# Switching from 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, a tenofovir prodrug, results in 90% lower tenofovir plasma concentrations than does tenofovir disproxil fumarate, thereby minimising bone and renal risks. We investigated the efficacy, safety, and tolerability of switching to a single-tablet regimen containing rilpivirine, emtricitabine, and tenofovir alafenamide compared with remaining on rilpivirine, emtricitabine, and tenofovir disoproxil fumarate.

**Methods** In this randomised, double-blind, multicentre, placebo-controlled, non-inferiority trial, HIV-1-infected adults were screened and enrolled at 119 hospitals in 11 countries in North America and Europe. Participants were virally suppressed (HIV-1 RNA <50 copies per mL) on rilpivirine, 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 either rilpivirine (25 mg), emtricitabine (200 mg), and tenofovir alafenamide (25 mg) or to remain on a single-tablet regimen of rilpivirine (25 mg), emtricitabine (200 mg), and tenofovir disoproxil fumarate (300 mg), with matching placebo, once daily for 96 weeks. Investigators, participants, study staff, and those assessing outcomes were masked to treatment group. All participants who received one dose of study drug and were on the tenofovir disoproxil fumarate regimen before screening were included in primary efficacy analyses. The primary endpoint was the proportion of participants with less than 50 copies per mL of plasma HIV-1 RNA at week 48 (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 NCT01815736.

**Findings** Between Jan 26, 2015, and Aug 25, 2015, 630 participants were randomised (316 to the tenofovir alafenamide group and 314 to the tenofovir disoproxil fumarate group). At week 48, 296 (94%) of 316 participants on tenofovir alafenamide and 294 (94%) of 313 on tenofovir disoproxil fumarate had maintained less than 50 copies per mL HIV-1 RNA (difference –0·3%, 95·001% CI –4·2 to 3·7), showing non-inferiority of tenofovir alafenamide to tenofovir disoproxil fumarate. Numbers of adverse events were similar between groups. 20 (6%) of 316 participants had study-drug related adverse events in the tenofovir alafenamide group compared with 37 (12%) of 314 in the tenofovir disoproxil fumarate group; none of these were serious.

**Interpretation** Switching to rilpivirine, emtricitabine, and tenofovir alafenamide was non-inferior to continuing rilpivirine, emtricitabine, tenofovir disoproxil fumarate 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.

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## Introduction

The need for lifelong antiretroviral therapy highlights the imperative for antiretroviral therapy regimens to maximise simplicity, safety, tolerability, and enduring antiviral efficacy.[1–3] Even effective regimens might need to be modified to reduce toxicity, to improve tolerability, to simplify adherence, to reduce cost, or to adjust to allow for concomitant medication or comorbid conditions.[1,4] The single-tablet regimen of the non-nucleoside reverse-transcriptase inhibitor (NNRTI) rilpivirine co-formulated with emtricitabine and tenofovir disoproxil fumarate has been used to simplify regimens and is a recommended alternative regimen for the treatment of HIV-1 infection.[5] Significant clinical improvements have been observed in virally suppressed HIV-infected patients switching to rilpivirine, emtricitabine, and tenofovir disoproxil fumarate from a ritonavir-boosted protease inhibitor and NNRTI-based regimens.[6] The efficacy and

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## Research in context

### Evidence before this study

We searched PubMed for clinical trials of tenofovir alafenamide and rilpivirine for the treatment of HIV-1 infection. Our search terms included "tenofovir alafenamide", "TAF", "rilpivirine", and "HIV" with articles restricted to clinical trials published in English between Jan 1, 1990 and Aug 4, 2016. The search yielded two trials that included participants treated concomitantly with tenofovir alafenamide and rilpivirine. In the first, bioequivalence of coformulated rilpivirine, emtricitabine, and tenofovir alafenamide was established in healthy volunteers using the references of single-agent rilpivirine and coformulated elvitegravir, cobicistat, emtricitabine, and tenofovir alafenamide. The second trial was a phase 3 clinical study that assessed switching from fixed-dose emtricitabine and tenofovir disoproxil fumarate to a fixed-dose combination of emtricitabine and tenofovir alafenamide, both with a third drug (n=663). Only nine (1%) participants in this study were taking rilpivirine and only three of those were randomly switched to tenofovir alafenamide. No study has examined clinical outcomes for treatment with coformulated rilpivirine, emtricitabine, and tenofovir alafenamide.

### Added value of this study

This large study reports the clinical outcome of the single-tablet regimen rilpivirine, emtricitabine, and tenofovir alafenamide in patients who were virally suppressed on rilpivirine, emtricitabine, and tenofovir disoproxil fumarate. Switching to a tenofovir alafenamide regimen was non-inferior to remaining on the tenofovir disoproxil fumarate regimen, and both maintained high levels of virological suppression at 48 weeks without evidence of treatment-emergent resistance. Participants who switched to the tenofovir alafenamide coformulation had significant improvements in measures of proteinuria and in bone mineral density. These findings are the first to provide favourable efficacy and safety of coformulated rilpivirine, emtricitabine, and tenofovir alafenamide.

