Atazanavir plus ritonavir or saquinavir, and lopinavir/ritonavir in patients experiencing multiple virological failures

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Objective: To evaluate atazanavir/ritonavir (ATV/RTV) (300/100 mg) once daily, atazanavir/saquinavir (ATV/SQV) (400/1200 mg) once daily, and lopinavir/ritonavir (LPV/RTV) (400/100 mg) twice daily, each with tenofovir (300 mg) once daily and a nucleoside reverse transcriptase inhibitor in treatment-experienced HIV-infected patients.

Methods: Randomized, open-label, 48-week multicenter trial of 358 randomized adult patients who had failed two or more prior HAART regimens with baseline HIV RNA $\geq$ 1000 copies/ml and CD4 cell count $\geq 50 \times 10^6$ cells/l.

Results: The primary efficacy endpoint [plasma HIV RNA reduction assessed by time-averaged difference (TAD)] was similar for ATV/RTV and LPV/RTV [TAD 0.13; 97.5% confidence interval, −0.12 to 0.39] at 48 weeks. Mean reductions from baseline for ATV/RTV and LPV/RTV were comparable at 1.93 and 1.87 $\log_{10}$ copies/ml, respectively. Mean CD4 cell count increases were 110 and 121 $\times 10^6$ cells/l for ATV/RTV, and LPV/RTV, respectively. The efficacy of ATV/SQV was lower than LPV/RTV by both these parameters. Declines in total cholesterol and fasting triglycerides were greater with ATV/RTV and ATV/SQV than with LPV/RTV ($P \leq 0.005$). Lipids in the LPV/RTV arm at week 48 generally increased from baseline. Lipid-lowering agents were used more frequently in the LPV/RTV arm than in the ATV arms ($P < 0.05$ versus ATV/RTV), as were antidiarrheal agents ($P \leq 0.04$ versus both ATV treatments). No new or unique safety findings emerged.

Conclusions: ATV boosted with RTV is as effective and well tolerated as LPV/RTV in treatment-experienced patients, with a more favorable impact on serum lipids. Pharmacokinetically enhanced ATV provides a suitable choice for therapy of treatment-experienced HIV-infected patients.

AIDS 2005, **19**:685–694

Keywords: antiretroviral therapy, atazanavir, lipids, lopinavir, protease inhibitors, ritonavir, saquinavir

Introduction

The use of highly active antiretroviral therapy (HAART) in the treatment of HIV infection has transformed HIV disease from a condition that often resulted in mortality within a few years to a chronic syndrome [1–4]. Effective long-term viral suppression and immunological recovery in HIV-infected patients, however, can be compromised

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Received: 4 August 2004; revised: 8 October 2004; accepted: 14 October 2004.

ISSN 0269-9370 © 2005 Lippincott Williams & Wilkins

by the pharmacological shortcomings of some HAART components, drug toxicities, and complicated dosing regimens that jeopardize treatment adherence [5–7]. Such limitations can lead to the emergence of viral resistance and treatment failure. For treatment-experienced patients, new treatment options become progressively limited as initial ones fail, and treatment failure rates increase as patients move to their second and third regimens [8–10].

The long-term success of many protease inhibitor (PI)-based therapies may be further compromised by metabolic abnormalities in the forms of dyslipidemia, lipodystrophy and insulin resistance, commonly associated with the use of this class of antiretroviral agent [11–13]. Increasing evidence suggests that PI-related hypercholesterolemia and hypertriglyceridemia may correlate with increased long-term cardiovascular risk for HIV-infected individuals [14–18].

Atazanavir is a potent, safe, and well-tolerated PI that is taken once daily and has a resistance profile distinct from other drugs in its class [19,20]. In a 48-week clinical trial with drug-naive patients, atazanavir-related changes in lipid concentrations were significantly less than those associated with nelfinavir [21].

Moreover, pharmacokinetic studies conducted in healthy individuals have demonstrated that boosting a 300 mg dose of atazanavir with 100 mg ritonavir once daily increases the trough plasma concentration of atazanavir by $\geq$ 5-fold compared with that for 400 mg atazanavir alone, without substantially increasing the maximum plasma concentration [22–24]. Boosting atazanavir with ritonavir has the potential to increase treatment potency, particularly against drug-resistant HIV-1 strains, without significantly raising the risk for toxicity, potentially allowing for two therapeutic options for this PI. The present study was undertaken to evaluate the efficacy and safety of both ritonavir-boosted atazanavir and a dual PI combination comprising atazanavir and saquinavir in comparison with ritonavir-boosted lopinavir, each administered with one nucleoside reverse transcriptase inhibitor (NRTI) and tenofovir. The study was conducted over 48 weeks in treatment-experienced HIV-infected patients who had failed multiple HAART regimens.

