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Atazanavir/Ritonavir vs Lopinavir/Ritonavir in Antiretroviral-Naïve HIV-1–Infected Patients: CASTLE 96 Week Efficacy and Safety

J-M. Molina,[1] J. Andrade-Villanueva,[2] J. Echevarria,[3] P. Chetchotisakd,[4] J. Corral,[5] N. David,[6] M. Mancini,[7] R. Yang,[7] D. McGrath,[7] J. Absalon[7]

[1]Hôpital Saint-Louis, Paris, France; [2]Hospital Civil De Guadalajara, Guadalajara, Mexico; [3]Hospital Nacional Cayetano Heredia, Peru; [4]Khonkaen University, Khonkaen, Thailand; [5]Hospital Interzonal Gral. De Agudos Oscar Alende, Buenos Aires, Argentina; [6]Brooklyn Medical Centre, Western Cape, South Africa; [7]Bristol-Myers Squibb, Wallingford, CT, USA

Judith Absalon, MD, MPH
Bristol-Myers Squibb
Wallingford, CT
USA
Tel: 203-677-3856
E-mail: judith.absalon@bms.com

ABSTRACT

Background

- ATV/RTV has similar efficacy to LPV/RTV with more favorable lipid and GI profiles in treatment-naïve HIV-infected patients after 48 weeks of therapy. Efficacy and safety through Week (Wk) 96 are presented.

Methods

- Randomized, open-label, prospective study of once-daily ATV/RTV vs twice-daily LPV/RTV, both with fixed-dose tenofovir/emtricitabine in 883 treatment-naïve patients. Analyses at Wk 96: % with HIV RNA < 50 copies/mL (c/mL), emergence of resistance, adverse events (AEs), Δ CD4 cell count and fasting lipids.

Results

- Overall 19% of subjects discontinued before Wk 96 (16% ATV/RTV, 21% LPV/RTV); 39 LPV/RTV subjects (9%) switched to tablet formulation after Wk 48.

Efficacy Results at Wk 96 - As-randomized Subjects

	ATV/RTV (n = 440)	LPV/ RTV (n = 443)	Difference Estimate (95% CI; *P* Value) ATV/RTV - LPV/RTV
HIV RNA < 50 c/mL, n/N (%) CVR NC = F (ITT)	327/440 (74)	302/443 (68)	6.1 (0.3 to 12.0; *P* < 0.05)
Qualifying HIV RNA ≥ 100,000 c/mL	165/223 (74)	149/225 (66)	
Baseline CD4 < 50 cells/mm^3	45/58 (78)	28/48 (58)	
VR-OC (OT)	326/365 (89)	302/345 (88)	1.6 (-3.1 to 6.2, *P* = NS)
CD4, mean change from baseline, cells/mm^3	268	290	-21.2 (-43.3 to 0.9; *P* = NS)

- Virologic failure was low in both arms (30/440 ATV/RTV, 29/443 LPV/RTV, 7%).
- Grades 2-4 related hyperbilirubinemia was greater on ATV/RTV (7% vs < 1%); grades 2-4 related diarrhea (12% vs 2%) and nausea (8% vs 4%) were greater on LPV/RTV.
- Mean percent Δ in fasting TGs and TC from baseline were significantly lower on ATV/RTV vs LPV/RTV (13% vs 50% and 13% vs 25%, respectively; *P* < 0.0001).

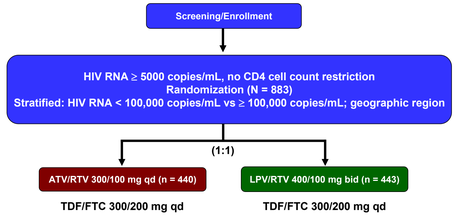
Conclusions

- Noninferiority of ATV/RTV vs LPV/RTV was confirmed at Wk 96. In the ITT analysis, ATV/RTV had higher response rates. This difference in response was driven by discontinuations among subjects on LPV/RTV. ATV/RTV continues to demonstrate a better lipid profile and fewer GI AEs vs LPV/RTV.

STUDY DESIGN

- International, multicenter, open-label, randomized, 96-week study to determine the comparative clinical efficacy and safety of ATV/RTV and LPV/RTV in treatment-naïve HIV-1–infected patients **(Figure 1)**.

Figure 1. Study Design



ATV/RTV, atazanavir/ritonavir; LPV/RTV, lopinavir/ritonavir; TDF, tenofovir; FTC, emtricitabine.

