



Switching from efavirenz, emtricitabine, and tenofovir disoproxil fumarate to tenofovir alafenamide coformulated with rilpivirine and emtricitabine in virally suppressed adults with HIV-1 infection: a randomised, double-blind, multicentre, phase 3b, non-inferiority study

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Summary

Background Tenofovir alafenamide is a prodrug that reduces tenofovir plasma concentrations by 90% compared with tenofovir disoproxil fumarate, thereby decreasing bone and renal risks. The coformulation of rilpivirine, emtricitabine, and tenofovir alafenamide has recently been approved, and we aimed to investigate the efficacy, safety, and tolerability of switching to this regimen compared with remaining on coformulated efavirenz, emtricitabine, and tenofovir disoproxil fumarate.

Methods In this randomised, double-blind, placebo-controlled, non-inferiority trial, HIV-1-infected adults were enrolled at 120 hospitals and outpatient clinics in eight countries in North America and Europe. Participants were virally suppressed (HIV-1 RNA <50 copies per mL) on efavirenz, emtricitabine, and tenofovir disoproxil fumarate for at least 6 months before enrolment and had creatinine clearance of at least 50 mL/min. Participants were randomly assigned (1:1) to receive a single-tablet regimen of rilpivirine (25 mg), emtricitabine (200 mg), and tenofovir alafenamide (25 mg) or to continue a single-tablet regimen of efavirenz (600 mg), emtricitabine (200 mg), and tenofovir disoproxil fumarate (300 mg), with matching placebo. Investigators, participants, study staff, and those assessing outcomes were masked to treatment group. The primary endpoint was the proportion of participants with plasma HIV-1 RNA of less than 50 copies per mL at week 48 (assessed by the US Food and Drug Administration snapshot algorithm), with a prespecified non-inferiority margin of 8%. This study was registered with ClinicalTrials.gov, number NCT02345226.

Findings Between Jan 26, 2015, and Aug 27, 2015, 875 participants were randomly assigned and treated (438 with rilpivirine, emtricitabine, and tenofovir alafenamide and 437 with efavirenz, emtricitabine, tenofovir disoproxil fumarate). Viral suppression at week 48 was maintained in 394 (90%) of 438 participants assigned to the tenofovir alafenamide regimen and 402 (92%) of 437 assigned to the tenofovir disoproxil fumarate regimen (difference -2.0%, 95.001% CI -5.9 to 1.8), demonstrating non-inferiority. 56 (13%) of 438 in participants in the rilpivirine, emtricitabine, and tenofovir alafenamide group experienced treatment-related adverse events compared with 45 (10%) of 437 in the efavirenz, emtricitabine, and tenofovir disoproxil fumarate group.

Interpretation Switching to rilpivirine, emtricitabine, and tenofovir alafenamide from efavirenz, emtricitabine, and tenofovir disoproxil fumarate was non-inferior in maintaining viral suppression and was well tolerated at 48 weeks. These findings support guidelines recommending tenofovir alafenamide-based regimens, including coformulation with rilpivirine and emtricitabine, as initial and ongoing treatment for HIV-1 infection.

Funding Gilead Sciences.

Introduction

Efavirenz and rilpivirine are non-nucleoside reverse transcriptase inhibitors (NNRTIs); efavirenz and rilpivirine coformulations with emtricitabine and tenofovir disoproxil fumarate are approved single-tablet regimens for the treatment of HIV-1 infection.¹ Compared with efavirenz, rilpivirine has fewer CNS-related side-effects, such as headache, impaired cognition, sleep disturbances, and suicide.²⁻⁴ However, rilpivirine must be taken with food

and is associated with several drug interactions that limit its use in some populations.⁵ Both rilpivirine and efavirenz, each coformulated with emtricitabine and tenofovir disoproxil fumarate, are alternative antiretroviral regimens in current US HIV treatment guidelines.⁶ Rilpivirine, emtricitabine, and tenofovir disoproxil fumarate remains a preferred regimen in European treatment guidelines for selected patients (CD4 count >200 per μ L and HIV RNA <100 000 copies per mL).⁷

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Research in context

Evidence before this study

We searched PubMed for clinical trials of regimen switches involving rilpivirine, efavirenz, and tenofovir alafenamide for the treatment of HIV-1 infection. Our search terms included "rilpivirine", "efavirenz", "tenofovir alafenamide", "TAF", "switch", and "HIV" with articles restricted to clinical trials published in English between Jan 1, 1990 and Sept 22, 2016. Only one study was found examining a switch from efavirenz-based to rilpivirine-based antiretroviral treatment. This open-label, single-arm study switched 49 patients from efavirenz, emtricitabine, and tenofovir disoproxil fumarate to rilpivirine, emtricitabine, and tenofovir disoproxil fumarate and 94% maintained viral suppression at week 48. Randomised, controlled trials examining switches from nevirapine-based and from protease inhibitor-based regimens have shown rilpivirine, emtricitabine, and tenofovir disoproxil fumarate to be non-inferior to continued treatment. No study has examined clinical outcomes for treatment with coformulated rilpivirine, emtricitabine, and tenofovir alafenamide, and no randomised controlled study has assessed the efficacy and safety of switching from treatment based on efavirenz and tenofovir disoproxil fumarate to that based on rilpivirine and tenofovir alafenamide.

