



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

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Summary

Lancet 2008; 372: 646–55

Published Online

August 2, 2008

DOI:10.1016/S0140-

6736(08)61081-8

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Background Atazanavir/ritonavir is as effective as lopinavir/ritonavir, with a more favourable lipid profile and less gastrointestinal toxicity, in treatment-experienced HIV-1-infected patients. We compared these two combinations directly in treatment-naive patients.

Methods In this open-label, international non-inferiority study, 883 antiretroviral-naive, HIV-1-infected patients were randomly assigned to receive atazanavir/ritonavir 300/100 mg once daily (n=440) or lopinavir/ritonavir 400/100 mg twice daily (n=443), in combination with fixed-dose tenofovir/emtricitabine 300/200 mg once daily. Randomisation was done with a computer-generated centralised randomisation schedule and was stratified by baseline levels of HIV RNA (viral load) and geographic region. The primary endpoint was the proportion of patients with viral load less than 50 copies per mL at week 48. The main efficacy analysis was done by intention to treat. This trial is registered with ClinicalTrials.gov, number NCT00272779.

Findings At week 48, 343 (78%) of 440 patients receiving atazanavir/ritonavir and 338 (76%) of 443 patients receiving lopinavir/ritonavir had achieved a viral load of less than 50 copies per mL (difference 1.7%, 95% CI -3.8 to 7.1). Mean increases from baseline in CD4 cell count were similar (203 cells per μ L in the atazanavir/ritonavir group vs 219 cells per μ L in the lopinavir/ritonavir group). 25 (6%) patients in the atazanavir/ritonavir group and 26 (6%) in the lopinavir/ritonavir group were virological failures by week 48. Only two patients, both in the atazanavir/ritonavir group, had non-polymorphic protease inhibitor resistance mutations emerge on treatment, which conferred phenotypic resistance to atazanavir in one patient. Serious adverse events were noted in 51 (12%) of 441 patients in the atazanavir/ritonavir group and in 42 (10%) of 437 patients in the lopinavir/ritonavir group. Fewer patients in the atazanavir/ritonavir group than in the lopinavir/ritonavir group experienced grade 2–4 treatment-related diarrhoea (10 [2%] vs 50 [11%]) and nausea (17 [4%] vs 33 [8%]). Grade 2–4 jaundice was seen in 16 (4%) of 441 patients in the atazanavir/ritonavir group versus none of 437 patients in the lopinavir/ritonavir group; grade 3–4 increases in total bilirubin were seen in 146 (34%) of 435 patients on atazanavir/ritonavir and in one (<1%) of 431 patients on lopinavir/ritonavir.

Interpretation In treatment-naive patients, atazanavir/ritonavir once-daily demonstrated similar antiviral efficacy to lopinavir/ritonavir twice-daily, with less gastrointestinal toxicity but with a higher rate of hyperbilirubinaemia.

Funding Bristol-Myers Squibb.

Introduction

Since the introduction of combination highly active antiretroviral therapy (HAART), there have been dramatic reductions in HIV-1-related morbidity and mortality in the developed world.^{1,2} While antiretroviral treatment strategies for HIV-infected patients continue to evolve, protease inhibitors (PIs) remain a cornerstone of HAART because of their recognised potency and high genetic barrier to antiretroviral resistance.³

Most current international guidelines recommend ritonavir-boosted PIs, including fixed-dose lopinavir/ritonavir and atazanavir, as preferred, or alternative third-agent HIV medications for the initiation of

HAART in antiretroviral-naive patients.^{4–6} The choice of drugs is governed by consideration of efficacy and assessment of differences among treatment options in terms of dosing convenience, tolerability, and longer-term safety concerns.^{7–9} For PI therapy, gastrointestinal tolerability and lipid profile are key considerations. Gastrointestinal intolerance is an established risk for treatment failure¹⁰ and PI-associated dyslipidaemia partly explains the increase in the risk for myocardial infarction observed in patients on HAART.^{3,4,7,11–13}

Atazanavir is a potent once-daily PI with proven efficacy in both treatment-experienced and treatment-naive

patients.^{14–18} It has a favourable impact on lipids in treatment-naïve patients¹⁹ and, even when boosted with ritonavir, results in better lipid profiles and improved gastrointestinal tolerability compared with lopinavir/ritonavir in treatment-experienced patients.^{4,17} The aim of the 96-week CASTLE study (BMS AI424138) is to examine the comparative clinical efficacy of once-daily atazanavir/ritonavir and twice-daily lopinavir/ritonavir, both given in combination with once-daily, fixed-dose tenofovir and emtricitabine, in treatment-naïve HIV-1-infected patients. Here, we report the 48-week primary efficacy and safety results of this study.

Methods

Participants

Patients were recruited from centres at 134 sites in 29 countries from November, 2005, through June, 2006, and were eligible for enrolment if they were infected with HIV-1, aged 18 years or older, naïve to antiretroviral therapy (<1 week previous antiretroviral exposure, except in setting of post-exposure prophylaxis or prevention of mother-to-child transmission, in which case <6 weeks of previous antiretroviral exposure was allowed), and had HIV-1 RNA of 5000 copies per mL or greater.

The study was done in accordance with Good Clinical Practice and the ethical principles in the Declaration of Helsinki. At each study site, the protocol, amendments, and informed consent received approval by the institutional review board/independent ethics committee before initiation.

