

Comparison of 48-week efficacy and safety of darunavir/ritonavir (DRV/r) with lopinavir/ritonavir (LPV/r) in LPV/r-naïve, treatment-experienced, patients: a randomised, controlled Phase III trial (TITAN)

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TITAN = TMC114/r In Treatment-experienced pAtients Naïve to lopinavir

TITAN (TMC114-C214): Study Design

- Phase III randomised, controlled trial with primary analysis at Week 48

Screening phase (4 weeks)

- Treatment-experienced, LPV-naïve
- VL $\geq 1,000$ copies/mL
- Stable HAART (≥ 12 wks) or STI (≥ 4 wks)

Treatment phase (96 weeks)

DRV/r 600/100mg bid
+ OBR

LPV/r* 400/100mg bid
+ OBR

785 screened, 595 patients
randomised and treated

- All patients received optimised background therapy
 - at least two or three ARVs from approved NRTI and/or NNRTI classes; enfuvirtide disallowed

*LPV/r patients were allowed to switch to new formulation upon its approval by the regulatory authorities; VL = viral load; DRV/r = darunavir with low-dose ritonavir, LPV/r = lopinavir with low-dose ritonavir

TITAN: study objectives

- **Primary objective**

- **demonstrate non-inferiority in confirmed VL <400 copies/mL with DRV/r vs LPV/r at Week 48**

- **Secondary objectives**

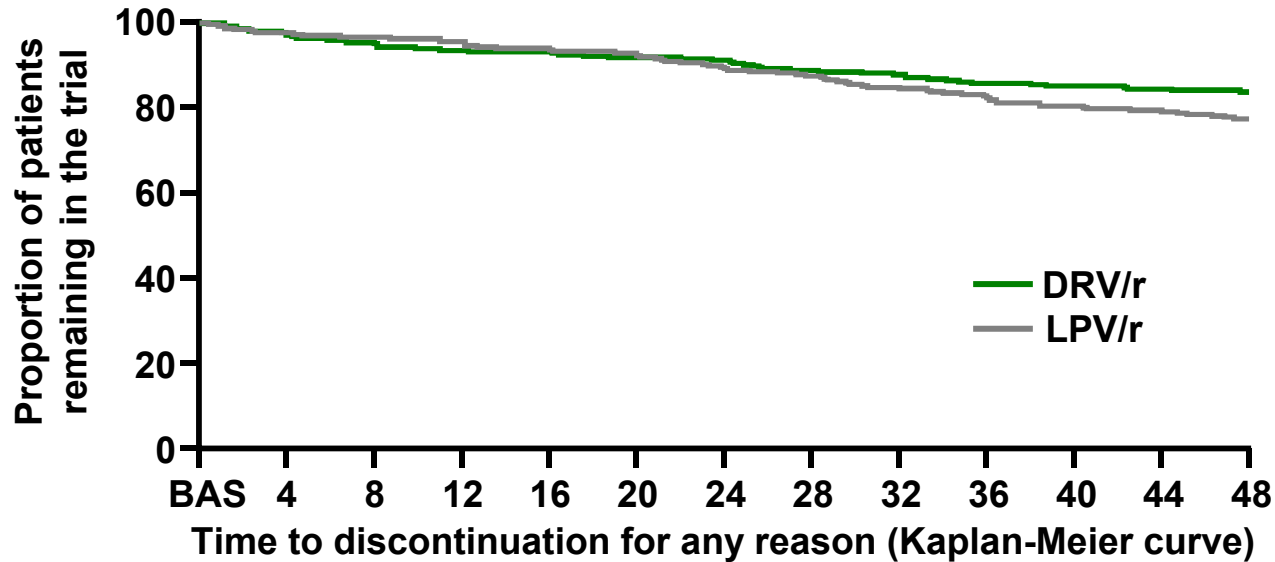
- **test for superiority of DRV/r over LPV/r in the event that the primary objective was achieved**
- **evaluate other virological and immunological parameters**
 - **VL <50 copies/mL**
 - **change in CD4 cell count**
- **evaluate efficacy, safety and tolerability over 96 weeks**