Methods

Patients

The study included men and non-pregnant women $\geq$ 16 years of age (or legal minimum age as locally required) who had failed two or more prior HAART regimens that included one or more NRTI, a non-nucleoside reverse transcriptase inhibitor (NNRTI) and PI. Patients were required to have a baseline plasma HIV RNA level $\geq$ 1000 copies/ml, a baseline CD4 cell count $\geq 50 \times 10^6$ cells/l, and to have previously responded to at least one HAART regimen with a 1.0 $\log_{10}$ copies/ml reduction in viral load or a decline in viral load to $<$ 400 copies/ml. Patients were also required to have levels of serum creatinine $<$ 1.5 times the upper limit of normal (ULN), serum lipase $<$ 1.4 $\times$ ULN, alanine aminotransferase and aspartate aminotransferase $<$ 3 $\times$ ULN, and total serum bilirubin $<$ 1.5 $\times$ ULN. Patients were excluded if they had previously used atazanavir, lopinavir/ritonavir or tenofovir $\geq$ 30 days, or saquinavir $\geq$ 30 days unless phenotypic testing (PhenoSense; ViroLogic, South San Francisco, California, USA) revealed continued sensitivity to saquinavir [$\leq$ 2.5 times the concentration required to inhibit 50% of HIV-1 replication (IC_{50}) of the control strain].

Study design and outcomes

The study incorporated a randomized, open-label, multicenter, three-arm design and was conducted by 83 investigators in Europe and North and South America. The study protocol and consent forms were reviewed and approved by independent ethics committee or institutional review board for each study center.

The primary efficacy analysis compared the magnitude and durability of the reduction in plasma HIV RNA from baseline, based on the time-averaged-difference (TAD) through week 48, between each atazanavir treatment group and the lopinavir/ritonavir treatment group. Secondary efficacy assessments included the change from baseline in plasma HIV RNA at week 2, the proportion of patients with plasma HIV RNA $<$ 400 or $<$ 50 copies/ml through week 48, and the change from baseline in CD4 cell count through week 48. Safety assessments included general safety and tolerability as well as the magnitude of changes in total cholesterol, high density lipoprotein cholesterol, fasting low-density lipoprotein (LDL) cholesterol and fasting triglycerides through week 48.

Treatment

Randomization was performed centrally and patients were assigned in a 1:1:1 ratio to (a) atazanavir 300 mg plus ritonavir 100 mg once daily, (b) atazanavir 400 mg plus saquinavir 1200 mg once daily or (c) lopinavir/ritonavir 400/100 mg twice daily. Patients in each group also received tenofovir 300 mg once daily plus one NRTI: didanosine 400 mg once daily (reduced total dosage to 200 and 250 mg once daily, depending on body weight, was recommended after the start of the trial because of pharmacokinetic interaction with tenofovir), stavudine 40 mg twice daily, lamivudine 150 mg twice daily, zidovudine 300 mg twice daily or abacavir 300 mg twice daily. The NRTI component was chosen on the basis of phenotypic sensitivity analyses carried out at screening. If this information was not available, patients were assigned to an NRTI that they had not taken before. During the initial 2 weeks of treatment, patients remained on their

previous NRTI while the PI or NNRTI component was replaced by study PI. Starting at week 3, patients were switched to the full study regimen (Fig. 1).

Assessment and monitoring

Enrolled patients underwent targeted physical examinations at baseline, weeks 2, 4, 8, 12 and 16, and every 8 weeks thereafter, and were evaluated for plasma HIV RNA levels, CD4 cell counts, adverse events and metabolic parameters. Plasma HIV RNA levels were also measured at week 1. At screening and baseline, HIV RNA levels were measured using standard Amplicor HIV-1 Monitor version 1.5 (accuracy range, 400–750000 copies/ml; Roche Molecular Systems, Branchburg, New Jersey, USA). On-study HIV RNA levels were measured using version 1.5 of the Roche Amplicor HIV-1 Monitor Ultra Sensitive assay (accuracy range, 50–75000 copies/ml). HIV RNA values $>$ 75000 copies/ml were tested reflexively using the standard Amplicor HIV-1 Monitor assay. Toxicities were graded according to the modified World Health Organization criteria.

Statistical analyses

Efficacy endpoints were assessed for all randomized patients with plasma HIV RNA levels and CD4 cell counts obtained through 4 days after the last dose of study therapy. The study incorporated a non-inferiority design with the primary comparisons made to the lopinavir/ritonavir reference arm. The planned sample size of 330 randomized patients (110 per treatment arm) provided 99% power to demonstrate that the TAD in reduction of HIV RNA ($\log_{10}$ copies/ml) from baseline through week 48 was similar (non-inferior) between each atazanavir arm versus lopinavir/ritonavir. Regimens were determined to be similar in the primary efficacy analysis if the upper 97.5% confidence interval (CI) for the TAD was $<$ 0.5 $\log_{10}$ copies/ml.