### Implications of all available evidence

Rilpivirine, emtricitabine, and tenofovir alafenamide is an effective, complete regimen with improved measures of renal and bone safety compared with rilpivirine, emtricitabine, and tenofovir disoproxil fumarate. These findings support guidelines recommending tenofovir alafenamide-based regimens, including coformulation with rilpivirine and emtricitabine, as initial and ongoing treatment for HIV-1 infection.

safety of rilpivirine in antiretroviral therapy-naive patients has been shown in randomised clinical trials, mostly with emtricitabine and tenofovir disoproxil fumarate as the NRTI backbone.[7–9]

Tenofovir alafenamide is a novel prodrug of tenofovir that is converted intracellularly to the active form; the resulting concentrations of tenofovir diphosphate in circulating lymphocytes are higher than those achieved with tenofovir disoproxil fumarate. Tenofovir alafenamide has a similar antiviral efficacy to tenofovir disoproxil fumarate at a lower dose, resulting in 91% lower plasma tenofovir exposures. Pivotal phase 3 studies established the virological non-inferiority of tenofovir alafenamide versus tenofovir disoproxil fumarate.[10–12] In these phase 3 studies, participants treated with tenofovir alafenamide consistently showed improvements in renal and bone health compared with those treated with tenofovir disoproxil fumarate.

The single-tablet regimen containing 25 mg rilpivirine, 200 mg emtricitabine, and 25 mg tenofovir alafenamide was approved by the US Food and Drug Administration (FDA) and the European Medicines Agency after demonstration of bioequivalent pharmacokinetics to rilpivirine and an approved emtricitabine and tenofovir alafenamide-containing regimen.[1,5,13]

We investigated the clinical efficacy, safety, and tolerability of switching to rilpivirine, emtricitabine, and tenofovir alafenamide versus remaining on rilpivirine, emtricitabine, and tenofovir disoproxil fumarate in HIV-1 infected, virally suppressed adults. An important secondary endpoint of this large, randomised controlled trial was to further explore the behaviour of markers of renal function and bone metabolism, seeking confirmation of the hypothesis that tenofovir alafenamide is associated with improvement in these markers compared with tenofovir disoproxil fumarate. Herein, we present the week 48 results of this study.

## Methods

### Study design and participants

GS-US-366-1216 is a phase 3b, randomised, double-blind, non-inferiority study done at 119 hospital sites in 11 countries in North America (Canada and the USA) and Europe (Belgium, France, Germany, Italy, the Netherlands, Spain, Sweden, Switzerland, and the UK). Study investigators enrolled participants who were HIV-1 infected adults (aged at least 18 years), virally suppressed with HIV-1 RNA less than 50 copies per mL on a stable regimen of coformulated rilpivirine, emtricitabine, 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 had no documented resistance to rilpivirine, emtricitabine, or tenofovir. 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 (1:1) participants to either switch to rilpivirine, emtricitabine, and tenofovir alafenamide or remain on rilpivirine, emtricitabine, and tenofovir disoproxil fumarate. A computer-generated randomisation allocation sequence was created by a third party and used block randomisation with a block size of 4 (Bracket, San Francisco, CA, USA). Participants received placebo tablets matching the alternative treatment and were instructed to take the study medications with food (without instructions with regard to caloric or nutritional content). All investigators, participants, and study staff giving treatment, assessing outcomes, and collecting data were masked to the treatment group. Investigators determined eligibility, and used a real-time interactive web response system to to assign participants, to obtain the patient number, and to receive the treatment assignment (provided and managed by Bracket).

### 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 or remained on a single-tablet regimen of 25 mg rilpivirine, 200 mg emtricitabine, and 300 mg tenofovir disoproxil fumarate. Laboratory tests included haematological analysis, serum chemistry tests, fasting lipid parameters, CD4 cell counts, measures of renal function (estimated glomerular filtration rate with the Cockroft-Gault equation), 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-1 RNA concentration (Roche TaqMan 2.0; Roche Diagnostics, Rotkreuz, Switzerland). Resistance testing consisted of genotyping and phenotyping of protease and reverse transcriptase (Monogram Biosciences, CA, USA) for any participant who had a confirmed HIV-1 RNA of at least 50 copies per mL and the confirmation of HIV-1 RNA of at least 400 copies per mL or having HIV-1 RNA of at least 400 copies per mL at week 48, or at the last visit on study drug. We collected all available historical genotypes before this study. In participants who had virological failure and developed resistance on study drug, and did not have historical genotype data available, proviral DNA genotyping (GenoSure Archive, Monogram Biosciences, CA, USA) was done retrospectively on the baseline sample. 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 centre masked to study group assignment read all scans (BioClinica, PA, USA). 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.[14] Two key safety endpoints were prespecified with multiplicity adjustments: percentage change from baseline in hip bone mineral density and spine bone mineral density at week 48. Additional efficacy endpoints included the treatment proportion of participants with plasma HIV-1 RNA of at least 50 copies per mL at week 48; the virological efficacy by subgroups stratified by age, sex, race, geographic region, and study medication adherence; the proportion of participants with plasma HIV-1 RNA of less than 50 copies per mL at week 48 when classifying missing cases as failures and missing cases as excluded; participants with HIV-1 RNA of less than 20 copies per mL 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.

### Statistical analysis

Assuming a response rate of 89% at week 48, we calculated that a sample size of 550 randomly assigned participants would be needed to achieve 85% power to detect non-inferiority at a one-sided α of 0·025.

The primary analysis was done in the full-analysis set (ie, all participants who were randomly assigned, had received at least one dose of the study drug and were on rilpivirine, emtricitabine, and tenofovir disoproxil fumarate before the screening visit) after all enrolled participants had completed their week 48 study visit or had prematurely discontinued the study drug. Additionally, the week 48 efficacy endpoint was analysed with an HIV-1 RNA cutoff of less than 20 copies per mL.

