Original article

96-Week resistance analyses of rilpivirine in treatment-naive, HIV-1-infected adults from the ECHO and THRIVE Phase III trials

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Background: In the ECHO/THRIVE 96-week efficacy analysis, the response rate was 78% with rilpivirine (RPV) and efavirenz (EFV) plus two nucleoside/nucleotide reverse transcriptase inhibitors.
Methods: For resistance analyses, virological failures (VFs) were genotyped and/or phenotyped at baseline and failure.
Results: In the overall 96-week resistance analyses, the proportion of VFs was higher with RPV (96/686, 14%) versus EFV (52/682, 8%), but similar within weeks 48–96 (22/686, 3% versus 16/682, 2%). In genotyped VFs, treatment-emergent non-nucleoside reverse transcriptase inhibitor (NNRTI) resistance-associated mutations (RAMs) were as common with RPV (46/86, 53%) versus EFV (20/42, 48%), but nucleoside/nucleotide reverse transcriptase inhibitor RAMs were more common with RPV (48/86, 56%) than EFV (11/42, 26%). In RPV VFs, E138K+M184I remained the most frequent combination. Among RPV VFs with phenotypic RPV resistance, cross-resistance was observed with nevirapine (16/35, 46%), EFV (30/35, 86%) and etravirine (32/35, 91%). Among patients with baseline viral load (VL)≤100,000 copies/ml, there were fewer VFs (RPV: 28/368, 8%; EFV: 20/329, 6%), fewer VFs with treatment-emergent NNRTI RAMs (RPV: 10/27, 37%; EFV: 6/17, 35%), and less phenotypic resistance to RPV and other NNRTIs, than in patients with baseline VL>100,000 copies/ml (VFs: 68/318, 21% [RPV], 32/353, 9% [EFV]; NNRTI RAMs: 36/59, 61% [RPV], 14/32, 56% [EFV]). Among RPV VFs with baseline VL≤100,000 copies/ml observed within weeks 48–96, only 1/7 had phenotypic resistance to RPV.
Conclusions: During the second year of treatment in ECHO/THRIVE, few VFs with emerging NNRTI RAMs (no new RPV RAMs) occurred.

Introduction

The non-nucleoside reverse transcriptase inhibitor (NNRTI) rilpivirine (RPV; TMC278, EDURANT®), combined with other antiretroviral drugs (ARVs) and as a single-tablet regimen with emtricitabine (FTC) and tenofovir disoproxil fumarate (TDF; COMPLERA® [US]/EVIPLERA® [EU], Gilead Sciences, Foster City, CA, USA), is approved in treatment-naive, HIV-1-infected adults in several countries worldwide, including the USA, Canada and Europe [1–4]. The pooled 48-week efficacy and safety outcomes of ECHO and THRIVE [5] were the basis of the regulatory approval of RPV. Both of these Phase III clinical trials assessed the efficacy and safety of 25 mg RPV once daily versus 600 mg efavirenz (EFV) once daily, each with a nucleoside/nucleotide reverse transcriptase inhibitor (NRTI) background regimen. Non-inferior efficacy of RPV versus EFV was demonstrated in each trial at 48 weeks [6,7]. In the pooled 96-week efficacy analyses of ECHO/THRIVE, 78% of RPV-treated and 78% of EFV-treated patients (difference [95% CI]: 0.0% [-4.4%, 4.4%]) had a viral load (VL)<50 copies/ml (intent-to-treat, time to loss of virological response) [8]. Among patients with baseline VL≤100,000 copies/ml, virological responses occurred in 84% of RPV- and 80% of EFV-treated patients (difference [95% CI] 4.0% [-1.7%, 9.7%]). Virological responses in the baseline VL>100,000 copies/ml subgroup were seen in 70% of RPV- versus 75% EFV-treated patients (difference [95% CI] -5.2% [-12.0%, 1.5%]). RPV was associated with significantly lower incidences of

adverse events leading to discontinuation, grade 2–4 adverse events at least possibly related to treatment (rash, dizziness and abnormal dreams/nightmares), and fewer grade 2–4 lipid abnormalities than EFV [8].

Many factors guide the selection and use of ARVs in HIV-1 infection [9,10]. In addition to efficacy and tolerability, important factors are the presence of resistance-associated mutations (RAMs) or the potential for emergence of RAMs likely to limit future treatment options [11–13]. Therefore, the characterization of the resistance profile of new ARVs is critical.

Data on the 48-week resistance analyses of ECHO/THRIVE have been published [14]. Briefly, among the RPV and EFV virological failures (VFs; that is, patients included in the resistance analysis), the proportions of RPV and EFV VFs with treatment-emergent NNRTI RAMs were comparable. However, the proportions of VFs with treatment-emergent NRTI RAMs were higher with RPV than with EFV. The most common treatment-emergent NNRTI RAMs and NRTI RAMs in RPV VFs were E138K and M184I, respectively. Analyses by baseline VL showed that the occurrence of RPV VFs with treatment-emergent NNRTI RAMs and NRTI RAMs was less frequent among patients with baseline VL≤100,000 versus >100,000 copies/ml. In patients with baseline VL≤100,000 copies/ml, the proportion of VFs with treatment-emergent NNRTI RAMs was similar between the RPV and EFV treatment groups, and the proportion of VFs with treatment-emergent NRTI RAMs was higher with RPV than with EFV. Phenotypic resistance to RPV was seen in half of the RPV VFs, and was more prevalent in patients with baseline VL>100,000 copies/ml versus baseline VL≤100,000 copies/ml. Among the RPV VFs with resistance to RPV, cross-resistance to nevirapine (NVP), etravirine (ETR) and EFV was common.

The aims of the present analyses are to report the virology and resistance findings of the VFs observed in the overall 96-week ECHO/THRIVE database, and to further evaluate these findings by time period (weeks 0–48 versus 48–96), and by baseline VL (≤100,000 and >100,000 copies/ml).

