Rilpivirine Versus Efavirenz in HIV-1–Infected Subjects Receiving Emtricitabine/Tenofovir DF: Pooled 96-Week Data from ECHO and THRIVE Studies

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Objectives: Week 96 efficacy and safety of the non-nucleoside reverse transcriptase inhibitor (NNRTI) rilpivirine (RPV) was compared to efavirenz (EFV) in subset of 1,096 subjects who received emtricitabine/tenofovir disoproxil fumarate (FTC/TDF) in pooled data from 2 phase 3 studies. **Methods:** ECHO and THRIVE are double-blind, double-dummy, randomized, active-controlled, non-inferiority phase 3 studies of RPV versus EFV plus 2 NRTIs in antiretroviral-naïve adult subjects. The primary and secondary endpoints were the proportion of subjects with HIV-1 RNA <50 copies/mL using an intent-to-treat, time to loss of virologic response (ITT-TLOVR) analysis at weeks 48 and 96, respectively. Safety, tolerability, immunologic response, adherence level, and other measures were also evaluated. **Results:** At week 48, noninferior efficacy of RPV+FTC/TDF over EFV+FTC/TDF was established, and at week 96 RPV+FTC/TDF remained noninferior (77% overall response rate in both groups). Through week 96, rates of virologic failure were higher in the RPV+FTC/TDF group, with low and similar rates of virologic failure and resistance mutations occurring during the second year of follow-up. Treatment with RPV+FTC/TDF was associated with a lower rate of discontinuation due to adverse events and grade 2–4 adverse events including dizziness, abnormal dreams/nightmares, rash, and lipid abnormalities. **Conclusions:** The pooled ECHO and THRIVE studies demonstrated noninferiority of RPV+FTC/TDF in achieving virologic response with safety and tolerability advantages over EFV+FTC/TDF through 96 weeks. Higher rates of virologic failure in the RPV+FTC/TDF group were balanced with higher rates of discontinuations due to adverse events in the EFV+FTC/TDF group. **Key words:** *efavirenz, emtricitabine, HIV-1 antiviral therapy, rilpivirine, tenofovir disoproxil fumarate*

For treatment-naïve patients infected with HIV-1, current treatment guidelines recommend initiation of highly active antiretroviral (ARV) treatment with the non-nucleoside reverse transcriptase inhibitor (NNRTI) efavirenz (EFV).[1,2] Efavirenz (Sustiva, Stocrin; Bristol-Myers Squibb Company) may be associated with neurological, psychological, and dermatological side effects that can lead to discontinuation of therapy and is potentially teratogenic (Pregnancy Category D). Alternative NNRTIs include nevirapine and rilpivirine. Nevirapine (Viramune, Boehringer Ingelheim) has been associated with hepatotoxicity, rash, and hypersensitivity reactions. Rilpivirine (RPV; Edurant, Janssen Therapeutics) was approved by the US Food and Drug Administration in May 2011 as a once-daily oral treatment for HIV-1 infection in

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combination with other ARV agents in ARV treatment–naïve adults.

Rilpivirine is a diarylpyrimidine derivative with a long terminal elimination half-life of 50 hours,[3,4] permitting once-daily dosing. RPV is primarily metabolized by the cytochrome P450 (CYP) 3A pathway. Therefore drugs that induce CYP3A can decrease plasma concentrations of RPV. RPV does not have a clinically relevant effect on the exposure of drugs metabolized by CYP enzymes.[4,5] Absorption of RPV is pH dependent, and coadministration with proton pump inhibitors may lead to decreased plasma concentrations of RPV; however only proton pump inhibitors are contraindicated, whereas spacing RPV apart from antacids and H2 antagonists allows for coadminstration. RPV-containing products (RPV or RPV/FTC/TDF) must be dosed with a meal, because RPV exposure is reduced when dosed in a fasted state or with a liquid nutritional supplement.[6] Rilpivirine does not exhibit teratogenicity in animals[4,7] and is categorized as a Pregnancy Category B drug.[4] Rilpivirine 25 mg plus emtricitabine 200 mg/tenofovir disoproxil fumarate 300 mg (FTC/TDF) coformulated as a single-tablet regimen (STR) (Complera, Eviplera; Gilead Sciences Inc.) was approved in the United States in August 2011 and the European Union in November 2011 for the treatment of HIV-1 infection in an adult treatment-naïve population. In both the United States and the European Union, the indication is restricted to those with baseline HIV-1 RNA levels <100,000 copies/mL. The US prescribing information notes the higher rate of virologic failure observed in patients with baseline HIV-1 RNA above this threshold.

