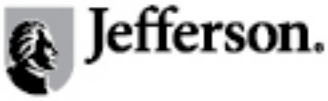

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Comparative gender analysis of the efficacy and safety of atazanavir/ritonavir and lopinavir/ritonavir at 96 weeks in the CASTLE study

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Objectives: To examine whether the overall results of the CASTLE study pertain to both genders, we analysed the efficacy and safety of atazanavir/ritonavir and lopinavir/ritonavir in 277 female and 606 male patients in the open-label, multinational trial over 96 weeks. The trial is registered with ClinicalTrials.gov, number NCT00272779.

Methods: Treatment-naive patients aged ≥18 years with HIV-1 RNA ≥5000 copies/mL were randomized to receive either atazanavir/ritonavir 300/100 mg once daily or lopinavir/ritonavir 400/100 mg twice daily, with fixed-dose tenofovir/emtricitabine 300/200 mg once daily.

Results: At week 96, confirmed virological response rates (HIV RNA <50 copies/mL; intent-to-treat analysis) were higher in women and men receiving atazanavir/ritonavir than those receiving lopinavir/ritonavir and lower in women than men in both treatment arms (67% of women and 77% of men on atazanavir/ritonavir and 63% of women and 71% of men on lopinavir/ritonavir). These differences were not observed in the on-treatment analysis. Mean change in CD4 cell count from baseline to week 96 was 265 cells/mm^3 for women and 269 cells/mm^3 for men on atazanavir/ritonavir and 298 cells/mm^3 for women and 286 cells/mm^3 for men on lopinavir/ritonavir. Discontinuation rates were higher in women than men in each treatment arm (22% of women and 15% of men on atazanavir/ritonavir and 29% of women and 18% of men on lopinavir/ritonavir). In women and men, grade 2–4 nausea and diarrhoea were more frequent in the lopinavir/ritonavir group; jaundice and hyperbilirubinaemia occurred more frequently in the atazanavir/ritonavir group.

Conclusions: Once-daily atazanavir/ritonavir is an effective and well-tolerated therapeutic option for women and men with HIV-1 infection. The sex-based differences in response may be due to higher discontinuation rates in women.

Keywords: antiretroviral therapy, protease inhibitors, HIV

Introduction

Of the estimated 35 million people living with HIV, almost half are women, and this proportion is increasing in several countries.[1,2] Of particular concern are the increases in HIV infection among young women, who now make up >60% of young adults aged 15–24 years living with HIV/AIDS.[1] Women account for ∼25% of new AIDS cases and more than one-third of new HIV diagnoses in the USA. African–American and Hispanic women represent a disproportionate percentage of the disease burden, constituting <25% of all US women, but accounting for 79% of new diagnoses.[3] Despite the changing epidemiology of HIV among women, they remain under-represented in most clinical HIV studies as few women enrol and continue in trials in the developed world.[4,5] Much of the data available on women with HIV are from studies carried out in resource-limited

settings. In addition, as most clinical studies have enrolled fewer women than men, treatment guidelines are based primarily on outcomes in men.

Recent studies highlight that despite initial concerns regarding potential differences in response to antiretroviral (ARV) therapy across gender, both men and women respond equally well to therapy. Differences in response typically occur due to a higher number of discontinuations among women as compared with men. When efficacy results are censored for discontinuations other than virological failure, women have responded as well as men in several clinical trials in both treatment-naive and treatment-experienced HIV-infected patients.[3,6–9] The reasons for the high number of discontinuations among women in HIV clinical trials are not known. Even though there do not appear to be significant differences in efficacy by sex, gender differences in toxicity and adverse reactions have been detected, despite the fact that no major study in treatment-naive patients has been designed or powered to detect gender differences.[5,6,8,10–13] As there are several issues that women must consider when incorporating a complex ARV regimen into their lives (including contraception, childbearing, breastfeeding and the potential for mother-to-child HIV transmission), it is imperative to define potential side effects that may affect the choice of treatment regimen.[3,14] HIV stigma and access to care may also affect outcomes for HIV-infected women.[3,15] For many women, fitting modern regimens and clinic visits into their busy schedules can be a challenge. Therefore, tailoring ARV treatment regimens to gender may optimize response, tolerability and adherence, and minimize toxicity.

