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Efficacy and Safety By Racial Group in ARV-Naïve Subjects Treated With Atazanavir/Ritonavir or Lopinavir/Ritonavir: 48-Week Results for the CASTLE Study (AI424138)

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BACKGROUND

Introduction

- Race-based differences in efficacy and safety have been reported among HIV-infected individuals receiving highly active antiretroviral therapy (HAART), but data from randomized clinical trials are limited.[1-3]
- Globally, there is a growing increase in obesity, diabetes, and the metabolic syndrome, and there are reports that certain ethnic groups may be more susceptible to the risks posed by these conditions.[4,5]
- Atazanavir-boosted with ritonavir (ATV/RTV) is a potent, generally well-tolerated, once-daily HIV-1 protease inhibitor (PI) extensively studied in treatment-naïve and treatment-experienced patients.[6-8]
- CASTLE demonstrated that in combination with tenofovir disoproxil fumarate/emtricitabine, ATV/RTV is noninferior to lopinavir/RTV (LPV) in antiviral efficacy in treatment-naïve patients at 48 weeks, with significantly less elevation of lipids and better gastrointestinal (GI) tolerability.[8]
- This large-scale study provides the opportunity to assess potential differences in treatment efficacy and safety among antiretroviral-naïve HIV-infected patients from a number of racial/ethnic backgrounds.

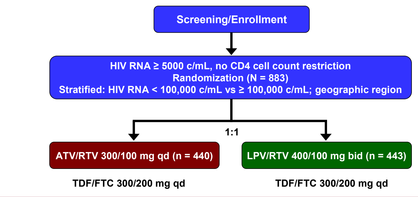
Objective

- To analyze the CASTLE 48-week efficacy and safety data by racial/ethnic group and to assess the virologic, immunologic, and safety profiles of both an ATV/RTV-based regimen and an LPV/RTV-based regimen.

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 treatment-naïve HIV-infected patients (**Figure 1**).
- The primary end point was proportion of patients with HIV RNA < 50 c/mL at Week 48.
- The proportion of patients with HIV RNA < 50 c/mL (confirmed virologic response [CVR], noncompleter equals failure [NC = F]), CD4 cell count changes, adverse events (AEs), and fasting lipid changes are presented by race through Week 48 for this analysis.
- Demographic data collected at baseline included race and ethnicity categorized as white, black, Asian, or other.

Figure 1. CASTLE Study Design[8]



RESULTS

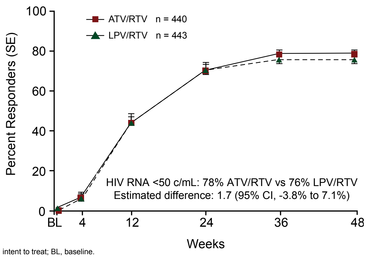
- Of 883 randomized patients, 48% were white, 18% were black, 9% were Asian, and 24% were other (comprising Hispanic/Latino 6%, Mestizo 67%, mixed race 27%).
- Racial/ethnic classification was similar between the 2 treatment arms.

Virologic and Immunologic Responses

Total Study Population

- In the primary analysis, once-daily ATV/RTV was noninferior to twice-daily LPV/RTV (**Figure 2**).

Figure 2. Overall CASTLE Population: Primary Efficacy End Point, ITT-CVR[8]



ITT, intent to treat; BL, baseline.

Racial/Ethnic Subgroups

- Virologic response rates to the regimens were consistently high across all racial/ethnic subgroups (**Table 1**).
- The magnitude of immunologic response (median increase in CD4 cell count) was lowest among black patients for both regimens (**Table 1**).

Table 1. Efficacy of Treatment by Race/Ethnicity: The Proportion of Patients With HIV RNA < 50 c/mL (CVR, NC = F) and CD4 Cell Count Changes From Baseline (cells/mm^3) at Week 48 in Different Race Groups Within the CASTLE Study

Randomized Patients, Race/Ethnicity	HIV RNA < 50 c/mL at Week 48: Responder/Evaluable (%); ITT		CD4 Cell Count Change From Baseline at Week 48 (cells/mm^3): Median (Q1, Q3) [N Observed]	
	ATV/RTV n = 440	LPV/RTV n = 443	ATV/RTV n = 440	LPV/RTV n = 443
All	343/440 (78)	338/443 (76)	191 (114, 271) [370]	200 (122, 291) [363]
White	159/207 (77)	162/221 (73)	226 (135, 313) [170]	204 (126, 299) [181]
Black	59/83 (71)	62/80 (78)	142 (85, 222) [66]	190 (133, 261) [65]
Asian	35/42 (83)	37/41 (90)	198 (135, 240) [36]	220 (100, 330) [37]
Other	90/108 (83)	77/101 (76)	188 (110, 255) [98]	193 (124, 274) [80]

Adverse Events

- AEs were not treatment-limiting in most cases; the incidence of AEs leading to discontinuation of study therapy was low in the overall population (2% ATV/RTV and 3% LPV/RTV).
  - More patients receiving ATV/RTV discontinued due to jaundice/hyperbilirubinemia (< 1% vs 0), while more patients receiving LPV/RTV discontinued due to diarrhea (< 1% vs 0).
- Grade 2 to 4 treatment-related AEs stratified by race/ethnicity and treatment arm are shown in **Table 2**.

Table 2. Grade 2 to 4 Treatment-Related AEs at Week 48 (Treated Patients) by Race/Ethnicity

	White		Black		Asian		Other	
	ATV/RTV	LPV/RTV	ATV/RTV	LPV/RTV	ATV/RTV	LPV/RTV	ATV/RTV	LPV/RTV
All n/N (%)	59/207 (29)	63/221 (29)	20/85 (24)	12/77 (16)	10/42 (24)	17/40 (43)	26/107 (24)	37/99 (37)
Diarrhea, %	4	14	1	5	0	10	< 1	10
Nausea, %	5	8	1	3	0	8	5	11
Jaundice, %	6	0	0	0	5	0	2	0

n/N indicates all AEs and selected AEs of clinical interest.