We tested the primary assessment of non-inferiority 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%. A planned independent data monitoring committee interim analysis was done after all enrolled participants had completed their week 24 study visit or had prematurely discontinued the study drug at week 24. An α penalty of 0·00001 was spent for this planned interim analysis. Therefore, the significance level for the two-sided non-inferiority test at week 48 was 0·04999, corresponding to a 95·001% CI. We constructed the two-sided 95·001% CIs based on the unconditional exact method using two inverted one-sided tests.[15] In the snapshot analysis of the full-analysis set, participants with HIV-1 RNA less than 50 copies per mL in the week 48 window (between days 295 and 378) were classified into three outcomes: less than 50 copies per mL at week 48; 50 copies per mL or more at week 48, participants

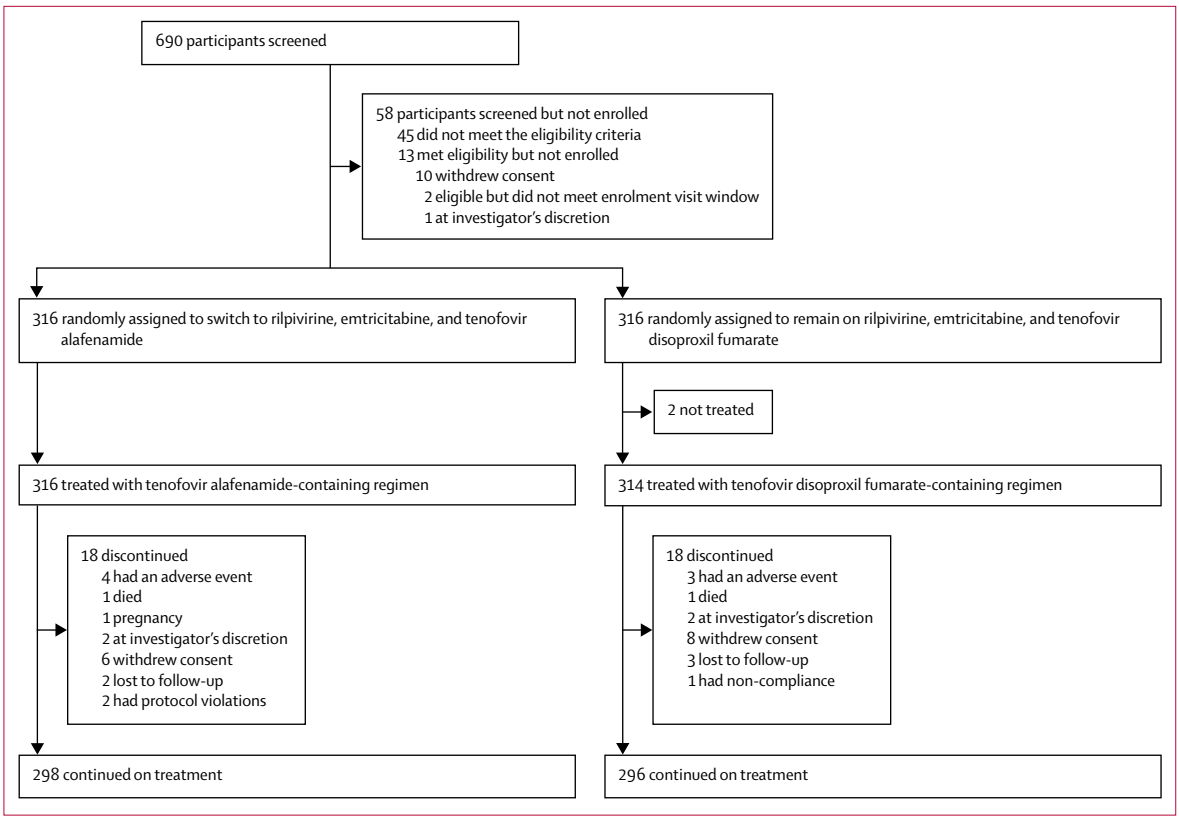


***Figure 1:*** **Trial profile**

| | Rilpivirine, emtricitabine, and tenofovir alafenamide (n=316) | Rilpivirine, emtricitabine, and tenofovir disoproxil fumarate (n=314) |
|---|---|---|
| Age (years) | 46 (37–53) | 44 (36–51) |
| Sex | | |
| Male | 275 (87%) | 289 (92%) |
| Female | 41 (13%) | 25 (8%) |
| Race | | |
| White | 238 (75%) | 235 (75%) |
| Black | 65 (21%) | 54 (17%) |
| Asian | 7 (2%) | 17 (5%) |
| Ethnicity | | |
| Hispanic or Latino | 40 (13%) | 53 (17%) |
| Body-mass index (kg/m²) | 25·7 (23·3–29·0) | 25·5 (23·0–27·8) |
| HIV-1 RNA <50 copies per mL | 307 (97%) | 312 (99%) |
| CD4 count (cells per μL) | 673 (521–877) | 668 (525–817) |
| Creatinine clearance by Cockcroft-Gault formula (mL/min) | 103·5 (88·5–119·8) | 99·7 (87·3–119·8) |
| Proteinuria by urinalysis (dipstick) | | |
| Grade 0 | 285 (90%) | 285 (91%) |
| Grade 1 | 31 (10%) | 28 (9%) |
| Grade 2 | 0 | 1 (<1%) |

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

***Table 1:*** **Baseline characteristics**

discontinued study drug before week 48 due to lack of efficacy, or participants discontinued study drug before week 48 with last HIV-1 RNA 50 copies per mL or more; and no virological data at week 48 if data were missing or participants discontinued study drug before week 48 with last available HIV-1 RNA measurement of less than 50 copies per mL. We also assessed the proportion of participants with plasma HIV-1 RNA of 50 copies per mL or more at week 48 by snapshot with a 4% margin for non-inferiority test.

