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Relationship between combination of baseline viral load and CD4 cell count, and Week 48 or 96 responses to rilpivirine (RPV) or efavirenz (EFV) in treatment-naïve HIV-1-infected adults: pooled analysis from the Phase III ECHO and THRIVE trials

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Introduction

- RPV (EDURANT®) is a new NNRTI approved in the USA, Canada and Europe, in combination with other antiretrovirals, for use in HIV-1-infected, treatment-naïve adults[1,2]
  - A single-tablet regimen of RPV, with tenofovir disoproxil fumarate (TDF) and emtricitabine (FTC) (Complera® [USA]; Eviplera® [EU]) has also been approved[3,4]
  - The European Medicines Agency approval of EDURANT® and Eviplera® is for patients with a viral load ≤100,000 copies/mL (c/mL).[2,4]
- These approvals were granted on the basis of the 48-week, primary analysis of the global Phase III, randomized, double-blind, double-dummy ECHO (TMC278-C209, NCT00540449)[5] and THRIVE (TMC278-C215, NCT00543725)[6] trials
  - RPV 25 mg qd had non-inferior efficacy to EFV 600 mg qd in each trial (primary objective)
  - RPV had significantly lower rates of grade 2–4 adverse events (AEs) at least possibly related to treatment, rash, dizziness and abnormal dreams/nightmares, and had significantly less lipid elevations than EFV.
- In the pooled, Week 96 analysis of these two trials, similar confirmed response rates (viral load <50 c/mL, intent-to-treat, time-to-loss-of-virologic-response [ITT-TLOVR]) were seen for RPV and EFV (78%).[7]
- Logistic regression with generalized additive models showed that the most important factors associated with increased likelihood in achieving virologic response with RPV or EFV at Week 48 in ECHO and THRIVE were higher treatment adherence, higher exposure to the drug and lower baseline viral load.[8]
- The current, post-hoc analysis, compares Week 48 and 96 responses (viral load <50 c/mL, ITT-TLOVR algorithm) and virologic outcomes within categories of baseline viral load and CD4 cell count, from a univariate perspective (without accounting for other predictors of response). Baseline viral load and CD4 cell count are factors readily known to a clinician when considering initiating treatment, while adherence and PK are not ascertainable when considering these regimens. In this analysis, 655/685 patients (96%) were >95% adherent as reported by the investigator on RPV, while 607/682 (89%) had >95% adherence on EFV.

Methods

- Patients (N=1368) were randomized 1:1 to receive RPV 25 mg qd or EFV 600 mg qd plus TDF/FTC (ECHO) or investigator-selected TDF/FTC, zidovudine/lamivudine (AZT/3TC) or abacavir/lamivudine (ABC/3TC) (THRIVE). Pooled data are presented.
- Patients were advised to take RPV/RPV placebo with food at the same time each day, and EFV/EFV placebo on an empty stomach, at bedtime.
- Randomization was stratified by baseline viral load:≤100,000; >100,000–≤500,000 and >500,000 c/mL (and by background regimen in THRIVE).Given the small size of the >500,000 c/mL subgroup, data are presented in two subgroups: ≤100,000 c/mL and >100,000 c/mL.
- Secondary objectives of the trials included an evaluation of efficacy and safety/tolerability over 96 weeks.

Results

Baseline characteristics

- Baseline patient demographics and disease characteristics were well-balanced between the two groups (**Table 1**).[7]
- There was a strong inverse correlation between baseline viral load and CD4 cell count e.g. for patients with CD4 cell count <50 cells/mm³ and 50–200 cells/mm³, 84% (59/70) and 64% (237/369), respectively, had a baseline viral load >100,000 c/mL.

Response to RPV or EFV by baseline viral load and CD4 cell count

- In patients with baseline viral load ≤100,000 c/mL, responses were high and in general similar between RPV and EFV (**Table 2** and **Figure 1A**)
  - RPV responses were all ≥90% at Week 48 and ≥84% at Week 96 (**Figure 1A**), except for lowest CD4 cell count category (<50 cells/mm³)
  - Given the correlation between baseline viral load and CD4 cell count, sample size in the CD4 cell count <50 cells/mm³ category (RPV N=6 and EFV N=5) is too small to draw conclusions.

