

Development of resistance in patients with virologic failure (VF) on darunavir/ritonavir (DRV/r) or lopinavir/ritonavir (LPV/r): results of a randomized, controlled, Phase III trial in treatment-experienced patients (TITAN)

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Introduction

- The new HIV-1 protease inhibitor (PI), darunavir (DRV; TMC114), has significant in-vitro antiretroviral (ARV) activity against both wild-type virus and multidrug-resistant HIV-1 strains.¹
- DRV possesses a high genetic barrier¹ defined as the drug's ability to delay the development of resistance and to retain antiviral activity despite the occurrence of mutations within the viral target protein.
- DRV/r at a dose of 600/100mg bid has been approved in the USA² and other countries including those in Europe³ for the treatment of HIV-1 infection in treatment-experienced adult patients.
- TITAN (TMC114-C214; TMC114/r In Treatment-experienced pAtients Naïve to LPV) is an ongoing Phase III trial designed to assess the efficacy and safety of DRV/r versus LPV/r in patients with a broad range of treatment experience, typical of that encountered in a clinical setting.⁴
- The emergence of resistance to highly active ARV therapy (HAART) presents a significant challenge to managing HIV-1 infection.
- This poster studies development of resistance in TITAN patients experiencing VF with DRV/r or LPV/r.

Methods

Design and patient population

- TITAN is a randomized, controlled, 96-week, ongoing Phase III trial designed to assess the efficacy and safety of DRV/r versus LPV/r in LPV-naïve, treatment-experienced, HIV-1-infected patients.
- The primary objective of the trial was to establish non-inferiority of DRV/r versus LPV/r at Week 48 with VL <400 copies/mL.
- Patients with HIV-1 RNA >1000 copies/mL and treated with their current HAART for ≥12 weeks were randomized to receive an optimized background regimen (OBR) consisting of 2–3 ARVs (NRTIs with or without NNRTIs; enfuvirtide was disallowed) plus either DRV/r 600/100mg bid or LPV/r 400/100mg bid (Figure 1)
- patients on a structured treatment interruption (STI) of ≥4 weeks were also permitted to enroll.
- Patients with previous or current use of LPV, DRV, tipranavir or enfuvirtide and current use of investigational ARV drugs were excluded from the trial.

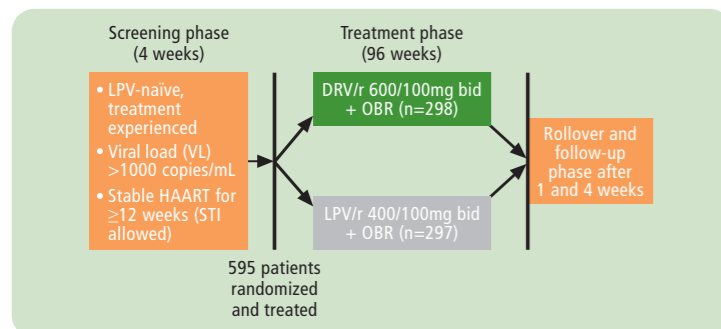


Figure 1. TITAN study design.

Virologic analysis

- Analyses were performed on the dataset from the primary analyses with a cut-off date of January 17 2007, at which time all patients had reached Week 48 of treatment or discontinued earlier.
- Viral phenotypic (Antivirogram[®]) and genotypic determinations were performed by Virco BVBA (Mechelen, Belgium).
- Phenotypic resistance was defined as having a fold-change in EC₅₀ (FC) above the biologic/clinical cut-off (Antivirogram[®]). The clinical cut-off of 10 was used for both DRV⁵ and LPV.⁶
- All lists of mutations were based on the IAS-USA lists.⁷
- The development of resistance at endpoint (i.e. the last available timepoint with a genotype/phenotype during the treatment period) compared with baseline was studied in patients who experienced VF
- the development of a mutation was defined as a mutation that could be detected by resistance testing at endpoint, but was not detected at baseline
- the loss of susceptibility to an ARV was defined as having a FC above the biologic/clinical cut-off at endpoint while not at baseline.

- VFs were defined as rebounders (loss of HIV-1 RNA <400 copies/mL) and those that were never suppressed (HIV-1 RNA <400 copies/mL never achieved).
- The time-to-loss of virologic response (TLOVR; non-VF censored) imputation method was used for the identification of VF, meaning that data were not imputed at timepoints after discontinuation for patients who discontinued for reasons other than VF (non-VF). Moreover, patients who discontinued before Week 16 were not taken into account to determine VF.
- As some patients in TITAN had decreased susceptibility to LPV at baseline despite being LPV/r naïve, a subanalysis was conducted that excluded patients with FC >10 to LPV. In addition, some patients in TITAN had previous use of two or more PIs; these patients were also excluded to provide another subanalysis.

Results

Baseline characteristics

- A total of 595 patients were randomized and treated, of these, 31% had not used PIs previously. Eighty-two percent of baseline isolates were susceptible to ≥4 PIs.
- Virologic baseline characteristics are shown in Table 1.