Analyses from the open-label, international CASTLE study provide much-needed data on the efficacy and tolerability of protease inhibitor (PI)-based regimens in female and male patients. Findings from a 48 week analysis, reported at the Seventeenth International AIDS Conference (2008), demonstrated that treatment-naive women receiving atazanavir/ritonavir or lopinavir/ritonavir (both in combination with tenofovir/emtricitabine) experienced a greater number of treatment-related adverse events and slightly lower virological response than males.[8] These data are consistent with the gender-based differences previously noted; however, these analyses were not preplanned or powered to identify differences in efficacy and safety. We report here results from an analysis assessing the efficacy, safety and tolerability of atazanavir/ritonavir and lopinavir/ritonavir in combination with tenofovir/emtricitabine in female and male patients enrolled in the CASTLE study through 96 weeks of treatment. In the overall CASTLE population, atazanavir/ritonavir was shown to be non-inferior to, with higher virological response rates than, lopinavir/ritonavir through 96 weeks of treatment. The difference in response rates in favour of atazanavir/ritonavir at 96 weeks was driven by a higher rate of discontinuation among patients receiving lopinavir/ritonavir. This was accompanied, in the overall population, by significantly less lipid elevation and better gastrointestinal tolerability in the atazanavir/ritonavir group than in the lopinavir/ritonavir group.[16,17]

Methods

Study design and participants

Details of the study design and participants were described previously by Molina *et al.*[17] Briefly, patients were eligible for enrolment if they were infected with HIV-1, were aged ≥18 years, were naive to ARV therapy (<1 week previous ARV experience or <6 weeks exposure for prophylaxis or prevention of mother-to-child transmission) and had HIV-1 RNA ≥5000 copies/mL. Patients were randomized to receive either atazanavir/ritonavir 300/100 mg once daily or lopinavir/ritonavir 400/100 mg twice daily, each given in combination with fixed-dose tenofovir/emtricitabine 300/200 mg once daily. Patients assigned to lopinavir/ritonavir were able to switch from the soft-gel capsule to the tablet formulation after 48 weeks. Randomization was in a 1:1 ratio, and was stratified for HIV-1 level (<100 000 or ≥100 000 copies/mL) and geographical region.

Research ethics

The study was conducted in accordance with good clinical practice and the ethical principles of the Declaration of Helsinki. The institutional review board/independent ethics committee at each study site approved the protocol, amendments and informed consent before initiation. The trial is registered with ClinicalTrials.gov, number NCT00272779.

Procedures

Study procedures were outlined in the previous publication[17] and continued as described for the duration of the 96 week study. Patients were assessed at screening, day 1 (baseline) and at weeks 2, 4, 12, 24, 36, 48, 60, 72, 84 and 96, or at early termination. 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 at all patient visits (except week 2).

The primary endpoint of the CASTLE study was the the proportion of patients with HIV-1 RNA <50 copies/mL at week 48, as reported by Molina *et al.*[16] In this paper, secondary efficacy endpoints for patients of female and male gender are reported, including the proportion of patients with HIV-1 RNA <50 copies/mL at week 96 and change in absolute CD4 cell count from baseline through week 96. Safety endpoints assessed at week 96 included frequency of adverse events, serious adverse events and discontinuation due to adverse events, and changes from baseline in fasting lipids over time.

