (ACTG 244/RV79) evaluated the response in zidovudine-treated subjects of a switch to zidovudine/didanosine or zidovudine/didanosine/nevirapine at the time of developing the 215Y or F mutations and compared this response with similarly treated controls in whom virus remained wild-type at this codon. After detection of the 215 mutation there was a median CD4+ cell decline of 49 and 35/μL/year in the zidovudine/didanosine and zidovudine/didanosine/nevirapine arms, respectively, in the group with the mutation mutant. This compares with the control group in which the change in therapy was associated with a median increase of 22 and 72 CD4+ cells/μL/year in the zidovudine/didanosine and zidovudine/didanosine/nevirapine arms, respectively, in follow-up. Although these data derive from a period when mono- and dual-nRTI therapies were standard, they highlight the role of the T215 Y/F mutation as a determinant of disease progression, which may be independent of resistance phenotype.

Mutations in the reverse transcriptase and protease genes as predictors of failure in protease inhibitor- and nRTI-experienced subjects.– Lorenzi et al evaluated mutations in the HIV-1 reverse transcriptase and protease as predictors of subsequent response to nelfinavir-based salvage therapies in 62 highly nRTI- and protease inhibitor-experienced subjects with a median baseline CD4+ cell count and plasma HIV-1 RNA viral load of 133/μL and 5.16 $\log_{10}$ copies/mL, respectively. Subjects had significant prior protease inhibitor and nRTI exposures, but few (<5%) had prior NNRTI exposure. Baseline mutations to nRTIs included zidovudine-associated mutations (80%), 184V (75%), 69D (11%); and to protease 46I/L (21%), 82A/T (45%), and 90M (39%). The D30N mutation associated with nelfinavir exposure was not recorded in any isolate at baseline. Salvage regimens comprised nelfinavir in combination with saquinavir/1 to 2 nRTIs (40%), or with NNRTI/nRTI (23%), or with 2 to 4 nRTIs (37%). At 4 to 12 weeks' follow-up, the median (range) decrease in plasma HIV-1 RNA levels was -0.38 (-3.17 to +1.09). Importantly, only 3% of subjects recorded plasma HIV-1 viral loads of <400 copies/mL. In multivariate analysis the baseline total number of mutations in the reverse transcriptase and protease was the only factor independently predictive of virologic response (univariate RR, 0.14 $\log_{10}$ per mutation; $P<0.0001$). The CD4+ cell count, baseline plasma HIV-1 RNA level, and CDC stage were not predictive of outcome **(Abstract 140)**. These data complement those of Race et al, who observed that the risk of phenotypic protease inhibitor cross-resistance in vitro increases as the number of protease mutations increases **(Abstract 119)**.

Phenotypic assays: drug susceptibilities as predictors of response to salvage regimens employing 6 or more antiretrovirals.– Among individuals failing current standard regimens and who have broad cross-class experience, the possibility of utilizing multiple agents in so-called mega-HAART regimens is being widely investigated. Miller et al evaluated baseline plasma HIV-1 drug susceptibilities, as determined by the Virco recombinant virus assay, in relation to response to treatment with 6 or more antiretrovirals in 24 highly antiretroviral-experienced subjects **(Abstract 130)**. The protease inhibitor regimens used included ritonavir/(nelfinavir or saquinavir) versus nelfinavir/indinavir. The NNRTIs used included efavirenz, nevirapine, or delavirdine. Baseline drug susceptibilities revealed resistance to zidovudine, abacavir, and NNRTIs in 15 (63%), 11 (46%), and 10 (42%) subjects, respectively. Resistance to 3 or more protease inhibitors was observed in 13 (54%) subjects, 6 of whom exhibited high-level cross-resistance. Subjects were followed up for a median of 8 months when an increase in CD4+ cell count >100/μL was recorded in 19 of 24 subjects. Defining a response as a sustained plasma HIV-1 viral load <500 copies/mL, the numbers of responders, nonsustained responders, and failures were 10 (50%), 8 (33%), and 6 (24%), respectively. Seven of 10 responders, and 0 of 6 failures were treated with a minimum of 4 "active" drugs. Thus for subjects treated with mega-HAART regimens, the inclusion of multiple agents to which HIV-1 isolates are susceptible will more likely be successful. These data suggest a role for phenotypic testing in optimizing such complex regimens and raise the possibility of simplifying such regimens by deleting drugs to which resistance is documented.

