Once-Daily Atazanavir/Ritonavir Compared With Twice-Daily Lopinavir/Ritonavir, Each in Combination With Tenofovir and Emtricitabine, for Management of Antiretroviral-Naive HIV-1–Infected Patients: 96-Week Efficacy and Safety Results of the CASTLE Study

Jean-Michel Molina, MD,† Jaime Andrade-Villanueva, MD,‡ Juan Echevarria, MD,§ Ploenchan Chetchotisakd, MD,‖ Jorge Corral, MD,¶ Neal David, FCFP,# Graeme Moyle, MD,** Marco Mancini, BS,†† Lisa Percival, MS,†† Rong Yang, PhD,†† Victoria Wirtz, MS,†† Max Lataillade, DO, MPH,†† Judith Absalon, MD, MPH,†† and Donnie McGrath, MD, MPH†† for the CASTLE Study Team*

Background: Once-daily atazanavir/ritonavir demonstrated similar antiviral efficacy to twice-daily lopinavir/ritonavir over 48 weeks, with less gastrointestinal disturbance and a better lipid profile, in treatment-naive patients.

Methods: International, multicenter, open-label, 96-week non-inferiority randomized trial of atazanavir/ritonavir 300/100 mg once daily vs lopinavir/ritonavir 400/100 mg twice daily, each in combination with fixed-dose tenofovir/emtricitabine 300/200 mg once daily, in antiretroviral-naive, HIV-1–infected patients. The primary end point was the proportion of patients with HIV RNA <50 copies/mL at 48 weeks. Results through 96 weeks are reported.

Results: Of 883 patients enrolled, 440 were randomized to atazanavir/ritonavir and 443 to lopinavir/ritonavir. At week 96, more patients receiving atazanavir/ritonavir achieved HIV RNA <50 copies/mL (74% vs 68%, $P < 0.05$) in the intent-to-treat analysis. On both regimens, 7% of subjects were virologic failures by 96 weeks. Bilirubin-associated disorders were greater in patients taking atazanavir/ritonavir. Treatment-related gastrointestinal adverse events were greater in patients taking lopinavir/ritonavir. Mean changes from baseline in fasting total cholesterol, non–high-density lipoprotein cholesterol, and triglycerides at week 96 were significantly higher with lopinavir/ritonavir ($P < 0.0001$).

Conclusions: Noninferiority of atazanavir/ritonavir to lopinavir/ritonavir was confirmed at 96 weeks. Atazanavir/ritonavir had a better lipid profile and fewer gastrointestinal adverse events than lopinavir/ritonavir.

Key Words: combination antiretroviral therapy, HIV-1, atazanavir/ritonavir, treatment-naive patients, CASTLE study

(*J Acquir Immune Defic Syndr* 2010;53:323–332)

Received for publication March 19, 2009; accepted October 26, 2009.

From the *Department of Infectious Diseases, Hospital Saint-Louis, AP-HP; †University of Paris-Diderot, Paris, France; ‡Unidad de NIH, Hospital Civil De Guadalajara, Guadalajara, Mexico; §Departamento de Enfermedades Infecciosas, Tropicales y Dermatológicas, Hospital Nacional Cayetano Heredia, Lima, Peru; ‖Department of Medicine, Khonkaen University, Khonkaen, Thailand; ¶Hospital Interzonal Gral. De Agudos Oscar Alende, Buenos Aires, Argentina; #Brooklyn Medical Centre, Western Cape, South Africa; **Kobler Clinic, St Stephens Centre, Chelsea and Westminster Hospital, London, UK; and ††Research and Development, Bristol-Myers Squibb, Wallingford, CT.

Members of the CASTLE Study Team are listed in Appendix.

Part of this research was presented as a poster at the 48th Annual Interscience Conference on Antimicrobial Agents and Chemotherapy and the Infectious Diseases Society of America, 46th Annual Meeting, Washington, DC, October 25–28, 2008.

Supported by the Bristol-Myers Squibb.

Conflict of interest: J.-M.M. has received consulting fees and lecture fees from GlaxoSmithKline, Abbott, Gilead, Tibotec, Pfizer, and Bristol-Myers Squibb. J.A.-V. has no conflict of interest to declare. J.E. has received research funding and honoraria from Bristol-Myers Squibb. P.C. has received travel grants from Bristol-Myers Squibb, Merck Sharpe & Dohme, Pfizer, Abbott, and Schering-Plough. J.C. has no conflict of interest to declare. N.D. has no conflict of interest to declare. G.M. has received research grants from Abbott Inc, Anormed Inc, Ardea, Bristol-Myers Squibb, GlaxoSmithKline, Gilead, Merck Inc, Pfizer Inc, Theratechnologies, and Tibotec/Johnson & Johnson. He has also received honoraria from Ardea, Bristol-Myers Squibb, GlaxoSmithKline, Gilead, Merck Inc, Panacos, Pfizer Inc, Theratechnologies, Tibotec/Johnson & Johnson, and Tobira Pharmaceuticals. M.M., L.P., R.Y., V.W., M.L., and D.M. are employees and stockholders of Bristol-Myers Squibb. J.A. was an employee of Bristol-Myers Squibb at the time when the study was conducted.

Correspondence to: Professor Jean-Michel Molina, MD, Department of Infectious Diseases, Hopital Saint-Louis 1, Av. C. Vellefaux, 75475 Paris Cedex 10, France (e-mail: jean-michel.molina@sls.ap-hop-paris.fr).

INTRODUCTION

The reductions in morbidity and mortality associated with combination highly active antiretroviral therapy (HAART) for HIV-1 infection in the developed world[1] indicate that components of these regimens will continue to be used for increasingly longer-term treatment of patients.

Globally, recommendations for the treatment of HAART-naive HIV-infected patients include regimens containing a ritonavir-boosted protease inhibitor (PI) or a nonnucleoside reverse transcriptase inhibitor combined with 2 nucleoside reverse transcriptase inhibitors (NRTIs).[2–5] Established efficacy and high genetic barrier to the emergence of resistance are key factors in the widespread inclusion of PIs in combination HAART regimens,[6] with most international guidelines recommending the use of atazanavir, darunavir, fosamprenavir, lopinavir, or saquinavir as the PIs of choice.[2–5]

Published reports of comparative trials of ritonavir-boosted PIs have demonstrated similar efficacy between agents over 48 weeks in antiretroviral-naive patients infected with HIV-1, including fosamprenavir and lopinavir,[7] darunavir and lopinavir,[8] atazanavir and lopinavir,[9] and saquinavir and lopinavir.[10] Efficacy profile alone is therefore not a key differentiating drug-related factor influencing choice of therapy—tolerability and toxicity are also important considerations that help to differentiate between treatment options.[11–14] In addition to efficacy and safety, factors such as pill burden and dosing frequency, which are known to impact adherence, and in turn treatment outcomes, need to be considered.[11]

The majority of clinical trials of HAART regimens report data from 48 weeks as the primary end point; however, data beyond the first year of therapy are important in differentiating ritonavir-boosted PI-containing HAART regimens with regard to continued efficacy, tolerability, and quality of life. The aim of the 96-week CASTLE study (BMS AI424138) was to examine the long-term comparative clinical efficacy and safety of once-daily atazanavir/ritonavir and twice-daily lopinavir/ritonavir, both given in combination with once-daily, fixed-dose tenofovir and emtricitabine, for the management of HIV-1 infection in antiretroviral treatment-naive patients through 96 weeks of therapy.