Added value of this study

To our knowledge, this is the first study of efficacy and safety of switching from efavirenz, emtricitabine, and tenofovir

disoproxil fumarate to rilpivirine, emtricitabine, and tenofovir alafenamide. The tenofovir alafenamide regimen was non-inferior to continuing the tenofovir disoproxil fumarate regimen and high rates of viral suppression were maintained for both at week 48. There was no treatment emergent resistance seen in participants receiving rilpivirine, emtricitabine, and tenofovir alafenamide. Measures of bone and renal safety were improved in the tenofovir alafenamide group, consistent with previously described safety benefits compared with tenofovir disoproxil fumarate. The long-term clinical significance of these findings remains to be determined.

Implications of all the available evidence

Switching to rilpivirine, emtricitabine, and tenofovir alafenamide from efavirenz, emtricitabine, and tenofovir disoproxil fumarate in virally suppressed patients is effective and associated with improved measures of bone and renal safety. No treatment-emergent resistance was detected for patients receiving rilpivirine, emtricitabine, and tenofovir alafenamide. These findings support guidelines recommending tenofovir alafenamide-based regimens, including coformulation with rilpivirine and emtricitabine, as initial and ongoing treatment for HIV-1 infection.

Regimens containing tenofovir alafenamide have high efficacy and improved renal and bone safety in clinical trials of HIV-infected, treatment-naïve, or virally suppressed participants.^{8–11} The single-tablet regimen containing rilpivirine (25 mg), emtricitabine (200 mg), and tenofovir alafenamide (25 mg) was approved in Europe and the USA based on the demonstration of bioequivalent pharmacokinetics to rilpivirine and an approved regimen containing emtricitabine and tenofovir alafenamide.^{6,12,13} We aimed to assess the clinical efficacy, safety, and tolerability of switching to rilpivirine, emtricitabine, and tenofovir alafenamide versus remaining on efavirenz, emtricitabine, and tenofovir disoproxil fumarate in HIV-infected, virally suppressed adults.

Methods

Study design and participants

GS-US-366-1160 is a phase 3b, randomised, double-blind, multicentre, non-inferiority study done at 120 sites in eight countries in North America (USA and Canada) and Europe (Belgium, France, Germany, Spain, Switzerland, and the UK). Study investigators enrolled participants who were HIV-infected adults (aged at least 18 years), virally suppressed (HIV-1 RNA <50 copies per mL) on a stable regimen of single-tablet efavirenz, emtricitabine, and tenofovir disoproxil fumarate for at least 6 months before screening, had

creatinine clearance of at least 50 mL/min (calculated by the Cockcroft–Gault equation), and no documented resistance to efavirenz, rilpivirine, emtricitabine, or tenofovir. Participants must have been willing to switch their regimens but were not required to have an indication for switching, such as drug-related toxicity, intolerance, comorbid condition, or preference for new treatment.^{5,6,14} This study was done in accordance with the Declaration of Helsinki and approved by central or site-specific review boards or ethics committees. All participants provided written informed consent.

Randomisation and masking

We randomly assigned participants (1:1) either to switch to rilpivirine, emtricitabine, and tenofovir alafenamide or to remain on efavirenz, emtricitabine, and tenofovir disoproxil fumarate. A computer-generated randomisation allocation sequence was created by a third party and used blocked randomisation with a block size of 4 (Bracket, San Francisco, USA). Participants received placebo tablets matching the alternative treatment and study drugs were administered twice daily. All investigators, participants, and study staff giving treatment, assessing outcomes, and collecting data were masked to treatment group. Investigators determined eligibility, obtained the patients' numbers, and used a real-time interactive web response system to receive treatment assignments.

Procedures

We did post-baseline study visits at weeks 4, 8, and 12, after which participants continued masked treatment with visits every 12 weeks until week 96. Participants either switched to a single-tablet regimen of 25 mg rilpivirine, 200 mg emtricitabine, and 25 mg tenofovir alafenamide, which was given with food, or remained on a single-tablet regimen of 600 mg efavirenz, 200 mg emtricitabine, and 300 mg tenofovir disoproxil fumarate, which was given on an empty stomach. Laboratory tests included haematological analysis, serum chemistry tests, fasting lipid parameters, CD4 cell counts, measures of renal function (creatinine clearance, urine protein to creatinine ratio, urine albumin to creatinine ratio, retinol binding protein to creatinine ratio, β 2-microglobulin to creatinine ratio; Covance Laboratories, IN, USA), and measurement of HIV RNA concentration (Roche TaqMan 2.0; Roche Diagnostics, Rotkreuz, Switzerland). HIV-1 resistance testing consisted of genotyping and phenotyping of protease and reverse transcriptase (Monogram Biosciences, CA, USA). Resistance testing was duplicated for any participant who had a confirmed plasma HIV-1 RNA of 50 copies per mL or more and the confirmation sample had HIV-1 RNA of at least 400 copies per mL or had HIV-1 RNA of 400 copies per mL or more at the discontinuation or last visit. We collected historical genotypes from samples taken before this study for all participants with available data (appendix p 1). In participants who had virological failure, developed resistance, and did not have historical genotype data available, proviral DNA genotyping with the GenoSure Archive assay (Monogram Biosciences, CA, USA) was done retrospectively on the baseline sample to assess pre-existing resistance. We did dual energy x-ray absorptiometry scans for hip and spine bone mineral density before drug administration at baseline and then every 24 weeks throughout the study. A centralised laboratory blinded to study group (BioClinica, PA, USA) read all scans. We assessed adverse events and concomitant drugs at each visit.