METHODS

ECHO and THRIVE were phase 3, double-blind, double-dummy, active-controlled randomized trials designed to assess the efficacy, safety, and tolerability of RPV 25 mg versus EFV 600 mg taken once daily with a nucleoside or nucleotide reverse transcriptase inhibitor (NRTI, NtRTI) background regimen for 96 weeks. In the THRIVE study, investigators could choose from 3 background NtRTI regimens (FTC/TDF, zidovudine/lamivudine [AZT/3TC], or abacavir/lamivudine [ABC/3TC]), whereas in the ECHO study, all individuals received FTC/TDF. In the THRIVE study, randomization was stratified by background regimen and screening HIV-1 RNA category (≤100,000 copies/mL, 100,001–500,000 copies/mL, and >500,000 copies/mL); in the ECHO study, randomization was stratified by screening HIV-1 RNA category only.

The ECHO study was conducted at 112 sites across 21 countries, and the THRIVE study was conducted at 98 sites across 21 countries. Subjects enrolled in both studies were HIV-1–infected treatment-naïve males or females at least 18 years of age with any CD4 cell count and pretreatment plasma HIV-1 RNA of at least 5,000 copies/mL with demonstrated viral sensitivity to the background NRTIs and without demonstrable non-nucleoside reverse transcriptase inhibitor (NNRTI) mutations. Subjects were excluded if they had active clinically significant disease, were infected with HIV-2, had renal impairment (estimated glomerular filtration rate [eGFR] based on creatinine <50 mL/min), or were pregnant or breastfeeding. RPV (or matching placebo) was recommended to be taken with a meal, preferably with breakfast, to simplify the ability to obtain C_{trough} drug levels during typical study visit times, whereas EFV (or matching placebo) was recommended to be taken on an empty stomach in the evening, consistent with the known side effects of the drug. Efficacy assessments in both studies included antiviral activity, immunologic changes, and evolution of HIV-1 genotypic and phenotypic characteristics. In addition, efficacy outcomes were stratified by level of adherence as reported by subjects using an abbreviated version of the validated and published Medication Adherence Self-Report Inventory (M-MASRI).

The protocols for both studies were reviewed and approved by independent ethics committees and local or central institutional review boards at participating sites, and the trial was undertaken in accordance with the principles of good clinical practice and the Declaration of Helsinki. All subjects provided written informed consent prior to participating in the studies. Investigators, the sponsor, and subjects participating in the trial were masked to NNRTI treatment assignment. Further details on the individual study designs, timing of assessments, and methods have been previously published.[8,9]

For both ECHO and THRIVE studies, the primary outcome was noninferiority between treatments at 48 weeks in the percentage of subjects receiving at least one dose of study drug with confirmed virologic response (HIV-1 RNA <50 copies/mL). Virologic response was defined by

the intent-to-treat time to loss of virologic response (ITT-TLOVR) algorithm.[10] For noninferiority, there was a 12% maximum allowable difference between treatments. The same statistical methodology was applied to the pooled analysis of the 96-week data for the FTC/TDF subset. Virologic failure was defined as (1) virologic response confirmed at 2 consecutive visits before week 96 and confirmed rebound at or before week 96, or (2) no confirmed response at all before week 96 with an increase in viral load ≥0.5 $\log_{10}$ copies/mL above the nadir (never suppressed). Plasma HIV-1 RNA was determined using a Roche Amplicor viral load assay.

In addition to the ITT-TLOVR analysis of these endpoints, an ITT-snapshot analysis based upon the last HIV-1 RNA value in the week 96 visit window (90 to 103 weeks) was performed. Virologic response was also analyzed using stratification by baseline HIV-1 RNA (≤100,000, 100,001–500,000, or >500,000 copies/mL) and by adherence level (>95% and ≤95%) using ITT-TLOVR methodology. Adherence data were self-reported using the M-MASRI questionnaire in which subjects self-report their adherence over the past 30 days by means of a horizontal visual analogue scale ranging from 0% to 100%. For individuals with confirmed virological failure, viral genotypic and phenotypic determinations were performed using the virco-TYPE HIV-1 resistance assay (Janssen Diagnostics BVBA, Beerse, Belgium) and Antivirogram.

Adverse events were coded using MedDRA (version 11.0), and severity of adverse events was evaluated according to the Division of AIDS grading scale.[11] Using all available data, the incidence of serious adverse events (SAEs), grade 2–4 treatment-related adverse events (AEs), AEs leading to discontinuation, treatment-related neurologic and psychiatric AEs, and treatment-related rash were compared between the RPV+FTC/TDF and EFV+FTC/TDF groups. Differences in grade 2–4 AEs, treatment-related neurologic or psychiatric AEs, and treatment-related rash were analyzed between groups using the Fisher exact test. Dual-energy x-ray absorptiometry (DEXA) was performed during substudies of ECHO and THRIVE to assess any changes in bone mineral density (BMD) and body fat distribution. Electrocardiogram (ECG) results were analyzed to determine whether QT interval prolongation occurred.

