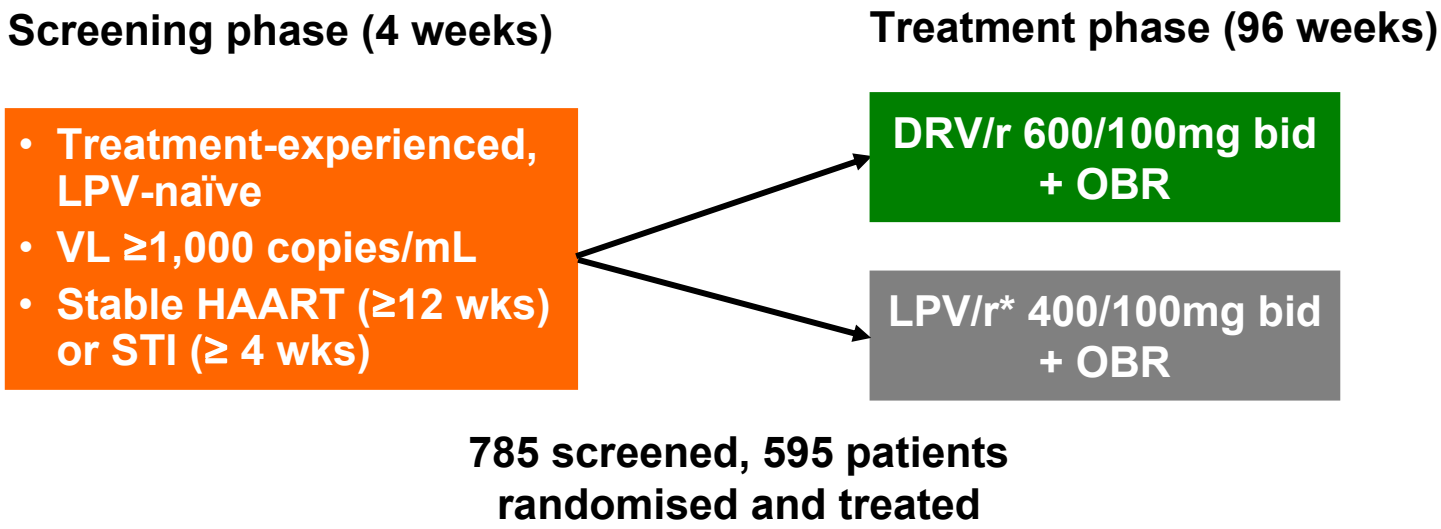
Comparison of 48-week efficacy and safety of darunavir/ritonavir (DRV/r) with lopinavir/ritonavir (LPV/r) in LPV/r-naïve, treatment-experienced, patients: a randomised, controlled Phase III trial (TITAN)

Valdez-Madruga J, Berger DS, McMurchie M, Suter F, Banhegyi D, Ruxrungtham K, Lefebvre E, De Paepe E, Tomaka F, De Pauw M, Vandevoorde A, Vangeneugden T, Spinosa-Guzman S

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**



- **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

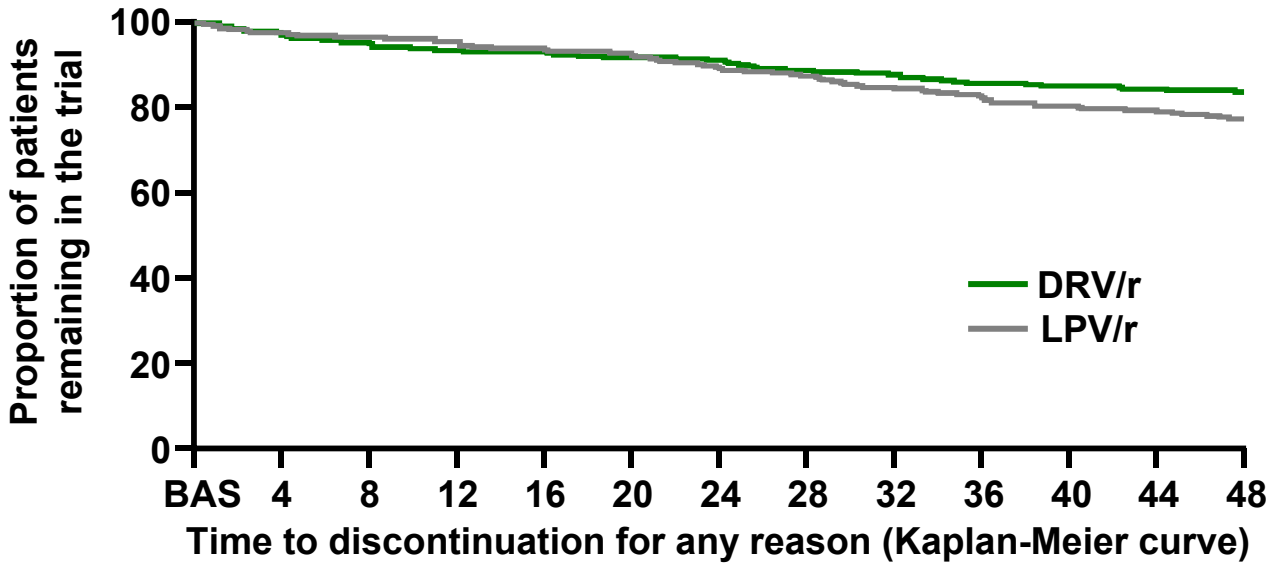
TLOVR = time to loss of virological response; CI = confidence interval

