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Factors affecting virologic response to darunavir/ritonavir and lopinavir/ritonavir in treatment-naïve HIV-1-infected patients in ARTEMIS at 96 weeks

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Introduction

- ARTEMIS (TMC114-C211; **A**nti**R**etroviral **T**herapy with TMC114 **E**xa**M**ined **I**n naïve **S**ubjects) is an ongoing, randomized, controlled, Phase III trial evaluating the efficacy and safety of darunavir (DRV; TMC114) with low-dose ritonavir (DRV/r) versus lopinavir (LPV)/r in treatment-naïve HIV-1-infected patients.[1]
- In the 96-week analysis,[2] 79% of DRV/r compared with 71% of LPV/r patients achieved HIV-1 RNA <50 copies/mL; intent-to-treat/time-to-loss of virologic response (ITT-TLOVR), p value for superiority = 0.012.
- Once-daily DRV/r was generally safe and well tolerated in the Week 96 analysis[2]
  - grade 2–4 diarrhea 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 (18% vs 28%, p=0.0016 and 4% vs 13%, p<0.0001, respectively).
- DRV/r at a dose of 800/100mg qd has been approved in both Europe and the US[3] for the treatment of HIV-1 infection in treatment-naïve adult patients.
- To determine the factors influencing virologic response to DRV/r in ARTEMIS, we examined the effect of different baseline and treatment factors (such as adherence) on HIV-1 RNA reduction to <50 copies/mL at Week 96 in different subgroups of patients in the trial.

Methods

Patients and study design

- Adult, HIV-1-infected, treatment-naïve patients with HIV-1 RNA ≥5000 copies/mL were randomized to receive DRV/r 800/100mg qd or LPV/r 800/200mg total daily dose
  - all patients receive a fixed-dose background regimen of tenofovir disoproxil fumarate (TDF) 300mg qd and emtricitabine (FTC) 200mg qd (TDF/FTC was provided by Gilead).
- The primary objective of the ARTEMIS study was to demonstrate non-inferiority of DRV/r qd versus LPV/r based on the primary endpoint, which was the proportion of patients with confirmed HIV-1 RNA <50 copies/mL.
- Detailed methodology of the ARTEMIS study has been reported previously.[1]
- For comparing proportions, unless otherwise stated (eg. using a model with certain covariates), chi-squared tests were used.

Definition of virologic response

ITT-TLOVR was used to define virologic response <50 copies/mL at Week 96

- In the TLOVR algorithm, a patient's response is considered to be >50 copies/mL at Week 96 if he/she
  - discontinued randomized treatment before Week 96, for any reason
  - had not achieved HIV-1 RNA levels below 50 copies/mL for at least two consecutive visits before Week 96 (never suppressed)
  - showed a rebound in HIV-1 RNA above 50 copies/mL for two consecutive visits by Week 96, after intitial suppression. Even if this rebound in HIV-1 RNA was temporary, this patient is still a failure by TLOVR.

Confirmed virologic response (CVR) NC=F

- CVR is the same as the standard ITT-TLOVR analysis, but does not include any temporary blips in HIV-1 RNA as failures. This method was used in the CASTLE study.[4] If a patient shows two consecutive HIV-1 RNA >50 copies/mL values during treatment, but then there is resuppression to <50 copies/mL on two consecutive visits, the patient is still classified as a success by this method.

Non-VF censored

- This analysis excludes patients who discontinued randomized treatment for any reason other than VF.

Multivariate analysis models

- Logistic regression models were implemented to investigate the associations between achieving HIV-RNA <50 copies/mL at Week 96 and treatment and prognostic covariates.
- Potential prognostic covariates included age, sex, race, region, adherence, baseline $\log_{10}$ HIV-1 RNA and baseline CD4 cell count.
- Treatment effect was measured by differences in the unadjusted and model-adjusted responses using TLOVR and TLOVR non-VF censored algorithms (excluding discontinuations for reasons other than VF to determine response).

Adherence

- The Modified Medication Adherence Self-Report Inventory (M-MASRI) questionnaire assessed adherence with trial medication by percentages of doses taken from Week 0 to Week 96
  - average adherence from Week 4 to Week 96 was used to assess overall adherence up to Week 96 or time of withdrawal in early terminations (mean adherence >95% [adherent] vs ≤95% [sub-optimally adherent]).

