

# Dose-ranging, randomized, clinical trial of atazanavir with lamivudine and stavudine in antiretroviral-naive subjects: 48-week results

Robert L. Murphy, Ian Sanne<sup>a</sup>, Pedro Cahn<sup>b</sup>, Praphan Phanuphak<sup>c</sup>,  
Lisa Percival<sup>d</sup>, Thomas Kelleher<sup>d</sup> and Michael Giordano<sup>d</sup>

**Objective:** To compare the efficiency and safety of atazanavir and nelfinavir in antiretroviral-naive patients.

**Design:** Randomization to atazanavir 400 mg or 600 mg once daily; nelfinavir 1250 mg twice a day, plus lamivudine and stavudine.

**Methods:** A blinded (to the atazanavir dose), 48-week trial in patients with HIV-1 RNA  $\geq 2000$  copies/ml, CD4 cell count  $\geq 100 \times 10^6$  cells/l. Primary end-point: change in HIV-1 RNA from baseline at 48 weeks. Secondary end-point: subjects with HIV-1 RNA  $< 400$ , and  $< 50$  copies/ml, CD4 cell count changes, adverse events.

**Results:** The 467 randomized subjects had comparable baseline characteristics across treatments. With atazanavir 400 mg, 600 mg and nelfinavir, respectively, mean changes in HIV-1 RNA ( $\log_{10}$  copies/ml) from baseline to 48 weeks were  $-2.51$ ,  $-2.58$ ,  $-2.31$ ; HIV-1 RNA  $< 400$  copies/ml [intent-to-treat population (ITT), non-completion = failure (NC = F)], 64%, 67%, 53%; HIV-1 RNA  $< 50$  copies/ml (ITT NC = F), 35%, 36%, 34%; mean CD4 cell count increased comparably at 48 weeks ( $234 \times 10^6$ ,  $243 \times 10^6$ ,  $211 \times 10^6$  cells/l). Adverse events were similar across treatments with the exception of diarrhea (more frequent with nelfinavir) and jaundice (more frequent with atazanavir). Mean changes from baseline to 48 weeks were: fasting low density lipoprotein cholesterol, +5.2%, +7.1% and +23.2% (at 56 weeks) and fasting triglycerides (48 weeks), +7.2%, +7.6% and +49.5%, in the atazanavir 400 mg, 600 mg, and nelfinavir groups, respectively ( $P < 0.01$ , atazanavir versus nelfinavir).

**Conclusions:** Atazanavir is a potent, safe, well tolerated, and effective once-daily protease inhibitor with low pill burden (two capsules/day). Lipid changes with atazanavir were significantly less than with nelfinavir, however, clinical significance of these findings in terms of decreased cardiovascular risk is unknown. © 2003 Lippincott Williams & Wilkins

*AIDS* 2003, **17**:2603–2614

**Keywords:** atazanavir, hyperlipidemia, protease inhibitors, cardiovascular disease, highly active antiretroviral therapy

---

From the Feinberg School of Medicine, Northwestern University, Chicago, Illinois, USA, the <sup>a</sup>WHC Infectious Diseases Clinical Trials Unit, Johannesburg, South Africa, <sup>b</sup>Fundacion Huesped, Buenos Aires, Argentina, <sup>c</sup>Chulalongkorn University, Bangkok, Thailand, and <sup>d</sup>Bristol-Myers Squibb Company, Wallingford, Connecticut, USA.

Correspondence to R. L. Murphy, John P. Phair Professor of Infectious Diseases, Northwestern University, 676 N. Saint Clair Street, Suite 200, Chicago, Illinois 60611, USA.

Received: 6 September 2002; revised: 8 May 2003; accepted: 13 May 2003.

DOI: 10.1097/01.aids.0000096930.51231.5d

## Introduction

Highly active antiretroviral therapy (HAART) has proved effective in suppressing HIV-1 replication and improving clinical outcome [1]. Low potency, variable pharmacokinetic characteristics, heavy pill burden, complex dosing requirements and metabolic toxicities, however, often limit the effectiveness of currently available protease inhibitor (PI)-based regimens, contributing to poor tolerability, suboptimal adherence and treatment failure [2]. Currently available PIs cause potentially serious metabolic complications, significantly elevating lipids and triglycerides [3,4] possibly contributing to lipodystrophy [5–7] and increasing cardiovascular disease risk [8]. The Adult AIDS Clinical Trials Group recommends [9] that PI-related dyslipidemia be treated according to general population guidelines [10]. However, lipid-lowering agents may introduce drug-related complications, as current PIs alter the metabolism of many of these agents, and their use potentially introduces additional complexity to already complicated HAART regimens [9]. There is a need for effective PIs with simplified dosing without elevations in lipid concentrations.

Atazanavir is a PI in clinical development with an *in vitro* 50% inhibitory concentration of 2.6–5.3 nM and a distinct resistance profile [11,12]. Its minimum serum concentration with sequential once-daily 400 mg dosing is greater than the protein binding-adjusted 50% inhibitory concentration for more than 36 h at steady state [13]. It has a low pill burden (two capsules/dose) [13–16]. Its inhibitory quotient range is higher than that of current PIs (10.2 to 25.5) [17]. *In vitro*, atazanavir-resistant variants emerge more slowly than do variants resistant to either ritonavir or nelfinavir, and variants of HIV-1 that are resistant to up to three current PIs retain sensitivity to atazanavir [18]. Atazanavir-resistant variants arising *in vivo* have a unique mutational pattern, including an I50L signature substitution. In an otherwise wild-type HIV-1 protease, the I50L substitution confers increased susceptibility of HIV-1 to other PIs, including amprenavir, but the clinical significance of this *in vitro* observation is not known. No cross-resistance has been observed between atazanavir and amprenavir *in vitro* in any of the isolates containing the I50L or I50V substitutions [19].

Comparative clinical trials show that atazanavir is safe, well tolerated and effective in rapidly and durably suppressing HIV-1 RNA and durably increasing CD4 cell count in both antiretroviral-naïve and -experienced subjects for 48 weeks [14,20,21]. Changes from baseline in lipid concentrations with atazanavir were not of a clinically significant magnitude, compared with the prompt, marked and sustained lipid elevations associated with comparator drugs. Based on safety and antiviral efficacy considerations, the 400 mg dose of

atazanavir once daily was chosen for evaluation in Phase III studies.

The objective of this clinical trial, Study AI424-008, was to compare the safety and efficacy of atazanavir, once daily at two different doses, with twice-daily nelfinavir, each administered with stavudine and lamivudine. Preliminary results from the present trial have been presented previously [22].

## Methods

### Study design

Study AI424-008 was a Phase II, 48-week, multinational, randomized, blinded (by atazanavir dose), active-controlled, three-arm study. The primary objective was to compare the antiviral efficacy of two dose levels of atazanavir (400 mg and 600 mg) once daily with nelfinavir (1250 mg) twice daily, each combined with the nucleoside reverse transcriptase inhibitors (NRTI) lamivudine and stavudine in antiretroviral-naïve subjects. Secondary objectives were comparison of their safety and tolerability, the differences in proportions of subjects with HIV-1 RNA levels < 400 and < 50 copies/ml, and differences in magnitude and durability of changes in CD4 cell counts. The atazanavir 400 mg group received once-daily atazanavir 400 mg, the atazanavir 600 mg group received once-daily atazanavir 600 mg, and the nelfinavir group received twice-daily nelfinavir 1250 mg (five 250-mg tablets twice a day), each plus lamivudine 150 mg and stavudine 40 mg twice a day. Stavudine doses were based on weight: subjects  $\geq 60$  kg at baseline received 40 mg, and those < 60 kg received 30 mg.