TITAN: baseline characteristics

	DRV/r* (n=298)	LPV/r (n=297)
Demographics		
Male, n (%)	229 (77)	241 (81)
Mean (±SD) age (years)	41 ± 9.0	41 ± 8.6
Disease characteristics		
Mean (± SD) baseline log_{10} VL	4.33 ± 0.79	4.28 ± 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 (%)		
NRTIs: ≥4	156 *(52)*	151 *(51)*
NNRTIs: ≥1	225 *(76)*	229 *(77)*
PIs: 0	94 *(32)*	93 *(31)*
PIs: 1	108 *(36)*	115 *(39)*
PIs: ≥2	*96 (32)*	89 *(30)*
Optimised background therapy		
Number of sensitive† NRTIs used, n (%)		
0	30 *(10)*	*42 (15)*
1	70 *(24)*	75 *(26)*
≥2	188 *(65)*	171 *(59)*
Geometric median FC (range)		
DRV	0.6 (0–37)	0.6 (0–44)
LPV	0.7 (0–74)	0.8 (0–74)

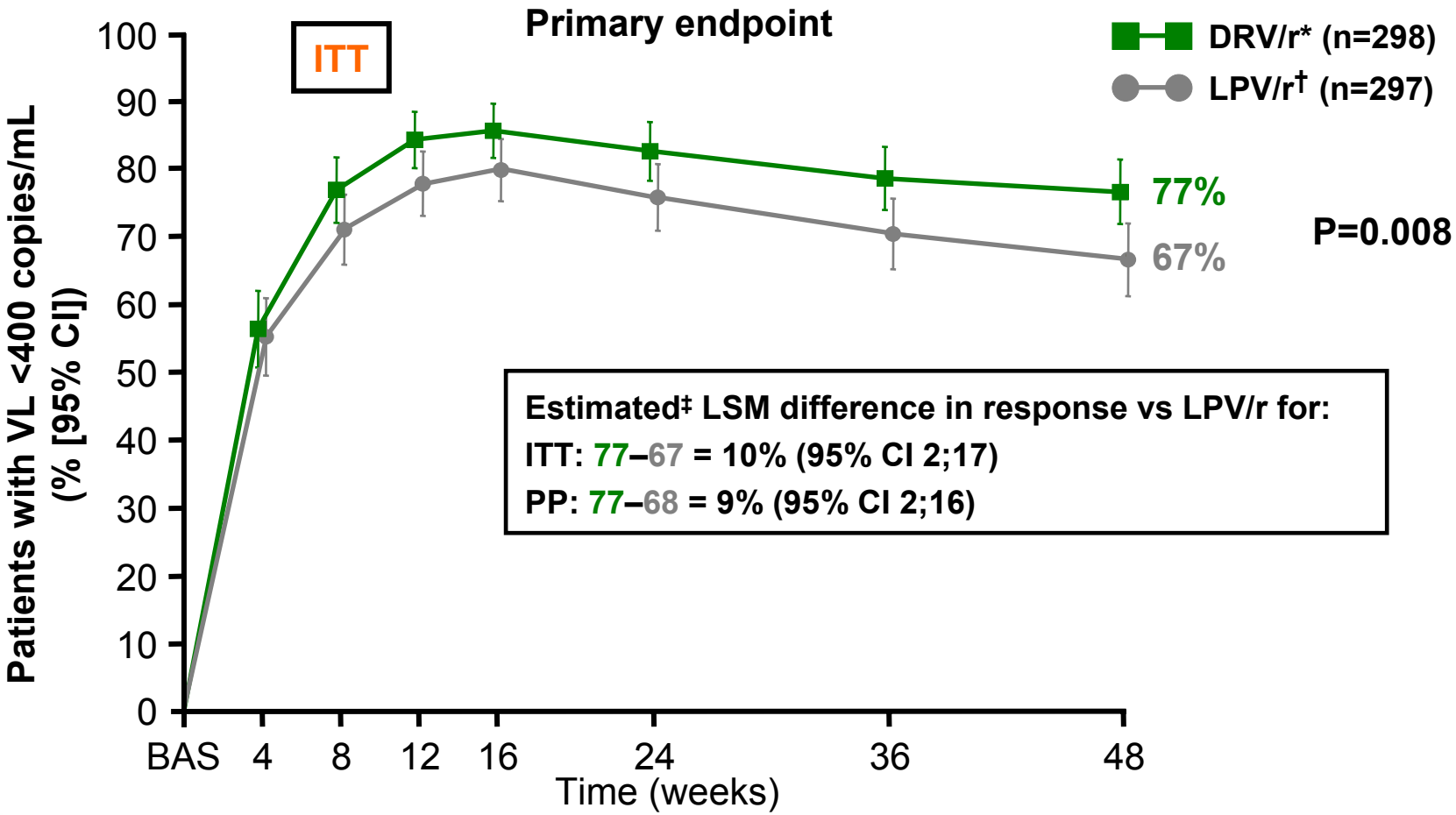
*DRV/r 600/100mg bid; †Phenotypes determined by Antivirogram®; FC = fold change in EC_{50}