The percentages of patients with HIV RNA levels $<$ 400 and $<$ 50 copies/ml were assessed as secondary efficacy

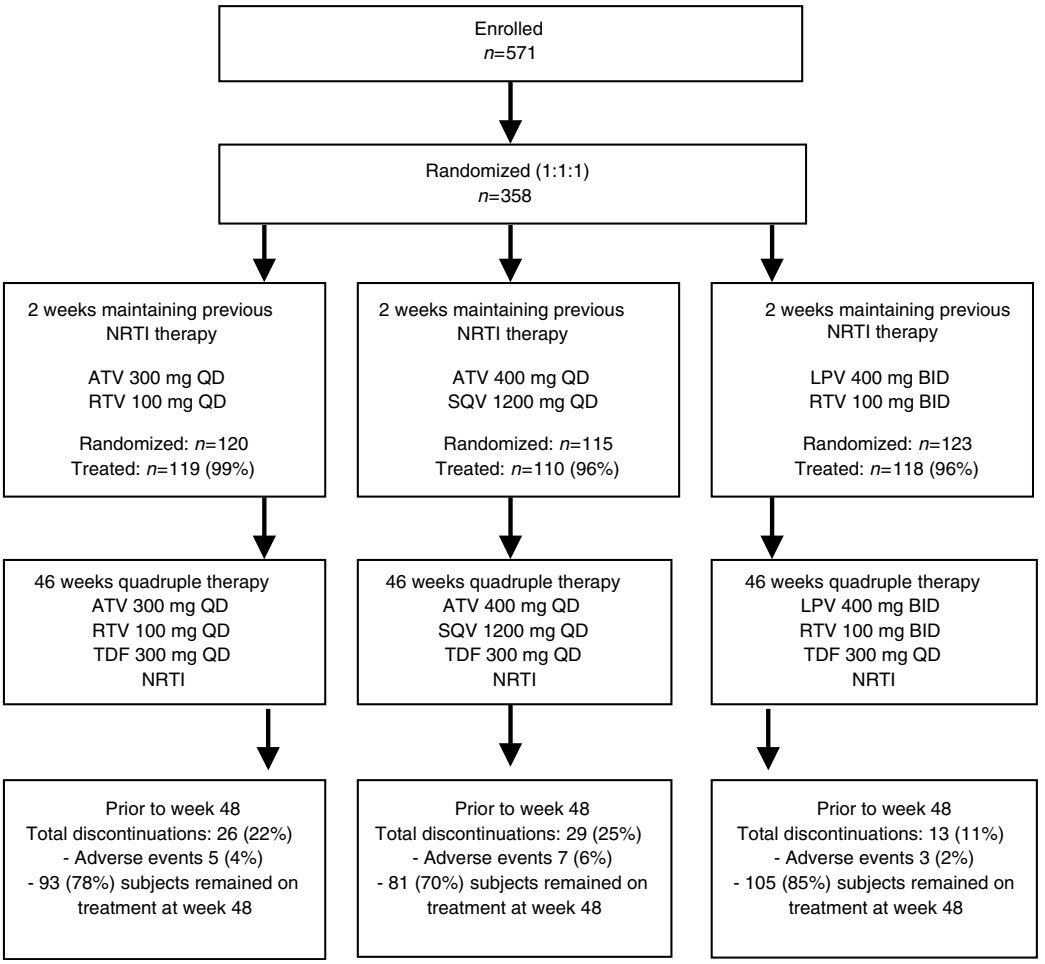

Fig. 1. Patient disposition. Differences in discontinuation rates likely correlated with open-label trial design and patient confidence in approved rather than experimental treatment. Of the 213 subjects not randomized, 194 did not satisfy the inclusion/exclusion criteria of the protocol and 11 withdrew consent. ATV, atazanavir; LPV, lopinavir; SQV, saquinavir; RTV, ritonavir; TDF, tenofovir; QD, once daily; BID, twice daily.

outcome measures using both intent-to-treat and as-treated analyses. The intent-to-treat analyses included all randomized patients in the denominator and counted as responders those patients with a minimum of two sequential HIV RNA measurements < 400 copies/ml (or < 50 copies/ml) maintained through week 48 without intervening replicated rebounds or treatment discontinuations. Patients who remained on study at week 48 were included in the as-treated analyses with response based only on the week 48 HIV RNA measurement being < 400 copies/ml (or < 50 copies/ml), or both previous and subsequent measurements < 400 copies/ml if the week 48 measurement was missing.

Assessment of safety endpoints included all treated patients. Serious adverse events and deaths were included without regard to treatment status at the time of onset for enrolled patients. Mean percentage changes from baseline and SE for lipid parameters were computed on the log scale and back transformed.

Results

A total of 571 patients were enrolled; 358 patients were randomized and 347 (97%) were treated (Fig. 1). The most frequent cause for non-randomization was failure to meet inclusion requirements (194; 34% of the total 571 enrolled). In general, baseline characteristics were comparable across treatment regimens. (Table 1).

The extent of prior treatment experience as well as baseline phenotypic and genotypic characteristics are shown in Table 1. Median prior exposures to any PI, NNRTI or NRTI were 2.5, 1.5 and 5.1 years, respectively. A total of 34% had taken a PI as part of their last HAART regimen prior to randomization (within the 3 months prior to study entry) whereas 60% had taken an NNRTI. The median numbers of baseline PI and NRTI mutations were two and three, respectively, for all treatment groups. The median time on study therapy was 48 weeks for all treatment groups.