Procedures

In this open-label, multicentre non-inferiority study, patients were randomly assigned in a one to one ratio to receive either atazanavir 300 mg (two 150 mg capsules) plus ritonavir 100 mg (one capsule) once daily, or fixed-dose lopinavir/ritonavir 400/100 mg (three 133/33·3 mg capsules [fixed-dose, soft-gel formulation]) twice daily, each given with tenofovir/emtricitabine 300/200 mg (one tablet) once daily. Throughout the first 48 weeks of the study, the protocol required patients to receive the capsule formulation of lopinavir/ritonavir. Randomisation was done with a computer-generated centralised randomisation schedule and was stratified by HIV RNA level at enrolment (<100 000 or ≥100 000 copies per mL) and geographic region (Africa, Asia, Europe, North America, South America).

Patients were assessed at screening, at day 1 (baseline), and at weeks 2, 4, 12, 24, 36, and 48, or at early termination. Resistance testing was done at baseline and during the study in any patient with a 0·5 log increase in HIV RNA from a previous scheduled HIV RNA test at week 12 or thereafter and who had a confirmatory HIV RNA of 400 copies per mL or greater, and in any patient with an HIV RNA of 400 copies per mL or greater at week 24 or anytime thereafter. Results of baseline resistance testing were not used to determine study eligibility since

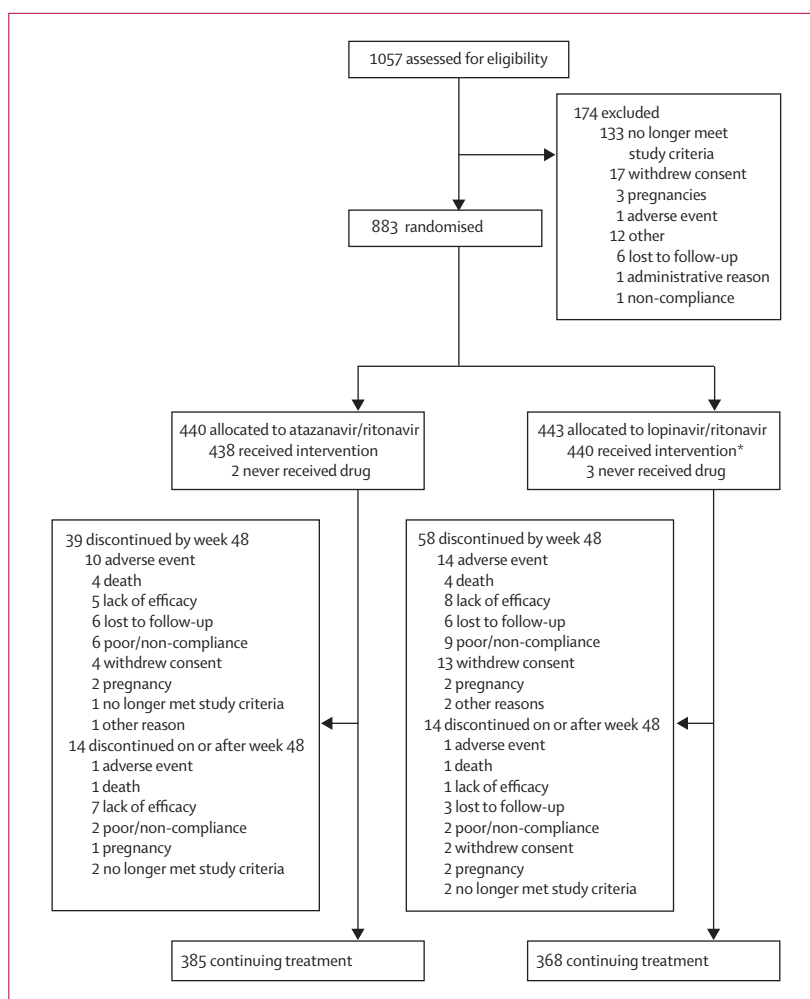


Figure 1: Trial profile

*Three patients erroneously received atazanavir/ritonavir.

	Atazanavir/ritonavir (N=440)	Lopinavir/ritonavir (N=443)	Overall (N=883)
Age (years)	34 (19–72)	36 (19–71)	35 (19–72)
Sex (female)	138 (31%)	139 (31%)	277 (31%)
CDC Class C AIDS	19 (4%)	24 (5%)	43 (5%)
HIV RNA (\log_{10} copies per mL)	5·01 (2·60–5·88)	4·96 (3·32–5·88)	4·98 (2·60–5·88)
HIV RNA $\geq 100\ 000$ copies per mL	225 (51%)	208 (47%)	433 (49%)
CD4 cell count (cells per μL)	205 (2–794)	204 (4–810)	205 (2–810)
CD4 count <50 cells per μL	58 (13%)	48 (11%)	106 (12%)
HBV positive	24 (5%)	20 (5%)	44 (5%)
HCV positive	40 (9%)	33 (7%)	73 (8%)
HIV subtype B	280 (67%)	276 (65%)	556 (66%)

Data are n (%) or median (range).

Table 1: Baseline characteristics of the as-randomised patients

resistance testing was not standard of care at the time of study initiation; samples were batched and not run in real time and were therefore not available to investigators at the time of screening.

At all patient visits (except week 2), vital signs and samples for plasma HIV RNA, CD4 cell count, and laboratory tests (serum chemistry and haematology, fasting lipid profile, urinalysis, hepatitis co-infection) were taken. Assays were done at a central laboratory that met Clinical Laboratory Improvement Amendments regulations or equivalent by country. HIV-1 RNA

concentrations were measured by qualitative PCR with the Roche Amplicor assay version 1.5 (Roche Molecular Systems, Branchburg, NJ, USA), standard assay at screening and baseline, and ultrasensitive protocol at all other visits. Phenotypic resistance to selected PIs, nucleoside reverse transcriptase inhibitors, and non-nucleoside reverse transcriptase inhibitors was tested with the PhenoSense HIV assay (Monogram Biosciences, San Francisco, CA, USA), and substitutions in the HIV reverse transcriptase and protease genomes were determined with the GeneSeq HIV assay (Monogram Biosciences). Hepatitis serologies were assessed at screening, week 48, or at early termination.