The trial was blinded only to the atazanavir dose. All other study drugs were administered open-label. Each atazanavir capsule contained 200 mg of drug. Patients were assigned in a 2:2:1 ratio (atazanavir 400 mg or 600 mg once daily or nelfinavir 1250 mg twice daily). Breaking the blind to treatment allocation was permitted in the event of a medical emergency for which knowledge of the investigational product would be critical to the subject's management or for atazanavir dose reductions.

### Selection of study population

Male and female HIV-1-infected patients were eligible for inclusion if they were at least 18 years of age and antiretroviral-naïve and had HIV-1 RNA levels of  $\geq 2000$  copies/ml and CD4 cell counts of  $\geq 100 \times 10^6$  cells/l (or  $\geq 75 \times 10^6$  cells/l in the absence of a prior AIDS diagnosis). Subjects were considered antiretroviral naïve if they had had  $\leq 30$  days' therapy with an NRTI, and/or  $\leq 7$  days' therapy with a non-nucleoside reverse transcriptase inhibitor or a PI,

provided the last dose was taken > 30 days before screening. Patients were excluded if they had a newly diagnosed HIV-1-related opportunistic infection, a suspected primary HIV-1 infection, a history of acute or chronic pancreatitis, proven or suspected hepatitis, or signs or symptoms of peripheral neuropathy grade 2 or higher at the time of screening. Women of child-bearing age were required to have a negative serum or urine pregnancy test within 72 h of commencing study medication.

Laboratory values measured within 14 days of the start of treatment had to be serum creatinine  $\leq 1.5$  times the upper limit of normal (ULN), total serum lipase  $\leq 1.4$  times ULN, liver enzymes [aspartate aminotransferase (AST), alanine aminotransferase (ALT), gamma-glutamyltransferase] < 3 times ULN and total bilirubin < 1.5 times ULN.

### Ethical approval

The trial was conducted in accordance with the Declaration of Helsinki. All patients gave written informed consent before participating. Institutional review boards and independent ethics committees approved the informed consent, the protocol and all protocol amendments prior to initiation of the trial.

### Assessments and monitoring

Subject evaluation occurred at screening, baseline, and weeks 4, 8, 12, 16, and 24 and every 8 weeks thereafter. Additional visits were permitted as required. Plasma HIV-1 RNA was determined by the AMPLICOR HIV-1 Monitor<sup>TM</sup> assay and by the AMPLICOR HIV-1 Monitor<sup>TM</sup> UltraSensitive assay, versions 1.0 and 1.5 (both Roche Molecular Systems; Branchburg, New Jersey, USA) on samples shipped at ambient temperature. Limits of quantification of the assays were 400 and 50 copies/ml, respectively. Version 1.0 assays were used on all samples from North America, and version 1.5 assays were used in Africa, Asia, Europe and South America. Because of the diverse capabilities of the 51 multinational centers, plasma samples were allowed to be shipped at ambient temperatures. If transport required more than 24 h, specimens were to be shipped frozen. The UltraSensitive assay, version 1.5, is more sensitive than other assays to non-subtype B virus, which is important in researching non-US or European populations. CD4 cell counts were determined by validated three-color flow cytometry measurements of circulating lymphocytes.

The safety of the study regimens was assessed using patients' medical history, physical examination, clinical laboratory test results and reported adverse events, which were recoded using an adaptation of the US Food and Drug Administration's Coding Symbols for Thesaurus of Adverse Reaction Terms, version III (COSTART III). Severity was evaluated according to

the modified World Health Organization criteria and rated on a scale of 1–4. The investigators were provided with a prescribed list of drug substitutions that were permitted to address toxicities, and investigators were required to consult with the medical monitor before restarting the study medications.

### Management of subjects with adverse events or intolerance

Subjects demonstrating toxicity or intolerance to stavudine could substitute zidovudine, and didanosine could be substituted for lamivudine. In subjects with grade 4 isolated hyperbilirubinemia (bilirubin levels 5–10 times ULN), the dose of atazanavir was withheld until repeat testing demonstrated hyperbilirubinemia of grade 3 or less. At that time, the atazanavir treatment was resumed, with the dose reduced by 200 mg. Subjects at any atazanavir dose level who re-experienced bilirubin elevations to > 10 times ULN were discontinued from the study. Subjects were allowed to discontinue the study under specific circumstances: major, serious and unexpected or life-threatening toxicity; pregnancy; need for a medication prohibited by the protocol; increase in viral load from a previously confirmed undetectable level to a detectable level; and personal request.

Samples for evaluation of total cholesterol, low density lipoprotein (LDL) cholesterol and triglyceride concentrations were collected from subjects in the fasting state. Lactate was evaluated at screening, baseline (day 1), weeks 2, 4, 8, 12, 16 and then every 8 weeks and at the final visit. Subjects returned for an unscheduled visit for lactate evaluation if grade 3 reduction in serum bicarbonate level occurred. Serum lactate levels were not collected in a standardized fashion for the period of time covered in this article. After week 72, serum lactate collection and measurement were standardized according to ACTG guidelines.

### Statistical analyses

The target sample size of 400 treated subjects was designed to provide at least 95% power for the primary analysis to demonstrate that the antiviral efficacy of any dose of atazanavir, in terms of the time-averaged difference (TAD) [23] of the HIV-1 RNA change from baseline over 48 weeks, was similar to that of nelfinavir. The power calculation assumed an upper 97.5% confidence limit of  $0.5 \log_{10}$  HIV-1 RNA copies/ml adjusted for two primary comparisons, a within-subject variance of  $0.5 \log_{10}$  copies HIV-1 RNA, a between-subject variance of  $0.8 \log_{10}$  copies HIV-1 RNA, and an equal effect for all atazanavir and nelfinavir regimens. The secondary analysis of the difference in the proportions of subjects with plasma HIV-1 RNA levels < 400 copies/ml at week 48 had 45% power to show that the pair-wise comparisons of atazanavir and nelfinavir regimens were similar to with-

in 12%. The efficacy data set included all randomized subjects. The safety data set included all treated subjects who received at least one dose of PI study medication. HIV-1 RNA values outside the upper (or lower) limit of quantification were assigned a value of 1 more (or less) than the limit.

Changes from baseline in HIV-1 RNA levels were compared using a 97.5% confidence interval for the TAD through 48 weeks. Analysis of the difference in the proportions of subjects with plasma HIV-1 RNA levels < 400 and < 50 copies/ml at 48 weeks was performed using a difference in proportions based on normal approximations. Randomized subjects were classified as virological responders if they remained on treatment and had a single HIV-1 RNA measurement < 400 or < 50 copies/ml closest to the scheduled visit and within a predefined visit window. The denominator was based on randomized subjects. Subjects considered failures in this analysis [intent-to-treat (ITT), non-completer = (NC = F)] were those with HIV-1 RNA > 400 or > 50 copies/ml and those who discontinued prior to their scheduled visit. Subjects who remained on treatment and did not have a week 48 measurement were classified as responders only if their previous and subsequent measurements were < 400 or < 50 copies/ml. The on-treatment analysis utilized the same response definition and included only subjects who remained on treatment in the denominator.

Changes from baseline in CD4 cell counts were compared using the TAD through 48 weeks. Lipid concentrations were compared using mean percent changes from baseline at 48 weeks based on t distributions. Fisher's exact test [24] was used to compare discrete variables (e.g., adverse events).