METHODS

A detailed description of the study methods has been published and a brief description of the 96-week methodology is provided below.[9]

Participants

Patients were eligible for this study if they were aged 18 years or greater, infected with HIV-1, naive to antiretroviral therapy (less than 1 week of previous antiretroviral exposure, except in the setting of postexposure prophylaxis or prevention of mother-to-child transmission, in which case less than 6 weeks of previous antiretroviral exposure was allowed), and had HIV-1 RNA of 5000 copies/mL or greater. Patients were recruited by 134 centers in 29 countries between November 2005 and June 2006.

This study was performed in accordance with Good Clinical Practice and the ethical principles of the Declaration of Helsinki. The protocol was approved by the institutional review board at each study site, and patients provided written-informed consent before participation in the study.

Procedures

The primary end point of the study was the proportion of patients with HIV RNA <50 copies/mL at week 48, and has previously been reported.[9] Secondary efficacy end points were the proportion of patients with HIV RNA <50 copies/mL at week 96, the proportion of patients with HIV RNA <400 copies/mL at weeks 48 and 96, change in CD4 cell count from baseline through week 96, log reduction in HIV RNA by week 96, and the antiretroviral resistance profiles of patients experiencing virologic failure. Adherence to study regimen to week 96 was also assessed. Safety end points included the incidence of adverse events and serious adverse events, discontinuations due to adverse events, laboratory abnormalities, and changes from baseline in fasting lipids over time. Patients assigned to lopinavir/ritonavir were able to switch from the soft-gel capsule to the tablet formulation after 48 weeks in the event of intolerance to the soft-gel capsule formulation or for subject convenience.

Statistical Analysis

Statistical methods for the week 48 analysis have been previously published.[9] The week 96 analyses used the same methods and are briefly summarized below.

Efficacy results are presented by the as-randomized treatment regimen [intention to treat (ITT)]. Safety results are presented by the as-treated treatment regimen (ie, by the treatment regimen actually received). Two-sided tests of statistical significance at the 0.05 level were used. The proportion of subjects with HIV RNA <50 copies/mL at week 96 was assessed with several algorithms and cohorts of randomized subjects. The 96-week principal analysis was based on the confirmed virologic response (CVR) noncompleter = failure (NC = F; ITT) definition of response. Supportive analyses used the CVR noncompleter = missing (NC = M), time to loss of virologic response (TLOVR: an ITT analysis that defines response as 2 consecutive on-treatment HIV RNA <50 copies/mL achieved and maintained through week 96 without intervening discontinuation and virologic rebound), and virologic response–observed cases (VR-OC) definitions of response.

The treatment regimens were compared using the difference in proportions (atazanavir/ritonavir – lopinavir/ritonavir) and 95% confidence interval (CI) based on a stratified normal approximation. Analyses were stratified by the same strata as randomization—that is, HIV RNA level at enrollment and geographic region. The atazanavir/ritonavir regimen was deemed to be noninferior to the lopinavir/ritonavir regimen if the lower CI for the difference in proportions was greater than −10%. The proportion of subjects with HIV RNA <400 copies/mL at week 96 was assessed analogously to the proportion with HIV RNA <50 copies/mL.

Observed values were used to summarize HIV RNA $\log_{10}$ levels, CD4 cell counts, and their changes from baseline through week 96. Mean CD4 changes from baseline at week 96 were compared between treatment regimens with 95% CIs based on stratified normal approximations using observed values. Descriptive analyses were performed for patients with HIV RNA <50 copies/mL at week 96 with CVR (NC = F) by prespecified baseline subgroups.

Genotypic and phenotypic resistance profiles were determined for patients who met criteria for virologic failure through week 96 as defined by CVR (NC = F) for HIV RNA

of 400 copies/mL or more. Virologic failure was defined as rebound after achieving a confirmed HIV RNA <400 copies/mL without resuppression, discontinuation due to insufficient HIV RNA response before week 96, or failure to achieve a confirmed HIV RNA of <400 copies/mL and on study at week 96.

The proportions of patients adherent to the regimens at week 96 were determined by comparing actual study medications received with those reported on the Multicenter AIDS Cohort Study (MACS) adherence questionnaire for treated patients with evaluable results.[15,16] Patients were considered adherent to regimen only when they were adherent to all drugs in the regimen. Nonadherence to a drug resulted when 1 of the following criteria was met: (1) patient took fewer medications than prescribed in the past 4 days; (2) patient took medication as prescribed in the past 4 days in an atypical pattern; (3) patient took fewer pills per dose than prescribed in the past 4 days; or (4) patient provided partial responses to adherence questions.

Analyses of fasting lipids over time excluded values obtained after the start of serum lipid reduction therapy. Mean percent changes in fasting lipids from baseline were compared between treatment regimens with 95% CIs based on stratified normal approximations.

Role of the Funding Source

The study design and analysis plan were developed by the study sponsor with input from prospective investigators. Decisions regarding the final protocol, data reviews, and publishing were made based on discussion between the sponsor and the study investigators. The corresponding author and the sponsor had full access to the data after official closure of the database, and the corresponding author had final responsibility for submitting the manuscript.

RESULTS

Demographics and Disposition of Patients

The disposition of patients is shown in Figure 1. Of 883 patients included in the efficacy analysis, 440 were randomized to atazanavir/ritonavir and 443 were randomized to lopinavir/ritonavir. Baseline characteristics were similar between the treatment groups and have been published previously.[9] Overall, 39 patients treated with lopinavir/ritonavir switched from the capsule to the tablet formulation between weeks 48 and 96. The mean/median time to tablet switch was 87 weeks. Most subjects who switched were men (N = 31)