Investigators determined the intensity of adverse events at each study visit with a modified WHO grading system, and determined the relation between adverse events and study therapy.²⁰

The primary endpoint was the proportion of patients with HIV RNA of less than 50 copies per mL at week 48. Secondary efficacy endpoints were the proportion of patients with HIV RNA less than 400 copies per mL at week 48, change in CD4 cell count from baseline through week 48, log reduction in HIV RNA by week 48, and the antiretroviral resistance profiles of patients experiencing virological failure. Safety endpoints included the incidence of adverse events, serious adverse events, discontinuations due to adverse events, laboratory abnormalities, and changes from baseline in laboratory tests over time.

Statistical analysis

Assuming a 70% response rate (ie, 70% of patients remaining on treatment for 48 weeks and HIV RNA <50 copies per mL) on both treatment regimens, a sample size of 882 randomised patients (441 per regimen) would provide 90% power to demonstrate that the atazanavir/ritonavir regimen is non-inferior to the lopinavir/ritonavir-based regimen.

Efficacy results are presented by the as-randomised 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 primary efficacy endpoint was assessed with several algorithms and cohorts. The principal analysis was done on a confirmed virological response, non-completer equals failure (CVR, NC=F) basis—an ITT definition of response. Supportive analyses were done with CVR, non-completer equals missing (CVR, NC=M); time to loss of virological response (TLOVR); and the virological response-observed cases (VR-OC) definitions of response. TLOVR is an ITT analysis that defines response as two consecutive on-treatment measurements of HIV RNA of less than 50 copies per mL achieved and maintained through week 48 without intervening discontinuation and virological rebound (ie, two consecutive on-treatment measurements of HIV RNA of 50 copies per mL or greater

	Atazanavir/ritonavir	Lopinavir/ritonavir	Atazanavir-lopinavir
CVR, NC=F*	343/440 (78%)	338/443 (76%)	1.7% (-3.8 to 7.1)
CVR, NC=M	343/398 (86%)	338/379 (89%)	-2.9% (-7.5 to 1.6)
TLOVR	343/440 (78%)	337/443 (76%)	1.9% (-3.6 to 7.4)
VR-OC	335/399 (84%)	333/382 (87%)	-3.5% (-8.7 to 1.8)

Data are number of responders/number assessable (%) or difference estimate (95% CI). Difference estimates are stratified by qualifying HIV RNA and region. CVR=confirmed virological response. NC=F=non-completer equals failure. NC=M=non-completer equals missing. TLOVR=time to loss of virological response. VR-OC=virological response-observed cases. *Primary analysis.

Table 2: Proportions of patients with HIV RNA below 50 copies per mL at week 48

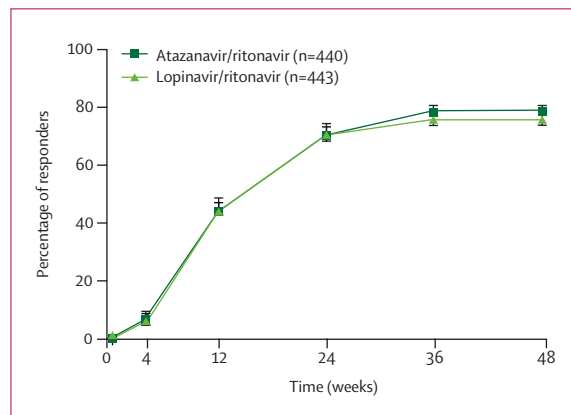


Figure 2: Proportion of patients with HIV RNA below 50 copies per mL at week 48 (ITT; CVR, NC=F analysis)
Error bars are SE.

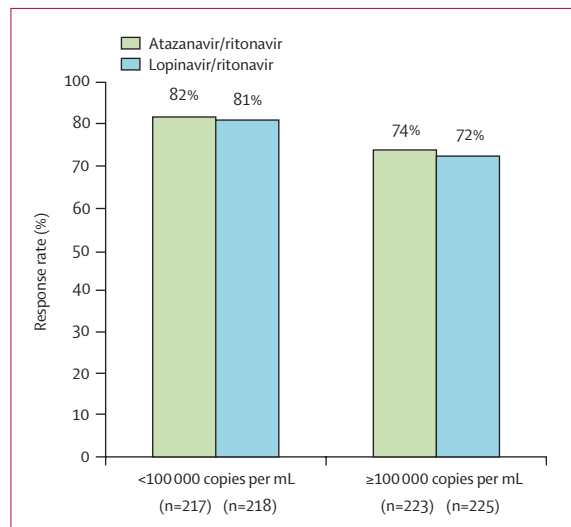


Figure 3: Proportion of patients with HIV RNA below 50 copies per mL at week 48 (ITT; CVR, NC=F analysis), by qualifying HIV-1 RNA

or last HIV RNA of 50 copies per mL or greater followed by discontinuation). CVR analyses use the same definitions of response and failure as TLOVR, but classify patients with confirmed re-suppression after virological rebound as responders. VR-OC is based on a single measurement of HIV RNA of less than 50 copies per mL at week 48.

Treatment regimens were compared by calculation of the difference in proportions (atazanavir/ritonavir–lopinavir/ritonavir) and 95% CI based on a stratified normal approximation. Analyses were stratified by the same strata as randomisation—ie, HIV RNA level at enrolment and geographic region. The proportion of patients with HIV RNA below 50 copies per mL was computed within each stratum, and combined by use of a weighted average with weights proportional to stratum size (Cochran-Mantel-Haenszel weighting). The atazanavir/ritonavir regimen was deemed to be non-inferior to the lopinavir/ritonavir regimen if the lower CI for the difference in proportions was greater than –10%.

