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ORIGINAL RESEARCH

Switching to coformulated rilpivirine (RPV), emtricitabine (FTC) and tenofovir alafenamide from either RPV, FTC and tenofovir disoproxil fumarate (TDF) or efavirenz, FTC and TDF: 96-week results from two randomized clinical trials*

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Objectives

The single-tablet regimen rilpivirine, emtricitabine and tenofovir alafenamide (RPV/FTC/TAF) for treatment of HIV-1-infected adults was approved based on bioequivalence. We assessed the clinical efficacy, safety and tolerability of switching to RPV/FTC/TAF from either RPV/FTC/tenofovir disoproxil fumarate (TDF) or efavirenz (EFV)/FTC/TDF.

Methods

We conducted two distinct randomized, double-blind, active-controlled, noninferiority trials in participants taking RPV/FTC/TDF (Study 1216) and EFV/FTC/TDF (Study 1160). Each study randomized virologically suppressed (HIV-1 RNA < 50 copies/mL) adults (1:1) to switch to RPV/FTC/TAF or continue their current regimen for 96 weeks. We evaluated efficacy as the proportion with HIV-1 RNA < 50 copies/mL using the Food and Drug Administration snapshot algorithm and prespecified bone and renal endpoints at week 96.

Results

We randomized and treated 630 participants in Study 1216 (RPV/FTC/TAF, $n = 316$; RPV/FTC/TDF, $n = 314$) and 875 in Study 1160 (RPV/FTC/TAF, $n = 438$; EFV/FTC/TDF, $n = 437$). In both studies, the efficacy of switching to RPV/FTC/TAF was noninferior to that of continuing baseline therapy at week 96, with respective percentages of patients with HIV RNA < 50 copies/mL being 89.2% versus 88.5% in Study 1216 [difference 0.7%; 95% confidence interval (CI) −4.3 to +5.8%] and 85.2% versus 85.1% in Study 1160 (difference 0%; 95% CI −4.8 to +4.8%). No participant on RPV/FTC/TAF developed treatment-emergent resistance versus two on EFV/FTC/TDF and one on RPV/FTC/TDF. Compared with continuing baseline therapy, significant improvements in bone mineral density and renal tubular markers were observed in the RPV/FTC/TAF groups ($P < 0.001$).

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Conclusions
Switching to RPV/FTC/TAF from RPV/FTC/TDF or EFV/FTC/TDF was safe and effective and improved bone mineral density and renal biomarkers up to 96 weeks with no cases of treatment-emergent resistance.

Keywords: bone mineral density, HIV, renal disease, rilpivirine, tenofovir alafenamide

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Introduction

Regimens in which a nonnucleoside reverse transcriptase inhibitor (NNRTI) is combined with two nucleos(t)ide reverse transcriptase inhibitors (NRTIs) remain among the most commonly prescribed regimens for the treatment of HIV-1 infection worldwide. The NNRTIs efavirenz (EFV) and rilpivirine (RPV) are each coformulated with the NRTIs emtricitabine (FTC) and tenofovir disoproxil fumarate (TDF) as complete single-tablet regimens (STRs): EFV/FTC/TDF and RPV/FTC/TDF, respectively. Where EFV/FTC/TDF was the first once-daily single-tablet regimen, the association of EFV with central nervous system (CNS)-related side effects has curtailed its use as better tolerated options, including RPV, have become available [1–3]. Subsequently, it has been found that regimens containing tenofovir alafenamide (TAF) have improved bone and renal safety compared with TDF-containing regimens, while maintaining excellent efficacy [4,5].

Rilpivirine/FTC/TAF is a preferred or alternative recommended treatment regimen for initial antiretroviral therapy in European and US treatment guidelines for patients with a CD4 cell count > 200 cells/μL and HIV RNA < 100 000 HIV-1 RNA copies/mL [6,7]. Whether to switch from an effective regimen remains of clinical interest.

We investigated the clinical efficacy, safety and tolerability of switching to RPV/FTC/TAF from a stable regimen of either RPV/FTC/TDF or EFV/FTC/TDF in HIV-1-infected, virally suppressed adults in two distinct but similarly designed randomized controlled trials. The primary 48-week endpoints were previously reported [5,8]. Herein, we present efficacy, safety and tolerability outcomes up to week 96.

Methods

Study design and participants

Details of the design, inclusion criteria and methodology of the trials have been previously reported [8,9]. Briefly, we conducted two randomized, double-blind, active-controlled, 96-week, phase 3b clinical studies in virologically suppressed (HIV-1 RNA < 50 copies/mL), HIV-1-infected adults with creatinine clearance (CrCl) > 50 mL/min as calculated by the Cockcroft–Gault equation [10], taking either RPV/FTC/TDF (25/200/300 mg) in Study 1216 or EFV/FTC/TDF (600/200/300 mg) in Study 1160 for at least 6 months. Each study randomized participants (1:1) to switch to RPV/FTC/TAF (25/200/25 mg) or to continue their current regimen for 96 weeks. Participants received placebo tablets matching the alternative treatment. The studies were undertaken in accordance with the Declaration of Helsinki and approved by central or site-specific review boards and ethics committees.

