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Gender-Based Differences in ARV-Naïve Patients Treated With Boosted Protease Inhibitors: Results From the CASTLE Study (AI424138)

Bristol-Myers Squibb
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BACKGROUND

Introduction

- Gender-based differences in efficacy and safety have been reported among HIV-infected individuals receiving highly active antiretroviral therapy (HAART) and may relate to sex-based differences in pharmacokinetic and pharmacodynamic drug handling.[1-4]
- It has been noted that women may experience higher toxicity profiles while receiving antiretroviral (ARV)-treatment regimens; however, data from randomized clinical trials are limited.[4,5]
- Women are recognized as the fastest growing population of patients with HIV/AIDS.[2]
- Gender differences affecting either response to, or safety of, ARV-treatment regimens may be important to consider when selecting regimens intended for long-term control of HIV infection, particularly among women.
- Atazanavir (ATV) is a potent, generally well-tolerated, once-daily HIV-1 protease inhibitor (PI) extensively studied in treatment-naïve and treatment-experienced patients and a common component of HAART.[6,7]
- The CASTLE study demonstrated that in combination with tenofovir disoproxil fumarate/emtricitabine, ATV/ritonavir (RTV) is noninferior to lopinavir (LPV)/RTV in antiviral efficacy in treatment-naïve patients at 48 weeks, with significantly less elevation of lipids and better gastrointestinal (GI) tolerability.[8]
- CASTLE is an international randomized clinical trial in 134 sites in 29 countries.[a]
- This large-scale study, which included male and female HIV-infected, ARV-naïve patients, affords the opportunity to assess potential gender differences in the efficacy and safety profiles of the 2 most commonly used PIs in HIV treatment.

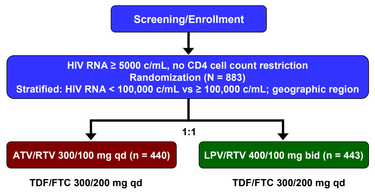
Objective

- To assess and compare the virologic, immunologic, and safety profiles of an ATV/RTV-based regimen with an LPV/RTV-based regimen by gender using 48-week data from the CASTLE study.

Methods

- CASTLE is a randomized, open-label, prospective study comparing once-daily ATV/RTV with twice-daily LPV/RTV, both in combination with fixed-dose tenofovir/emtricitabine (TDF/FTC) in 883 treatment-naïve HIV-infected patients (**Figure 1**).

Figure 1. CASTLE Study Design[3]



- Through the first 48 weeks of the study, the protocol required patients to receive the capsule formulation of LPV/RTV.
- The primary end point was the proportion of patients with HIV RNA < 50 c/mL at Week 48.
- Secondary assessments included CD4 cell count change and safety parameters (adverse events [AEs] and laboratory tests [eg, serum chemistry and hematology, fasting lipid profile]).
- Treatment comparisons by gender were prespecified; however, comparisons of lipid parameters by gender were post hoc analyses.

RESULTS

- Baseline patient characteristics by gender are presented in **Table 1**.
- Of the 883 randomized patients within CASTLE, 277 patients (31%) overall were female. Baseline characteristics were comparable by gender for both arms (**Table 1**).

Table 1. CASTLE Study Baseline Characteristics By Gender

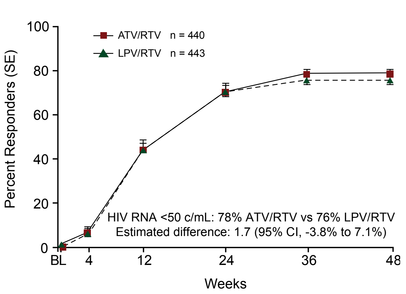
	ATV/RTV n = 440		LPV/RTV n = 443	
	Female n = 138	Male n = 302	Female n = 139	Male n = 304
Age, median years (min, max)	33 (20, 56)	35 (19, 72)	37 (19, 63)	36 (19, 71)
Region, n (%)				
Africa	33 (24)	34 (11)	41 (29)	24 (8)
Asia	15 (11)	24 (8)	12 (9)	28 (9)
Europe	15 (11)	50 (17)	13 (9)	53 (17)
North 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 $\log_{10}$ c/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 ≥ 100,000 c/mL, n (%)	56 (40)	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)

CDC, Centers for Disease Control and Prevention.

Virologic and Immunologic Responses

- Overall, once-daily ATV/RTV-based HAART demonstrated similar efficacy to twice-daily LPV/RTV-based HAART: 78% of patients on ATV/RTV and 76% on LPV/RTV achieved HIV RNA < 50 c/mL at Week 48 (difference estimate 1.7% [95% CI, -3.8% to 7.1%]) using an intent-to-treat (ITT) analysis, confirmed virologic response (CVR) noncompleter = failure (NC = F).

Figure 2. Overall CASTLE Population: Primary Efficacy End Point, ITT-CVR[3]



BL, baseline.

- Virologic response rates were consistently high in both male and female patients (**Table 2**).
- Overall, mean CD4 cell count changes from baseline at Week 48 were 203 cells/mm^3 on ATV/RTV and 219 cells/mm^3 on LPV/RTV. These results were consistent in both male and female patients (**Table 2**).