Descriptive analyses were done for patients with HIV RNA below 50 copies per mL at week 48 with CVR, NC=F by prespecified baseline subgroups. The association between response rates and baseline CD4 cell count was assessed post hoc for each regimen with the Cochran-Armitage trend test. Mean changes in CD4 cell counts from baseline at week 48 were compared between treatment regimens with 95% CIs based on stratified normal approximations and observed values.

Genotypic and phenotypic resistance profiles were determined for patients who met criteria for virological failure through week 48 as defined by CVR, NC=F for HIV RNA of 400 copies per mL or greater. Virological failure was defined as rebound after achieving a confirmed viral load of less than 400 copies per mL without re-suppression, discontinuation due to insufficient viral load response before week 48, or failure to achieve a confirmed viral load of less than 400 copies per mL on study and at week 48. Genotypic resistance was assessed by searching for all PI-resistance mutations, and selected reverse transcriptase inhibitor-resistance mutations in the most current version of the International AIDS Society-USA (IAS-USA) list²¹ and the Stanford HIV Drug Resistance Database. PI-resistance substitutions were categorised as polymorphic or non-polymorphic. Polymorphic substitutions were defined as either PI-resistance substitutions not listed in IAS-USA or PI-resistance substitutions listed as minor in IAS-USA that had mutation scores of 0 for all PIs, according to values assigned by the Stanford database. Non-polymorphic substitutions listed in IAS-USA were further categorised as either major or minor using both IAS-USA and Stanford classifications, with the Stanford database taking precedence because of its mutation scoring algorithm.

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

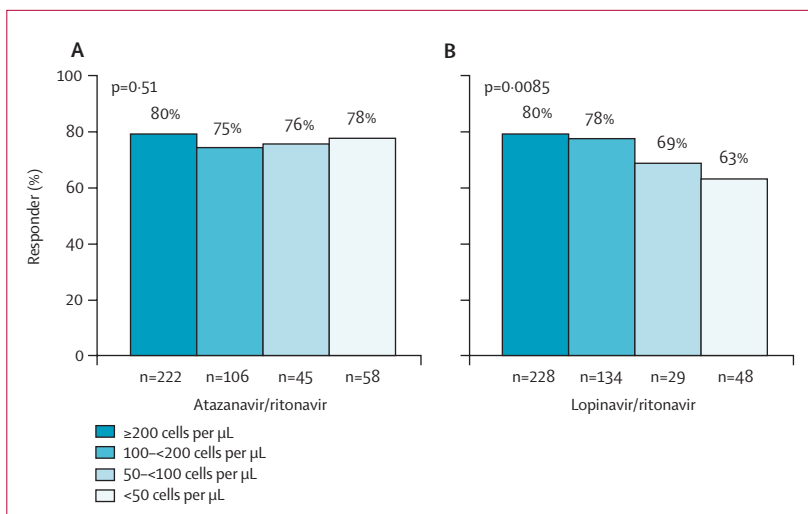


Figure 4: Response rate (ITT; CVR, NC=F; HIV RNA below 50 copies per mL at week 48) by baseline CD4 cell count in (A) the atazanavir/ritonavir group and (B) the lopinavir/ritonavir group. p values for response by baseline CD4 cell count calculated with Cochran-Armitage trend tests.

95% CIs based on stratified normal approximations and last observation carried forward (LOCF).

The proportions of patients adherent to the regimen at week 48 were determined by comparing actual study medications received with those reported on the Multicenter AIDS Cohort Study (MACS) adherence questionnaire.^{22,23} The denominator was based on patients who received any study medication at week 48. Patients were classified as non-adherent to a drug if they took fewer medications than prescribed in the past 4 days, took medication as prescribed in the past 4 days in an atypical pattern, took fewer pills per dose than prescribed in the past 4 days, or provided partial responses to adherence questions. Patients had to be adherent to all drugs in the regimen to be categorised as adherent to the regimen. Patients who did not report any drugs in the regimen on MACS were deemed to be non-adherent.

Statistical analyses were done with SAS version 9. This study is registered with ClinicalTrials.gov, number NCT00272779.

Role of the funding source

The study sponsor developed the study design and analysis plan 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

883 HIV-infected, treatment-naive patients were randomised and analysed for efficacy (figure 1). Three patients randomised to receive lopinavir/ritonavir received atazanavir/ritonavir for the duration of the

For the Stanford HIV Drug Resistance Database see <http://hivd.stanford.edu>

	Atazanavir/ ritonavir (N=440)	Lopinavir/ ritonavir (N=443)
CVR-defined virological failure*	25 (6%)	26 (6%)
Rebound after achieving confirmed viral load <400 copies per mL without re-suppression	10	17
Discontinued due to insufficient viral load response†	4	6
Failure to achieve confirmed viral load <400 copies per mL and on study at week 48	11	3
Assessed for treatment-emergent drug-associated substitutions‡	19	20
Any PI substitution	10	8
Polymorphic	8	8
Non-polymorphic	2§	0
Emtricitabine-associated substitutions (M184I/V)	5	4
Tenofovir-associated substitutions (K65R/K70E)	1	0
Thymidine analogue mutations	1	1

*Excludes two patients with baseline phenotypic resistance to atazanavir/ritonavir and lopinavir/ritonavir.
†Discontinuations due to insufficient viral load response were as judged by investigators. ‡Six patients in each group did not have paired baseline and on-treatment genotypes available for analysis. §Patient 1: N88S, M46I. Patient 2: L10F, V32I, K43T, M46I, A71I, G73S, L90M.

