Rilpivirine vs. efavirenz-based single-tablet regimens in treatment-naive adults: week 96 efficacy and safety from a randomized phase 3b study

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Objectives: To compare efficacy, safety, tolerability, and patient-reported outcomes between two single-tablet regimens, rilpivirine/emtricitabine/tenofovir disoproxil fumarate (RPV/FTC/TDF) and efavirenz/emtricitabine/tenofovir disoproxil fumarate (EFV/FTC/TDF), in HIV-1-infected, treatment-naive adults.

Design: This was a phase 3b, 96-week, randomized, open-label, international, noninferiority trial.

Methods: A total of 799 participants were randomized (1 : 1) to receive RPV/FTC/TDF or EFV/FTC/TDF. The primary efficacy endpoint evaluated proportions of participants with HIV-1 RNA less than 50 copies/ml using the Snapshot algorithm. Additional assessments included $CD4^+$ cell counts, genotypic/phenotypic resistance, adverse events, patient-reported outcomes, and quality of life questionnaires.

Results: At week 96, trial completion rates were 80.2% (316/394; RPV/FTC/TDF) and 74.0% (290/392; EFV/FTC/TDF). Overall, RPV/FTC/TDF was noninferior to EFV/FTC/TDF [HIV-1 RNA <50 copies/ml: 77.9 vs. 72.4%, respectively; difference −5.5; 95%CI (−0.6, 11.5); $P = 0.076$]. RPV/FTC/TDF was significantly more efficacious compared with EFV/FTC/TDF in participants with baseline HIV-1 RNA equal to or less than 100 000 copies/ml (78.8 vs. 71.2%; $P = 0.046$) and in those with $CD4^+$ cell count greater than 200 cells/μl (80.6 vs. 73.0%; $P = 0.018$). There was no significant between-group difference in the $CD4^+$ cell count increase (278 ± 189 vs. 259 ± 191 cells/μl; $P = 0.17$). Few participants developed resistance after week 48 (1.0% RPV/FTC/TDF; 0.3% EFV/FTC/TDF). Compared with EFV/FTC/TDF, RPV/FTC/TDF was associated with fewer adverse event-related discontinuations (3.0 vs. 11.0%; $P<0.001$), significantly fewer adverse events due to central nervous system issues and rash, greater improvements in patient-reported symptoms, and significant improvements in the SF-12v2 quality of life questionnaire mental health composite score ($P = 0.014$).

Conclusion: In treatment-naive, HIV-1-infected participants, 96-week RPV/FTC/TDF treatment demonstrated noninferior efficacy and better tolerability than EFV/FTC/TDF.

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Introduction

In HIV-1-positive individuals, antiretroviral treatment with single-tablet regimens (STRs) has been shown to improve virologic suppression, treatment adherence, quality of life (QoL), and treatment satisfaction, and to reduce the rate of virologic failure, compared with multi-tablet regimens [1–3]. In 2011, the once-daily STR comprising 25 mg rilpivirine (RPV), 200 mg emtricitabine (FTC), and 300 mg tenofovir disoproxil fumarate (TDF; RPV/FTC/TDF; Complera in United States, Eviplera in European Union) was approved to treat HIV-1 infections in treatment-naive adults in the United States and European Union [4,5]. In 2013, the indication was expanded to include virologically suppressed patients without resistance to regimen components who wish to replace their current, stable regimen. For treatment-naive patients, RPV/FTC/TDF is indicated for those with HIV-1 RNA load equal to or less than 100 000 copies/ml at therapy initiation.

Initial approval of RPV/FTC/TDF was based on two double-blind, double-dummy studies (ECHO and THRIVE) that demonstrated noninferior efficacy, improved tolerability, and fewer adverse event-related discontinuations following treatment with RPV vs. efavirenz (EFV) when administered in combination with two nucleoside or nucleotide reverse transcriptase inhibitors (N[t]RTIs) [6–9].

The single-tablet regimen trial (STaR) was a 96-week, open-label study designed to directly compare the safety and efficacy of the two STRs, RPV/FTC/TDF and co-formulated EFV, emtricitabine (FTC), and tenofovir disoproxil fumarate (EFV/FTC/TDF; Atripla) in HIV-1-infected treatment-naive adults. At the week 48 primary endpoint, RPV/FTC/TDF demonstrated noninferior efficacy and a low rate of resistance development in individuals with less than 100 000 copies/ml [10]. Additionally, RPV/FTC/TDF showed better tolerability [11] and was associated with fewer patient-reported neuropsychiatric and gastrointestinal symptoms compared with EFV/FTC/TDF (Gilead data on file; manuscript in preparation). Thus, this STR may be a suitable long-term therapy for treatment-naive, HIV-positive participants.