Outcomes

The primary outcome was the proportion of participants who had plasma HIV-1 RNA of less than 50 copies per mL at week 48 as defined by the US Food and Drug Administration snapshot algorithm.¹⁵ Two key safety endpoints were prespecified with multiplicity adjustments: hip bone mineral density and spine bone mineral density. Additional efficacy endpoints included the proportion of participants with at least 50 copies per mL plasma HIV-1 RNA at week 48; virological efficacy by subgroups stratified by age, sex, race, geographic region, and study medication adherence; the proportion of participants with HIV-1 RNA of less than 50 copies per mL at week 48 when classifying missing as failure and missing as excluded; participants with less than 20 copies per mL HIV-1 RNA at week 48 by snapshot; and change in CD4 cell count from baseline at week 48.

Safety evaluations included standard laboratory testing and adverse events coded with version 19.0 of the Medical Dictionary for Regulatory Activities (MedDRA).

Statistical analysis

Assuming a response rate of 89% at week 48, we calculated that a sample size of 800 randomly assigned participants would achieve at least 95% power to detect non-inferiority at a one-sided α of 0.025. A sample size of 400 participants per group would achieve at least 95% power to detect non-inferiority margin of 4% for the primary efficacy endpoint.

We did the primary endpoint analysis using the full analysis set (all participants who were randomly assigned and had received at least one dose of the study drug) after all enrolled participants had completed their week 48 study visit or had prematurely discontinued study drug. We also analysed the primary efficacy endpoint using the per-protocol analysis set (participants in the full analysis set who had not committed any major protocol violations). Major protocol violations included the violation of the key entry criteria, including not receiving efavirenz, emtricitabine, and tenofovir disoproxil fumarate for at least 6 months, not having documented plasma HIV-1 RNA of less than 50 copies per mL for at least 6 months, having documented resistance to any of the study drugs, or taking prohibited medications. Additionally, we analysed the week 48 efficacy endpoint with a HIV-1 RNA cutoff of less than 20 copies per mL. The primary assessment of non-inferiority was tested with a conventional 95% CI approach for the difference in response rates (tenofovir alafenamide regimen minus tenofovir disoproxil fumarate regimen) with a prespecified non-inferiority margin of 8%. The independent data monitoring committee performed a planned interim analysis, during which an α penalty of 0.00001 was spent. Therefore, the significance level for the two-sided non-inferiority test at week 48 was 0.04999, corresponding to a 95.001% CI. The two-sided 95.001% CIs were constructed on the basis of the unconditional exact method with two inverted one-sided tests.¹⁶ If non-inferiority in the tenofovir alafenamide group was established, an assessment of superiority would be done with the same 95.001% CI. If the lower bound of the 95.001% CI was greater than 0, then superiority of the tenofovir alafenamide regimen would be established. We used Fisher's exact test as a secondary superiority assessment. In the snapshot analysis of the full analysis set, participants with plasma HIV-1 RNA of less than 50 copies per mL in the week 48 window (between days 295 and 378) were classified into three outcomes: HIV-1 RNA of less than 50 copies per mL; 50 copies per mL HIV-1 RNA including at least 50 copies per mL plasma at week 48, participants who discontinued study drug before week 48 because of a lack of efficacy, or participants who discontinued study drug before week 48; or no virological data in the week 48 if data were missing or participants discontinued study drug before to week 48

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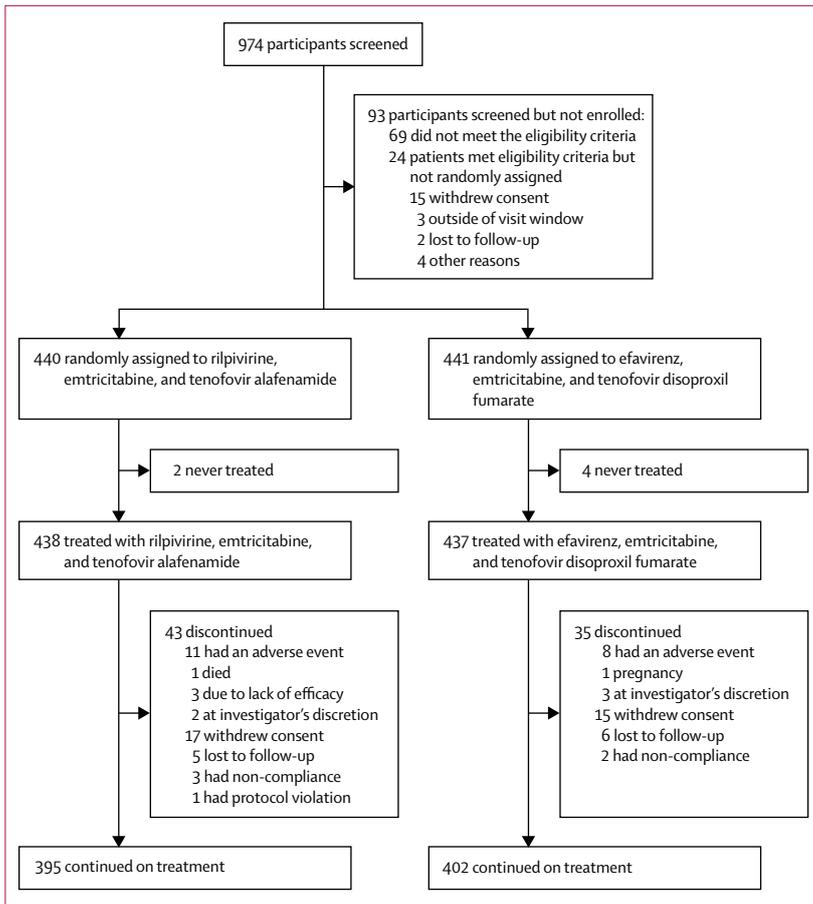