Statistical analyses

We assessed efficacy by examining the proportion in each group with plasma HIV-1 RNA < 50 copies/mL at week 96 [US Food and Drug Administration (FDA)-defined snapshot algorithm [11]] and evaluated noninferiority with a two-sided 95% confidence interval (CI) for the difference in response rates (RPV/FTC/TAF minus either RPV/FTC/TDF or EFV/FTC/TDF) with a prespecified noninferiority margin of 8%. Safety endpoints included percentage change from baseline in hip and spine bone mineral density (BMD) and percentage change or change from baseline in renal parameters [CrCl, urine albumin to creatinine ratio (UACR), retinol-binding protein to creatinine ratio (RBP:Cr) and β2-microglobulin to creatinine ratio (β2M:Cr)] at week 96. We measured fasting lipids [total cholesterol, low-density lipoprotein (LDL) cholesterol, high-density lipoprotein (HDL) cholesterol and triglycerides] at baseline and every 24 weeks up to week 96. We used the Wilcoxon rank sum test to compare differences between treatment groups for continuous laboratory test results (SAS version 9.4; SAS Institute, Cary, NC). We coded adverse events with the Medical Dictionary for Regulatory Activities (MedDRA® version, 20.0 www.meddra.org).

Results

Between 26 January and 27 August 2015, we randomized and initiated study treatments in 630 participants in Study 1216 (RPV/FTC/TAF, $n = 316$; RPV/FTC/TDF, $n = 314$) and 875 in Study 1160 (RPV/FTC/TAF, $n = 438$; EFV/FTC/TDF, $n = 437$). Baseline characteristics were similar between the RPV/FTC/TAF groups and either the

RPV/FTC/TDF or EFV/FTC/TDF group, with the exception of sex in Study 1216, which enrolled more women in the RPV/FTC/TAF group than in the RPV/FTC/TDF group (Table 1). Median time on the regimen prior to randomization was 2.4 years [interquartile range (IQR) 1.6–3.2 years] in Study 1216 and 6.5 years (IQR 4.2–8.5 years) in Study 1160. At the time of analysis, 87% of participants in Study 1216 and 84% of those in Study 1160 remained on their randomly assigned treatment. The reasons for discontinuation were similar across treatment arms in each study (Figure 1).

In both studies, the efficacy of switching to RPV/FTC/TAF was noninferior to that of continuing baseline therapy at week 96. In Study 1216, 89.2% of participants on RPV/FTC/TAF versus 88.5% of those on RPV/FTC/TDF had HIV-1 RNA < 50 copies/mL by FDA snapshot [difference in percentages 0.7%; 95% confidence interval (CI) −4.3 to +5.8%] at week 96 (Table 2). High rates of virological suppression were also seen at week 96 in Study 1160, with 85.2% of participants on RPV/FTC/TAF versus 85.1% of those on EFV/FTC/TDF having HIV-1 RNA < 50 copies/mL (difference in percentages 0%; 95% CI −4.8 to +4.8%) at week 96.

The percentages of participants with HIV-1 RNA ≥ 50 copies/mL at week 96 were low in both studies: in Study 1216, percentages were 0.6% for RPV/FTC/TAF versus 1.0% for RPV/FTC/TDF (difference in percentages −0.3%; 95% CI −2.2 to +1.5%), and in Study 1160 they were 0.7% for RPV/FTC/TAF versus 0.9% for EFV/FTC/TDF (difference in percentages −0.2%; 95% CI −1.7 to +1.2%). Efficacy was also similar in a prespecified analysis using the lower threshold for virological suppression of HIV-1 RNA < 20 copies/mL (Study 1216: 85.8% for RPV/FTC/TAF versus 86.3% for RPV/FTC/TDF; difference −0.5%; 95% CI −6.0 to +5.0%; Study 1160: 83.1% for RPV/FTC/TAF versus 83.5% for EFV/FTC/TDF; difference in percentages −0.4%; 95% CI −5.5 to +4.6%).

Subgroup analyses comparing rates of virological suppression at week 96 within prespecified subgroups (age, sex, race, region, and study drug adherence) showed no differences between treatments in either study (Fig. S1). CD4 cell counts were maintained across all treatments up to week 96. The mean (standard deviation) changes from baseline in CD4 cell counts at week 96 in Study 1216 were +12 (180.6) cells/μL for the RPV/FTC/TAF group and +16 (171.9) cells/μL for the RPV/FTC/TDF group ($P = 0.77$), and in Study 1160 they were +12 (199.8) cells/μL for the RPV/FTC/TAF group and +6 (153.2) cells/μL for the EFV/FTC/TDF group ($P = 0.64$).