Methods

Trial design and treatment

Details of the ECHO and THRIVE trials (ClinicalTrials.gov numbers NCT00540449 and NCT00543725) have been published [6,7]. These were multicentre, international, Phase III, randomized, double-blind, double-dummy trials in treatment-naive, HIV-1-infected adults. Patients had baseline VL≥5,000 copies/ml, and showed sensitivity (virco™TYPE HIV-1; Janssen Diagnostics BVBA, Beerse, Belgium) to the background NRTIs. An important exclusion criterion was the presence of ≥1 NNRTI RAM from a list of 39 [6,7,15]. Patients received either RPV 25 mg once daily or EFV 600 mg once daily, and a background NRTI regimen; TDF/FTC in ECHO [6], and investigator-selected NRTIs (TDF/FTC, zidovudine/lamivudine [3TC], or abacavir/3TC) in THRIVE [7].

Virology assessments

Plasma samples were collected at screening, baseline, at regular intervals throughout the trials and at the final/withdrawal visit. VL was evaluated using the COBAS Amplicor HIV-1 Monitor Test (version 1.5; Roche Diagnostics, Basel, Switzerland).

Samples for viral genotypic and phenotypic analyses were taken at screening/baseline and at selected visits at/after the failure time point. Genotypic analyses were conducted by population sequencing (virco™TYPE HIV-1, Janssen Diagnostics BVBA) of the amino acids 1–400 of the HIV-1 reverse transcriptase. Phenotypic resistance (Antivirogram®; Janssen Diagnostics BVBA) to an NNRTI was determined as a fold-change (FC) above the biological cutoff (BCO; >3.3 for EFV; >6.0 for NVP; >3.7 for RPV [16]) or the lower clinical cutoff (>3.2 for ETR).

Data analyses and definition of VF

The resistance analyses of the 96-week database were performed on the pooled intent-to-treat ECHO/THRIVE populations. To capture all emergence of resistance, VF was defined broadly as either: first achieving two consecutive VL values <50 copies/ml then having two consecutive (or only one if treatment was stopped) VL values ≥50 copies/ml (rebounder); or never achieving two consecutive VL values <50 copies/ml and having an increase in VL≥0.5 $\log_{10}$ copies/ml above the nadir (never suppressed). In the resistance analyses, the time of failure visit was defined as the first visit at/after VF with genotypic data. Post hoc statistical comparisons were conducted as appropriate using Fisher's Exact test at a 5% significance level and without correction for multiplicity.

Some analyses included the entire dataset, and others were limited to the first year (weeks 0–48, that is, including all patients with VF up to and including the 48-week visit), or the second year (weeks 48–96, that is, including all patients with VF post the 48-week visit and up to and including the 96-week visit) of the trials. The allocation of the VFs to the week 0–48 and 48–96 periods was done using the 48-week and 96-week visits as cutoff dates, and consequently, one of the RPV-treated patients who experienced VF after the 96-week visit was not included in the analyses by trial periods (weeks 0–48 and 48–96). Subanalyses of these two trial periods by baseline VL

categories (≤100,000 and >100,000 copies/ml) were also included. Because randomization was stratified by baseline VL (≤100,000, >100,000 to ≤500,000, and >500,000 copies/ml) data were also evaluated for patients in the baseline VL category >500,000 copies/ml for a limited number of end points. Patients in the latter category are also included within the >100,000 copies/ml group in our subanalyses.

Resistance analyses and identification of RAMs

In the 96-week database, genotypic data were available for 86/96 RPV VFs and 42/52 EFV VFs, and phenotypic data were available for 81/96 RPV VFs and 41/52 EFV VFs (missing genotype and phenotype were usually due to VL≤500 copies/ml).

The lists of 20 NRTI RAMs [17], 48 NNRTI RAMs [15,18] and 16 RPV RAMs (K101E/P, E138A/G/K/Q/R, V179L, Y181C/I/V, Y188L, H221Y, F227C and M230I/L) [14,17,19,20] were used in this report.

Results

VFs

In the 96-week resistance analyses, significantly more patients had VF (see definition in *Methods*) with RPV (96/686, 14%) than with EFV (52/682, 8%; $P<0.0001$). In patients with baseline VL≤100,000 copies/ml, the proportion of VFs was comparable between RPV (28/368, 8%) and EFV (20/329, 6%; $P=0.46$), but was higher among patients with VL>100,000 copies/ml with RPV (68/318, 21%) than with EFV (32/353, 9%; $P<0.0001$; Table 1). The proportion of VFs was also higher with RPV (17/69, 25%) than with EFV (11/83, 13%) in patients with baseline VL>500,000 copies/ml.

The analysis by trial period showed that the majority of VFs occurred within weeks 0–48 (RPV: 73/686, 11%; EFV: 36/682, 5%). Within weeks 48–96, the numbers of VFs in the subgroup of patients with baseline VL≤100,000 copies/ml were low (RPV: 7/368, 2% and EFV: 6/329, 2%; Table 1).

The VFs that were classified as never suppressed occurred essentially within weeks 0–48 (RPV: 43/686, 6%; EFV: 17/682, 3%), while only one (<1%) in each treatment group was observed within weeks 48–96. The proportions of RPV and EFV VFs that were rebounders within weeks 0–48 (RPV: 30/686, 4%; EFV: 19/682, 3%) and within weeks 48–96 (RPV: 21/686, 3%: EFV: 15/682, 2%) were similar (RPV, $P=0.25$; EFV, $P=0.60$; Table 1). Within the latter period, the median VLs (IQR Q1–Q3) at the time of failure were 2,400 (1,690–5,260) versus 1,060 (484–6,250) copies/ml for the RPV VFs with baseline VL≤100,000 or >100,000 copies/ml, respectively.