TITAN: baseline characteristics

	DRV/r* (n=298)	LPV/r (n=297)
Demographics		
Male, n (%)	229 (77)	241 (81)
Mean (\pm SD) age (years)	41 \pm 9.0	41 \pm 8.6
Disease characteristics		
Mean (\pm SD) baseline log ₁₀ VL	4.33 \pm 0.79	4.28 \pm 0.81
Median CD4 (cells/mm ³ [range])	235 (3–831)	230 (2–1,096)
CDC class C, n (%)	101 (34)	94 (32)
History of ARV treatment		
Structured treatment interruption, n (%)	64 (22)	71 (24)
Previous ARV experience, n (%)		
<i>NRTIs: \geq4</i>	156 (52)	151 (51)
<i>NNRTIs: \geq1</i>	225 (76)	229 (77)
<i>PIs: 0</i>	94 (32)	93 (31)
<i>PIs: 1</i>	108 (36)	115 (39)
<i>PIs: \geq2</i>	96 (32)	89 (30)
Optimised background therapy		
Number of sensitive [†] NRTIs used, n (%)		
0	30 (10)	42 (15)
1	70 (24)	75 (26)
\geq 2	188 (65)	171 (51)
Geometric median FC (range)		
DRV	0.6 (0–37)	0.6 (0–44)
LPV	0.7 (0–74)	0.8 (0–74)

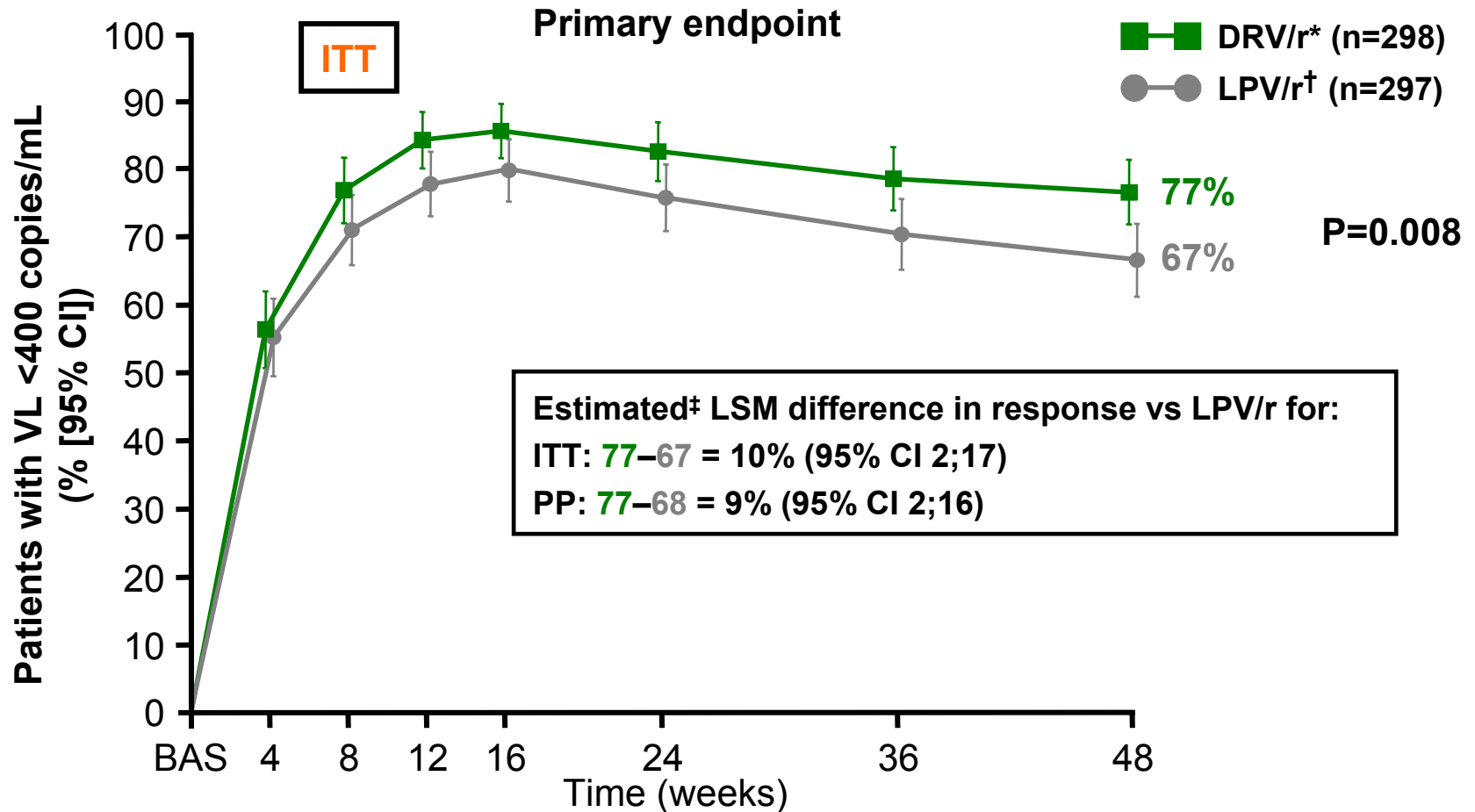
*DRV/r 600/100mg bid; [†]Phenotypes determined by Antivirogram[®]; FC = fold change in EC₅₀