In this manuscript, we report the efficacy, safety, resistance, and patient-reported outcomes (PROs) from the STaR trial collected through week 96.

Methods

Study design and procedures

Design of this study has been reported in more detail previously [11]. In brief, this phase 3b, 96-week, international, open-label study (GS-US-264-0110, NCT01309243, EUDRACT 2010-024007-27) compared the safety and efficacy of once-daily single-tablet regimens of coformulated 25 mg RPV, 200 mg FTC, and 300 mg TDF (taken with a meal) and coformulated 600 mg EFV, 200 mg FTC, and 300 mg TDF (taken on an empty stomach, preferably at bedtime) in HIV-1-infected, antiretroviral treatment-naive adults (HIV-1 RNA $\geq$2500 copies/ml) without resistance to any study drug component and who lacked the RPV mutations K101E/P, E138A/G/K/Q/R, Y181C/I/V, and H221Y. The participants were randomized by HIV-1 RNA level strata at screening ($\leq$100 000 and >100 000 copies/ml). HIV-1 RNA levels were assessed using COBAS AMPLICOR Monitor Version 1.5 (Roche Diagnostics, Basel, Switzerland).

Efficacy parameters

The primary efficacy endpoint was the proportion of participants with HIV-1 RNA less than 50 copies/ml determined using Snapshot analysis [12] at week 48. Secondary objectives included efficacy using Snapshot and changes from baseline in $CD4^+$ cell count at week 96. Additional analyses included efficacy stratified by HIV-1 RNA ($\leq$100 000 or >100 000 copies/ml) or $CD4^+$ cell count ($\leq$200 or >200 cells/μl) at screening and efficacy by time to loss of virologic response (TLOVR) analysis [13] with baseline HIV-1 RNA levels included in the model ($\leq$100 000 copies/ml vs. >100 000 copies/ml). Patient reported outcomes (PROs) included the HIV symptom index questionnaire (HIV SIQ) [14], the HIV treatment satisfaction questionnaire (HIVTSQ) [15,16], and a QoL assessment, performed by means of SF-12v2 [17]. Treatment adherence was assessed by means of pill count and by participant self-report, assessed through an abbreviated version of the medication adherence self-report inventory with visual analogue scale [18].

Drug resistance

At screening, protease/reverse transcriptase genotyping was performed using the GeneSeq assay (Monogram Biosciences, South San Francisco, California, USA). The postbaseline resistance analysis population (RAP) included isolates from individuals with HIV-1 RNA at least 400 copies/ml and either suboptimal virologic response (less than 1 $\log_{10}$ decrease in HIV-1 RNA from baseline at week 8 confirmed at the subsequent visit)

or confirmed virologic rebound (HIV-1 RNA $\geq$50 copies/ml at two consecutive visits after reaching HIV-1 RNA <50 copies/ml or $\geq$1 $\log_{10}$ increase in HIV-1 RNA from nadir at two consecutive visits). Isolates from individuals who were on study drugs, had not been analyzed previously, and had HIV-1 RNA at least 400 copies/ml at weeks 48 or 96 or their last study visit were also analyzed for resistance development. Postbaseline genotypic and phenotypic testing was done for protease transcriptase and reverse transcriptase using the PhenoSense GT assay (Monogram Biosciences).

Safety evaluation

Data on treatment-emergent adverse events (TEAEs) and laboratory findings were collected up to 30 days after the last dose of study drug. Specific TEAEs of importance were based on adverse effects described in at least one label for a RPV- or EFV-containing product, focusing on nervous system disorders, psychiatric disorders, and rash (Supplemental Table 1, http://links.lww.com/QAD/A794). Creatinine clearance (Cockcroft-Gault formula using observed body weight) and the level of lipids in plasma (triglycerides and the total; HDL, high-density lipoprotein; and LDL, low-density lipoprotein cholesterol – collected in the fasted state) were also monitored.