Treatment-emergent NNRTI and NRTI RAMs

In the 96-week resistance analyses, among the 86 RPV VFs with genotypes the proportions of RPV VFs with ≥1 treatment-emergent NNRTI, NRTI and a combination of an NNRTI RAM with an NRTI RAM were 46/86 (53%), 48/86 (56%) and 43/86 (50%), respectively. Compared with RPV VFs, a similar proportion of the 42 EFV VFs with genotypes had treatment-emergent NNRTI RAMs (20/42, 48%; $P=0.58$), but a smaller proportion had treatment-emergent NRTI RAMs (11/42, 26%; $P=0.0023$), and consequently

Table 1. Proportion of VFs by type, trial period and baseline VL, at time of failure

	RPV patients			EFV patients		
	Baseline VL≤100,000 copies/ml	Baseline VL>100,000 copies/ml	All	Baseline VL≤100,000 copies/ml	Baseline VL>100,000 copies/ml	All
Overall 96-week analysis						
All	28/368 (8)	68/318 (21)	96/686 (14)	20/329 (6)	32/353 (9)	52/682 (8)
Never suppressed	10/368 (3)	34/318 (11)	44/686 (6)	4/329 (1)	14/353 (4)	18/682 (3)
Rebounders	18/368 (5)	34/318 (11)	52/686 (8)	16/329 (5)	18/353 (5)	34/682 (5)
Weeks 0–48						
All	20/368 (5)	53/318 (17)	73/686 (11)	14/329 (4)	22/353 (6)	36/682 (5)
Never suppressed	10/368 (3)	33/318 (11)	43/686 (6)	4/329 (1)	13/353 (4)	17/682 (3)
Rebounders	10/368 (3)	20/318 (6)	30/686 (4)	10/329 (3)	9/353 (3)	19/682 (3)
Weeks 48–96[a]						
All	7/368 (2)	15/318 (5)	22/686 (3)	6/329 (2)	10/353 (3)	16/682 (2)
Never suppressed	0/368	1/318 (<1)	1/686 (<1)	0/329	1/353 (<1)	1/682 (<1)
Rebounders	7/368 (2)	14/318 (4)	21/686 (3)	6/329 (2)	9/353 (3)	15/682 (2)

Data are number of virological failures (VFs)/number of patients (%). [a]One VF in the rilpivirine (RPV) group is not reported in the trial period because the time of failure occurred after the 96-week visit (Table 5). EFV, efavirenz; VL, viral load.

Table 2. Proportion of VFs with treatment-emergent[a] NNRTI RAMs and NRTI RAMs by trial period and baseline VL, at time of failure

	RPV VFs			EFV VFs		
	Baseline VL≤100,000 copies/ml	Baseline VL>100,000 copies/ml	All	Baseline VL≤100,000 copies/ml	Baseline VL>100,000 copies/ml	All
Overall 96-week analysis						
No RAMs	13/27 (48)	14/59 (24)	27/86 (31)	10/17 (59)	8/25 (32)	18/42 (43)
NNRTI RAMs	10/27 (37)	36/59 (61)	46/86 (53)	6/17 (35)	14/25 (56)	20/42 (48)
NRTI RAMs	12/27 (44)	36/59 (61)	48/86 (56)	2/17 (12)	9/25 (36)	11/42 (26)
NNRTI+NRTI RAMs	9/27 (33)	34/59 (58)	43/86 (50)	1/17 (6)	7/25 (28)	8/42 (19)
Weeks 0–48						
No RAMs	10/19 (53)	9/48 (19)	19/67 (28)	5/11 (45)	5/17 (29)	10/28 (36)
NNRTI RAMs	7/19 (37)	32/48 (67)	39/67 (58)	5/11 (45)	11/17 (65)	16/28 (57)
NRTI RAMs	8/19 (42)	33/48 (69)	41/67 (61)	2/11 (18)	7/17 (41)	9/28 (32)
NNRTI+NRTI RAMs	6/19 (32)	31/48 (65)	37/67 (55)	1/11 (9)	7/17 (41)	8/28 (29)
Weeks 48–96[b]						
No RAMs	3/7 (43)	5/11 (45)	8/18 (44)	5/6 (83)	3/8 (38)	8/14 (57)
NNRTI RAMs	2/7 (29)	4/11 (36)	6/18 (33)	1/6 (17)	3/8 (38)	4/14 (29)
NRTI RAMs	3/7 (43)	3/11 (27)	6/18 (33)	0/6 (0)	2/8 (25)	2/14 (14)
NNRTI+NRTI RAMs	2/7 (29)	3/11 (27)	5/18 (28)	0/6 (0)	0/8 (0)	0/14 (0)

Data are number of virological failures (VFs)/number of VFs with genotypic data (%). [a]Mutations absent prior to treatment (screening or baseline) and present at time of failure (virco™TYPE HIV-1). [b]One VF in the rilpivirine (RPV) group is not reported in the trial period because the time of failure occurred after the 96-week visit (Table 5). EFV, efavirenz; NNRTI, non-nucleoside reverse transcriptase inhibitor; NRTI, nucleoside/nucleotide reverse transcriptase inhibitor; RAM, resistance-associated mutations; VL, viral load.

also fewer had a combination of an NNRTI RAM with an NRTI RAM (8/42, 19%; *P*=0.0023; Table 2).

Among patients with baseline VL≤100,000 copies/ml, the proportions of RPV (10/27, 37%) and EFV (6/17, 35%) VFs with treatment-emergent NNRTI RAMs were comparable. Among patients with baseline VL>100,000 copies/ml, the proportion of RPV VFs with NNRTI RAMs (36/59, 61%) was similar to that of EFV VFs (14/25, 56%; *P*=0.061; Table 2). Because only few VFs occurred within weeks 48–96, comparison of the proportion of RPV VFs with treatment-emergent NNRTI or NRTI RAMs between the two trial periods was difficult. Some variation was found between the proportion of RPV VFs with NNRTI RAMs within weeks 0–48 (39/67, 58%) and within weeks 48–96 (6/18, 33%; *P*=0.81); a similar observation was made with EFV VFs. As in weeks 0–48 (RPV: 41/67, 61% and EFV: 9/28, 32%), the number of VFs with NRTI RAMs within weeks 48–96 was higher in RPV (6/18, 33%) than EFV (2/14, 14%) VFs (*P*=0.41).