Results

Patient disposition and baseline characteristics

- Demographic data and disease characteristics were well balanced across the treatment arms at baseline (Table 1).

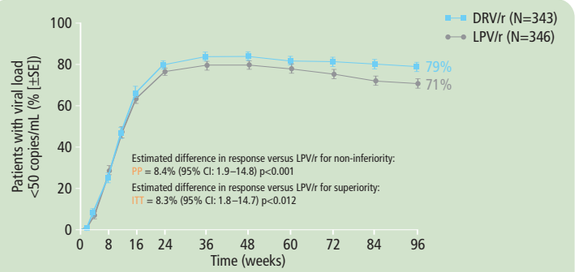
Table 1. ARTEMIS: baseline characteristics.

	DRV/r (N=343)	LPV/r (N=346)
Baseline demographics		
Male, n (%)	239 (70)	241 (70)
Mean age, years (±SD)	35.5 (9)	35.3 (9)
Black, n (%)	80 (23)	71 (21)
Caucasian, n (%)	137 (40)	153 (44)
Hispanic, n (%)	77 (22)	77 (22)
Oriental/Asian, n (%)	44 (13)	38 (11)
Baseline disease characteristics		
Median CD4 cell count, cells/mm³ (range)	228 (4–750)	218 (2–714)
Median $\log_{10}$ HIV-1 RNA, copies mL (SD)	4.86 (0.64)	4.84 (0.60)
Median duration of HIV infection, years (SD)	2.4 (3.6)	2.5 (3.6)

SD = standard deviation

Overall response and response by adherence

- The overall response rate and the percentage of responders are shown in Figure 1 and Table 2, respectively.



*Estimated from a logistic regression model including treatment and stratification factors (baseline $\log_{10}$ viral load and baseline CD4 cell count); SE = standard error; PP = per protocol; CI = confidence interval

Figure 1. Proportion of patients in ARTEMIS with HIV-1 RNA <50 copies/mL to Week 96 (ITT-TLOVR).*

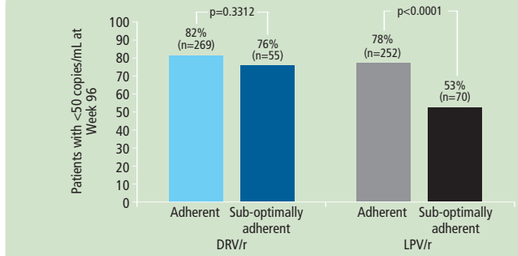
- When response was assessed by adherence, there was no statistically significant difference in response (HIV-1 RNA <50 copies/mL) at Week 96 between adherent patients in the DRV/r and LPV/r treatment groups.

Table 2. Percentage of responders (<50 copies/mL) at Week 96 by population.

ARTEMIS	DRV/r n/N (%)	LPV/r n/N (%)	DRV/r–LPV/r (%)*	p value‡
ITT-TLOVR	271/343 (79.0)	245/346 (70.8)	8.2	<0.05
CVR, NC=F	276/343 (80.5)	254/346 (73.4)	7.0	<0.05
Non-VF censored	271/292 (92.8)	245/281 (87.2)	5.6	<0.05

*Summary statistics; ‡Chi-squared test
NC=F = non-completor=failure

- However, in sub-optimally adherent patients, those receiving DRV/r had a greater response at Week 96 than those receiving LPV/r (Figure 2).



Note: adherence based on average % adherence Week 4 through Week 96

Figure 2. Proportion of patients in ARTEMIS with HIV-1 RNA <50 copies/mL by average adherence.

- In the DRV/r group, sub-optimally adherent patients had similar rates of response (76%) compared with adherent patients (82%; p=0.3312).
- In the LPV/r group, sub-optimally adherent patients had statistically lower rates of response (53%) than adherent patients (78%; p<0.0001).

Multivariate analysis

- In the multivariate analyses, the difference in response (HIV-1 RNA <50 copies/mL) favoring DRV/r was maintained after adjusting for baseline and treatment factors (Figure 3).