- Overall, the incidences of jaundice and hyperbilirubinemia (all grades) were lowest in blacks (2% and 4%, respectively) and highest in Asians (26% and 40%, respectively) in the ATV/RTV group.
- **Table 3** shows all grade and grade 3 to 4 laboratory abnormalities in bilirubin.

Table 3. Percentage of Patients in Each Racial/Ethnic Group With All Grade and Grade 3 to 4 (≥ 2.6 × ULN) Laboratory Abnormalities in Bilirubin (Direct and Total Bilirubin)

	White (%)	Black (%)	Asian (%)	Other (%)
All Grade				
Direct bilirubin				
ATV/RTV	90	71	88	88
LPV/RTV	13	9	13	5
Total bilirubin				
ATV/RTV	89	64	93	87
LPV/RTV	4	5	10	3
Grade 3 to 4				
Direct bilirubin				
ATV/RTV	14	5	5	3
LPV/RTV	< 1	3	3	0
Total bilirubin				
ATV/RTV	37	25	38	31
LPV/RTV	< 1	0	0	0

ULN, upper limit of normal.

- **Table 4** provides the percentage of patients with grade 3 to 4 laboratory abnormalities by race/ethnicity (aspartate transaminase [AST], alanine transaminase [ALT], total cholesterol, and triglycerides).

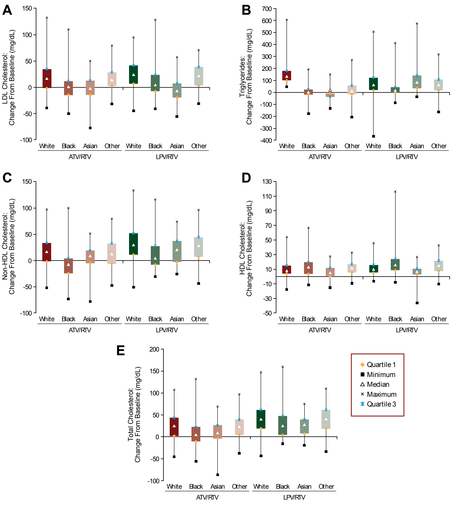
Table 4. Percentage of Patients With Grade 3 to 4 Laboratory Abnormalities for AST, ALT, Total Cholesterol, and Triglycerides by Race/Ethnicity

Abnormality	White (%)	Black (%)	Asian (%)	Other (%)
AST				
ATV/RTV	2	4	0	2
LPV/RTV	< 1	0	0	0
ALT				
ATV/RTV	2	2	0	2
LPV/RTV	< 1	1	8	0
Total cholesterol				
ATV/RTV	9	7	0	6
LPV/RTV	21	12	15	16
Triglycerides				
ATV/RTV	< 1	0	0	< 1
LPV/RTV	4	0	8	3

Lipid Parameters

- The percent increase in total cholesterol from baseline to Week 48 was 19% among blacks and Asians (both groups) receiving LPV/RTV, compared with 3% and 6%, respectively, for ATV/RTV.
- In the LPV/RTV group white patients had a 27% increase in total cholesterol and patients in the other racial/ethnic group had a 30% increase, compared with 15% and 17% increases, respectively, for patients in the white and other racial/ethnic groups receiving ATV/RTV.
- The most notable racial/ethnic trend in the data was an increase in triglycerides from baseline to Week 48 in the LPV/RTV group noted as a 100% increase in Asian patients and 60% increases in the white and other racial/ethnic groups.
- By contrast, triglyceride levels increased by 17% in whites, 0% in blacks, 21% in Asian, and 11% in the other racial/ethnic group treated with ATV/RTV.
- **Figure 3** shows change from baseline in fasting lipids (mg/dL) at Week 48 by treatment regimen and race/ethnicity.

Figure 3. Change From Baseline at Week 48 in LDL Cholesterol (A), Triglycerides (B), Non-HDL Cholesterol (C), HDL Cholesterol (D), and Total Cholesterol (E) (mg/dL) by Treatment Regimen and Race/Ethnicity



CONCLUSIONS

- Both once-daily ATV/RTV and twice-daily LPV/RTV regimens demonstrated overall high levels of virologic response and robust increases in CD4 cell count, but the regimens varied in efficacy and immunologic response by race/ethnicity.
- As anticipated, direct hyperbilirubinemia occurred more frequently with ATV/RTV than with LPV/RTV, but was not treatment-limiting.
- The rates of direct hyperbilirubinemia (all grade and grade 3-4) were slightly higher among whites than other ethnic groups, but were consistent with previous studies of ATV/RTV.
- As anticipated, patients on ATV/RTV had fewer gastrointestinal AEs regardless of race/ethnicity; among patients receiving LPV/RTV diarrhea was highest for white patients (14%) and lowest for black patients (5%).
- Patients receiving ATV/RTV had less elevation in total cholesterol, non-HDL cholesterol, and triglycerides regardless of race/ethnicity.
- The impact on some lipid parameters varied widely by race/ethnicity for ATV/RTV and LPV/RTV: Asian patients receiving LPV/RTV had a 100% increase in triglycerides, whereas black patients receiving ATV/RTV had no increase.
- While both ATV/RTV and LPV/RTV regimens show high levels of efficacy in all race/ethnicities at 48 weeks, variations in safety profiles, particularly gastrointestinal tolerability and increases in lipid parameters, discriminated between the 2 boosted PIs.
- These differences provide important information for clinicians to consider when selecting regimens intended for long-term control of HIV infection.

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