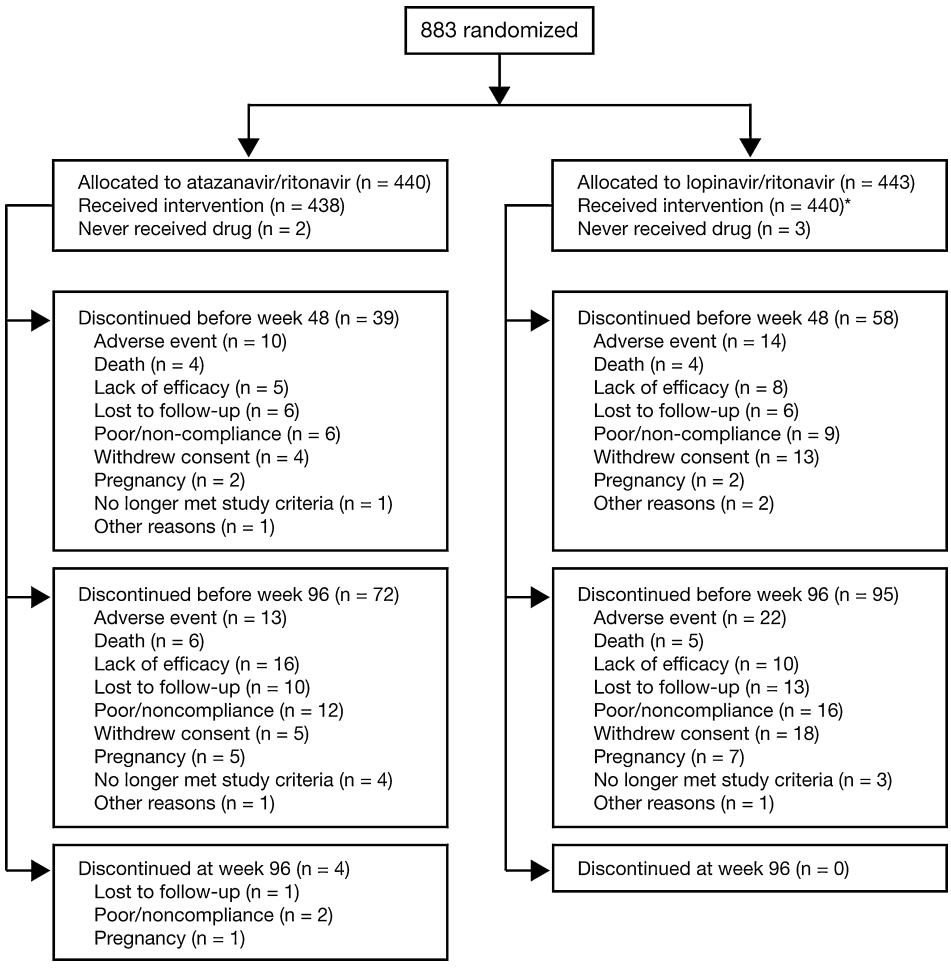

FIGURE 1. Patient disposition. *Three patients erroneously received atazanavir/ritonavir. Lack of efficacy was defined by the investigator and could include reasons such as adverse events and poor adherence, and was not limited only to evidence of increasing HIV RNA. Reasons for withdrawal of consent—atazanavir: nonspecific (2), relocation (2), adverse event (1); lopinavir: nonspecific (9), relocation (3), lopinavir tablet preference (3), adverse event (2), wanted daily regimen (1).

with the majority of subjects being from Asia (N = 14) and South America (N = 16).

Of the 438 patients who received study treatment in the atazanavir/ritonavir group, 72 (16%) discontinued before week 96 compared with 95 (22%) of the 440 patients who received study treatment in the lopinavir/ritonavir group; a greater proportion of these discontinuations in the lopinavir/ritonavir group was due to adverse events and withdrawal of consent (Fig. 1). Three (<1%) patients taking atazanavir/ritonavir discontinued due to jaundice/hyperbilirubinemia compared with none taking lopinavir/ritonavir. None of these discontinuations on atazanavir/ritonavir occurred between weeks 48 and 96. More patients taking lopinavir/ritonavir than atazanavir/ritonavir discontinued due to diarrhea [7 (1.6%) vs 0], with 2 discontinuations occurring between weeks 48 and 96. Renal adverse events led to discontinuation for 1 patient on each regimen, only during the first 48 weeks (Fanconi syndrome with atazanavir/ritonavir, proteinuria with lopinavir/ritonavir).

Efficacy

At week 48, the noninferiority of atazanavir/ritonavir to lopinavir/ritonavir was demonstrated, with similar proportions of patients in each group achieving the primary end point.[9] At week 96, in the ITT analysis CVR (NC = F), 74% of patients in the atazanavir/ritonavir group achieved the end point of HIV RNA <50 copies/mL compared with 68% ($P < 0.05$) of patients in the lopinavir/ritonavir group (Table 1, Fig. 2). The atazanavir/ritonavir regimen met the criterion for noninferiority to the lopinavir/ritonavir-based regimen in this analysis and in the supportive efficacy analyses (CVR NC = M, TLOVR, VR-OC) (Table 1, Fig. 2).

The proportion of patients who achieved HIV RNA <400 copies/mL by the CVR (NC = F) analysis was 80% among patients taking atazanavir/ritonavir and 74% among patients taking lopinavir/ritonavir; the difference estimate was 5.1% (95% CI, –0.4% to 10.6%). Similar findings were observed in the additional analyses.

Responses by qualifying HIV RNA strata were higher for atazanavir/ritonavir than lopinavir/ritonavir for those patients with qualifying HIV RNA of <100 000 copies/mL and those with HIV RNA of 100,000 copies/mL or more (Fig. 3). There was no difference between groups in log reduction in HIV RNA from baseline to week 96 (mean HIV RNA reduction on atazanavir/lopinavir 3.21 $\log_{10}$ copies/mL vs 3.19 $\log_{10}$ copies/mL on lopinavir/ritonavir). Similar mean

TABLE 1. Proportion of Patients With HIV RNA <50 Copies/mL at Week 96

	Responder/Evaluable (%)		Difference Estimate (95% CI)
End point	ATV/RTV, N = 440	LPV/RTV, N = 443	ATV/RTV − LPV/RTV
CVR (NC = F)	327/440 (74)	302/443 (68)	6.1 (0.3, 12.0)
CVR (NC = M)	327/360 (91)	302/340 (89)	1.8 (−2.6, 6.3)
TLOVR	308/440 (70)	281/443 (63)	6.6 (0.4, 12.7)
VR-OC	326/365 (89)	302/345 (88)	1.6 (−3.1, 6.2)

Data are number of responders/number assessable (%) or difference estimate (95% CI). Difference estimates are stratified by qualifying HIV RNA and region.

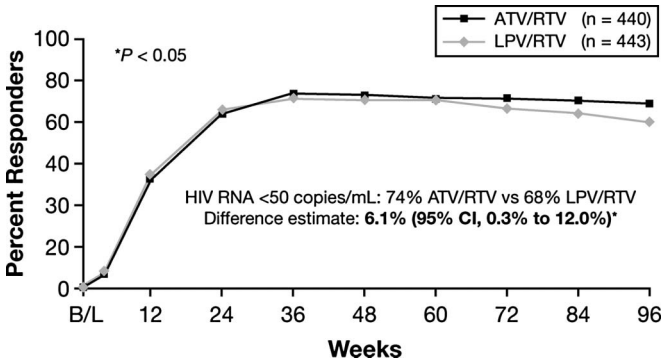

FIGURE 2. Proportion of patients with HIV RNA <50 copies/mL at week 96 (ITT; CVR, NC = F analysis). ATV/RTV, atazanavir/ritonavir; LPV/RTV, lopinavir/ritonavir; B/L, baseline.

increases from baseline to week 96 in CD4 cell count were achieved with both regimens (268 cells/μL in the atazanavir/ritonavir group and 290 cells/μL in the lopinavir/ritonavir group; difference −21.2 cells/μL; 95% CI, –43.3 to 0.9).

Response rates (HIV RNA <50 copies/mL) were consistent on atazanavir/ritonavir across all the baseline CD4 subgroups, and were consistently higher than those achieved with lopinavir/ritonavir across all baseline CD4 subgroups (Fig. 4). In patients with baseline CD4 < 50 cells/μL, 78% responded in the atazanavir/ritonavir group compared with 58% in the lopinavir/ritonavir group (Table 2). Similarly, higher responses were demonstrated in patients with baseline HIV RNA 100,000 copies/mL or more and CD4 < 100 cells/μL randomized to atazanavir/ritonavir (71%) than lopinavir/ritonavir (61%) (Table 2).