## Results

### Baseline characteristics

A total of 467 patients were randomly assigned to the regimens: atazanavir 400 mg (181 patients), atazanavir 600 mg (195 patients) or nelfinavir (91 patients). Three patients in the atazanavir 400 mg group did not initiate treatment. Subject disposition at 48 weeks is shown in Table 1. Time on therapy was comparable across the atazanavir and nelfinavir treatment regimens (mean of 49.1 to 49.8 weeks across the three groups). The reasons for discontinuation were comparable across treatment groups. There were 54 (12%) discontinuations prior to week 48, 19 (4%) due to adverse events that were also comparable across treatment groups.

Baseline characteristics and demographics are shown in Table 2. Demographic characteristics were comparable across regimens. Mean HIV-1 RNA level was 4.74 (SE, 0.03) log<sub>10</sub> copies/ml, and the mean CD4 cell count was 295 (SE, 7) × 10<sup>6</sup> cells/l.

### Antiretroviral and immunological efficacy

Mean changes over time in HIV-1 RNA are shown in Fig. 1a. The primary end-point was week 48. At week 24, mean changes from baseline (SE) in both the atazanavir 400 mg and 600 mg groups were -2.54 (0.07) log<sub>10</sub> copies/ml, and in the nelfinavir group they were -2.42 (0.09) log<sub>10</sub> copies/ml. These changes were sustained at 48 weeks. The similarity of the atazanavir and nelfinavir regimens in reducing HIV-1 RNA from baseline to 48 weeks is shown in Table 3. Cutoff for the limit of quantification constrains the measurement of the actual decline in viral load. Fig. 1b shows treatment responses over time for ITT NC = F analysis.

**Table 1. Subject disposition in Trial A1424-008 at 48 weeks.**

	Subjects [n (%)]		
	Atazanavir (once daily)		Nelfinavir (twice a day)
	400 mg (n = 181)	600 mg (n = 195)	1250 mg (n = 91)
Randomized			
Never treated	3 (2)	—	—
Treated	178 (98)	195 (100)	91 (100)
Discontinued prior to week 48	22 (12)	21 (11)	11 (12)
Adverse event	7 (4)	9 (5)	3 (3)
Death	1 (< 1)	1 (< 1)	—
Disease progression, relapse	1 (< 1)	1 (< 1)	—
Lost to follow-up	5 (3)	7 (4)	2 (2)
Non-compliance	2 (1)	2 (1)	1 (1)
Pregnancy	2 (1)	—	1 (1)
Subject withdrew	2 (1)	—	1 (1)
Treatment failure/lack of efficacy	2 (1)	1 (< 1)	3 (3)
Completed 48 weeks	156 (86)	174 (89)	80 (88)

**Table 2. Baseline characteristics and demographics of the randomized patient population in Trial A1424-008.**

Characteristic	Atazanavir (once daily)		Nelfinavir (twice a day)	Total
	400 mg (n = 181)	600 mg (n = 195)	1250 mg (n = 91)	(n = 467)
Age (years)				
Mean (SE)	34.3 (0.7)	34.7 (0.6)	35.3 (1.0)	34.7 (0.4)
Range	18–64	18–58	19–69	18–69
Sex [n (%)]				
Male	110 (61)	125 (64)	57 (63)	292 (63)
Female	71 (39)	70 (36)	34 (37)	175 (37)
Race [n (%)]				
White	100 (55)	104 (53)	52 (57)	256 (55)
Black/mixed	47 (26)	59 (30)	24 (26)	130 (28)
Asian/Pacific Islander	27 (15)	25 (13)	12 (13)	65 (14)
Hispanic/Latino	7 (4)	6 (3)	3 (3)	15 (3)
American/Alaskan Native	–	1 (< 1)	–	1 (< 1)
Region [n (%)]				
Europe	53 (29)	61 (31)	28 (31)	142 (30)
Africa	38 (21)	40 (21)	23 (25)	101 (22)
North America	26 (14)	31 (16)	11 (12)	68 (15)
South America	40 (22)	38 (19)	17 (19)	95 (20)
Asia	24 (13)	25 (13)	12 (13)	61 (13)
Injecting drug use [n (%)]	11 (6)	16 (8)	6 (7)	33 (7)
AIDS [n (%)]	18 (10)	24 (12)	9 (10)	51 (11)
Plasma HIV RNA (log <sub>10</sub> copies/ml) [mean (SE)]	4.74 (0.05)	4.73 (0.05)	4.73 (0.07)	4.74 (0.03)
CD4 cell count (× 10 <sup>6</sup> cells/l) [mean (SE)]	294 (12)	302 (11)	283 (16)	295 (7)
Total cholesterol (mg/dl) [mean (SE, n)] <sup>a</sup>	168.0 (2.9, 178)	168.6 (2.9, 195)	164.5 (3.9, 91)	–
Fasting LDL cholesterol (mg/dl) [mean (SE, n)] <sup>a</sup>	99.3 (2.4, 136)	102.4 (2.7, 164)	96.8 (3.8, 75)	–
Fasting triglycerides (mg/dl) [mean (SE, n)] <sup>a</sup>	128.2 (7.7, 139)	121.0 (8.0, 167)	107.8 (6.0, 77)	–

CD4 cell counts increased continuously throughout the 48 weeks, except for a slight decrease from week 40 to week 48 with nelfinavir (Fig. 1c). Mean increases in CD4 cell count are shown in Table 3.