Multinucleoside Resistance

Data continue to emerge relating to groups of mutations in the HIV-1

reverse transcriptase associated with multi-nRTI resistance. The following mutations, when occurring in a background of zidovudine resistance mutations (+/- the M184V mutation), are associated with moderate to high levels of cross-resistance to all currently available nucleoside analogs: single, double, or triple codon insertions at codons 68-69 (including S/SS/SA/SE/SAG), T69D/N/S/A, and the V75M mutation **(Abstracts 122, 123, 133, 135, S34)**.

RT codon 68 and 69 insertions. Lukashov and Ross described 7 isolates demonstrating 2 codon insertions between reverse transcriptase codons 68 and 69 **(Abstracts 122, 123)**. The treatment histories in these subjects varied, but most had previously received lamivudine and 5 of 7 had received zidovudine. Notably 2 of 7 subjects had only received stavudine and lamivudine in combination. In the isolates from these latter 2 subjects the 2 codon insertion (S-A) was observed in the absence of the typical zidovudine-associated resistance mutations.

The Q151M resistance complex.– The complete Q151M reverse transcriptase resistance complex (A62V, V75I, F77L, F116Y, and Q151M) is associated with a relatively high level of resistance to all currently available nRTIs. The occurrence of this complex in whole or part is typically observed in viral isolates that do not display mutations associated with resistance to other nRTIs. Two uncommon viral isolates were described in which the Q151M mutation was observed to emerge in association with multiple zidovudine mutations or where the complete Q151M complex was observed in association with the M184V mutation **(Abstract 121)**. Recombinant virus susceptibility assays demonstrated that the complete Q151M complex + M184V demonstrated greater resistance than the Q151M + zidovudine resistant complex.

Two studies described the diminished in vitro susceptibilities of recombinant HIV-1 isolates bearing the Q151M multi-nRTI resistance mutation **(Abstracts 113, 124)**. Notably, none of the 5 recombinant viruses examined by Van et al was susceptible to abacavir, with 3 of 5 isolates displaying high-level abacavir resistance. However, Anton et al described that isolates bearing the Q151M mutation exhibited only minor (2.5-fold) decreases in susceptibility to both adefovir and PMPA **(Abstract 124)**.

Impact of multidrug resistance in clinical trials.– Poorer response to salvage therapy with abacavir, efavirenz, and amprenavir was observed with each of the following baseline reverse transcriptase mutations or mutation complexes, (3 zidovudine-associated mutations (+/- 184V mutation), the T69D mutation, the 68-69 insertion variants, and the Q151M complex **(Abstract 133)**. Montoya et al described early failure in 2 of 6 subjects on a salvage regimen of adefovir, efavirenz, didanosine, and hydroxyurea in association with the presence at baseline of reverse transcriptase mutations 41L, 69D/S/A, and 215Y in combination **(Abstract 135)**.

Cross-Resistance

Protease inhibitor cross-resistance.– Race et al evaluated in vitro resistance to indinavir, saquinavir, ritonavir, nelfinavir, and amprenavir of HIV-1 isolates derived from 108 plasma samples from subjects failing protease-containing regimens, principally indinavir, ritonavir, and saquinavir. The drug susceptibility assay used was a novel single-cycle recombinant virus assay (scRVA). The incidence of cross-resistance among the currently available protease inhibitors was high, 60% to 90%. However, the level of cross-resistance to amprenavir was somewhat lower (37% to 40%). Resistance to indinavir was strongly associated with resistance to both ritonavir and nelfinavir. Over 80% of isolates with the mutations V54 + A82 + (I10 or V/Y71) were resistant to 4 or 5 protease inhibitors. Overall, a correlation was noted between the number of protease mutations observed and the number of protease inhibitors to which an isolate was resistant **(Abstract 119)**.

