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Characterization of virologic failures on darunavir/ritonavir in the randomized, controlled, Phase III TITAN trial in treatment-experienced patients

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Introduction

- The emergence of resistance to highly active antiretroviral therapy (HAART) presents a significant challenge to managing HIV-1 infection. Characterizing the development of resistance to new antiretrovirals (ARVs) is needed to help improve treatment decisions.
- The new HIV-1 protease inhibitor (PI) darunavir (DRV; TMC114) has significant in-vitro ARV activity against both wild-type virus and multidrug-resistant HIV-1 strains.[1] DRV has a high genetic barrier, which delays the development of resistance and allows the retention of antiviral activity despite the occurrence of mutations within the target viral protein.
- DRV with low-dose ritonavir (DRV/r) at a dose of 600/100mg bid has been approved in the USA[2] and the EU[3] for the treatment of HIV-1 infection in treatment-experienced adult patients.
- In the ongoing Phase III TITAN trial (TMC114-C214), results of the 48-week primary analysis showed that treatment with DRV/r 600/100mg bid achieved both primary (noninferiority) and secondary (superiority) virologic endpoints versus lopinavir/ritonavir (LPV/r) 400/100mg bid in patients with a broad range of treatment experience.[4]
- At Week 48 in the TITAN trial, 71% of DRV/r patients achieved full virologic suppression (HIV RNA <50 copies/mL) compared to 60% of LPV/r patients.[4]
- The present analyses characterized the development of resistance in TITAN patients experiencing virologic failure (VF) with DRV/r or LPV/r.

Methods

Design and patient population

- TITAN is an international, 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.[4]
- Patients with HIV-1 RNA >1000 copies/mL and treated with their current HAART for ≥12 weeks were randomized to receive either DRV/r 600/100mg bid or LPV/r 400/100mg bid, plus an optimized background regimen (OBR, at least two ARVs [NRTIs and/or NNRTIs]; enfuvirtide (ENF) was disallowed) (Figure 1). Initially, patients on a structured treatment interruption of ≥4 weeks were also permitted to enroll.
- Patients with previous or current use of LPV, DRV, tipranavir (TPV) or ENF and current use of investigational ARV drugs were excluded from the trial.

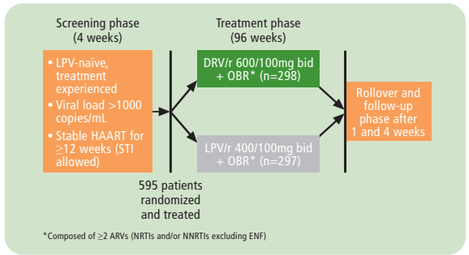

Figure 1. TITAN study design.

Virologic analysis

- Analyses were performed on the dataset from the primary analyses with a cut-off date of 17 January 2007, when all patients had reached Week 48 of treatment or discontinued earlier.
- VFs were defined as rebounders (loss of HIV-1 RNA <400 copies/mL) and never suppressed patients (never achieved HIV-1 RNA <400 copies/mL). Moreover, patients who discontinued before Week 16 were not taken into account to determine VF.
- The time-to-loss of virologic response (TLOVR; non-VF censored) imputation method was used for the analysis of virologic response, meaning that data were not imputed at timepoints after discontinuation for patients who discontinued for reasons other than VF (non-VF).
- Viral phenotypic (Antivirogram®) and genotypic determinations were performed by Virco BVBA (Mechelen, Belgium).
- Phenotypic resistance was defined as having a fold-change in EC_{50} (FC) above the biologic/clinical cut-off (Antivirogram®). The clinical cut-off of 10 was used for both DRV[5] and LPV[6], and 3 for TPV.[7] The biologic cut-offs 2.2, 2.4, 2.4, 2.2 and 1.8 were used for amprenavir (APV), atazanavir (ATV), indinavir (IDV), nelfinavir (NFV) and saquinavir (SQV), respectively.
- All lists of mutations were based on the IAS-USA lists.[8]
- The development of resistance at endpoint (EP; i.e. the last available timepoint with a genotype/phenotype during the treatment period) compared with baseline (BL) was studied in patients who experienced VF
  - the development of a mutation was defined as the detection of a mutation by resistance testing at EP, but not at BL
  - the loss of susceptibility to an ARV was defined as having a FC above the biologic/clinical cut-off at EP while not at BL.
- In parallel with the phenotypic analysis, a genotypic interpretation was performed using the Agence Nationale de Recherches sur le Sida (ANRS) system HIV-1 genotypic drug resistance interpretation algorithm of 2007.[9]

Results

Baseline characteristics

- Of the 595 patients who were randomized and treated, 31% had not used PIs previously. A total of 82% of BL isolates were susceptible to ≥4 PIs.
- BL characteristics were similar between the two treatment groups with a median of 0 primary PI mutations, 4 PI resistance-associated mutations (RAMs) and 2 NRTI RAMs, a median FC of 0.6 for DRV and 0.75 for LPV, and a median phenotypic sensitivity score of the underlying therapy of 2.[10]

Virologic failures

- More patients receiving LPV/r failed to respond to treatment or experienced rebound, compared with those patients receiving DRV/r. The VF rate with LPV/r was two-fold higher than with DRV/r (Figure 2a).

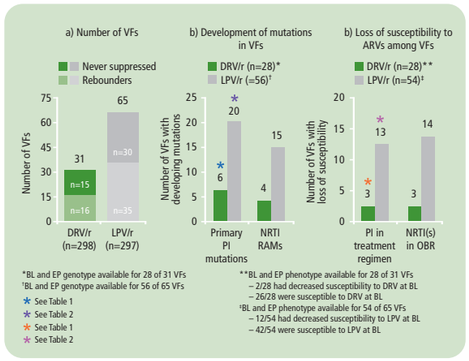

Figure 2. Number of VFs and resistance development in VFs.