Key bone measures were prespecified in secondary endpoint analyses. We assessed the difference in percentage change from baseline for spine and hip bone mineral density between treatment groups using an ANOVA model. A sample size of 300 participants (150 per treatment group) would provide at least 90% power to detect a 1·38% difference between treatment groups in the percentage change of hip and spine bone mineral density from baseline to week 48 assuming a SD for bone mineral density of 3·33%[16] and the two-sided *t* test was done at an α of 0·05. If non-inferiority of the primary efficacy endpoint was established, multiplicity adjustments were done for the safety endpoints with a fallback procedure[17] in the sequential order given below with prespecified two-sided α levels: hip bone mineral density (α=0·025) and spine bone mineral density (α=0·025). The adjusted

α levels were dependent on the results from preceding tests. For both safety endpoints, two-sided superiority tests were done. We assessed differences between groups in the distribution of clinical hip and spine bone mineral density status (normal: bone status bone mineral density T-score ≥–1, osteopenia: bone mineral density T-score from ≥–2·5 to <–1, and osteoporosis: bone mineral density T-score <–2·5), adjusting for baseline bone mineral density clinical status.

We summarised the safety data in the safety analysis set (all randomly assigned participants who received at least one dose of study drug) with descriptive statistics. Study drug adherence was computed as the number of pills taken divided by number of pills prescribed. For 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 and per-protocol sets by treatment group with descriptive statistics using on-treatment data. We constructed the differences at baseline and changes from baseline in CD4 cell count between treatment groups and the associated 95% CI with an ANOVA model, including treatment as a fixed effect in the model. We generated p values for comparison between treatment groups from the ANOVA model as well.

We summarised baseline characteristics with descriptive statistics. For categorical data, we calculated p values with the Cochran-Mantel-Haenszel test (general association statistic was used for nominal data, row mean scores differ statistic was used for ordinal data) for treatment comparison. For continuous data, we calculated p values by use of the two-sided Wilcoxon rank sum test for treatment comparison. SAS software, version 9.4, was used for all statistical analyses. This study is registered with ClinicalTrials.gov, number NCT02345262.

### Role of the funding source

The funder collected and analysed the data, interpreted the results, and helped to write the report. All authors had full access to the study data. CO and HC had final responsibility to submit for publication.

## Results

Between Jan 26, 2015, and Aug 25, 2015, 690 participants were screened for this study and 632 were randomly assigned; 630 received at least one dose of study drug (figure 1). Of these 630 participants, 316 were randomised to switch to the tenofovir alafenamide regimen. The remaining 314 participants remained on their previous tenofovir disoproxil fumarate regimen. Baseline demographics were balanced between the two treatment groups with the exception of sex; more participants were female in the tenofovir alafenamide group than in the tenofovir disoproxil fumarate group (table 1).

| | Rilpivirine, emtricitabine, and tenofovir alafenamide (n=316) | Rilpivirine, emtricitabine, and tenofovir disoproxil fumarate (n=313)* | Tenofovir alafenamide *vs* tenofovir disoproxil fumarate | |
|---|---|---|---|---|
| | | | p value† | Difference in percentages (95·001% CI)‡ |
| HIV-1 RNA <50 copies per mL | 296 (94%) | 294 (94%) | 1·00 | –0·3% (–4·2 to 3·7) |
| HIV-1 RNA ≥50 copies per mL | 2 (1%) | 0 | 0·50 | 0·6% (–0·6 to 2·3) |
| HIV-1 RNA ≥50 copies per mL | 2 (1%) | 0 | .. | .. |
| Discontinued because of a lack of efficacy | 0 | 0 | .. | .. |
| Discontinued because of adverse events or death and last available HIV-1 RNA ≥50 copies per mL | 0 | 0 | .. | .. |
| Discontinued because of other reasons§ and last available HIV-1 RNA ≥50 copies per mL | 0 | 0 | .. | .. |
| No virological data | 18 (6%) | 19 (6%) | .. | .. |
| Discontinued because of adverse events or death and last available HIV-1 RNA <50 copies per mL | 5 (2%) | 4 (1%) | .. | .. |
| Discontinued because of other reasons§ and last available HIV-1 RNA <50 copies per mL | 12 (4%) | 11 (4%) | .. | .. |
| Missing data for study drug | 1 (<1%) | 4 (1%) | .. | .. |
| HIV-1 RNA <50 copies per mL with missing cases counted as failures¶ | 301 (95%) | 297 (95%) | 0·86 | 0·4% (–3·0 to 4·0) |
| HIV-1 RNA <50 copies per mL with missing data counted as excluded¶ | 301/304 (99%) | 297/297 (100%) | 0·25 | –1·0% (–2·9 to 0·3) |

