Efficacy and Safety of Boosted Once-Daily Atazanavir and Twice-Daily Lopinavir Regimens in Treatment-Naïve HIV-1 Infected Subjects

CASTLE: 48-Week Results

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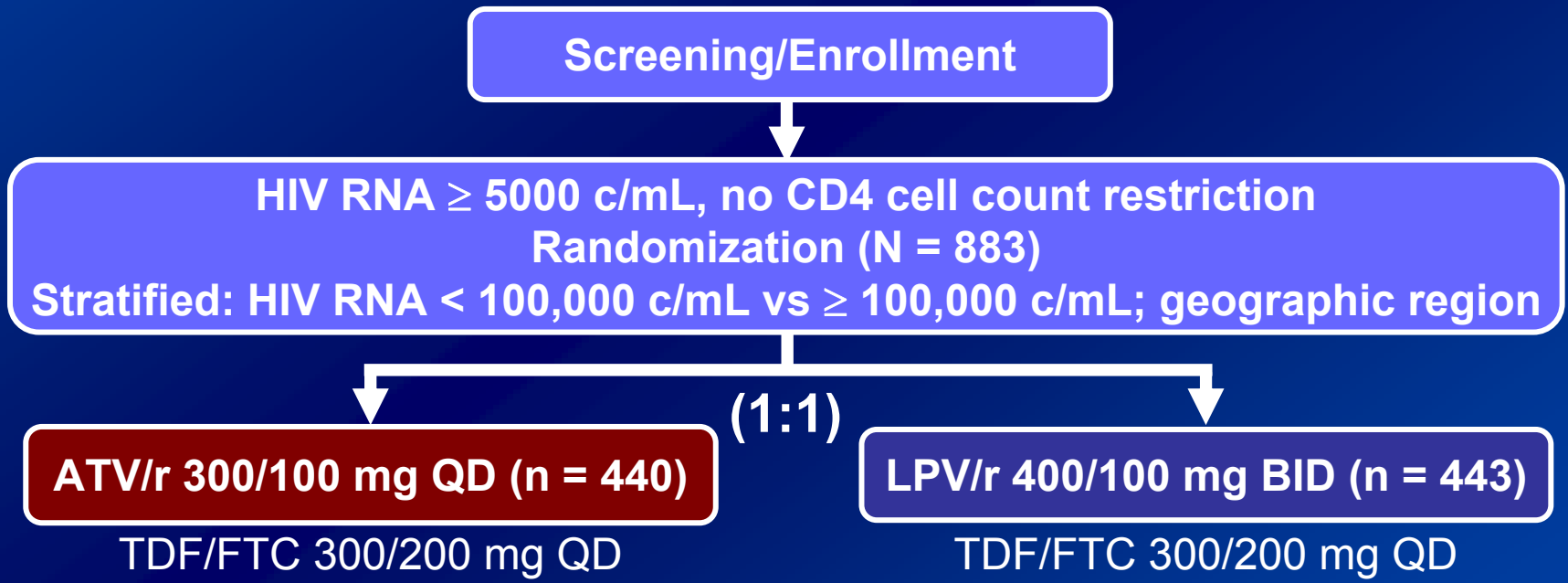
Study Design

International, multicenter, open-label, randomized, 96-week study to determine the comparative clinical efficacy and safety of ATV/r and LPV/r in treatment-naïve HIV-1 infected subjects



Study Objectives

Primary end point:

- **Proportion of subjects with HIV RNA < 50 c/mL at week 48**
  - Principal analysis: ITT-Confirmed Virologic Response (CVR) - (NC = F)
  - Supportive analyses:
    - ITT-TLOVR
    - On-treatment-Virologic Response Observed Cases (OT-VROC)

Primary objective:

- **Demonstrate noninferiority of ATV/r once daily vs LPV/r twice daily based on primary end point**
  - Δ -10%, ATV/r - LPV/r

Secondary end points:

- **Immunologic response**
- **Safety and tolerability**
- **Changes in fasting lipids**
- **Resistance**