TITAN: study completion/withdrawal



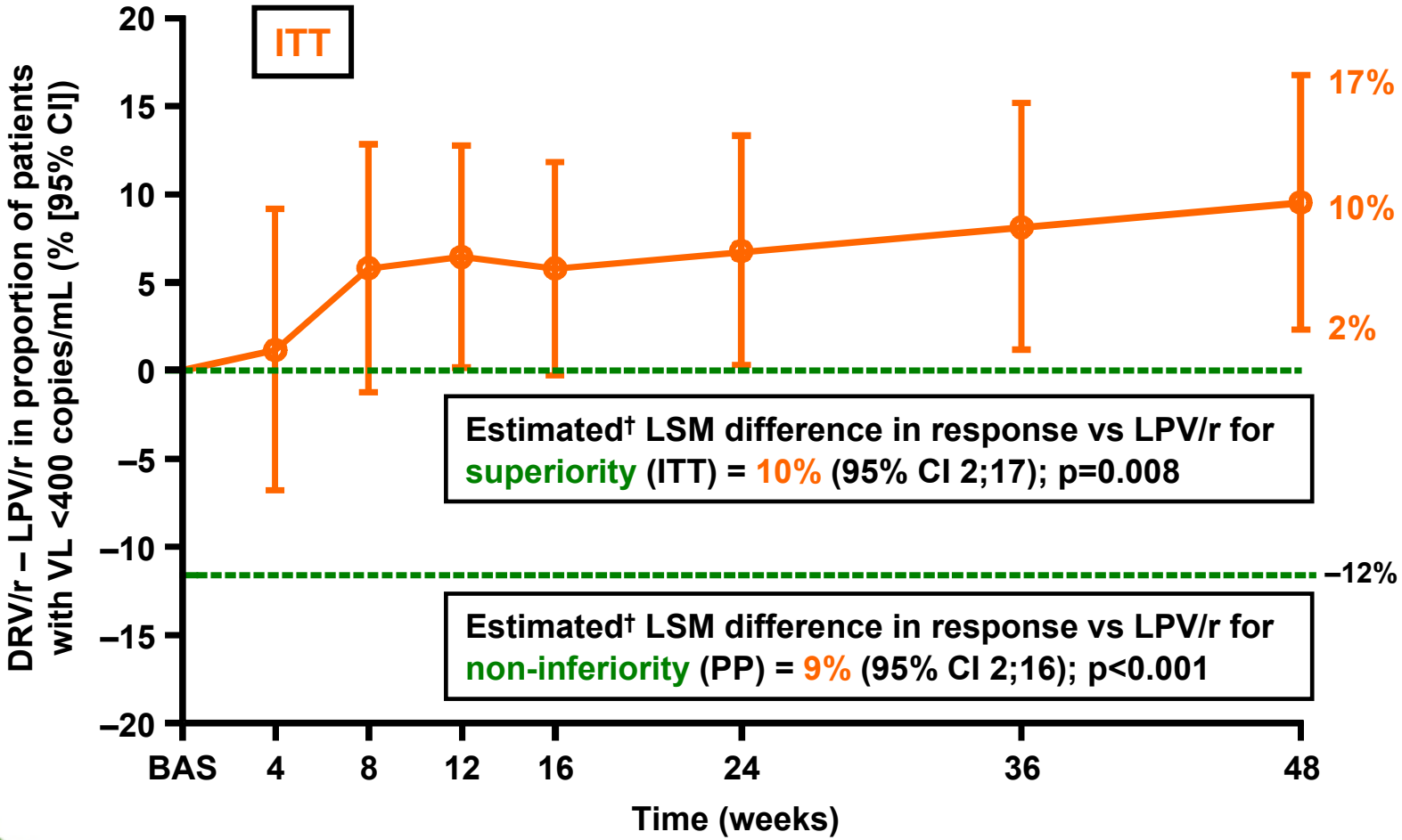
Incidence (%)	DRV/r*	LPV/r
Randomised – not treated	4	5
Randomised – treated	298	297
Discontinued – treated	62 (20.8%)	86 (29.0%)
AE/HIV-related event	20 (6.7%)	21 (7.1%)
Lost to follow-up	10 (3.4%)	10 (3.4%)
Withdrew consent	9 (3.0%)	10 (3.4%)
Virological failure	4 (1.3%)	34 (11.4%)
Non-compliance	11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