Data are n (%). *One participant was randomly assigned and dosed but was taking co-formulated efavirenz, emtricitabine, and tenofovir disoproxil fumarate instead of co-formulated emtricitabine, rilpivirine, and tenofovir disoproxil fumarate and was excluded from the full-analysis set. †p values for the superiority test comparing the percentages of participants with less than 50 copies per mL HIV-1 RNA or at least 50 copies per mL HIV-1 RNA between treatment groups were from the Fisher's exact test. ‡Differences in percentages of participants with less than 50 copies per mL HIV-1 RNA or at least 50 copies per mL HIV-1 RNA between treatment groups and their 95·001% CIs were calculated on the basis of an unconditional exact method with two inverted one-sided tests. §Other reasons include participants who discontinued study drug at investigator's discretion, withdrawal of consent, loss to follow-up, non-compliance with study drug, protocol violation, and 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's exact test to compare the two treatment groups; and difference in percentages of patients with less than 50 copies per mL HIV-1 RNA between treatment groups and its 95% CIs were calculated on the basis of an unconditional exact method with two inverted one-sided tests.

***Table 2:*** **Virological outcomes at week 48**

Switching to tenofovir alafenamide was non-inferior to continuing tenofovir disoproxil fumarate for the primary outcome HIV-1 RNA of less than 50 copies per mL at week 48 (FDA snapshot algorithm); viral suppression was maintained in 296 (94%) of 316 participants in the tenofovir alafenamide group and in 294 (94%) of 313 participants in the tenofovir disoproxil fumarate group (adjusted difference –0·3%, 95·001% CI –4·2 to 3·7; table 2). On the basis of the snapshot algorithm, few participants had HIV-1 RNA of 50 copies per mL or more: two (1%) of 316 participants in the tenofovir alafenamide and none of the 313 participants in the tenofovir disoproxil fumarate group (adjusted difference 0·6%, –0·6 to 2·3, p=0·50). Since the upper bound of this two-sided 95·001% CI of the difference between

See Online for appendix

| | Rilpivirine, emtricitabine and tenofovir alafenamide (n=316) | Rilpivirine, emtricitabine and tenofovir disoproxil fumarate (n=314) |
|---|---|---|
| Any adverse event | 254 (80%) | 254 (81%) |
| Grade 3 or 4 adverse events | 17 (5%) | 10 (3%) |
| Serious adverse events* | 18 (6%) | 12 (4%) |
| Study-drug-related adverse events | 20 (6%) | 37 (12%) |
| Study-drug-related serious adverse events | 0 | 0 |
| Any adverse event leading to study drug discontinuation† | 4 (1%) | 3 (1%) |
| Adverse event in ≥5% of participants | | |
| Upper respiratory tract infection | 27 (9%) | 26 (8%) |
| Diarrhoea | 23 (7%) | 26 (8%) |
| Nasopharyngitis | 22 (7%) | 24 (8%) |
| Headache | 15 (5%) | 17 (5%) |
| Bronchitis | 12 (4%) | 18 (6%) |
| Sinusitis | 12 (4%) | 18 (6%) |

Data are n (%). *Serious adverse events were defined as per-protocol events and were judged to be so by the investigator. †Adverse-event-related study drug discontinuations in the tenofovir alafenamide group include gastroesophageal reflux disease (n=1), hiatus hernia and ulcerative oesophagitis (n=1), fatigue (n=1), and suicidal depression (n=1). Adverse-event-related study drug discontinuations in the tenofovir disoproxil fumarate group include drug hypersensitivity (n=1), increased alanine aminotransferase and increased aspartate aminotransferase (n=1), and chronic myeloid leukaemia (n=1).

***Table 3:*** **Adverse events**

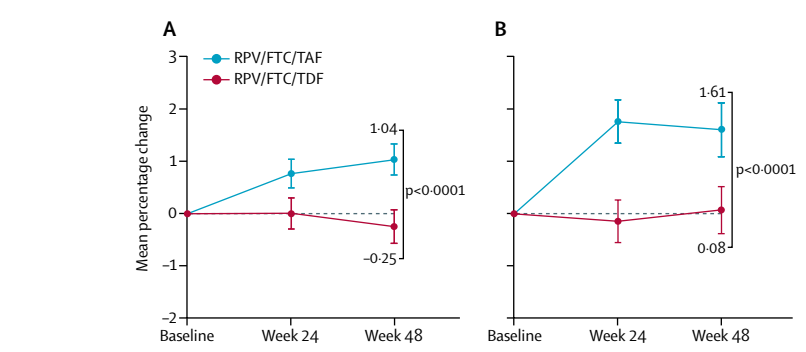


***Figure 2:*** **Mean percentage change from baseline to week 24 and 48 in hip bone mineral density (A) and lumbar spine bone mineral density (B) by dual energy x-ray absorptiometry**
Error bars show 95% CIs. RPV/FTC/TAF=rilpivirine, emtricitabine, and tenofovir alafenamide. RPV/FTC/TDF=rilpivirine,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

treatment groups was less than the prespecified 4% margin, results of this prespecified secondary efficacy endpoint outcome also showed non-inferiority of the tenofovir alafenamide regimen with regard to virological failure compared with the tenofovir disoproxil fumarate regimen. In the per-protocol analysis, 287 (99%) of 289 participants in the tenofovir alafenamide group and 280 (100%) of 280 participants in the tenofovir disoproxil fumarate group maintained viral suppression (adjusted difference –0·7%, –2·5 to 0·7). Results from the analyses of missing cases counted as failures or exclusions were consistent with the primary endpoint (table 2). The proportions of participants with viral suppression (HIV-1 RNA <50 copies per mL) in the full-analysis set were similar between age, sex, race, geographic region, and adherence rate subgroups (appendix p 5). Viral suppression with HIV-1 RNA cutoff at less than 20 copies per mL was noted in 290 (92%) of 316 participants in the tenofovir alafenamide group and 283 (90%) of 313 participants in the tenofovir disoproxil fumarate group (difference 1·4%, –3·2 to 6·0). Mean changes from baseline in CD4 cell counts were similar between groups: +9 cells per µL (SD 160) for the tenofovir alafenamide group and –1 cell per µL (SD 153) for the tenofovir disoproxil fumarate group (p=0·41).