Statistical analysis

Efficacy and safety analyses were similar to those used in the week 48 analysis [11] and included participants who were randomized and received at least one dose of study medication (Full Analysis Set and Safety Populations, respectively). The proportions of participants with virologic success and failure were analyzed using a Cochran–Mantel–Haenszel test, stratified by baseline HIV-1 RNA levels ($\leq$100 000 vs. >100 000 copies/ml). For assessments based on the Snapshot algorithm, RPV/FTC/TDF was considered noninferior to EFV/FTC/TDF if the lower bound of the 95% confidence interval (CI) of the between-treatment difference (RPV/FTC/TDF–EFV/FTC/TDF) was greater than −12%. If noninferiority was demonstrated, and if the lower bound of the 95% CI of the between-treatment difference was more than 0 (consistent with $P<0.05$ at $\alpha=0.05$, two-sided), then RPV/FTC/TDF was deemed superior to EFV/FTC/TDF. Changes from baseline in $CD4^+$ cell counts were compared using an analysis of variance (ANOVA), with treatment and baseline HIV-1 RNA levels ($\leq$100 000 or >100 000 copies/ml) as fixed effects. In this manuscript, with the exception of the HIV snapshot results, missing data were excluded from the analyses. Between-treatment comparisons for incidence of TEAEs of importance were performed using the Fisher's exact test. Changes from baseline in fasting lipid parameters were analyzed with ANOVA, with treatment as a fixed effect in the model. HIV SIQ changes from baseline and between-treatment differences were evaluated using the McNemar test and the Cochran–Mantel–Haenszel test with modified ridit scores, respectively; changes from baseline and between-treatment differences for SF-12v2 were compared using the Wilcoxon signed-rank test and the χ^2-square test, respectively. For HIVTSQ, total treatment satisfaction scores were compared using an ANOVA with treatment as a fixed effect.

Results

Baseline characteristics

Of the 799 randomized participants, 786 received at least one dose of study drug (the Full Analysis Set and Safety Population were the same). Week 96 completion rates were 80.2% (316/394; RPV/FTC/TDF) and 74.0% (290/392; EFV/FTC/TDF). Baseline

Table 1. Virologic outcomes at week 96, Snapshot analysis (Full Analysis Set), *n* (%).

	RPV/FTC/TDF, $N=394$		EFV/FTC/TDF, $N=392$
Virologic success			
(HIV-1 RNA <50 copies/ml)	307 (77.9)		284 (72.4)
Difference (95%CI)		5.5 (−0.6,11.5)	
P-value		0.076	
Virologic failure	37 (9.4)		23 (5.9)
Difference (95%CI)		3.7 (−0.1,7.4)	
P-value		0.052	
HIV-1 RNA $\geq$50 copies/ml	6 (1.5)		6 (1.5)
Treatment discontinuation due to lack of efficacy	16 (4.1)		4 (1.0)
Treatment discontinuation due to other reasons[a] and last available HIV-1 RNA $\geq$50 copies/ml	15 (3.8)		13 (3.3)
No data in the study window	50 (12.7)		85 (21.7)
Treatment discontinuation due to adverse event or death	12 (3.0)		42 (10.7)
Treatment discontinuation due to other reasons[†] and last available HIV-1 RNA <50 copies/ml	31 (7.9)		37 (9.4)
Missing data during study window while receiving study drug	7 (1.8)		6 (1.5)

P-values refer to the superiority comparisons (Cochran–Mantel–Haenszel test), conducted because between-treatment differences fulfilled the noninferiority criterion of the lower bound of the 95% CI being greater than −12%. CI, confidence interval; EFV/FTC/TDF, efavirenz/emtricitabine/tenofovir disoproxil fumarate; RPV/FTC/TDF, rilpivirine/emtricitabine/tenofovir disoproxil fumarate.
[a]Other reasons may include loss to follow-up, consent withdrawal, nonadherence, protocol violation and other reasons.

Table 2. Participants achieving HIV-1 RNA less than 50 copies/ml by baseline HIV-1 RNA at week 96 by Snapshot analysis, stratified by HIV-1 RNA and $CD4^+$ cell count (Full Analysis Set), *n* (%).