Both studies were registered with the US National Institutes of Health via ClinicalTrials.gov (NCT00540449 [ECHO] and NCT00543725 [THRIVE]), as well as the European Union Drug Regulating Authorities Clinical Trials (EUDRACT) database (2007–002646–38 [ECHO] and 2007–002647–25 [THRIVE]).

RESULTS

A total of 690 subjects were randomized and treated in the ECHO study, of whom 346 received RPV and 344 received EFV. In the THRIVE study, 678 subjects were randomized and treated, of whom 340 received RPV and 338 received EFV. Of these, 204 subjects received RPV with FTC/TDF and 202 subjects received EFV with FTC/TDF (representing 60% of the study population). Thirty percent of the THRIVE study population (204 subjects) received AZT/3TC as their background regimen at study entry and 10% (68 subjects) received ABC/3TC.

Overall in the 2 trials, baseline demographics and disease characteristics were similar between the RPV+FTC/TDF and EFV+FTC/TDF groups (**Table 1**). The majority of the 1,096 subjects were White (63% RPV, 61% EFV) and male (78% RPV, 79% EFV), and the median age at baseline was 36 years in both treatment groups. The median baseline HIV-1 RNA was 5.0 $\log_{10}$ copies/mL in both groups, and median CD4 cell count was 247 cells/mm^3 in the RPV+FTC/TDF group and 261 cells/mm^3 in the EFV+FTC/TDF group. The same percentage of subjects in both treatment groups (33%) had a prior history of neurological or psychiatric illnesses.

At week 96, the same percentage of subjects in the RPV+FTC/TDF and EFV+FTC/TDF groups experienced virologic response based on both ITT-TLOVR and ITT-snapshot analysis methods (77%),[12] confirming the noninferiority of the RPV regimen to the EFV regimen (**Table 2**). Based on ITT-TLOVR analysis of the percentage of subjects with HIV-1 RNA <50 copies/mL, RPV+FTC/TDF was noninferior to EFV+FTC/TDF at both weeks 48 and 96 (–0.4 treatment difference; 95% CI, –5.4 to 4.6). At the primary endpoint of week 48, RPV+FTC/TDF demonstrated a virologic response rate (83%) that was noninferior to EFV+FTC/TDF (82%).[12] Mean increases from baseline to week 96 in CD4 cell count were similar in both groups (+226 cells/mm^3 in the RPV group and +222 cells/mm^3 in the EFV group).

Virologic response at week 96 was also analyzed across 3 baseline HIV-1 RNA strata; results indicated that RPV+FTC/TDF was noninferior to EFV+FTC/

Table 1. Baseline demographics, disease characteristics, and laboratory values for pooled FTC/TDF subset in ECHO/THRIVE studies

Characteristic	RPV+FTC/TDF (n = 550)	EFV+FTC/TDF (n = 546)
Subject demographics		
Female, %	22	21
Median age (range), years	36 (18–78)	36 (19–69)
Median BMI (range), kg/m^2	24 (16–55)	24 (16–44)
Race, %		
White	63	61
Black or African American	24	23
Asian	10	13
Other[a]	1	1
Missing	2	1
Hispanic ethnicity	24	27
Disease characteristics		
Median HIV-1 RNA (range), $\log_{10}$ copies/mL	5 (2–7)	5 (3–7)
Baseline HIV-1 RNA ≤100,000 copies/mL	288 (52.4%)	255 (46.7)
Baseline HIV-1 RNA >100,000 copies/mL	262 (47.6%)	291 (52.3%)
Median CD4 cell count (range), cells/mm^3	247 (1–888)	261 (1–857)
CD4 cell count <200 cells/mm^3, %	33	30
CDC Category C, %	5.3	6.4
Prior history of neurologic or psychiatric illness, %	33	33
Laboratory parameters, mean (95% CI)		
Fasting lipid parameters, mg/dL[b]		
Total cholesterol	161.7 (158.8-164.7)	161.3 (158.4-164.3)
HDL cholesterol	41.3 (40.3-42.4)	39.6 (38.7-40.5)
LDL cholesterol	96.7 (94.2-99.2)	96.3 (93.6-99.0)
Triglycerides	124.5 (117.7-131.3)	131.5 (123.8-139.3)
Hepatic and renal parameters		
AST, U/L	32.9 (30.7-35.2)	35.6 (30.8-40.4)
ALT, U/L	32.5 (30.5-34.6)	38.3 (31.4-45.2)
Creatinine, mg/dL	0.85 (0.84-0.86)	0.85 (0.84-0.86)
GFR, mL/min/1.73 m^2 [c]	108.3 (106.4-110.1)	108.1 (106.4-109.8)

Note: ALT = alanine aminotransferase; AST = aspartate aminotransferase; BMI = body mass index; EFV = efavirenz; FTC/TDF = emtricitabine/tenofovir disoproxil fumarate; GFR = glomerular filtration rate; HDL = high-density lipoprotein; LDL = low-density lipoprotein; RPV = rilpivirine.

