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Efficacy and Safety of Atazanavir/RTV vs. Lopinavir/RTV in Treatment-Naïve Patients with Advanced Disease: CASTLE Study 96-Week Results

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BACKGROUND

Introduction

- Atazanavir (ATV) is a potent, well-tolerated, once-daily HIV-1 protease inhibitor (PI) with established efficacy in both treatment-naïve and treatment experienced patients[1,2]
- The CASTLE study was an international, randomized, open-label, prospective study comparing the efficacy and safety of ATV/ritonavir (RTV) with that of lopinavir (LPV)/RTV (both given in combination with tenofovir/emtricitabine [TDF/FTC]) in treatment-naïve patients
- In the 96 Week analysis of CASTLE, the ATV/RTV-based regimen was shown to be noninferior in antiviral efficacy to the LPV/RTV-based regimen with better gastrointestinal (GI) tolerability and a better lipid profile[3]
- Efficacy and safety in patients with advanced HIV disease (low CD4 cell count and/or high HIV RNA) are of clinical interest and importance

Objective

- To explore the impact of baseline CD4 cell count and HIV RNA levels on virologic, immunologic, and safety profiles of ATV/RTV and LPV/RTV, both in combination with TDF/FTC, in treatment-naïve HIV-infected patients

Methods

- CASTLE was a 96 Week, randomized, open-label, prospective study comparing once-daily ATV/RTV (300/100 mg qd [n = 440]) with twice-daily LPV/RTV (400/100 mg bid [n = 443]), both in combination with fixed-dose TDF/FTC (300/200 mg qd) in 883 antiretroviral therapy (ART)-naïve HIV-infected patients
- Patients were stratified according to HIV RNA (< 100,000 copies/mL or ≥ 100,000 copies/mL) and geographic region
- The primary end point was the proportion of patients with HIV RNA < 50 copies/mL at Week 48
- Secondary assessments included proportion of patients with HIV RNA < 50 copies/mL at Week 96, CD4 cell count change, and safety parameters
- Pre-specified subgroup analyses to assess the impact of baseline CD4 cell count and HIV RNA levels on virologic response and changes in CD4 cell count were performed according to the following strata:
  - CD4 count (cells/mm^3): < 50; 50 to < 100; 100 to < 200, and ≥ 200
  - HIV RNA (copies/mL) < 100,000; 100,000 to <500,000, and ≥ 500,000
- Pre-specified subgroup analyses to assess the impact of baseline CD4 cell counts and HIV RNA levels together on virologic response were performed by CD4 counts (cells/mm^3) < 100 and ≥ 100 and HIV RNA (copies/mL) < 100,000 and ≥ 100,000
- Post hoc subgroup analyses to assess the impact of baseline CD4 cell count and HIV RNA on safety parameters were performed according to the same strata

RESULTS

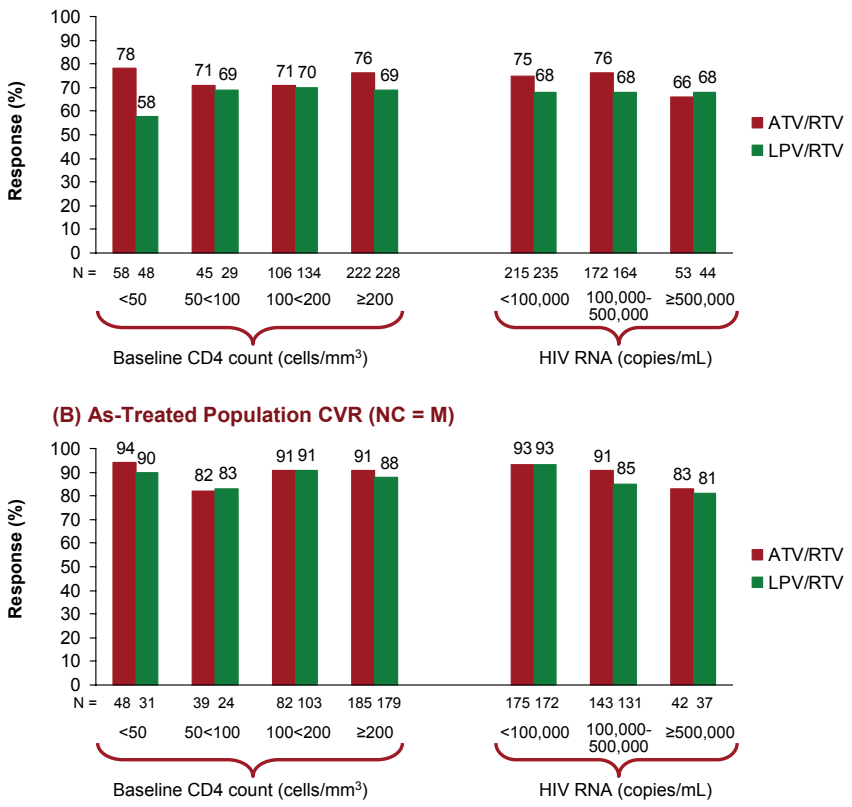
Patient Demographics and Disposition

- Patient characteristics (age, sex, and region) by baseline CD4 cell count and HIV RNA levels have been previously presented[4]
- Baseline characteristics were similar in the two treatment groups[4]