Stratification	HIV-1 RNA <50 copies/ml		
	RPV/FTC/TDF ($N = 394$)		EFV/FTC/TDF ($n = 392$)
By baseline HIV-1 RNA copies/ml			
≤100 000, *n*	260		250
n, %	205 (78.8)		178 (71.2)
Difference (95%CI)		7.6 (0.2, 15.1)	
P-value		0.046	
>100 000, *n*	134		142
n, %	102 (76.1)		106 (74.6)
Difference (95%CI)		1.5 (−8.7,11.6)	
P-value		0.78	
>100 000 to ≤500 000, *n*	98		117
n, %	80 (81.6)		88 (75.2)
Difference (95%CI)		6.4 (−4.5, 17.4)	
P-value		0.26	
>500 000, *n*	36		25
n, %	22 (61.1)		18 (72.0)
Difference (95%CI)		−10.9 (−34.6, 12.8)	
P-value		0.38	
By baseline $CD4^+$ cell count (cells/μl)			
≤200, *n*	53		51
n, %	32 (60.4)		35 (68.6)
Difference (95%CI)		−8.0 (−26.7,10.7)	
P-value		0.40	
>200, *n*	341		341
n, %	275 (80.6)		249 (73.0)
Difference (95%CI)		7.7 (1.3,14.0)	
P-value		0.018	

P-values refer to the superiority comparisons (Cochran–Mantel–Haenszel test), conducted because between-treatment differences fulfilled the noninferiority criterion of the lower bound of the 95% CI being greater than −12%. CI, confidence interval; EFV/FTC/TDF, efavirenz/emtricitabine/tenofovir disoproxil fumarate; RPV/FTC/TDF, rilpivirine/emtricitabine/tenofovir disoproxil fumarate.

demographic and clinical characteristics, reported previously, were similar between the two groups [12]. Briefly, the overall mean ± SD (standard deviation) age was 37 ± 11 years, and the study population predominantly consisted of male [92.9% (730/786)] and white participants [67.2% (528/786)]. The mean ± SD HIV-1 RNA was 4.8 ± 0.6 $\log_{10}$ copies/ml. A total of 510 (64.9%) participants had HIV-1 RNA or less than 100 000 copies/ml, 215 (27.4%) had more than 100 000 and/or less than 500 000 copies/ml, and 61 (7.8%) had more than 500 000 copies/ml. The overall mean ± SD $CD4^+$ cell count was 391 ± 183 cells/μl.

Efficacy

At week 96, trial completion rates were 80.2% (316/394; RPV/FTC/TDF) and 74.0% (290/392; EFV/FTC/TDF) and RPV/FTC/TDF was noninferior to EFV/FTC/TDF [difference 5.5%, 95% (CI −0.6 to 11.5%); superiority test *P*-value: 0.076; Table 1]. For comparison, those rates at week 48 were 85.8 and 81.6%, respectively [difference 4.1%, 95% CI (−1.1 to 9.2%); superiority test *P*-value: 0.12] [11].

Overall virologic failure rates via Snapshot analysis at week 96 (9.4 vs. 5.9%: Table 1) were similar to those observed at week 48 [RPV/FTC/TDF: 8.1% (32/394); EFV/FTC/TDF: 5.1% (20/392); difference 3.2%, 95% (CI −0.3 to 6.7%); superiority test *P*-value: 0.071]. Participants in the RPV/FTC/TDF group that had HIV-1 RNA less than 100 000 copies/ml demonstrated a significant difference in virologic success vs. EFV/FTC/TDF (78.8 vs. 71.2%, superiority test *P*-value: 0.046; Table 2). In addition, an analysis based on the baseline $CD4^+$ cell count strata (equal to or less than 200 cells/μl vs. >200 cells/μl) showed significant differences in virologic success in those with more than 200 cells/μl [80.6% (RPV/FTC/TDV) vs. 73.0% (EFV/FTC/TDF), superiority test *P*-value: 0.018; Table 2]. Discontinuation rates due to lack of efficacy were 4.1% (16/394) and 1.0% (4/392), respectively. Of the 16 study participants in the RPV/FTC/TDF arm who discontinued due to lack of efficacy, five had baseline HIV-1 RNA greater than 100 000–500 000 copies/ml and eight had baseline HIV-1 RNA greater than 500 000 copies/ml. In the EFV/FTC/TDF, of the four participants who discontinued due to lack of efficacy, three had baseline HIV-1 RNA equal to or less than 100 000 copies/ml and one had baseline HIV-1 RNA greater than 500 000 copies/ml. Adherence was similar between the two groups as assessed via pill count (RPV/FTC/TDF, 96.8%; EFV/FTC/TDF, 96.4%) or M-MASRI (44% in each group reported never missing a dose when asked at week 96).