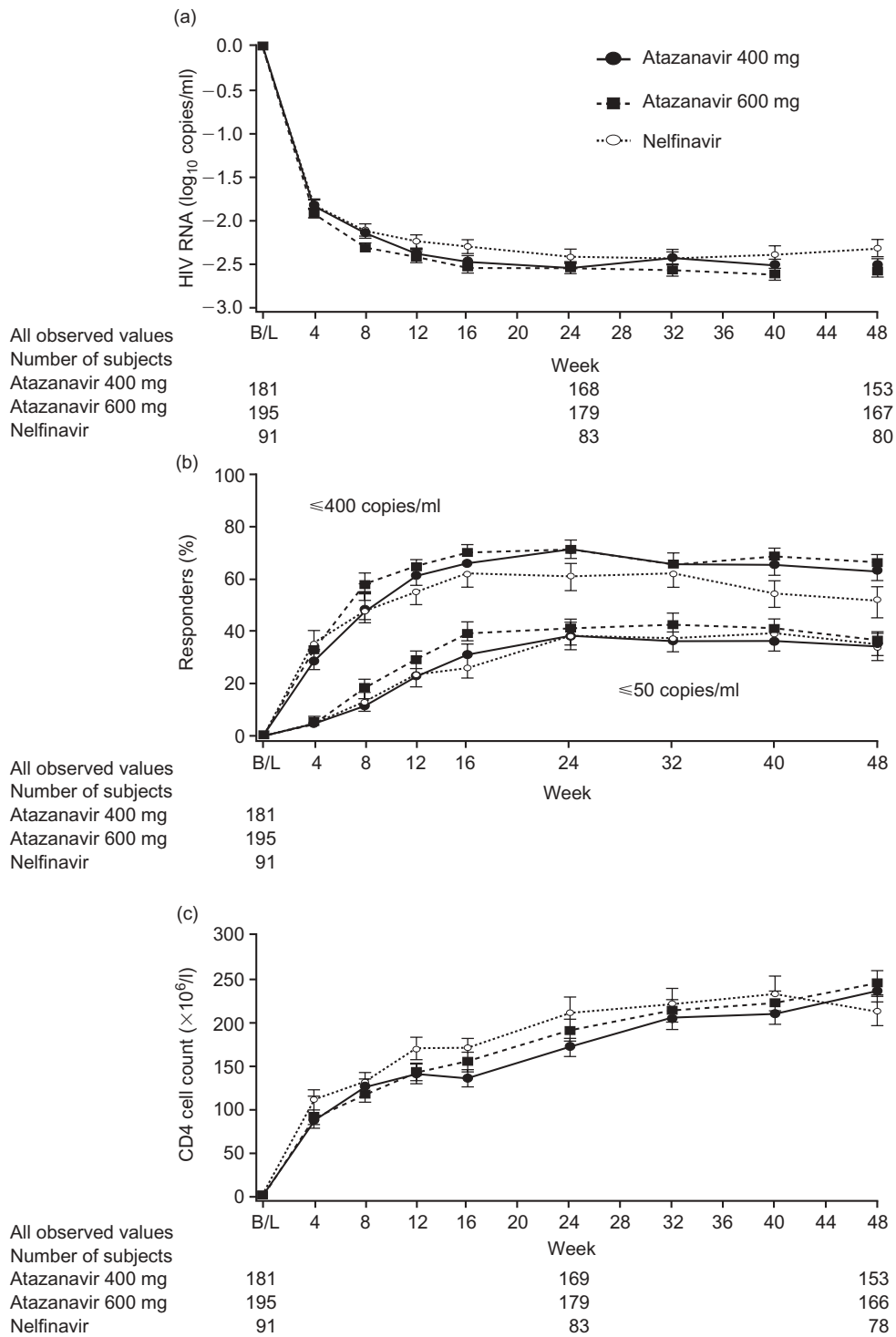
### Safety

Adverse events reported with a frequency of  $\geq 15\%$  with any treatment are shown in Table 4. The incidence of adverse events was comparable across regimens with the exception of diarrhea and jaundice. Diarrhea occurred significantly more frequently in the nelfinavir group than in either of the atazanavir groups ( $P < 0.0001$ ). Jaundice occurred only with atazanavir, at an incidence of 11% in the 400-mg group and 20% in the 600-mg group ( $P < 0.0001$ , each atazanavir regimen versus nelfinavir). Scleral icterus occurred only with atazanavir treatment, at an incidence of 9% in the 400-mg group ( $P = 0.002$ , atazanavir 400 mg versus nelfinavir) and of 12% in the 600-mg group ( $P = 0.0001$ , atazanavir versus nelfinavir). Lipodystrophy as a clinical adverse event, as assessed by the investigator, was reported in seven subjects (4%) in the atazanavir 400-mg group, seven subjects (4%) in the 600-mg group and in two (2%) in the nelfinavir group. Although there is currently no case definition for lipodystrophy, all but one of these events were reported as grade 1 or 2. The one exception, grade 3 to 4, occurred in a patient treated with atazanavir 600 mg.

A total of 27 (6%) subjects discontinued due to one or

more adverse events: nine subjects (5%) in the atazanavir 400-mg group, 14 (7%) in the atazanavir 600-mg group and four (4%) in the nelfinavir group. These 27 subjects reported 47 adverse events as leading to discontinuation, and 39 were considered at least possibly related to the study drug. Four atazanavir subjects (two in the 400-mg group and two in the 600-mg group) discontinued due to lactic acidosis or symptomatic hyperlactatemia (SHL) ranging from grade 1 to 3. Four atazanavir subjects in the 600-mg group discontinued due to hyperbilirubinemia that was attributed to the study drug. Two atazanavir subjects (one in each dose group) discontinued as a result of lipodystrophy that was attributed to the study drug. There were three deaths in the study, two in the atazanavir 600-mg group due to lactic acidosis on days 276 and 347, and one in the atazanavir 400-mg group from suicide at day 77.

Grade 3 to 4 laboratory abnormalities are shown in Table 5. Grade 3 to 4 elevations in total bilirubin were dose related and occurred most frequently in the atazanavir-treated subjects: 41% (400-mg group) and 58% (600-mg group), versus 4% in the nelfinavir group. Bilirubin elevations were reversible and predominantly indirect and unconjugated. Grade 3 to 4 elevations in AST and ALT were infrequent across treatment groups, and, as a marker of hepatotoxicity, showed no correlation with grade 3 to 4 elevations in total and indirect bilirubin.



**Fig. 1. Treatment responses through 48 weeks.** (A) Mean change (SE) in HIV-1 RNA from baseline through 48 weeks. At 48 weeks,  $P < 0.05$ , atazanavir 600 mg versus nelfinavir. (B) Virological responses through 48 weeks (ITT, NC = F analysis). At 48 weeks, HIV RNA  $< 400$  copies/ml,  $P < 0.05$ , atazanavir 600 mg versus nelfinavir. (C) Mean change in CD4 cell count through 48 weeks.

Lactic acidosis syndrome or SHL developed in seven subjects, three in the atazanavir 400-mg group and four in the atazanavir 600-mg group, for 19.6 cases per 1000 subject years; two of these died (both in the

atazanavir 600-mg group). Lactic acidosis was reported by the investigators based on the presence of elevated lactate, presence of metabolic acidosis and typical symptoms [25,26]. Several lactic acidosis cases presented

**Table 3. Efficacy end-points at 48 weeks.**

Week 48 end-point	Subjects [n (%)]		
	Atazanavir (once daily)		Nelfinavir (twice a day)
	400 mg (n = 181)	600 mg (n = 195)	1250 mg (n = 91)
Mean change in HIV-1 RNA [log <sub>10</sub> copies/ml (SE)]	-2.51 (0.07) (n = 153)	-2.58 <sup>a</sup> (0.06) (n = 167)	-2.31 (0.10) (n = 80)
Proportion HIV-1 RNA < 400 copies/ml			
Intent-to treat (NC = F) [n (%)]	116/181 (64)	130/195 (67) <sup>b</sup>	48/91 (53)
On treatment	116/156 (74) <sup>b</sup>	130/174 (75) <sup>b</sup>	48/80 (60)
Proportion HIV-1 RNA < 50 copies/ml			
Intent-to-treat (NC = F)	63/181 (35)	71/195 (36)	31/91 (34)
On treatment	63/156 (40)	71/174 (41)	31/80 (39)
Mean change in CD4 cell count (× 10 <sup>6</sup> cells/l)	+234 (n = 153)	+243 (n = 166)	+211 (n = 78)

<sup>a</sup>*P* < 0.025, time-averaged difference through week 48, atazanavir versus nelfinavir. <sup>b</sup>*P* < 0.05, atazanavir versus nelfinavir.

**Table 4. Adverse events and laboratory abnormalities reported as adverse events<sup>a</sup>.**

Adverse event	Subjects [n (%)]		
	Atazanavir (once daily)		Nelfinavir (twice a day)
	400 mg (n = 178)	600 mg (n = 195)	1250 mg (n = 91)
Diarrhea	36 (20) <sup>b</sup>	29 (15) <sup>b</sup>	51 (56)
Infection	75 (42)	107 (55)	44 (48)
Headache	45 (25)	52 (27)	24 (26)
Peripheral neurological symptoms	32 (18)	42 (22)	19 (21)
Rash	39 (22)	34 (17)	17 (19)
Nausea	38 (21)	35 (18)	16 (18)
Pain, abdomen	33 (19)	43 (22)	12 (13)
Flu syndrome	30 (17)	25 (13)	9 (10)
Cough increased	27 (15)	28 (14)	8 (9)
Hyperbilirubinemia	43 (24)	62 (32)	3 (3)
Jaundice	20 (11) <sup>b</sup>	39 (20) <sup>b</sup>	–

<sup>a</sup>Grade 1 to 4 adverse events occurring in ≥ 15% of treated subjects in any treatment group. <sup>b</sup>*P* < 0.0001 versus nelfinavir.