Table 1. Baseline characteristics by treatment arm.

Characteristic	ATV/RTV ($n = 120$)	ATV/SQV ($n = 115$)	LPV/RTV ($n = 123$)
Gender (% male)	80	77	78
Mean age [years (SE)]	41 (0.8)	42 (0.8)	40 (0.7)
Race [No. (%)]			
White	75 (63)	70 (61)	71 (58)
Hispanic/Latino	27 (23)	26 (23)	27 (22)
Black	18 (15)	16 (14)	21 (17)
Other	0	3 (3)	4 (3)
AIDS [No. (%)]	33 (28)	33 (29)	36 (29)
Median HIV RNA ($\log_{10}$ copies/ml)	4.44	4.42	4.47
Median CD4 cell count ($\times 10^6$ cells/l)	317	286	283
Patients treated for HBV or HCV [No. (%)]			
Positive[a]	20 (17)	20 (18)	18 (15)
Negative	96 (81)	88 (80)	94 (80)
Missing data	3	2	6
Prior antiretroviral use, (median years)			
PI	2.5	2.4	2.6
NRTI	5.2	4.9	5.1
NNRTI	1.5	1.7	1.3
Preceding therapy [No. (%)]			
PI	43 (36)	34 (30)	44 (36)
NNRTI	73 (61)	73 (63)	69 (56)
PI mutations [No. (%)][b]			
0	18 (15)	11 (10)	12 (10)
1–2	49 (41)	54 (47)	53 (43)
3–4	23 (19)	22 (19)	26 (21)
≥ 4	30 (25)	28 (24)	32 (26)
Phenotypic sensitivity to administered PI (ATV or LPV) [No. (%)][c]			
≤ 2.5	88 (73)	84 (73)	88 (72)
> 2.5–5.0	11 (9)	16 (14)	8 (7)
> 5.0–10.0	9 (8)	6 (5)	10 (8)
> 10	12 (10)	8 (7)	15 (12)
Missing	0	1	2

ATV, atazanavir; HBV, hepatitis B; HCV, hepatitis C; LPV, lopinavir; NRTI, nucleoside reverse transcriptase inhibitor; NNRTI, non-nucleoside reverse transcriptase inhibitor; PI, protease inhibitor; SQV, saquinavir; RTV, ritonavir.
[a]Patients were included in the positive group if they were hepatitis B surface antigen positive or hepatitis C antibody positive.
[b]Median number of PI mutations was two for all groups; median number of NRTI mutations was three for all groups. The PI mutations consisted of the 'Stanford Panel' of 16 ATV- or LPV-associated mutations (amino acid residues 10, 20, 24, 32, 33, 36, 46, 48, 50, 54, 63, 71, 73, 82, 84, 90).
[c]Values at screening, expressed as multiples of the median inhibitory concentration IC_{50} of the control strain and are given only for the PI, ATV and LPV appropriate to the respective treatment groups.

Virological efficacy

The antiviral efficacy of atazanavir/ritonavir was demonstrated to be not inferior to lopinavir/ritonavir for the TAD primary efficacy endpoint through week 48. The atazanavir/ritonavir versus lopinavir/ritonavir TAD estimate was 0.13 (97.5% CI, −0.12 to 0.39), meeting the criterion for similarity (non-inferiority) between the two regimens, while the response to atazanavir/saquinavir was significantly lower than lopinavir/ritonavir (TAD estimate 0.33; 97.5% CI, 0.07 to 0.60). The mean reductions from baseline in HIV RNA at 48 weeks were 1.93 $\log_{10}$ copies/ml for the atazanavir/ritonavir treatment arm, 1.55 $\log_{10}$ copies/ml for the atazanavir/saquinavir treatment arm and 1.87 $\log_{10}$ copies/ml for the lopinavir/ritonavir treatment arm (Fig. 2).

As measured during the first 2 weeks of study treatment prior to optimization of the nucleoside/nucleotide backbones, the intrinsic antiviral activities of all three new PI components were comparable. Through this 2-week period, the observed mean reductions in HIV RNA from baseline were 1.18, 1.14 and 1.30 $\log_{10}$ copies/ml for the atazanavir/ritonavir, atazanavir/saquinavir and lopinavir/ritonavir treatment arms, respectively.

Both the intent-to-treat and as-treated analyses of the percentages of patients with HIV RNA < 400 and < 50 copies/ml supported the conclusion of comparable efficacy between atazanavir/ritonavir and lopinavir/ritonavir (see Fig. 2b and Table 2). The response rates for the atazanavir/saquinavir treatment regimen were lower than those for the lopinavir/ritonavir arm.