Virological and Immunologic Responses

- In the entire population, 74% of the patients receiving ATV/RTV and 68% of the patients receiving LPV/RTV achieved a confirmed virologic response (CVR) (HIV RNA < 50 copies/mL, intent-to-treat [ITT]) at Week 96 (difference estimate 6.1% [95% CI 0.3% to 12.0%], p < 0.05)
  - 78% of the patients receiving ATV/RTV and 76% of the patients receiving LPV/RTV achieved a CVR (HIV RNA < 50 copies/mL, ITT) at Week 48 (primary endpoint)
- Analyses of CVR according to CD4 cell count and HIV RNA strata at baseline are summarized in **Figures 1A and B**

Figure 1. CVR (HIV RNA < 50 copies/mL) by Baseline CD4 Cell Counts and HIV RNA Strata at Week 96 in (A) the ITT Population CVR (NC = F) and (B) the As-Treated Population CVR (NC = M)



- In patients with the lowest baseline CD4 cell count (< 50 cells/mm^3)
  - ITT analysis: CVR was 78% (45/58) versus 58% (28/48) for ATV/RTV and LPV/RTV, respectively
  - As-treated (AT) analysis: CVR was 94% (45/48) versus 90% (28/31) for ATV/RTV and LPV/RTV, respectively
- In patients with the highest baseline HIV RNA (≥ 500,000 copies/mL)
  - ITT analysis: CVR was 66% (35/53) versus 68% (30/44) for ATV/RTV and LPV/RTV, respectively
  - AT analysis: CVR was 83% (35/42) versus 81% (30/37) for ATV/RTV and LPV/RTV, respectively
- Patients with both baseline CD4 < 100 cells/mm^3 and HIV RNA ≥ 100,000 copies/mL, 59/83 (71%) on ATV/RTV and 39/64 (61%) on LPV/RTV achieved HIV RNA < 50 copies/mL (CVR, ITT)
- Higher response rates (ITT) at lower baseline HIV RNA were seen for ATV/RTV vs. LPV/RTV
- Discontinuations and virologic failures based on CVR treatment outcomes are summarized in **Table 1**

Table 1. Discontinuations and Virologic Failures Based on CVR Treatment Outcomes Through Week 96

	By Baseline CD4 Count Strata (cells/mm^3)				By Baseline HIV RNA Strata (copies/mL)		
	<50	50 – < 100	100 – < 200	≥ 200	< 100,000	100,000 - < 500,000	≥ 500,000
Discontinuations, n/N (%)							
ATV/RTV	9/58 (16)	5/45 (11)	16/106 (15)	27/222 (12)	29/215 (13)	21/172 (12)	8/53 (15)
LPV/RTV	16/48 (33)	2/29 (7)	24/134 (18)	42/228 (18)	53/235 (23)	25/164 (15)	7/44 (16)
Virologic Failure, n/N (%)							
ATV/RTV	4/58 (7)	8/45 (18)	15/106 (14)	24/222 (11)	22/215 (10)	21/172 (12)	10/53 (19)
LPV/RTV	4/48 (8)	7/29 (24)	15/134 (11)	27/228 (12)	21/235 (9)	25/164 (15)	7/44 (16)

Virologic failure is defined as patients who never suppressed on the study through Week 96, discontinued due to insufficient viral load response through Week 96, or rebounded without resuppression.

- In patients with the lowest baseline CD4 count (< 50 cells/mm^3), there were twice as many discontinuations on LPV/RTV (16/48 [33 %]) than on ATV/RTV (9/58 [16 %]) through Week 96
- The reasons for discontinuations in patients with the lowest baseline CD4 count (< 50 cells/mm^3) included:
  - ATV/RTV: 2% (1/58) adverse events, 3% (2/58) death, 2% (1/58) withdrew consent, 2% (1/58) nonadherent
  - LPV/RTV: 13% (6/48) adverse events, 4% (2/48) death, 6% (3/48) withdrew consent, 6% (3/48) nonadherent

- Analysis of mean change in CD4 cell count according to baseline CD4 count strata and HIV RNA strata are summarized in **Table 2**

Table 2. Mean Change in CD4 Cell Count (cells/mm^3) from Baseline to Week 96 by Baseline CD4 Count and HIV RNA Strata