TITAN: study completion/withdrawal



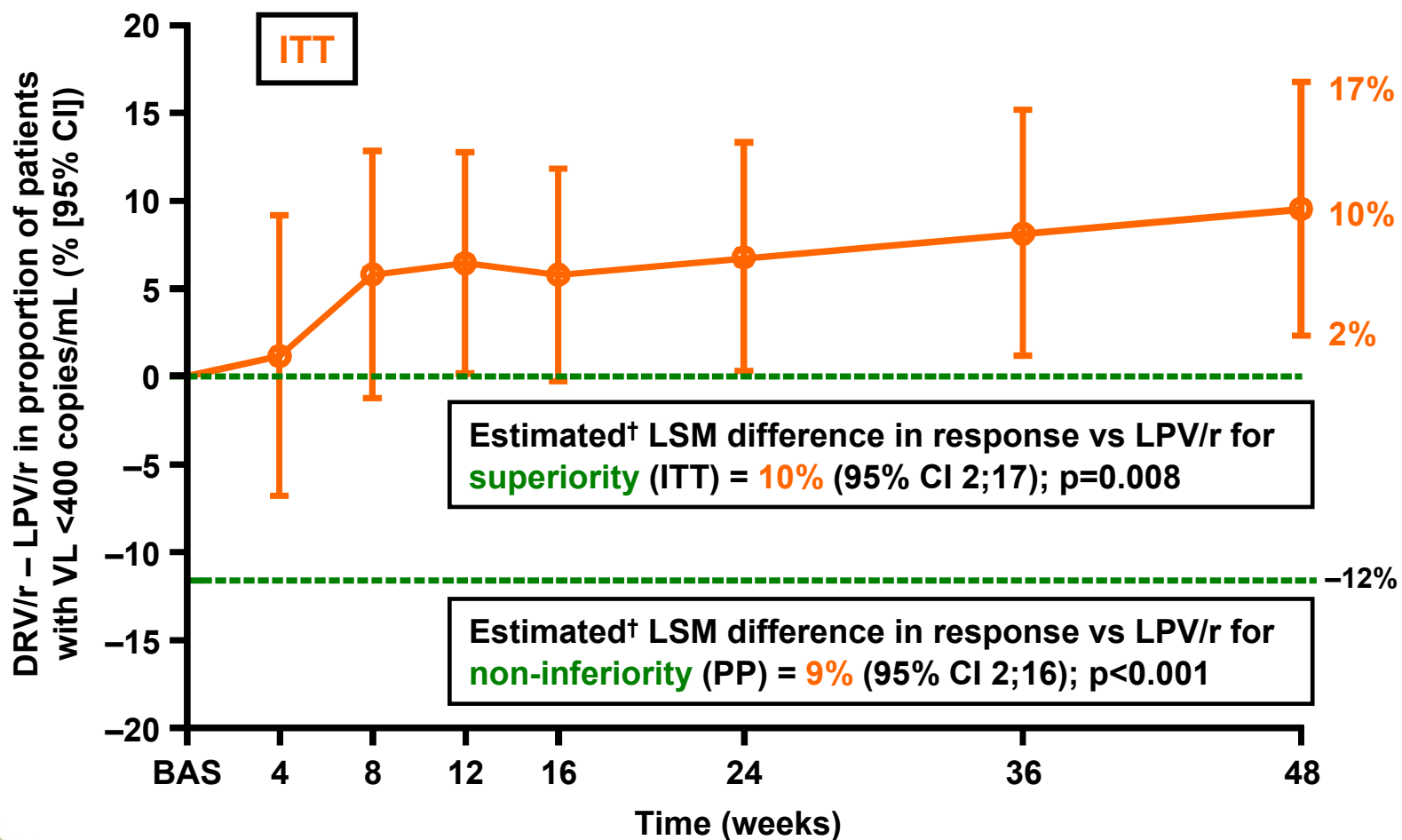
Incidence (%)	DRV/r*	LPV/r
Randomised – not treated	4	5
Randomised – treated	298	297
Discontinued – treated	62 (20.8%)	86 (29.0%)
AE/HIV-related event	20 (6.7%)	21 (7.1%)
Lost to follow-up	10 (3.4%)	10 (3.4%)
Withdrew consent	9 (3.0%)	10 (3.4%)
Virological failure	4 (1.3%)	34 (11.4%)
Non-compliance	11 (3.7%)	4 (1.3%)
Other	8 (2.7%)	7 (2.4%)

