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Incidence of rash in the 96-week analysis of the pooled, Phase III, randomised, double-blind ECHO and THRIVE trials

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Introduction

- Rilpivirine (RPV; EDURANT®), a new NNRTI, in combination with other antiretrovirals (ARVs) and the single-tablet regimen of RPV with tenofovir disoproxil fumarate (TDF) and emtricitabine (FTC) are approved for use in HIV-1-infected, treatment-naïve adults in the USA, Canada and Europe (viral load ≤100,000 copies/mL).[1–4]
- Noninferior efficacy of RPV 25 mg qd compared to efavirenz (EFV) 600 mg qd was confirmed in the Phase III, randomised, double-blind, ECHO (TMC278-C209, NCT00540449) and THRIVE (TMC278-C215, NCT00543725) trials. A higher rate of virologic failure was seen with RPV than with EFV among patients with baseline viral load >100,000 copies/mL
  - RPV had significantly lower rates of discontinuations due to adverse events (AEs), grade 2–4 AEs at least possibly related to treatment, rash, dizziness and abnormal dreams/nightmares, and had significantly less lipid elevations than EFV.[5–7]
- Rash is a commonly-described side effect of HIV therapy
  - NNRTIs exhibit a class effect with regard to skin-related adverse effects, varying from a mild morbilliform rash to Stevens-Johnson syndrome (SJS).[8]
- The current, post-hoc, pooled 96-week analysis of the ECHO and THRIVE studies provides an in-depth assessment of incident rash that occurred in the studies.

Methods

- Patients (N=1,368) were randomised 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).
- Patients were advised to take RPV/RPV placebo with a meal, and EFV/EFV placebo on an empty stomach, at bedtime.
- The incidence of AEs was assessed at each visit via patient interview.
- Management of rash was at the discretion of the investigator and followed generally accepted medical standards (**Table 1**).

Table 1. Grading and management of rash in the ECHO and THRIVE trials.

Division of AIDS toxicity grade	Definitions	Action regarding ARV medication
1	Localised macular rash	Continue ARV or have ARV medication interrupted at the discretion of the investigator
2	Diffuse macular, maculopapular or morbilliform rash or target lesions	Continue ARV or have ARV medication interrupted at the discretion of the investigator
3*	Diffuse macular, maculopapular, or morbilliform rash with vesicles or limited number of bullae	Permanently discontinue ARV medication
	Superficial mucous membrane ulceration limited to one site	Refer to dermatologist
	Cutaneous reaction/rash with at least one of raised liver enzymes/serum sickness-like reaction/eosinophilia/fever	
4*	Extensive or generalised bullous lesions	Permanently discontinue ARV medication
	SJS	Refer to dermatologist
	Mucosal membrane ulceration (two or more sites)	
	Toxic epidermal necrolysis	

*Local safety assessment and daily follow-up for the next 5 days

Results

Baseline characteristics

- Demographics and baseline disease characteristics were well balanced between treatment groups (**Table 2**).

Table 2. Demographics and baseline characteristics.

Baseline parameter	RPV N=686	EFV N=682
Female, %	24	24
Male, %	76	76
Median age, years (range)	36 (18–78)	36 (19–69)
Race, %		
Caucasian	61	60
Black	24	23
Asian	11	14
Other races/not stated	3	3
Median log_{10} viral load, copies/mL (range)	5 (2–7)	5 (3–7)
Baseline viral load copies/mL, % >100,000 copies/mL*	46	52
Median CD4⁺ cell count, cells/mm³ (range)	249 (1–888)	260 (1–1,137)
Hepatitis B or C co-infection, %	7	9

*Median baseline viral load, copies/mL (interquartile range [IQR]) in patients with baseline viral load >100,000 copies/mL was RPV 235,000 (152,000–443,000 copies/mL) vs EFV 236,000 (150,000–460,000 copies/mL), and in patients with baseline viral load ≤100,000 copies/mL it was RPV 37,000 (18,000–59,000 copies/mL) vs EFV 34,000 (16,000–62,000 copies/mL)

Rash analysis

- The median (range) treatment duration was 104 (0–135) weeks in the RPV group and 104 (0–136) weeks in the EFV group.

Table 3. Overall incidence of rash (any type).