We did resistance analysis for two participants, one in each group. No emergent resistance developed to either treatment regimen. The participant in the tenofovir alafenamide group had re-emergence of archived mutations Met41Lys, Glu44Asp, Asp67Asn, Val118Ile, Leu210Trp, and Thr215Tyr that confer resistance to tenofovir and the participant did not re-suppress (HIV-1 RNA of less than 50 copies per mL). The participant in the tenofovir disoproxil fumarate group had no resistance detected and did achieve resuppression on continued therapy. Seven participants had evidence of resistance to study drugs in their historical genotypes: four in the tenofovir alafenamide group (two with Met184Val, one with Glu138Ala, and one with Lys101Glu+Glu138Lys) and three in the tenofovir disoproxil fumarate group (one Met184Val and two Glu138Ala; appendix p 1). One participant with Met184Val in the tenofovir alafenamide group discontinued study drug at week 4 with less than 50 copies per mL HIV-1 RNA; all other participants had less than 50 copies per mL HIV-1 RNA at week 48. 17 participants had Lys103Asn pre-existing in their historical genotypes (ten in the tenofovir alafenamide group and seven in the tenofovir disoproxil fumarate group). One participant in each group with Lys103Asn discontinued study drug with HIV-1 RNA less than 50 copies per mL before week 48. All other participants with Lys103Asn present by historical genotype had less than 50 copies per mL HIV-1 RNA at week 48.

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 uncommon. Participants in the tenofovir alafenamide group had a lower incidence of drug-related adverse events than did those in the tenofovir disoproxil fumarate group. One participant (<1%) in each treatment group had a study drug-related

adverse event leading to discontinuation: fatigue in the tenofovir alafenamide group and hypersensitivity in the tenofovir disoproxil fumarate group. Two individuals died in the study, one in each treatment group: cardiac arrest in the tenofovir alafenamide group and carbon monoxide poisoning in the tenofovir disoproxil fumarate group. Neither death was considered treatment related. 40 (13%) of 315 participants in the tenofovir alafenamide group had grade 3 or 4 laboratory abnormalities compared with 19 (6%) of 313 in the tenofovir disoproxil fumarate group. This difference was driven by the higher incidence of grade 3 or 4 creatine kinase (14 [4%] of 315 *vs* six [2%] of 313) and LDL abnormalities (12 [4%] of 307 *vs* two [<1%] of 303).

Hip and spine bone mineral density in the tenofovir alafenamide group increased from baseline to weeks 24 and 48 but changes were minimal in the tenofovir disoproxil fumarate group (p<0·0001 for difference in changes between groups; figure 2, appendix p 2). A greater proportion of participants in the tenofovir alafenamide group than in the tenofovir disoproxil fumarate group had increases in bone mineral density that exceeded a 3% minimum threshold;[16] 27 (16%) of 168 participants versus seven (4%) of 165 participants at the hip, and 47 (27%) of 172 versus 19 (11%) of 168 at the spine (p<0·0001 for the difference in distribution between treatment groups). All fracture adverse events, reported for four (1%) of 316 participants in the tenofovir alafenamide group and five (2%) of 314 in the tenofovir disoproxil fumarate group, were the result of trauma and considered unrelated to treatment.

No cases of proximal tubulopathy were reported in either group, and no study participants discontinued as a result of study-drug-related renal adverse events. One participant in the tenofovir alafenamide group had an acute kidney injury associated with pneumonia, rhabdomyolysis, and drug abuse that was considered unrelated to study drug; treatment was not discontinued. Increases from baseline in median creatinine clearance were seen at week 4 and persisted through week 48 for the tenofovir alafenamide group compared with minimal changes from baseline in the tenofovir disoproxil fumarate group (week 48: 4·5 mL/min *vs* 0·7 mL/min, p=0·0024; appendix p 3). At 48 weeks, quantitative proteinuria (total urinary protein and albumin to urine creatinine ratios) decreased in the tenofovir alafenamide group whereas increases were noted in the tenofovir disoproxil fumarate (p<0·0001 for both, table 4). Tubular proteinuria (retinol binding protein and β-2 microglobulin to urine creatinine ratios) also improved with in the tenofovir alafenamide group compared with that in the tenofovir disoproxil fumarate group (p<0·0001 for both, table 4).