Statistical analysis

Statistical methods for the week 96 analysis have been previously published[17] and are briefly summarized below. Efficacy results are presented by the as-randomized treatment regimen [intent-to-treat (ITT)]. Safety results are presented by the as-treated treatment regimen (i.e. by the treatment regimen actually received). The gender analysis was not powered to detect statistical differences, and no statistical comparisons between treatment arms or between genders were carried out for this report. The proportion of patients with HIV RNA <50 copies/mL at week 96 was assessed with several algorithms and cohorts of randomized patients. The principal analysis was based on the confirmed virological response (CVR) non-completer=failure (NC=F; ITT) definition of response. Supportive analyses used the virological response-observed cases (VR-OC) definitions of response and a *post hoc* cross-sectional analysis at week 96 in the as-treated population. Observed values were used to summarize CD4 cell counts and their changes from baseline through week 96.

Categories of fasting lipid parameters were tabulated through week 96 using observed values. Categories for cholesterol and triglycerides were defined according to the US National Cholesterol Education Program (NCEP) Adult Treatment Panel (ATP) III guidelines.[18] Analyses of fasting lipids over time excluded values obtained after patients commenced lipid-lowering agents.

Table 1. Baseline characteristics and demographics for female and male patients randomized in CASTLE

	ATV/RTV, $N=440$		LPV/RTV, $N=443$	
	female, $n=138$	male, $n=302$	female, $n=139$	male, $n=304$
Age, median years (min, max)	33 (20, 56)	35 (19, 72)	37 (19, 63)	36 (19, 71)
Region, *n* (%)				
Africa	33 (24)	34 (11)	41 (29)	24 (8)
Asia	15 (11)	24 (8)	12 (9)	28 (9)
Europe	15 (11)	50 (17)	13 (9)	53 (17)
North America	7 (5)	60 (20)	9 (6)	60 (20)
South America	68 (49)	134 (44)	64 (46)	139 (46)
CDC class C AIDS, *n* (%)	4 (3)	15 (5)	5 (4)	19 (6)
HIV RNA $\log_{10}$ copies/mL, median (min, max)	4.87 (2.60, 5.88)	5.06 (3.05, 5.88)	4.87 (3.69, 5.88)	5.00 (3.32, 5.88)
HIV RNA $\geq$100 000 copies/mL, *n* (%)	56 (41)	169 (56)	57 (41)	151 (50)
CD4 cells/mm^3, median (min, max)	196 (8, 794)	208 (2, 760)	190 (11, 416)	210 (4, 810)
CD4 $<$50 cells/mm^3, *n* (%)	15 (11)	43 (14)	15 (11)	33 (11)
Hepatitis B and/or C co-infection, *n* (%)	15 (11)	46 (15)	11 (8)	40 (13)

ATV, atazanavir; LPV, lopinavir; RTV, ritonavir.

Results

Disposition and baseline data

Of the 883 HIV-infected, treatment-naive patients randomized within CASTLE, 277 (31%) were female and 606 (69%) were male. Few women from developed nations were enrolled in the CASTLE study; 6% of women were from North America, compared with 48% from South America and 27% from Africa. Other baseline characteristics for female and male patients were comparable across the two treatment arms (Table 1).

Thirty-one (22%) women in the atazanavir/ritonavir group and 40 (29%) women in the lopinavir/ritonavir group discontinued through week 96 (Figure 1). Discontinuation rates were lower for male patients; 15% and 18% in the atazanavir/ritonavir and lopinavir/ritonavir groups, respectively. The reasons for discontinuation were similar between the two treatment groups. However, more women in the lopinavir/ritonavir group than in the atazanavir/ritonavir group withdrew as a result of suboptimal adherence (eight versus four) or withdrawn consent (nine versus three). Other common reasons for discontinuation were adverse events, lack of efficacy and pregnancy (Figure 1). Adverse events had only a minor influence on discontinuation rates for both treatment groups, with six (4%) women in each group, seven (2%) men in the atazanavir/ritonavir group and 16 (5%) men in the lopinavir/ritonavir group withdrawing before week 96 for this reason.