Resistance

Virologic failure [using CVR (NC = F)] occurred in similar numbers of patients in each group (Table 3). Overall, 11 patients taking atazanavir/ritonavir and 8 patients taking

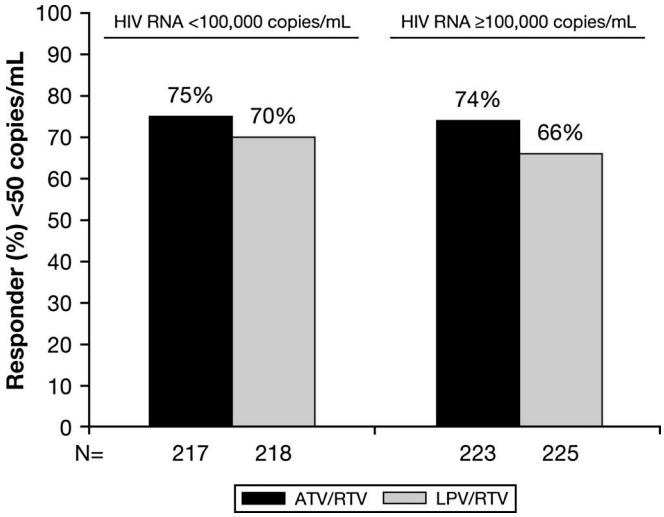

FIGURE 3. Proportion of patients with HIV RNA <50 copies/mL at week 96 (ITT; CVR, NC = F analysis), by qualifying HIV-1 RNA. ATV/RTV, atazanavir/ritonavir; LPV/RTV, lopinavir/ritonavir.

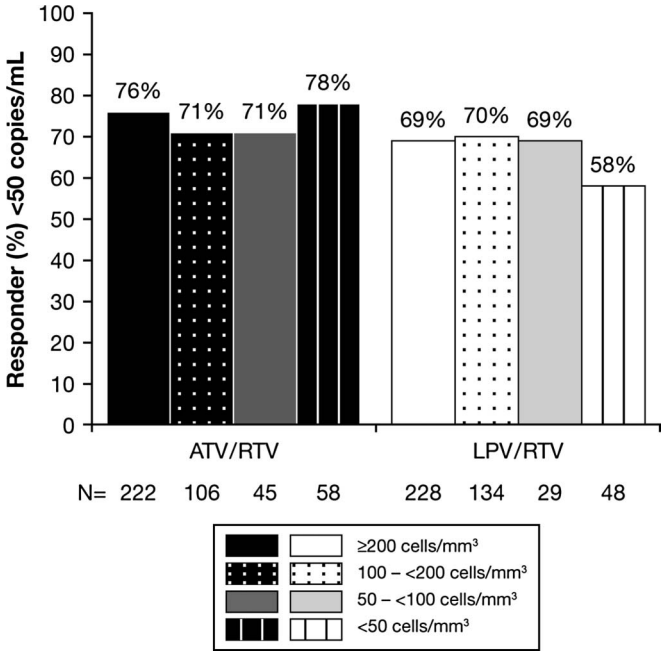

FIGURE 4. Proportion of patients with HIV RNA <50 copies/mL at week 96 (ITT; CVR, NC = F analysis), by baseline CD4 cell count. ATV/RTV, atazanavir/ritonavir; LPV/RTV, lopinavir/ritonavir.

lopinavir/ritonavir who met criteria for virologic failure at week 48 were not virologic failures at week 96.

Among patients with virologic failure at week 48 or week 96 without baseline phenotypic resistance to their on-treatment PI, 3 developed major or minor PI substitutions through week 96. One patient in the atazanavir/ritonavir group had major and minor PI substitutions emerge and ultimately failed at week 67. This patient had baseline T12A/S, I13I/V, M36I, N37D, I62V, L63P, A71A/T, I72V, and I93L, with atazanavir fold-change of 0.78. In addition, 1 patient in the lopinavir/ritonavir group had minor PI substitutions emerge while on study. This patient had multiple major and minor substitutions (L10L/I, V32I, I54I/V, A71I, G73G/S and V82V/A, L89V, and L90M) without phenotypic resistance to lopinavir/ritonavir at baseline (LPV FC 6.09). An additional patient in the atazanavir/ritonavir group reported as a virologic failure at week 48 with an N88S substitution, associated with atazanavir resistance, subsequently achieved an HIV RNA <50 copies/mL at week 96 without a change in study regimen. No patient on either regimen with virologic failure that had a wild-type isolate at baseline developed genotypic or phenotypic resistance to atazanavir/ritonavir or lopinavir/ritonavir.

Adherence

Patients in both the atazanavir/ritonavir and lopinavir/ritonavir treatment arms had similarly low rates of nonadherence (ie, <100% adherent) from week 4 to week 96 of the study. At study visits through week 96, across both treatment arms, 80% to 88% of patients were adherent to their treatment regimen (at week 96, adherence rates were 82% for atazanavir/ritonavir and 84% for lopinavir/ritonavir). For both regimens, the main reason for noncompletion of the MACS questionnaire was discontinuation of study medication [71/439 patients (16%) taking atazanavir/ritonavir and 90/433 patients (21%) taking lopinavir/ritonavir at week 96]. For patients who included reasons for nonadherence at week 96, the most common were "ran out of pills" in the atazanavir/ritonavir treatment group and "simply forgot" in the lopinavir/ritonavir treatment group.

Safety

The safety analysis was conducted on data from 878 treated patients (441 in the atazanavir/ritonavir group and 437 in the lopinavir/ritonavir group; 2 and 3 randomized patients on the atazanavir/ritonavir and lopinavir/ritonavir regimens, respectively, were never treated and 3 patients randomized to lopinavir/ritonavir received atazanavir/ritonavir). There were no unexpected safety events, adverse events were not treatment limiting in most cases, and the majority were mild to moderate in intensity.

There were no additional deaths after 48 weeks of the study. Serious adverse events were reported in 14% and 11% of patients on the atazanavir/ritonavir and lopinavir/ritonavir

TABLE 2. Treatment Outcomes at Week 96 Among Patients With Advanced Disease

	ATV/RTV, N = 440		LPV/RTV, N = 443	
	n (%)		n (%)	
	CD4 < 50 cells/μL, n = 58	CD4 < 100 cells/μL and HIV RNA ≥100,000 copies/mL, n = 83	CD4 < 50 cells/μL, n = 48	CD4 < 100 cells/μL and HIV RNA ≥100,000 copies/mL, n = 64
Virologic response CVR (NC = F)	45 (78)	59 (71)	28 (58)	39 (61)
Virologic failure	4 (7)	11 (13)	4 (8)	10 (16)
Discontinued	9 (16)	13 (16)	16 (33)	15 (23)
Adverse events	1 (2)	1 (1)	6 (13)	5 (8)
Death	2 (3)	3 (4)	2 (4)	1 (2)
Withdrew consent	1 (2)	1 (1)	3 (6)	4 (6)
Nonadherent	1 (2)	3 (4)	3 (6)	3 (5)
Other*	4 (7)	5 (6)	2 (4)	2 (3)

*Other includes pregnancy, no longer meets study criteria, lost to follow-up.
ATV/RTV, atazanavir/ritonavir; LPV/RTV, lopinavir/ritonavir.