Genotypes and phenotypes of efavirenz resistance and cross- resistance.– Bachelor et al, employing data derived from 3 clinical trials, described rebound in plasma HIV-1 viral load in subjects on efavirenz-based regimens in association with the emergence of the sentinel K103N RT mutation alone or more frequently when paired with the L100I, V108I, or P225H mutations **(Abstract 109)**. The resistance profiles to currently available NNRTIs of recombinant viruses carrying the above mutations were examined **(Abstract 110)**. Recombinant viruses carrying the K103N mutation alone displayed 19-, 40-, and 24-fold reductions in susceptibilities to efavirenz, nevirapine, and delavirdine, respectively. The level of NNRTI cross-resistance was further increased in mutants carrying the K103N mutation in combination with the L100I, V108I, or P225H mutations. Thus recombinant viruses bearing the K103N mutation in isolation or paired with L100I, V108I, or P225H mutations were cross-resistant in vitro to all currently available NNRTIs. The combination L100I/ K103N carried the highest level of cross-resistance to currently available NNRTIs.

Virologic Failure of Indinavir-Based Therapies with "Wild- Type" Rebound of HIV-1 RNA in Plasma

Several studies dealt with the observation of "wild-type" protease sequences in subjects with rebound of plasma HIV-1 RNA levels on indinavir-containing regimens. ACTG 343 previously demonstrated the high failure rate of induction/maintenance strategies in zidovudine-experienced subjects. Havlir et al presented updated data from ACTG 343, describing 9 and 17 subjects with virologic rebound who received indinavir and zidovudine/lamivudine/indinavir, respectively, and comparing these with 10 controls in whom virologic suspension was maintained **(Abstract LB12)**. These 26 isolates were susceptible to indinavir using the ViroLogic phenotype assay. The only protease inhibitor-associated mutation observed was the M46L change in 1 of 26 subjects. Among isolates exposed to lamivudine, 14 of 17 (82%) possessed the 184V mutation and were resistant. Although mean random indinavir levels in the rebound and control groups were comparable, the percent of subjects with at least one indinavir level below detection was higher in the triple-drug failure group.

Similar findings were described by Descamps et al who presented an analysis of the Trilege study in which a comparable induction/maintenance strategy was evaluated in antiretroviral-naive subjects **(Abstract 493)**. Among 29 subjects taking indinavir/zidovudine or indinavir/zidovudine/lamivudine who experienced on-treatment rebound in plasma HIV-1 RNA, "wild-type" protease sequence was observed in 28 (97%). More detailed pharmacokinetic profiles in these subjects revealed at least one indinavir level below detection limits (0.5 ng/mL) in 13 of 26 subjects, while 4 of 26 had subtherapeutic indinavir levels.

These observations were consistent with those of Holder et al who found no indinavir-associated resistance mutations in 69% to 78% of isolates derived from indinavir-treated subjects experiencing an on-treatment rebound in plasma viral RNA, while reverse transcriptase mutations were observed in more than 70% of such isolates (492). Importantly, it does not appear that this phenomenon is restricted to indinavir as wild-type protease rebound in plasma has been observed in 90% of protease inhibitor-naive subjects in whom amprenavir/zidovudine/lamivudine therapy is failing **(Abstract 118)**.

Activity of Adefovir Dipivoxil Against Zidovudine and Zidovudine/Lamivudine-Resistant Isolates

Adefovir dipivoxil (bis-POM PMEA) is the oral prodrug of adefovir, a nucleotide reverse transcriptase inhibitor (nRTI) with in vitro potency equivalent to current nRTIs. While isolates possessing zidovudine resistance mutations show diminished susceptibility to adefovir, this resistance may be reduced significantly by the incorporation of the M184V reverse transcriptase mutation, associated with lamivudine resistance. Notably, the presence of the M184V mutation in isolation renders HIV-1 isolates approximately 2-fold more susceptible to adefovir than wild-type virus **(Abstracts 124, 137)**.