Table 1. Baseline viral load and CD4 cell count.[7]

	RPV (N=686)	EFV (N=682)
Median $\log_{10}$ baseline viral load, c/mL (range)	5 (2–7)	5 (3–7)
Baseline viral load c/mL, % >100,000 c/mL	46	52
Median baseline viral load, c/mL (IQR)		
Median baseline viral load >100,000 c/mL	235,000 (152,000–443,000)	236,000 (150,000–460,000)
Median baseline viral load ≤100,000 c/mL	37,000 (18,000–59,000)	34,000 (16,000–62,000)
Median baseline CD4 cell count, cells/mm³ (range)	249 (1–888)	260 (1–1137)

IQR = interquartile range

- In the subset of patients with baseline viral load >100,000 c/mL, overall response rates tended to increase with increasing CD4 cell count, to a greater extent in the RPV group than in the EFV group (**Figure 1B**)
  - In patients with baseline CD4 cell count >200 cells/mm³, responses were similar between the treatment groups.
- Overall across baseline viral loads, lower responses were seen in both treatment groups (and lower with RPV than EFV) in the CD4 cell count <50 cells/mm³ category (**Table 2**)
  - Apart from baseline viral load, other factors affecting treatment response such as adherence and RPV PK (as per GAM analysis) may have confounded this finding, particularly in this small subgroup: e.g. in the subset with >95% adherence in terms of drug intake, response rates were RPV 62% vs EFV 78% at Week 96.

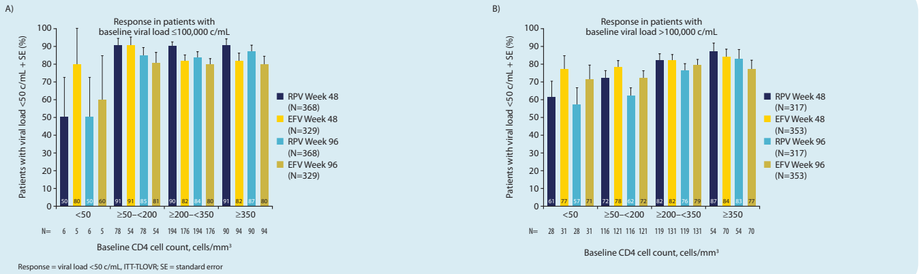
Table 2. Response by baseline viral load or CD4 cell count.

	RPV 25 mg qd (N=686)		EFV 600 mg qd (N=682)	
Week 48	**N**	**Response, %**	**N**	**Response, %**
Baseline viral load, c/mL				
≤100,000	368	90	330	84
>100,000	318	77	352	81
Baseline CD4 cell count, cells/mm³				
<50	34	59	36	78
≥50–<200	194	80	175	82
≥200–<350	313	87	307	82
≥350	144	90	164	83
Week 96				
Baseline viral load, c/mL				
≤100,000	368	84	329	80
>100,000	318	70	353	75
Baseline CD4 cell count, cells/mm³				
<50	34	56	36	69
≥50–<200	194	71	175	75
≥200–<350	313	81	307	79
≥350	144	85	164	79

Virologic outcomes at Weeks 48 and 96 by baseline viral load and CD4 cell count

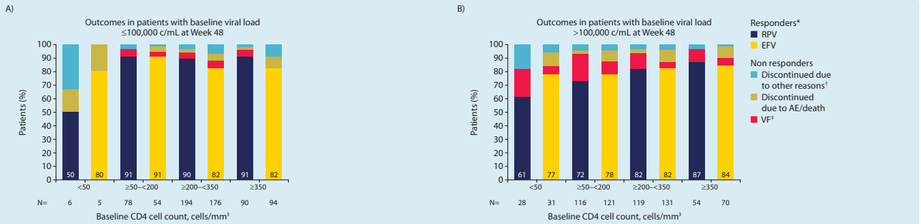
- For patients with baseline viral load ≤100,000 c/mL, in general a comparable and low percentage of patients with virologic failure (VF) was observed in the RPV group and in the EFV group, while slightly fewer patients discontinued due to AEs/deaths or other reasons on RPV than on EFV (**Figures 2A** and **3A**)
  - Of the six patients receiving RPV with baseline viral load ≤100,000 c/mL and CD4 cell count <50 cells/mm³ none had VF at Weeks 48 or 96.
- A numerically higher rate of VF was reported for patients with a baseline viral load >100,000 c/mL receiving RPV compared with those receiving EFV (**Figures 2B** and **3B**).The difference between the treatment groups was more noticeable with lower baseline CD4 cell count.
- For patients with baseline viral load >100,000 c/mL, the rate of discontinuation due to an AE or death was higher with EFV compared with RPV. In general, the rate of discontinuation due to other reasons was similar across RPV and EFV treatment groups (**Figures 2B** and **3B**), yet in both baseline viral load categories was disproportionately higher in the CD4 <50 cells/mm³ for RPV vs EFV (overall 21% vs 6% at Weeks 48 and 96). For either baseline viral load treatment group, there was no discernible impact of baseline CD4 cell count on the rate of discontinuations due to AEs.