TABLE 3. Treatment-Emergent Resistance Through Week 96 in Isolates from Patients With Virologic Failure

		ATV/RTV, N = 438*	LPV/RTV, N = 443
Virologic failure (HIV RNA ≥400 copies/mL)*		28 (6%)	29 (7%)
Paired genotypes		26	26
Major PI substitution†		1‡	0
Minor PI substitution†		1‡	1§
PI polymorphisms† (without major or minor PI substitutions)		11	14
Wild type†		14	11
M184I/V		5	7
K65R		1	0
TAMs (M41L, D67N, K70R, L210W, T215FY, K219EQ)		1	3
Paired phenotypes		25	23
PI phenotypic resistance	ATV/RTV FC >5.2	1	0
	LPV/RTV FC >9	0	1
	Other boosted PIs	2	4
RTI phenotypic resistance	FTC FC >3.5 or 3TC FC >3.5	5	5
	TDF FC >1.4	0	2
	Other NRTIs	3	5

*As-randomized subjects without baseline phenotypic resistance to on-treatment PI.
†IAS-USA PI mutations classified as major (D30N, V32I, M46IL, I47AV, G48V, I50LV, I54ALMSTV, L76V, V82AFLST, I84V, N88DS, L90M) or minor (L10FIRV, V11I, L24I, L33F, E35G, K43T, F53LY, Q58E, A71ITV, G73ACST, T74P, N83D, L89V) according to the Stanford HIV Database.
‡Single subject with both major and minor substitutions: L10F, V32I, K43T, M46I, A71I, G73S, L90M; 1 additional subject in ATV/RTV arm with emergent major PI substitutions at week 48 not listed at week 96 due to subsequent virologic resuppression without a change in regimen.
§Baseline PI substitutions: V32I, I54IV, V82VA, L90M, L10LI, A71I, G73GS, L89V (LPV FC 6.09); additional minor PI substitutions at virologic failure: L10V, V11I (LPV FC 69).
FC, fold change; FTC, emtricitabine; IAS, International AIDS Society; PI, protease inhibitor; TAMs, thymidine analogue mutations; TDF, tenofovir disoproxil fumarate; ATV/RTV, atazanavir/ritonavir; LPV/RTV, lopinavir/ritonavir.

TABLE 4. Grades 2–4 Adverse Events Through Week 96

	ATV/RTV (N = 441), n (%)	LPV/RTV (N = 437), n (%)
Grades 2–4 adverse events in ≥2% of patients		
All adverse events	283 (64)	282 (65)
Bronchitis	17 (4)	15 (3)
Nasopharyngitis	15 (3)	19 (4)
Herpes zoster	13 (3)	15 (3)
Upper respiratory tract infection	13 (3)	21 (5)
Influenza	10 (2)	15 (3)
Gastroenteritis	9 (2)	5 (1)
Pharyngitis	9 (2)	5 (1)
Tonsillitis	9 (2)	4 (<1)
Urinary tract infection	9 (2)	11 (3)
Sinusitis	7 (2)	9 (2)
Pneumonia	3 (<1)	10 (2)
Diarrhea	30 (7)	73 (17)
Nausea	23 (5)	37 (8)
Vomiting	15 (3)	18 (4)
Abdominal pain	11 (2)	12 (3)
Hyperbilirubinemia	33 (7)	2 (<1)
Jaundice	18 (4)	0
Headache	28 (6)	22 (5)
Back pain	16 (4)	5 (1)
Rash	13 (3)	8 (2)
Depression	12 (3)	7 (2)
Pyrexia	9 (2)	13 (3)
Grades 2–4 treatment-related adverse events		
Overall (through week 96)	133 (30)	140 (32)
That occurred in ≥2% of patients		
Hyperbilirubinemia	33 (7)	1 (<1)
Jaundice	18 (4)	0 (0)
Nausea	18 (4)	33 (8)
Diarrhea	11 (2)	54 (12)*
Headache	6 (1)	9 (2)
Rash	10 (2)	4 (<1)

*The rate of Grades 2–4 treatment-related diarrhea after switch was 0% in patients (n = 39) who switched to the lopinavir/ritonavir tablet formulation between weeks 48 and 96. Diarrhea (all grades) after switch was reported in 1/39 (3%) patients.
ATV/RTV, atazanavir/ritonavir; LPV/RTV, lopinavir/ritonavir.

regimens, respectively, with an individual incidence of <1% in either regimen. Few were considered to be related to the study drugs.

The overall incidence of Grades 2–4 treatment–related adverse events was 30% and 32% in those patients on the atazanavir/ritonavir and lopinavir/ritonavir regimens, respectively (Table 4). Most of these were reported by 2% of patients or less on either regimen, and few were considered by the investigators to be related to the study drug (Table 4). More patients in the lopinavir/ritonavir treatment arm experienced gastrointestinal adverse events compared with the atazanavir/ritonavir arm. In addition, a larger proportion of subjects taking lopinavir/ritonavir (24%) compared with atazanavir/ritonavir (12%) required the use of antidiarrheal agents. Hepatobiliary adverse events were experienced by more patients in the atazanavir/ritonavir group than the lopinavir/ritonavir group. Three patients discontinued due to jaundice/hyperbilirubinemia through week 48 with no additional discontinuations due to hyperbilirubinemia occurring between weeks 48 and 96. Among patients who switched to the lopinavir/ritonavir tablet formulation (n = 39), the incidence of Grades 2–4 treatment–related adverse events after switch was 8%. There were no Grades 2–4 treatment–related adverse events of diarrhea after switch; diarrhea (all grades) was reported in 1/39 patients (3%) after switch.

The incidences of selected Grades 3–4 laboratory abnormalities are shown in Table 5. Elevations in total bilirubin were predictably higher in patients taking atazanavir/ritonavir than lopinavir/ritonavir (44% vs <1%). Grades 3–4 increases in alanine aminotransferase concentration were reported in 3% and 2% of patients taking atazanavir/ritonavir and lopinavir/ritonavir, respectively; Grades 3–4 elevations of aspartate aminotransferase were reported in 3% and 1% of patients taking atazanavir/ritonavir and lopinavir/ritonavir, respectively. Grades 3–4 elevations in serum creatinine were <1% in both regimens. Mean change from baseline to week 96 in serum creatinine was 0.04 mg/dL or less in both regimens, and substitution of tenofovir/emtricitabine for decline in

TABLE 5. Selected Grades 3–4 Laboratory Abnormalities Through Week 96

	ATV/RTV (N = 441), n (%)	LPV/RTV (N = 437), n (%)
Total bilirubin elevation (>2.5 × ULN)	192/435 (44)	3/431 (<1)
ALT elevation (>5 × ULN)	11/435 (3)	7/431 (2)
AST elevation (>5 × ULN)	11/435 (3)	5/430 (1)
Total cholesterol (≥240 mg/dL)	47/434 (11)	108/428 (25)
Triglycerides (≥751 mg/dL)	3/434 (<1)	18/428 (4)
Hyperglycemia (≥251 mg/dL)	3/434 (<1)	2/428 (<1)
Creatinine (3.1–6 × ULN)	1/435 (<1)	2/431 (<1)

ALT, alanine aminotransferase; AST, aspartate aminotransferase; ATV/RTV, atazanavir/ritonavir; LPV/RTV, lopinavir/ritonavir; ULN, upper limit of normal.

renal function was <1% overall. The median calculated creatinine clearance percent change from baseline was −1% in patients in the atazanavir/ritonavir arm and −2% in the lopinavir/ritonavir arm. At week 96, the proportion of patients with >50% reduction from baseline in creatinine clearance was 0% in the atazanavir/ritonavir arm and <1% in the lopinavir/ritonavir arm.