These in vitro data were supported by the 48-week results of GS-96-408, in which the relative benefits of adding adefovir (n=219) or placebo (n=223) to stable background therapy were evaluated. At 24 weeks' follow-up, plasma HIV-1 RNA levels remained unchanged in the placebo group, while the addition of adefovir produced a modest (0.4 $\log_{10}$ copies/mL) decrease in plasma HIV-1 RNA levels that was sustained for 32 to 48 weeks. However, the virology substudy of 31 patients showed that among subjects remaining on stable background therapy, the degree of suppression of plasma HIV-1 RNA levels differed according to baseline reverse transcriptase genotype, M184V (-0.54 $\log_{10}$) > wild-type >M184V + $\geq$ 1 zidovudine mutation >$\geq$ 1 zidovudine mutation (+0.16 $\log_{10}$ copies/mL). Interestingly, zidovudine-associated mutations emerged after 24 weeks on adefovir-containing regimens among subjects treated also with zidovudine or stavudine **(Abstracts 124, 137)**.

Abacavir Efficacy in Relation to Baseline Reverse Transcriptase Genotypic Profiles

Lanier et al evaluated virologic outcomes at 12 to 24 weeks in nRTI-experienced subjects who received abacavir-based therapies **(Abstract 134)**. This study evaluated 88 subjects previously enrolled variously in CNA 2003, 3001, 3002, and 3009 studies in which abacavir was added to stable background therapy (comprising nRTIs, NNRTIs, or protease inhibitors). Median CD4+ cell counts and plasma HIV-1 RNA levels ranged from 146 to 492/μL and 3.52 to 4.83 $\log_{10}$ copies/mL, respectively. At 12 to 24 weeks' follow-up the percentage of subjects achieving plasma HIV-1 RNA levels below 400 copies/mL with baseline reverse transcriptase genotypes was 54% (wild-type), 68% (M184V alone), 55% (1 or 2 mutations), and 8% (3 or more mutations), respectively. Thus, although the presence of the M184V mutation in isolation at baseline conferred a modest 2-fold decrease in susceptibility to abacavir relative to wild-type, this alone did not appear to affect the proportion of subjects in whom plasma HIV-1 RNA levels were <400 copies/mL in follow-up. However, the presence of 3 or more reverse transcriptase mutations at baseline, a history of receiving 3 or more antiretrovirals, and a history of receiving

antiretrovirals for more than 18 months were each associated with a poorer response to abacavir (P= 0.001).

Utility of Resistance Testing in Clinical Management

The impact of HIV-1 genotyping on clinical decision making and virologic outcomes was evaluated in the Genotypic Antiretroviral Resistance Testing (GART) study **(Abstract LB8)**. In this study 153 subjects with a greater than 3-fold increase in plasma HIV-1 RNA after 16 weeks on standard protease inhibitor-based therapies were enrolled. There were 2 study arms. In the GART arm, the patient's physician could choose to follow the recommendations of an individualized GART report. This report was prepared by individuals familiar with interpretation of HIV-1 genotypic data and also considered the subjects antiretroviral histories, CD4+ cell counts, and plasma HIV-1 RNA levels. In the no-GART arm, the patient's physician made treatment decisions without the GART report. The primary endpoint was the change in HIV-1 viral load as an average of the 4- and 8-week changes from baseline.

At entry, 78 and 75 subjects were enrolled in the GART and no-GART arms, respectively. The mean entry CD4+ cell counts and median plasma HIV-1 RNA levels were 230/μL and 4.6 $\log_{10}$ copies/mL, respectively. At entry, most subjects were receiving lamivudine plus (stavudine or zidovudine) plus (indinavir or nelfinavir). In the GART and no-GART arms, the first protease inhibitor-based regimen was failing in 53% and 44% of subjects, respectively. Baseline genotypic data revealed that 73% of isolates had 1 major mutation in both reverse transcriptase and protease genes, 20% had 1 major mutation in the reverse transcriptase gene alone, and 5% had no major mutations in either gene. The major reverse transcriptase mutations were M184V (82%) and 215Y/F (61%). The major protease mutations included D30N (14%), V82A/I/D (34%), and L90M (31%). The plasma HIV-1 RNA responses in the GART and no-GART arms were -1.17 $\log_{10}$ and -0.51 $\log_{10}$ copies/mL from baseline (P=0.001). This difference between the 2 arms remained significant when controlling for subject demographic group, the number of baseline antiretrovirals, the CD4+ cell count and plasma HIV-1 RNA level at baseline, and the study week of follow-up.