Up to 96 weeks, eight participants with protocol-defined virological failure met the criteria for resistance analysis in Study 1216: three (0.9%) in the RPV/FTC/TAF

Table 1 Baseline characteristics

	Study 1216 (baseline regimen RPV/FTC/TDF)		Study 1160 (baseline regimen EFV/FTC/TDF)	
Randomized treatment	**RPV/FTC/TAF (*n* = 316)**	**RPV/FTC/TDF (*n* = 314)**	**RPV/FTC/TAF (*n* = 438)**	**EFV/FTC/TDF (*n* = 437)**
Age (years) [median (IQR)]	46 (37, 53)	44 (36, 51)	49 (42, 55)	48 (41, 54)
Male [*n* (%)]	275 (87)	289 (92)	373 (85)	390 (89)
Race/ethnicity [*n* (%)]				
White	238 (75)	235 (75)	291 (66)	292 (67)
Black or African descent	65 (21)	54 (17)	118 (27)	120 (27)
Asian	7 (2)	17 (5)	9 (2)	8 (2)
Latino/Hispanic	40 (13)	53 (17)	79 (18)	78 (18)
Region [*n* (%)]				
USA	222 (70)	226 (72)	351 (80)	345 (79)
Non-USA*	94 (30)	88 (28)	87 (20)	92 (21)
CD4 count (cells/μL) [median (IQR)]	673 (521, 877)	668 (525, 817)	673 (507, 887)	666 (505, 820)
Duration of baseline regimen at enrolment (years) [median (IQR)]†	2.3 (1.5, 3.3)	2.5 (1.6, 3.2)	6.5 (4.5, 8.2)	6.6 (4.1, 8.7)
CrCl (mL/min) [median (IQR)]	104 (89, 120)	100 (87, 120)	110 (91, 132)	108 (92, 133)
Proteinuria grade [*n* (%)]				
1	31 (10)	28 (9)	26 (6)	36 (8)
2	0	1 (< 1)	2 (< 1)	1 (< 1)
3	0	0	0	0
Diabetes mellitus [*n* (%)]	5 (2)	10 (3)	26 (6)	24 (5)
Hypertension [*n* (%)]	66 (21)	55 (18)	118 (27)	122 (28)

CrCl, creatinine clearance; EFV, efavirenz; FTC, emtricitabine; IQR, interquartile range; RPV, rilpivirine; TAF, tenofovir alafenamide; TDF, tenofovir disoproxil fumarate.
*Includes Canada and Europe.
†A single-tablet regimen of RPV/FTC/TDF for Study 1216 and a single-tablet regimen of EFV/FTC/TDF for Study 1160.