Efficacy

In the CVR analysis (NC=F; ITT), 67% of women and 77% of men receiving atazanavir/ritonavir and 63% of women and 71% of men receiving lopinavir/ritonavir achieved HIV-1 RNA $<$50 copies/mL at 96 weeks of treatment (Figure 2). CVR rates were generally lower in female patients than male patients in both treatment arms. Virological response rates in the VR-OC analysis were comparable between treatment groups and between genders (86% of women and 91% of men on atazanavir/ritonavir and 89% of women and 87% of men on lopinavir/ritonavir achieved HIV-1 RNA $<$50 copies/mL) at 96 weeks of treatment (Figure 2). Response rates (HIV RNA $<$50 copies/mL) by cross-sectional analysis at 96 weeks in the as-treated population were 69% (95/138) of female patients and 77% (234/303) of male patients for atazanavir/ritonavir and 63% (88/139) of female patients and 70% (210/298) of male patients for lopinavir/ritonavir.

The mean change in CD4 cell count from baseline to week 96 was similar between the two treatment groups, at 265 cells/mm^3 in female patients and 269 cells/mm^3 in male patients on atazanavir/ritonavir and 298 cells/mm^3 in female patients and 286 cells/mm^3 in male patients on lopinavir/ritonavir.

Safety

Eight hundred and seventy-eight subjects received study drug and were included in safety analyses. Three subjects were randomized to lopinavir/ritonavir but received atazanavir/ritonavir during the entire treatment period. No unexpected adverse events occurred, and adverse events were not treatment limiting in most cases. Two (1%) deaths occurred among women in the study, both in the lopinavir/ritonavir group. Four men (1%) in the lopinavir/ritonavir group and six men (2%) in the atazanavir/ritonavir treatment group died during the study. None of the deaths were considered to be related to the study drugs. Serious adverse events were reported by 20 (14%) women and 43 (14%) men in the atazanavir/ritonavir group and 17 (12%) women and 33 (11%) men in the lopinavir/ritonavir group. All but a few serious adverse events were reported by $<$1% of the population. There were no reports of myocardial infarction in either treatment group.

883 patients randomized

440 patients allocated to atazanavir/ritonavir			443 patients allocated to lopinavir/ritonavir		
138 women		302 men	139 women		304 men
138	Treated	300	139	Treated	301
31 (22%)	Discontinuations	45 (15%)	40 (29%)	Discontinuations	55 (18%)
8 (6%)	Lack of efficacy[a]	8 (3%)	6 (4%)	Lack of efficacy[a]	4 (1%)
6 (4%)[b]	Adverse event	7 (2%)[c]	6 (4%)[d]	Adverse event	16 (5%)[e]
5 (4%)	Pregnancy[f]	0	7 (5%)	Pregnancy[f]	0
4 (3%)	Poor/non-compliance	8 (3%)	8 (6%)	Poor/non-compliance	8 (3%)
3 (2%)	Withdrew consent	2 (<1%)	9 (6%)	Withdrew consent	9 (3%)
2 (1%)	Lost to follow-up	8 (3%)	1 (<1%)	Lost to follow-up	12 (4%)
1 (<1%)	No longer meets study criteria	3 (<1%)	0	No longer meets study criteria	3 (<1%)
0	Death	6 (2%)	2 (1%)	Death	3 (<1%)
0	Other	1 (<1%)	1 (<1%)	Other	0
2 (1%)[g]	Discontinued at week 96	2 (<1%)[h]	0	Discontinued at week 96	0

Figure 1. Trial profile for female and male patients in the CASTLE study. [a]Insufficient viral load response determined by investigators. [b]Two cases of rash, one case of tuberculosis (TB), one case of thrombocytopenia, one gastrointestinal problem and one gastrointestinal problem plus dizziness, jaundice, hepatomegaly and hyperbilirubinaemia. [c]Two cases of jaundice, two gastrointestinal problems, one case of abdominal pain, one case of *Mycobacterium* infection and one case of Fanconi syndrome. [d]Two cases of TB, one case of hypersensitivity, one case of hypertrophic cardiomyopathy, one case of rash and one case of proteinuria. [e]Seven cases of diarrhoea, one case of furnicle, one case of major depression, one case of rash, one case of rhabdomycosis, one case of lipoma, two cases of hyperlipidaemia, one case of lipodystrophy and one case of Kaposi's sarcoma. [f]Protocol-defined for discontinuation. [g]One pregnancy and one poor/non-compliance. [h]One lost to follow-up and one poor/non-compliance.