Figure 1: Trial profile

with last available HIV-1 RNA of less than 50 copies per mL. We also assessed the proportion of participants with at least 50 copies per mL HIV-1 RNA by snapshot with a 4% margin for non-inferiority test.

Key bone safety measures were prespecified in secondary endpoint analyses. We assessed the between group difference in percentage change from baseline for spine and hip bone mineral density with an analysis of variance model. A sample size of 750 participants (375 per treatment group) would provide at least 95% power to detect a 1.38% difference between treatment groups in percentage change of hip and spine bone mineral density from baseline to week 48 assuming an SD of 3.4% percentage change in bone mineral density of 3.34%¹⁷ and the two-sided α level of 0.05. If non-inferiority of the primary efficacy endpoint was established, multiplicity adjustments were done for the key bone safety endpoints with a fallback procedure¹⁸ in the sequential order given below with prespecified two-sided α levels: hip bone mineral density ($\alpha=0.02$) and spine bone mineral density ($\alpha=0.02$). The adjusted α levels were dependent on the results from preceding tests. For key bone safety endpoints, we did two-sided superiority tests. We also assessed differences between groups in the distribution

	Rilpivirine, emtricitabine, tenofovir alafenamide (n=438)	Efavirenz, emtricitabine, tenofovir disoproxil fumarate (n=437)
Age (years)	49 (42–55)	48 (41–54)
Sex		
Male	373 (85%)	390 (89%)
Female	65 (15%)	47 (11%)
Ethnic origin		
White	291 (66%)	292 (67%)
Black	118 (27%)	120 (28%)
Asian	9 (2%)	8 (2%)
Ethnicity		
Hispanic or Latino	79 (18%)	78 (18%)
Body-mass index (kg/m ²)	26.1 (23.4–29.4)	25.9 (23.7–28.6)
HIV-1 RNA <50 copies per mL	430 (98%)	432 (99%)
CD4 count (cells per μ L)	673 (507–887)	666 (505–820)
Creatinine clearance by Cockcroft-Gault formula (mL/min)	110.4 (91.4–132.0)	107.6 (91.6–132.7)
Proteinuria by urinalysis (dipstick)		
Grade 0	410 (94%)	400 (91%)
Grade 1	26 (6%)	36 (8%)
Grade 2	2 (<1%)	1 (<1%)

Data are median (IQR) or n (%).

Table 1: Baseline demographic and clinical characteristics

of clinical hip and spine bone mineral density status (normal bone status: bone mineral density T-score at least -1 ; osteopenia: bone mineral density T-score from -2.5 to -1 , and osteoporosis: bone mineral density T-score less than -2.5) at weeks 24 and 48, adjusting for baseline bone mineral density clinical status.

We summarised the safety data in the safety analysis set with descriptive statistics. We computed study drug adherence as number of pills taken divided by number of pills prescribed. For percentage change from baseline in proteinuria, the differences between treatment groups were analysed with rank analysis of covariance. For other continuous laboratory test results, we used Wilcoxon rank sum testing.

We summarised changes in CD4 cell count from baseline to week 48 in the full analysis set by treatment group with descriptive statistics using on-treatment data.

Baseline demographic and clinical characteristics were summarised with descriptive statistics. For categorical data, we calculated the p values from the Cochran-Mantel-Haenszel test (general association statistic for nominal data, row mean scores differ statistic for ordinal data). For continuous data, p value was from the two-sided Wilcoxon rank sum test. We used SAS, version 9.4, for all analyses.

An independent data monitoring committee reviewed interim study results when all participants had reached

week 24. This study was done according to protocol without substantial deviations and is registered with ClinicalTrials.gov, number NCT02345226.

Role of the funding source

Gilead Sciences funded the study, collected, and analysed the data, interpreted the results, and helped to write the report. EDJ enrolled participants, analysed the data, and independently interpreted the results, and edited and approved the manuscript. MR, GC, PR, ALM, AM, CTM, JdW, H-JS, J-MM, FAP, and IPV enrolled participants, reviewed and interpreted analyses of data, and edited and approved the draft manuscript. HC, AC, and EQ designed the study. YPL performed the data analyses, which were reviewed and interpreted by DP, AC, DSG, EQ, and HC. The first draft was written by EDJ and HC. All authors contributed to edits of the final report. EDJ and HC made the decision to submit the manuscript for publication.

Results

Between Jan 26, 2015, and Aug 27, 2015, 974 participants were screened, and 875 were randomly assigned and received at least one dose of study drug (figure 1). Of these 875 participants, 438 were randomly assigned to switch to rilpivirine, emtricitabine, and tenofovir alafenamide. The remaining 437 participants remained on their previous regimen of efavirenz, emtricitabine, and tenofovir disoproxil fumarate. Baseline demographics were balanced between the two treatment groups (table 1).