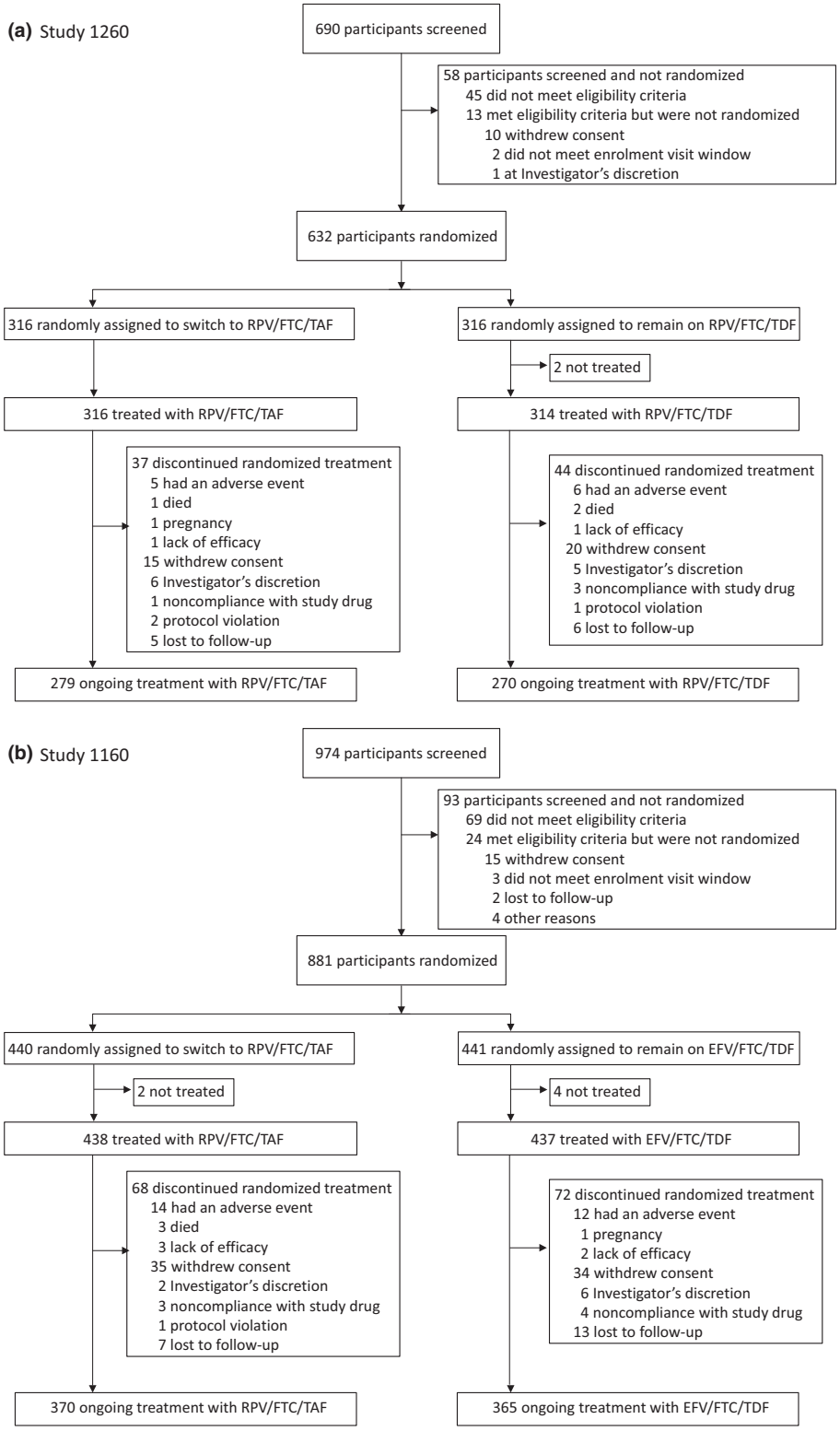

Fig. 1 Disposition of study participants at week 96. (a) Study 1216: Switch to rilpivirine, emtricitabine and tenofovir alafenamide (RPV/FTC/TAF) from RPV/FTC/tenofovir disoproxil fumarate (TDF). (b) Study 1160: switch to RPV/FTC/TAF from efavirenz (EFV)/FTC/TDF.

Table 2 Virological outcomes at week 96

	Study 1216		Study 1160	
	RPV/FTC/TAF (n = 316)	RPV/FTC/TDF (n = 313)	RPV/FTC/TAF (n = 438)	EFV/FTC/TDF (n = 437)
HIV-1 RNA < 50 copies/mL	282 (89.2)	277 (88.5)	373 (85.2)	372 (85.1)
Difference in percentages < 50 copies/mL (95% CI)	0.7% (−4.3 to 5.8%)† (P = 0.80)*		0.0% (−4.8 to 4.8%)† (P = 1.00)*	
HIV-1 RNA ≥ 50 copies/mL	2 (0.6)	3 (1.0)	3 (0.7)	4 (0.9)
Difference in percentages ≥ 50 copies/mL (95% CI)	−0.3% (−2.2 to 1.5%)† (P = 0.69)*		−0.2% (−1.7 to 1.2%)† (P = 0.73)*	
HIV-1 RNA ≥ 50 copies/mL in week 96 window	1 (0.3)	1 (0.3)	0	0
Discontinued study drug because of lack of efficacy	1 (0.3)	0	3 (0.7)	2 (0.5)
Discontinued study drug because of AE/death and last available HIV-1 RNA ≥ 50 copies/mL	0	0	0	0
Discontinued study drug for other reasons‡ and last available HIV-1 RNA ≥ 50 copies/mL	0	2 (0.6)	0	2 (0.5)
No virological data in week 96 window	32 (10.1)	33 (10.5)	62 (14.2)	61 (14.0)
Discontinued study drug because of AE/death and last available HIV-1 RNA < 50 copies/mL	5 (1.6)	8 (2.6)	16 (3.7)	11 (2.5)
Discontinued study drug for other reasons‡ and last available HIV-1 RNA < 50 copies/mL	24 (7.6)	25 (8.0)	45 (10.3)	50 (11.4)
Missing data during window but on study drug	3 (0.9)	0	1 (0.2)	0

The week 96 window was between days 631 and 714 (inclusive). Results are n (%) unless stated otherwise.
AE, adverse event; CI, confidence interval; EFV, efavirenz; FTC, emtricitabine; RPV, rilpivirine; TAF, tenofovir alafenamide; TDF, tenofovir disoproxil fumarate.
*P-values for the superiority test comparing the percentages of participants with HIV-1 RNA < 50 or ≥ 50 copies/mL were from the Fisher exact test.
†Differences in percentages of participants with HIV-1 RNA < 50 or ≥ 50 copies/mL between treatment groups and their 95% CIs were calculated based on an unconditional exact method using two inverted one-sided tests.
‡Discontinuation for other reasons includes participants who discontinued the study drug for the following reasons: investigator's discretion, withdrew consent, lost to follow-up, noncompliance with study drug, protocol violation, pregnancy, and study terminated by sponsor.