Table 3: Treatment-emergent resistance through week 48 in isolates from patients with virological failure

	Atazanavir/ritonavir (N=441)	Lopinavir/ritonavir (N=437)
Grade 2–4 adverse events in ≥2% of patients		
Herpes zoster	9 (2%)	14 (3%)
Influenza	6 (1%)	9 (2%)
Nasopharyngitis	8 (2%)	11 (3%)
Bronchitis	7 (2%)	11 (3%)
Upper respiratory tract infection	7 (2%)	12 (3%)
Diarrhoea	24 (5%)	66 (15%)
Nausea	21 (5%)	36 (8%)
Vomiting	10 (2%)	16 (4%)
Abdominal pain	9 (2%)	10 (2%)
Hyperbilirubinaemia	26 (6%)	1 (<1%)
Jaundice	16 (4%)	0
Headache	27 (6%)	16 (4%)
Rash	13 (3%)	7 (2%)
Back pain	10 (2%)	4 (<1%)
Pyrexia	6 (1%)	12 (3%)
Hypertriglyceridaemia	4 (<1%)	18 (4%)
Grade 2–4 treatment-related adverse events		
Overall (through week 48)	115 (26%)	129 (30%)
That occurred in ≥2% of patients		
Jaundice	16 (4%)	0
Nausea	17 (4%)	33 (8%)
Diarrhoea	10 (2%)	50 (11%)
Rash	14 (3%)	9 (2%)

Data are n (%).

Table 4: Grade 2–4 adverse events through week 48

study because of a central drug-assignment error. For the purposes of efficacy analyses, these patients were deemed to have been treated as randomised (ie, were

included in the lopinavir/ritonavir group) but were grouped as-treated with atazanavir/ritonavir in the safety analyses. Five patients randomly assigned to the atazanavir/ritonavir group and seven to lopinavir/ritonavir had been exposed to antiretroviral therapy at baseline as part of post-exposure prophylaxis or prevention of mother-to-child transmission.

Baseline demographics were much the same in the two treatment groups (table 1). 39 (9%) of the 438 individuals who received study treatment in the atazanavir/ritonavir group and 58 (13%) of 440 patients who received study treatment in the lopinavir/ritonavir group discontinued before week 48; similar proportions of these discontinuations in each group were due to adverse events (figure 1). There were more discontinuations due to jaundice on atazanavir/ritonavir than on lopinavir/ritonavir (three [<1%] vs none) and more due to diarrhoea on lopinavir/ritonavir than on atazanavir/ritonavir (four [<1%] vs none). One patient on each regimen discontinued due to a renal adverse event (Fanconi syndrome on atazanavir/ritonavir, proteinuria on lopinavir/ritonavir). At week 48, 330 (82%) of 401 patients on atazanavir/ritonavir and 316 (84%) of 378 patients on lopinavir/ritonavir were still adherent to the regimen.

At baseline, nine (2%) patients in the atazanavir/ritonavir group and 11 (3%) of those in the lopinavir/ritonavir group had major PI-resistance substitutions; 136 (31%) and 168 (39%) had minor PI-resistance substitutions, respectively. Two patients in the atazanavir/ritonavir group had baseline phenotypic resistance to atazanavir/ritonavir, lopinavir/ritonavir (Monogram PhenoSense clinical cutoffs, fold change [FC] atazanavir/ritonavir 19 and 10; lopinavir/ritonavir 39 and 9), and emtricitabine (FC 44 and 64). One of these patients also had baseline resistance to tenofovir (FC 1.74).

At week 48, similar proportions of patients in each group had achieved the primary endpoint as assessed with the principal ITT analysis of CVR, NC=F (table 2, figure 2). The atazanavir/ritonavir regimen met the criterion for non-inferiority to the lopinavir/ritonavir-based regimen (table 2, figure 2). The three patients randomised to lopinavir/ritonavir who received atazanavir/ritonavir were all primary endpoint treatment successes. The non-inferiority of the atazanavir/ritonavir-based regimen to the lopinavir/ritonavir-based regimen was confirmed by the supportive analyses (table 2).

Treatment regimens were comparable in terms of the mean increase from baseline to week 48 in CD4 cell count (203 cells per µL in the atazanavir/ritonavir group and 219 cells per µL in the lopinavir/ritonavir group; difference -16.4 cells per µL, 95% CI -35.9 to 3.1). There was no difference between groups in log reduction in HIV RNA from baseline and week 48 (data not shown).

Treatment response (HIV RNA <50 copies per mL) at week 48 using CVR, NC=F as assessed by strata of viral

load at enrolment and baseline CD4 cell count subgroups are shown in figures 3 and 4. Responses stratified by qualifying HIV RNA strata were consistent between groups, with some diminution in response rates in those with qualifying HIV RNA of 100 000 copies per mL or more in both groups (figure 3). The association between response rate and baseline CD4 cell count was assessed post hoc within each regimen. These analyses indicated that lower response rates were associated with lower baseline CD4 cell counts for lopinavir/ritonavir ($p=0.0085$; figure 4B) but not for atazanavir/ritonavir ($p=0.51$; figure 4A). Seven (12%) of the 58 patients in the atazanavir/ritonavir group and six (13%) of 48 in the lopinavir/ritonavir group with CD4 cell counts below 50 cells per μL were virological failures by week 48; six (10%) of those in the atazanavir/ritonavir group and 11 (23%) of those in the lopinavir/ritonavir group discontinued before confirmed virological suppression; of these patients, none in the atazanavir/ritonavir group and five in the lopinavir/ritonavir group discontinued because of adverse events.