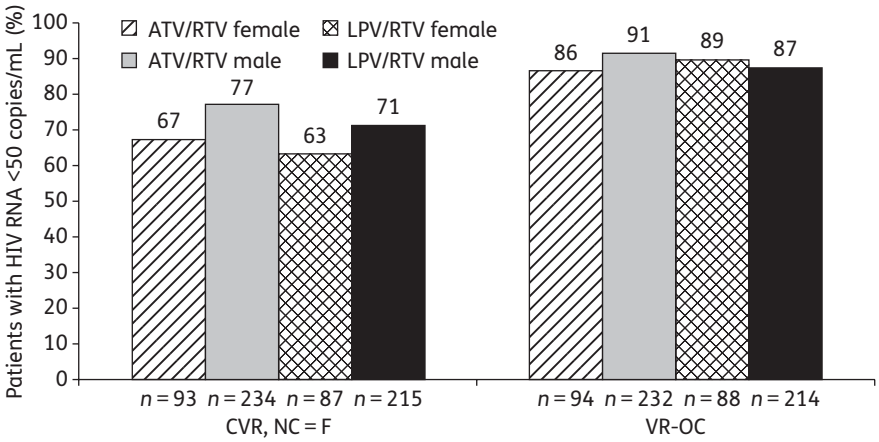

Figure 2. CVR (HIV RNA <50 copies/mL) at week 96 in the ITT (NC=F) and VR-OC (on-treatment) analyses. Response rates (HIV RNA <50 copies/mL) by cross-sectional analysis at 96 weeks in the as-treated population were: atazanavir/ritonavir (ATV/RTV), 69% of female patients and 77% of male patients; and lopinavir/ritonavir (LPV/RTV), 63% of female patients and 70% of male patients.

Table 2. Selected grade 2–4 treatment-related adverse events in female and male patients in each treatment group through week 96

	ATV/RTV		LPV/RTV	
Adverse events, *n* (%)	female, *n*=138	male, *n*=303	female, *n*=139	male, *n*=298
Any adverse event	45 (33)	88 (29)	46 (33)	94 (32)
Nausea	10 (7)	8 (3)	19 (14)	14 (5)
Diarrhoea	4 (3)	7 (2)	13 (9)	41 (14)
Hyperbilirubinaemia[a]	15 (11)	29 (10)	1 (<1)	1 (<1)
Jaundice/scleral icterus	6 (4)	15 (5)	0	0
Rash[b]	7 (5)	7 (2)	4 (3)	6 (2)
Vomiting	2 (1)	3 (<1)	3 (2)	4 (1)

ATV, atazanavir; LPV, lopinavir; RTV, ritonavir.
[a]Hyperbilirubinaemia also includes blood bilirubin abnormal, blood bilirubin increased, blood bilirubin unconjugated and blood bilirubin unconjugated increased from the INVESTIGATIONS system organ class.
[b]Rash includes dermatitis allergic, prurigo, psoriasis, rash, rash erythematous, rash generalized, rash maculopapular, rash papular, rosacea and urticaria.