**Table 5. Grade 3 to 4 laboratory abnormalities.**

	Subjects [n (%)]		
	Atazanavir (once daily)		Nelfinavir (twice a day)
	400 mg (n = 178)	600 mg (n = 195)	1250 mg (n = 91)
Hemoglobin	–	1/195 (< 1)	3/91 (3)
White blood cell count	–	1/195 (< 1)	–
Neutrophils	3/176 (2)	7/195 (4)	7/91 (8)
Platelets	–	2/195 (1)	1/91 (1)
Aspartate aminotransferase	5/177 (3)	6/195 (3)	5/91 (5)
Alanine aminotransferase	8/177 (5)	10/195 (5)	7/91 (8)
Elevated total bilirubin	73/177 (41)	113/195 (58)	4/91 (4)

as part of a syndrome of other mitochondrial-related disorders, including pancreatitis and hepatotoxicity. Lactic acidosis was reported in subjects in Europe (two), South America (two), Asia (two) and Africa (one). All lactic acidosis cases were female, and all but

one was overweight (body mass index > 25 kg/m<sup>2</sup>) or obese (body mass index > 30 kg/m<sup>3</sup>). Lactic acidosis tended to occur late in the course of the study (> 30 weeks). A multivariate analysis did not identify increased risk of lactic acid syndrome/SHL for the

atazanavir 400 mg ( $P = 0.55$ ), atazanavir 600 mg ( $P = 0.31$ ) or with the combined atazanavir groups ( $P = 0.35$ ) compared to the nelfinavir group.

### Changes in lipid profiles

Significant differences were observed in percent changes from baseline in serum lipid profiles between atazanavir and nelfinavir. Baseline total cholesterol, fasting LDL cholesterol and fasting triglyceride concentrations were similar across treatment groups, as shown in Table 2. Percent changes from baseline through 48 weeks are shown in Figs 2a, b and c. At 48 weeks, the mean percent increases from baseline ( $\pm$  SE computed on the log scale) in the atazanavir 400-mg, atazanavir 600-mg and nelfinavir groups, respectively, were as follows: total cholesterol, 5.1 (3.5, 6.7), 5.9 (4.6, 7.1), 24.6 (22.0, 27.3); fasting LDL cholesterol (values at 56 weeks), 5.2 (2.5, 7.9), 7.1 (4.2, 10.1), 23.2 (18.4, 28.2); fasting triglycerides, 7.2 (1.3, 13.3), 7.6 (3.1, 12.2), 49.5 (38.3, 61.6) ( $P < 0.01$ , all comparisons to baseline;  $P < 0.01$ , atazanavir versus nelfinavir at week 48). Increases in high density lipoprotein cholesterol were comparable across treatment groups.

At baseline, the proportions of subjects with total cholesterol values in the various categories defined by the National Cholesterol Education Program (NCEP), Adult Treatment Panel III (ATP III), guidelines [10] were comparable across regimens. At baseline, 79–83% of subjects had total cholesterol levels classified as desirable ( $< 200$  mg/dl). At week 48, 75% of subjects in the atazanavir 400-mg group had maintained desirable total cholesterol concentrations. In the nelfinavir group, the proportion with desirable total cholesterol decreased from 82% at baseline to 49% at 48 weeks.

## Discussion

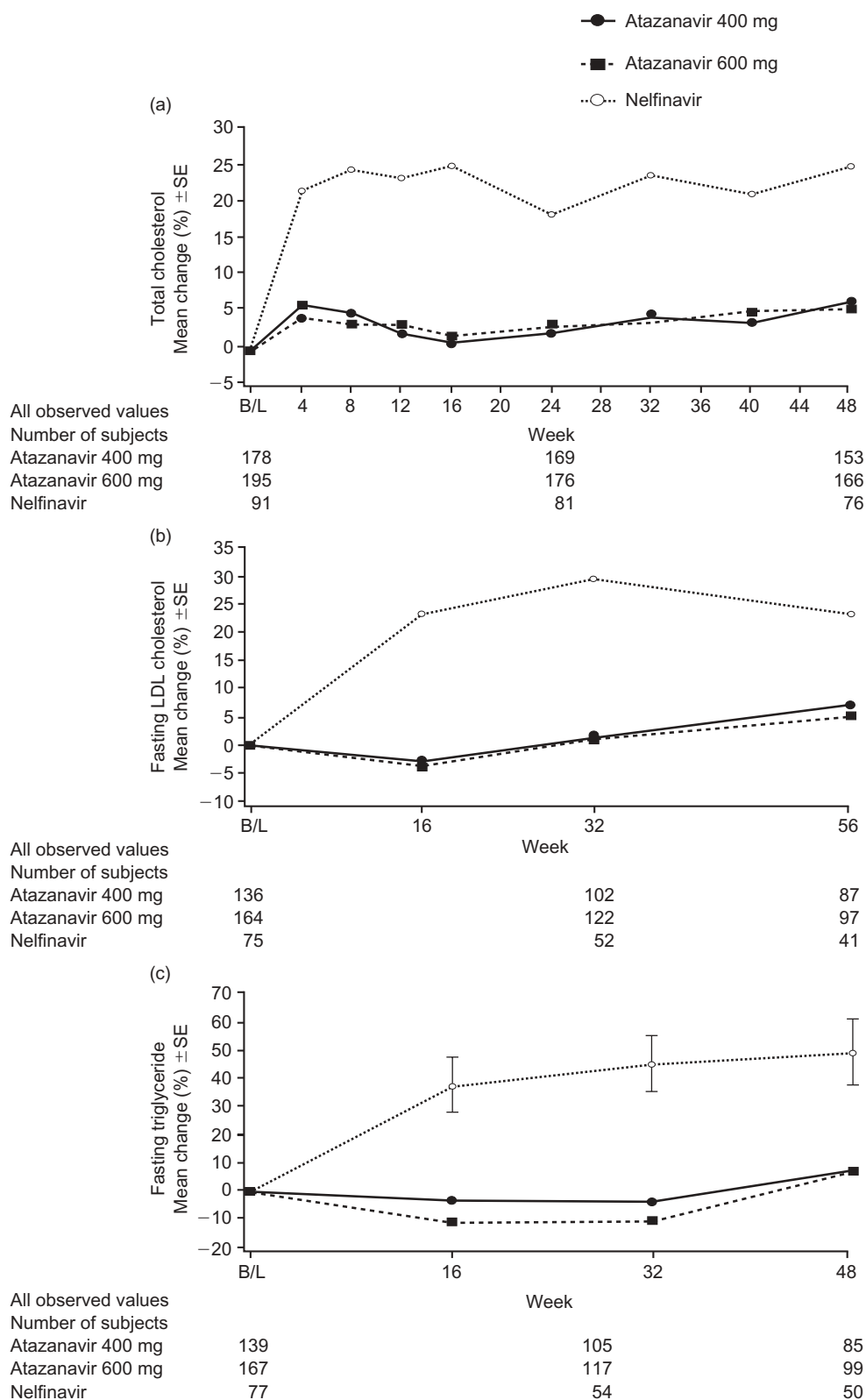
Study AI424-008 demonstrates that a HAART regimen with atazanavir 400 mg or 600 mg once daily is comparable in safety and has similar antiviral efficacy to nelfinavir twice daily, each in combination with lamivudine and stavudine through 48 weeks. AI424-008 is one of the first trials using a once-daily PI with a low pill burden, of two capsules/day. As in other indications, the simplicity of this dosing schedule, with a low incidence of side effects and better tolerability, is expected to encourage adherence and improve virological outcomes [27], leading to more durable HIV-1 suppression and a delay in the emergence of drug-resistant variants [28–30].