Virological failure (using CVR, $\text{NC}=\text{F}$) occurred in similar numbers of patients in each group (table 3). Two patients taking atazanavir/ritonavir had non-polymorphic PI-resistance mutations emerge on treatment. In one patient the N88S substitution, associated with atazanavir resistance, emerged. At the time of failure the isolate remained sensitive to atazanavir/ritonavir (atazanavir $\text{FC } 3.71$) and developed increased susceptibility to fosamprenavir, darunavir, and lopinavir/ritonavir. The patient subsequently experienced virological re-suppression without change in regimen to a viral load of less than 50 copies per mL. Of note, the N88S substitution was also recorded in one baseline isolate of a patient randomised to atazanavir/ritonavir (atazanavir $\text{FC } 1.38$); this patient achieved viral suppression to HIV RNA below 50 copies per mL at week 36, and remained suppressed throughout the study period. The second patient receiving atazanavir/ritonavir with emergent non-polymorphic PI-resistance mutations had six PI mutations at baseline, and rebounded rapidly at week 24 after suppression to an HIV RNA of less than 50 copies per mL, suggesting that failure was due to re-emergence of archived resistance mutations and previous exposure of the virus to PIs.

The safety population consisted of 878 treated patients—441 in the atazanavir/ritonavir group and 437 in the lopinavir/ritonavir group. There were no unexpected safety events, and adverse events were not treatment limiting in most cases. 13 deaths were reported: six in the atazanavir/ritonavir group, six in the lopinavir/ritonavir group, and one patient who was enrolled but died before randomisation. None were deemed to be related to the study drug.

Serious adverse events were noted in 51 (12%) patients in the atazanavir/ritonavir group and in 42 (10%) patients in the lopinavir/ritonavir group. All serious adverse

	Atazanavir/ritonavir	Lopinavir/ritonavir
Total bilirubin elevation ($\geq 2.6 \times \text{ULN}$)	14/435 (34%)	1/431 (<1%)
Alanine aminotransferase increase ($\geq 5.1 \times \text{ULN}$)	8/435 (2%)	6/431 (1%)
Aspartate aminotransferase increase ($\geq 5.1 \times \text{ULN}$)	9/435 (2%)	2/430 (<1%)
Total cholesterol ($\geq 240 \text{ mg/dL}$)	30/434 (7%)	77/428 (18%)
Triglycerides ($\geq 751 \text{ mg/dL}$)	2/434 (<1%)	15/428 (4%)

Data are n/N (%). ULN=upper limit of normal.

Table 5: Selected grade 3–4 laboratory abnormalities in $\geq 2\%$ patients through week 48

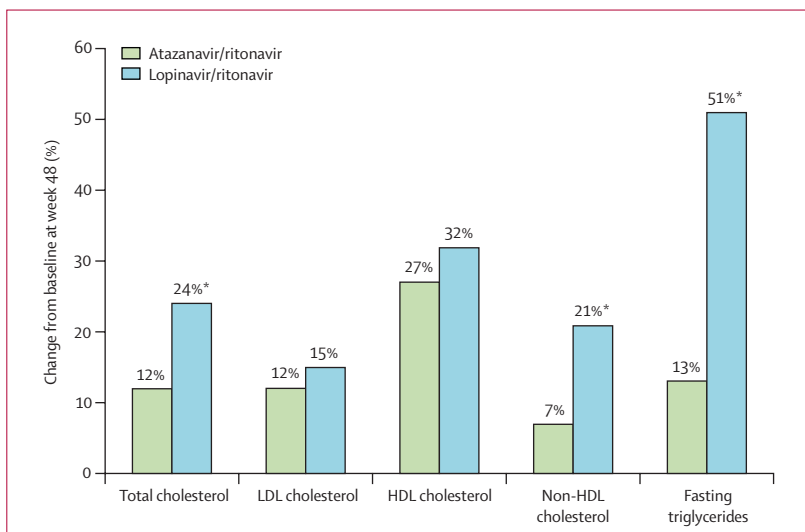


Figure 5: Percentage change in fasting lipids over 48 weeks (last observation carried forward)
* $p < 0.0001$.

events were reported by less than 1% of patients on either regimen with the exception of diarrhoea, which was reported by six (1%) patients in the lopinavir/ritonavir group and by two (<1%) in the atazanavir/ritonavir group. Few of these serious adverse events were deemed to be related to the study drug. Grade 2–4 adverse events, including those deemed to be treatment related, are shown in table 4. Of note, more patients on lopinavir/ritonavir experienced grade 2–4 treatment-related nausea and diarrhoea than did those in the atazanavir/ritonavir group; more patients on lopinavir/ritonavir required initiation of anti-diarrhoeal medications than did patients on atazanavir/ritonavir (94 [22%] vs 41 [9%]).

The incidence of grade 3–4 increases in alanine aminotransferase and aspartate aminotransferase concentrations was low on each regimen (table 5), but grade 3–4 increases ($2.6 \times$ upper limit of normal or greater) in total bilirubin occurred much more frequently in the atazanavir/ritonavir group than in the lopinavir/ritonavir group (table 5). 16 (4%) patients in the atazanavir/ritonavir group had grade 4 increases, compared with none in the lopinavir/ritonavir group. There was little change from baseline to week 48 in serum creatinine ($\leq 0.5 \text{ mg/L}$ on both regimens). The median percentage changes from baseline in the calculated creatinine clearance (Cockcroft-Gault formula)

