

# Genotypic and phenotypic characterization of HIV-1 isolates obtained from patients failing rilpivirine (RPV, TMC278) in the Phase III studies ECHO and THRIVE: 48 week analysis

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## Introduction

- ECHO (TMC278-C209, NCT00540449) and THRIVE (TMC278-C215, NCT00543725) were 96-week, Phase III, randomized (1:1), double-blind, double-dummy trials in treatment-naïve, HIV-1-infected adults
  - The trials compared RPV 25 mg qd (N = 686), an investigational NNRTI, and efavirenz (EFV) 600 mg qd (N = 682) both in combination with two N(t)RTIs (ECHO: TDF/FTC; THRIVE: Investigator's choice of TDF/FTC [60%]; AZT/3TC [30%]; ABC/3TC [10%]).<sup>1</sup>
- In the pooled Week 48 primary analysis, RPV 25 mg qd had non-inferior efficacy to EFV 600 mg qd (primary objective)
  - 84% of patients in the RPV group and 82% of patients in the EFV group achieved viral load (VL) < 50 c/mL (difference in response: 2.0% [95% confidence interval (CI): -2.0%, 6.0%]; intent-to-treat, time-to-loss-of virologic-response [ITT-TLOVR] algorithm)
  - Responses in the baseline (BL) VL ≤ 100K c/mL subgroup were 90% (RPV; N' = 368) and 84% (EFV; N' = 330) (difference: 6.6% [1.6%; 11.5%]) and in the BL VL > 100K c/mL subgroup were 77% (RPV; N' = 318) vs 81% (N' = 352; EFV) (difference: -3.6% [-9.8%; 2.5%])
  - RPV had significantly lower rates of grade 2-4 adverse events at least possibly related to treatment (16% vs 31%), rash, dizziness, abnormal dreams/nightmares, and significantly lower lipid elevations than EFV.<sup>1</sup>
- RPV is being developed as a single-agent tablet and a fixed-dose single-tablet regimen with TDF/FTC.<sup>2</sup>
- Here we present a genotypic and phenotypic characterization of HIV-1 isolated from patients with virologic failure (VF) in ECHO and THRIVE.

## Results

Table 1. Incidence of VF\* by BL VL category.

Time of failure	Pooled RPV patients (N = 686)			Pooled EFV patients (N = 682)		
	BL VL ≤ 100K c/mL N = 368	BL VL > 100K c/mL N = 318	All N = 686	BL VL ≤ 100K c/mL N = 330	BL VL > 100K c/mL N = 352	All N = 682
All	19/368 (5)	53/318 (17)	72/686 (10)	16/330 (5)	23/352 (7)	39/682 (6)
Rebounders <sup>1</sup>	9/19 (47)	20/53 (38)	29/72 (40)	12/16 (75)	8/23 (35)	20/39 (51)
Never suppressed <sup>2</sup>	10/19 (53)	33/53 (62)	43/72 (60)	4/16 (25)	15/23 (65)	19/39 (49)
B subtype <sup>1</sup>	13/19 (68)	42/53 (79)	55/72 (76)	13/16 (81)	15/23 (65)	28/39 (72)
Subtype non-B	6/19 (32)	11/53 (21)	17/72 (24)	3/16 (19)	8/23 (35)	11/39 (28)
TDF/FTC regimen <sup>3</sup>	17/19 (90)	45/53 (85)	62/72 (86)	9/16 (56)	18/23 (78)	27/39 (69)
ABC/3TC regimen <sup>3</sup>	1/19 (5)	0	1/72 (1)	2/16 (13)	2/23 (9)	4/39 (10)
AZT/3TC regimen <sup>3</sup>	1/19 (5)	8/53 (15)	9/72 (13)	5/16 (31)	3/23 (13)	8/39 (21)
With genotypic data	N = 16	N = 46	N = 62	N = 12	N = 16	N = 28