	RPV N=686	EFV N=682
Rash regardless of causality, n (%)		
Any grade	79 (12)	179 (26)
Grade 1	59 (9)	119 (17)
Grade 2	21 (3)	75 (11)
Grade 3	2 (0.3)	6 (1)
At least one serious AE	0	2 (0.3)
Leading to discontinuation	1 (0.1)	12 (2)
Rash at least possibly related to treatment, n (%)		
Any grade	29 (4)	103 (15)
Grade 1	22 (3)	52 (8)
Grade 2	9 (1)	55 (8)
Grade 3	1 (0.1)	5 (1)
At least one serious AE	0	1 (0.1)
Leading to discontinuation	1 (0.1)	11 (2)

- The incidence of rash (any type, any grade, regardless of causality) was 12% (n=79/686) in the RPV group vs 26% (n=179/682) in the EFV group (p<0.0001, Fisher's exact test, preplanned analysis) (**Table 3**).
- Most rashes were mild-to-moderate (grade 1–2; none were grade 4), discontinuations were infrequent and only two rashes were considered to be serious (**Table 3**).
- Of the two patients in the EFV group who had rash reported as serious AEs, one patient had grade 3 generalised rash (onset Day 10), which was reported to be very likely related to study medication by the investigator, required supportive care (but was not hospitalised) and led to permanent discontinuation as required per protocol. The other patient had grade 2 rash (onset Day 15), reported to be doubtfully related to study medication by the investigator, which led to temporary discontinuation of study medication.
- Treatment-related rash events (described as 'at least possibly related to treatment') were reported at both a lower incidence (p<0.0001, preplanned analysis) and a lower grade in the RPV group than in the EFV group.
- The most common designated rash diagnoses are provided in **Table 4**.
- No cases of SJS or toxic epidermal necrolysis were reported in either group.

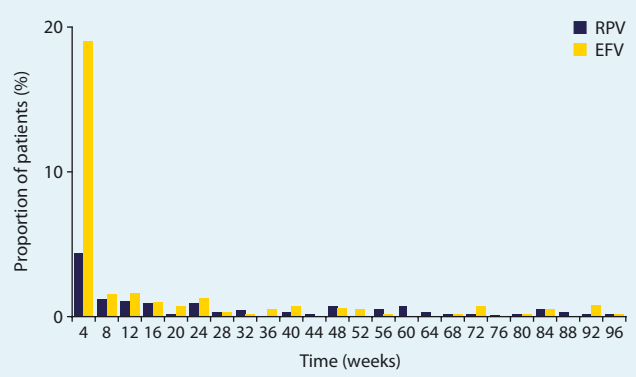
Table 4. Most common designated rash diagnoses (by investigator; occurring in >5 patients).

Incidence, n (%)	RPV N=686	EFV N=682
Rash (not further specified)	41 (6)	93 (14)
Pruritus	23 (3)	34 (5)
Prurigo	6 (1)	0
Papular rash	4 (1)	12 (2)
Maculopapular rash	3 (0.4)	15 (2)
Pruritic rash	4 (1)	9 (1)
Erythema	7 (1)	9 (1)
Allergic dermatitis	2 (0.3)	6 (1)
Macular rash	2 (0.3)	8 (1)
Urticaria	2 (0.3)	6 (1)
Generalised rash	0	7 (1)

Rash (any type, any cause) incidence over time

- The incidence of rash was highest in the first 4 weeks, with a much lower incidence in the RPV than the EFV group. Few new rash AEs occurred in either group thereafter and with comparable incidence in the RPV and EFV groups (**Figure 1**).

Figure 1. Incidence of treatment-emergent rash events over time.



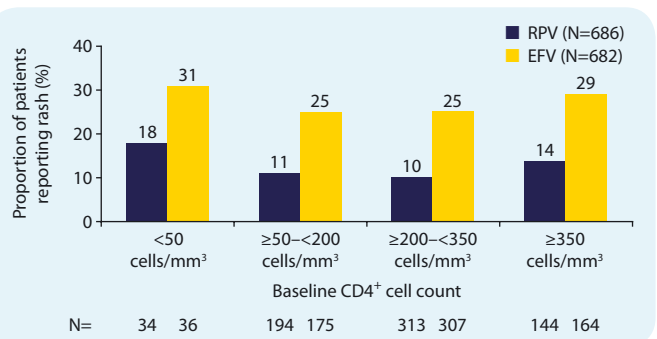
Incidence = new AEs only (i.e., those with onset in the corresponding time period). AEs considered 'new' are those with no time-period overlaps (on the preferred term level)
Percentages are calculated versus the number of patients in the treatment phase at that timepoint