Within weeks 48–96, combinations of an NNRTI RAM with an NRTI RAM were only seen in RPV VFs (5/18, 28%), and were similarly distributed among patients with baseline VL>100,000 copies/ml (3/11, 27%) and baseline VL≤100,000 copies/ml (2/7, 29%; Table 2).

There were few RPV VFs with ≥3 NNRTI RAMs (9/86, 11%), and most were observed within weeks 0–48 among the patients with baseline VL>100,000 copies/ml. There were also fewer EFV VFs with multiple NNRTI RAMs within weeks 48–96 than within weeks 0–48 (Table 3). A higher proportion of RPV VFs had ≥2 NNRTI RAMs (4/18, 22%) compared with EFV VFs (1/14, 7%) within weeks 0–48.

The treatment-emergent NNRTI RAMs observed in ≥2 RPV VFs were V90I, L100I, K101E, E138K/Q, V179I, Y181C, V189I, H221Y and F227C (Table 4). In the overall week 96 analysis, the most frequent combination of an NNRTI RAM with an NRTI RAM remained E138K+M184I in RPV VFs, and K103N remained the most frequent RAM in EFV VFs [14]. In the overall week 96 analyses, the most common combination of RAMs observed in the RPV VFs, E138K+M184I/V [14], was more frequently observed in RPV VFs with baseline VL>100,000 copies/ml (22/59, 37%) than in RPV VFs with baseline VL≤100,000 copies/ml (7/27, 26%). The highest frequency was found in RPV VFs with baseline VL>500,000 copies/ml (10/17, 59%). Within weeks 48–96, the most frequent treatment-emergent NNRTI and NRTI RAMs in the RPV VFs were E138K (3/18, 17%) and M184I (4/18, 22%). E138K and M184I/V were usually observed in combination: two VFs with E138K+M184I and one with E138K+M184V; their RPV FC values were 1.4, 6.5 and 10.9 (Table 5). Two NNRTI RAMs (K103N, G190E) not previously described in the 48-week analysis [14] were observed in single RPV VFs within 48–96 weeks (Table 4). Both

Table 3. Proportion of VFs by number of treatment-emergent[a] NNRTI RAMs per VF by trial period and baseline VL, at time of failure

	RPV VFs			EFV VFs		
NNRTI RAMs, *n*	Baseline VL≤100,000 copies/ml	Baseline VL>100,000 copies/ml	All	Baseline VL≤100,000 copies/ml	Baseline VL>100,000 copies/ml	All
Overall 96-week analysis						
0	17/27 (63)	23/59 (39)	40/86 (47)	11/17 (65)	11/25 (44)	22/42 (52)
1	6/27 (22)	16/59 (27)	22/86 (26)	5/17 (29)	8/25 (32)	13/42 (31)
2	3/27 (11)	12/59 (20)	15/86 (17)	1/17 (6)	3/25 (12)	4/42 (10)
≥3	1/27 (4)	8/59 (14)	9/86 (11)	0/17 (0)	3/25 (12)	3/42 (7)
Weeks 0–48						
0	12/19 (63)	16/48 (33)	28/67 (42)	6/11 (55)	6/17 (35)	12/28 (43)
1	4/19 (21)	15/48 (31)	19/67 (28)	4/11 (36)	6/17 (35)	10/28 (36)
2	2/19 (11)	10/48 (21)	12/67 (18)	1/11 (9)	3/17 (18)	4/28 (14)
≥3	1/19 (5)	7/48 (15)	8/67 (12)	0/11 (0)	2/17 (12)	2/28 (7)
Weeks 48–96[b]						
0	5/7 (71)	7/11 (64)	12/18 (67)	5/6 (83)	5/8 (63)	10/14 (71)
1	1/7 (14)	1/11 (9)	2/18 (11)	1/6 (17)	2/8 (25)	3/14 (21)
2	1/7 (14)	2/11 (18)	3/18 (17)	0/6 (0)	0/8 (0)	0/14 (0)
≥3	0/7 (0)	1/11 (9)	1/18 (6)	0/6 (0)	1/8 (13)	1/14 (7)

Data are number of virological failures (VFs)/number of VFs with genotypic data (%). [a]Mutations absent prior to treatment (screening or baseline) and present at time of failure (virco™TYPE HIV-1). [b]One VF included in the 96-week database was not reported with the weeks 48–96 because the time of failure occurred after the 96-week visit (Table 5). EFV, efavirenz; NNRTI, non-nucleoside reverse transcriptase inhibitor; RAM, resistance-associated mutation; RPV, rilpivirine; VL, viral load.

were found in RPV VFs with a baseline VL>100,000 copies/ml (Table 5). The presence of K103N or G190E was not associated with an increase in RPV FC (2.6 and 1.4, respectively). E138Q was observed in combination with M184I (RPV FC=3.2). The Y188L mutation recently described to be associated with decreased phenotypic susceptibility to RPV [19], and recently included as one of the RPV RAMs [20], was not detected among the treatment-emergent NNRTI RAMs (Tables 4 and 5). Patient self-reported adherence questionnaires indicated <95% adherence for 7/18 (39%) of RPV VFs occurring within weeks 48–96, and 4/7 of these RPV VFs had no treatment-emergent RAMs (Table 5). Within weeks 48–96, three out of four RPV VFs with pre-existing RAMs at baseline (that is, V90I+A62V or V179I) had no treatment-emergent RAMs at failure (Table 5).