TITAN: viral load <400 copies/mL to Week 48 (TLOVR)



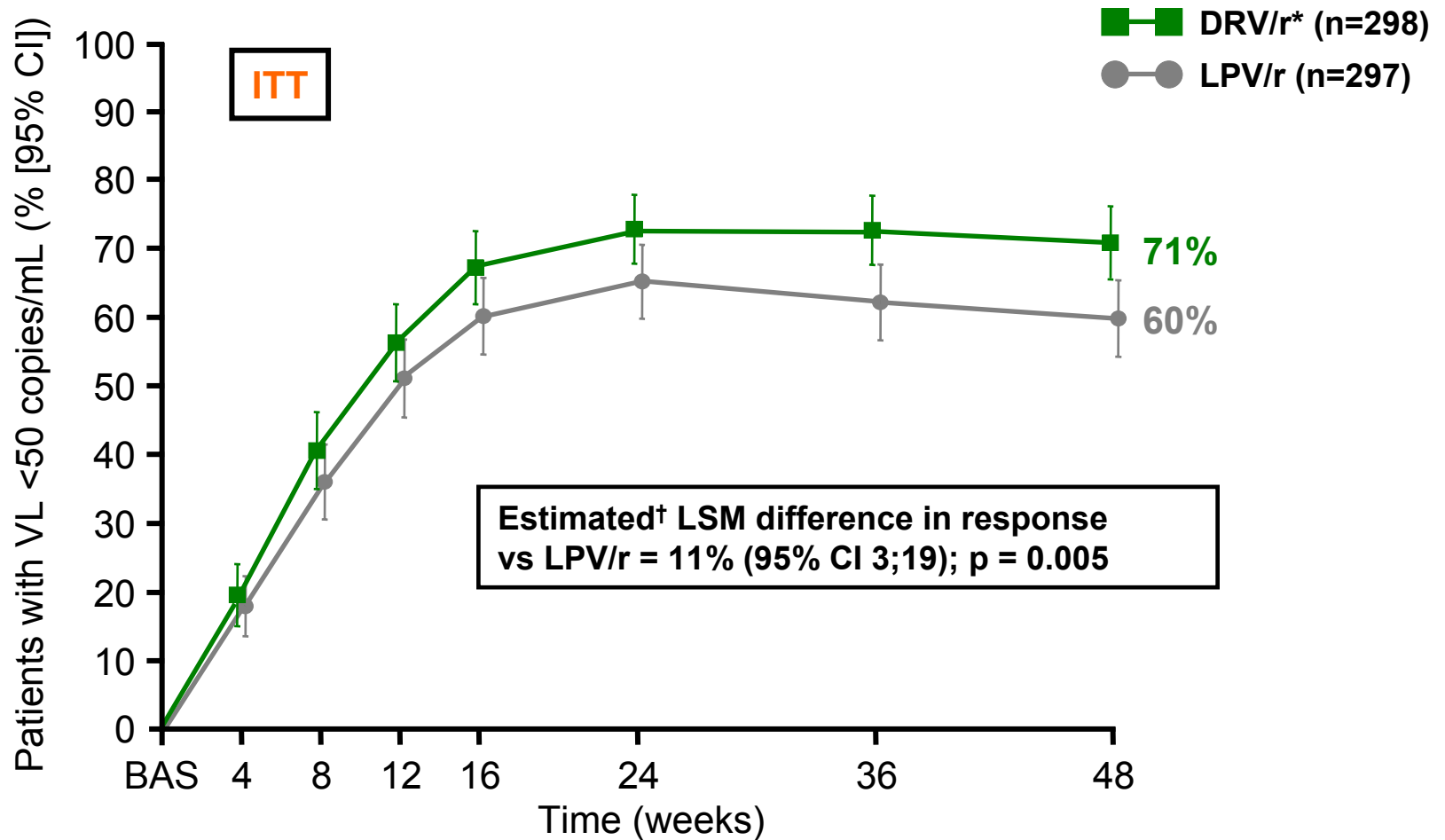
LSM= least square mean; *DRV/r 600/100mg bid, n=286 for PP; †n=293 for PP; ‡Estimated from a logistic regression model including treatment and stratification factors: baseline log₁₀ VL and use of NNRTIs in the optimised background regimen

TITAN: difference (DRV/r–LPV/r) in viral load <400 copies/mL to Week 48 (TLOVR)