Subjects randomized to an atazanavir arm experienced significantly better virologic outcome in some analyses. At 48 weeks, the decline in HIV-1 RNA level was similar between the atazanavir 400-mg group and the

nelfinavir group, but, in the atazanavir 600-mg group it was significantly greater than that in the nelfinavir group ( $P < 0.025$ ). The proportions of virological responders were generally comparable across treatment groups. However, in the ITT analysis at 48 weeks, a significantly greater proportion in the atazanavir 600-mg group than in the nelfinavir group achieved HIV-1 RNA levels  $< 400$  copies/ml ( $P < 0.05$ ). In the on-treatment analysis, the proportion of responders at HIV-1 RNA  $< 400$  copies/ml was also significantly greater in the atazanavir 400-mg and 600-mg treatment groups than in the nelfinavir treatment group at 48 weeks ( $P < 0.05$ , both atazanavir groups versus nelfinavir). Durable increases in CD4 cell count from baseline were comparable in the three treatment groups at 48 weeks. Efficacy results for atazanavir confirm the findings from previous trials in antiretroviral-naïve subjects (trial AI424-007) [14] and in antiretroviral-experienced subjects (trial AI424-009) [20].

Atazanavir was well tolerated at both doses, and its safety was comparable to that of nelfinavir. The incidence of diarrhea was greater in the nelfinavir group than in both atazanavir groups ( $P < 0.0001$ ). Reversible, dose-related elevations of indirect, unconjugated bilirubin were reported with greater frequency with atazanavir, and although asymptomatic, resulted in treatment discontinuation in four subjects in the atazanavir 600 mg group. Elevated bilirubin was not associated with hepatotoxicity as assessed by grade 3 to 4 elevations of ALT and AST. In the presence of elevated bilirubin, measurement of serum aminotransferases increases the sensitivity of detecting the presence or absence of liver damage. In acute hepatocellular necrosis caused by drug-induced hepatitis, elevated bilirubin levels are accompanied by a significant elevation in levels of ALT and AST [31]. Grade 3 to 4 elevations of ALT and AST with atazanavir treatment were infrequent and comparable to nelfinavir. Preclinical studies have shown that atazanavir-associated bilirubin elevations may be attributable to inhibition of uridine diphosphate glucuronosyltransferase 1A1 [16], a mechanism similar to that described for the reversible elevations in bilirubin associated with Gilbert's syndrome, which are of little clinical significance [32]. This is also the apparent mechanism for reversible bilirubin elevations reported with indinavir treatment [33]. Although the discontinuation rate for adverse events was similar across all treatment groups, the incidence of jaundice was 11% and 20% in the atazanavir 400-mg and 600-mg treatment groups, respectively. This observation accounted, in part, for the decision to carry the 400-mg dose to phase III clinical trials.

Lactic acidosis developed in seven subjects receiving atazanavir and contributed to two deaths in the study. Lactic acidosis has been reported in patients receiving



**Fig. 2. Mean percent changes in lipid variables from baseline through 48 weeks, all observed values, last observation carried forward analysis.** (a) Total cholesterol. At 48 weeks,  $P < 0.0001$ , atazanavir 400 mg and 600 mg versus nelfinavir. (b) Fasting LDL cholesterol. At 48 weeks,  $P < 0.001$ , atazanavir 400 mg versus nelfinavir;  $P < 0.01$  atazanavir 600 mg versus nelfinavir. (c) Fasting triglyceride. At 48 weeks,  $P < 0.001$ , atazanavir 400 mg versus nelfinavir;  $P < 0.0001$ , atazanavir 600 mg versus nelfinavir.

HAART, particularly in obese women, and is typically associated with the nucleoside components of the regimen [34]. In this study, which involved a 4:1 randomization to atazanavir- compared to nelfinavir-based treatment and all patients received the same nucleoside components, there were no identified risk factors for development of lactic acidosis.

Dyslipidemia occurs with current PIs and is implicated in development of cardiovascular disease. Dyslipidemia may coincide with PI-associated fat redistribution [3–8,35–40]. In contrast to the prompt, marked, sustained and potentially clinically relevant increases in serum lipid and triglyceride concentrations observed with nelfinavir, significantly smaller elevations in total cholesterol, fasting LDL cholesterol or fasting triglyceride concentrations above baseline occurred with atazanavir treatment through 48 weeks ( $P < 0.01$ ). Relatively small increases in lipid parameters may actually represent a return to pre-HAART lipid levels as suggested in a recent report from the Multicenter AIDS Cohort Study [41].

Current guidelines recommend that PI-associated dyslipidemia be treated to reduce the risk of cardiovascular events [9]. For the general population, the NCEP ATP III classifies total cholesterol of  $< 200$  mg/dl as desirable, 200–239 mg/dl as borderline high, and  $\geq 240$  mg/dl as high. [10]. Total cholesterol levels within the range of borderline high to high values can develop in HIV-1-infected patients treated with current PIs [37,42]. In the present study, 17–21% of subjects had borderline high or high total cholesterol values at baseline. At weeks 24 and 48, 40% and 51% had developed borderline high or high total cholesterol concentrations, respectively, in the nelfinavir group, compared with 21% and 28% in the atazanavir groups. The Adult AIDS Clinical Trials Group recommends that PI-associated dyslipidemia be treated according to the NCEP recommendations, stressing the paramount importance of avoiding drug–drug interactions [9]. The 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors (the ‘statins’) are the most commonly used agents for such treatment. Significant drug interactions arise when PIs and statins are co-administered, as many statins are metabolized by the cytochrome P450 isoenzyme CYP 3A4, which the PIs inhibit [43,44]. Ritonavir and saquinavir co-administered with atorvastatin or simvastatin increase their serum concentrations 31-fold [43], and similar elevations have been reported with nelfinavir and lopinavir/ritonavir [43, 45]. Elevated levels of statins have been associated with an array of toxicities, including rhabdomyolysis [46].

In the present study, the increases in serum lipids that occurred in the nelfinavir treatment arm were similar in magnitude to those that have been observed with many of the current PIs [3,5,42,47–52]. Although the

lipid changes induced by PIs and other agents used to treat HIV may have clinical consequences in the HIV population, the clinical significance of these findings in terms of increased cardiovascular risk is not known. The need to treat dyslipidemia introduces additional complexity and pill burden to already complex HAART regimens, potentially further reducing adherence. Less-than-perfect adherence leads to the emergence of drug-resistant HIV-1 variants [53]. Boosting of a primary PI with ritonavir can reduce the number of required daily doses, but it also increases the total pill burden and the severity of metabolic side effects such as dyslipidemia, as well as introducing new side effects [54]. Atazanavir offers an alternative strategy to ritonavir boosting, since it is effective taken once daily, with a low pill burden (two capsules/day) and the changes in lipids and triglycerides associated with its use are significantly less than those observed with other PIs, including nelfinavir.

Although there was no case definition for a lipodystrophy endpoint, two subjects, one each in the atazanavir 400-mg and 600-mg treatment groups, were discontinued from treatment because of investigator-assessed lipodystrophy. Based on the low incidence of lipodystrophy in this study, blinded only as to atazanavir dose, conclusions concerning the two PIs and lipodystrophy could not be made.

In summary, this trial in antiretroviral-naïve subjects demonstrates that atazanavir once daily has safety, tolerability and efficacy comparable to nelfinavir twice daily through 48 weeks. Atazanavir rapidly and durably suppresses HIV-1 RNA levels and durably increases CD4 cell count. Atazanavir was significantly less likely than nelfinavir to cause diarrhea. Reversible, unconjugated hyperbilirubinemia, not associated with hepatotoxicity, was the most frequently reported laboratory abnormality in atazanavir-treated subjects. Changes in lipid and triglyceride levels with atazanavir treatment are of a significantly smaller magnitude than the prompt, marked, and sustained elevations observed with nelfinavir.