There were 42/86 (49%) RPV VFs with at least 1 of the 16 RPV RAMs (see *Methods*); most were observed within weeks 0–48 (37/42, 88%). Nine RPV RAMs were identified in the RPV VFs in the overall 96-week resistance analysis all within weeks 0–48, and four of those nine were also detected within weeks 48–96. Most of the RPV RAMs were observed in patients with a baseline VL>100,000 copies/ml (33/59, 56%; Tables 4 and 5).

Phenotypic analysis and cross-resistance in VFs

In the 96-week resistance analyses, there were 35/81 (43%) RPV VFs with phenotypic resistance to RPV (RPV FC>BCO). Of those, 35, 16, 30 and 32 were cross-resistant to NVP, EFV and ETR, respectively. Of the 17/41 EFV VFs resistant to EFV, 15, 1 and 0 were cross-resistant to NVP, ETR and RPV, respectively. Phenotypic resistance was less common among RPV VFs with baseline VL≤100,000 copies/ml versus >100,000 copies/ml. For EFV VFs, there was no apparent relationship between baseline VL and phenotypic resistance (data not shown).

Discussion

ECHO and THRIVE assessed the efficacy and tolerability of once-daily RPV versus EFV in ARV treatment-naive patients, both combined with an NRTI background regimen. After both 48 and 96 weeks, the efficacy analyses showed that the response rate was high and non-inferior for RPV versus EFV [5–8]. At the end of the 96-week trial period, the efficacy in ECHO/THRIVE remained comparable to that of other recent studies of ARVs in HIV-1-infected, ARV-naive patients [21–23].

The data from the 96-week resistance analyses of ECHO/THIVE confirmed those of the 48-week resistance analyses [14]. The key resistance findings in the second year (weeks 48–96) of ECHO/THRIVE were: similar proportions of RPV and EFV VFs with resistance to their treatment NNRTI, although a higher

Table 4. Proportion of RPV and EFV VFs with treatment-emergent[a] NNRTI RAMs by trial period and baseline VL, at time of failure

	RPV VFs			EFV VFs		
	Baseline VL ≤100,000 copies/ml	Baseline VL >100,000 copies/ml	All	Baseline VL ≤100,000 copies/ml	Baseline VL >100,000 copies/ml	All
Overall 96-week analysis						
Any NNRTI RAMs	10/27 (37)	36/59 (61)	46/86 (53)	6/17 (35)	14/25 (56)	20/42 (48)
Any RPV RAMs	9/27 (33)	33/59 (56)	42/86 (49)	1/17 (6)	2/25 (8)	3/42 (7)
E138K[b]	7/27 (26)	24/59 (41)	31/86 (36)	0/17 (0)	1/25 (4)	1/42 (2)
K101E[b]	2/27 (7)	6/59 (10)	8/86 (9)	1/17 (6)	1/25 (4)	2/42 (5)
H221Y[b]	0/27 (0)	7/59 (12)	7/86 (8)	0/17 (0)	0/25 (0)	0/42 (0)
Y181C[b]	1/27 (4)	5/59 (9)	6/86 (7)	0/17 (0)	0/25 (0)	0/42 (0)
V90I	2/27 (7)	4/59 (7)	6/86 (7)	0/17 (0)	1/25 (4)	1/42 (2)
V189I	0/27 (0)	6/59 (10)	6/86 (7)	0/17 (0)	0/25 (0)	0/42 (0)
E138Q[b]	1/27 (4)	2/59 (3)	3/86 (3)	0/17 (0)	0/25 (0)	0/42 (0)
F227C[b]	0/27 (0)	2/59 (3)	2/86 (2)	0/17 (0)	0/25 (0)	0/42 (0)
L100I	1/27 (4)	1/59 (2)	2/86 (2)	0/17 (0)	1/25 (4)	1/42 (2)
V179I	1/27 (4)	1/59 (2)	2/86 (2)	0/17 (0)	0/25 (0)	0/42 (0)
K101P[b]	0/27 (0)	1/59 (2)	1/86 (1)	0/17 (0)	0/25 (0)	0/42 (0)
Y181I[b]	0/27 (0)	1/59 (2)	1/86 (1)	0/17 (0)	0/25 (0)	0/42 (0)
M230L[b]	0/27 (0)	1/59 (2)	1/86 (1)	0/17 (0)	0/25 (0)	0/42 (0)
K103N	0/27 (0)	1/59 (2)	1/86 (1)	6/17 (35)	8/25 (32)	14/42 (33)
V106A	0/27 (0)	1/59 (2)	1/86 (1)	0/17 (0)	0/25 (0)	0/42 (0)
V106I	0/27 (0)	1/59 (2)	1/86 (1)	0/17 (0)	0/25 (0)	0/42 (0)
V108I	0/27 (0)	1/59 (2)	1/86 (1)	0/17 (0)	2/25 (8)	2/42 (5)
G190E	0/27 (0)	1/59 (2)	1/86 (1)	0/17 (0)	1/25 (4)	1/42 (2)
F227L	0/27 (0)	1/59 (2)	1/86 (1)	0/17 (0)	0/25 (0)	0/42 (0)
V106M	0/27 (0)	0/59 (0)	0/86 (0)	0/17 (0)	3/25 (12)	3/42 (7)
K101Q	0/27 (0)	0/59 (0)	0/86 (0)	0/17 (0)	1/25 (4)	1/42 (2)
V179D	0/27 (0)	0/59 (0)	0/86 (0)	0/17 (0)	1/25 (4)	1/42 (2)
Y188C	0/27 (0)	0/59 (0)	0/86 (0)	0/17 (0)	2/25 (8)	2/42 (5)
Y188H	0/27 (0)	0/59 (0)	0/86 (0)	0/17 (0)	1/25 (4)	1/42 (2)
P225H	0/27 (0)	0/59 (0)	0/86 (0)	0/17 (0)	1/25 (4)	1/42 (2)
K238T	0/27 (0)	0/59 (0)	0/86 (0)	0/17 (0)	1/25 (4)	1/42 (2)
Weeks 0–48						
Any NNRTI RAMs	7/19 (37)	32/48 (67)	39/67 (58)	5/11 (45)	11/17 (65)	16/28 (57)
Any RPV RAMs	6/19 (32)	31/48 (65)	37/67 (55)	1/11 (9)	1/17 (6)	2/28 (7)
E138K[b]	5/19 (26)	22/48 (46)	27/67 (40)	0/11 (0)	1/17 (6)	1/28 (4)
K101E[b]	2/19 (11)	6/48 (13)	8/67 (12)	1/11 (9)	0/17 (0)	1/28 (4)
Y181C[b]	1/19 (5)	5/48 (10)	6/67 (9)	0/11 (0)	0/17 (0)	0/28 (0)
H221Y[b]	0/19 (0)	6/48 (13)	6/67 (9)	0/11 (0)	0/17 (0)	0/28 (0)
V90I	1/19 (5)	4/48 (8)	5/67 (7)	0/11 (0)	1/17 (6)	1/28 (4)
V189I	0/19 (0)	5/48 (10)	5/67 (7)	0/11 (0)	0/17 (0)	0/28 (0)
E138Q[b]	0/19 (0)	2/48 (4)	2/67 (3)	0/11 (0)	0/17 (0)	0/28 (0)
L100I	1/19 (5)	1/48 (2)	2/67 (3)	0/11 (0)	1/17 (6)	1/28 (4)
V179I	1/19 (5)	1/48 (2)	2/67 (3)	0/11 (0)	0/17 (0)	0/28 (0)
K101P[b]	0/19 (0)	1/48 (2)	1/67 (1)	0/11 (0)	0/17 (0)	0/28 (0)
Y181I[b]	0/19 (0)	1/48 (2)	1/67 (1)	0/11 (0)	0/17 (0)	0/28 (0)
F227C[b]	0/19 (0)	1/48 (2)	1/67 (1)	0/11 (0)	0/17 (0)	0/28 (0)
M230L[b]	0/19 (0)	1/48 (2)	1/67 (1)	0/11 (0)	0/17 (0)	0/28 (0)
V106A	0/19 (0)	1/48 (2)	1/67 (1)	0/11 (0)	0/17 (0)	0/28 (0)
V108I	0/19 (0)	1/48 (2)	1/67 (1)	0/11 (0)	1/17 (6)	1/28 (4)
F227L	0/19 (0)	1/48 (2)	1/67 (1)	0/11 (0)	0/17 (0)	0/28 (0)
K103N	0/19 (0)	0/48 (0)	0/67 (0)	5/11 (45)	6/17 (35)	11/28 (39)
V106M	0/19 (0)	0/48 (0)	0/67 (0)	0/11 (0)	3/17 (18)	3/28 (11)
K101Q	0/19 (0)	0/48 (0)	0/67 (0)	0/11 (0)	1/17 (6)	1/28 (4)