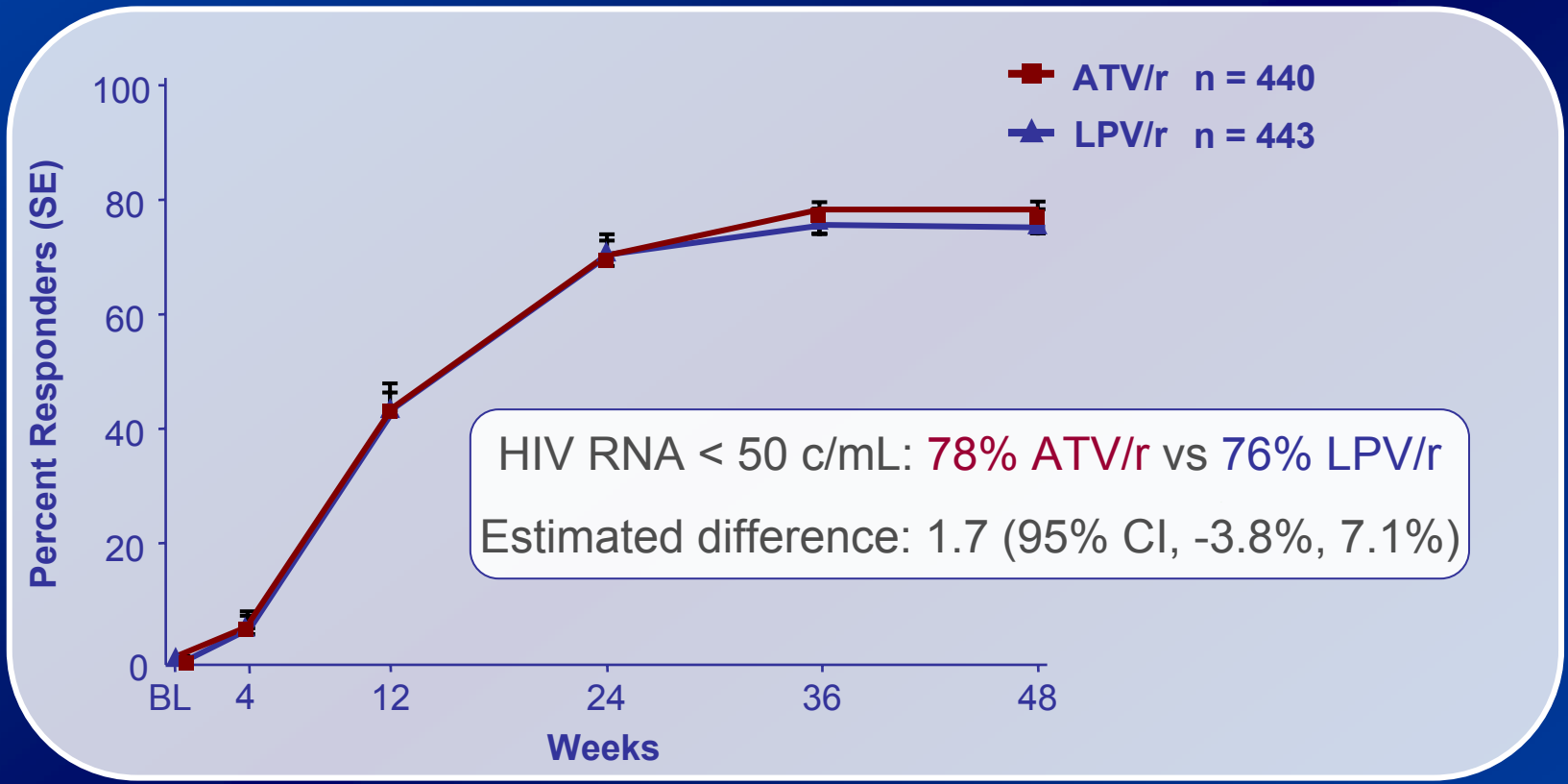
Baseline Characteristics

	ATV/r n = 440	LPV/r 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 $\log_{10}$ c/mL, median (min-max)	**5.01** (2.60-5.88)	**4.96** (3.32-5.88)
HIV RNA ≥ 100,000 c/mL, n (%)	**225** (51)	**208** (47)
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 co-infection, n (%)	**61** (14)	**51** (12)