## Acknowledgements

The authors thank the following for their contributions to this study: M. Flepp, B. Hirschel, Y. Mouton, W. Rozenbaum, C. Trepo, A. Sonnerborg, K. Lidman, A. Plettenberg, H.-J. Stellbrink, F. Bergmann, W. Brocckhaus, N. Clumeck, Prof. Hemmer, M.A. Fischl, G. Friedland, K. Henry, J.R. Kostman, N. Nassar, M. O’Hearn, M.G. Sension, G. Sepulveda, M. Wohlfeiler, O. Klein, J. Wechsler, D. Wright, B. Gamulo Yangco, C. Zala, P. Patterson, W. Belloso, E. Ralph, F. Smaill, M. Arlotti, R. Esposito, K. Zachary, L. Minoli, S.

Suwanagool, R. Rubio Garcia, E. Van Wijngaerden, R. Wood, S. Miller, J. Furtado, A. Almeida, M.P. Souza Lima, D. Salmon, B. Grinsztejn, J. Santana, V. Pokrovsky.

## References

1. Hammer SM, Squires KE, Hughes MD, Grimes JM, Demeter LM, Currier JS, *et al.* for the AIDS Clinical Trials Group 320 Study Team. **A controlled trial of two nucleoside analogues plus indinavir in persons with human immunodeficiency virus infection and CD4 cell counts of 200 per cubic millimeter or less.** *N Engl J Med* 1997, **337**:725–733.
2. Montaner JSG, Reiss P, Cooper D, Vella S, Harris M, Conway B, *et al.* **A randomized, double-blind trial comparing combinations of nevirapine, didanosine, and zidovudine for HIV-infected patients: the INCAS Trial.** *JAMA* 1998, **279**:930–937.
3. Moyle GJ, Baldwin C. **Lipid abnormalities during saquinavir soft-gel-based highly active antiretroviral therapy [letter].** *J Acquir Immune Defic Syndr* 1999, **21**:423–424.
4. Purnell JQ, Zambon A, Knopp RH, Pizzuti DJ, Achari R, Leonard JM, *et al.* **Effect of ritonavir on lipids and post-heparin lipase activities in normal subjects.** *AIDS* 2000, **14**:51–57.
5. Mulligan K, Grunfeld C, Tai VW, Algren H, Pang M, Chernoff DN, *et al.* **Hyperlipidemia and insulin resistance are induced by protease inhibitors independent of changes in body composition in patients with HIV infection.** *J Acquir Immune Defic Syndr* 2000, **23**:35–43.
6. Ho TTY, Chan KCW, Wong KH, Lee SS. **Abnormal fat distribution and use of protease inhibitors.** *Lancet* 1998, **351**:1736–1737.
7. Martinez E, Mocroft A, García-Viejo MA, Pérez-Cuevas JB, Blanco JL, Mallolas J, *et al.* **Risk of lipodystrophy in HIV-1-infected patients treated with protease inhibitors: a prospective cohort study.** *Lancet* 2001, **357**:592–598.
8. Tsiodras S, Mantzoros C, Hammer S, Samore M. **Effects of protease inhibitors on hyperglycemia, hyperlipidemia, and lipodystrophy: a 5-year cohort study.** *Arch Intern Med* 2000, **160**:2050–2056.
9. Dubé MP, Sprecher D, Henry WK, Aberg JA, Torriani FJ, Hodis HN, *et al.* for the Adult AIDS Clinical Trial Group Cardiovascular Disease Focus Group. **Preliminary guidelines for the evaluation and management of dyslipidemia in adults infected with human immunodeficiency virus and receiving antiretroviral therapy: recommendations of the Adult AIDS Clinical Trial Group Cardiovascular Disease Focus Group.** *Clin Infect Dis* 2000, **31**:1216–1224.
10. Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults. **Executive summary of the third report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III).** *JAMA* 2001, **285**:2486–2497.
11. Gong Y-F, Robinson B, Rose R, Deminie C, Spicer T, Markowitz M, *et al.* **Antiviral activity and resistance profile of an HIV-1 protease inhibitor BMS-232632.** *38th Interscience Conference on Antimicrobial Agents and Chemotherapy.* San Diego, September 1998 [abstract I-79].
12. Rabasseda X, Silvestre J, Castañer J. **BMS-232632.** *Drugs of the Future* 1999, **24**:375–380.
13. O'Mara EM, Smith J, Olsen SJ, Tanner T, Schuster AE, Kaul S. **BMS-232632: single and multiple oral dose safety and pharmacokinetic study in healthy volunteers.** *Sixth Conference on Retroviruses and Opportunistic Infections.* Chicago, January–February 1999 [abstract 604].
14. Squires K, Gatell J, Piliro P, Sanne I, Wood R, Schnittman SM. **AI424-007: 48-week safety and efficacy results from a phase II study of a once-daily HIV-1 protease inhibitor (PI), BMS-232632.** *Eighth Conference on Retroviruses and Opportunistic Infections.* Chicago, February 2001 [abstract 15].
15. Sanne I, Piliro P, Wood R, Kelleher T, Cross A, Mongillo A, *et al.* **Safety and antiviral efficacy of a novel once-daily HIV-1 protease inhibitor BMS-232632: preliminary results from a phase II clinical trial.** *Seventh Conference on Retroviruses and Opportunistic Infections.* San Francisco, January–February 2000 [abstract 672].
16. O'Mara E, Mummaneni V, Randall D, Sagali N, Olsen S, Tanner T, *et al.* **BMS-232632: a summary of multiple dose pharmacokinetic, food effect and drug interaction studies in healthy subjects.** *Seventh Conference on Retroviruses and Opportunistic Infections.* San Francisco, January–February 2000.
17. Piliro P. **The utility of inhibitory quotients in determining relative potency of protease inhibitors.** *AIDS* 2002, **16**:799–800.
18. Gong Y-F, Robinson BS, Rose RE, Deminie C, Spicer TP, Stock D, *et al.* **In vitro resistance profile of the human immunodeficiency virus type 1 protease inhibitor BMS-232632.** *Antimicrob Agents Chemother* 2000, **44**:2319–2326.
19. Colonna RJ, Friborg J, Rose RE, Lam E, Parkin N. **Identification of amino acid substitutions correlated with reduced atazanavir susceptibility in patients treated with atazanavir containing regimens [abstract 4].** *Antivir Ther* 2002, **7**(suppl 1):S6.
20. Haas DW, Zala C, Schrader S, Thiry A, McGovern R, Schnittman S. **Atazanavir plus saquinavir once daily favorably affects total cholesterol (TC), fasting triglyceride (TG), and fasting LDL cholesterol (LDL) profiles in patients failing prior therapy (trial AI424-009, week 48).** *Ninth Conference for Retroviruses and Opportunistic Infections.* Seattle, February 2002 [abstract 42].
21. Piliro PJ, Cahn P, Pantaleo G, Gatell J, Squires K, Percival L, *et al.* **Atazanavir: a once-daily protease inhibitor with a superior lipid profile—results of clinical trials beyond week 48.** *Ninth Conference on Retroviruses and Opportunistic Infections.* Seattle, February 2002 [abstract 706-T].
22. Sanne I, Cahn P, Percival L, Phanuphak P, Kelleher TGM, Pantaleo G. **Comparative results (phase II 48-week): BMS-232632, stavudine, lamivudine as HAART for treatment-naïve HIV(+) patients (AI424-008).** *41st Interscience Conference on Antimicrobial Agents and Chemotherapy.* Chicago, December 2001 [abstract I-667].
23. Diggle PJ, Liang K-Y, Zeger SL. *Analysis of Longitudinal Data.* New York: Oxford University Press; 1994.
24. Fleiss JL. *Statistical Methods for Rates and Proportions.* New York: John Wiley & Sons; 1981.
25. Braunwald E, Hauser SL, Fauci AS, Kasper DL, Longo DL, Jameson JL, *et al.* (eds) *Harrison's Principles of Internal Medicine.* New York: McGraw-Hill; 2001.
26. DiPiro JT, Talbert RL, Yee GC, Matzke GR, Wells BG, Posey LM, *et al.* (eds) *Pharmacotherapy. A Pathophysiologic Approach.* Stamford: Appleton & Lange; 1999.
27. Dusing R. **Adverse events, compliance, and changes in therapy.** *Curr Hypertens Rep* 2001, **3**:488–492.
28. Greenberg RN. **Overview of patient compliance with medication dosing: a literature review.** *Clin Ther* 1984, **6**:592–599.
29. Paterson DL, Swindells S, Mohr J, Brester M, Vergis EN, Squier C, *et al.* **Adherence to protease inhibitor therapy and outcomes in patients with HIV infection.** *Ann Intern Med* 2000, **133**:21–30.
30. Eldred LJ, Wu AW, Chaisson RE, Moore RD. **Adherence to antiretroviral and pneumocystis prophylaxis in HIV disease.** *J Acquir Immune Defic Syndr* 1998, **18**:117–125.
31. Pratt DS, Kaplan MM. **Evaluation of liver function.** In *Harrison's Principles of Internal Medicine.* Edited by Braunwald E, Fauci AS, Kasper DL, Hauser SL, Longo DL, Jameson JL. New York: McGraw-Hill; 2002:1711–1715.
32. Kaplan M, Hammerman C, Rubaltelli FF, Vilei MT, Levy-Lahad E, Renbaum P, *et al.* **Hemolysis and bilirubin conjugation in association with UDP-glucuronosyltransferase 1A1 promoter polymorphism.** *Hepatology* 2002, **35**:905–911.
33. Zucker S, Qin X, Rouster S, Yu F, Green R, Keshavan P, *et al.* **Mechanism of indinavir-induced hyperbilirubinemia.** *Proc Natl Acad Sci USA* 2001, **98**:12671–12676.
34. John M, Mallal S. **Hyperlactatemia syndromes in people with HIV infection.** *Curr Opin Infect Dis* 2002, **15**:23–29.
35. Gervasoni C, Ridolfo AL, Trifirò G, Santambrogio S, Norbiato G, Musiccò M, *et al.* **Redistribution of body fat in HIV-infected women undergoing combined antiretroviral therapy.** *AIDS* 1999, **13**:465–471.
36. Benson JO, McGhee K, Coplan P, Grunfeld C, Robertson M, Brodovicz KG, *et al.* **Fat redistribution in indinavir-treated patients with HIV infection: A review of postmarketing cases.** *J Acquir Immune Defic Syndr* 2000, **25**:130–139.
37. Carr A, Samaras K, Burton S, Law M, Freund J, Chisholm DJ, *et al.* **A syndrome of peripheral lipodystrophy, hyperlipidaemia**