[†]Estimated from a logistic regression model including treatment and stratification factors: baseline log₁₀ VL and use of NNRTIs in the optimised background regimen

TITAN: viral load <50 copies/mL to Week 48 (TLOVR) – all patients



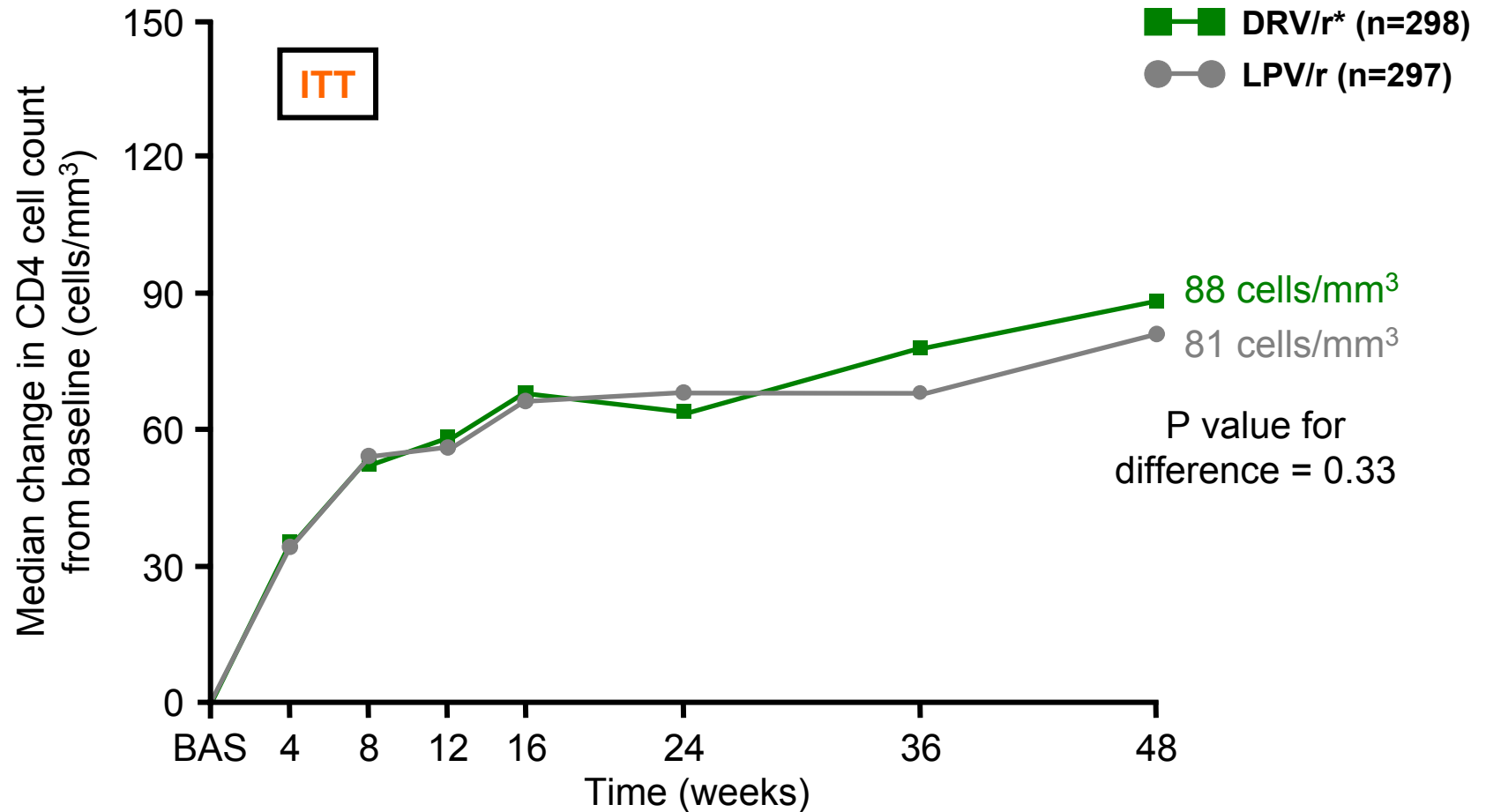
*DRV/r 600/100mg bid; [†]Estimated from a logistic regression model including treatment and stratification factors: baseline log₁₀ VL and use of NNRTIs in the optimised background regimen

TITAN: viral load <50 copies/mL at Week 48 by baseline LPV FC (TLOVR)

