

Adherence to darunavir/ritonavir and lopinavir/ritonavir in treatment-naïve, HIV-infected patients in ARTEMIS: 96-week data

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Introduction

- The efficacy and safety of darunavir with low-dose ritonavir (DRV/r) 800/100mg qd versus lopinavir with low-dose ritonavir (LPV/r) in treatment-naïve, HIV-infected patients is being examined in the ongoing, Phase III ARTEMIS (TMC114-C211; AntiRetroviral Therapy with TMC114 Examined In naïve Subjects) trial.
- Based on the 48-week results of this trial,¹ once-daily DRV/r is
 - approved for use in treatment-naïve, HIV-1-infected adult patients in the USA² and in Europe³
 - listed as a preferred protease inhibitor (PI) component of therapy for treatment-naïve patients in the US Department of Health and Human Services (DHHS)⁴ and International AIDS Society-USA (IAS-USA) guidelines.⁵
- At Week 96, DRV/r 800/100mg qd showed significantly greater virological response rates than LPV/r 800/200mg total daily dose⁶
 - 79% of DRV/r patients achieved HIV-1 RNA <50 copies/mL (intent-to-treat analysis of time-to-loss of virological response [ITT-TLOVR], Food and Drug Administration algorithm for definition of virological response) versus 71% of LPV/r patients (difference = 8.3%, p value for superiority = 0.012; ITT-TLOVR).
- Once-daily DRV/r was generally safe and well tolerated in the Week 96 analysis, with few treatment discontinuations due to adverse events (AEs) (5% for DRV/r vs 10% for LPV/r)
 - grade 2–4 diarrhoea at least possibly related to treatment occurred less frequently with DRV/r than LPV/r (4% vs 11%; p<0.001)
 - grade 2–4 triglyceride and total cholesterol laboratory abnormalities were reported less frequently with DRV/r than LPV/r (4% vs 13%, p<0.0001 and 18% vs 28%, p=0.0016, respectively).
- Adherence to antiretroviral (ARV) treatment is a strong predictor of long-term treatment response⁷
 - in the Week 48 analyses of ARTEMIS, adherence correlated with both efficacy and safety outcomes. However, suboptimal adherence (≤95%) resulted in higher virological response rates with DRV/r than with LPV/r⁸
 - an updated analysis of adherence in ARTEMIS, up to Week 96, is presented.

Methods

Study design

- Details of the ARTEMIS study methodology have been reported previously.¹
- Treatment-naïve, HIV-1-infected adult patients with HIV-1 RNA >5,000 copies/mL were randomised to receive DRV/r 800/100mg qd or LPV/r 800/200mg total daily dose (Figure 1).
- Patients also received a fixed-dose background regimen of tenofovir disoproxil fumarate (TDF) 300mg qd and emtricitabine (FTC) 200mg qd.
- Written informed consent was obtained from all patients. The study protocol was reviewed and approved by the appropriate institutional ethics committees and health authorities, and was conducted in accordance with the Declaration of Helsinki.

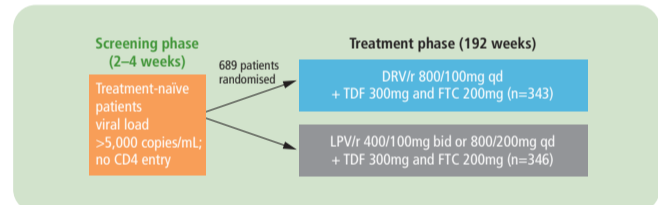


Figure 1. ARTEMIS study design.

Efficacy and safety assessments

- The primary endpoint was the proportion of patients with HIV-1 RNA <50 copies/mL (TLOVR) at Week 48
 - the primary objective was to demonstrate non-inferiority of DRV/r qd versus LPV/r based on the primary endpoint.
- Secondary objectives included: long-term safety, tolerability and durability of virological responses; testing for superiority of virological response if non-inferiority of DRV/r versus LPV/r was established; pharmacokinetics; immunological response; and quality of life.