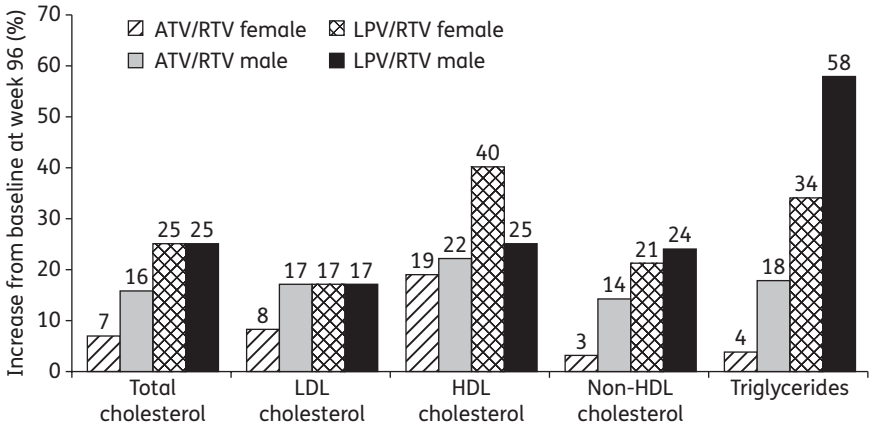

Figure 3. Mean percentage change in fasting lipid concentrations in female and male patients from baseline through week 96 (as-treated). ATV, atazanavir; LPV, lopinavir; RTV, ritonavir.

The proportion of women experiencing any grade 2–4 treatment-related adverse event was identical in both treatment groups, at 33% (Table 2). Twenty-nine percent of men in the atazanavir/ritonavir arm and 32% of men in the lopinavir/ritonavir-treatment arm experienced grade 2–4 treatment-related adverse events. Grade 2–4 treatment-related nausea and diarrhoea were more common among women and men in the lopinavir/ritonavir group than in the atazanavir/ritonavir group; however, jaundice/scleral icterus and hyperbilirubinaemia occurred more frequently in women and men receiving atazanavir/ritonavir than in those receiving lopinavir/ritonavir. Grade 2–4 treatment-related rash occurred in 5% and 3% of women and 2% and 2% of men receiving atazanavir/ritonavir and lopinavir/ritonavir, respectively.

Figure 3 shows that the mean percentage changes in fasting lipid concentrations over 96 weeks were generally greater in women and men receiving lopinavir/ritonavir than in those receiving atazanavir/ritonavir. In the atazanavir/ritonavir arm, mean changes from baseline in all lipid parameters were lower in women than in men. In the lopinavir/ritonavir arm, mean changes from baseline were lower in women than in men for non-high-density lipoprotein (non-HDL) cholesterol and triglycerides, higher for women than men for HDL cholesterol and similar in women and men for total cholesterol and low-density lipoprotein (LDL) cholesterol. More women and men receiving lopinavir/ritonavir (9%) than atazanavir/ritonavir (2%) initiated lipid-lowering therapy after the start of study therapy. Women and men in both treatment groups had optimal median fasting total cholesterol, HDL cholesterol, non-HDL cholesterol and LDL cholesterol concentrations at week 96 as defined by the NCEP ATP III guidelines. Men receiving lopinavir/ritonavir had median fasting triglyceride concentrations (177 mg/dL) above the NCEP ATP III guidelines at 96 weeks.

Discussion

The findings of this analysis of response to therapy across male and female genders were consistent with the overall results for the CASTLE study.[17] In the ITT analysis, women and men

receiving atazanavir/ritonavir had higher virological response rates than those receiving lopinavir/ritonavir, and women in either treatment arm had lower virological response rates than men. Through 96 weeks of treatment, gastrointestinal tolerability was better and there was less elevation of lipids among women and men receiving atazanavir/ritonavir than those receiving lopinavir/ritonavir, which is similar to the trend observed in the overall population.[17] It is possible that increased gastrointestinal toxicity contributed to the higher rate of treatment discontinuation in the lopinavir/ritonavir group; however, this requires further investigation.