Patient population	Response rate (%)				Non-inferiority p value †	Superiority p value †
	DRV/r*	LPV/r	DRV/r–LPV/r	95% CI †		
Overall (n=595)	71	60	11	3 – 19	<0.0001	0.005
LPV FC ≤40 (n=569)	70	60	10	2 – 18	<0.0001	0.013
LPV FC ≤10 (n=524)	70	63	7	-1 – 16	<0.0001	0.068

*DRV/r 600/100mg bid †Estimated from a logistic regression model including treatment and stratification factors: baseline log₁₀ HIV-RNA and use of NNRTIs in the optimised background regimen

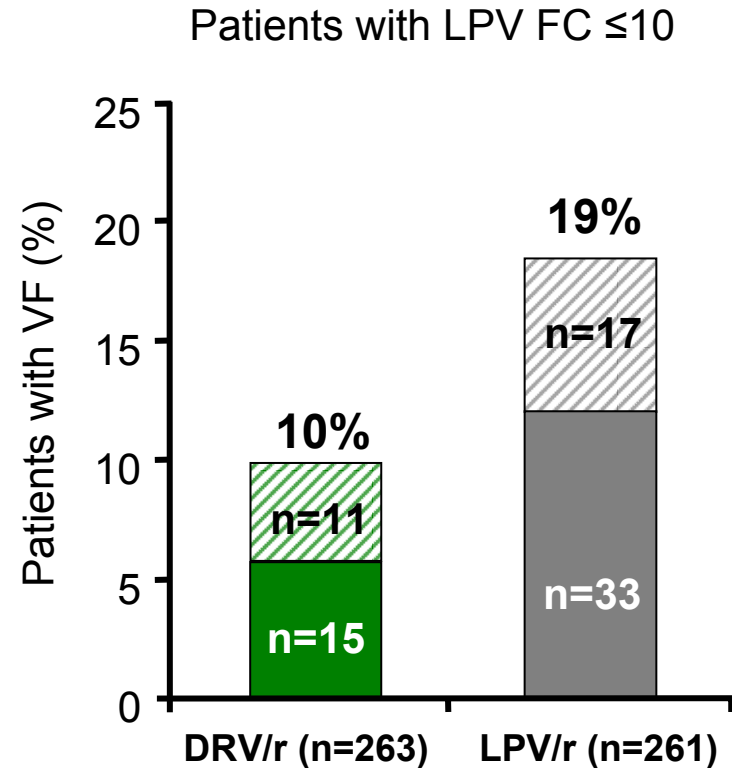
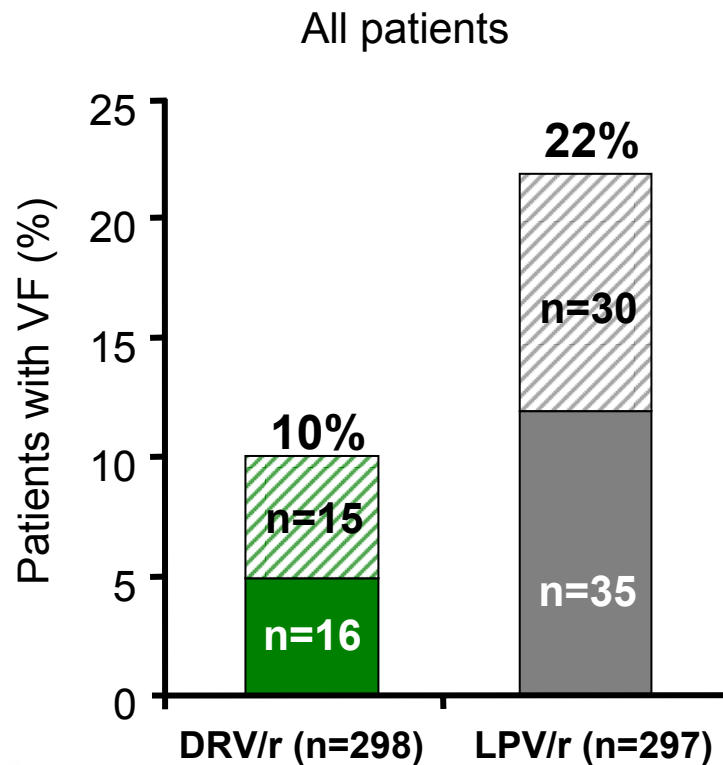
TITAN: median change in absolute CD4 cell count to Week 48 (NC=F)