Viral suppression was maintained in 90% of participants switching to the rilpivirine, emtricitabine, and tenofovir alafenamide group and in 92% of those who continued on the efavirenz, emtricitabine, and tenofovir disoproxil fumarate regimen (table 2).

Switching to rilpivirine, emtricitabine, and tenofovir alafenamide was non-inferior to continuing efavirenz, emtricitabine, and tenofovir disoproxil fumarate for the primary outcome at week 48 (US Food and Drug Administration snapshot algorithm). 1% of participants in the tenofovir alafenamide group and 1% of participants in the tenofovir disoproxil fumarate group had HIV-1 RNA of 50 copies per mL or more (table 2). The upper bound of this two-sided 95·001% confidence interval of the difference between treatment groups was less than the prespecified 4% margin, demonstrating non-inferiority of a switch to tenofovir alafenamide versus continuing tenofovir disoproxil fumarate for the secondary outcome of viral failure. In the per-protocol analysis, 377 (99%) of 380 participants in the tenofovir alafenamide group and 397 (99%) of 400 in the tenofovir disoproxil fumarate group maintained viral suppression (percentage difference -0·0%, 95·001% CI -1·7 to 1·5). Results from the analyses in which missing cases were counted as failures or excluded were consistent with the primary endpoint (table 2). Rates of viral suppression (HIV-1 RNA <50 copies per mL) in the full analysis

	Rilpivirine, emtricitabine, tenofovir alafenamide (n=438)	Efavirenz, emtricitabine, tenofovir disoproxil fumarate (n=437)		Tenofovir alafenamide regimen vs tenofovir disoproxil fumarate regimen
			p value	Difference in percentages (95·001% CI)
FDA snapshot algorithm				
HIV-1 RNA <50 copies per mL	394 (90%)	402 (92%)	0·35	-2·0% (-5·9 to 1·8)
HIV-1 RNA ≥50 copies per mL	5 (1%)	4 (1%)	1·00†	0·2% (-1·4 to 1·8)*
HIV-1 RNA ≥50 copies per mL	2 (<1%)	3 (1%)
Discontinued due to lack of efficacy	2 (<1%)	0
Discontinued due to adverse events or death and last available HIV-1 RNA ≥50 copies per mL	0	0
Discontinued due to other reasons† and last available HIV-1 RNA ≥50 copies per mL	1 (<1%)	1 (<1%)
No virological data	39 (9%)	31 (7%)
Discontinued due to adverse events or death and last available HIV-1 RNA <50 copies per mL	12 (3%)	6 (1%)
Discontinued due to other reasons† and last available HIV-1 RNA <50 copies per mL	23 (5%)	20 (5%)
Missing data but on study drug	4 (1%)	5 (1%)
Analysis with missing cases counted as failures‡				
HIV-1 RNA <50 copies per mL	403 (92%)	407 (92%)	0·61	-1·1% (-4·7 to 2·4)
Analysis with missing cases counted as excluded‡				
HIV-1 RNA <50 copies per mL	403/405 (100%)	407/410 (99%)	1·00	0·2% (-1·1 to 1·7)

Data are n (%) or n/N (%), unless otherwise specified. FDA=US Food and Drug Administration. *p values for the superiority test comparing the percentages of participants with HIV-1 RNA of less than 50 copies per mL or HIV-1 RNA of at least 50 copies per mL between treatment groups were from the Fisher exact test; differences in percentages of participants with HIV-1 RNA of less than 50 copies per mL or HIV-1 RNA of at least 50 copies per mL between treatment groups and their 95·001% CIs were calculated based on an unconditional exact method with two inverted one-sided tests. †Other reasons include participants who discontinued study drug due to investigator's discretion, withdrawal of consent, loss to follow-up, non-compliance with study drug, protocol violation, or pregnancy. ‡p value, difference in percentages, and 95% CIs were based on a dichotomised response: success (HIV-1 RNA <50 copies per mL) or failure (HIV-1 RNA ≥50 copies per mL or missing) for missing cases counted as failed or excluded cases; p values were from the Fisher exact test to compare the two treatment groups; difference in percentages of participants with HIV-1 RNA of less than 50 copies per mL between treatment groups and its 95% CI were calculated based on an unconditional exact method with two inverted one-sided tests.

Table 2: Virological outcomes at week 48

set were similar for subgroups of age, sex, race, and geographic region (appendix p 5). In those with a study drug adherence of at least 95%, a lower percentage of participants in the tenofovir alafenamide group had HIV-1 RNA of less than 50 copies per mL compared with the tenofovir disoproxil fumarate group: 301 (91%) of 331 versus 341 (95%) of 359 (percentage difference -4·0%, 95% CI -8·1 to -0·2). This difference was driven by a higher rate of discontinuations due to non-virological failure reasons in the tenofovir alafenamide group than in the tenofovir disoproxil fumarate group: 17 (5%) of 331 versus ten (3%) of 359. Viral suppression (with cutoff