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



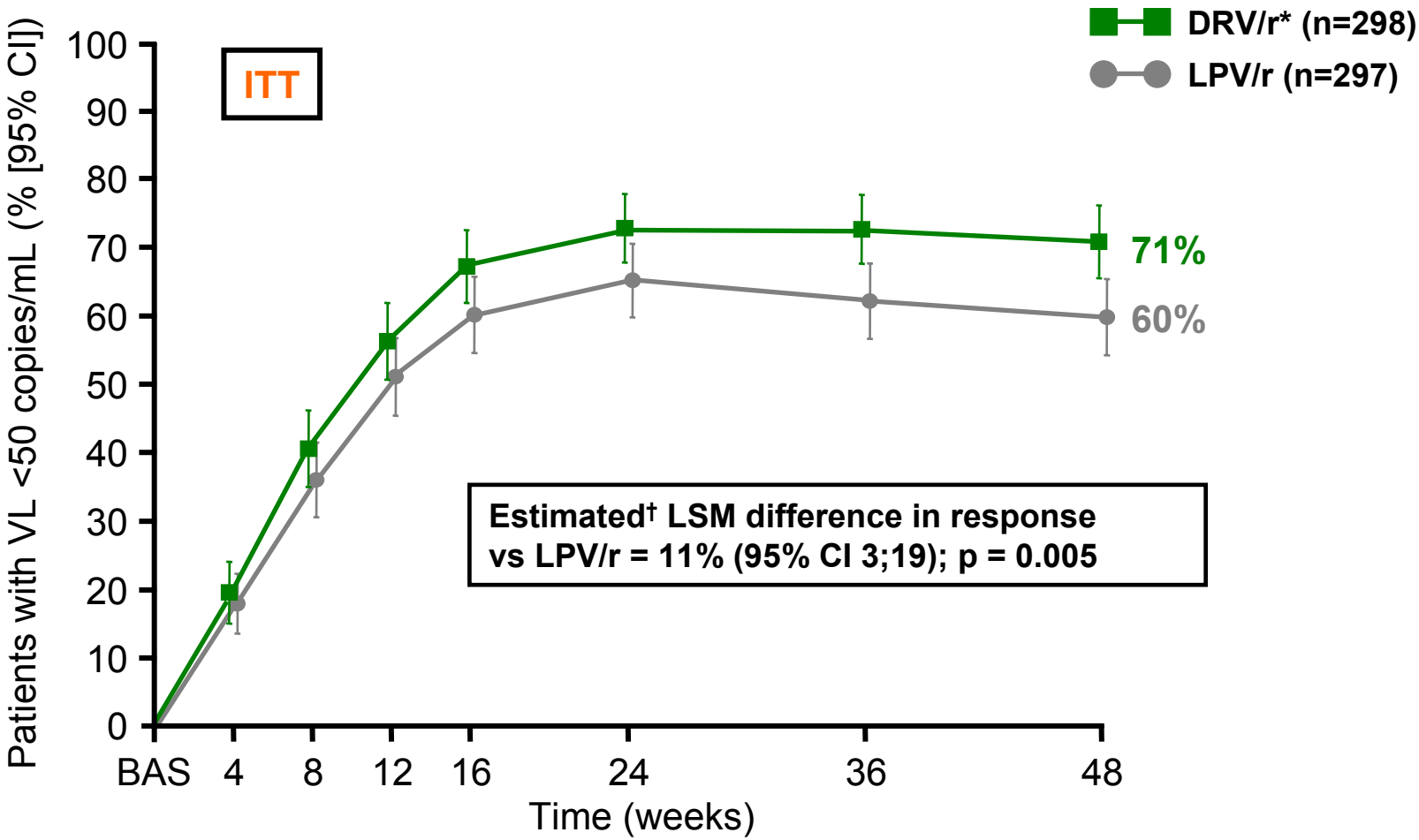
LSM= least square mean; *DRV/r 600/100mg bid, n=286 for PP; †n=293 for PP; ‡Estimated from a logistic regression model including treatment and stratification factors: baseline $\log_{10}$ VL and use of NNRTIs in the optimised background regimen

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 $\log_{10}$ VL and use of NNRTIs in the optimised background regimen