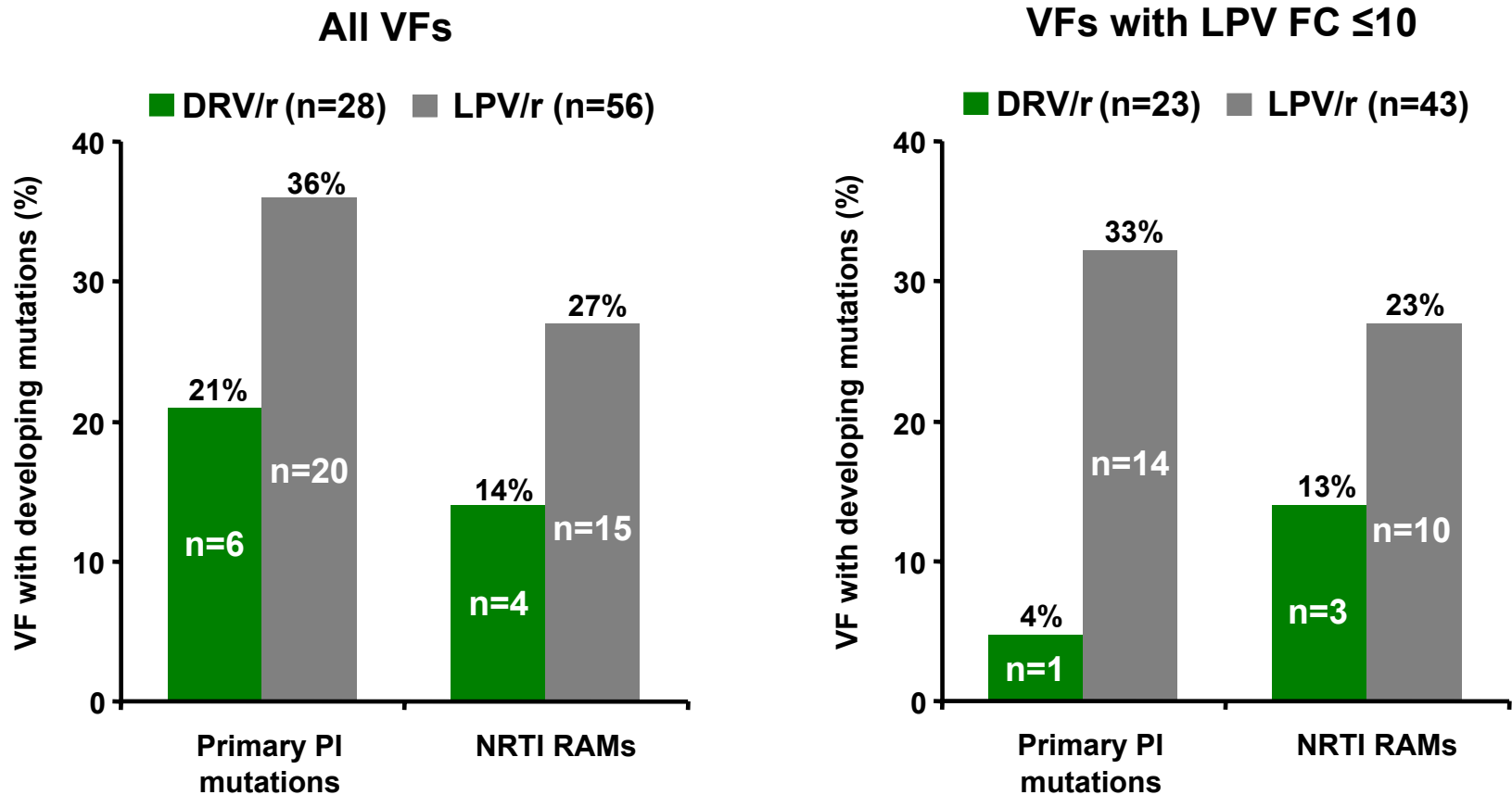
*DRV/r 600/100mg bid

TITAN: virological failure rates (ITT-TLOVR)

- Patients with virological failure (VF; >400 copies/mL) consisted of non-responders (■) and rebounders (▨)