\*Determined in the ITT population including data beyond 48 weeks (First achieved 2 consecutive VL values < 50 c/mL followed by VL value(s) ≥ 50 c/mL; <sup>1</sup>Never achieving < 50 c/mL and with a VL increase ≥ 0.5 log<sub>10</sub> c/mL above nadir; <sup>2</sup>Proportion of B subtype at baseline was 70% in the RPV group and 68% in the EFV group; <sup>3</sup>Distribution of background regimen was approximately: TDF/FTC (80%); AZT/3TC (15%); ABC/3TC (5%) in the Pooled ECHO and THRIVE trials

Table 2. Incidence of treatment-emergent\* NNRTI and N(t)RTI RAMs by BL VL.

Incidence, n (%)	RPV N = 686		EFV N = 682	
	All	BL VL ≤ 100K c/mL N = 368	All	BL VL > 100K c/mL N = 318
All VF with genotypic data <sup>1</sup>	N = 62	N = 28	N = 28	N = 28
NNRTI RAM	39 (63)	15 (54)	15 (54)	15 (54)
N(t)RTI RAM	42 (68)	9 (32)	8 (29)	8 (29)
NNRTI and N(t)RTI RAM	37 (60)	8 (29)	8 (29)	8 (29)
BL VL ≤ 100K c/mL	N = 16	N = 12	N = 12	N = 12
NNRTI RAM	6 (38)	5 (42)	5 (42)	5 (42)
N(t)RTI RAM	7 (44)	2 (17)	2 (17)	2 (17)
NNRTI and N(t)RTI RAM	5 (32)	1 (8)	1 (8)	1 (8)
BL VL > 100K c/mL	N = 46	N = 16	N = 16	N = 16
NNRTI RAM	33 (72)	10 (63)	10 (63)	10 (63)
N(t)RTI RAM	35 (76)	7 (44)	7 (44)	7 (44)
NNRTI and N(t)RTI RAM	32 (70)	7 (44)	7 (44)	7 (44)

\*Not present at screening or baseline and present at time of failure while on treatment; <sup>1</sup>At time of failure; Ns are small and caution should be taken when interpreting rates

Figure 1. Proportion of treatment-emergent\* NNRTI and N(t)RTI RAMs by BL VL.

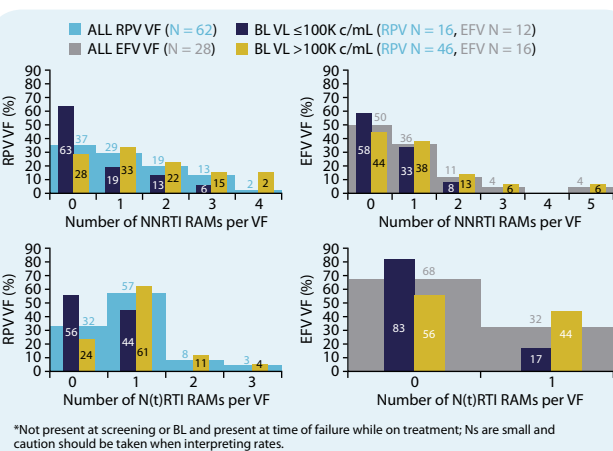
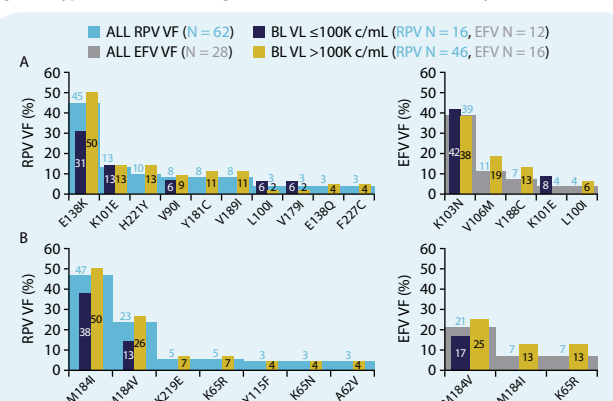


Figure 2. Type of treatment-emergent\* A) NNRTI and B) N(t)RTI RAMs by BL VL.