OBJECTIVES

Primary Objective

- Demonstrate noninferiority of ATV/RTV once daily versus LPV/RTV twice daily based on primary end point
  - Δ -10%, ATV/RTV - LPV/RTV

Primary End Point

- Proportion of subjects with HIV RNA < 50 copies/mL at Week 48
  - Principal analysis: confirmed virologic response, noncompleter = failure (CVR, NC = F) – intent-to-treat (ITT)
  - Supportive analyses:
    - Time to loss of virologic response (TLOVR – ITT)
    - Virologic response-observed cases (VR-OC) – on-treatment (OT)

Secondary End Points

- Proportion of subjects with HIV RNA < 50 copies/mL at Week 96
- Changes from baseline in absolute CD4 count through Week 96
- Resistance profiles; virologic failures; genotypic and phenotypic testing
- Adverse events (AEs)
- Changes in fasting lipids; fasting lipid National Cholesterol Education Program (NCEP) shift, and ratios

RESULTS

Table 1. Baseline Characteristics

	ATV/RTV (n = 440)	LPV/RTV (n = 443)
Age, median (min, max)	34 (19, 72)	36 (19, 71)
Female, n (%)	138 (31)	139 (31)
CDC Class C AIDS, n (%)	19 (4)	24 (5)
HIV RNA $\log_{10}$ copies/mL, median (min, max)	5.01 (2.60, 5.88)	4.96 (3.32, 5.88)
HIV RNA ≥ 100,000 copies/mL, n (%)[a]	223 (51)	225 (51)
CD4 cells/mm^3, median (min, max)	205 (2, 794)	204 (4, 810)
CD4 < 50 cells/mm^3, n (%)	58 (13)	48 (11)
Hepatitis B and/or C coinfection, n (%)	61 (14)	51 (12)

[a]Qualifying HIV RNA.

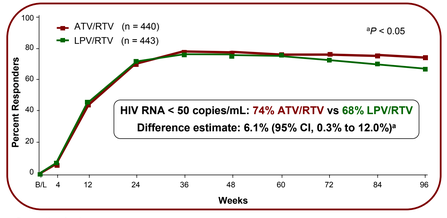
Table 2. Disposition

		ATV/RTV n (%)	LPV/RTV n (%)[a]	Total N (%)
Randomized		440	443	883
Treated		438 (> 99)	440 (> 99)	878 (99)
Discontinued before Week 96		72 (16)	95 (21)	167 (19)
AEs		13 (3)	22 (5)	35 (4)
Death		6 (1)	5 (1)	11 (1)
Lack of efficacy (Investigator specified term)[b]		16 (4)	10 (2)	26 (3)
Other		1 (< 1)	1 (< 1)	2 (< 1)
Lost to follow-up		10 (2)	13 (3)	23 (3)
Poor/Noncompliance		12 (3)	16 (4)	28 (3)
Pregnancy		5 (1)	7 (2)	12 (1)
No longer meets study criteria		4 (< 1)	3 (< 1)	7 (< 1)
Withdrew consent[c]		5 (1)	18 (4)	23 (3)

[a]39 subjects on LPV/RTV switched to tablet formulation between Weeks 48 and 96.
[b]Lack of efficacy was defined by the Investigator and could include reasons such as low adherence, AEs, etc, in addition to increasing viral load as the reason for treatment discontinuation.
[c]Reasons for withdrawal of consent—ATV: nonspecific (2), relocation (2), AE (1); LPV: nonspecific (9), relocation (3), LPV tablet preference (3), AE (2), wants daily regimen (1).

RESULTS

Figure 2. HIV RNA < 50 copies/mL (CVR, NC = F)



Supportive Analyses:
ITT–TLOVR: HIV RNA < 50 copies/mL: ATV/RTV 70%, LPV/RTV 63%; 6.6% (0.4% to 12.7%).
OT–VR-OC: HIV RNA < 50 copies/mL: ATV/RTV 89%, LPV/RTV 88%; 1.6% (-3.1% to 6.2%).