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



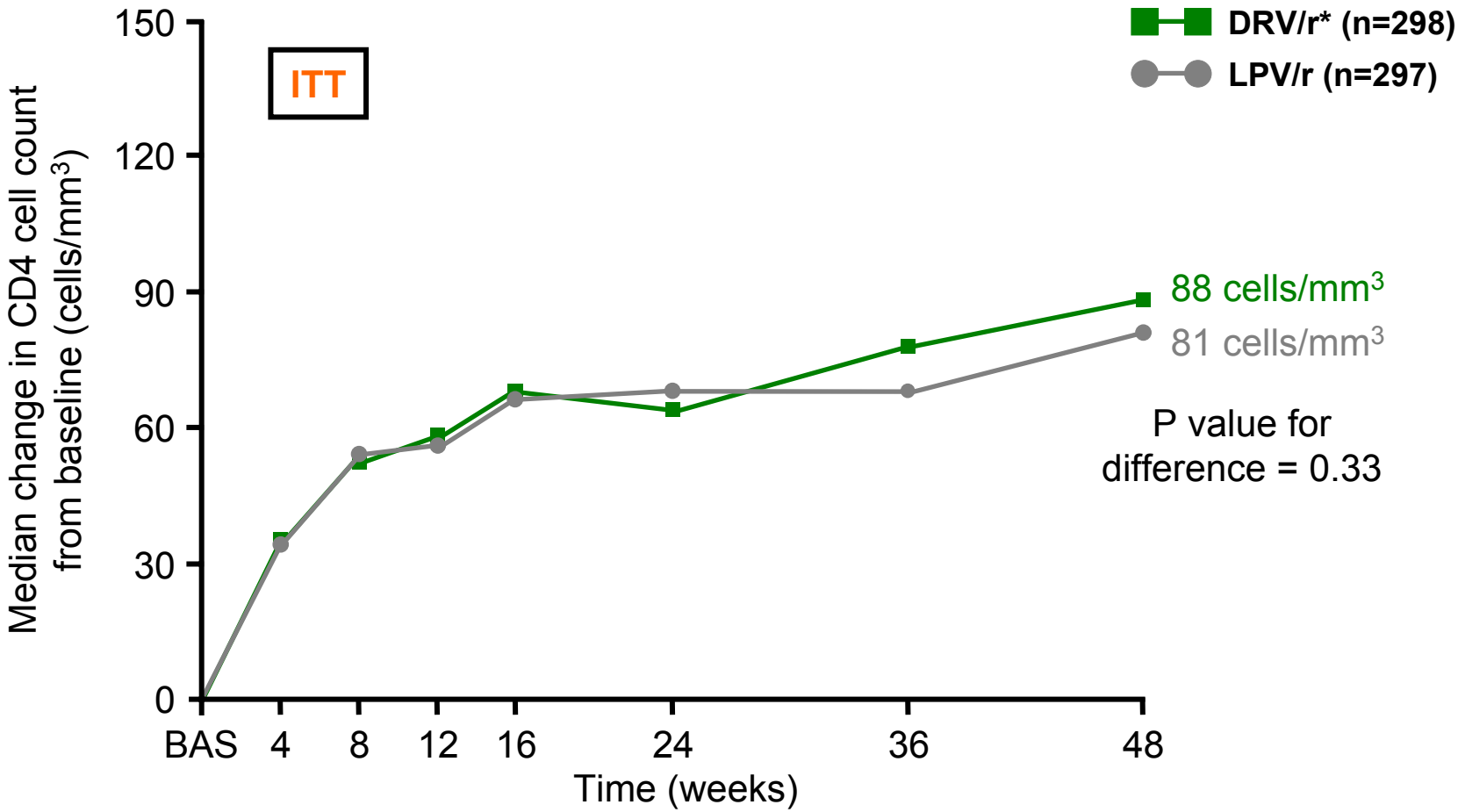
*DRV/r 600/100mg bid; †Estimated from a logistic regression model including treatment and stratification factors: baseline $\log_{10}$ VL and use of NNRTIs in the optimised background regimen

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 $\log_{10}$ HIV-RNA and use of NNRTIs in the optimised background regimen

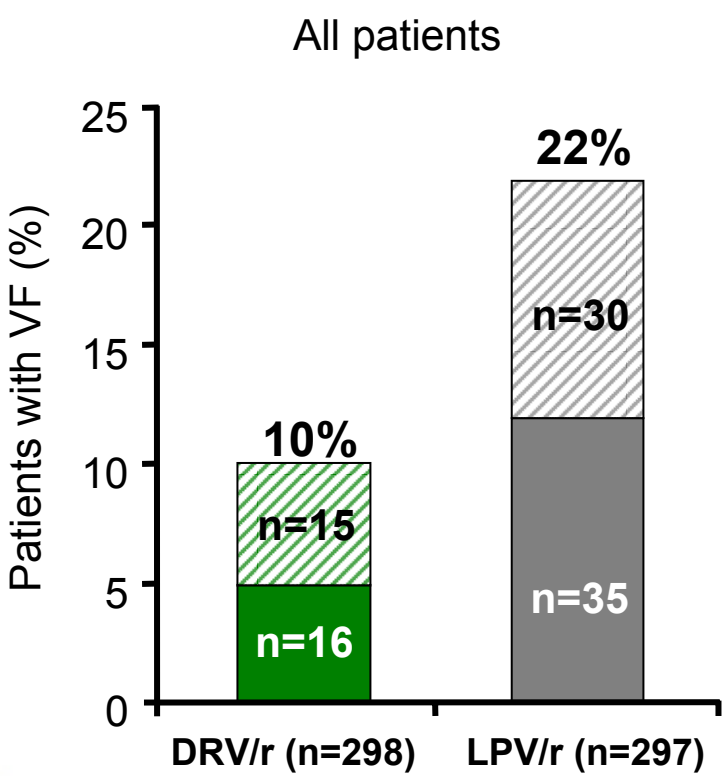
TITAN: median change in absolute CD4 cell count to Week 48 (NC=F)