The change in plasma viral RNA from baseline was related to the number of active drugs prescribed in each arm, ranging from +0.14 to -1.25 $\log_{10}$ copies/mL for the use of ≤ 1 to ≥ 4 active drugs, respectively. Three or more active drugs were used in 86% and (50% of GART and no-GART arms, respectively. However, within the GART arm, in only 54% of cases did the physician actually prescribe the recommended GART regimen. When the data were analyzed by GART adherence, the effect of GART report is more obvious with >80% and <1% adherence associated with -1.47 $\log_{10}$ and 0.0 $\log_{10}$ copies/mL changes in plasma HIV-1 RNA from baseline, respectively (P=0.006). These data highlight the utility of appropriately applied genotypic interpretations as an adjunct to standard care in individuals failing current standard therapies.

Virologic Response in Specific Body Compartments

Seminal Plasma

Depasquale et al examined the protease sequences in blood and seminal plasma in 10 antiretroviral-naive subjects treated with amprenavir-based therapy who had detectable viral load in seminal plasma at baseline **(Abstract LB11)**. A rebound of viral load in seminal and blood plasma in 2 patients was associated with amprenavir-associated mutations L10I and I50V in both blood and seminal plasma virus. In 2 patients HIV RNA rebound in blood and seminal plasma was associated with amprenavir mutations only in virus in blood plasma. In 1 subject the L90M mutation was observed transiently in seminal plasma only.

Cerebrospinal Fluid

Stavudine/lamivudine/nelfinavir, viral load response, and stavudine levels.– Haas et al evaluated the impact of stavudine/lamivudine/nelfinavir on cerebrospinal fluid (CSF) and plasma viral load in 3 HIV seropositive, antiretroviral-naive subjects, using highly intensive sampling of CSF and plasma at baseline and after 4 to 7 days of therapy **(Abstract 405)**. For these 3 subjects the "day 0" plasma HIV-1 RNA levels ranged from 4.69 to 4.87 $\log_{10}$ copies/mL and the mean CSF RNA levels were 3%, 45%, and 93% of plasma levels, respectively. In follow-up, day 4 to 7, the plasma HIV-1 RNA levels fell by 1.33, 0.81, 1.11 $\log_{10}$ copies/mL, and CSF levels fell by 0.81, 1.18, and 0.037, respectively. The CSF:plasma ratios of declines were 0.61, 1.48, and 0.32. CSF levels of stavudine varied among subjects but were approximately 39% of plasma levels. These data suggest, at least in the short term, that variable rates of HIV-1 RNA decay may occur in CSF in individuals taking potent antiretroviral therapies.

Indinavir levels in CSF and serum and relation to viral load.– Letendre et al compared CSF and serum indinavir levels with plasma HIV-1 RNA levels in 22 HIV seropositive subjects on stable therapy with indinavir plus 2

nRTIs. Subjects had a median CD4+ cell count of 243/μL and median plasma and CSF RNA levels of 3.1 and 2.3 $\log_{10}$ copies/mL, respectively **(Abstract 407)**. Samples were drawn at differing times along the dose interval. Serum indinavir and plasma HIV-1 RNA levels were inversely correlated (P=0.03). No correlation was evident between CSF indinavir and HIV-1 RNA levels; however, 18 of 22 CSF samples had <200 copies/mL. CSF indinavir levels demonstrated less variation than serum indinavir levels and were approximately 6% (5% to 9%) of serum levels. This study demonstrated appreciable penetration of indinavir into the CSF.

Ritonavir/saquinavir, viral load response, and protease inhibitor levels.– In the Prometheus study, Gisolf et al evaluated differing viral load responses in CSF and plasma in 27 HIV-1 seropositive subjects who received twice daily regimens of ritonavir/saquinavir (400/400 mg), with or without stavudine **(Abstract 403)**. At week 12 in the ritonavir/saquinavir and ritonavir/saquinavir/stavudine groups, 4 of 14 (29%) and 12 of 13 (92%) subjects, respectively, had CSF viral loads below quantification (P=0.001). In 21 of 25 subjects, CSF protease inhibitor levels were below detectable limits. These data suggest that the CSF penetration of ritonavir and saquinavir when used in combination may be suboptimal.