group and five (1.6%) in the RPV/FTC/TDF group. No participant on RPV/FTC/TAF had treatment-emergent resistance and two of the three participants analysed resuppressed to HIV RNA < 50 copies/mL while continuing RPV/FTC/TAF. The third had mutations detected at the time of virological failure; these mutations were pre-existing at study enrolment, as shown by retrospective proviral DNA genotyping of the baseline sample (M41L, E44D, D67N, V118I, L210W and T215Y) as previously described [9]. Two participants on RPV/FTC/TDF resuppressed to HIV RNA < 50 copies/mL without treatment-emergent resistance while continuing RPV/FTC/TDF. One participant on RPV/FTC/TDF had treatment-emergent resistance detected at week 84 with reverse transcriptase mutations K65R, M184V, K219K/E, K103N and Y181C conferring phenotypic resistance to FTC and RPV. Retrospective proviral DNA genotyping of the baseline sample showed that M184V and K103N were pre-existing at baseline. One participant on RPV/FTC/TDF had a mutation detected at week 84 that was retrospectively found to be pre-existing in the baseline sample (K103N) and subsequently discontinued study medications. The final RPV/FTC/TDF participant had wild-type virus at their last visit on study medications.

Ten participants with virological failure met the criteria for resistance analysis in Study 1160: eight (1.8%) in the RPV/FTC/TAF group and two (0.5%) in the EFV/FTC/TDF group. No participant on RPV/FTC/TAF had treatment-emergent resistance and seven of the eight participants subsequently resuppressed to HIV-1 RNA < 50 copies/mL while continuing RPV/FTC/TAF. Two participants on RPV/FTC/TAF had detectable resistance mutations at virological failure that were pre-existing at study entry as shown by retrospective proviral DNA genotyping of the baseline sample as previously described: one with K219K/E and K103N who resuppressed on continued RPV/FTC/TAF and one with V90V/I, K103N and E138E/A [8]. Two participants on EFV/FTC/TDF had treatment-emergent resistance. One developed resistance-associated mutations M184V, V106I/L and Y188L as previously described and the other developed resistance-associated mutations K101K/E, K103N and P225P/H.

All treatments were well tolerated and most adverse events were mild or moderate in severity and not related to study drugs. Adverse events led to discontinuation of the study drug for 11 participants in Study 1216; five (1.6%) on RPV/FTC/TAF and six (1.9%) on RPV/FTC/TDF. Only one (drug hypersensitivity in the RPV/FTC/TDF group) was considered related to the study drug by the investigator. Four of these discontinuations occurred after week 48, including one in a participant in the RPV/FTC/TAF group who developed a solitary cutaneous Kaposi's sarcoma

lesion and was switched to a nonstudy regimen at the discretion of the investigator. Adverse events led to discontinuation of the study drugs for 26 participants in Study 1160; 14 (3.2%) on RPV/FTC/TAF and 12 (2.7%) on EFV/FTC/TDF. Seven of these discontinuations occurred after week 48, including one for Fanconi syndrome in a participant on EFV/FTC/TDF, which was considered related to the study medication. This diagnosis was preceded by several days of nausea and vomiting from ureterolithiasis, and concomitant with acute prerenal failure and metabolic acidosis, which were unrelated to study drugs. The study drug was discontinued, ureterolithiasis was surgically removed and the adverse events resolved. Three deaths occurred in Study 1216: from suicide, carbon monoxide poisoning and methamphetamine overdose. Four deaths occurred in Study 1160: from hypertensive cardiovascular disease, sepsis, pneumonia attributable to lung cancer and cocaine and methamphetamine overdose. No death was considered related to the study drugs.

In each study, increases from baseline in the mean per cent change of hip and spine BMD were observed at week 48 following switch to RPV/FTC/TAF [8,9]. Improvements continued up to week 96 and were significant compared with minimal changes in BMD with continuation of the baseline regimen (Figure 2; $P < 0.001$). Fractures were infrequent, being reported in similar numbers in the different treatment groups in both studies [Study 1216: nine (2.8%) for RPV/FTC/TAF and seven (2.2%) for RPV/FTC/TDF ($P = 0.80$); Study 1160: 14 (3.2%) for RPV/FTC/TAF and six (1.4%) for EFV/FTC/TDF ($P = 0.11$)]. Most were the result of an acute trauma, with the exception of two participants in Study 1160; one on RPV/FTC/TAF with pathological fractures attributable to bone metastases from prostate cancer, and one on EFV/FTC/TDF with a nontraumatic foot fracture.