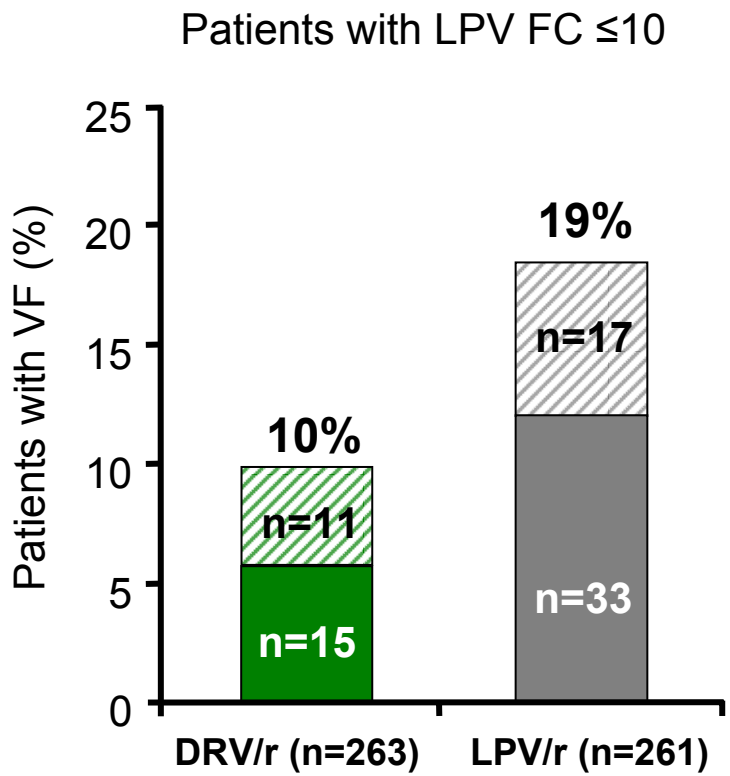


*DRV/r 600/100mg bid

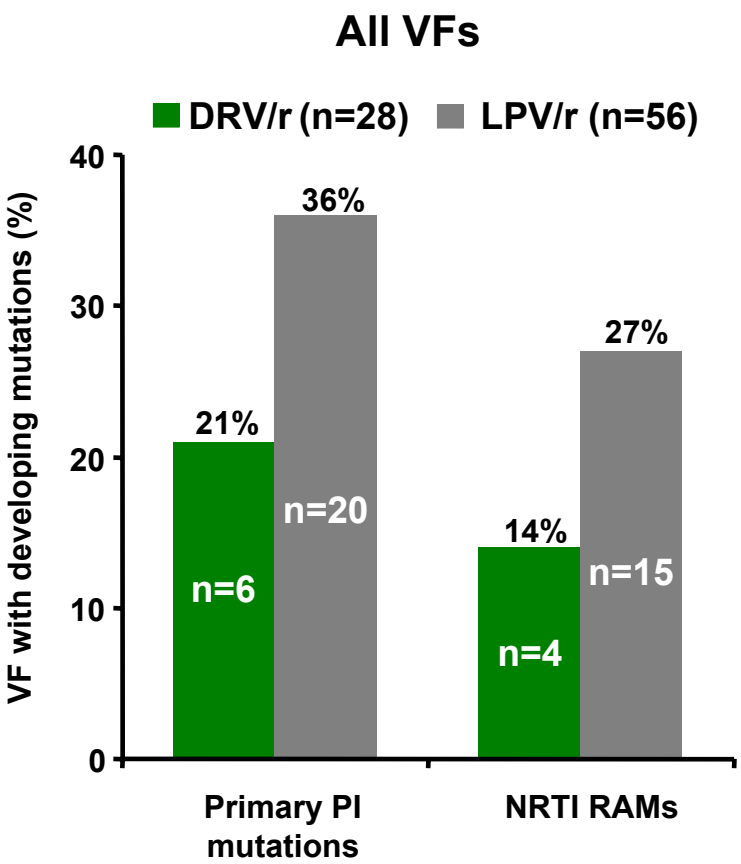
TITAN: virological failure rates (ITT-TLOVR)