	Rilpivirine, emtricitabine, tenofovir alafenamide (n=438)	Efavirenz, emtricitabine, tenofovir disoproxil fumarate (n=437)
Any adverse event	351 (80%)	323 (74%)
Study drug-related adverse events	56 (13%)	45 (10%)
Grade 3 or 4 adverse events	27 (6%)	25 (6%)
Serious adverse events	24 (6%)	25 (6%)
Study drug-related serious adverse events	0	1 (<1%)
Premature study drug discontinuation*†	11 (3%)	8 (2%)
Most common adverse events (≥5%)		
Upper respiratory tract infection	44 (10%)	42 (10%)
Nasopharyngitis	34 (8%)	19 (4%)
Cough	26 (6%)	15 (3%)
Headache	24 (6%)	17 (4%)
Diarrhoea	21 (5%)	32 (7%)
Arthralgia	20 (5%)	24 (5%)

Data are n (%). *Adverse event-related discontinuations in the rilpivirine/emtricitabine/tenofovir alafenamide group included anaemia (n=1), diarrhoea (n=1), vomiting (n=1), constipation (n=1), fatigue (n=2), ulcer haemorrhage (n=1), localised infection (n=1), multiple fractures (n=1), road traffic accident (n=1), dysgeusia (n=1), headache (n=1), somnolence (n=1), anxiety (n=1), cough (n=1), decreased glomerular filtration rate (n=1), and generalised pruritus (n=1). †Adverse event-related discontinuations in the efavirenz/emtricitabine/tenofovir disoproxil fumarate group included atrial fibrillation (n=1), diarrhoea (n=1), vomiting (n=1), abdominal distension (n=1), abdominal pain (n=1), constipation (n=1), dysphagia (n=1), gastro-oesophageal reflux disease (n=1), nausea (n=1), hypersensitivity (n=1), sinusitis (n=1), arthralgia (n=1), confusional state (n=1), insomnia (n=1), asthma (n=1), and rash (n=1).

Table 3: Adverse events

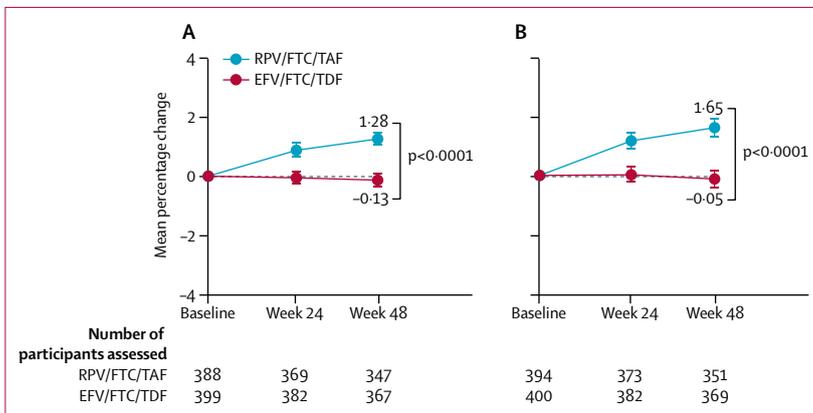


Figure 2: Mean percentage change from baseline to week 24 and week 48 in hip bone mineral density (A) and lumbar spine bone mineral density (B) by dual energy x-ray absorptiometry
 Error bars show 95% CIs. RPV/FTC/TAF=rilpivirine, emtricitabine, and tenofovir alafenamide. EFV/FTC/TDF=efavirenz, emtricitabine, and tenofovir disoproxil fumarate.

of HIV-1 RNA <20 copies per mL) was noted in 379 (87%) of 438 participants in the tenofovir alafenamide group and 395 (90%) of 437 in the tenofovir disoproxil fumarate group (percentage difference -3.9%, 95% CI -8.2 to 0.5). Mean increases in CD4 counts were similar between groups: 23 cells per μL (SD 156) for the tenofovir alafenamide group and 12 cells per μL (SD 153) for the tenofovir disoproxil fumarate group ($p=0.31$).

We analysed resistance in participants with confirmed virological rebound: six in the tenofovir alafenamide group and two in tenofovir disoproxil fumarate group. No emergent resistance was detected in the tenofovir

alafenamide group. Four participants were later re-suppressed to less than 50 copies per mL without changing study drugs and two participants had detectable resistance substitutions that were pre-existing at study entry, one with Lys70Lys/Glu, Lys103Lys/Asn, and Pro225Pro/His in their historical genotype, Lys219Lys/Glu, Lys103Lys/Asn, and Pro225Pro/His by their baseline archive test, and Lys219Lys/Glu and Lys103Asn at week 8; and one with Lys103Lys/Asn and Glu138Glu/Ala at week 36 and their baseline visit with HIV-1 RNA of 54200 copies per mL. One participant in the tenofovir disoproxil fumarate developed emergent resistance to emtricitabine (Met184Val) and rilpivirine (Val106Ile/Leu and Tyr188Leu) at week 24. Three participants had evidence of resistance to study drugs in their historical genotypes: two in the tenofovir alafenamide group (one Lys103Asn and one Glu138Ala) and one in the efavirenz/emtricitabine/tenofovir disoproxil fumarate group with Lys103Asn. All three of these participants discontinued at week 36 or week 48 with HIV-1 RNA of less than 50 copies per mL.