There were no cases of proximal renal tubular disorders in Study 1216. One participant who received EFV/FTC/TDF in Study 1160 acquired Fanconi syndrome at week 70 which was considered related to the study drugs by the investigator. In Study 1216, participants who switched to RPV/FTC/TAF had an increase in CrCl at week 96 compared with those who continued RPV/FTC/TDF (Table 3). In Study 1160, there was a larger median decrease in CrCl for participants who switched to RPV/FTC/TAF than in those who continued EFV/FTC/TDF. Participants who switched to RPV/FTC/TAF had little change from baseline in UACR and RBP:Cr and a decrease from baseline in the β2M:Cr ratio at week 96, compared with

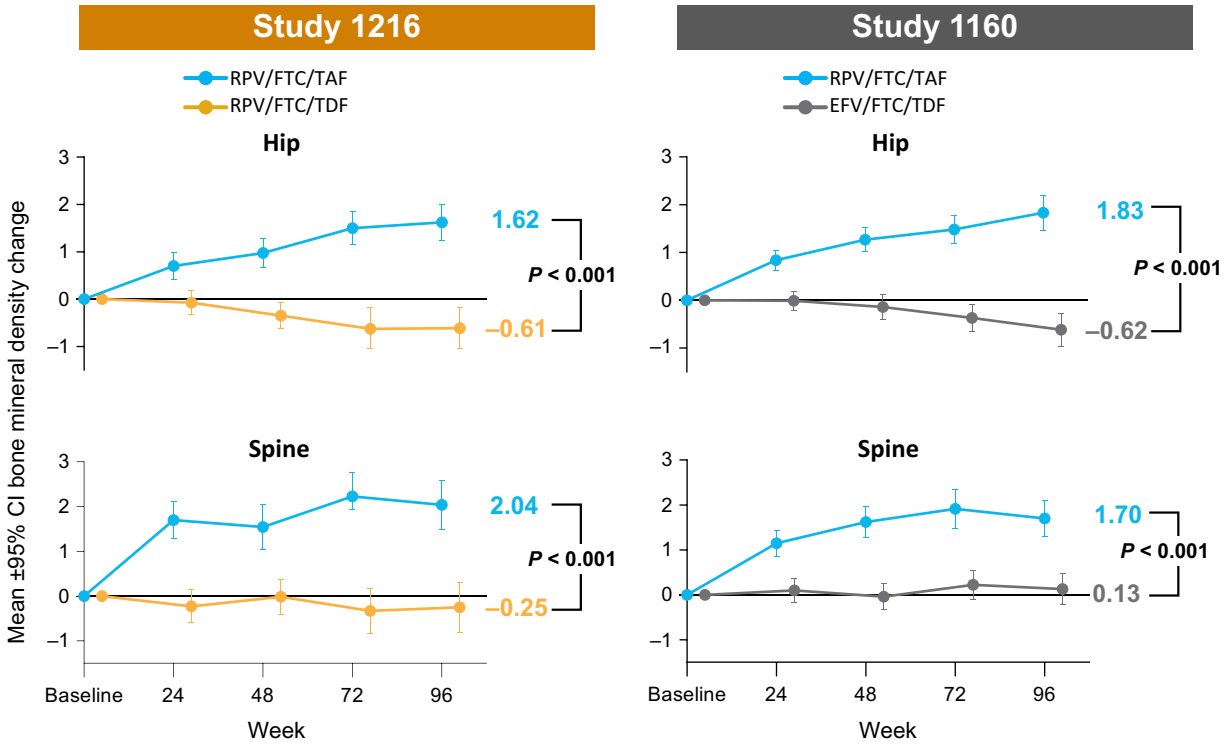

Figure 2 Changes in bone mineral density (BMD) at the hip and spine from baseline to week 96. BMD, bone mineral density; CI, confidence interval. *P*-values are from the analysis of variance (ANOVA) model including treatment as a fixed effect.

Table 3 Changes in creatinine clearance (CrCl) and renal biomarkers from baseline to week 96

	Study 1216			Study 1160		
Renal assessments	RPV/FTC/TAF (n = 316)	RPV/FTC/TDF (n = 314)	P-value	RPV/FTC/TAF (n = 438)	EFV/FTC/TDF (n = 437)	P-value
CrCl by Cockroft–Gault (mL/min)						
Baseline	103.5 (88.5, 119.8)	99.7 (87.3, 119.8)	0.47	110.4 (91.4, 132.0)	107.6 (91.6, 132.7)	0.63
Change at week 96	5.9 (−3.0, 13.3)	−0.2 (−8.8, 8.1)	< 0.001	−4.6 (−13.6, 5.4)	−1.1 (−10.3, 6.6)	0.004
UACR						
Baseline	5.5 (3.7, 10.0)	5.4 (3.8, 9.2)	0.98	6.9 (4.2, 13.6)	6.4 (4.3, 11.8)	0.40
Percentage change at week 96	9.3 (−29.0, 57.9)	32.9 (−12.5, 102.7)	< 0.001	−1.0 (−40.4, 57.1)	39.6 (−4.7, 136.8)	< 0.001
RBP to creatinine ratio						
Baseline	101.2 (70.5, 157.6)	111.1 (75.8, 196.9)	0.12	115.8 (75.0, 254.4)	131.8 (82.7, 265.7)	0.14
Percentage change at week 96	6.5 (−31.7, 57.8)	55.8 (2.5, 137.9)	< 0.001	−7.3 (−49.8, 42.2)	87.1 (13.4, 202.5)	< 0.001
β2-microglobulin to creatinine ratio						
Baseline	111.6 (67.0, 260.0)	116.1 (61.7, 326.1)	0.72	130.1 (69.0, 498.6)	153.6 (78.8, 480.8)	0.13
Percentage change at week 96	−15.5 (−60.7, 29.2)	43.7 (−24.5, 182.3)	< 0.001	−31.7 (−76.7, 16.7)	68.4 (−19.1, 203.2)	< 0.001