Data are number of virological failures (VFs)/number of VFs with genotypic data (%). [a]Mutations absent prior to treatment (screening or baseline) and present at time of failure (virco™TYPE HIV-1). [b]Rilpivirine (RPV) resistance-associated mutations (RAMs). [c]One VF included in the 96-week database was not reported with the weeks 48–96 because the time of failure occurred after the 96-week visit (Table 5). EFV, efavirenz; NNRTI, non-nucleoside reverse transcriptase inhibitors; VL, viral load.

Table 4. Continued.

	RPV VFs			EFV VFs		
	Baseline VL ≤100,000 copies/ml	Baseline VL >100,000 copies/ml	All	Baseline VL ≤100,000 copies/ml	Baseline VL >100,000 copies/ml	All
V179D	0/19 (0)	0/48 (0)	0/67 (0)	0/11 (0)	1/17 (6)	1/28 (4)
Y188C	0/19 (0)	0/48 (0)	0/67 (0)	0/11 (0)	2/17 (12)	2/28 (7)
Y188H	0/19 (0)	0/48 (0)	0/67 (0)	0/11 (0)	1/17 (6)	1/28 (4)
G190E	0/19 (0)	0/48 (0)	0/67 (0)	0/11 (0)	1/17 (6)	1/28 (4)
P225H	0/19 (0)	0/48 (0)	0/67 (0)	0/11 (0)	1/17 (6)	1/28 (4)
K238T	0/19 (0)	0/48 (0)	0/67 (0)	0/11 (0)	1/17 (6)	1/28 (4)
Weeks 48–96[c]						
Any NNRTI RAMs	2/7 (29)	4/11 (36)	6/18 (33)	1/6 (17)	3/8 (38)	4/14 (29)
Any RPV RAMs	2/7 (29)	2/11 (18)	4/18 (22)	0/6 (0)	1/8 (13)	1/14 (7)
E138K[b]	1/7 (14)	2/11 (18)	3/18 (17)	0/6 (0)	0/8 (0)	0/14 (0)
E138Q[b]	1/7 (14)	0/11 (0)	1/18 (6)	0/6 (0)	0/8 (0)	0/14 (0)
H221Y[b]	0/7 (0)	1/11 (9)	1/18 (6)	0/6 (0)	0/8 (0)	0/14 (0)
F227C[b]	0/7 (0)	1/11 (9)	1/18 (6)	0/6 (0)	0/8 (0)	0/14 (0)
V90I	1/7 (14)	0/11 (0)	1/18 (6)	0/6 (0)	0/8 (0)	0/14 (0)
K103N	0/7 (0)	1/11 (9)	1/18 (6)	1/6 (17)	2/8 (25)	3/14 (21)
V106I	0/7 (0)	1/11 (9)	1/18 (6)	0/6 (0)	0/8 (0)	0/14 (0)
V189I	0/7 (0)	1/11 (9)	1/18 (6)	0/6 (0)	0/8 (0)	0/14 (0)
G190E	0/7 (0)	1/11 (9)	1/18 (6)	0/6 (0)	0/8 (0)	0/14 (0)
K101E	0/7 (0)	0/11 (0)	0/18 (0)	0/6 (0)	1/8 (13)	1/14 (7)
V108I	0/7 (0)	0/11 (0)	0/18 (0)	0/6 (0)	1/8 (13)	1/14 (7)
Y188H	0/7 (0)	0/11 (0)	0/18 (0)	0/6 (0)	1/8 (13)	1/14 (7)

proportion of RPV VFs had ≥2 NNRTI RAMs; a limited number of RPV VFs with RPV RAMs; and the confirmation of the RPV resistance profile.