Table 2. Efficacy of Treatment by Gender: Proportion of Patients With HIV RNA < 50 c/mL and CD4 Cell Count Changes From Baseline at Week 48

Randomized Patients	HIV RNA < 50 c/mL (CVR NC = F) at Week 48: Responder/Evaluable (%)		Mean CD4 Cell Count Change From Baseline [SE], cells/mm^3		Absolute CD4 Cell Count at Week 48 [SE], cells/mm^3	
Gender	ATV/RTV	LPV/RTV	ATV/RTV	LPV/RTV	ATV/RTV	LPV/RTV
Female	105/138 (76)	101/139 (73)	199 [11.8]	221 [12.5]	406 [16.5]	417 [15.4]
Male	238/302 (79)	237/304 (78)	205 [8.7]	219 [8.9]	418 [12.2]	448 [12.0]

Adverse Events

- AEs were not treatment-limiting in most cases.
- The rates of select GI grade 2 to 4 treatment-related AEs, by gender and treatment arm, are shown in **Table 3**.

Table 3. Safety of Treatment by Gender: Grade 2 to 4 Treatment-Related AEs Through Week 48—Treated Patients: All AEs and Selected AEs of Clinical Interest

	All Grade 2 to 4 Treatment-Related AEs		Diarrhea		Nausea		Vomiting	
Gender	ATV/RTV n/N (%)	LPV/RTV n/N (%)	ATV/RTV n/N (%)	LPV/RTV n/N (%)	ATV/RTV n/N (%)	LPV/RTV n/N (%)	ATV/RTV n/N (%)	LPV/RTV n/N (%)
Female	42/138 (30)	45/139 (32)	4/138 (3)	13/139 (9)	9/138 (7)	19/139 (14)	1/138 (< 1)	3/139 (2)
Male	73/303 (24)	84/298 (28)	6/303 (2)	37/298 (12)	8/303 (3)	14/298 (5)	3/303 (< 1)	3/298 (1)

- GI adverse events generally occurred at higher frequencies in patients on the LPV/RTV rather than the ATV/RTV regimen.
- In the LPV/RTV-treatment group there appeared to be a tendency for women to experience more nausea and men to experience more diarrhea.
- Other grade 2 to 4 treatment-related GI AEs were reported by ≤ 1% of men or women in either treatment arm through 48 weeks.
- Grade 2 to 4 treatment-related jaundice was reported in 4% of male patients and 3% of female patients receiving ATV/RTV, and in no patients receiving LPV/RTV.
- The rates of other grade 2 to 4 treatment-related AEs differed less than 5% between genders within system organ class for both regimens.

Lipid Parameters

- Differences have been reported between ATV/RTV and LPV/RTV at 48 weeks in the overall CASTLE population in terms of changes in lipid profile from baseline.[8]
  - Mean percent increases in fasting total cholesterol, non–high-density lipoprotein cholesterol (non–HDL-C), and triglycerides (TGs) were higher with LPV/RTV than ATV/RTV (all $P < 0.0001$).
  - More patients taking LPV/RTV (8%) than ATV/RTV (2%) initiated lipid-lowering therapy.
- Post hoc analyses of 48-week data show that the changes in fasting total cholesterol, non–HDL-C, and TGs remained lower on ATV/RTV than LPV/RTV, regardless of gender (**Table 4**).

Table 4. Change in Fasting Lipid Parameters From Baseline at Week 48 By Treatment Group and Gender

	Female				Male			
Fasting Lipid	ATV/RTV		LPV/RTV		ATV/RTV		LPV/RTV	
mg/dL	Median (min, max)	Change From BL	Median (min, max)	Change From BL	Median (min, max)	Change From BL	Median (min, max)	Change From BL
TC	164 (85, 313)	10	182 (73, 368)	29	166 (77, 305)	23	186 (94, 312)	38
HDL-C	47 (28, 89)	8	50 (19, 135)	13	44 (24, 91)	9	46 (19, 92)	9
Non–HDL-C	117 (50, 255)	0	130 (40, 327)	18	119 (26, 259)	13	139 (42, 272)	26
LDL-C	104 (35, 251)	5	108 (24, 238)	12	100 (23, 286)	12	108 (85, 128)	17
TG	97 (40, 324)	17	133 (44, 506)	34	140 (35, 609)	19	180 (42, 773)	64

TC, total cholesterol; LDL-C, low-density lipoprotein cholesterol.

CONCLUSIONS

- In treatment-naïve patients, once-daily ATV/RTV demonstrated similar antiviral efficacy to twice-daily LPV/RTV, and both regimens were associated with robust increases in CD4 cell count, regardless of gender.
- Once-daily ATV/RTV was associated with a lower incidence of GI-related AEs and a significantly better lipid profile than LPV/RTV, regardless of gender.
- ATV/RTV is an effective once-daily boosted PI regimen that in combination with other ARVs is well tolerated and is appropriate for use in HIV-infected treatment-naïve female and male patients.

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[a]Countries of research: Argentina, Australia, Austria, Belgium, Brazil, Canada, Chile, Colombia, Costa Rica, Dominican Republic, France, Germany, Guatemala, Hong Kong, Indonesia, Mexico, The Netherlands, Panama, Peru, Portugal, Puerto Rico, Singapore, South Africa, Spain, Taiwan, Province of China, Thailand, United Kingdom, United States.