Values are median (IQR). P-values were from the two-sided Wilcoxon rank sum test to compare the two treatment groups.
EFV, efavirenz; FTC, emtricitabine; IQR, interquartile range; RBP, retinol-binding protein; RPV, rilpivirine; TAF, tenofovir alafenamide; TDF, tenofovir disoproxil fumarate; UACR, urine albumin to creatinine ratio.

increases from baseline in these measures for those who remained on treatment with RPV/FTC/TDF or EFV/FTC/TDF.

In Study 1216, fasting total cholesterol, direct LDL cholesterol, HDL cholesterol and triglycerides had modest increases in participants who switched to RPV/FTC/TAF and remained stable in those who continued RPV/FTC/TDF (Table 4). There was a difference in the median change in total to HDL cholesterol ratio measured for participants who switched to RPV/FTC/TAF compared with those who continued RPV/FTC/TDF (Table 4). Median total to HDL cholesterol ratios were not significantly different between the treatment groups at week 96 (3.7 for RPV/FTC/TAF and 3.6 for RPV/FTC/TDF; P = 0.46). While on the study, a larger proportion of participants in the RPV/FTC/TAF group (8%) began lipid-lowering drugs than in the RPV/FTC/TDF group (3%; P = 0.002). In Study 1160, switching to RPV/FTC/TAF was associated with decreases in fasting total and HDL cholesterol at week 96; lipids remained stable in the EFV/FTC/TDF group (Table 4). Neither the change from baseline nor the median total to HDL cholesterol ratio was significantly different at week 96 (median at week 96, 3.6 for RPV/FTC/TAF and 3.5 for EFV/FTC/TDF; P = 0.25). Similar proportions of participants in the RPV/FTC/TAF (5%) and EFV/FTC/TDF (6%) groups began lipid-lowering drugs (P = 0.56) over the course of the study.

Discussion

These two phase 3 studies showed that switching to coformulated RPV/FTC/TAF from either RPV/FTC/TDF or EFV/FTC/TDF was noninferior for maintaining virological suppression, and was durable for at least 96 weeks compared with continuing either baseline regimen. Virological failure was rare in all treatment groups (≤ 1%). The majority of participants not included as successes in the FDA snapshot algorithm discontinued treatment prior to week 96 for nonvirological reasons with last on-treatment HIV-1 RNA < 50 copies/mL. No treatment-emergent resistance was detected in participants who switched to RPV/FTC/TAF.

Improvements in BMD and urine biomarkers of renal safety were seen in the RPV/FTC/TAF groups over those whose treatment contained TDF. Bone density continued to improve to at least 96 weeks. Also, the improvements in measures of quantitative and tubular proteinuria in the TAF-treated compared with the TDF-treated groups were consistent with prior studies, and these benefits were evident for the duration of follow-up [4,5].

No renal tubular disorders were reported for any participant taking RPV/FTC/TAF, while one case of Fanconi syndrome occurred in a participant on EFV/FTC/TDF. This event was precipitated by prerenal acute kidney injury, which can cause elevated plasma concentrations of tenofovir as renal clearance of this TDF metabolite declines. TAF use results in 91% lower plasma concentrations of tenofovir than TDF and thus renal toxicities have rarely been seen in patients taking TAF [12,13]. Participants switching from EFV/FTC/TDF to RPV/FTC/TAF in Study 1160 did have an immediate small increase in serum creatinine consistent with inhibition by RPV of creatinine secretion in the renal tubule [14]. The median change in serum creatinine at week 4 was 0.05 mg/dL for RPV/FTC/TAF versus 0.02 mg/dL for EFV/FTC/TDF (P < 0.001) and remained stable from week 12 to week 96.