Visit-by-visit data suggests a maximal rate of virologic success after 24 weeks of treatment in both groups

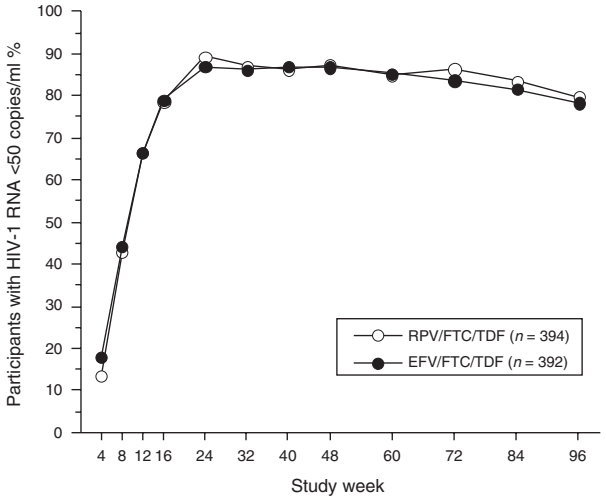

Fig. 1. Virologic success* by visit (missing data equals failure, Full Analysis Set). *Virologic success was defined as HIV-1 RNA less than 50 copies/ml. EFV/FTC/TDF, efavirenz/emtricitabine/tenofovir disoproxil fumarate; RPV/FTC/TDF, rilpivirine/emtricitabine/tenofovir disoproxil fumarate.

(>85%), with a slow decline over the subsequent 72 weeks and no between-group differences (Fig. 1).

The Snapshot analysis of virologic failure demonstrated a significant difference between treatment groups in participants who had HIV-1 RNA greater than 500 000 copies/ml [RPV/FTC/TDF: 33.3% (12/36); EFV/FTC/TDF: 8.0% (2/25); difference 25.3%, 95% CI (6.6–44.0%); superiority test *P*-value: 0.022] and those with $CD4^+$ cell count or less than 200 cells/μl [RPV/FTC/TDF: 30.2% (16/53); EFV/FTC/TDF: 9.8% (5/51); difference 20.5%, 95% CI (5.136.0%); superiority test *P*-value: 0.010].

The TLOVR analysis demonstrated that the RPV/FTC/TDF group had a significantly higher proportion of participants who achieved and maintained virologic success through week 96 than the EFV/FTC/TDF group [79.4 vs. 73.0%; difference 6.6%, 95% CI (0.7–12.6%; $P = 0.030$]. In both groups, the mean $CD4^+$ cell counts increased markedly from baseline to week 96 (RPV/FTC/TDF: 278 ± 189 cells/μl; EFV/FTC/TDF: 259 ± 191 cells/μl), but without a significant between-group difference ($P = 0.17$). This outcome is similar to the one observed at week 48, where an increase in $CD4^+$ cell count in both groups was also observed (RPV/FTC/TDF, 200 ± 159 cells/μl; EFV/FTC/TDF, 191 ± 144 cells/μl; $P = 0.34$).

Resistance development

As reported in more detail previously [19], the RAP through week 96 included 24 of 394 participants (6.1%) receiving RPV/FTC/TDF and nine of 392 participants (2.3%) receiving EFV/FTC/TDF (see Supplemental Table 3, http://links.lww.com/QAD/A794). In the RPV/FTC/TDF arm, 21 of 394 participants (5.3%; 88% of RAP) developed non-nucleoside reverse-transcriptase inhibitors (NNRTI) and/or NRTI resistance mutations and 20 of 21 isolates had both NNRTI and NRTI genotypic and/or phenotypic resistance. In the EFV/FTC/TDF arm, isolates from four of 392 participants (1.0%; 44% of RAP) developed NNRTI and/or NRTI resistance mutations. Few participants developed resistance after week 48 (1.0% RPV/FTC/TDF; 0.3% EFV/FTC/TDF). When stratified by baseline HIV-1 RNA equal to or less than or greater than 100 000 copies/ml, nine of 260 (3.5%) vs. 12 of 134 (9.0%) RPV/FTC/TDF-treated participants and 3 of 250 (1.2%) vs. one of 142 (0.7%) EFV/FTC/TDF-treated participants developed resistant isolates, respectively.