Disposition

	ATV/r n = 440 n (%)	LPV/r n = 443 n (%)
Randomized	**440**	**443**
Treated	**438** (99)	**440** (99)
Discontinued before week 48	**39** (9)	**58** (13)
AEs	**10** (2)	**14** (3)
Death	**4** (< 1)	**4** (< 1)
Lack of efficacy	**5** (1)	**8** (2)
Lost to follow-up	**6** (1)	**6** (1)
Poor/noncompliance	**6** (1)	**9** (2)
Withdrew consent	**4** (< 1)	**13** (3)
Other (pregnancy, no longer meets study criteria, other)	**4** (< 1)	**4** (<1)

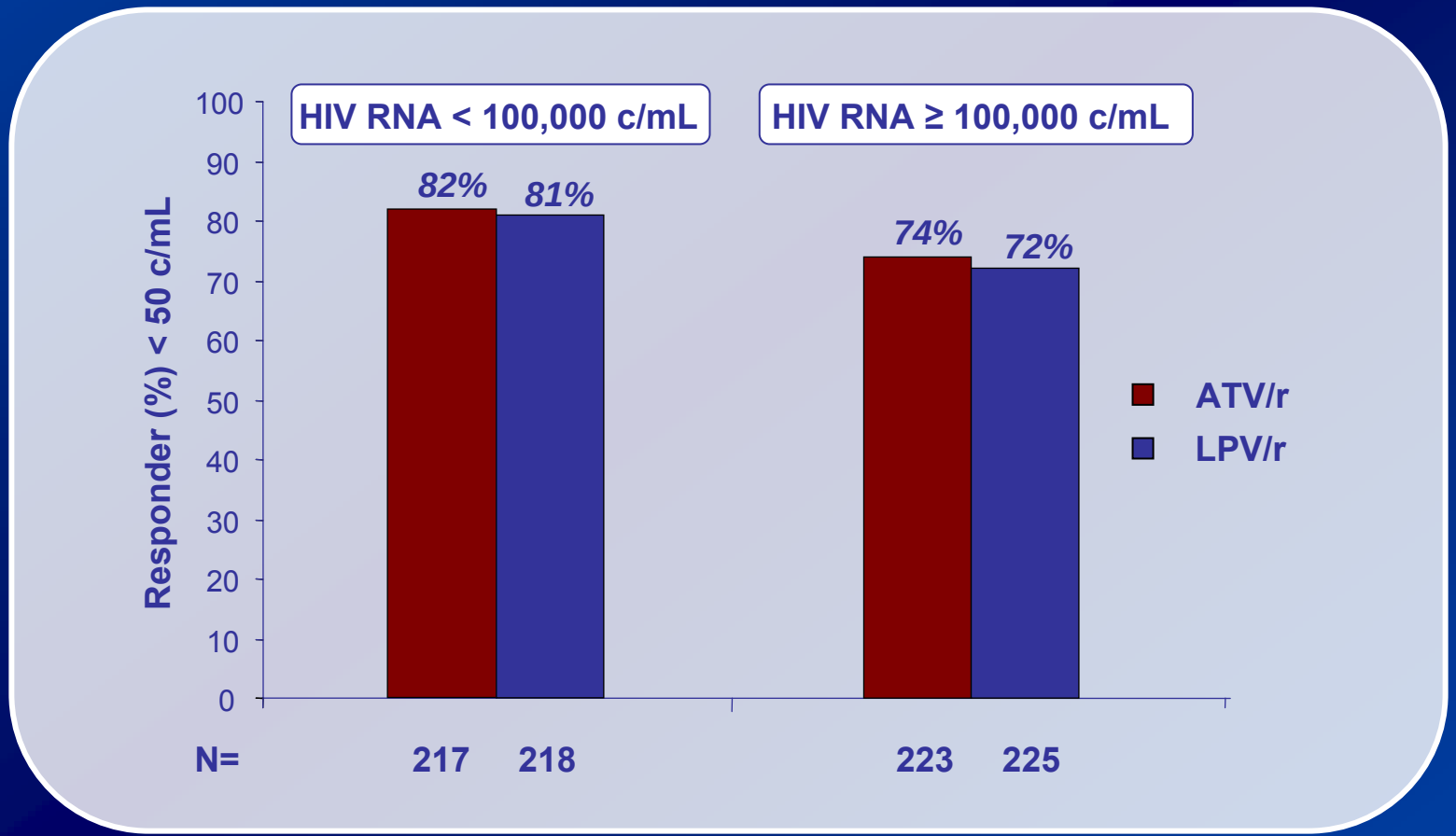
Primary Efficacy End Point
ITT-Confirmed Virologic Response (NC = F)