Adherence assessments

- Adherence was assessed using the Modified Medication Adherence Self-Report Inventory (M-MASRI) validated questionnaire; a key endpoint was
 - percentage of doses of DRV/r and LPV/r taken (within the correct time frame) during the previous 30 days.
- Data were collected at Weeks 4, 12, 24, 36, 48, 60, 72, 84 and 96.
- At each timepoint, rates were transformed into a binary variable (adherent [≥95%] and suboptimally adherent [≤95%]); as this adherence level is widely accepted as being required to achieve optimal ARV efficacy⁹
 - average adherence from Week 4 to Week 96 was used to assess overall adherence up to Week 96 or time of withdrawal for early terminations.
- Confirmed virological responses and AEs were tabulated over time by adherence.
- Between-group comparisons and within-group comparisons versus baseline were assessed by Pearson's chi-square test or the Fisher's exact test (if one or more of the cells had an expected frequency of five or less).
- Patient-perceived degree of distress caused by symptoms and side effects and their impact on adherence was assessed by a modified version of the validated Memorial Symptom Assessment Scale – Short Form.

Results

Patient disposition and baseline characteristics

- Six hundred and eighty-nine patients (DRV/r: n=343; LPV/r: n=346) were randomised and treated.
- Demographical data and disease characteristics were well balanced across the treatment arms at baseline (Table 1).

Table 1. Demographical and baseline characteristics.

	DRV/r (n=343)	LPV/r (n=346)
Demographics		
Male, n (%)	239 (70)	241 (70)
Mean age, years (±SD)	35.5 (9)	35.3 (9)
Race, n (%)		
Black	80 (23)	71 (21)
Caucasian	137 (40)	153 (44)
Hispanic	77 (22)	77 (22)
Oriental/Asian	44 (13)	38 (11)
Other	4 (1)	5 (1)
Missing	1 (1)	2 (1)
Disease characteristics		
Mean known duration of infection, years (±SD)	2.4 (3.6)	2.5 (3.6)
Mean baseline log ₁₀ HIV RNA (±SD)	4.86 (0.64)	4.84 (0.60)
Median CD4 cell count, cells/mm ³ (range)	228 (4–750)	218 (2–714)

SD = standard deviation

Adherence

- Median self-reported adherence was 100% at all timepoints for both groups. The mean adherence ranged from 97.4% to 97.9% (DRV/r) and 96.3% to 97.7% (LPV/r) from Week 4 to Week 96.
- The proportion of patients with a mean Week 4–96 adherence within various cut-off values are shown in Figure 2
 - further statistical analysis of the subcategories below 95% adherence were not valid due to the low patient numbers.

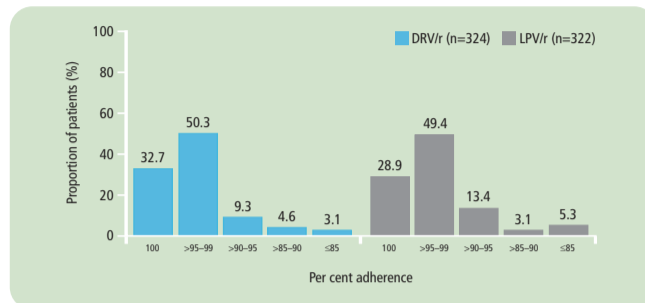


Figure 2. Proportion of patients versus per cent adherence for various cut-off values.

- Overall adherence was high; 83% (DRV/r) and 78% (LPV/r) of patients were adherent i.e. had a Week 4–96 mean adherence of >95%
 - values ranged from 81% to 90% for DRV/r patients and 74% to 89% for LPV/r patients over time (Figure 3)
 - no statistically significant difference between the treatment groups was seen at any timepoint.

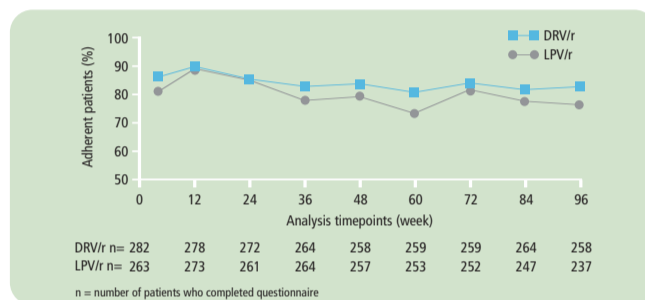


Figure 3. M-MASRI: proportion of adherent patients by analysis timepoint.

Adherence and efficacy

- Confirmed virological response rates at Week 96 (viral load <50 copies/mL, ITT-TLOVR) in patients reporting adherence (Week 4–96 mean adherence >95%) versus suboptimal adherence (Week 4–96 mean adherence ≤95%) by treatment are shown in Figure 4.
- Response rates (<50 copies/mL) in adherent patients were similar in DRV/r and LPV/r patients: 82% (221/269) and 78% (196/252), respectively.
- In patients reporting suboptimal adherence, however, a lower response (<50 copies/mL) at Week 96 was seen with LPV/r (53%) compared with DRV/r (76%) patients (p<0.01).