Adjunctive Agents

Interleukin-2 Therapy

Clinical trials employing interleukin-2 (IL-2) in conjunction with anti- retroviral therapy in order to enhance immune recovery and as a possible means of purging latent HIV-1 from the resting CD4+ T-cell reservoir were presented. In 4 studies presented at the Conference, the combination of antiretroviral therapy with IL-2 resulted in substantial CD4+ cell count increases and no significant viral rebounds relative to antiretroviral therapy alone **(Abstracts 354, 355, 356, 357)**. For example, Losso et al related data from a randomized, dose-ranging open-label trial employing antiretroviral therapy with and without subcutaneous IL-2 in 73 patients with baseline CD4+ cell counts above 350/μL (mean, 506/μL) and a mean plasma HIV-1 RNA level of 2.96 $\log_{10}$ **(Abstract 354)**. At week 24, CD4+ cell count increases were significantly greater (200/μL versus <50/μL) with the IL-2-containing regimen than with antiretroviral therapy alone (P<0.001). At the same time, the percentages of patients with plasma HIV-1 RNA below 500 copies/mL were equivalent (70% versus 62%, respectively, P=0.46). The most common adverse effects were fever, malaise, and rash.

To examine the potential of concurrently administered IL-2 and antiretroviral therapy in eliminating latent HIV-1 reservoirs, Prins et al related data collected from a study combining IL-2 and OKT-3 with antiretroviral therapy with the intent to test the above hypothesis **(Abstract LB6)**. Three patients with long-term antiretroviral suppression of plasma HIV-1 RNA levels (a range of 9 to 15 months of therapy resulting in <5 copies/mL for 34 to 37 weeks) were enrolled and treated with OKT-3 and IL-2. While HIV-1 replication was transiently stimulated in these patients as reflected by plasma HIV-1 RNA levels increasing above measurable levels, the number of resting lymphocytes harboring HIV-1 DNA remained <1 per 10^6 cells in 2 of the patients. Unfortunately, significant lymphopenia and other adverse effects resulted from the treatment.

Hydroxyurea-Containing Therapies

Primary infection.– Zala et al evaluated the impact of stavudine/didanosine/nevirapine with and without hydroxyurea in 22 subjects treated within 6 months of HIV-1 infection **(Abstract 399)**. At 24 and 36 weeks the numbers of subjects with plasma HIV-1 RNA levels <50 copies/mL in '+' hydroxyurea and '-' hydroxyurea arms were 8 of 10 and 7 of 8, and 5 of 6 and 4 of 5, respectively. The relative increases in CD4+ cell counts at 36 weeks in the '+' hydroxyurea and '-' hydroxyurea arms were + 175 and + 415/μL. Notably 1 subject, treated approximately 1 month after a confirmed diagnosis of primary infection with stavudine/didanosine/nevirapine without hydroxyurea and who had suppression of plasma HIV-1 RNA levels to below 50 copies/mL on treatment at 8 weeks, stopped his therapy after 20 weeks. To date, 18 weeks after stopping therapy, this subject still had plasma HIV-1 RNA levels below the limit of detection.

Treatment of established disease with hydroxyurea/didanosine.– In a complex study, Frank et al evaluated the relative merits of didanosine monotherapy versus various combination regimens of hydroxyurea with didanosine, including the delayed or immediate addition of hydroxyurea to didanosine therapy **(Abstract 402)**. Seventy-two subjects with a median CD4+ cell count of 370/μL and a median $\log_{10}$ plasma HIV-1 RNA level of 4.42 were enrolled. All were didanosine-naive, and 45% were antiretroviral-naive. This study noted no effect of 4 weeks of hydroxyurea monotherapy on plasma viral load, and a greater reduction in plasma viral load at 8 weeks in the hydroxyurea/didanosine arm than in the didanosine monotherapy arm, 1.57

and 0.83 $\log_{10}$, respectively (P=0.01). No significant change was observed in plasma viral load 12 weeks after hydroxyurea was added to didanosine monotherapy.