Fasting total cholesterol, direct LDL, HDL, and triglycerides increased in the tenofovir alafenamide group at week 48 and remained stable in the tenofovir disoproxil fumarate group (appendix p 4). However, the change in the total cholesterol to HDL ratio was similar in the two groups at week 48 (median change 0·1, p=0·18). During the study, 13 (4%) of 316 participants in the tenofovir alafenamide group began lipid-lowering drugs compared with two (1%) of 314 in the tenofovir disoproxil fumarate group (p=0·0067).

| | Rilpivirine, emtricitabine, and tenofovir alafenamide (n=316) | Rilpivirine, emtricitabine, and tenofovir disoproxil fumarate (n=314) | p value |
|---|---|---|---|
| **Creatinine clearance* (mL/min)** | | | |
| Baseline | 103·5 (88·5 to 119·8) | 99·7 (87·3 to 119·8) | 0·47 |
| Change at week 48 | 4·5 (–4·1 to 12·3) | 0·7 (–6·6 to 8·1) | 0·0024 |
| **Urine protein to creatinine ratio (mg/g)** | | | |
| Baseline | 53·2 (35·5 to 88·7) | 50·0 (36·4 to 80·6) | 0·69 |
| Percentage change at week 48 | –18·8 (–47·4 to 26·8) | 7·3 (–31·4 to 63·0) | <0·0001 |
| **Urine albumin to creatinine ratio (mg/g)** | | | |
| Baseline | 5·5 (3·7 to 10·0) | 5·4 (3·8 to 9·2) | 0·98 |
| Percentage change at week 48 | –7·8 (–34·2 to 27·6) | 16·8 (–19·6 to 64·0) | <0·0001 |
| **Urine β-2 microglobulin to creatinine ratio (μg/g)** | | | |
| Baseline | 111·6 (67·0 to 260·0) | 116·1 (61·7 to 326·1) | 0·72 |
| Percentage change at week 48 | –29·0 (–63·8 to 10·8) | 12·0 (–40·6 to 119·4) | <0·0001 |
| **Urine retinol-binding protein to creatinine ratio (μg/g)** | | | |
| Baseline | 101·2 (70·5 to 157·6) | 111·1 (75·8 to 196·9) | 0·12 |
| Percentage change at week 48 | –18·0 (–43·7 to 19·6) | 21·5 (–17·3 to 84·2) | <0·0001 |

Data are median (IQR). *As calculated by the Cockcroft-Gault formula. p values were from the two-sided Wilcoxon rank sum test to compare the two treatment groups.

*Table 4:* **Changes in quantitative measures of proteinuria from baseline to week 48**

## Discussion

At week 48 after switching from single-tablet rilpivirine, emtricitabine, tenofovir disoproxil fumarate, single tablet rilpivirine, emtricitabine, and tenofovir alafenamide was associated with a low rate of virological failure (<1%) and no evidence of treatment-emergent resistance. Noteworthy, is the continued viral suppression in participants with pre-existing Lys103Asn mutations. The efficacy analysis where missing cases were counted as excluded further emphasises the finding that few participants experienced virological failure. The high rate of viral suppression occurred in the context of simple instructions of study drug administration with food, without specific caloric or fat intake information.

The adverse event profiles were similar between the two treatment groups throughout the 48 weeks. Switching to single-tablet rilpivirine, emtricitabine, and tenofovir alafenamide was associated with significant improvements in hip and spine bone mineral density compared with the single-tablet tenofovir disoproxil fumarate regimen. Our results are consistent with previous findings of improved bone density when switching from a regimen containing tenofovir disoproxil fumarate to one containing tenofovir alafenamide.[11,12]

Although no participants developed tubulopathy in this study, long-term tenofovir disoproxil fumarate use

might impair kidney function.[18–20] This study assessed clinical laboratory evidence of tenofovir disoproxil fumarate-associated nephrotoxicity by use of tests for proteinuria (urine protein to creatinine ratio) and albuminuria (urine albumin to creatinine ratio) with validated thresholds associated with elevated risk for adverse clinical outcomes[21] recommended by guidelines for both HIV-infected[22] and HIV-uninfected[23] patients. This study also assessed tubular proteinuria by measuring urine retinol binding protein to creatinine ratio and β-2 microglobulin to creatinine ratio,[22] markers specific for proximal renal tubular dysfunction and recommended for monitoring tenofovir nephrotoxicity in the current Infectious Diseases Society of America guidelines. Although participants randomly assigned in this study had minimal-to-no renal impairment at entry (creatinine clearance ≥50 mL/min), increases in creatinine clearance and improvements in glomerular and tubular proteinuria were observed after switching to rilpivirine, emtricitabine, and tenofovir alafenamide, suggesting a lower risk for nephrotoxicity compared with remaining on the tenofovir disoproxil fumarate regimen. These improvements in markers of renal function are similar to those of another large tenofovir disoproxil fumarate to tenofovir alafenamide switch study in a population of participants with a creatinine clearance of at least 50 mL per min at study baseline[11] as well as those of a switch study in a population with renal impairment (creatinine clearance 30–69 mL per min) at baseline.[24] Assessment of potential long-term renal and bone benefit of rilpivirine, emtricitabine, and tenofovir alafenamide will require further follow-up. Nonetheless, this study reinforces the previous association of lower plasma tenofovir concentrations with improved clinical bone and renal parameters with tenofovir alafenamide-based regimens.