Both treatments were well tolerated, with most adverse events reported as mild or moderate in severity. The types of adverse events were similar between the groups (table 3). Adverse events leading to study drug discontinuation were reported in 11 (3%) of 438 participants in the tenofovir alafenamide group and eight (2%) of 437 in the tenofovir disoproxil fumarate group. The incidence of any study drug-related adverse events was similar between groups (table 3). Five (1%) of 438 participants in the tenofovir alafenamide group and seven (2%) of 437 in the tenofovir disoproxil fumarate group had adverse events considered related to study drug that led to discontinuation. One participant in the tenofovir alafenamide group died; this event was related to cocaine and methamphetamine overdose. Laboratory abnormalities were similar in both treatment groups, with a similar incidence of grade 3 or 4 laboratory adverse events: 43 (10%) of 437 participants in the tenofovir alafenamide group versus 39 (9%) of 434 participants in the tenofovir disoproxil fumarate group.

At week 48, bone mineral density at the hip and spine increased in the tenofovir alafenamide group but remained stable or decreased at both sites in the tenofovir disoproxil fumarate group (figure 2, appendix p 2). At week 48, bone mineral density clinical status (osteopenia or osteoporosis) at the hip had improved in 15 participants in the tenofovir alafenamide group compared with nine participants in the tenofovir disoproxil fumarate group and in the spine in 27 participants compared with six ($p=0.0037$ for the difference between groups). Eight participants in the tenofovir alafenamide group and four participants in the tenofovir disoproxil fumarate group had fractures. One pathological fracture occurred secondary to bone metastasis; all other fractures were trauma-related and considered unrelated to treatment.

No cases of proximal tubulopathy were reported by the investigator in either group. One 74-year-old man in the tenofovir alafenamide group discontinued study drug because of a decreased creatinine clearance without evidence of proteinuria or glycosuria. This patient had a previous history of hypertension and screening creatinine clearance of 54.2 mL/min. This adverse event was considered related to study drug, with the lowest creatinine clearance being 26.4 mL/min. Study drug was discontinued and the patient initiated non-study drug treatment with another tenofovir alafenamide-containing single-tablet regimen (elvitegravir, cobicistat, emtricitabine, and tenofovir alafenamide). Creatinine clearance returned to baseline (51.7 mL/min) after 4 weeks. For both treatment groups, median creatinine clearance decreased at week 4 and was stable from weeks 12 through 48. At week 48, median decreases from baseline in creatinine clearance were greater in the tenofovir alafenamide group than in the tenofovir disoproxil fumarate group (table 4, appendix p 3). At 48 weeks, all measures of quantitative proteinuria (ratios of total urinary protein, albumin, retinol binding protein and β 2-microglobulin to urine creatinine) improved with tenofovir alafenamide compared with tenofovir disoproxil fumarate ($p < 0.0001$ for all ratios).

Switching to tenofovir alafenamide led to decreases in fasting total cholesterol and HDL at week 48; lipids remained stable in the tenofovir disoproxil fumarate group (appendix p 4). Similar changes in total cholesterol to HDL ratio were observed between the two groups at week 48 (median change 0.1 for tenofovir alafenamide and 0 for tenofovir disoproxil fumarate, $p = 0.20$). 16 (4%) of 438 in the tenofovir alafenamide group initiated treatment with lipid-modifying agents between entry and week 48 compared with 17 (4%) of 437 in the tenofovir disoproxil fumarate group; $p = 0.86$.

Discussion

To our knowledge, this is the first randomised, controlled trial to assess the safety and efficacy of switching to the single-tablet regimen rilpivirine, emtricitabine and tenofovir alafenamide from efavirenz, emtricitabine, and tenofovir disoproxil fumarate. Switching to the tenofovir alafenamide regimen was non-inferior to continuing the tenofovir disoproxil fumarate regimen and was associated with a low rate of virological failure (<1%). There was no evidence of treatment-emergent resistance in participants who switched to the tenofovir alafenamide regimen through to week 48. Of note, to accommodate the double-blind, placebo-controlled study design, participants switched from a stable, once-daily regimen to two study drug tablets taken twice daily administered with different food schedules. The study drug administration complexity could have influenced tolerability and adherence and potentially affected viral suppression.

The adverse event profiles were similar between the two treatment groups through to week 48, probably reflecting tolerance for the well characterised adverse

	Rilpivirine, emtricitabine, tenofovir alafenamide (n=438)	Efavirenz, emtricitabine, tenofovir disoproxil fumarate (n=437)	p value
Creatinine clearance by Cockcroft-Gault (mL/min)			
Baseline	110.4 (91.4 to 132.0)	107.6 (91.6 to 132.7)	0.63
Change at week 48	-4.1 (-12.7 to 4.6)	-0.6 (-7.8 to 6.7)	<0.0001
Urine protein to creatinine ratio (mg/g)			
Baseline	63.3 (40.8 to 105.4)	62.2 (40.7 to 108.7)	0.91
Percentage change at week 48	-30.0% (-54.4 to 18.9)	-2.0% (-35.6 to 42.0)	<0.0001
Urine albumin to creatinine ratio (mg/g)			
Baseline	6.9 (4.2 to 13.6)	6.4 (4.3 to 11.8)	0.40
Percentage change at week 48	-13.5% (-47.5 to 25.3)	12.2% (-20.0 to 55.6)	<0.0001
Urine β-2 microglobulin to creatinine ratio (μg/g)			
Baseline	130.1 (69.0 to 498.6)	153.6 (78.8 to 480.8)	0.13
Percentage change at week 48	-41.0% (-74.5 to 0.8)	17.1% (-34.1 to 135.7)	<0.0001
Urine retinol-binding protein to creatinine ratio (μg/g)			
Baseline	115.8 (75.0 to 254.4)	131.8 (82.7 to 265.7)	0.14
Percentage change at week 48	-27.6% (-58.8 to 4.2)	29.1% (-13.4 to 96.8)	<0.0001
Data are median (IQR).			