	By Baseline CD4 Count Strata (cells/mm^3)				By Baseline HIV RNA Strata (copies/mL)		
	<50	50 - < 100	100 - < 200	≥ 200	< 100,000	100,000 - < 500,000	≥ 500,000
ATV/RTV	271 (n = 46)	296 (n = 37)	258 (n = 79)	266 (n = 174)	249 (n = 163)	281 (n = 132)	299 (n = 41)
LPV/RTV	338 (n = 29)	297 (n = 22)	294 (n = 97)	277 (n = 169)	258 (n = 159)	312 (n = 123)	354 (n = 35)

Tolerability and Safety

- The incidence of all treatment-related grade 2 to 4 adverse events and selected grade 2 to 4 treatment-related adverse events (AEs) of clinical interest through Week 96 are summarized by baseline CD4 cell count strata (**Figure 3 and Table 3**) and baseline HIV RNA strata (**Table 4**)

Figure 3. All Grade 2-4 Treatment-Related Adverse Events through Week 96 by Baseline CD4 Count and Baseline HIV RNA

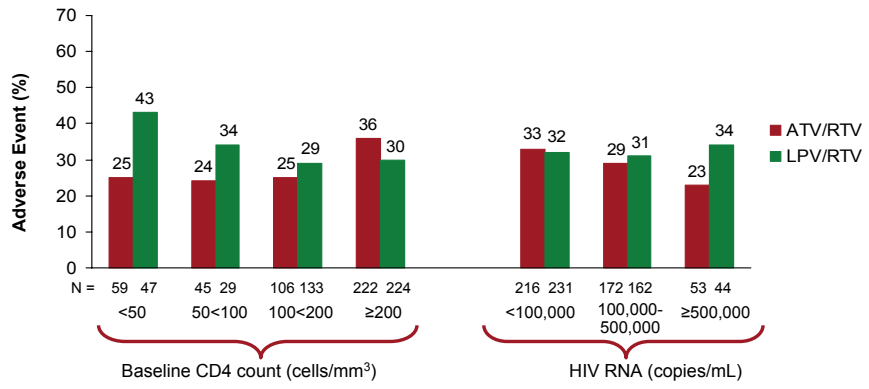


Table 3. Grade 2-4 Treatment-Related Adverse Events [n (%)] through Week 96 by Baseline CD4 Cell Count Strata

	ATV/RTV				LPV/RTV			
CD4 cell count (cells/mm^3)	<50	50-<100	100-<200	≥200	<50	50-<100	100-<200	≥200
	n = 59	n = 45	n = 106	n = 222	n = 47	n = 29	n = 133	n = 224
All	15 (25)	11 (24)	26 (25)	80 (36)	20 (43)	10 (34)	39 (29)	68 (30)
Jaundice	1 (2)	0	3 (3)	13 (6)	0	0	0	0
Diarrhea	0	1 (2)	3 (3)	7 (3)	8 (17)	3 (10)	13 (10)	29 (13)
Nausea	2 (3)	0	6 (6)	10 (5)	5 (11)	2 (7)	9 (7)	16 (7)

All adverse events and selected adverse events of clinical interest are in as-treated population.

Table 4. Grade 2-4 Treatment-Related Adverse Events [n (%)] through Week 96 by HIV RNA Strata

	ATV/RTV			LPV/RTV		
HIV RNA (copies/mL)	<100,000	100,000 - <500,000	≥ 500,000	<100,000	100,000 - <500,000	≥ 500,000
	n = 216	n = 172	n = 53	n = 231	n = 162	n = 44
All	71 (33)	50 (29)	12 (23)	75 (32)	50 (31)	15 (34)
Jaundice	9 (4)	7 (4)	2 (4)	0	0	0
Diarrhea	7 (3)	4 (2)	0	29 (13)	20 (12)	5 (11)
Nausea	10 (5)	8 (5)	0	18 (8)	13 (8)	2 (5)

All adverse events and selected adverse events of clinical interest are in as-treated population.

- A higher incidence of grade 2 to 4 treatment-related AEs was observed with LPV/RTV vs. ATV/RTV at low baseline CD4 cell counts (< 100 cells/mm^3)

CONCLUSIONS

- This subgroup analysis of CASTLE confirms that ATV/RTV is an effective and well-tolerated once-daily treatment that is appropriate for use in advanced HIV-infected treatment-naïve patients
- ATV/RTV demonstrated high response rates (ITT) across all CD4 cell count strata
- ATV/RTV demonstrated similar antiviral efficacy to LPV/RTV (AT) across all CD4 cell count strata
- More grades 2-4 treatment-related AEs were observed with LPV/RTV at low baseline CD4 cell counts
- Similar rates of grades 2-4 treatment-related AEs were observed with ATV/RTV across baseline CD4 and HIV RNA strata

REFERENCES

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