- Fewer VFs on DRV/r than on LPV/r developed primary PI mutations or NRTI RAMs (Figure 2b).
- In the DRV/r group, 6 VFs developed a primary PI mutation (Figure 2b)
  - in 1 of the 6 DRV/r VFs, the L90M mutation that was detected at EP and not at BL was already detected in the screening sample
  - in the other 5 VFs, the following primary PI mutations (all DRV RAMs) developed: V32I (in 3 patients), I47V and L76V (in 2 patients) and I54L (in 1 patient). The 5 patients had previously used 2–6 PIs.
- In the LPV/r group, 20 VFs developed a primary PI mutation (Figure 2b)
  - in 1 of the 20 LPV/r VFs, the primary PI mutation M46I that was detected at EP and not at BL was already detected in the screening sample
  - in the other 19 VFs, the following primary PI mutations developed: M46I (in 6 patients), M46L and L76V (in 4 patients), L33F, I47A, I47V, V82A and I84V (in 2 patients) and V32I, I50V and I54M (in 1 patient). All these mutations are described as LPV RAMs.[11]
- Based on Antivirogram, in the DRV/r group, 3 VFs lost susceptibility to DRV; in the LPV/r group, 13 VFs lost susceptibility to LPV (Figure 2c).
- Among the DRV/r VFs, the majority retained susceptibility to PIs, based on phenotypic Antivirogram data (Figure 3). More VFs on LPV/r than on DRV/r lost susceptibility to the PI studied or any other PI (Figure 3).
- The same conclusion could be drawn from the ANRS HIV-1 genotypic drug resistance interpretations instead of the phenotypes (Figure 4).

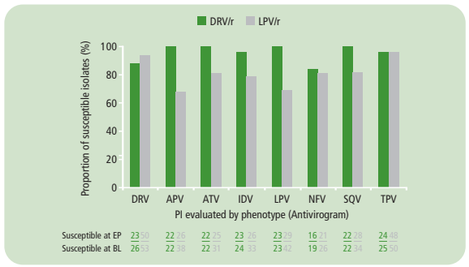

Figure 3. Proportion of isolates remaining susceptible to PIs upon VF (phenotypic Antivirogram data).

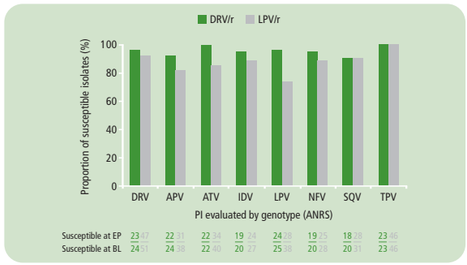

Figure 4. Proportion of isolates remaining susceptible to PIs upon VF (genotypic ANRS data).

- Tables 1 and 2 present an overview of the resistance data of all VFs on DRV/r or LPV/r treatment, respectively, showing the BL PI RAMs, the PI RAMs including the primary PI mutations that developed at EP relative to BL, and the phenotype (Antivirogram) and genotypic interpretation (ANRS) from the BL and EP sample.

Table 1. Overview of resistance data of all VFs in the DRV/r group.

VFs with developing primary PI mutation(s)

VFs without developing primary PI mutation(s)

*Mutation already present at screening
RB = rebounder; NS = never suppressed patient; BL = baseline; EP = endpoint; AVG = Antivirogram
Light green indicates previous use of 1 PI; dark green indicates previous use of ≥2 PIs
Primary PI mutations are shown in bold in the 'Developing PI RAMs' column
For Antivirogram data: FC values above the biological/clinical cut-off (decreased susceptibility) are shown in red; BL to EP changes from susceptible to decreased susceptibility are highlighted in yellow
For ANRS resistance interpretations calls: The calls intermediate (I) and resistant (R) are shown in red; BL to EP changes from susceptible (S) to I or R, or from I to R are highlighted in yellow

Table 2. Overview of resistance data of all VFs in the LPV/r group.

VFs with developing primary PI mutation(s)

Table 2 (cont'd). Overview of resistance data of all VFs in the LPV/r group.

VFs without developing primary PI mutation(s)

*Mutation already present at screening
RB = rebounder; NS = never suppressed patient; BL = baseline; EP = endpoint; AVG = Antivirogram
Light green indicates previous use of 1 PI; dark green indicates previous use of ≥2 PIs
Primary PI mutations are shown in bold in the 'Developing PI RAMs' column
For Antivirogram data: FC values above the biological/clinical cut-off (decreased susceptibility) are shown in red; BL to EP changes from susceptible to decreased susceptibility are highlighted in yellow
For ANRS resistance interpretations calls: The calls intermediate (I) and resistant (R) are shown in red; BL to EP changes from susceptible (S) to I or R, or from I to R are highlighted in yellow

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.
- Fewer VFs receiving DRV/r developed primary PI mutations and NRTI RAMs compared with VFs receiving LPV/r.
- More VFs on LPV/r than on DRV/r lost susceptibility to any other PI. Among the DRV/r VFs, the majority retained susceptibility to PIs. The findings based on phenotypic data (Antivirogram) were also confirmed by genotypic interpretation (ANRS).
- In summary, these TITAN study findings suggest that
  - DRV/r is more effective than LPV/r
  - upon VF, DRV/r is better than LPV/r in preventing the development of resistance
  - cross-resistance between DRV and other PIs was less frequent than that of LPV in this population of less treatment-experienced patients.

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