Table 1. Baseline characteristics

	DRV/r (n=298)	LPV/r (n=297)
Median number of mutations at baseline ¹ (range)		
Primary PI	0 (0–6)	0 (0–6)
PI RAMS	4 (0–17)	4 (0–14)
DRV RAMS	0 (0–5)	0 (0–4)
LPV RAMS	1 (0–11)	1 (0–9)
NRTI RAMS	2 (0–7)	2 (0–8)
Proportion of patients with ≥3 DRV RAMS, n (%)	12 (4.1)	11 (3.7)
Proportion of patients with ≥6 LPV RAMS, n (%)	32 (10.8)	35 (11.8)
Median phenotypic sensitivity score of OBR (range)	2 (0–3)	2 (0–4)
Median FC (range)		
DRV	0.60 (0.1–37.4)	0.60 (0.1–43.8)
LPV	0.70 (0.4–74.4)	0.80 (0.3–74.5)
DRV FC >10, n (%)	5 (1.7)	4 (1.4)
LPV FC >10, n (%)	29 (9.9)	29 (10.0)
LPV FC >40, n (%)	5 (1.7)	8 (2.8)

RAMs = resistance-associated mutations

- All patients were LPV-naïve at study entry; baseline characteristics showed that
- at baseline, 98.5% of patients were fully susceptible to DRV (FC ≤10) and 90.0% of patients were fully susceptible to LPV (FC ≤10)
- baseline demographics and treatment history were similar between treatment groups.
- This suggests that DRV has a higher genetic barrier to the development of resistance than LPV.

Overall efficacy results

- More DRV/r than LPV/r patients achieved VL <400 copies/mL at Week 48 (Figure 2). DRV/r was proven to be noninferior to LPV/r, as determined by the primary endpoint (VL <400 copies/mL). Results of a secondary analysis showed that DRV/r was superior to LPV/r at this timepoint.⁴

Virologic failures

- More patients receiving LPV/r failed to respond to treatment or rebounded compared to those receiving DRV/r (Figure 3a). The VF rate with LPV/r was two-fold higher than with DRV/r
- in patients with LPV FC ≤10 (Figure 3b) or those with previous use of none or only one PI (Figure 3c), still twice as many patients receiving LPV/r failed to respond or rebounded compared to those receiving DRV/r.

Development of mutations in VFs

- Fewer VFs on DRV/r than on LPV/r developed primary PI mutations or NRTI RAMS (Figure 4a)
- this difference remained or became more apparent when patients with LPV FC >10 (Figure 4b) or those with previous use of two or more PIs (Figure 4c) were excluded from the analysis
- only one of the VFs on DRV/r treatment with LPV FC ≤10 and none of the VFs on DRV/r treatment with previous use of ≤1 PI developed a primary PI mutation. On the contrary, 14/43 (33%) VFs on LPV/r treatment with LPV FC ≤10 and 10/31 (32%) VFs on LPV/r treatment with previous use of ≤1 PI developed a primary PI mutation.

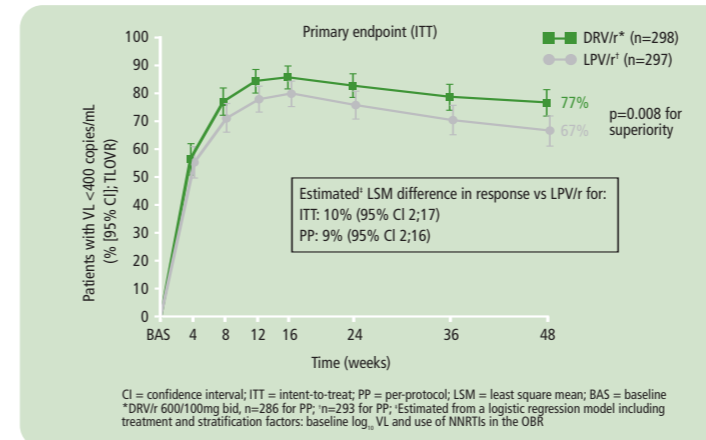


Figure 2. Proportions of DRV/r and LPV/r patients with VL <400 copies/mL to Week 48 (TLOVR-ITT).

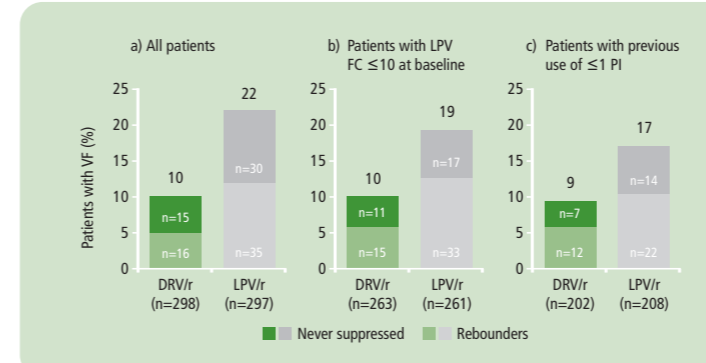


Figure 3. Proportions of DRV/r and LPV/r patients with VF.