\*Not present at screening or BL and present at time of failure while on treatment in at least two patients; Ns are small and caution should be taken when interpreting rates.

Table 3. Complete genotypic resistance profile of RPV VFs by BL VL.

Genotypes RPV VF (BL VL ≤ 100K c/mL)	RPV	EFV	ETR	NVP	AZT	3TC	ABC	FTC	TDF
K219E	8.6	1.2	1.8	1.8	0.2	37.2	0.9	19.3	0.3
Y90I/V	8.1	7.8	22.5	3.6	0.5	32.2	1.3	57.1	0.4
E138K	2.6	5.2	7.1	4.3	0.5	62.5	1.3	32.9	0.3
V179I	2.0	1.8	1.5	3.0	0.7	0.3	0.6	0.5	0.2
M184I	1.8	1.9	1.4	2.6	0.6	10.9	1.8	17.4	0.4
E138K	1.6	1.2	2.5	0.8	0.6	34.9	1.7	24.9	0.6
L100I/L	1.5	3.2	2.9	5.0	0.4	21.9	1.0	32.4	0.4
K101E/K	1.0	2.5	3.1	1.9	0.4	29.2	1.9	19.8	0.5
Genotypes RPV VF (BL VL > 100K c/mL)									
V90I	621.3	4.4	311.9	75.0	1.6	54.9	3.8	36.4	1.2
K101P/T	138.1	313.6	9.1	63.4	0.4	44.3	0.5	33.3	0.2
L100I	64.4	35.7	63.9	32.8	1.7	53.3	2.3	23.0	1.1
E138K	31.6	7.3	17.1	6.5	0.9	78.1	3.1	40.4	0.4
V108I	28.3	14.4	32.4	79.0	0.5	104.2	1.7	28.7	0.7
V106A	21.2	6.0	1.5	57.1	0.2	19.3	0.9	5.3	0.4
E138K	21.2	10.2	15.0	13.9	0.7	59.0	1.9	24.8	0.6
F227C	17.5	41.7	13.7	56.7	0.2	63.8	1.1	40.8	0.3
K101E	17.0	19.3	12.7	58.7	0.6	103.7	2.7	50.0	0.7
V90I/V	13.1	5.3	7.0	5.7	0.7	54.9	1.9	36.4	0.8
K101E	10.0	4.3	14.0	51.3	0.3	12.6	6.6	24.9	1.5
E138K	9.6	4.4	12.1	5.4	2.2	70.8	4.2	60.9	0.9
E138E/K	9.0	13.0	14.0	25.4	0.7	45.9	1.7	25.6	0.5
E138K	8.8	3.8	4.9	1.6	0.3	62.4	1.4	27.9	0.5
E138K	8.7	5.7	14.6	6.7	0.7	32.3	3.0	27.6	0.5
E138K	8.3	3.7	9.1	2.1	0.7	144.6	3.3	55.5	0.6
V90I	7.9	4.5	8.1	10.0	1.1	37.8	2.5	24.2	0.5
E138K	7.8	6.7	11.8	2.8	0.6	19.5	1.2	13.3	0.6
E138K	7.5	3.3	10.8	4.4	1.1	72.7	3.2	28.7	0.5
V90I	6.9	2.2	8.0	1.3	1.0	106.2	1.6	37.0	0.7
E138K	6.5	2.1	6.7	1.4	1.5	57.7	4.2	22.9	0.6
V90I	6.3	3.8	6.2	1.2	0.4	36.5	2.1	26.5	0.7
K101E/K	5.9	7.1	11.1	4.3	0.4	1.5	1.5	16.9	0.2
K101E/K	5.4	7.2	9.4	4.1	0.6	144.6	0.8	47.4	1.0
V106I	5.1	4.9	15.4	65.3	0.7	29.7	2.6	50.9	0.3
E138K	5.1	4.0	4.6	1.1	1.1	28.4	1.4	19.6	0.5
E138K	4.9	4.9	6.4	1.9	1.0	52.7	2.5	24.2	0.6
K101E	4.6	5.0	3.0	2.1	0.4	26.6	0.4	23.1	0.2
K101E	4.6	3.8	4.1	4.1	0.7	22.2	1.5	22.1	0.6
E138K	3.6	1.8	4.0	1.2	0.3	22.8	5.7	16.4	1.8
E138K	1.8	0.8	0.9	0.9	0.8	53.3	1.2	23.0	0.5
M184I	1.7	1.4	2.4	0.9	0.5	39.4	1.0	23.8	0.7
V90I	1.4	1.6	2.5	0.7	0.6	37.5	1.0	15.6	0.2
V179A/V	1.3	0.8	0.8	1.3	1.1	0.3	0.5	1.4	0.5
M184V	1.3	1.1	1.3	1.2	0.5	103.7	2.3	50.0	0.9
V179I	0.8	0.6	0.8	0.3	0.6	0.6	0.5	0.8	0.5
V179I	0.7	1.3	0.9	1.4	1.9	0.7	0.8	1.0	0.8
M184I	0.5	1.3	1.1	0.3	0.6	7.3	1.3	19.8	0.4
V106I	0.4	0.5	0.8	0.7	1.1	0.6	0.4	1.0	0.7