Figure 1. Response in patients with baseline viral load A) ≤100,000 c/mL and B) >100,000 c/mL by baseline CD4 cell count at Weeks 48 and 96.



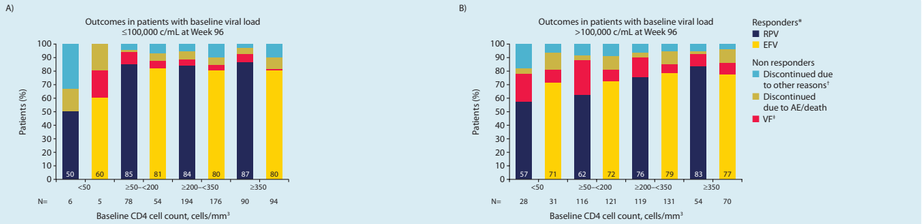
Response = viral load <50 c/mL, ITT-TLOVR; SE = standard error

Figure 2. Virologic outcomes at Week 48 in patients with baseline viral load A) ≤100,000 c/mL and B) >100,000 c/mL by baseline CD4 cell count.



*Patients with viral load <50 c/mL, ITT-TLOVR; †Lost to follow-up, non-compliance, withdrew consent, ineligible to continue, sponsor's decision;
‡Determined by TLOVR in the ITT population: confirmed response before Week 48 and confirmed rebound at or before Week 48, or no response before Week 48

Figure 3. Virologic outcomes at Week 96 in patients with baseline viral load A) ≤100,000 c/mL and B) >100,000 c/mL by baseline CD4 cell count.



*Patients with viral load <50 c/mL, ITT-TLOVR; †Lost to follow-up, non-compliance, withdrew consent, ineligible to continue, sponsor's decision;
‡Determined by TLOVR in the ITT population: confirmed response before Week 96 and confirmed rebound at or before Week 96, or no response before Week 96

Conclusions

- Responses with RPV were numerically higher than EFV responses in patients with both baseline viral load ≤100,000 c/mL and CD4 cell count ≥200 cells/mm³.
- Overall, non-inferiority (12% margin) between groups was met in patients with baseline viral load >100,000 c/mL (any CD4 cell count), i.e. differences in responses between treatment groups (95% CI) at Week 48 and 96 were –3.7% (–9.9%; 2.5%) and –5.2% (–12.0%; 1.5%), respectively. RPV responses were numerically lower than EFV responses in patients with baseline viral load >100,000 c/mL and CD4 cell count <200 cells/mm³, but in patients with a CD4 cell count >200 cells/mm³ and baseline viral load >100,000 c/mL, the response rates were similar.
- A higher baseline viral load or a lower CD4 cell count were partially predictive of response with RPV or EFV at Week 48 and 96 (lower for RPV than EFV).
- The effect of CD4 cell count on treatment response was largely, but not completely explained by the effect of baseline viral load (given the low rate of VF in patients with low viral load and low CD4 cell count).
- These results demonstrate that in patients with baseline viral load ≤100,000 c/mL and CD4 cell count >50 cells/mm³ or with baseline viral load >100,000 c/mL and CD4 cell count >200 cells/mm³, RPV gave good response rates
  - The reasons for discontinuation were different between the groups, with more VFs on RPV and more discontinuations due to AEs on EFV, especially for patients with baseline viral load >100,000 c/mL
  - Note that results in some baseline viral load/CD4 subgroups should be interpreted with caution because of small sample sizes, in particular the subgroup with a CD4 cell count <50 cells/mm³.

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