IMMUNE RECONSTITUTION

Several presentations elucidated a more detailed picture of the immunologic ramifications of potent antiretroviral therapy. The major themes in this area were outlined in a symposium by Autran **(Abstract S44)**. These include (1) the long-term characteristics of naive CD4+ cell regeneration and (2) the restoration of recall antigen and HIV-1 specific responsiveness.

Potent Antiretroviral Therapy and Naive CD4+ T-cell Regeneration

As demonstrated by Autran et al long-term naive CD4+ T-cell regeneration is dependent on viral suppression rather than the degree of HIV-1 disease at baseline **(Abstract S44)**. After 2 years of potent antiretroviral therapy, no plateau in the increase of naive CD4+ cells has yet been observed. Moreover, it was estimated that in order to attain normal levels of naive cells, the duration of HIV-1 suppression would be approximately 12 months if basal CD4+ cell counts were above 400/μL or 6 to 8 years if basal CD4+ cell counts were below 100/μL. In addition to long-term HIV-1 suppression, naive CD4+ cell regeneration is also dependent on retained thymic function, this based on a lack of naive cell recovery in patients with Hodgkin's disease who underwent thymic irradiation.

Potent Antiretroviral Therapy and Response to Recall Antigens

The observation that the early initiation of potent antiretroviral therapy prevents loss of responsiveness to mitogens and recall antigens was made by several groups **(Abstracts 322, 324, S44)**. For example, a presentation by Carvelain et al demonstrated that the T-cell response to cytomegalovirus (CMV) 2 years after initiation of highly active antiretroviral therapy (HAART) in patients with advanced disease (mean CD4+ cell count of 369/μL) was 64% versus 100% in patients with early (mean CD4+ cell count of 851/μL) HIV-1 disease **(Abstract 324)**. Similarly, in a study by Schrier et al the responsiveness to CMV in patients with advanced disease (CD4+ cell count <100/μL) increased from 15% before active antiretroviral therapy to approximately 70% after initiation of therapy **(Abstract 325)**. As with other studies, the immune recovery was related to the amplitude of CD4+ cell response rather than the plasma HIV-1 RNA level **(Abstracts 325, 326)**.

The clinical correlation of the above-mentioned increases of in vitro CMV specific immune reactivity after active antiretroviral therapy was demonstrated by Jouan et al in a study that enrolled 47 HAART-treated patients with prior CMV retinitis **(Abstracts S44)**. Of these subjects, only 2 had CMV relapses in 20 months. No specific CMV reactivity was demonstrable in these 2 individuals. Antigen-specific immune restoration, therefore, appears to be functional and may allow for the subsequent withdrawal of prophylactic antimicrobial regimens.

HIV-1 Specific Immune Response

The initiation of potent antiretroviral therapy early in acute HIV-1 infection results in a significant increase in HIV-1 specific immune responses **(Abstracts 23, 324, S44)**. Autran et al presented a study of 52 patients treated with HAART for 2 to 3 years after being initiated in primary, intermediate (CD4+ cell count 250-400/μL), and advanced (CD4+ cells <250/μL) HIV-1 disease **(Abstract S44)**. Recovery of HIV p24 antigen response was only observed in subjects in whom therapy was initiated in primary infection (approximately 50% recovered p24 antigen reactivity), but not in the latter 2 groups **(Abstracts 324, S44)**. In a study of 11 acutely infected patients presented by Malhotra et al, the initiation of indinavir/zidovudine/lamivudine resulted in a significant 6-fold enhanced p24 antigen lymphoproliferative response relative to untreated controls **(Abstract 23)**.

Although an absence of restored HIV-1 and other antigen specific immune responses was observed in patients with established disease, Autran et al were able to demonstrate that in some cases, this deficit could be reversed in vitro by interleukin-12. **(Abstracts 324, S44)**.

CONCLUSION

The Conference has once again provided the field with a full description of the current state-of-the-art of antiretroviral chemotherapy and has highlighted the future directions of drug development and clinical research. It is hoped that the blueprint provided for the development of new agents, combinations and strategies to maximize antiviral potency, simplify regimens, and minimize toxicities will contribute to sustaining and furthering the progress in reducing morbidity and mortality from HIV disease witnessed in recent years. ■

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