Post-hoc exploratory analyses were performed to evaluate the effects on virological response of (a) baseline phenotypic sensitivity to the randomized PI and (b) the number of PI mutations at baseline, using the 'Stanford Panel' of 16 atazanavir- or lopinavir-associated mutations (amino acid residues 10, 20, 24, 32, 33, 36, 46, 48, 50, 54, 63, 71, 73, 82, 84, 90). For the purposes of these analyses, a cutoff of 2.5, consistent with the

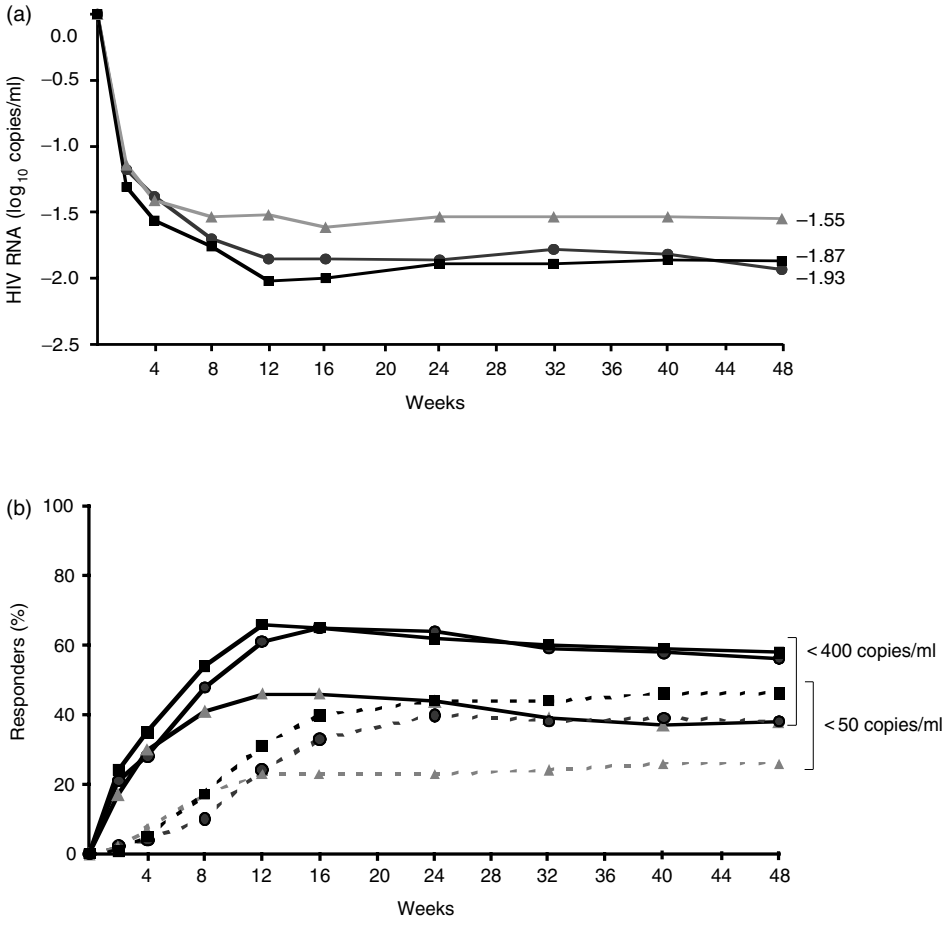

Fig. 2. Mean change from baseline to week 48. (a) Change in HIV RNA level. (b) Change in virological response in an intent-to-treat analysis. Solid lines correspond to percentage of responders at a limit of quantification of 400 copies/ml. Dotted lines correspond to percentage of responders at a limit of quantification of 50 copies/ml. atazanavir/ritonavir (●; $n = 120$); atazanavir/saquinavir (▲; $n = 115$); lopinavir/ritonavir (■; $n = 123$).

Table 2. Virological efficacy by the number of baseline protease inhibitor mutations at week 48[a].

	ATV/RTV			ATV/SQV			LPV/RTV		
	Overall $n = 120$	< 4 PI mutations $n = 80$	≥ 4 PI mutations $n = 40$	Overall $n = 115$	< 4 PI mutations $n = 77$	≥ 4 PI mutations $n = 38$	Overall $n = 123$	< 4 PI mutations $n = 76$	≥ 4 PI mutations $n = 47$
HIV RNA [mean change from baseline ($\log_{10}$ copies/ml)]	−1.93	−2.13	−1.38	−1.55	−1.98	−0.42	−1.87	−2.10	−1.47
Responders: intent-to-treat (% of patients)[b]									
< 400 copies/ml	56	70	28	38	53	8	58	68	40
< 50 copies/ml	38	44	25	26	38	3	46	55	30
Responders: as-treated (% of patients)[c]									
< 400 copies/ml	71[d]			53[e]			66[f]		
< 50 copies/ml	52[d]			38[e]			54[f]		