[a]Other = American Indian or Alaska Native, Native Hawaiian or Other Pacific Islander, Asian/Black, or African American/White.

[b]Test results were not available for a small number of subjects. The number of observations for RPV+FTC/TDF ranged from 465 to 472 and for EFV+FTC/TDF it ranged from 445 to 459.

[c]GFR is calculated using Modification of Diet for Renal Disease (MDRD) formula.

Sources: Nelson et al., 2011.[12]

TDF in those with baseline HIV-1 RNA ≤100,000 copies/mL (83% RPV vs 80% EFV; 95% CI, –3.9 to 9.1) and 100,001–500,000 copies/mL (74% RPV vs 73% EFV; 95% CI, –7.8 to 9.0), but not in subjects with baseline HIV-1 RNA above 500,000 copies/mL (60% RPV vs 75% EFV; 95% CI, –31.0 to 1.8).[12]

A majority of subjects in both groups (≥81%) had adherence levels >95%. Adherence was one of the most important factors associated with virologic response. When both baseline HIV-1 RNA and M-MASRI adherence level were considered in the analysis of virologic response using the ITT-TLOVR analysis method, lower virologic responses in both groups at week 96 were observed among subjects with suboptimal adherence (≤95%) and high baseline HIV-1 RNA (>100,000 copies/mL) (**Table 3**).[12,13]

Table 2. Virologic outcome at week 96 by baseline HIV-1 RNA for pooled FTC/TDF subset in ECHO/THRIVE studies (ITT-TLOVR analysis)

	Pooled		Baseline HIV-1 RNA ≤100,000 copies/mL		Baseline HIV-1 RNA >100,000 copies/mL	
Response category, n (%)	RPV (n = 550)	EFV (n = 546)	RPV (n = 288)	EFV (n = 255)	RPV (n = 262)	EFV (n = 291)
Responder	423 (76.9)	422 (77.3)	241 (83.7)	206 (80.8)	182 (69.5)	216 (74.2)
Virologic failure	63 (11.5)	28 (5.1)	17 (5.9)	6 (2.4)	46 (17.6)	22 (7.6)
Rebounder	33 (6.0)	20 (3.7)	12 (4.2)	6 (2.4)	21 (8.0)	14 (4.8)
Re-suppressed	14 (2.5)	7 (1.3)	4 (1.4)	3 (1.2)	10 (3.8)	4 (1.4)
Never suppressed	30 (5.5)	8 (1.5)	5 (1.7)	0	25 (9.5)	8 (2.7)
Initial lack of response	4 (0.7)	1 (0.2)	0	0	4 (1.5)	1 (0.3)
Death	0	4 (0.7)	0	0	0	4 (1.4)
Discontinued due to AE	20 (3.6)	44 (8.1)	12 (4.2)	17 (6.7)	8 (3.1)	27 (9.3)
Discontinued due to other reason than AE	44 (8.0)	48 (8.8)	18 (6.3)	26 (10.2)	26 (9.9)	22 (7.6)

Note: AE = adverse event; EFV = efavirenz; FTC/TDF = emtricitabine/tenofovir disoproxil fumarate; ITT-TLOVR = intent-to-treat, time to loss of virologic response; RPV = rilpivirine.

Table 3. Virologic response and virologic failure at week 96, by self-reported M-MASRI adherence and baseline HIV-1 RNA for pooled FTC/TDF subset in ECHO/THRIVE studies (ITT-TLOVR analysis)

Treatment group	Baseline HIV-1 RNA, copies/mL	M-MASRI adherence category >95%	M-MASRI adherence category ≤95%
Virologic response			
RPV+FTC/TDF	Overall (N = 540)	81%	56%
	≤100,000 (n = 288)	87%	63%
	>100,000 (n = 262)	74%	50%
EFV+FTC/TDF	Overall (N = 546)	83%	67%
	≤100,000 (n = 255)	87%	62%
	>100,000 (n = 291)	80%	70%
Virologic failure			
RPV+FTC/TDF	Overall (N = 540)	9.8%	19.1%
	≤100,000 (n = 288)	3.7%	18.8%
	>100,000 (n = 262)	16.9%	19.4%
EFV+FTC/TDF	Overall (N = 546)	4.7%	6.9%
	≤100,000 (n = 255)	2.9%	0%
	>100,000 (n = 291)	6.3%	11.4%

Note: EFV = efavirenz; FTC/TDF = emtricitabine/tenofovir disoproxil fumarate; ITT-TLOVR = intent-to-treat, time to loss of virologic response; M-MASRI = Modified Medication Adherence Self-Report Inventory; RPV = rilpivirine.
Source: Nelson et al., 2011.[12]

At week 96, based on the ITT-TLOVR analysis, the proportion of subjects with virologic failure in the resistance analysis was higher in the RPV+FTC/TDF group (14%) versus the EFV+FTC/TDF group (7%) (**Table 4**).[12] These data are consistent with those observed at week 48 (11.5% vs 4.2%, respectively), with notably fewer virologic failures observed in year 2 (2.7% vs 2.6%, respectively) in the resistance analysis.