We observed increases in fasting total cholesterol, LDL cholesterol, and triglycerides in the group taking rilpivirine, emtricitabine, and tenofovir alafenamide, and more participants in this group were started on lipid-lowering therapy than in the tenofovir disoproxil fumarate group. The magnitude of the observed changes in the tenofovir alafenamide group are consistent with previous findings[11,12] and smaller than those observed in several small studies that have attempted to isolate the effect of tenofovir disoproxil fumarate on lipids.[25–27] Importantly, in our study and other studies, no treatment differences were observed in total cholesterol to HDL ratio, which is associated with cardiovascular risk.[28] The mechanism by which tenofovir disoproxil fumarate lowers plasma cholesterol levels (total cholesterol, LDL, and HDL) is unknown but is thought to be related to greater plasma tenofovir concentrations with tenofovir disoproxil fumarate than with tenofovir alafenamide.[29] This off-target action of tenofovir disoproxil fumarate is mitigated or eliminated when tenofovir alafenamide is used without a resultant change in the total cholesterol to HDL ratio or atherosclerotic cardiovascular disease risk.[30] Whether the lipid reductions that result from tenofovir disoproxil fumarate use translate to a change in cardiovascular event frequency has not been studied.

This study has a few important limitations. First, the study was powered for the primary efficacy endpoint and, therefore, might fail to detect rare clinical safety events. Second, surrogate markers were used to assess kidney and bone safety and few clinical events were found throughout the 48 weeks. Other limitations include a small proportion of study participants with advanced HIV disease and a small proportion of women in the rilpivirine, emtricitabine, and tenofovir disoproxil fumarate group.

Results from this study complement a parallel study assessing the effect of switching to rilpivirine, emtricitabine, and tenofovir alafenamide from a regimen of efavirenz, emtricitabine, and tenofovir disoproxil fumarate (NCT02345226). The totality of data from these two studies and other similar studies comparing tenofovir disoproxil fumarate-based regimens with those containing tenofovir alafenamide[10–12] provides important evidence to guide clinical treatment strategies for treatment-naive or virally suppressed individuals with HIV-1 infection.

Overall, virally suppressed, HIV-1 infected participants who switched to rilpivirine, emtricitabine, and tenofovir alafenamide maintained viral suppression at 48 weeks with low rates of virological failure, good tolerability, and improvements in measures of bone and renal safety compared with rilpivirine, emtricitabine, and tenofovir disoproxil fumarate. These findings support guidelines recommending tenofovir alafenamide-based regimens, including coformulation with rilpivirine and emtricitabine, as initial and ongoing treatment for HIV-1 infection.

#### Contributors

CO, EDJ, MR, GC, PR, ALM, AM, BV, JdW, JR, AL, BR, DP, AT, and MS enrolled participants, analysed data and independently interpreted the results, and edited and approved the report. AC, EQ, and HC designed the study. HCL performed the data analyses, which were reviewed and interpreted by DP, AC, EQ, DSG, and HC. The first draft was written by CO and HC. All authors were involved in the development of the primary manuscript, interpretation of data, have read and approved the final version. All authors contributed to edits of the final report.

#### Declaration of interests

CO has received research grants, personal fees, and non-financial support for lectureships and serving on advisory boards from Gilead, Merck Sharp & Dohme, Bristol-Myers Squibb, ViiV Healthcare, and Janssen. 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 for Gilead, ViiV Healthcare, GlaxoSmithKline, Pfizer, Janssen, and Merck. PR receives research support from AbbVie, Bristol-Myers Squibb, Gilead Sciences, GlaxoSmithKline, 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 has received consultancy payments and speaking fees from Bristol-Myers Squibb, Gilead, ViiV Healthcare, Merck Sharp & Dohme, AbbVie, and

Janssen-Cilag. AM reports receiving grants and personal fees from Gilead; grants from ViiV Healthcare, Merck, MBS; and personal fees from ViiV Healthcare and Merck. JdW has acted as consultant for Abbott Laboratories Canada and served on advisory boards for Abbott Laboratories, Bristol-Myers Squibb, Gilead, Tibotec, and ViiV Healthcare. JdW has acted as consultant for Abbott Laboratories Canada and served on advisory boards for Abbott Laboratories, Bristol-Myers Squibb, Gilead, Tibotec, and ViiV Healthcare. JdW has served on advisory boards as a speaker and consultant; has received conference attendance fees from AbbVie, ViiV Healthcare, and Merck; and has received payment for conducting HIV research from Gilead. JR reports receiving personal fees from Abbott, Hexal, Merck, Gilead, AbbVie, Janssen-Cilag, Merck Sharp & Dohme, Bristol-Myers Squibb, ViiV Healthcare, Cipla, and Bionor. AL has acted as consultant or participated in advisory boards as speaker or in the conduct of clinical trials for Abbot Laboratories, Bristol-Myers Squibb, Gilead, Merck Sharp & Dohme, ViiV Healthcare, Pfizer, and AbbVie. BR reports grants from Gilead; grants from Merck Sharp & Dohme; advisory board membership from Gilead, AbbVie, Merck Sharp & Dohme, Bristol-Myers Squibb, and Jansen-Cilag; personal fees from Gilead, and Bristol-Myers Squibb, outside of the submitted work. DPod has received research grants and honoraria for advisories and conferences from Boehringer Ingelheim, GlaxoSmithKline, ViiV Healthcare, Pfizer, Bristol-Myers Squibb, Abbott Laboratories, Gilead, Janssen, and Merck Sharp & Dohme. AT has received research support from Gilead and personal fees from Gilead, Janssen, and GlaxoSmithKline. MS reported receiving adviser fees and travel grants from AbbVie, Gilead, Janssen-Cilag, Merck Sharp & Dohme, and ViiV Healthcare. DPor, HCL, AC, EQ, DS, and HC are employees of Gilead and hold stock interest in the company. BV declares no competing interests.

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