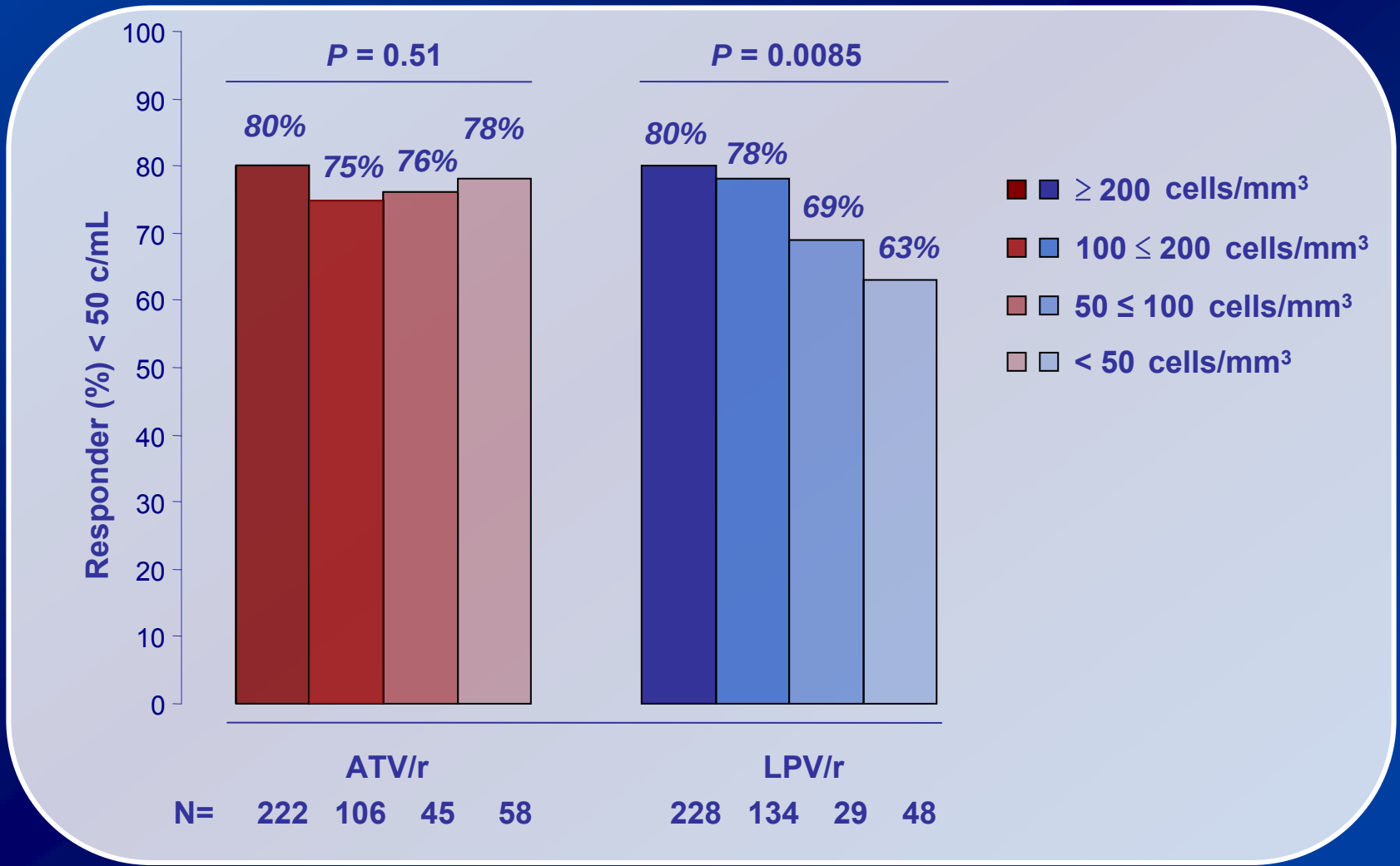
ATV/r has non-inferior antiviral efficacy compared with LPV/r