In the 96-week resistance analyses, the overall proportion of VFs was higher with RPV (96/686, 14%) versus EFV (52/682, 8%). However, in contrast with the data observed during the first year (weeks 0–48; RPV: 73/686, 11% versus EFV: 36/682, 5%), in the second year the proportions of both RPV and EFV VFs were lower and similar (RPV: 22/686, 3% and EFV: 16/682, 2%). Almost all the VFs observed during the second year were rebounders.

In line with the data observed in the 48-week resistance analyses [14], the 96-week resistance analyses showed that the proportion of RPV (46/86, 53%) and EFV (20/42, 48%) VFs with treatment-emergent NNRTI RAMs were comparable, and that NRTI RAMs emerged more frequently in RPV (48/86, 56%) than in EFV (11/42, 26%) VFs. The majority of treatment-emergent NNRTI RAMs and NRTI RAMs were observed during the first year of the trials (overall and within each baseline VL subgroup) probably because there were very few VFs during the second year. The 96-week resistance analysis confirmed that lower baseline VL was associated with fewer VFs and that the RPV resistance profile is independent of the baseline VL [14]. The most frequent treatment-emergent NNRTI RAMs in RPV and EFV VFs were E138K and K103N, respectively, during both the first and the second year of the trials. The 96-week resistance analyses confirmed the pattern of resistance to RPV described in the 48-week resistance analyses [14] as no new RPV RAMs were observed during the second year of the trials. In the 96 week ECHO and THRIVE studies, RPV VFs without treatment-emergent mutations or RPV VFs with NNRTI RAMs that were not RPV RAMs (such as K103N, V106I, V179I or V189I) were observed. These VFs retained susceptibility to RPV and ETR (Table 5) [14,16]. These treatment failures may be attributed to loss of sensitivity to the background regimen (for those VFs with an NRTI RAM) or to episodes of poor adherence to treatment [8].

The EFV resistance findings observed in ECHO/THRIVE agreed with previous data [24] and the pattern of resistance to EFV continued to be distinct from that of RPV.

In the 96-week resistance analyses, E138K was always found in combination with an NRTI RAM in RPV VFs. The most common NRTI RAMs were M184I and M184V; both known to confer resistance to 3TC and FTC [25,26]. As previously described in the 48-week resistance analyses, the most common combination of an NNRTI RAM with an NRTI RAM

Table 5. Genotypic and phenotypic profiles of the RPV VFs occurring within weeks 48–96 and post week 96 by BL VL, at time of failure

ID	Background regimen	Failure VL, copies/ml	Genotype		HIV-1 subtype	FC in 50% effective concentration[a]								
			NNRTI RAM	NRTI RAM		RPV	EFV	ETR	NVP	3TC	FTC	TDF	ABC	AZT
Weeks 48–96 and BL VL≤100,000 copies/ml														
1	TDF/FTC	84	V90I, E138K[b]	M184I	B	**6.5**	**6.9**	**7.3**	2.3	**70.0**	**48.5**	0.7	2.3	0.7
2[c]	TDF/FTC	82	E138Q[b]	M184I	B	3.2	2.6	**4.6**	1.1	**68.9**	**30.6**	0.4	1.5	0.7
3	AZT/3TC	6,640	(V90I)	(A62V)	AE	2.0	2.4	2.3	2.7	0.6	0.8	0.5	0.6	1.0
4[c]	TDF/FTC	3,880	–	M184I/M	B	1.9	1.2	0.9	0.5	NA	**3.6**	0.3	0.5	0.8
5	TDF/FTC	1,750	–	–	C	1.7	0.6	1.0	1.8	0.8	1.6	0.5	0.6	1.3
6[c]	ABC/3TC	1,510	–	–	C	1.5	1.4	1.1	2.7	0.9	1.6	0.7	0.8	1.5
7	TDF/FTC	38,800	–	–	C	0.8	0.7	0.8	1.5	1.3	1.6	1.4	0.5	0.7
Weeks 48–96 and BL VL>100,000 copies/ml														
8[c]	ABC/3TC	1,230	E138K[b], H221Y[b]	M184V	B	**10.9**	**8.1**	**7.7**	**7.8**	**93.7**	**48.5**	0.8	2.6	0.8
9	TDF/FTC	524	K103N, V189I	M184V	C	2.6	**14.2**	0.6	**61.1**	**30.6**	**35.3**	0.2	0.6	0.7
10[c]	TDF/FTC	112	–	–	B	2.3	2.3	1.5	2.3	0.9	1.1	0.8	1.0	1.1
11[c]	TDF/FTC	3,940	–	–	B	1.4	1.0	1.1	0.7	0.4	0.5	0.4	0.2	1.5
12	AZT/3TC	1,060	(V90I), E138K[b], (V179I), G190E/G, F227C[b]/F	M184I	B	1.4	1.6	2.5	0.7	**37.5**	**15.6**	0.2	1.0	0.6
13[c]	AZT/3TC	8,560	–	–	B	1.4	1.2	1.2	0.8	0.8	1.2	0.7	0.7	0.5
14	TDF/FTC	68,300	–	–	C	1.4	1.1	1.2	0.7	1.4	2.0	0.8	0.7	0.7
15	TDF/FTC	772	V106I	–	B	1.3	1.3	1.6	2.0	0.8	0.5	0.4	0.4	1.1
16	AZT/3TC	24,600	–	–	B	1.3	1.1	0.9	2.5	0.9	0.9	0.7	0.5	1.3
17	TDF/FTC	133	(V179I)	–	B	1.0	0.7	1.4	0.9	0.9	1.2	0.8	0.4	1.0
18	TDF/FTC	97	(V179I)	–	B	NA	NA	NA	NA	NA	NA	NA	NA	NA
Post week 96 and BL VL≤100,000 copies/ml														
19	ABC/3TC	123	E138K[b]	M184I, K219E	B	**10.5**	2.6	**5.6**	0.7	**34.9**	**34.8**	0.1	1.9	0.8