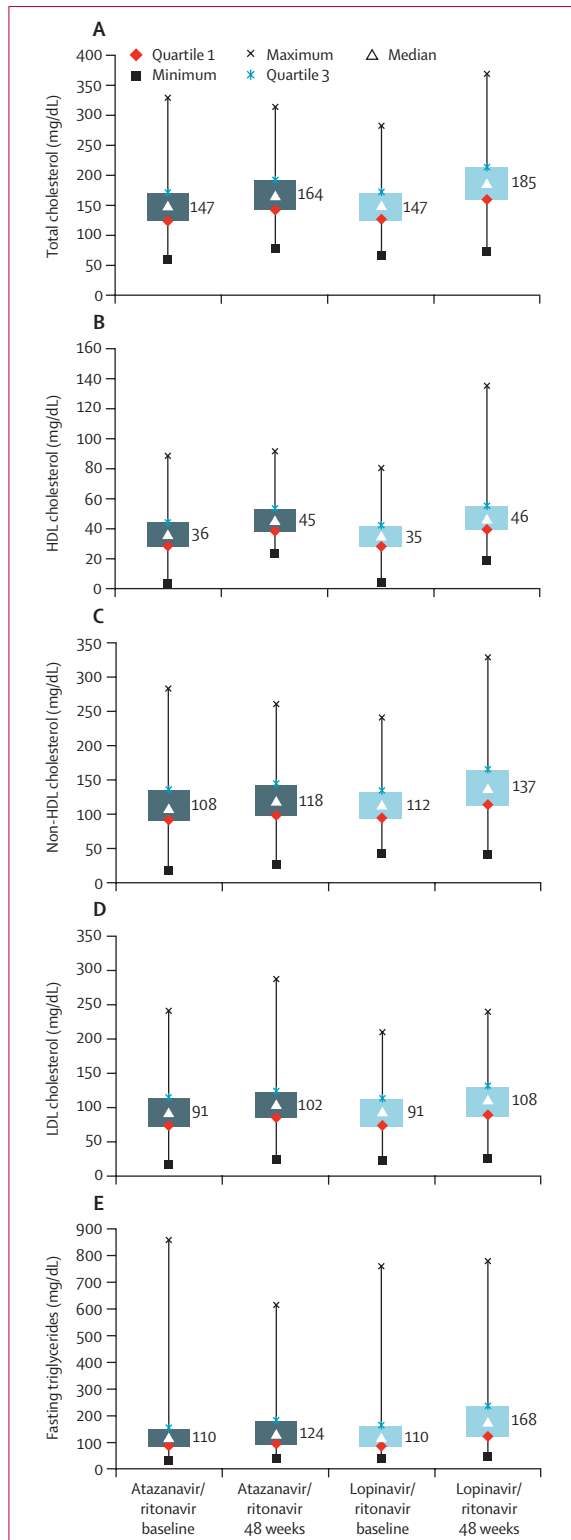


Figure 6: Total cholesterol (A), HDL cholesterol (B), non-HDL cholesterol (C), LDL cholesterol (D), and fasting triglycerides (E) at baseline and week 48 Data points represent median values; box plots represent interquartile range; whiskers indicate minimum and maximum values. Data available for 441 patients on atazanavir/ritonavir and 437 on lopinavir/ritonavir.

at week 48 were -1% (IQR -11 to 8) on atazanavir/ritonavir and -1% (-11 to 11) on lopinavir/ritonavir.

Mean percentage changes in fasting total cholesterol, non-HDL cholesterol, and triglycerides from baseline at week 48 were significantly higher on lopinavir/ritonavir than on atazanavir/ritonavir ($p < 0.0001$ for these three types of lipid; figure 5). Plasma lipid values at baseline and at week 48 are shown in figure 6. Through week 48, more patients on lopinavir/ritonavir than on atazanavir/ritonavir used lipid-lowering therapy (33 [8%] vs 10 [2%]).

Discussion

Our data show that once-daily ritonavir-boosted atazanavir is non-inferior in terms of efficacy to twice-daily ritonavir-boosted lopinavir, both in combination with once-daily tenofovir/emtricitabine for the initial treatment of antiretroviral-naïve HIV-1-infected patients over 48 weeks. Response rates were consistent with those seen in other studies of atazanavir/ritonavir¹⁸ and lopinavir/ritonavir²⁴⁻²⁷ in treatment-naïve patients, after allowing for differences in study designs and populations.

In addition to high antiviral response rates, increases in CD4 cell count—an important measure of immune reconstitution—were seen with both regimens by 48 weeks. Both regimens were effective in patients with high viral loads, although response rates were lower in patients with higher viral load in both groups. Although analyses of the relation between efficacy and baseline CD4 cell count were done post hoc, the antiviral efficacy of atazanavir/ritonavir was maintained irrespective of baseline CD4 cell count, while reduced response rates were seen with lower baseline CD4 cell counts for patients on lopinavir/ritonavir. Variation in response rates for lopinavir/ritonavir has been noted before; in study M98-863, a large randomised, controlled trial that compared lopinavir/ritonavir with nelfinavir in treatment-naïve patients,²⁸ lower response rates (where a response was deemed to be HIV RNA < 400 copies per mL) were observed among treatment-naïve patients receiving lopinavir/ritonavir with CD4 cell counts below 50 cells per μL at baseline than in those with higher counts, although the differences in response were not statistically significant.²⁸ A trial in treatment-naïve patients that compared lopinavir/ritonavir with darunavir/ritonavir showed lower response rates among patients with CD4 cell counts below 50 cells per μL than in those with higher CD4 cell counts with both drug combinations.²⁵ However, other studies of lopinavir/ritonavir have not reported this variation based on baseline CD4 cell counts.^{26,27} In this study, nearly a quarter of patients on lopinavir/ritonavir with a baseline CD4 cell count below 50 cells per μL discontinued before confirmed virological suppression, and of these, half did so due to an adverse event. By contrast, no patients with a baseline CD4 cell count below this

threshold on atazanavir/ritonavir discontinued because of an adverse event, suggesting that the reduced response rates seen among patients with low CD4 cell counts and advanced HIV-related immune suppression on lopinavir/ritonavir might be due mainly to intolerance.