Mean percent changes in lipids from baseline at week 96 were significantly higher ($P < 0.0001$) in patients taking lopinavir/ritonavir than atazanavir/ritonavir for fasting total cholesterol, non–high-density lipoprotein (HDL) cholesterol, and triglycerides (Fig. 5). Mean percent changes in low-density lipoprotein (LDL) cholesterol were similar between the 2 treatment groups. In addition, more patients on the atazanavir/ritonavir regimen than the lopinavir/ritonavir regimen had optimal lipids at week 96 as defined by the National Cholesterol Education Program Adult Treatment Panel III for total cholesterol, non-HDL cholesterol, LDL cholesterol, triglycerides, and total cholesterol:HDL cholesterol ratio.[17] Shifts up of 1 category or more in NCEP for total cholesterol occurred in 16% of patients taking atazanavir compared with 29% taking lopinavir/ritonavir; 32% vs 40%, respectively, for LDL cholesterol; and 23% vs 49%, respectively, for triglycerides. A total cholesterol:HDL cholesterol ratio >5 was recorded in 17% of patients in the atazanavir/ritonavir group at week 96 compared with 23% at baseline, and in 27% of patients in the lopinavir/ritonavir group (also 27% at baseline). Fewer patients taking atazanavir/ritonavir (2%) than lopinavir/ritonavir (9%) initiated lipid-reduction therapy after start of study therapy.

DISCUSSION

The 96-week data from this noninferiority study confirm the similar virologic efficacy of once-daily ritonavir-boosted atazanavir to twice-daily ritonavir-boosted lopinavir, both in combination with tenofovir/emtricitabine, for the treatment of antiretroviral-naive HIV-1 adults that was previously established at week 48.[9] The difference in response between the regimens in the ITT analysis in favor of the atazanavir/ritonavir-based regimen at 96 weeks was driven by a similar virologic response rate with a higher rate of discontinuations among patients taking lopinavir/ritonavir. This was based on a combination of adverse events and withdrawal of consent, both of which were higher among the patients in the lopinavir/ritonavir group compared with those in the atazanavir/ritonavir group. Both atazanavir/ritonavir and lopinavir/ritonavir, in combination with tenofovir/emtricitabine, had similarly high rates of adherence in this trial, as measured by the MACS survey (>80%) throughout this study, and thus adherence differences cannot explain the differences in response between the 2 groups.

The CASTLE study is the first comparative study to confirm the durability of the once-daily atazanavir/ritonavir regimen in treatment-naive patients through 96 weeks, with noninferiority to, and higher response rates than, twice-daily lopinavir/ritonavir.

Response rates in this 96-week study were consistent with those seen in other studies of atazanavir/ritonavir[18] and lopinavir/ritonavir[7,8,19,20] in treatment-naive patients, after taking differences in study designs and populations into

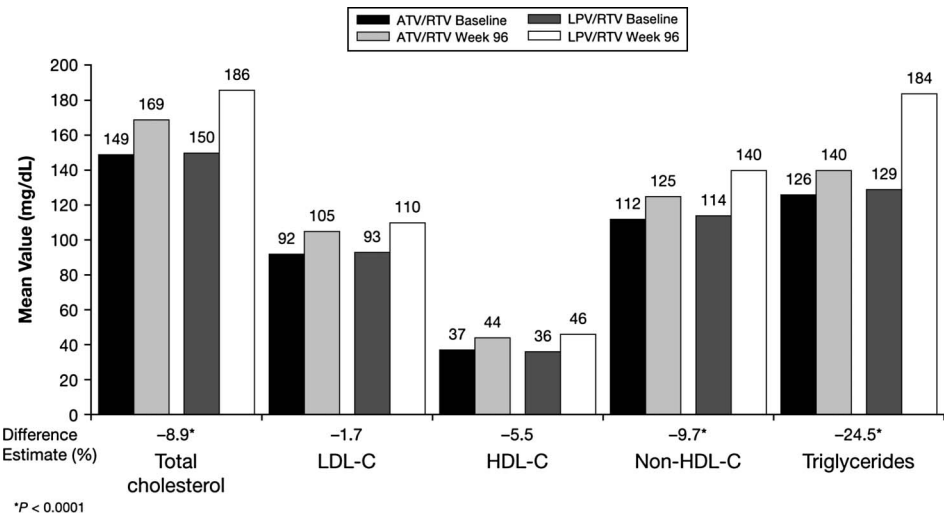

FIGURE 5. Mean fasting lipids at baseline and week 96. ATV/RTV, atazanavir/ritonavir; LPV/RTV, lopinavir/ritonavir; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol.

consideration. Similarly, the efficacy results are consistent with those reported for other long-term studies of PIs.[21–24] Both the atazanavir/ritonavir and lopinavir/ritonavir regimens resulted in similar increases in CD4 cell counts over 96 weeks. Response rates of HIV RNA <50 copies/mL were achieved at consistent levels across all baseline CD4 cell counts in both treatment groups, with results that were higher in the atazanavir/ritonavir group than the lopinavir/ritonavir group due to a higher rate of discontinuations among patients taking lopinavir/ritonavir. In addition, both regimens were effective in patients with high baseline HIV RNA; response rates were somewhat lower in patients with higher baseline HIV RNA in both treatment groups. More patients with advanced disease (CD4 <50 cells/μL and HIV RNA 100,000 copies/mL or more) responded among those treated with atazanavir/ritonavir than with lopinavir/ritonavir. A poorer response to lopinavir/ritonavir in patients with more advanced disease compared with those with lower HIV RNA and CD4 cell counts has also been reported in other studies.[8,25,26]

As expected, there was a low rate of virologic failure during treatment with these boosted PI regimens. These findings are consistent with data from other studies.[7,8,20] The rates of development of resistance to PIs over the course of the study were low, with only a single patient in each treatment group with virologic failure at 96 weeks developing phenotypic resistance to a study PI. The emergence of NRTI substitutions was also low, with 5 patients in each treatment group developing phenotypic resistance to emtricitabine and 2 patients on lopinavir/ritonavir with phenotypic resistance to tenofovir disoproxil fumarate.

The main difference between the regimens in this study was related to their safety and tolerability. Adverse events and toxicity are the most common causes of treatment failure, and among the PIs gastrointestinal tolerability is an established risk for this outcome.[27] In this study, more patients in the lopinavir/ritonavir group than the atazanavir/ritonavir group withdrew consent, and more discontinued treatment due to adverse events. Furthermore, the patients in the lopinavir/ritonavir group experienced a higher rate of gastrointestinal intolerability than those in the atazanavir/ritonavir group. Of note, no patients in the atazanavir/ritonavir arm discontinued treatment due to diarrhea, and a greater proportion of patients given lopinavir/ritonavir who remained in the study required antidiarrheal medication compared with those given atazanavir/ritonavir. Although patients treated with atazanavir/ritonavir had a higher rate of bilirubin abnormalities, only few (3) patients discontinued treatment as a result, none of them between weeks 48 and 96.

As expected, lopinavir/ritonavir resulted in higher increases in lipids compared with atazanavir/ritonavir. Drug-related dyslipidemia is associated with increased cardiovascular risk in patients on PI-containing regimens.[6,28–30] Some PIs are known to increase total cholesterol and LDL cholesterol levels,[31] with a dose–response effect from ritonavir, although as seen in this study, the lipid profile changes are not consistent among different PIs. Although the ritonavir daily dose in the lopinavir/ritonavir arm was twice as high as in the atazanavir/ritonavir arm, total exposure to ritonavir was comparable between the treatment arms [geometric mean ratio for area under the concentration curve over 24 hours (AUC_{0-24}) was 0.84; 90% CI, 0.61–1.15].[32] The similarity in AUC_{0-24} for ritonavir with both treatment regimens suggests that the higher rates of metabolic and gastrointestinal abnormalities observed in the twice-daily lopinavir/ritonavir arm compared with the atazanavir/ritonavir arm must be in part related to the lopinavir component of the fixed-dose lopinavir/ritonavir regimen.