ATV, atazanavir; LPV, lopinavir; SQV, saquinavir; RTV, ritonavir.
[a]The mutations consisted of the 'Stanford Panel' of 16 atazanavir- or lopinavir-associated mutations (amino acid residues 10, 20, 24, 32, 33, 36, 46, 48, 50, 54, 63, 71, 73, 82, 84, 90).
[b]Atazanavir/ritonavir versus lopinavir/ritonavir difference estimate for HIV RNA < 400 copies/ml was −1.9 (95% CI, −14.3 to 10.6) and for HIV RNA < 50 copies/ml was −8.0 (95% CI, −20.4 to 4.4); atazanavir/saquinavir versus lopinavir/ritonavir difference estimate for HIV RNA < 400 copies/ml was −19.5 (95% CI, −32.2 to −6.8) and for HIV RNA < 50 copies/ml was −19.4 (95% CI, −31.7 to −7.2).
[c]Atazanavir/ritonavir verus lopinavir/ritonavir difference estimate for HIV RNA < 400 copies/ml was 5.3 (95% CI, −7.7 to 18.3) and for HIV RNA $<$ 50 copies/ml was −2.7 (95% CI, −16.6 to 11.3); atazanavir/saquinavir versus lopinavir/ritonavir difference estimate for HIV RNA < 400 copies/ml was −12.6 (95% CI, −26.8 to 1.6) and for HIV RNA < 50 copies/ml was −16.0 (95% CI, −30.5 to −1.5).
[d]Overall $n = 93$.
[e]Overall $n = 81$.
[f]Overall $n = 105$.

protocol-defined inclusion/exclusion criteria, was used uniformly for all tested drugs. In the atazanavir/ritonavir and lopinavir/ritonavir arms, patients with viral strains sensitive to their randomized PI ($\leq 2.5 \times IC_{50}$ control) experienced comparable mean declines in plasma HIV RNA levels at week 48 (2.12 and 2.09 $\log_{10}$ copies/ml, respectively). A lesser mean decline was noted for patients treated with atazanavir/saquinavir (1.86 $\log_{10}$ copies/ml). Patients resistant to their randomized PI ($> 2.5 \times IC_{50}$ control) experienced lesser declines in plasma HIV RNA levels than sensitive patients. However, the declines experienced by patients treated with atazanavir/ritonavir and lopinavir/ritonavir remained comparable, whereas atazanavir/saquinavir, again, was less effective (mean declines 1.17, 1.27, and 0.46 $\log_{10}$ copies/ml, respectively).

Similarly, when virological response was stratified according to the number of PI mutations at baseline, atazanavir/ritonavir and lopinavir/ritonavir treatment resulted in comparable reductions in HIV RNA at week 48 as well as comparable proportions of patients in response. Atazanavir/saquinavir treatment was less effective on both measures (Table 2). Patients with ≥ 4 PI mutations at baseline experienced lesser declines in HIV RNA at week 48 than those with fewer baseline mutations. However, the declines remained comparable between the atazanavir/ritonavir and lopinavir/ritonavir treatment groups.

Immunological efficacy

At week 48, mean increases in CD4 cell count for patients treated with atazanavir/ritonavir and lopinavir/ritonavir were 110 and 121 $\times 10^6$ cells/l, respectively; atazanavir/saquinavir-treated patients experienced a mean increase from baseline in CD4 cell count that was lower than that for patients receiving either of the other regimens (72×10^6 cells/l). Through week 48, the atazanavir/ritonavir versus lopinavir/ritonavir and atazanavir/saquinavir versus lopinavir/ritonavir TAD estimates were −17.5 (95% CI, −45.6 to 10.6) and −47.6 (95% CI, −79.2 to −16.1), respectively.

Adverse events

The overall incidence of adverse events (investigator reported) was comparable among treatment regimens, with >80% of patients on each regimen reporting at least one adverse event. Treatment-related grade 2–4 adverse events were experienced by 34 patients (29%) treated with atazanavir/ritonavir, 29 patients (26%) treated with atazanavir/saquinavir and 29 patients (25%) treated with lopinavir/ritonavir. (Table 3) Two deaths were reported, one in the atazanavir/saquinavir group and one in the lopinavir/ritonavir group; neither was considered to be related to study medication. A total of 37 patients experienced one or more serious adverse events, including 12 (10%) in the atazanavir/ritonavir group, 14 (12%) in the atazanavir/saquinavir group and 11 (9%) in the lopinavir/ritonavir group. The majority of serious adverse events was considered unrelated to study medication, and no unexpected drug-related toxicities were reported.