Table 4: Changes in quantitative measures of renal functions from baseline to week 48

effect profile of efavirenz, included in the regimens of all patients before randomisation. Switching to rilpivirine, emtricitabine, and tenofovir alafenamide led to improvements in hip and spine bone density at week 48. Although direct comparison of tenofovir alafenamide with tenofovir disoproxil fumarate cannot be made in the current study, these benefits are consistent with previous studies of virally suppressed patients who switched from a regimen containing tenofovir disoproxil fumarate to one with tenofovir alafenamide.^{9,11}

Rilpivirine's inhibition of organic cation transporter 2 reduces the tubular secretion of creatinine, thus raising serum creatinine concentrations without affecting glomerular filtration.^{19,20} For participants switching to rilpivirine, emtricitabine, and tenofovir alafenamide, a small creatinine clearance decrease was observed at week 4 and remained stable from week 12 to week 48. In parallel, improvements in measures of proteinuria were noted, suggesting a lower potential for nephrotoxicity of rilpivirine, emtricitabine, tenofovir alafenamide than with efavirenz, emtricitabine, and tenofovir disoproxil fumarate. Chronic use of tenofovir disoproxil fumarate is associated with declines in kidney function,²¹⁻²³ and the renal safety implications for switching to the tenofovir alafenamide regimen are encouraging. Longer term assessment will confirm whether these improved bone and renal measures decrease comorbidities.

We observed lower fasting total cholesterol and HDL cholesterol levels in the rilpivirine, emtricitabine, tenofovir alafenamide group than in the efavirenz, emtricitabine, and tenofovir disoproxil fumarate group at week 48, consistent with previous observations after discontinuation of efavirenz.^{24,25} However, the lipid changes in this study were small, and no difference in

the total cholesterol to HDL ratios between treatment groups was observed. In previous single-variable studies, the off-target lipid-lowering effect of tenofovir disoproxil fumarate was lost when switching to tenofovir alafenamide.^{8,26} The efavirenz to rilpivirine switch and subsequent change in lipids makes the interpretation of any tenofovir-related lipid effect less clear in the current study.

There are important limitations of this study worth noting. The study was powered for the primary efficacy endpoint and might fail to detect rare clinical safety events. Other limitations include the fact that a small proportion of enrolled study participants had advanced HIV disease or renal dysfunction.

Results from this study complement a parallel study in which participants switched to rilpivirine, emtricitabine, and tenofovir alafenamide from a stable regimen of rilpivirine, emtricitabine, tenofovir disoproxil fumarate.²⁷ Together, these studies present the first clinical outcomes data assessing the use of coformulated rilpivirine, emtricitabine, and tenofovir alafenamide.

Overall, virally suppressed, HIV-infected individuals who switched to rilpivirine, emtricitabine, and tenofovir alafenamide maintained viral suppression at 48 weeks similarly to those who remained on efavirenz, emtricitabine, and tenofovir disoproxil fumarate. The rilpivirine, emtricitabine, and tenofovir alafenamide single-tablet regimen was well tolerated and associated with significant improvements in measures of bone and renal safety. Virally suppressed individuals can be switched from efavirenz, emtricitabine, and tenofovir disoproxil fumarate to rilpivirine, emtricitabine, and tenofovir alafenamide without a loss of efficacy.

Contributors

All authors were involved in the development of the primary manuscript, interpretation of data, have read and approved the final version, and have met the criteria for authorship as established by the ICMJE. EDJ, MR, GC, PR, ALM, AM, CTM, JdW, H-JS, J-MM, FAP, and IPV enrolled participants, analysed data and independently interpreted the results, and edited and approved the report. EQ and HC designed the study. YPL did the data analyses, which were reviewed and interpreted by DP, AC, EQ, DSG, and HC. The first draft was written by EDJ and HC. All authors contributed to edits of the final report.

Declaration of interests

This study was sponsored by Gilead Sciences (Gilead). EDJ has received research grant support from and has served on the speaker's bureau and advisory boards for Gilead and Janssen. MR reports receiving grants from Gilead Sciences. GC reports payment for conducting HIV drug research from Gilead, ViiV Healthcare, GlaxoSmithKline (GSK), Pfizer, Janssen, and Merck. PR receives research support from AbbVie, Bristol-Myers Squibb, Gilead, GSK, Idenix, Janssen, and Merck; consulting fees from AbbVie, Gilead, and Janssen, and serves on the speakers' bureau for AbbVie, Gilead Sciences, Janssen, and ViiV Healthcare. ALM received grants, personal fees and non-financial support from Gilead Sciences, grants and personal fees from ViiV Healthcare, Janssen, and Merck, and grants from Bristol-Myers Squibb. AM received grants and personal fees from Gilead, ViiV Healthcare, and Merck and grants from Bristol-Myers Squibb. CTM has received research grants and personal fees from Gilead and Janssen; and speaker's bureau fees from fees from AbbVie, Theratechnologies, Janssen, ViiV Healthcare, and Gilead. JdW has acted as consultant for Abbott Laboratories Canada and served on advisory boards for Abbott

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