No new or unexpected safety concerns emerged between 48 and 96 weeks, and the gastrointestinal and lipid safety profiles of atazanavir/ritonavir remained more favorable than those of lopinavir/ritonavir at 96 weeks. Events leading to study drug discontinuation in both regimens were consistent with the known side-effect profiles of the study drugs and comparison/backbone treatments.

The open-label design of this study is a limitation. In addition, patients in the lopinavir/ritonavir treatment group were only allowed to switch from the capsule to the tablet formulation after 48 weeks. Although this allowed for a direct comparison between atazanavir/ritonavir and a single formulation of lopinavir/ritonavir for the first 48 weeks of the study, the lack of comparative data against the newer tablet formulation of lopinavir/ritonavir throughout the study may be relevant, particularly as the capsule formulation is no longer available. However, several factors argue against the significance of any possible effects of the lopinavir/ritonavir formulation: first, only 3 patients discontinued treatment before week 48 because of a preference for the lopinavir/ritonavir tablet, and second, the 2 formulations have been shown to have similar safety and tolerability profiles.[19] Finally, the similarly high adherence rates for both the atazanavir/ritonavir and lopinavir/ritonavir regimens before and after week 48 also suggest that pill burden and tolerability were not limiting factors in these treatment-naive patients. It is unlikely, therefore, that study outcomes were affected as a result of the limited availability of the lopinavir/ritonavir tablet formulation.

The results of this long-term comparative study reinforce the use of once-daily atazanavir/ritonavir as a recommended first-line treatment option for HIV-1 infection. Atazanavir/ritonavir is noninferior to ritonavir-boosted twice-daily lopinavir, but with a more favorable overall safety profile, and, importantly, a better lipid profile than lopinavir/ritonavir in treatment-naive patients. This regimen is therefore an appropriate therapeutic option for antiretroviral-naive HIV-1–infected patients, and is highly effective in patients with advanced disease, as measured by baseline low CD4 and high HIV RNA levels.

ACKNOWLEDGMENTS

We thank the investigators, study coordinators, site and data managers, and patients for their contributions. We also thank the Bristol-Myers Squibb team members: A. Rightmire, C. Day, M. Ricciuti, M. Mathew, R. Bertz, M. Child, C. Tasker, A. Gadoury, P. Mrowiec, M. DeGrosky, and A. Gopinathan. Editorial support was provided by Cheryl Jenkins and Jean Turner at PAREXEL and was funded by Bristol-Myers Squibb.

J.-M.M., J.A.-V., J.E., P.C., J.C., N.D., G.M., M.M., L.P., R.Y., V.W., M.L., D.M.G., and J.A. all provided scientific input

into the study design and study protocol. J.A. assisted in writing the first draft of the manuscript. All authors assessed clinical data from the study and reviewed and edited the manuscript. All investigators were involved in enrollment of patients. R.Y. did all statistical analyses.