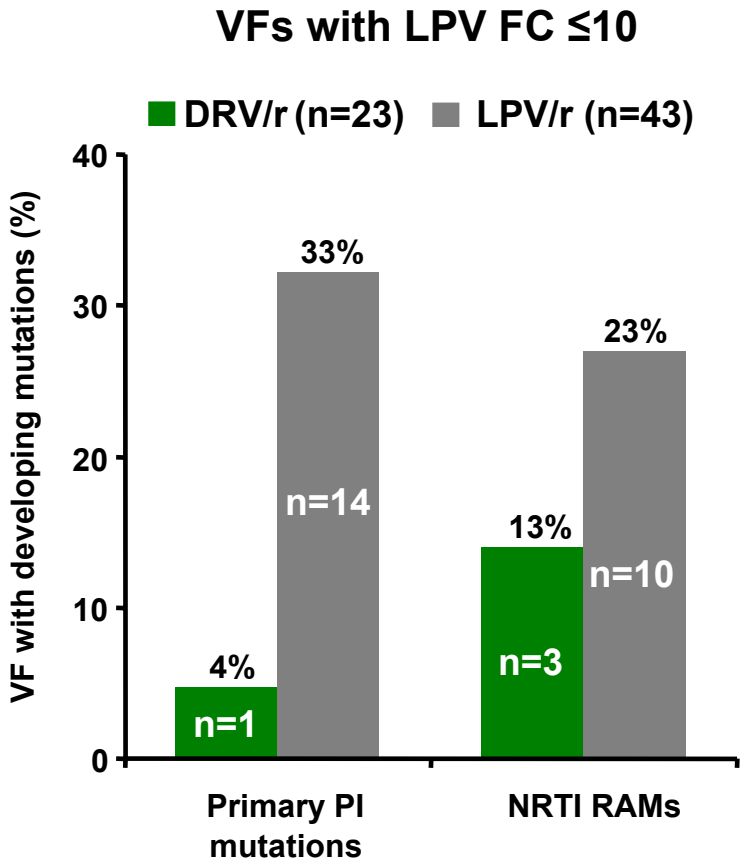
- **Patients with virological failure (VF; >400 copies/mL) consisted of non-responders (■) and rebounders (▨)**





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

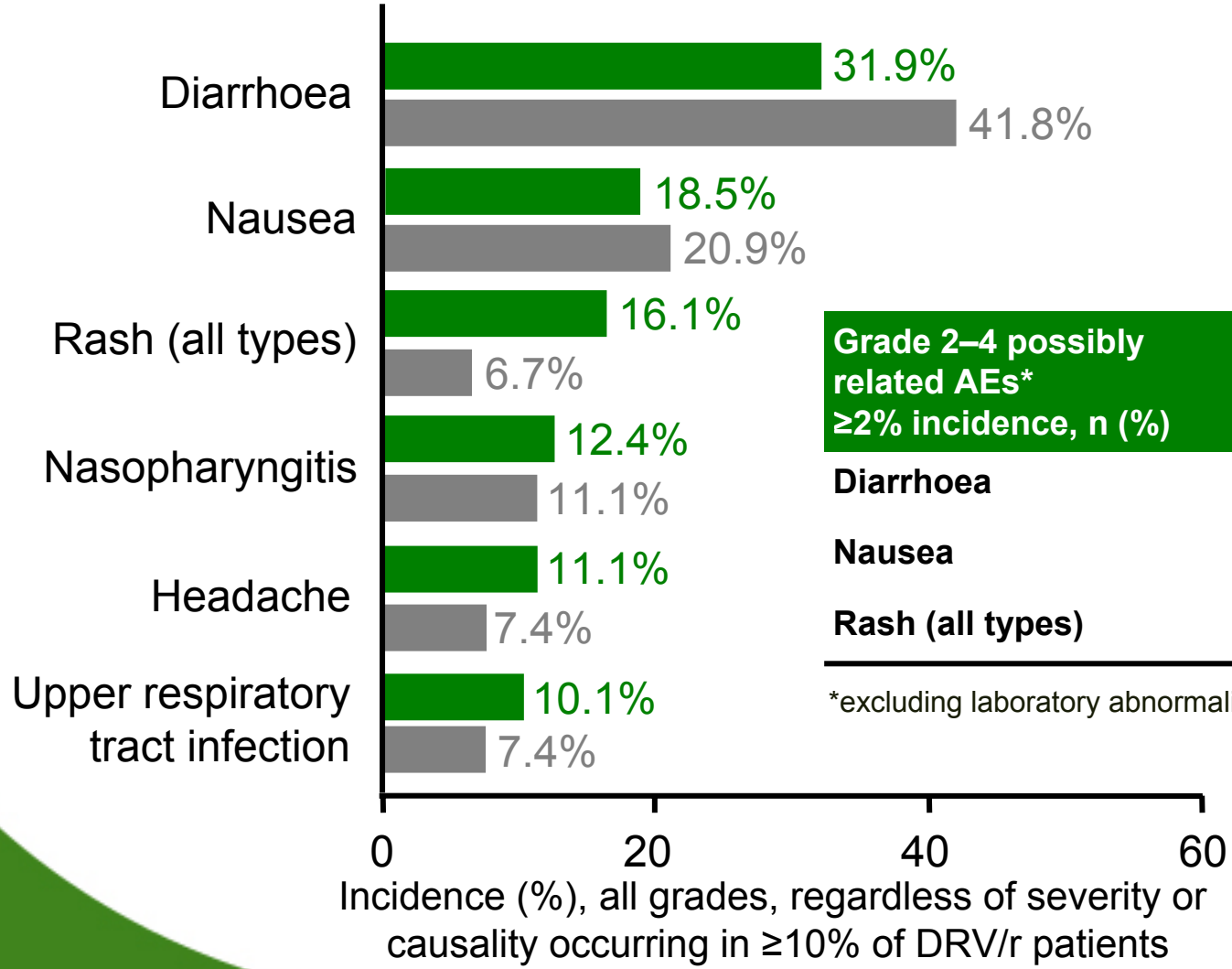




For more details – please see poster WEPEB038
de Bethune et al.