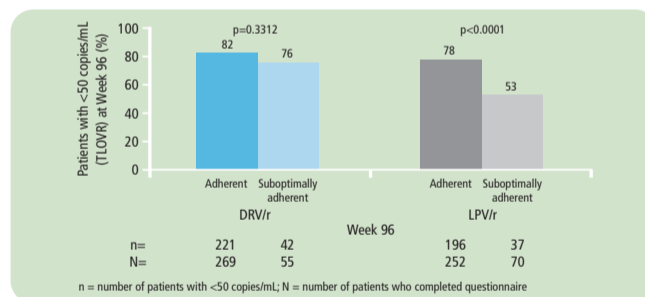


Figure 4. M-MASRI: confirmed virological response at Week 96 (viral load <50 copies/mL, TLOVR) by mean Week 4 to Week 96 adherence.

- In a logistical regression model including both treatment effect and adherence, confirmed virological response rates (viral load <50 copies/mL, ITT-TLOVR) were higher in the adherent versus suboptimally adherent groups (odds ratio [OR]: 2.3 [1.5–3.4]). The response rate was also higher in DRV/r-treated patients compared with LPV/r-treated patients (OR: 1.6 [1.09–2.3])
 - a smaller difference in virological response for adherent versus suboptimally adherent patients was reported for DRV/r than for LPV/r (DRV/r: 7% difference [82% vs 76%, p=0.3312]; LPV/r: 25% difference [78% vs 53%], p<0.0001).

Adherence and safety

- In order to correspond with the period of self-rated adherence, AEs with an onset date within 30 days before each timepoint were analysed. For example, Week 96 AEs referred to events which occurred between 30 days before Week 96 and the Week 96 visit.
- At most timepoints, in both adherent and suboptimally adherent patients, the percentage of patients with at least one AE was higher in the LPV/r arm than in the DRV/r arm (Figure 5).
- Suboptimally adherent patients reported more AEs than adherent patients in both treatment arms for the majority of timepoints (Figure 5).

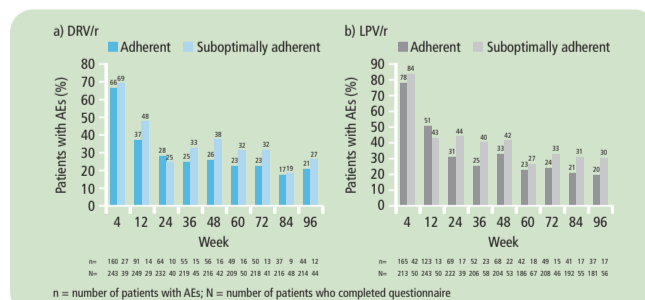


Figure 5. Percentage of patients with at least one AE by adherence and analysis timepoint for a) DRV/r and b) LPV/r treated patients.

- At Week 96, the proportion of patients with gastrointestinal (GI) AEs (regardless of severity or causality), in the overall population was 61% and 75% in the DRV/r and LPV/r groups, respectively.
- GI AEs were most frequently observed in the first 12 weeks of therapy. Fewer GI events were reported in patients receiving DRV/r compared with LPV/r (Figure 6).
- At Week 4, GI events with onset during the previous 30 days were reported in a similar proportion of adherent and suboptimally adherent; DRV/r: 37% and 39%, respectively; LPV/r: 52% and 52%, respectively.
- At Week 12, GI events were reported in fewer adherent patients compared with suboptimally adherent patients: 7% vs 28%, respectively, for DRV/r and 13% vs 23%, respectively, for LPV/r (Figure 6).

- The lower number of GI events reported after Week 12 made it difficult to assess their impact on adherence after this timepoint.

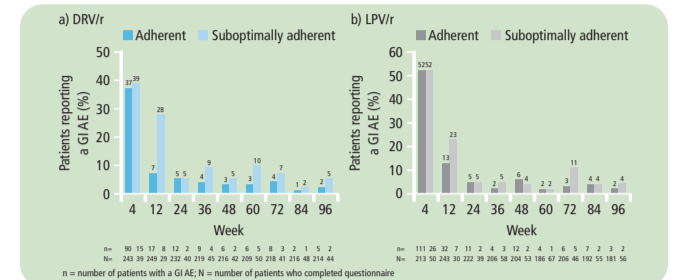


Figure 6. Proportion of patients with at least one GI AE regardless of causality or severity by adherence and analysis timepoint for a) DRV/r and b) LPV/r treated patients.