In Study 1216, there were small increases from baseline in fasting total cholesterol, direct LDL cholesterol,

Table 4 Changes in fasting lipids from baseline to week 96

	Study 1216			Study 1160		
Metabolic assessment	RPV/FTC/TAF (n = 316)	RPV/FTC/TDF (n = 314)	P-value	RPV/FTC/TAF (n = 438)	EFV/FTC/TDF (n = 437)	P-value
Total cholesterol (mg/dL)						
Baseline	173 (152, 196)	167 (152, 188)	0.07	191 (170, 211)	192 (167, 215)	0.88
Change at week 96	19 (4, 34)	3 (−12, 18)	< 0.001	−13 (−32, 10)	−3 (−19, 15)	< 0.001
Direct LDL cholesterol (mg/dL)						
Baseline	109 (89, 129)	105 (89, 123)	0.12	115 (97, 135)	117 (97, 139)	0.46
Change at week 96	15 (2, 28)	3 (−9, 15)	< 0.001	−2 (−20, 14)	0 (−13, 13)	0.22
HDL cholesterol (mg/dL)						
Baseline	47 (39, 56)	46 (38, 55)	0.34	52 (43, 65)	53 (44, 63)	0.99
Change at week 96	2 (−2, 8)	0 (−5, 6)	0.006	−4 (−11, 1)	0 (−6, 6)	< 0.001
Triglycerides (mg/dL)						
Baseline	101 (74, 147)	100 (72, 148)	0.47	116 (83, 175)	116 (79, 170)	0.36
Change at week 96	16 (−14, 53)	3 (−27, 35)	< 0.001	1 (−34, 24)	4 (−25, 35)	0.14
Total to HDL cholesterol ratio						
Baseline	3.6 (2.9, 4.5)	3.5 (2.9, 4.5)	0.60	3.6 (2.9, 4.3)	3.5 (2.9, 4.4)	0.95
Change at week 96	0.2 (−0.3, 0.5)	0 (−0.4, 0.5)	0.03	0.1 (−0.4, 0.5)	0 (−0.5, 0.4)	0.06

Values are median (IQR). P-values are from the two-sided Wilcoxon rank sum test to compare the two treatment groups.
HDL, high-density lipoprotein; IQR, interquartile range; LDL, low-density lipoprotein; EFV, efavirenz; FTC, emtricitabine; RPV, rilpivirine; TAF, tenofovir alafenamide; TDF, tenofovir disoproxil fumarate.

HDL cholesterol, and triglycerides in participants who substituted TAF for TDF. Treatment with TDF-containing regimens has consistently been associated with lower lipids compared with non-TDF-containing regimens, an effect thought to be a dose-related effect of plasma tenofovir on reducing select lipid parameters [15–18]. The changes in fasting lipids seen in Study 1216 are consistent with differences seen in treatment-naïve patients as well as in other studies evaluating the switch to TAF from TDF while maintaining other antiretroviral regimen components [4,5].

Although there were modest increases in lipids, their clinical significance is unclear. There were no clinically meaningful differences in the total cholesterol to HDL cholesterol ratio, which is incorporated into cardiovascular clinical risk predictors for HIV-infected and uninfected individuals [19,20]. Lipid differences of similar magnitude between TAF- and TDF-treated participants have resulted in no differences in atherosclerotic cardiovascular disease (ASCVD) estimated cardiovascular risk, or eligibility for statins [21].

In comparison, participants in Study 1160 switched two component drugs of their antiretroviral regimen, both from EFV to RPV and from TDF to TAF. In aggregate, eliminating the lipid-elevating influence of EFV [22] in favour of the more lipid-neutral RPV [23] outweighed the modest effect of switching from TDF to TAF.

These studies have important limitations. Each was powered for a primary efficacy endpoint and may be unable to detect rare clinical safety events. For example, EFV is associated with short- and long-term neuropsychiatric adverse effects and with an increase in suicidality in some reports [1,22,24], yet adverse event profiles and discontinuations were similar between the treatment groups of Study 1160. As neuropsychiatric symptoms may emerge early in treatment and lead to EFV discontinuation [24,25], compared with the general population, our study population may be enriched for participants who tolerate EFV, as they were taking it for a median of 6.5 years prior to study enrolment. This may further limit the study's ability to detect a safety difference. Other limitations include study participants being predominantly male and relatively healthy with only a small proportion having advanced HIV disease.

Overall, virologically suppressed HIV-1-infected adults who switched to RPV/FTC/TAF from either RPV/FTC/TDF or EFV/FTC/TDF maintained virological suppression over 96 weeks with low rates of virological failure. There was no treatment-emergent resistance to study medications in participants treated with RPV/FTC/TAF. The regimen of RPV/FTC/TAF had improved bone and renal safety profiles as well as excellent tolerability. These findings reinforce guidelines recommending use of RPV/FTC/TAF for treatment of HIV-1 infection and support switching virologically suppressed patients on current NNRTI-containing regimens to RPV/FTC/TAF for long-term patient safety.

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Supporting Information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Fig. S1. Forest plot of treatment difference in HIV-1 RNA < 50 copies/mL at week 96 (snapshot algorithm) by subgroup.