In addition to exploring the impact of adherence on response, we evaluated its impact on virologic failure rates. Adherence significantly impacted the virologic failure rates (ITT-TLOVR analysis) at week 96 for both drugs. Virologic failure rates were higher in the RPV+FTC/TDF group compared to the EFV+FTC/TDF group regardless of adherence category (>95% or ≤95%). However in subjects with lower baseline HIV-1 RNA (≤100,000 copies/mL) and good adherence (>95%), virologic failure rates were similar and low (3.7% in the RPV group and 2.9% in the EFV group) (**Table 3**).

Through 96 weeks, a similar proportion of subjects in both groups with virologic failure in the resistance analysis developed NNRTI mutations (55% in the RPV group and 50% in the EFV group). However, a greater proportion developed NtRTI mutations with RPV+FTC/TDF (58%) than with EFV+FTC/TDF (27%) (**Table 4**).[14,15] The most frequently occurring NtRTI resistance-associated mutation in both groups was M184I. The most frequently occurring NNRTI resistance-associated mutations were E138K (RPV group) and K103N (EFV group). The mutations E138K and M184I were the most common mutations observed together in the RPV+FTC/TDF group.

Rilpivirine plus FTC/TDF demonstrated a more favorable overall safety profile through week 96. The overall incidence of treatment-related grade 2–4 AEs during both years of the studies was higher in the EFV+FTC/TDF group (33%) versus the RPV+FTC/TDF group (17%) ($P < .0001$) (**Table 5**). The majority of AEs occurred in the first year of the studies; through year 2, the incidence of treatment-related grade 2–4 AEs was low and similar in both groups. Similar percentages of subjects in both groups experienced serious AEs through 96 weeks (9.5% RPV and 11% EFV). A significantly smaller percentage of subjects in the RPV+FTC/TDF group had AEs of dizziness, abnormal dreams or nightmares, somnolence, and rash (any severity grade) ($P < .05$ for each event type) (**Table 5**). There were significantly fewer discontinuations due to AEs overall ($P = .001$) and fewer discontinuations due to rash in the RPV+FTC/TDF group ($P = .003$).

Table 4. Summary of resistance findings at week 96 for pooled FTC/TDF subset in ECHO/THRIVE studies

	RPV+FTC/TDF (n = 550)			EFV+FTC/TDF (n = 546)		
	Time of failure					
Resistance category	All	Year 1	Year 2	All	Year 1	Year 2
Virologic failure, %	14.2%	11.5%	2.7%	6.8%	4.2%	2.6%
Rebounder, %	7.3%	4.7%	2.5%	4.8%	2.4%	2.4%
Virologic failure with resistance data, n	71	59	12	30	18	12
No emergent NNRTI or NtRTI RAMs, %	33%	31%	50%	43%	39%	50%
Any emergent NNRTI and/or NtRTI RAMs, n (%)	47 (66)	41 (70)	6 (50)	17 (57)	11 (61)	6 (50)
Any emergent[a] NNRTI RAMs, n (%)	39 (55)	34 (58)	5 (42)	15 (50)	11 (61)	4 (33)
Most frequent NNRTI RAM, n (%)	E138K	E138K	E138K	K103N	K103N	K103N
	26 (37)	24 (41)	2 (17)	10 (33)	7 (39)	3 (25)
Any emergent[a] NtRTI RAMs, n (%)	41 (58)	36 (61)	5 (42)	8 (27)	6 (33)	2 (17)
Most frequent NtRTI RAM, n (%)	M184I	M184I	M184I	M184I	M184V	M184I
	30 (42)	26 (44)	4 (33)	4 (13)	2 (11)	2 (17)

Note: EFV = efavirenz; NNRTI = non-nucleoside reverse transcriptase inhibitor, NtRTI = nucleotide reverse transcriptase inhibitor; RAM = resistance-associated mutation; RPV = rilpivirine.