- Total distress scores from a list of 39 symptoms were generally higher in LPV/r versus DRV/r patients, and were higher in suboptimally adherent compared with adherent patients in both arms (data not shown).

Adherence and demographics/baseline characteristics

- Some differences in adherence to both DRV/r and LPV/r were seen with both race and geographical region (Figure 7).
- Mean Week 4–96 adherence to both DRV/r and LPV/r differed by race (Figure 7a); suboptimal adherence data were as follows
 - Black patients, DRV/r: 26%; LPV/r: 41%
 - Caucasians, DRV/r: 15%; LPV/r: 15%
 - Other races, DRV/r: 13%; LPV/r: 19%.
- Geographical differences in mean Week 4–96 adherence to both DRV/r and LPV/r were also observed (Figure 7b)
 - patients in Asia, Central and South America, and Europe generally had higher adherence to both DRV/r and LPV/r than patients in North America and South Africa
 - across most regions evaluated, adherence was generally higher for DRV/r than LPV/r.
- Other baseline characteristics and demographics, including gender and age, were not significant predictors of adherence.

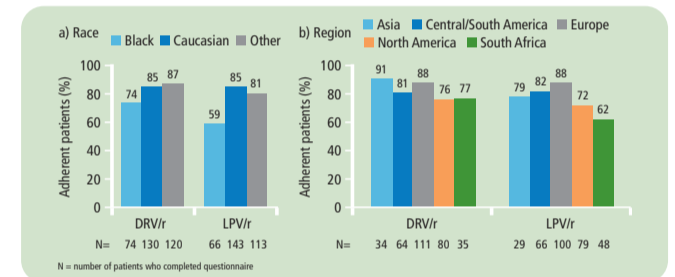


Figure 7. Percentage of adherent patients at Week 96 by a) race and b) geographical region.

Validity of M-MASRI adherence measurements

- The correlation between self-adherence measurements with self-reported missed doses due to symptoms (Weeks 4–96), and with plasma drug concentrations (Weeks 4–48) were tested by Kappa statistics
 - both endpoints (p<0.001 and p<0.01, respectively) correlated well with self-reported adherence from the M-MASRI, suggesting validity of this assessment.
- Patients reporting at least one missed dose due to symptoms listed in the symptoms questionnaire were more likely to self-report suboptimal adherence (Kappa coefficients ranged from 0.16 [at Week 96] to 0.32 [at Week 24], p<0.001 at all timepoints).
- With regards to pharmacokinetic data at Week 48
 - in the DRV/r arm, of the 36 suboptimally adherent patients, 11% (n=4) had a DRV plasma concentration below the limit of detection (10ng/mL) (vs 4% [n=7] of the 199 adherent patients) (all available data)
 - in the LPV/r arm, of the 49 suboptimally adherent patients 14% (n=7) had a LPV plasma concentration below the limit of detection (10ng/mL) (vs 4% [n=7] of the 189 adherent patients) (all available data).

Conclusions

- The Week 96 analysis of ARTEMIS demonstrated that adherence to ARV therapy correlated with efficacy and safety outcomes
 - virological response rates were generally higher in adherent versus suboptimally adherent patients
 - suboptimally adherent patients reported a higher incidence of AEs (mainly GI) and symptoms or symptom-related perceived distress associated with ARV therapy
 - variability of adherence levels was observed across regional and ethnic subgroups – these results confirm those reported at Week 48.⁹
- High virological response rates were seen at Week 96, which were similar between treatment arms for patients adherent to therapy.
- The efficacy of once-daily DRV/r in suboptimally adherent patients was minimally compromised compared with adherent patients (76% vs 82%).
- Suboptimal adherence to DRV/r had less effect on virological response than suboptimal adherence to LPV/r (7% vs 25% difference in response compared with adherent patients, respectively).
- Although adherence tended to be higher in the DRV/r arm, when the virological response was adjusted for differences in adherence, DRV/r treatment was still associated with a significantly greater virological response compared with LPV/r.
- Suboptimally adherent patients reported higher incidence of AEs and GI AEs, suggesting that tolerability may also be a significant driver of lower adherence.
- The better efficacy of DRV/r compared with LPV/r when adherence is compromised, may result from several factors including
 - the longer half-life of ritonavir-boosted DRV versus LPV (15 hours vs 5–6 hours)¹⁰
 - DRV's stronger binding affinity and lower dissociation rate from the HIV-1 protease compared with LPV.¹¹

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Medical writing support was provided by Gardiner-Caldwell Communications; this support was funded by Tibotec.