Lipids

Lipid concentrations generally decreased on both atazanavir regimens, whereas lipid concentrations generally increased on lopinavir/ritonavir, with a notable 30%

Table 3. Treatment-related grade 2–4 adverse events reported for ≥ 3% of patients in any treatment arm listing serum lipids[a]

	ATV/RTV ($n = 119$)	ATV/SQV ($n = 110$)	LPV/RTV ($n = 118$)
Adverse event [No. (%)]			
Jaundice	7 (6)[*]	2 (2)	0
Lipodystrophy	6 (5)	4 (4)	5 (4)
Myalgia	5 (4)	0	0
Icterus eye	4 (3)	0	0
Diarrhea	3 (3)	7 (6)	13 (11)[**]
Nausea	3 (3)	9 (8)	2 (2)
Fatigue	1 (< 1)	3 (3)	1 (< 1)
Peripheral neurological symptom	1 (< 1)	2 (2)	3 (3)
Vomiting	0	4 (4)	1 (< 1)
Rash	0	3 (3)	1 (< 1)
Mean percentage change baseline to week 48			
Total cholesterol	−8	−4	+6[***]
High density lipoprotein cholesterol	−7	+4	+2
Fasting low density lipoprotein cholesterol	−10	−3	+1
Fasting triglycerides	−4	−14	+30[***]

ATV, atazanavir; LPV, lopinavir; SQV, saquinavir; RTV, ritonavir.
[a]Grading according to World Health Organisation modified criteria; excluding patients on lipid-lowering therapy.
[*]$P = 0.01$, versus lopinavir/ritonavir.
[**]$P = 0.01$, versus atazanavir/ritonavir.
[***]$P \leq 0.005$, both atazanavir regimens versus lopinavir/ritonavir.

increase in fasting triglycerides (Table 3). The differences in total cholesterol and fasting triglycerides levels between the lopinavir/ritonavir treatment arm and each of the two atazanavir treatment arms were statistically significant ($P \leq 0.005$) at week 48. The decline observed in fasting LDL cholesterol on both atazanavir-containing regimens was not statistically significant (at the 5% level) compared with the small increase that occurred on the lopinavir/ritonavir-containing regimen. In the atazanavir/ritonavir, atazanavir/saquinavir and lopinavir/ritonavir treatment groups, respectively, median total cholesterol levels were 183, 166 and 178 mg/dl at baseline and 165, 156 and 188 mg/dl at week 48; median high density lipoprotein cholesterol levels were 38, 40 and 37 mg/dl at baseline and 37, 39 and 40 mg/dl at week 48; median fasting LDL cholesterol levels were 100, 96 and 103 mg/dl at baseline and 93, 89 and 99 mg/dl at week 48; and median fasting triglycerides levels were 164, 153 and 163 mg/dl at baseline and 137, 106 and 179 mg/dl at week 48. The percentages of atazanavir/ritonavir-treated patients who were within the National Cholesterol Education Program Adult Treatment Panel (NCEP ATP) III [25] desirable and optimal ranges for total cholesterol (< 200 mg/dl) and fasting LDL cholesterol (< 130 mg/dl), respectively, increased from 60% and 73% at baseline to 83% and 84% at week 48. Similarly, the respective values for the atazanavir/saquinavir treatment group increased from 72% and 80% at baseline to 86% and 87% at week 48. In contrast, the percentage of patients in the lopinavir/ritonavir treatment group with desirable total cholesterol and optimal fasting LDL cholesterol decreased from 69% and 81%, respectively, at baseline to 62% and 74%, respectively, at week 48. In multiple regression analyses, no effect of on-study NRTI (e.g., didanosine, stavudine) on lipid concentrations was observed (data not shown).

Lipid-lowering agents (atorvastatin, lovastatin, pravastatin, bezafibrate, fenofibrate, gemfibrozil) were used by comparable proportions of patients in each of the treatment arms at baseline (6%, atazanavir/ritonavir; 7%, atazanavir/saquinavir; 5%, lopinavir/ritonavir). Consistent with the relative effects of the treatment regimens on lipid levels, lipid-lowering therapy was initiated during the study by 3% of patients treated with atazanavir/ritonavir, 5% of patients treated with atazanavir/saquinavir and 14% of patients treated with lopinavir/ritonavir. During the entire course of the study, lipid-lowering therapy was used by 8% of patients treated with atazanavir/ritonavir, 12% of patients treated with atazanavir/saquinavir and 19% of patients treated with lopinavir/ritonavir ($P < 0.05$ versus atazanavir/ritonavir).

Laboratory abnormalities

Grade 3–4 bilirubin elevations (≥ 2.6 × ULN) occurred with greater frequency in patients receiving atazanavir: 49% of patients in the atazanavir/ritonavir group (9%, grade 4), 20% of the patients in the atazanavir/saquinavir group (2%, grade 4), and < 1% of the patients in the lopinavir/ritonavir group. In contrast, grade 3–4 elevations in hepatic transaminases (≥ 5.1 × ULN) occurred infrequently in all treatment groups and at comparable rates (elevated alanine aminotransferase 4% in the atazanavir/ritonavir group, 4% in the atazanavir/saquinavir group, 3% in the lopinavir/ritonavir group; elevated aspartate aminotransferase 3% in the atazanavir/

ritonavir group, 2% in the atazanavir/saquinavir group, 3% in the lopinavir/ritonavir group). These elevations were transient and infrequently clinically significant. Elevated transaminases were more common in patients who entered the study with abnormal values, especially those with a history of hepatitis B or C.