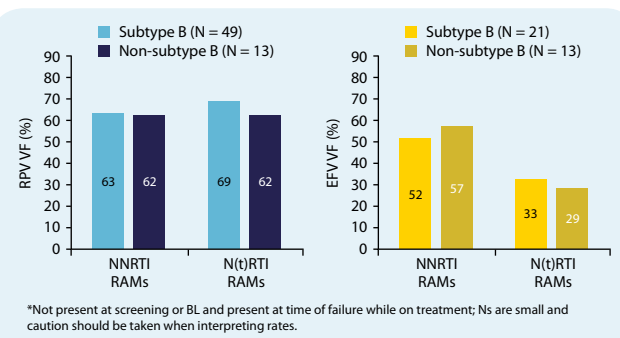
FC = fold change in 50% effective concentration; BCO = biological cut off (3.7 for RPV as determined by Antivirogram®).

Table 4. Most frequent treatment-emergent combinations of NNRTI and N(t)RTI RAMs in RPV VFs (N=37\*).

RPV VF <sup>1</sup>	n (%)	RPV FC Median (IQ1-IQ3)	FC > BCO	BL VL ≤ 100K c/mL n
<b>E138K + M184I (all)</b>	<b>17 (46)</b>	<b>8.1 (6.3-9.0)</b>	<b>15</b>	<b>2</b>
Exclusively	6 (16)	6.5 (4.9-8.7)	5	1
Plus other RT RAMs	11 (30)	8.3 (6.9-13.1)	10	1
<b>E138K + M184V (all)</b>	<b>8 (22)</b>	<b>7.9 (4.6-15.4)</b>	<b>6</b>	<b>1</b>
Exclusively	3 (8)	2.6 (1.8-6.5)	1	1
Plus other RT RAMs	5 (14)	9.6 (8.3-21.2)	5	0
<b>E138K + K101E + M184I (all)</b>	<b>4 (11)</b>	<b>3.5 (1.3-5.7)</b>	<b>2</b>	<b>2</b>
Exclusively	1 (3)	5.4	1	0
Plus other RT RAMs	3 (8)	1.5 (1.0-5.9)	1	2
<b>E138K + K101E + M184V + other RT RAMs</b>	<b>2 (5)</b>	<b>3.5 (1.0-5.9)</b>	<b>1</b>	<b>1</b>
<b>K101E + M184I exclusively</b>	<b>2 (5)</b>	<b>4.6 (4.6-4.6)</b>	<b>2</b>	<b>0</b>
<b>K101E + M184V + other RT RAMs</b>	<b>1 (3)</b>	<b>17</b>	<b>1</b>	<b>0</b>