- and insulin resistance in patients receiving HIV protease inhibitors. *AIDS* 1998, **12**:F51–F58.
38. Berger A. **Protease inhibitors may cause fat abnormalities and heart disease.** *BMJ* 1998, **317**:100.
  39. Penzak SR, Chuck SK. **Hyperlipidemia associated with HIV protease inhibitor use: pathophysiology, prevalence, risk factors and treatment.** *Scand J Infect Dis* 2000, **32**:111–123.
  40. Carr A, Samaras K, Chisholm DJ, Cooper DA. **Pathogenesis of HIV-1-protease inhibitor-associated peripheral lipodystrophy, hyperlipidaemia, and insulin resistance.** *Lancet* 1998, **351**:1881–1883.
  41. Riddler S, Smit E, Li R, Cole S, Chmiel J, Dobs A, et al. **Serum lipids and antiretroviral therapy among HIV-infected men.** *Tenth Conference on Retroviruses and Opportunistic Infections*. Boston, February 2003 [abstract 750].
  42. Stein JH, Klein MA, Bellehumeur JL, McBride PE, Wiebe DA, Otvos JD, et al. **Use of human immunodeficiency virus-1 protease inhibitors is associated with atherogenic lipoprotein changes and endothelial dysfunction.** *Circulation* 2001, **104**:257–262.
  43. Clumeck N. **Stavudine plus a non-thymidine nucleoside reverse transcriptase inhibitor as a backbone for highly active antiretroviral therapy.** *Antivir Ther* 1998, **3**(suppl 4):39–43.
  44. Lennernäs H, Fager G. **Pharmacodynamics and pharmacokinetics of the HMG-CoA reductase inhibitors. Similarities and differences.** *Clin Pharmacokinet* 1997, **32**:403–425.
  45. Hsyu P, Lewis R, Schultz M, Lillibridge J, Kerr B. **Pharmacokinetic interactions between nelfinavir and two HMG-CoA reductase inhibitors simvastatin and atorvastatin.** *40th Interscience Conference on Antimicrobial Agents and Chemotherapy*. Toronto, September 2000 [abstract 425].
  46. Dresser GK, Spence JD, Bailey DG. **Pharmacokinetic-pharmacodynamic consequences and clinical relevance of cytochrome P450 3A4 inhibition.** *Clin Pharmacokinet* 2000, **38**:41–57.
  47. Berthold HK, Parhofer KG, Ritter MM, Addo M, Wasmuth JC, Schliefer K, et al. **Influence of protease inhibitor therapy on lipoprotein metabolism.** *J Intern Med* 1999, **246**:567–575.
  48. Behrens G, Dejam A, Schmidt H, Balks HJ, Brabant G, Körner T, et al. **Impaired glucose tolerance, beta cell function and lipid metabolism in HIV patients under treatment with protease inhibitors.** *AIDS* 1999, **13**:F63–F70.
  49. Rockstroh JK, Bergmann F, Wiesel W, Rieke A, Thiesen A, Fätkenheuer G, et al. for the German Ritonavir/Indinavir Study Group. **Efficacy and safety of twice daily first-line ritonavir/indinavir plus double nucleoside combination therapy in HIV-infected individuals.** *AIDS* 2000, **14**:1181–1185.
  50. Danner SA, Carr A, Leonard JM, Lehman LM, Gudiol F, Gonzales J, et al. for the European-Australian Collaborative Ritonavir Study Group. **A short-term study of the safety, pharmacokinetics, and efficacy of ritonavir, an inhibitor of HIV-1 protease.** *N Engl J Med* 1995, **333**:1528–1533.
  51. Pernerstorfer-Schoen H, Jilma B, Perschler A, Wichlas S, Schindler K, Schindl A, et al. **Sex differences in HAART-associated dyslipidaemia.** *AIDS* 2001, **15**:725–734.
  52. Roberts AD, Muesing RA, Parenti DM, Hsia J, Wasserman AG, Simon GL. **Alterations in serum levels of lipids and lipoproteins with indinavir therapy for human immunodeficiency virus-infected patients.** *Clin Infect Dis* 1999, **29**:441–443.
  53. Chesney MA. **Factors affecting adherence to antiretroviral therapy.** *Clin Infect Dis* 2000, **30**(suppl 2):S171–S176.
  54. Gatanaga H, Aizawa S, Kikuchi Y, Tachikawa N, Genka I, Yoshizawa S, et al. **Anti-HIV effect of saquinavir combined with ritonavir is limited by previous long-term therapy with protease inhibitors.** *AIDS Res Hum Retroviruses* 1999, **15**:1493–1498.