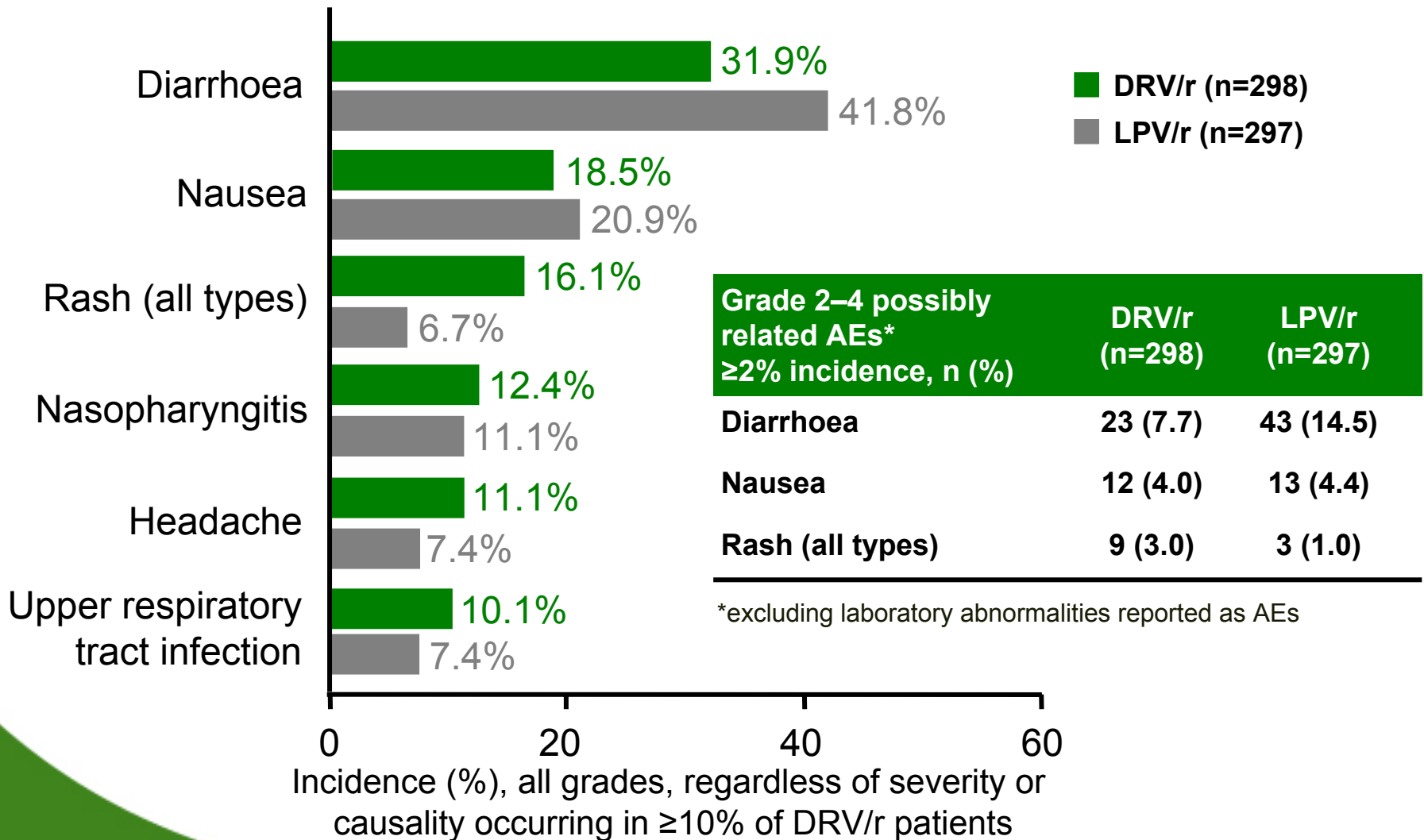


TITAN: development of primary PI mutations and NRTI RAMs upon treatment failure



For more details – please see poster **WEPEB038**
de Bethune et al.

TITAN: most common AEs



TITAN: grade 2–4 laboratory abnormalities ($\geq 2\%$ incidence)

Grade 2–4 laboratory abnormalities [†] Incidence, n (%)	DRV/r* (n=298)	LPV/r (n=297)
Total cholesterol	94 (31.5)	86 (29.0)
Triglycerides	57 (19.1)	75 (25.3)
Low-density lipoprotein	56 (18.8)	50 (16.8)
Pancreatic amylase	33 (11.1)	26 (8.8)
Hyperglycaemia	26 (8.7)	28 (9.4)
Alanine aminotransferase	26 (8.7)	26 (8.8)
Aspartate aminotransferase	20 (6.7)	26 (8.8)
Pancreatic lipase	14 (4.7)	11 (3.7)

*DRV/r 600/100mg bid; [†]By decreasing darunavir/r frequency

TITAN: conclusions

In this treatment-experienced, LPV-naïve population:

- **DRV/r was not only non-inferior, but virologically superior to LPV/r**
- **DRV/r was safe and well tolerated**
- **DRV/r provided better protection of the NRTI and the PI classes upon failure versus LPV/r**

TITAN: acknowledgments

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