Safety and tolerability

The two treatment groups had similar proportions of participants with at least one TEAE (RPV/FTC/TDF, 91.9%; EFV/FTC/TDF, 93.9%) or at least one treatment-emergent severe adverse event (TESAE; 9.1 vs. 12.2%). Through week 96, 10.2% of RPV/FTC/TDF-treated and 16.6% of EFV/FTC/TDF-treated participants experienced a grade 3–4 TEAE, with 0.8 and 2.0% participants, respectively, reporting a life-threatening (grade 4) event and 2.3 and 5.6% experiencing a grade 3–4 TEAE deemed related to study drug. For TEAEs of importance, the rates of nervous system disorders, psychiatric disorders, and rash events were each significantly lower in the RPV/FTC/TDF group, compared with the EFV/FTC/TDF group (Table 3). See Supplemental Table 2, http://links.lww.com/QAD/A794, for the list of most frequently reported TEAEs by system organ class and preferred term.

Table 3. Most frequently reported TEAEs of importance[a] (any grade, >5% of participants in either group, safety population), *n* (%).

System organ class	RPV/FTC/TDF	EFV/FTC/TDF	*P*-value
Preferred term	*N* = 394	*N* = 392	
Nervous system events	107 (27.2)	186 (47.4)	<0.001[b]
Dizziness	27 (6.9)	90 (23.0)	
Headache	56 (14.2)	62 (15.8)	
Somnolence	10 (2.5)	30 (7.7)	
Psychiatric events	111 (28.2)	192 (49.0)	<0.001[b]
Abnormal dreams	23 (5.8)	101 (25.8)	
Anxiety	28 (7.1)	37 (9.4)	
Depression	36 (9.1)	47 (12.0)	
Insomnia	45 (11.4)	59 (15.1)	
Rash events	62 (15.7)	95 (24.2)	0.003[b]
Rash[c]	31 (7.9)	52 (13.3)	

EFV/FTC/TDF indicates efavirenz/emtricitabine/tenofovir disoproxil fumarate; RPV/FTC/TDF, rilpivirine/emtricitabine/tenofovir disoproxil fumarate; TEAE, treatment-emergent adverse event. [a]Full list of items is provided in Supplemental Table 1, http://links.lww.com/QAD/A794.
[b]Statistical comparison refers to prespecified TEAE subsets within each system organ class.
[c]Preferred term rash was used when a more specific type of rash was not indicated by the investigator.

Table 4. Most frequently reported TEAEs leading to permanent study drug discontinuation by system organ class and time of discontinuation[a] (Safety Population), *n* (%).

System organ class	RPV/FTC/TDF ($N=394$) Weeks				EFV/FTC/TDF ($N=392$) Weeks			
	1–4	5–48	49–96	Total	1–4	5–48	49–96	Total
Psychiatric disorders	0	1	0	1 (0.3)	5	11	8	24 (6.1)
Nervous system disorders	0	2	1	3 (0.8)	5	2	1	8 (2.0)
Skin and subcutaneous tissue disorders (e.g. rash)	0	0	0	0	7	0	0	7 (1.8)
Clinical laboratory investigations	0	2	2	4 (1.0)	0	2	0	2 (0.5)
General disorders (e.g. fatigue)	0	0	0	0	3	1	1	5 (1.3)
Gastrointestinal disorders	0	1	0	1 (0.3)	1	2	0	3 (0.8)

EFV/FTC/TDF, efavirenz/emtricitabine/tenofovir disoproxil fumarate; RPV/FTC/TDF, rilpivirine/emtricitabine/tenofovir disoproxil fumarate; TEAE, treatment-emergent adverse event. [a]Permanent study drug discontinuation could be due to greater than 1 TEAE; system organ classes with at least four TEAEs overall are listed.

Through week 96, significantly fewer participants receiving RPV/FTC/TDF (3.0%) permanently discontinued study drug due to a TEAE, compared with EFV/FTC/TDF (11.0%; $P<0.001$). In the EFV/FTC/TDF group, the most frequent TEAE leading to discontinuation was a psychiatric event; in the RPV/FTC/TDF group, no single TEAE led to permanent discontinuation in more than one participant (Table 4). In both groups, permanent study drug discontinuations were more frequent during weeks 5–48 than before or after that period (Table 4). All discontinuations due to skin and subcutaneous tissue disorders (i.e. rash) were recorded during the first 4 weeks of treatment, all occurring in the EFV/FTC/TDF group (Table 4).