- The median (range) time to rash onset was 10.5 (1–502) and 11 (1–280) days with RPV (n=34) and EFV (n=119), respectively. The median duration of rash was 18 (2–605) days with RPV (n=37) and 10 (1–746) days with EFV (n=123).
- There were only eight additional patients in the RPV group and 10 additional patients in the EFV group that reported rash events in the Week 96 pooled analysis compared with the Week 48 pooled analysis.
- There were no additional serious rash AEs or rash AEs leading to permanent discontinuation in the Week 96 pooled analysis compared to the Week 48 pooled analysis. The last case of rash leading to discontinuation was one case observed in the RPV group with an onset on Day 86.

Subgroup analyses of rash (any type) incidence

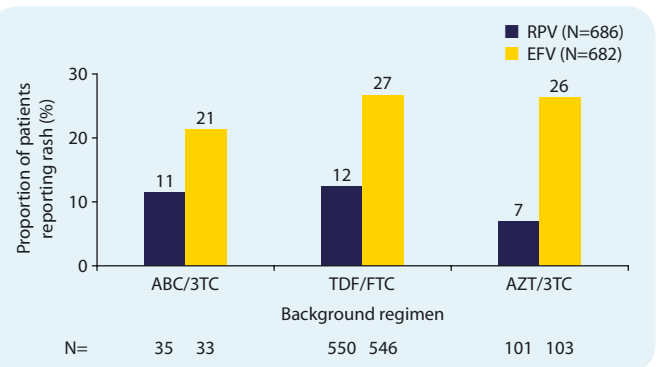
- Baseline CD4⁺ cell count was not predictive of rash in either treatment group (**Figure 2**).

Figure 2. Treatment-emergent rash (any type, any cause) by baseline CD4⁺ cell count.



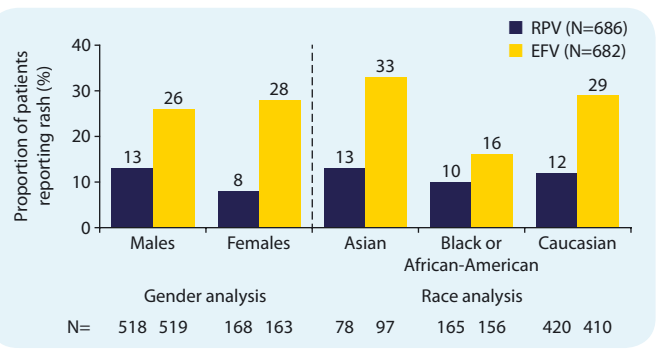
- There was a lower incidence of rash with RPV than with EFV in each N(t)RTI subgroup (**Figure 3**). In the RPV group, rash (any type) was also reported less frequently in the AZT/3TC subgroup (7%) than in the TDF/FTC subgroup (12%).

Figure 3. Incidence of treatment-emergent rash (any type, any cause) by treatment and background regimen at baseline.



- Overall, there was a comparable incidence of rash events in female and male patients. A slightly higher incidence of rash occurred in males than females in the RPV group (13% vs 8% respectively); the incidence was similar between the genders in the EFV group (26% vs 28% respectively) (**Figure 4**).
- The incidence of rash did not vary by race in the RPV group (**Figure 4**).
- Comparison of rash incidence by age group was not relevant due to the low number of patients aged ≥55 years.

Figure 4. Treatment-emergent rash (any type, any cause) by gender and race at screening.



Conclusions

- In the Week 96 analysis of the pooled ECHO and THRIVE trials, there was a significantly lower incidence of rash (any type) and a lower rate of discontinuations due to rash with RPV compared with EFV.
- Most rashes in both treatment groups were grades 1–2, and no cases of SJS or toxic epidermal necrolysis were reported in either group.
- Rash generally occurred within the first 4 weeks of treatment, with very few rashes appearing during the second year of treatment.
- Each subgroup analysis (baseline CD4⁺ cell count, N(t)RTI background, gender and race) revealed a numerically lower incidence of rash for RPV than EFV. Females and patients receiving an AZT/3TC background had the lowest incidence of rash in the RPV group while black/African American patients had the lowest incidence among races within the EFV group.

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