Consistent with other studies in treatment-naive patients,^{24–26} our data suggest that, in patients without evidence of baseline resistance, there is a low rate of virological failure during treatment with regimens containing a boosted PI. Rates of virological failure were much the same in both groups, as were the rates at which treatment resistance developed; there were few instances of the emergence of resistance to protease inhibitors, and the rate of emergence of the M184V mutation—a substitution that confers resistance to emtricitabine—was similar with both regimens. However, over the course of the study, two patients in the atazanavir/ritonavir group developed non-polymorphic mutations compared with none in the lopinavir/ritonavir group.

Advances made in the management of HIV infection have resulted in a fundamental shift in the profile of the disease in the developed world to a potentially chronic and manageable condition.^{1,29} Treatment regimens for the management of HIV infection must now provide a high level of antiviral efficacy and be shown to offer durable efficacy, a good tolerability and safety profile, and simple dosing to ensure treatment success and patient adherence in the long term. The results of this study show that regimens based on both atazanavir/ritonavir and lopinavir/ritonavir provide high antiretroviral efficacy and low rates of virological failure over 48 weeks in treatment-naive patients. Overall patient discontinuation rates were low and no unexpected safety events were noted. Adverse events were—in most cases—not treatment limiting. The proportion of patients with abnormal levels of alanine and aspartate aminotransferases was consistent between the two regimens and the incidence of abnormal bilirubin was predictably higher on atazanavir/ritonavir than on lopinavir/ritonavir.^{14,18} Although hyperbilirubinaemia and jaundice may be of concern because of their potential effect on patient quality of life, only three patients (<1%) discontinued treatment with atazanavir/ritonavir due to jaundice in the 48 weeks reported here, indicating that hyperbilirubinaemia does not have a significant effect on atazanavir tolerability.

Perhaps the greatest concern for physicians and patients in selecting a PI-based HAART regimen in treatment-naive patients is the potential risk of long-term adverse effects associated with PI-related dyslipidaemia and negative vasculature effects.^{4,12,30} Several mechanisms that could contribute to cardiovascular and cerebrovascular changes in HIV-infected patients on antiretroviral therapy have been reported, including the accelerated accumulation

of lipids in vessel walls. However, these mechanisms do not seem to be class specific.³⁰ Our results suggest that atazanavir/ritonavir had a significantly better lipid profile than did lopinavir/ritonavir; fewer patients on atazanavir/ritonavir required lipid-lowering therapy than did those on lopinavir/ritonavir. Whether these differences in lipid profiles will confer additional benefits in decreasing cardiovascular or cerebrovascular risk has yet to be elucidated.

Atazanavir/ritonavir exhibited less gastrointestinal toxicity than did the lopinavir/ritonavir regimen; more patients taking lopinavir/ritonavir initiated anti-diarrhoeal medication than did those on atazanavir/ritonavir. Inadequate adherence to HAART is affected by many factors, such as tolerability of therapy, pill burden, dosing frequency, food requirements, and safety concerns,⁷ and the risk of gastrointestinal side-effects ranks highly among patient concerns and preferences for third-agent HIV medications.³¹ Indeed, treatment-related diarrhoea is emerging as a risk factor for treatment failure.¹⁰ Recent clinic-based studies have shown that the safety and tolerability profile of atazanavir/ritonavir can lead to lower rates of treatment change in treatment-naive patients than with other third-agent HIV medications.^{32,33} Atazanavir/ritonavir also offers once-daily dosing and the lowest pill burden of available PIs, satisfying another criterion of patient preference and contributing to convenience of therapy.

Limitations of this study include its open-label design and the fact that patients were limited to using the three capsules, twice daily formulation of lopinavir/ritonavir during the 48-week assessment period, rather than the newer tablet formulation of two tablets twice daily. However, the low rates of discontinuation due to adverse events in these treatment-naive patients suggest that this formulation was not an issue, and the similar adherence rates for the regimens also suggest that pill burden was not a limiting factor. A study that compared the soft-gel capsules with the tablet form showed no statistically significant differences between the two formulations in terms of the number of patients discontinuing due to gastrointestinal adverse events or other adverse events, or in the incidence of treatment-emergent diarrhoea of any severity.²⁷ These data, in conjunction with the low discontinuation rate seen here, suggest that the use of lopinavir/ritonavir tablets would not have affected the study outcomes. One should also note that not permitting patients to switch formulations during the assessment period permitted a true comparison of consistent regimens from start of treatment through to week 48.

In summary, the results of this study support the use of once-daily atazanavir/ritonavir as a recommended first-line treatment option, with a number of patient benefits over the currently recommended ritonavir-boosted twice-daily lopinavir for the treatment of HIV-infected antiretroviral-naive patients.

Contributors

J-MM, JA-V, JE, PC, JC, ND, GM, MM, LP, RY, AT, and DMG all provided scientific input into the study design and study protocol. J-MM, RY, AT, LP, and DMG 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 enrolment of patients. RY and AT did all statistical analyses.

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Conflict of interest statement

J-MM has received consulting fees and lecture fees from GlaxoSmithKline, Abbott, Gilead, Tibotec, Pfizer, and Bristol-Myers Squibb. PC has received travel grants from Bristol-Myers Squibb, Merck Sharpe & Dohme, Pfizer, Abbott, and Schering-Plough. JE has received research funding and honoraria from Bristol-Myers Squibb. GM 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. MM, LP, RY, AT, and DMG are employees of Bristol-Myers Squibb. LP, MM, and DMG are stockholders of Bristol-Myers Squibb. JA-V, DN, and JC declare that they have no conflict of interest.

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, A Gopinathan, and J Absalon. Editorial support was provided by Cheryl Jenkins (Parexel, Worthing, UK) and was funded by Bristol-Myers Squibb.

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