The virological responses observed in the 96 week CASTLE study are comparable to those reported for other studies of atazanavir/ritonavir[19,20] and lopinavir/ritonavir[21,22] after taking into account the different study designs and subjects. The findings are also consistent with those reported for studies of other PIs.[6,21–24] Findings from our CVR analysis suggest that the efficacy of atazanavir/ritonavir and lopinavir/ritonavir may be lower in women than in men. However, these differences were not observed in the VR-OC on-treatment analysis, which showed that all observed virological response rates were comparable between treatment groups and between genders after 96 weeks of treatment. These findings are consistent with the overall results for the CASTLE study in which the difference in response between treatment arms in the ITT analysis at 96 weeks was driven by a similar virological response rate with a higher rate of discontinuation among patients receiving lopinavir/ritonavir.[17] In this analysis, the difference in virological response observed between genders in the ITT analysis at 96 weeks may have been due to the higher rate of discontinuation among women than among men in each treatment arm. Similar differences in response to once- or twice-daily lopinavir/ritonavir and tenofovir/emtricitabine between men and women have been reported,[25] while other studies have found no gender-related differences in response rates to fosamprenavir/ritonavir[26] and darunavir/ritonavir[6,27] in treatment-naive patients or combination ARV regimens in general.[28]

In our study, a greater proportion of women than men discontinued the study before week 96 in both treatment groups, a trend that has also been observed in previous studies.[5–9] This difference in the rate of discontinuation was partly driven by pregnancy (4%–5%) among women in both treatment groups. In addition, more women (6%) than men (3%) discontinued due to suboptimal adherence in the lopinavir/ritonavir arm. Whether the difference in compliance between women in the two treatment arms and between women and men is related to the higher rate of gastrointestinal side effects with lopinavir/ritonavir is unknown. There are several factors that may influence women's compliance with HIV regimens, including busy daily schedules, childcare responsibilities, social relationships, emotional well-being and therapy-induced changes in body appearance, such as weight gain.[29]

It is not known why women discontinue clinical trials more frequently than men. The Gender, Race and Clinical Experience (GRACE) study, which assessed darunavir/ritonavir (plus investigator-selected background regimens) in 287 and 142 treatment-experienced HIV-infected men and women, respectively, found a similar trend. At 48 weeks there was a higher-than-expected rate of discontinuation due to loss of follow-up, relocation and withdrawal of consent.[5] Although the numbers of women in clinical trials is increasing, their numbers remain low at only 20% in the AIDS Clinical Trials Group (ACTG5142) study,[30] 22% in the KLEAN study,[21] 30% in the ARTEMIS study[22] and 31% in the CASTLE study.[16]

There are several factors exclusive to women that may influence the decision to enrol in, or continue to participate in, a clinical study. Women of childbearing potential need to consider what contraception they would use when participating in clinical studies as few ARV drugs are indicated for concomitant use with contraceptive drugs.[3,31–33] Several PIs may increase or decrease the levels of contraceptives and may result in adverse events.[14] The potential teratogenic risk if pregnancy should occur may also deter women from enrolling or continuing in clinical studies. Nonetheless, for HIV-infected women who want to become pregnant, ARV therapy can reduce the risk of mother-to-child HIV transmission.[3,14] HIV-infected women are also more likely to have financial problems or experience discrimination than HIV-infected men and this may influence a woman's willingness to participate in a clinical study.[34] However, most of these data are obtained from studies carried out in the developing world. Until more women from the developed world participate in clinical studies, the reasons for fewer enrolments and more discontinuations among women than among men will not be fully understood.

Limitations of the study include its open-label design, and the fact that it was not specifically designed or powered to investigate the influence of gender on outcomes. A larger number of female patients would enable more meaningful comparisons between the two treatment groups.

In summary, the results of this study show that atazanavir/ritonavir is an effective once-daily boosted PI regimen that in combination with other ARVs is well tolerated and appropriate for use in HIV-infected women and men. The lower response rates observed in women than in men may have been due to higher discontinuation rates in women in both treatment arms, suggesting the need for additional research to understand the reasons why women are less likely to complete clinical trials.

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C. Jenkins and J. Turner, of PAREXEL, provided assistance in preparing and editing the manuscript.

Author contributions

D. M. and R. Y. provided scientific input into the study design and study protocol. R. Y. did all the statistical analyses. All authors assessed clinical data from the study and contributed to the drafting and editing of the manuscript.

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