\*All RPV VFs with at least one emerging NNRTI and N(t)RTI RAM; <sup>1</sup>The RPV FC in HIV-1 site-directed mutants were E138K + M184I (6.7), K101E + M184I (5.8), E138K + M184V (3.1), K101E + M184V (2.2), E138K (2.8), K101E (2.4), M184I (1.5) and M184V (0.8). Ns are small and caution should be taken when interpreting rates; FC = fold change in 50% effective concentration; IQ = interquartile range; BCO = biological cut off (3.7 for RPV as determined by Antivirogram®).

Figure 3. Proportion of treatment-emergent\* NNRTI and N(t)RTI RAMs by HIV-1 Subtype.



\*Not present at screening or BL and present at time of failure while on treatment; Ns are small and caution should be taken when interpreting rates.

- B and non-subtype B VFs did not exhibit specific patterns of NNRTI or N(t)RTI RAMs.

Table 5. Proportion of VF with NNRTI cross-resistance\* by BL VL.

Time of VF, %	RPV				EFV			
	BL VL ≤ 100K c/mL Resistant to RPV <sup>1</sup> N = 2	BL VL > 100K c/mL Sensitive to RPV <sup>1</sup> N = 14	BL VL ≤ 100K c/mL Resistant to RPV <sup>1</sup> N = 29	BL VL > 100K c/mL Sensitive to RPV <sup>1</sup> N = 17	BL VL ≤ 100K c/mL Resistant to EFV <sup>2</sup> N = 6	BL VL > 100K c/mL Sensitive to EFV <sup>2</sup> N = 6	BL VL ≤ 100K c/mL Resistant to EFV <sup>2</sup> N = 10	BL VL > 100K c/mL Sensitive to EFV <sup>2</sup> N = 10
Resistant to NVP	0	0	48	0	100	0	100	20
Resistant to EFV	50	7	90	6	100	0	100	0
Resistant to ETR	50	7	93	12	0	0	0	0

\*Determined by Antivirogram®; <sup>1</sup>RPV biological cut-off (BCO) = 3.7 (Antivirogram®); Ns are small and caution should be taken when interpreting rates.

## NNRTI RAMs associated with decreased susceptibility to RPV

- Considering all of the available cell culture and clinical data, any of the following amino acid substitutions, when present at baseline, are likely to decrease the antiviral activity of RPV: E138A/G/K/Q/R, K101E/P, H221Y, Y181C/I/V.<sup>4</sup> To this list, the FDA added V179L, F227C, and M230I/L in the US Prescribing Information.

Table 6. VFs with NNRTI RAMs: Median FC for the antiretrovirals in the treatment groups.

Median FC* (Q1-Q3)	RPV VFs with NNRTI RAMs		EFV VFs with NNRTI RAMs	
	BL VL ≤ 100K c/mL N = X	BL VL > 100K c/mL N = X	BL VL ≤ 100K c/mL N = X	BL VL > 100K c/mL N = X
<b>NNRTIs</b>				
RPV <sup>1</sup>	1.6 (0.9-2.3)	5.6 (1.4-9.6)	1.2 (0.7-1.6)	1.5 (0.9-1.8)
ETR	1.5 (1.1-2.7)	6.3 (1.3-12.1)	1.1 (0.6-2.5)	1.1 (0.9-1.6)
EFV	1.2 (0.9-2.2)	3.9 (1.3-6.0)	2.6 (1.1-20.3)	2.2 (1.5-34.2)
NVP	1.5 (0.7			