Supporting Analyses:
ITT-TLOVR: HIV RNA < 50 c/mL: ATV/r 78%, LPV/r 76%; 1.9 (-3.6, 7.4)
OT-VROC: HIV RNA < 50 c/mL: ATV/r 84%, LPV/r 87%; -3.5 (-8.7, 1.8)

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

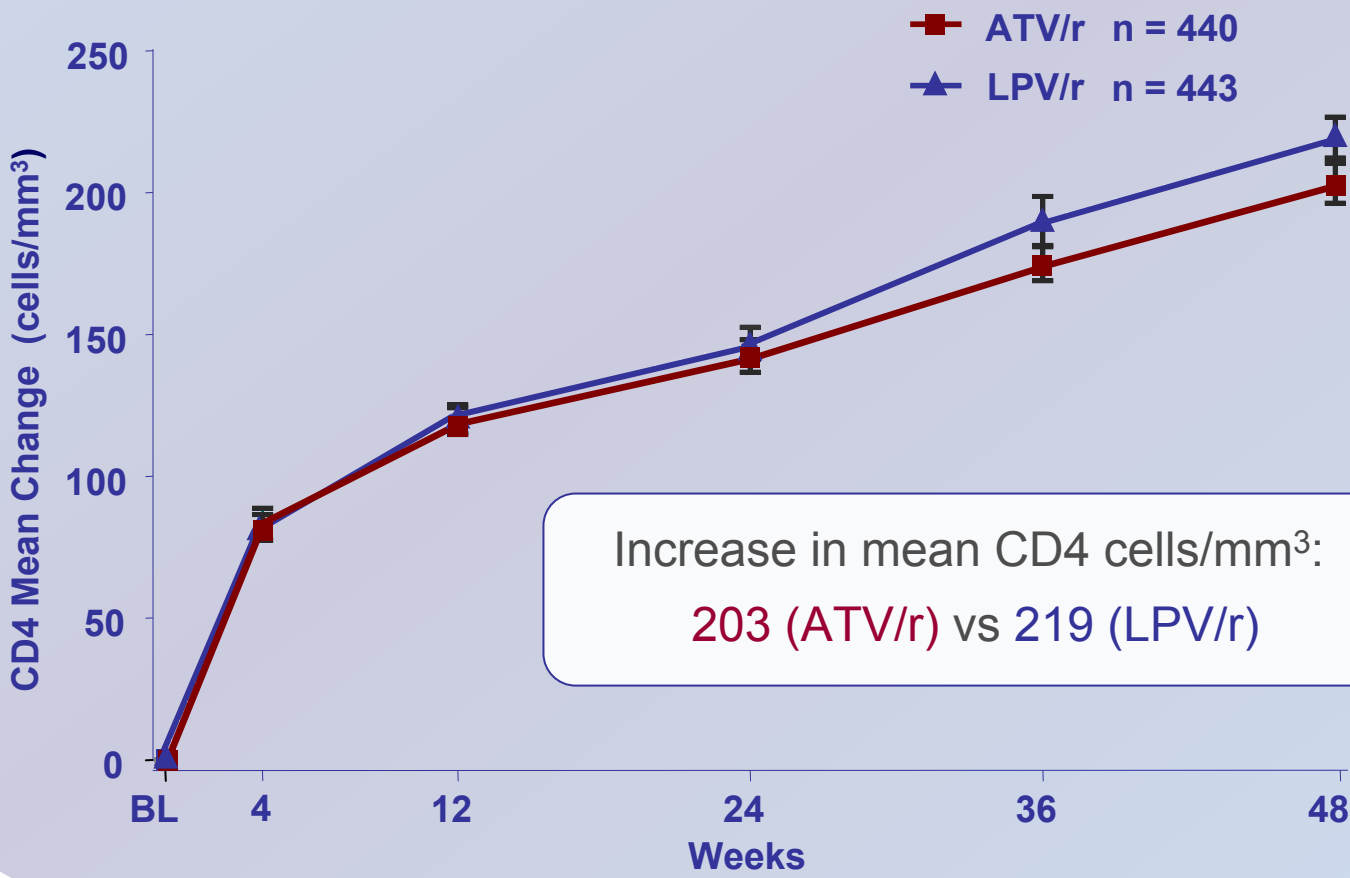


Response Rate by Baseline CD4 Cell Count - Post Hoc Analysis



P-values are from Cochran-Armitage trend test

CD4 Mean Change



Adverse Events Summary

		ATV/r n = 441 n (%)	LPV/r n = 437 n (%)
Serious Adverse Events (SAEs)		51 (12)	42 (10)
All grade 2-4 treatment-related AEs[a]		115 (26)	129 (30)
Grade 2-4 treatment-related AEs ≥ 3%[a,b]	Jaundice	16 (4)	0
	Nausea	17 (4)	33 (8)
	Diarrhea	10 (2)	50 (11)
	Rash	14 (3)	9 (2)

- Renal all grade AEs: 2% in both arms

[a] Through 48 weeks.
[b] Excluding laboratory abnormalities reported as AEs.