Figure 3. ITT-Confirmed Virologic Response (NC = F) by Qualifying HIV Viral Load

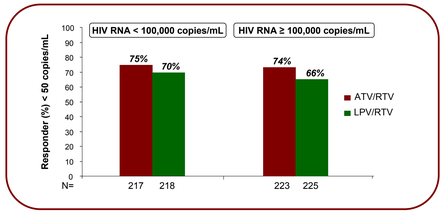
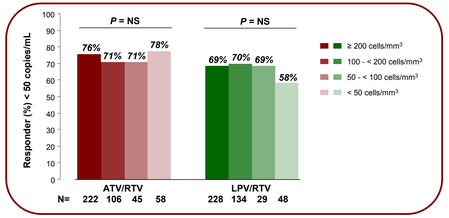


Table 3. Emergence of Resistance

		ATV/RTV (n = 438)	LPV/RTV (n = 443)
Virologic failure (subjects without baseline phenotypic PI resistance) through Week 96[a]		28 (6%)	29 (7%)
Paired genotypes		26	26
Major PI substitution[b]		1[c]	0
Minor PI substitution[b]		1[c]	1[d]
M184I/V		5	7
K65R		1	0
TAMs (M41L, D67N, K70R, L210W, T215FY, K219EQ)		1	3
Paired phenotypes		25	23
PI phenotypic resistance	ATV/RTV FC > 5.2	1	0
	LPV/RTV FC > 9	0	1
	Other RTV-boosted PIs	2	4
RTI phenotypic resistance	FTC FC > 3.5 or 3TC FC > 3.5	5	5
	TDF FC > 1.4	0	2
	Other NRTIs	3	5

[a]As-randomized subjects without baseline phenotypic resistance to on-treatment PI.
[b]IAS-USA PI mutations classified as major (D30N, V32I, M46I/L, I47A/V, G48V, I50LV, I54ALMSTV, L76V, V82AFLST, I84V, N88DS, L90M) or minor (L10FIRV, V11I, L24I, L33F, E35G, K43T, F53LY, Q58E, A71ITV, G73ACST, T74P, N83D, L89V) according to the Stanford HIV Database.
[c]Single subject with both major and minor substitutions: L10F, V32I, K43T, M46I, A71I, G73S, L90M; 1 additional subject on ATV/RTV with emergent major PI substitutions at Week 48 not listed at Week 96 due to subsequent virologic re-suppression.
[d]Baseline PI substitutions: V32I, I54IV, V82VA, L90M L10LI, A71I, G73GS, L89V (LPV FC 6.09); additional minor PI substitutions at virologic failure: L10V, V11I (LPV FC 69).

Figure 4. ITT-Confirmed Virologic Response (NC = F) by Baseline CD4 Cell Count



P values are from Cochran-Armitage trend test.

Table 4. CVR (HIV RNA < 50 copies/mL) Treatment Outcomes at Week 96 Among Subjects With Advanced Disease

	ATV/RTV (n = 440) n (%)		LPV/RTV (n = 443) n (%)	
	CD4 < 50[a] (n = 58)	CD4 < 100[a] and HIV RNA ≥ 100,000[b] (n = 83)	CD4 < 50[a] (n = 48)	CD4 < 100[a] and HIV RNA ≥ 100,000[b] (n = 64)
Virologic response CVR (NC = F)	45 (78)	59 (71)	28 (58)	39 (61)
Virologic failure	4 (7)	11 (13)	4 (8)	10 (16)
Discontinued	9 (16)	13 (16)	16 (33)	15 (23)
AEs	1 (2)	1 (1)	6 (13)	5 (8)
Death	2 (3)	3 (4)	2 (4)	1 (2)
Withdrew consent	1 (2)	1 (1)	3 (6)	4 (6)
Nonadherent	1 (2)	3 (4)	3 (6)	3 (5)
Other[c]	4 (7)	5 (6)	2 (4)	2 (3)

[a]CD4 cell count in cells/mm^3.
[b]HIV RNA in copies/mL.
[c]Other includes: pregnancy, subject no longer meets study criteria, lost to follow-up.

Figure 5. As-randomized CD4 Mean Change From Baseline

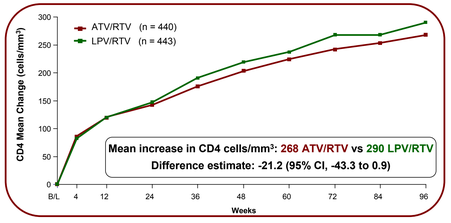


Table 5. Adverse Events Summary

		ATV/RTV (n = 441)	LPV/RTV (n = 437)
Serious adverse events (SAEs), n (%)		63 (14)	50 (11)
Grade 2-4 treatment-related AEs[a], n (%)		133 (30)	140 (32)
Grade 2-4 treatment-related AEs ≥ 3%[a,b], n (%)	Jaundice	18 (4)	0
	Nausea	18 (4)	33 (8)
	Diarrhea	11 (2)	54 (12)

- 39 (9%) subjects on ATV/RTV versus 96 (22%) subjects on LPV/RTV initiated antidiarrheal medications
- 7 subjects discontinued due to diarrhea (all on LPV/RTV)
  - 2 between Weeks 48 and 96
- 3 discontinuations on ATV/RTV due to jaundice/hyperbilirubinemia
  - None between Weeks 48 and 96
- Renal all-grade AEs: 4% in both arms
  - 1 discontinuation due to renal AE in each arm

[a]Through 96 weeks.
[b]Excluding laboratory abnormalities reported as AEs.