REFERENCES

1. Crum NF, Riffenburgh RH, Wegner S, et al. Comparisons of causes of death and mortality rates among HIV-infected persons: analysis of the pre-, early, and late HAART (highly active antiretroviral therapy) eras. *J Acquir Immune Defic Syndr*. 2006;41:194–200.
2. Department of Health and Human Services. Panel on Antiretroviral Guidelines for Adults and Adolescents. *Guidelines for the use of Antiretroviral Agents in HIV-1–Infected Adults and Adolescents*. 2008. Available at: http://aidsinfo.nih.gov/contentfiles/AdultandAdolescentGL.pdf. Accessed February 23, 2009.
3. Gazzard B, Bernard AJ, Boffito M, et al. British HIV Association (BHIVA) guidelines for the treatment of HIV-infected adults with antiretroviral therapy (2006). *HIV Med*. 2006;7:487–503.
4. Hammer SM, Saag MS, Schechter M, et al. Treatment for adult HIV infection: 2006 recommendations of the International AIDS Society-USA panel. *JAMA*. 2006;296:827–843.
5. EACS Guidelines. The European AIDS Clinical Society. Available at: www.eacs.eu/guide/index.htm. Accessed April 23, 2008.
6. Walmsley S. Protease inhibitor-based regimens for HIV therapy: safety and efficacy. *J Acquir Immune Defic Syndr*. 2007;45(Suppl 1):S5-S13.
7. Eron J Jr, Yeni P, Gathe J Jr, et al. The KLEAN study of fosamprenavir-ritonavir versus lopinavir-ritonavir, each in combination with abacavir-lamivudine, for initial treatment of HIV infection over 48 weeks: a randomised non-inferiority trial. *Lancet*. 2006;368:476–482.
8. Ortiz R, DeJesus E, Khanlou H, et al. Efficacy and safety of once-daily darunavir/ritonavir versus lopinavir/ritonavir in treatment-naive HIV-1-infected patients at week 48. *AIDS*. 2008;22:1389–1397.
9. Molina JM, Andrade-Villanueva J, Echevarria J, et al. Once-daily atazanavir/ritonavir versus twice-daily lopinavir/ritonavir, each in combination with tenofovir and emtricitabine, for management of antiretroviral-naive HIV-1-infected patients: 48 week efficacy and safety results of the CASTLE study. *Lancet*. 2008;372:646–655.
10. Walmsley S, Avihingsanon A, Slim J, et al. Gemini: a noninferiority study of saquinavir/ritonavir versus lopinavir/ritonavir as initial HIV-1 therapy in adults. *J Acquir Immune Defic Syndr*. 2009;50:367–374.
11. Conway B. The role of adherence to antiretroviral therapy in the management of HIV infection. *J Acquir Immune Defic Syndr*. 2007; 45(Suppl 1):S14-S18.
12. Molina JM, Journot V, Morand-Joubert L, et al. Simplification therapy with once-daily emtricitabine, didanosine, and efavirenz in HIV-1-infected adults with viral suppression receiving a protease inhibitor-based regimen: a randomized trial. *J Infect Dis*. 2005;191:830–839.
13. Molina JM, Journot V, Furco A, et al. Five-year follow up of once-daily therapy with emtricitabine, didanosine and efavirenz (Montana ANRS 091 trial). *Antivir Ther*. 2007;12:417–422.
14. Waters L, Nelson M. Why do patients fail HIV therapy? *Int J Clin Pract*. 2007;61:983–990.
15. Kleeberger CA, Phair JP, Strathdee SA, et al. Determinants of heterogeneous adherence to HIV-antiretroviral therapies in the Multicenter AIDS Cohort Study. *J Acquir Immune Defic Syndr*. 2001;26:82–92.
16. Chesney MA, Ickovics JR, Chambers DB, et al. Self-reported adherence to antiretroviral medications among participants in HIV clinical trials: the AACTG adherence instruments. Patient Care Committee & Adherence Working Group of the Outcomes Committee of the Adult AIDS Clinical Trials Group (AACTG). *AIDS Care*. 2000;12:255–266.
17. National Cholesterol Education Program, National Heart, Lung, and Blood Institute, National Institutes of Health. 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). September, 2002. National Institutes of Health (NIH), Publication No. 02–5215.
18. Malan DR, Krantz E, David N, et al. Efficacy and safety of atazanavir, with or without ritonavir, as part of once-daily highly active antiretroviral therapy regimens in antiretroviral-naive patients. *J Acquir Immune Defic Syndr*. 2008;47:161–167.
19. Gathe J, da Silva B, Loutfy M. Study M05–730 primary efficacy results at week 48: phase 3, randomized, open-label study of lopinavir/ritonavir tablets once daily vs twice daily, co-administered with tenofovir and emtricitabine in ARV-naive HIV-1-infected subjects. Presented at: 15th Conference on Retrovirus and Opportunistic Infections (CROI); February 3–6, 2008; Boston, MA.
20. Smith K, Fine D, Patel P. Efficacy and safety of abacavir/lamivudine combined to tenofovir/emtricitabine in combination with once-daily lopinavir/ritonavir through 48 weeks in the HEAT study. Presented at: 15th Conference on Retrovirus and Opportunistic Infections (CROI); February 3–6, 2008; Boston, MA.
21. Ananworanich J, Gayet-Ageron A, Ruxrungtham K, et al. Long-term efficacy and safety of first-line therapy with once-daily saquinavir/ritonavir. *Antivir Ther*. 2008;13:375–380.
22. Gathe JC Jr, Wood R, Sanne I, et al. Long-term (120-week) antiviral efficacy and tolerability of fosamprenavir/ritonavir once daily in therapy-naive patients with HIV-1 infection: an uncontrolled, open-label, single-arm follow-on study. *Clin Ther*. 2006;28:745–754.
23. Mills A, Nelson M, Jayaweera D, et al. ARTEMIS: efficacy and safety of darunavir/ritonavir (DRV/r) 800/100 mg once-daily vs lopinavir/ritonavir (LPV/r) in treatment-naive, HIV-1-infected patients at 96 wks. Presented at: 48th Interscience Conference on Antimicrobial Agents and Chemotherapy (ICAAC 2008); October 25–28, 2008; Washington, DC. Abstract H-1250c.
24. Murphy RL, da Silva BA, Hicks CB, et al. Seven-year efficacy of a lopinavir/ritonavir-based regimen in antiretroviral-naive HIV-1-infected patients. *HIV Clin Trials*. 2008;9:1–10.
25. Riddler SA, Haubrich R, DiRienzo AG, et al. Class-sparing regimens for initial treatment of HIV-1 infection. *N Engl J Med*. 2008;358:2095–2106.
26. Sierra Madero J, Villasis A, Medez P, et al. A prospective, randomized, open label trial of efavirenz versus lopinavir/ritonavir based HAART among antiretroviral therapy naïve, HIV infected individuals presenting for care with CD4 cell counts $<200/mm^3$ in Mexico. Presented at: XVII International AIDS Conference; August 2–8, 2008; Mexico City. Abstract TUAB0104.
27. Carr A, Amin J. Reasons for treatment success with initial ART: an analysis of 2,635 participants in 64 randomized, controlled trials and 14 prospective cohorts. Presented at: 15th Conference on Retrovirus and Opportunistic Infections (CROI); February 3–6, 2008; Boston, MA. Abstract 782.
28. Friis-Moller N, Sabin CA, Weber R, et al. Combination antiretroviral therapy and the risk of myocardial infarction. *N Engl J Med*. 2003;349: 1993–2003.
29. Friis-Moller N, Reiss P, Sabin CA, et al. Class of antiretroviral drugs and the risk of myocardial infarction. *N Engl J Med*. 2007;356:1723–1735.
30. Law MG, Friis-Moller N, El Sadr WM, et al. The use of the Framingham equation to predict myocardial infarctions in HIV-infected patients: comparison with observed events in the D:A:D Study. *HIV Med*. 2006;7:218–230.
31. Fontas E, van Leth F, Sabin CA, et al. Lipid profiles in HIV-infected patients receiving combination antiretroviral therapy: are different antiretroviral drugs associated with different lipid profiles? *J Infect Dis*. 2004;189:1056–1074.
32. Zhu L, Liao S, Child M, et al. CASTLE Study: pharmacokinetics and inhibitory quotient of atazanavir/ritonavir 300/100 mg once daily compared to lopinavir/ritonavir 400/100 mg twice daily, each in combination with fixed dose tenofovir-emtricitabine once daily, are supportive of 48 week efficacy and safety in HIV-1 infected, treatment-naïve subjects. Presented at: 9th International Workshop on Clinical Pharmacology of HIV Therapy; April 7–9, 2008; New Orleans, LA.

APPENDIX

CASTLE Study Team

Argentina—J. Benetucci, A. Casiro, I. Cassetti, J. Corral, J. Galindez, N. Luna, S. Lupo, E. Pallone, C. Rodriguez. *Australia*—D. Baker, N. Roth, C. Workman. *Austria*—N. Vetter. *Belgium*—J. Pelgrom. *Brazil*— J.L. Andrade,

M. Da Eira, B. Grinsztejn, R. De Jesus Pedro, F. Rangel, R. Zajdenverg. *Canada*—J.-G. Baril, F. Crouzat, R. LeBlanc, C. Tremblay. *Chile*—L. Bavestrello Fernandez, P. Gaete Gutierrez, L. Noriega, C. Perez. *Columbia*—O. Sussmann. *Costa Rica*—G. Herrera. *Dominican Republic*— E. Koenig. *France*—J.-F. Bergmann, P. Dellamonica, C. Katlama, J.-M. Molina, D. Vittecoq, L. Weiss. *Germany*—K. Arasteh, G. Faetkenheuer, J. Rockstroh, A. Stoehr. *Guatemala*—E. Arathoon, J.-F. Garcia, C. Mejia-Villatoro. *Hong Kong*—P. Li. *Indonesia*—S. Djauzi. *Italy*— A. Antinori, A. Lazzarin, A. D'Arminio Monforte, G. Penco, V. Vullo. *Mexico*—M. Magana Aquino, G. Amaya, J. Andrade-Villanueva, D. Jorge, J. Sierra, J. Carlos Tinoco, I. Zavala. *Netherlands*—I.M. Hoepelman, S. Van Der Geest. *Panama*—C. Alfredo, N. Sosa. *Peru*—R. Cabello, J. Echevarria, A. La Rosa, R. Salazar. *Portugal*—F. Antunes. *Puerto Rico*—S. Saavedra, G. Sepulveda. *Singapore*—L. Lin. *Spain*—J. Arribas, B. Clotet, J. Gatell, P. Miralles, F. Pulido Ortega, A. Rivero, I. Santos Gil, J. Santos Gonzalez. *South Africa*—N. David, C. Firnhaber, D. Johnson, E. Krantz, G. Latiff, D. Malan, D. Martin, J. Pitt, M. Zeier. *Thailand*—P. Chetchotisakd, K. Supparatpinyo. *Taiwan*—S.-M. Hsieh, Y.-C. Liu, W.W. Wong. *UK*—J. Ainsworth, M. Johnson, G. Moyle, G. Scullard, I. Williams. *USA*—D. Brand, F. Cruickshank, E. DeJesus, C. McDonald, R. Myers, S. Reddy, M. Sension, D. Ward.