[a]At least one emergent NNRTI RAM[15] or IAS-USA NtRTI RAM.[14]

Table 5. Treatment-emergent adverse events and grade 2–4 laboratory abnormalities occurring in ≥2% of subjects for pooled FTC/TDF subset in ECHO/THRIVE studies

Adverse event or laboratory abnormality	RPV+FTC/TDF (n = 550)	EFV+FTC/TDF (n = 546)	*P* value[a]
Adverse events (%)[b]			
Any serious adverse events (AEs)	9.5	11.2	–
Grade 2–4 treatment-related AEs	17	33	<.0001
Any treatment-related neurological AE[c]	17	37	<.0001
Somnolence	3	6	.0159
Dizziness	8	26	<.0001
Disturbance in attention	1	2	.0291
Grade 2-4 treatment-related neurological AE[c]	3	12	–
Any treatment-related psychiatric AE[c]	16	27	<.0001
Abnormal dreams/nightmares	9	15	.0029
Grade 2-4 treatment-related psychiatric AE	7	11	–
Any treatment-related rash	5	16	<.0001
Discontinued due to AEs	4	9	.0011
Rash	0.2	2.0	.0032
Depression	0.4	0.7	.45
	(n = 549)	(n = 536)	
Laboratory abnormalities, n (%)			
Grade 2–4	203 (37.0)	273 (50.9)	<.001
Hypophosphatemia	76 (13.8)	80 (15.0)	.665
Pancreatic amylase	48 (8.7)	53 (9.9)	.532
Hyperglycemia (fasted)	42 (7.7)	30 (5.6)	.182
ALT	38 (6.9)	59 (11.0)	.019
AST	36 (6.6)	59 (11.0)	.010
Hyperbilirubinemia (indirect)[d]	27 (4.9)	5 (0.9)	<.001
LDL, derived (fasted)	35 (6.4)	91 (17.0)	<.001
Total cholesterol (fasted)	34 (6.2)	109 (20.4)	<.001

Note: ALT = alanine aminotransferase; AST = aspartate aminotransferase; EFV = efavirenz; FTC = emtricitabine; LDL = low-density lipoprotein; RPV = rilpivirine; TDF = tenofovir disoproxil fumarate.

[a]*P* values are based on the Fisher Exact test for non-missing categorical variables.

[b]Includes all available safety data.

[c]Well-described AEs known to be associated with current non-nucleoside reverse transcriptase inhibitors.

[d]Of these 32 subjects with bilirubin abnormalities, 4 in the RPV+FTC/TDF group (0.7%) and 3 in the EFV+FTC/TDF group (0.6%) also had elevated direct bilirubin (*P* = .0723).

Source: Nelson et al., 2011.[12]

The proportion of subjects with laboratory abnormalities was significantly lower in the RPV+FTC/TDF group, including grade 2–4 laboratory abnormalities (37% RPV group and 51% EFV group; $P < .001$) (**Table 5**). The most common grade 2–4 laboratory abnormalities occurring in >10% of subjects were elevated total cholesterol and low-density lipoprotein (LDL) cholesterol (20% and 17%, respectively, in the EFV group), hypophosphatemia (14% RPV group and 15% EFV group), and transaminase elevations (11% EFV group) (**Table 5**).

There were no discontinuations due to renal AEs. There was minimal change in mean serum creatinine in both groups: 0.12 mg/dL (RPV) and 0.05 mg/dL (EFV). Mean change from baseline to week 96 in estimated glomerular filtration rate (eGFR) was –14.0 mL/min/1.73 m^2 (95% CI, –15.33 to –12.71) in the RPV+FTC/TDF group and –5.3 mL/min/1.73 m^2 (95% CI, –6.76 to –3.84) in the EFV+FTC/TDF group. Grade 2–4 serum creatinine elevations were rare in both groups (1.1% RPV group and 0.7% EFV group). Of graded serum creatinine

elevations, grade 1 elevations occurred in significantly more subjects receiving RPV+FTC/TDF (35 of 41 subjects) versus EFV+FTC (4 of 8 subjects) (P = .04). One subject in the RPV+FTC/TDF group experienced grade 3 serum creatinine elevation, and 1 subject in the EFV+FTC/TDF subject had grade 4 serum creatinine elevation. There were no discontinuations due to renal AEs. There was minimal change in mean serum creatinine in both groups: 0.12 mg/dL (RPV) and 0.05 mg/dL (EFV).

Grade 3–4 elevations in transaminases occurred in 1.5% of subjects receiving RPV+FTC/TDF and in 2.7% of those receiving EFV+FTC/TDF. Grade 2–4 hyperbilirubinemia occurred in 32 subjects across both treatment groups (27 RPV and 5 EFV; P < .001). Of those subjects in the RPV+FTC/TDF group, 27 had elevated indirect bilirubin and 4 also had elevated direct bilirubin (vs 5 and 3 subjects, respectively, EFV) (**Table 5**). There were no reported cases of jaundice or scleral icterus in either group. Low and similar proportions of subjects in both treatment groups discontinued due to hepatic laboratory abnormalities (0.7% in the RPV group and 1.3% in the EFV group).