Table 6. Selected Grade 3-4 Laboratory Abnormalities

	ATV/RTV (n = 441) n (%)	LPV/RTV (n = 437) n (%)
Total bilirubin elevation (> 2.5 × ULN)	192 (44)	3 (< 1)
ALT elevation (> 5 × ULN)	11 (3)	7 (2)
AST elevation (> 5 × ULN)	11 (3)	5 (1)
Total cholesterol (TC) (≥ 240 mg/dL)	47 (11)	108 (25)
Triglycerides (TG) (≥ 751 mg/dL)	3 (< 1)	18 (4)
Hyperglycemia (≥ 251 mg/dL)	3 (< 1)	2 (< 1)

- Change from baseline at 96 weeks in renal function:
  - Median calculated creatinine clearance: -1% ATV/RTV and -2% LPV/RTV

Table 7. As-treated Mean Fasting Lipids at Baseline and Week 96

	ATV/RTV (n = 441)			LPV/RTV (n = 437)			
Mean Value (mg/dL)	B/L (SE)	Wk 96 (SE)	Δ	B/L (SE)	Wk 96 (SE)	Δ	Difference Estimate (95% CI) ATV/RTV - LPV/RTV
TC	149 (1.8)	169 (2.0)	13%	150 (1.7)	186 (2.4)	25%	-8.9%[a] (-11.6% to -6.1%)
LDL-C	92 (1.5)	105 (1.7)	14%	93 (1.4)	110 (2.0)	17%	-1.7% (-5.9% to 2.6%)
HDL-C	37 (0.6)	44 (0.6)	21%	36 (0.6)	46 (0.8)	29%	-5.5% (-10.0% to -0.8%)
Non–HDL-C	112 (1.5)	125 (1.9)	11%	114 (1.5)	140 (2.3)	23%	-9.7%[a] (-13.0% to -6.3%)
TG	126 (3.7)	140 (4.1)	13%	129 (3.9)	184 (5.9)	50%	-24.5%[a] (-29.9% to -18.8%)

- Values presented are observed values. Analyses using last observation carried forward (LOCF) are consistent with the above results. Values were excluded after the start of serum lipid reduction therapy.
[a]*P* < 0.0001.

Table 8. Fasting Lipids: NCEP and Ratios

	ATV/RTV (n = 441)		LPV/RTV (n = 437)	
NCEP shifts up (≥ 1 category)				
TC	16%		29%	
LDL-C	32%		40%	
TG	23%		49%	
	Baseline	Week 96	Baseline	Week 96
Total:HDL-C ratio > 5	23%	17%	27%	27%

- 2% of subjects on ATV/RTV versus 9% of subjects on LPV/RTV initiated lipid-lowering drugs on study.

CONCLUSIONS

- Noninferiority of once-daily ATV/RTV compared with twice-daily LPV/RTV was confirmed at Week 96
- In the ITT analysis, ATV/RTV had higher response rates than LPV/RTV
  - This difference, not observed in the on-treatment analysis, was driven by similar virologic efficacy and a higher rate of discontinuations among patients receiving LPV/RTV
- High response rates with ATV/RTV were demonstrated irrespective of disease severity at baseline (high viral load, low CD4 count)
- Virologic failure rates were low and the emergence of resistance was infrequent with both regimens
- ATV/RTV had a better lipid profile and more favorable gastrointestinal tolerability than LPV/RTV
  - Mean changes from baseline in fasting TC, non–HDL-C, and TG at Week 96 were significantly higher in patients receiving LPV/RTV than those receiving ATV/RTV
  - Fewer gastrointestinal events were experienced by patients receiving ATV/RTV than those receiving LPV/RTV
- No new or unexpected safety events were identified
- Once-daily ATV/RTV plus TDF/FTC demonstrated durable antiviral efficacy and safety. This regimen is an appropriate therapeutic option for antiretroviral-naïve HIV-1–infected patients.