Two participants died during the study (one due to suicide, one due to septic shock), both in the EFV/FTC/TDF group; neither death was deemed related to study drug. By week 96, grade 3 treatment-emergent laboratory anomalies (TELAs) were experienced by 13.2 and 12.9% of RPV/FTC/TDF- and EFV/FTC/TDF-treated participants, respectively; rates of grade 4 TELAs were 8.7 and 7.2%. Fewer than 5% of participants in either group experienced a grade 3 or grade 4 TELA for any individual parameter, except for creatine kinase (RPV/FTC/TDF: 6.9%; EFV/FTC/TDF: 7.5%).

The median changes from baseline to week 96 in creatinine clearance were −5.2 ml/min in the RPV/FTC/TDF group and +4.3 ml/min in the EFV/FTC/TDF group. Three individuals, all of whom were black, permanently discontinued study drug due to renal disorders: two of them, one in each study arm, discontinued during the first 48 weeks due to renal failure, which resolved after stopping the treatment (further details in Cohen *et al.* [11]); the third, in the EFV/FTC/TDF group, discontinued treatment during week 74 due to proteinuria and hypoproteinemia (see Supplemental Data for details, http://links.lww.com/QAD/A794). At week 96, proteinuria was observed in 1.5 and 3.0% RPV/FTC/TDF- and EFV/FTC/TDF-treated participants, respectively. Laboratory results did not reveal patterns that would indicate proximal renal tubulopathy in either group.

At week 96, compared with the RPV/FTC/TDF group, the EFV/FTC/TDF group had a significantly greater increase in mean ± SD total cholesterol (25 ± 32 mg/dl EFV/FTC/TDF vs. 3 ± 33 mg/dl RPV/FTC/TDF; $P<0.001$), LDL cholesterol (15 ± 28 vs. 2 ± 27 mg/dl; $P<0.001$), and HDL cholesterol (9 ± 11 vs. 2 ± 10 mg/dl; $P<0.001$). Changes in triglyceride levels were not significantly different between the groups (8 ± 111 mg/dl RPV/FTC/TDF vs. −5 ± 69 mg/dl EFV/FTC/TDF; $P=0.090$). The mean ± SD change in total/HDL cholesterol ratio in both groups was −0.2 ± 1.1.

At week 96, participants in the RPV/FTC/TDF group reported a significant reduction in occurrence of 18 out of 20 HIV SIQ symptoms vs. baseline ($P\leq0.039$), and participants in the EFV/FTC/TDF group reported a significant reduction in seven out of 20 symptoms ($P\leq0.033$; see Supplemental Figure 1, http://links.lww.com/QAD/A794). Significant between-group differences in the distribution of symptom occurrence vs. baseline (no change, gain, or loss) were found for eight symptoms (fatigue; sleep difficulties; feeling sad or depressed; problems with having sex; pain, numbness or tingling in hands or feet; hair loss or changes; fevers, chills, or sweats; cough or trouble catching breath), all favoring RPV/FTC/TDF (see Supplemental Figure 1, http://links.lww.com/QAD/A794).

Overall satisfaction with treatment at week 96 was high in both groups, as indicated by mean HIVTSQ scores at least 57. For all eight subdomains of the SF-12v2, a QoL measure, mean scores at week 96 were similar between treatment groups (data not shown). The between-group difference in the median change from baseline at week 96 for the physical health composite score was not significant [0.3 (RPV/FTC/TDF) vs. 1.0 (EFV/FTC/TDF); $P=0.062$], but the difference for the mental health composite score was, favoring RPV/FTC/TDF (2.4 vs. 0.0; $P=0.014$).

Discussion

Results of this trial indicate that in treatment-naive, HIV-1-infected participants, 96-week RPV/FTC/TDF treatment demonstrated noninferior efficacy and better tolerability than EFV/FTC/TDF. Week 96 data for the overall study population from this open-label study are in agreement with previously reported findings at week 48 [11] and with earlier double-blind studies [6–9].