Discussion

The management of HIV-infected patients who have experienced prior virological failure is challenging and often not successful. Overt or achieved resistance to components of the potential new regimen, drug intolerance, inconvenience of remaining treatment options and variable drug pharmacokinetics all contribute to the low rates of antiretroviral suppression observed in patients beyond their initial treatment regimen.

Results from the 48-week trial reported here demonstrate the similar virological and immunological efficacy in treatment-experienced patients of HAART regimens containing atazanavir 300 mg boosted with ritonavir 100 mg once daily and lopinavir 400 mg boosted with ritonavir 100 mg twice daily. The efficacy of atazanavir/ritonavir and lopinavir/ritonavir was seen in the overall treatment population through comparable reductions in HIV RNA levels and increases in CD4 cell counts as well as in patients sensitive or resistant to their randomized PI and in patients with < 4 and ≥ 4 PI mutations at baseline. In contrast, the dual PI combination of atazanavir and saquinavir was less effective than lopinavir/ritonavir as assessed by all these efficacy measures. The reduced efficacy of the atazanavir/saquinavir arm may be related to decreased atazanavir serum levels as a result of a pharmacokinetic interaction with tenofovir [26]. Efficacy of the PI component of each study arm at 2 weeks prior to the addition of tenofovir and a new NRTI support the conclusion that ritonavir-boosted atazanavir and ritonavir-boosted lopinavir have similar intrinsic potency.

All treatments were generally safe and well tolerated and no new or unique safety findings emerged. Serious adverse events were infrequent and comparable across treatment regimens with few discontinuations owing to adverse events. Diarrhea was significantly more frequent in patients receiving ritonavir-boosted lopinavir than in patients receiving ritonavir-boosted atazanavir, prompting significantly greater use of antidiarrheal agents in the lopinavir/ritonavir arm. In contrast, jaundice and scleral icterus were more frequent in patients receiving ritonavir-boosted atazanavir than in patients receiving either atazanavir/saquinavir or ritonavir-boosted lopinavir, but did not result in any treatment discontinuations. Elevated bilirubin, a common side effect of atazanavir treatment, was observed more frequently in both atazanavir arms than in the lopinavir/ritonavir arm and was also most pronounced in patients receiving ritonavir-boosted atazanavir. These results were not surprising as atazanavir exposure would be expected to increase with ritonavir boosting. Bilirubin elevations, however, were not associated with hepatotoxicity in any treatment arm and neither elevated bilirubin nor the associated symptoms of jaundice and scleral icterus resulted in any treatment discontinuation.

One potential challenge to the use of ritonavir as a boosting agent is the correlation between ritonavir and lipid elevations. Although the majority of PI drugs have been linked to the development of some degree of dyslipidemia, the negative impact on lipids appears more severe for ritonavir than for other PI [27,28]. Coadministration of ritonavir at $\leq$ 200 mg with PI that include indinavir, lopinavir and saquinavir has been shown to produce increases in serum lipids [29–33]. In the case of ritonavir-boosted lopinavir, higher lopinavir trough concentrations have also been positively correlated with lipid elevations [30]. The adverse effects of PI drugs and boosted PI regimens on serum lipids are reflected by the rise in the percentage of HIV-infected patients receiving lipid-lowering therapy. A review of California Medicaid claims showed a significant increase in the percentage of patients taking PI drugs who received lipid-lowering drugs over the first 5 years that PI were available, while HIV-infected patients who were not treated with PI showed significantly less use of lipid-lowering agents over the same time period [34].

In this trial, treatment with atazanavir boosted with ritonavir did not result in the deleterious lipid elevations commonly observed with ritonavir or ritonavir-boosted PI. In contrast, the lipid effects of atazanavir boosted with ritonavir were more consistent with the lipid effects observed when atazanavir is administered as the sole PI [21,35] or in combination with saquinavir as part of a HAART regimen [36] (and as seen in the results of the present study). In comparison with lopinavir/ritonavir, atazanavir boosted with ritonavir significantly reduced total cholesterol and fasting triglycerides. In addition, significantly fewer patients on atazanavir/ritonavir required lipid-lowering therapy than patients on lopinavir/ritonavir.

In summary, atazanavir boosted with ritonavir once daily is as effective in treatment-experienced patients as a currently accepted standard of care (lopinavir/ritonavir twice daily). The increased exposure to atazanavir associated with ritonavir boosting was safe and well tolerated, with no unexpected or late-emerging adverse events. Furthermore, atazanavir boosted with ritonavir was not associated with adverse lipid effects observed with ritonavir and other PI, and its use resulted in a reduced need for both concomitant lipid-lowering and antidiarrheal medications. Given the fact that atazanavir boosted with ritonavir is effective when administered once daily, its use may decrease pill burden, promote

adherence and enhance long-term treatment success. Atazanavir boosted with ritonavir once daily is an effective and tolerable option for antiretroviral therapy-experienced patients with HIV infection.

Sponsorship: This study was wholly funded by Bristol-Myers Squibb.

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