[a]Fold change (FC) values in bold denote phenotypic resistance (that is, FC> biological/lower clinical cutoff; Antivirogram®); resistance-associated mutations (RAMs) displayed in parenthesis were those present at baseline (BL)/screening (patients with the non-nucleoside reverse transcriptase inhibitor (NNRTI) RAMs V90I/V, V106I, V179I and V189I/V were allowed to enrol in the trials [15]. [b]Rilpivirine (RPV) RAMs. [c]Indicates that the patient M-MASRI adherence was reported <95%. ABC, abacavir; AE, CRF01_AE; AZT, zidovudine; EFV, efavirenz; ETR, etravirine; FTC, emtricitabine; NA, not available in the week 96 database; NRTI, nucleoside/nucleotide reverse transcriptase inhibitor; NVP, nevirapine; TDF, tenofovir disoproxil fumarate; VF, virological failure; VL, viral load; 3TC, lamivudine.

in RPV VFs was E138K+M184I [14]. This combination of E138K+M184I is more commonly found in RPV VFs with baseline VL>500,000 copies/ml compared with RPV VFs with baseline VL≤100,000 copies/ml. This observation is in line with the previously described lower virological success of RPV versus EFV in this highest baseline VL category [8]. In the second year of the trials, 3 of the 18 RPV VFs had E138K, all 3 also had M184I or M184V, of whom 2 (1 with M184I and 1 with M184V) were resistant to RPV. We previously hypothesized that the high frequency of M184I/V observed in VFs treated with RPV and FTC, and its combination with E138K, suggested a role for M184I in resistance to RPV. This hypothesis was supported by HIV-1 site-directed mutant analyses and several other phenotypic assays [14,16,27]. These *in vitro* assessments demonstrated that the combination of E138K+M184I enhanced resistance to RPV compared with E138K alone. No consensus was reached on the effect of this combination of mutations on viral fitness as both a decrease in replication fitness [27] and fitness compensation [28,29] were described. Recently, it was demonstrated that, *in vitro*, the E138K mutation decreased rates of polymerization, impaired the HIV-1 ribonuclease H activity, and conferred ETR resistance through the p51 HIV-1 reverse transcriptase subunit, while the combination E138K+M184I enhanced dNTP usage via both HIV-1 reverse transcriptase subunits [30]. Another *in vitro* study established

that HIV-1 proviral mutants with M184I and E138K may pre-exist in reservoirs as a result of APOBEC3 editing [31]. Currently, E138K is not a commonly observed NNRTI RAM. Its prevalence was reported as <1% in three recent studies: one on US clinical samples from a large HIV-1-infected patient population [20], one on Spanish clinical samples from HIV-1-infected patients who experienced VF on NNRTI-based therapies [32] and one based on the data available in the Frankfurt Resistance Database [33]. The low frequency of E138K in treatment-naive, HIV-1-infected patients was also confirmed by ultra-deep sequencing analyses of a pertinent selection of clinical isolates from treatment-naive patients in which E138K was not detected [34–36].

RPV VFs with phenotypic resistance to RPV had evidence of cross-resistance to EFV, ETR and NVP. These results are supported by recent data showing the cross resistance to EFV, NVP, ETR and RPV of an HIV-1 proviral clone containing the mutations K101E, E138K and Y181C [37]. The high level of cross-resistance observed in these trials between ETR and RPV may be the result of both compounds belonging to the DAPY class [38,39]. As in the 48-week resistance analyses, the number of RPV VFs with phenotypic resistance to RPV, ETR or EFV was lower in patients with baseline VL≤100,000 versus >100,000 copies/ml. Conversely, the EFV VFs with phenotypic resistance to EFV or NVP were not resistant to RPV and ETR [14]. Guidelines recommend performing clinical resistance testing before starting or switching treatments so that an appropriate regimen can be selected for HIV-1-infected patients [9,10,40].

Summarizing the 96-week resistance analyses, there were more VFs in the RPV than in the EFV group, mainly due to those occurring during the first year (week 0–48) of the trials. In patients with baseline VL≤100,000 copies/ml, the proportions of VFs were similar between treatments for both the first and the second year of the trials. A similar proportion of RPV and EFV VFs with treatment-emergent NNRTI RAMs and more RPV than EFV VFs with NRTI RAMs were observed. The majority of RAMs were seen in never suppressed VFs during the first year of the trials. Although higher baseline VL was associated with a higher number of RPV VFs with treatment-emergent NNRTI RAMs, the NNRTI RAMs observed were the same in both baseline VL subgroups. In RPV VFs, the combination of E138K+M184I was the most common co-emergence of an NNRTI RAM with an NRTI RAM. Overall, the results of the 96-week resistance analyses extended the 48-week resistance findings, and demonstrated that few RPV RAMs emerged in the few VFs taking place during the second year of the ECHO/THRIVE trials. Nine of the 16 RPV RAMs (K101E, K101P, E138K, E138Q, Y181C, Y181I, H221Y, F227C and M230L) were identified as treatment-emergent in the RPV VFs. All RPV RAMs were observed during the first year of the trials, with no new ones identified during the second year.

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