The rate of virologic success at week 96 observed for RPV/FTC/TDF (78%) was nominally greater than that observed for RPV-containing regimens in the ECHO and THRIVE trials (76%) [7], whereas the rate observed for EFV/FTC/TDF (72%) was nominally lower than that of the EFV-containing regimens in the double-blind studies (77%) [7]. These nominal, relatively small differences in success rates between our trial and the ECHO and THRIVE studies may be a reflection of differences in trial design (open label vs. blinded) or a consequence of random fluctuations. Visit-by-visit data (Fig. 1) suggest a similar dynamic of virologic success over the 96 weeks of treatment between the two groups. Significant differences in virologic success between subgroups with equal to or less than 100 000 HIV-1 RNA copies/ml and greater than 200 $CD4^+$ cells/μl (Table 2) could be related to the higher rate of discontinuations due to adverse events in the EFV/FTC/TDF group. In addition, the higher virologic failure rates observed for RPV/FTC/TDF-treated participants with baseline HIV-1 RNA greater than 500 000 copies/ml and $CD4^+$ cell count equal to or less than 200 cells/μl were mainly due to a higher rate of discontinuation due to lack of efficacy in this group. However, the efficacy analyses in individuals with high baseline HIV-1 RNA levels and low $CD4^+$ cell counts were limited by a small number of participants in those categories. Compared with the results of the ECHO and THRIVE trials [6–9], the STaR week 96 data suggest a more favorable profile for RPV/FTC/TDF for participants with HIV-1 RNA equal to or less than 100 000 copies/ml (Tables 1 and 2).

Overall rates of resistance development through week 96 in the STaR study were low (5.3% RPV/FTC/TDF; 1.0% EFV/FTC/TDF) with infrequent emergent resistance after week 48 (1.0% RPV/FTC/TDF; 0.3% EFV/FTC/TDF) [19]. However, a greater proportion of study participants who met the criteria for resistance analysis developed resistance in the RPV/FTC/TDF arm (88%) compared with the EFV/FTC/TDF arm (44%). In this trial, resistance development was lower compared with the previous phase 3 studies conducted using the components of these two regimens (8.0% RPV + FTC/TDF; 3.1% EFV + FTC/TDF) [20]. Within the RPV/FTC/TDF arm, resistance was more frequent in individuals with baseline HIV-1 RNA greater than 100 000 copies/ml than those with HIV-1 RNA or less than 100 000 copies/ml [10,19].

This study also confirms the overall better safety and tolerability profile of RPV/FTC/TDF vs. EFV/FTC/TDF over 96 weeks of treatment, especially in terms of neuropsychiatric adverse effects and rash. Several sources, including approved labeling, a systematic review [21], and ECHO and THRIVE data [22], describe nervous system and psychiatric disorders as generally developing during the first days of treatment with EFV and resolving within 2–4 weeks. Data from the current study, however, show that the majority of TEAEs occurred during the first 48 weeks of treatment [23] and discontinuations due to these TEAEs were not limited to the earliest weeks of treatment. This is consistent with the Leutscher *et al.* study [24], which found that more than half of EFV-related discontinuations due to neuropsychiatric adverse events occurred after 12 months of treatment; however, that study was a retrospective chart review, which limits comparability with the current prospective, randomized, open-label trial. Patient-reported data on treatment satisfaction (HIVTSQ), disease symptoms (HIV SIQ), and the mental health composite score (SF-12) also indicate better tolerability of RPV/FTC/TDF compared with EFV/FTC/TDF.

A decreased eGFR observed in the RPV/FTC/TDF group is consistent with RPV's inhibition of the renal tubular secretion of creatinine in the kidney (Gilead, data on file, 2010) [25], which has not been associated with the development of renal failure or chronic kidney disease. This interpretation is supported by the pattern of the early decrease in creatinine clearance in the RPV/FTC/TDF group that occurred at week 4 and then remained stable thereafter (data not shown). Moreover, proteinuria rates were low in both treatment arms and no episode of proximal renal tubulopathy was observed during the trial.

An important limitation of this trial was the open-label design, which may have contributed to bias in assessment of outcomes, particularly those related to safety and tolerability. In addition, the study sample was predominantly male (93%) and white (67%), which, although a common characteristic of recent HIV trials, is not reflective of the global, US, or European HIV-positive populations [26].

In conclusion, results of this randomized trial indicate that RPV/FTC/TDF STR is an effective option for first-line therapy in treatment-naive patients infected with HIV-1, with better tolerability than EFV/FTC/TDF.

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Conflicts of interest

Disclaimers: This study was sponsored by Gilead Sciences, Inc. The authors declare the following potential conflicts of interest:

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