Subjects receiving RPV+FTC/TDF experienced significantly fewer treatment-emergent lipid abnormalities compared with subjects receiving EFV+FTC/TDF over 96 weeks. More subjects receiving RPV+FTC/TDF had desirable levels of total cholesterol (<200 mg/dL) and LDL cholesterol (<130 mg/dL) at week 96 (P < .002 for grade 0 of both parameters) (**Figure 1**). Mean changes from baseline in total cholesterol, LDL cholesterol, high-density lipoprotein (HDL) cholesterol, and triglycerides were significantly greater in the EFV+FTC/TDF group than in the RPV+FTC/TDF group (P < .001 for all comparisons, Wilcoxon rank-sum test). There was no significant difference between the arms in total cholesterol/HDL cholesterol ratio at week 96. Significantly fewer subjects receiving RPV+FTC/TDF utilized lipid-lowering therapies during the study (3% RPV+FTC/TDF vs 6% EFV+FTC/TDF; P = .025).

QT interval corrected according to Fridericia's formula (QTcF) increased over time up to week 96 for both the RPV+FTC/TDF and EFV+FTC/TDF groups, with no relevant difference between treatment groups.

DEXA scans were obtained at study baseline, week 48, and week 96 (or at the time of withdrawal for subjects who discontinued after 64 weeks) to evaluate changes in BMD and body fat distribution in a subset of subjects.[16] At both weeks 48 and 96, median change from baseline in total body BMD was similar between RPV+FTC/TDF and EFV+FTC/TDF (week 48: –1.4% and –1.5%; week 96: –1.7% and –1.8%, respectively). Median increase from baseline in limb fat at week 96 was higher in the RPV+FTC/TDF group (+1,032 g; interquartile range [IQR], 153–2,125 g) than in the EFV+FTC/TDF group (+772 g; –IQR, 174–2,093 g), but this difference was not statistically significant

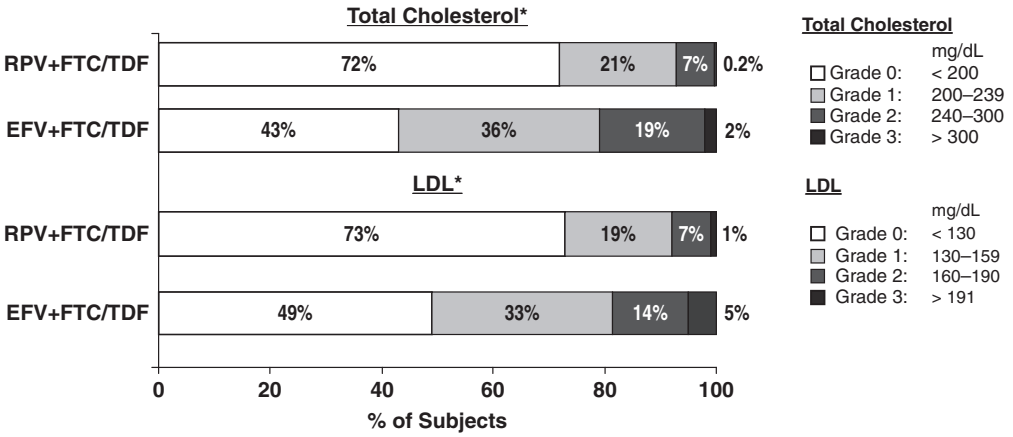

Figure 1. Changes through 96 weeks in total cholesterol and low-density lipoprotein (LDL) cholesterol for pooled FTC/TDF subset in ECHO/THRIVE studies. EFV = efavirenz; FTC = emtricitabine; RPV = rilpivirine; TDF = tenofovir disoproxil fumarate. *P value <.002 for all comparisons by individual grades (RPV+FTC/TDF vs EFV+FTC/TDF) using the the Fisher exact test. Source: Nelson et al., 2011.[12]

($P \geq .072$). Within-group limb-fat change from baseline to weeks 48 and 96 were statistically significant in both groups ($P < .0001$, Wilcoxon signed-rank test).

DISCUSSION

Rilpivirine coadministered with FTC/TDF showed sustained overall efficacy that was noninferior to EFV+FTC/TDF over 96 weeks by ITT-TLOVR and ITT-snapshot analyses (77% response rate at week 96 in both groups for both analyses). These results are consistent with those attained at 48 weeks (83% and 82% with virologic response, respectively, based on ITT-TLOVR).[17] To evaluate factors associated with achieving virologic response, pooled data for the FTC/TDF subset have been analyzed using multivariate analysis, which excluded subjects who discontinued for reasons other than virologic failure. Week 48 data were used in the multivariate analysis, because week 96 plasma concentrations of RPV were not available to include in the model. The analysis indicated that higher treatment adherence (>95%), higher exposure to the drug, and lower baseline viral load (≤100,000 copies/mL) predicted increased likelihood of achieving virologic response at week 48 in both study arms; in the RPV+FTC/TDF arm, baseline CD4 was also a predictor of response.[12] Similar results were seen with an analysis on the full pooled week 48 dataset from the ECHO and THRIVE studies.[18]

The week 96 results within the pooled FTC/TDF subset were consistent with the multivariate analysis of week 48 results; 87% of subjects in both groups with baseline HIV-1 RNA ≤ 100,000 copies/mL and adherence >95% achieved virologic response by week 96 (**Table 3**).