*Johnson et al. Top HIV Med 2006; 14:125–130

TITAN: most common AEs



DRV/r (n=298)

LPV/r (n=297)

Grade 2–4 possibly related AEs* ≥2% incidence, n (%)	DRV/r (n=298)	LPV/r (n=297)
Diarrhoea	23 (7.7)	43 (14.5)
Nausea	12 (4.0)	13 (4.4)
Rash (all types)	9 (3.0)	3 (1.0)

*excluding laboratory abnormalities reported as AEs

TITAN: grade 2–4 laboratory abnormalities (≥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

- **The patients and their families for their participation and support during the study**
- **TMC114-C214 study team and the investigators and co-investigators**
  - **Argentina**: Pedro Cahn, Arnaldo Casiró, Isabel Cassetti, Daniel David, Marcelo Losso and Sergio Lupo
  - **Australia**: David Cooper, Robert Finlayson, Jenny Hoy, Patricia Martinez, Marilyn McMurchie and Cassy Workman;
  - **Austria**: Armin Rieger and Norbert Vetter
  - **Belgium**: Nathan Clumeck, Jean-Christophe Goffard and Lutgarde Lynen
  - **Brazil**: Clovis Da Cunha, Beatriz Grinsztejn, Claudio Gonsalez, Jose Valdez-Madruga, Rogerio de Jesus Pedro, Jose Henrique Pilotto,
  - Mauro Schechter and Artur Timerman
  - **Canada**: John Gill, Norbert Gilmore, Don Kilby, Patrice Junod, Anita Rachlis, Benoit Trottier, Chris Tsoukas and Sharon Walmsley
  - **Chile**: Juan Ballesteros, Rebeca Northland and Carlos Pérez
  - **Denmark**: Henrik Nielsen
  - **France**: Jacques Durant, Pierre-Marie Girard, Christine Katlama, Christian Michelet, Jean-Michel Molina, Gilles Pialoux, Christophe Piketty, Dominique Salmon, Daniel Vittecoq and Patrick Yeni
  - **Germany**: Keikawus Arasteh, Gerd Fätkenheuer, Heribert Knechten, Antonius Mutz, Carl Knud Schewe, Dieter Schuster, Albrecht Stoehr and Andreas Trein
  - **Greece**: George Panos
  - **Guatemala**: Eduardo Arathoon and Carlos Mejia-Villatoro
  - **Hungary**: Denes Banhegyi
  - **Italy**: Andrea Antinori, Giampiero Carosi, Roberto Esposito, Adriano Lazzarin, Francesco Mazzotta, Anna Maria Orani, Stefano Rusconi,
  - Laura Sighinolfi and Fredy Suter
  - **Malaysia**: Adeeba Kamarulzaman and Christopher Lee
  - **Mexico**: Jaime Andrade
  - **Netherlands**: Kees Brinkman, Bart Rijnders and Herman Sprenger
  - **Panama**: Nestor Sosa
  - **Portugal**: Teresa Branco, António Diniz and Rui Sramento e Castro
  - **Puerto Rico**: Javier Morales Ramirez
  - **Russia**: Oleg Kozyrev, Grigory Moshkovich, Alexander Pronin, Oleg Romanenko, Elena Vinogradova and Alexey Yakovlev
  - **South Africa**: Ezio Baraldi, Francesca Conradie, Gulam Hoosan Latiff, Lerato Mohapi, Catherine Orrell, Osman Ebrahim and David Spencer
  - **Spain**: Jose Ramon Arribas, Angel Daniel Podzamczer and Maria Perez-Elias
  - **Switzerland**: Milos Opravil
  - **Thailand**: Ploenchan Chetchotisakd, Kiat Ruxrungtham, Wichai Techasathit and Chaiwat Ungsedhapand (key coordinator)
  - **United Kingdom**: Philippa Easterbrook and Anton Pozniak
  - **United States**: Ben Barnett, John Baxter, Paul Benson, Daniel S Berger, Jack Bissett, Cynthia Brinson, Alfred Burnside, Thomas Campbell, Amy Colson, Frederick Cruickshank, Edwin DeJesus, Robin Dretler, Robert Eng, Charles Farthing, Jeffrey Fessel, Michael Frank, David Hardy, Dushyantha Jayaweera, Thomas Jefferson, Harold Katner, Clifford Kinder, Harry Lampiris, Marc LaRiviere, Jason Leider, Steven Marlowe, Cynthia Mayer, David McDonough, Jose Montero, Karam Mounzer, Robert Myers, Dorece Norris, Frank Palella, Gerald Pierone, Bruce Rashbaum, Afsoon Roberts, Barry Rodwick, Peter Ruane, Kunthavi Sathasivam, Stefan Schneider, Shannon Schrader, Anita Scribner, Michael Sension, Peter Shalit, William Short, Stephen Smith, Alan Taege, Melanie Thompson, Timothy Wilkin and Bienvenido Yangco.

Supported by Tibotec