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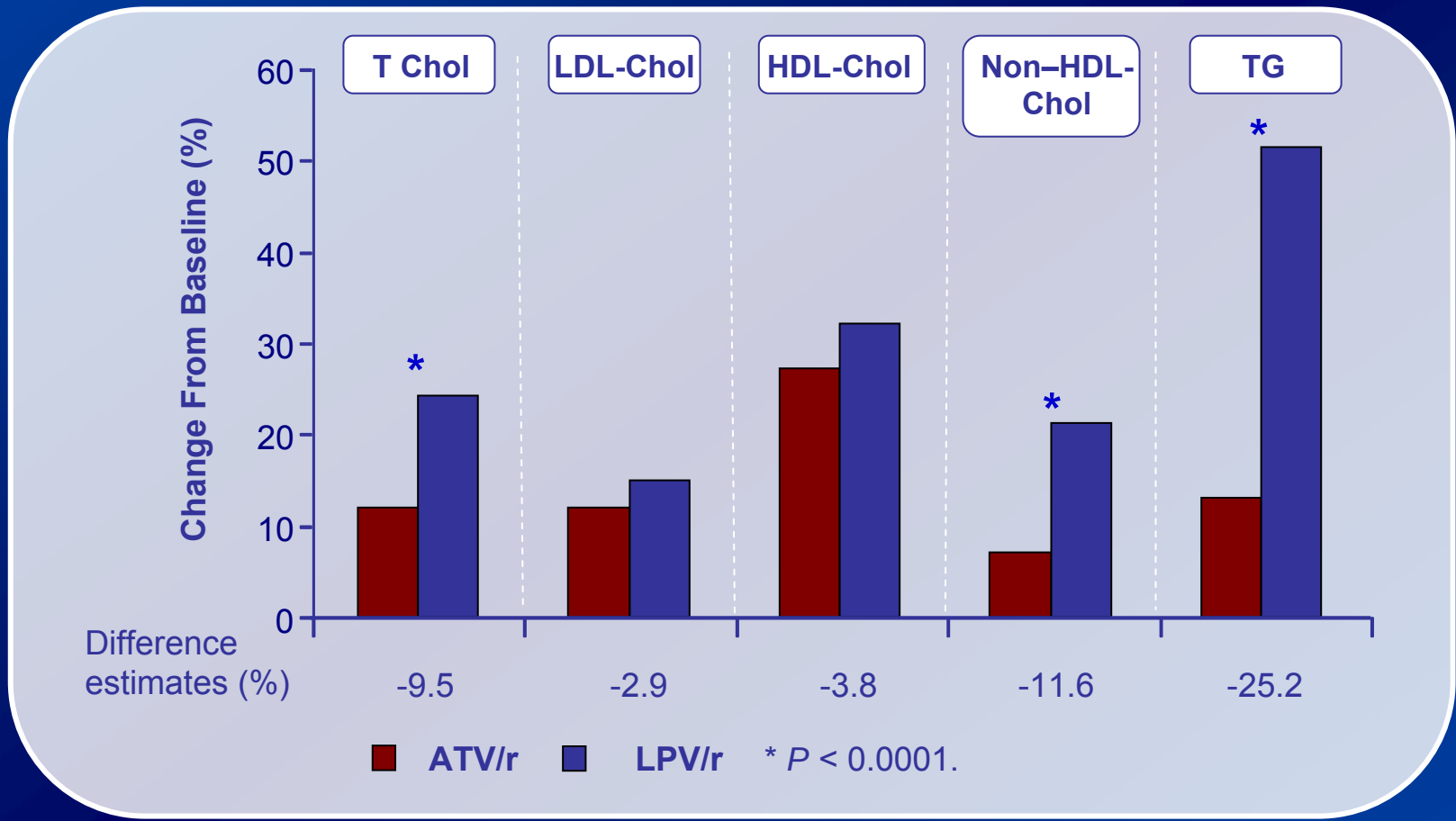
Selected Grade 3-4 Laboratory Abnormalities

	ATV/r n = 441 n (%)	LPV/r n = 437 n (%)
Total bilirubin elevation (> 2.5 × ULN)	146 (34)	1 (<1)
ALT elevation (> 5 × ULN)	8 (2)	6 (1)
AST elevation (> 5 × ULN)	9 (2)	2 (<1)
Total cholesterol (≥ 240 mg/dL)	30 (7)	77 (18)
Triglycerides (≥ 751 mg/dL)	2 (<1)	15 (4)
Hyperglycemia (≥ 251 mg/dL)	1 (<1)	1 (<1)

- Change from baseline at 48 weeks in renal function:
  - Mean serum creatinine: + 0.05 mg/dL ATV/r, + 0.02 mg/dL LPV/r
  - Median calculated creatinine clearance: 1% decrease in both arms

Fasting Lipids Mean Percent Changes From Baseline (LOCF)



- 2% of ATV/r vs 7% of LPV/r subjects initiated lipid-lowering therapy during the study

Conclusions

- **Once-daily ATV/r demonstrated non-inferior antiviral efficacy to twice-daily LPV/r, both in combination with TDF/FTC, in treatment-naïve patients**
- **In patients with advanced disease, ATV/r was highly effective in achieving virus undetectability**
- **Both regimens were generally well-tolerated with low rates of discontinuation**
  - Jaundice and hyperbilirubinemia were more commonly reported for ATV/r
  - Nausea and diarrhea occurred with greater frequency on LPV/r
- **ATV/r had a significantly better lipid profile (TC, TG, non-HDL) compared to LPV/r**
- **Once-daily ATV/r plus TDF/FTC is an appropriate therapeutic option for treatment-naïve patients**

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