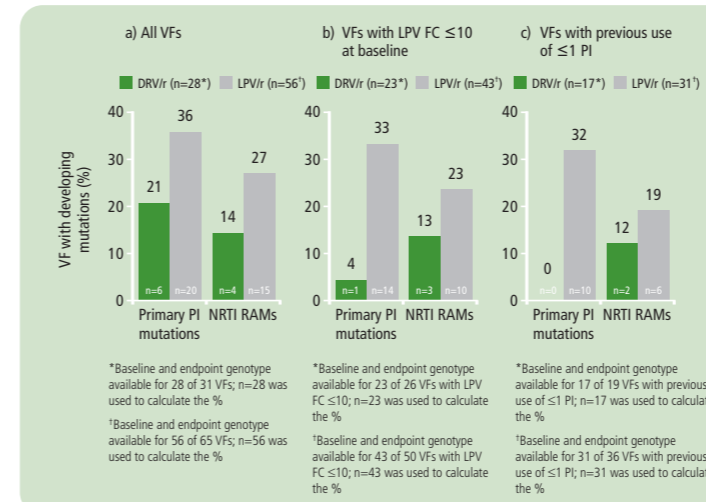


Figure 4. Development of primary PI mutations and NRTI RAMS upon VF.

- Analyses to identify the protease mutations that developed in >10% of VFs showed that the V321 mutation developed in 11% (3/28) of the VFs on DRV/r treatment and that the M46I and I54V mutations developed in 13% (7/56) and 14% (8/56), respectively, of the VFs on LPV/r treatment.

Loss of susceptibility to ARVs in VFs

- A smaller proportion of patients failing on DRV/r than on LPV/r lost susceptibility relative to baseline to the assigned study PI or NRTI(s) used in the background regimen (Figure 5a)
- the result was similar when patients with LPV FC >10 (Figure 5b) or those with previous use of two or more PIs (Figure 5c) were excluded from the analysis
- none of the VFs on DRV/r treatment with LPV FC ≤10 or with previous use of ≤1 PI lost susceptibility to DRV. On the contrary, 13/42 (31%) VFs on LPV/r treatment with LPV FC ≤10 and 8/30 (27%) VFs on LPV/r treatment with previous use of ≤1 PI lost susceptibility to LPV.

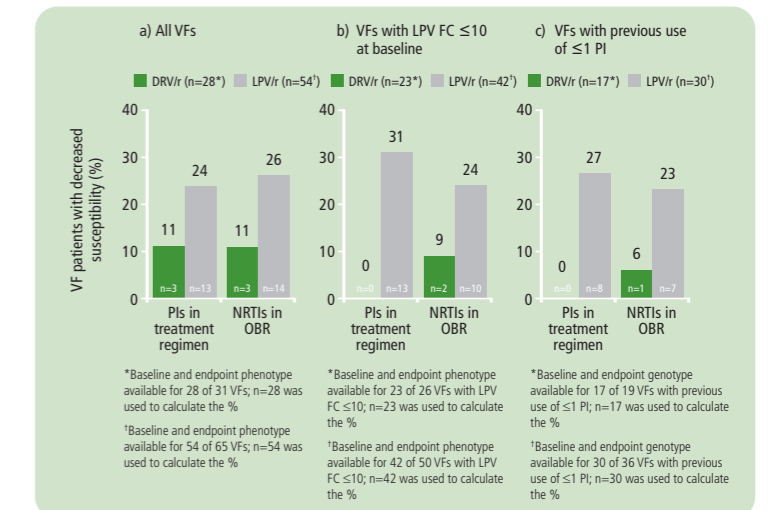


Figure 5. Loss of susceptibility to ARVs in VFs upon VF.

Conclusions

- In this LPV-naïve, treatment-experienced TITAN patient population, twice as many patients receiving LPV/r had VF compared with those receiving DRV/r
- even after excluding patients with LPV FC >10 or those with previous use of two or more PIs, twice as many patients receiving LPV/r had VF compared with those receiving DRV/r.
- Fewer VFs receiving DRV/r developed primary PI mutations and NRTI RAMS compared with VFs receiving LPV/r
- this conclusion remains true when patients with LPV FC >10 or patients who previously used ≥2 PIs were excluded.
- Compared with LPV/r and following VF, DRV/r-based therapy was associated with lower rates of loss of susceptibility to the PI or NRTI(s) in the treatment regimen. These findings suggest that in the TITAN study, DRV/r was more effective than LPV/r at protecting the treatment "backbone" and more likely to retain phenotypic susceptibility upon VF
- when patients with LPV FC >10 or patients who previously used ≥2 PIs were excluded, none of the VFs on DRV/r treatment lost susceptibility to DRV, while loss of LPV susceptibility was still observed in VFs on LPV/r treatment
- when patients with LPV FC >10 or patients who previously used ≥2 PIs were excluded, VFs receiving LPV/r still experienced a greater loss of susceptibility to NRTIs in the treatment regimen compared with DRV/r.
- These findings suggest that DRV has a high genetic barrier to the development of resistance and that the earlier use of DRV/r may better preserve future treatment options.

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