There was no significant difference between groups at week 96 for virologic response rates (ITT-TLOVR) and mean CD4 cell counts. There were more virologic failures with RPV+FTC/TDF through week 96, but in year 2 the proportion of subjects with virologic failure was low in both groups (2.7% RPV and 2.6% EFV) (**Table 4**). Whereas K103N was the most frequently occurring resistance-associated mutation with EFV+FTC/TDF, the mutations E138K and M184I were the most common mutations observed together with RPV+FTC/TDF. The M184I mutation alone likely did not impact RPV susceptibility in vitro. The higher frequency of E138K and M184I among virologic failures in the RPV+FTC/TDF group is potentially due to in vitro reduced susceptibility of the single mutants to RPV and FTC and the enhanced resistance to RPV for the double mutant at the cost of viral fitness.[19] However, 2 other groups have published viral fitness data that suggest a fitness compensation for the double mutant versus the single mutant.[20,21]

RPV plus FTC/TDF was associated with a lower incidence of treatment-related grade 2–4 overall AEs, including dizziness, abnormal dreams/nightmares, rash leading to discontinuation, and lipid abnormalities. One of the chief concerns with EFV-containing regimens is central nervous system toxicity, which is generally described as occurring soon after initiation of treatment and resolving after 2 to 4 weeks.[22] However, recent publications suggest that these toxicities may persist well beyond the first months of treatment.[23–27] The majority of the treatment-related neurological or psychiatric AEs occurred during the first 4 weeks of the ECHO and THRIVE studies[27]; from week 4 to week 12, there was little difference between the groups receiving RPV versus EFV in the incidence of new treatment-related neurological or psychiatric AEs.[27] For treatment-related neurologic AEs, the incidence during the first 12 weeks was 16% and 36% in subjects receiving RPV and EFV, respectively.[27] For treatment-related psychiatric AEs, the incidence during the first 12 weeks was 12% and 21% in subjects receiving RPV and EFV, respectively.[27] The early emergence and ongoing prevalence of neuropsychiatric AEs in the group receiving EFV is consistent with other data indicating discontinuation of EFV-containing regimens due to these AEs can occur months to years after their initial development.[26]

The observed changes in serum creatinine with RPV were likely related to changes in tubular secretion of creatinine. RPV inhibits organic cation transporter 2 (OCT2), a tubular secretion transporter, and results in early small serum creatinine elevations that plateau thereafter. In the THRIVE study, cystatin C, a more specific marker for renal function that is not affected by changes in tubular secretion of creatinine, was used to evaluate change in renal function. An increase in cystatin C clearance (GFR_{cyst}, Hoek formula)[9] was observed through week 24 despite an increase in serum creatinine, which supports the conclusion that the observed changes in serum creatinine with RPV

were likely related to changes in tubular secretion of creatinine.[12]

One of the potential limitations of the present analysis of 96-week data was that subjects included in the analyses were a subset from the ECHO and THRIVE studies; however this was a large sample with more than 1,000 subjects. Another limitation was that subjects in the pooled FTC/TDF subset with very high baseline viral load (>500,000 copies/mL) could not be evaluated critically as a subset because there were too few subjects in that category.

Adherence significantly impacted the virologic failure rates (ITT-TLOVR analysis) at week 96 for both drugs. Virologic failure rates were higher with RPV+FTC/TDF compared to EFV+ FTC/TDF group regardless of adherence category (>95% or ≤95%). However, in subjects with lower baseline HIV-1 RNA (≤100,000 copies/mL) and good adherence (>95%), virologic failure rates were similar and low (3.7% in the RPV+FTC/TDF group and 2.9% in the EFV+FTC/TDF group). The impact of adherence in the study may differ with adherence obtained when these drug combinations are taken as once-daily STRs (Atripla and Complera), due to differences in pill burden when the components are coadministered individually. In addition, due to the double-blind, double-dummy design of the ECHO and THRIVE studies, the pill burden was even greater and the multiple-pill dosing schedule required by the study protocols was more complex than that required with an STR.

Additional data are being collected on the efficacy, safety, and tolerability of RPV versus EFV in combination with FTC/TDF in an ongoing phase 3b, randomized, open-label study in which approximately 700 ARV treatment–naïve adult subjects are randomized to receive either Atripla or FTC/RPV/TDF as an STR for 96 weeks (NCT01309243, EUDRACT 2010–024007–27).

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