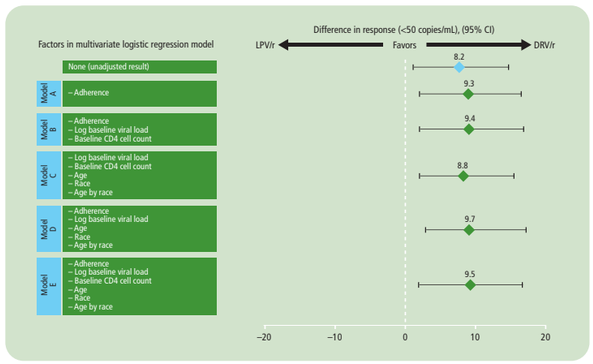


Figure 3. Multivariate analysis of response (<50 copies/mL) by model at Week 96.

- In the multivariate analysis, the full model (N=643) included treatment, adherence, age, race, baseline $\log_{10}$ HIV-1 RNA, and baseline CD4 cell count
  - region was initially included in the model, but was found to be significantly correlated with race, and therefore was removed.
- In the final reduced model, treatment effect was also examined; the analysis of main effects is shown (Table 3a). The response and difference in response was calculated for the final reduced model (Table 3b)
  - significantly more treatment-naïve patients achieved HIV-1 RNA <50 copies/mL with once-daily DRV/r compared with LPV/r.

Table 3. Statistical analysis of the final reduced model.

a) Analysis of main effects

Effect	Odds ratio for success* (95% CI)	p value
Treatment (DRV/r vs LPV/r)	1.6 (1.1–2.4)	0.0147
Mean adherence (Week 0–Week 96),† %	1.9 (1.4–2.6)	<0.0001
Baseline $\log_{10}$ HIV-1 RNA, copies/mL‡	0.56 (0.41–0.76)	0.0003

*Success = <50 copies/mL; †Per 10% change in adherence; ‡Per increase of one $\log_{10}$

b) Adjusted treatment effect§

N	DRV/r (%)	LPV/r (%)	DRV/r–LPV/r (95% CI)	p value for superiority
643	81.7	73.5	8.2 (1.5–14.9)	0.016

§Final reduced model included treatment, adherence, age, race, baseline $\log_{10}$ HIV-1 RNA, adherence-by-baseline $\log_{10}$ HIV-1 RNA and age by race

Repeat analysis in the non-VF censored population

Multivariate analysis

- The analysis of main effects was performed in non-VF censored patients (excludes all patients who discontinued for reasons other than true VF), and the reduced model results are shown (Table 4a)
  - significantly more treatment-naïve patients achieved HIV-1 RNA <50 copies/mL with once-daily DRV/r compared with LPV/r (Table 4b).

Table 4. Statistical analysis of the final reduced model in the non-VF censored population.

a) Analysis of main effects

Effect*	Odds ratio for success‡ (95% CI)	p value
Treatment (DRV/r vs LPV/r)	2.2 (1.2–4.1)	0.0096
Mean adherence (Week 0–Week 96),† %	1.1 (0.60–2.0)	0.7471
Baseline $\log_{10}$ HIV-1 RNA, copies/mL¶	0.30 (0.19–0.49)	<0.0001

*Age, race, and age by race also included in final model; ‡Success = <50 copies/mL; †Per 10% change in adherence; ¶Per increase of one $\log_{10}$

b) Adjusted treatment effect#

N	DRV/r (%)	LPV/r (%)	DRV/r–LPV/r (95% CI)	p value for superiority
549	94.2	87.9	6.3 (1.3–11.3)	0.014

#Final reduced model included treatment, adherence, baseline $\log_{10}$ HIV-1 RNA, age, race and age by race

Conclusions

- In ARTEMIS at 96 weeks, significantly more treatment-naïve patients achieved HIV-1 RNA <50 copies/mL with once-daily DRV/r 800/100mg compared with LPV/r 800/200mg total daily dose, even after adjusting for baseline predictors of response (i.e. adherence, age, race and baseline HIV-1 RNA).
- These results were also seen when patients who discontinued for adverse events or other reasons were excluded from the analysis (non-VF censored population).
- Sub-optimal adherence to DRV/r did not compromise virologic response, whereas patients receiving LPV/r who had sub-optimal adherence were significantly more likely to fail therapy.
- The efficacy benefit of DRV/r over LPV/r in the ARTEMIS trial was driven primarily by virologic endpoints. This efficacy benefit was not primarily caused by differences in discontinuations for adverse events or other reasons.

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