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Emtricitabine and tenofovir alafenamide *vs* emtricitabine and tenofovir disoproxil fumarate for HIV pre-exposure prophylaxis (DISCOVER): primary results from a randomised, double-blind, multicentre, active-controlled, phase 3, non-inferiority trial

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Summary

Background Tenofovir alafenamide shows high antiviral efficacy and improved renal and bone safety compared with tenofovir disoproxil fumarate when used for HIV treatment. Here, we report primary results from a blinded phase 3 study evaluating the efficacy and safety of pre-exposure prophylaxis (PrEP) with emtricitabine and tenofovir alafenamide versus emtricitabine and tenofovir disoproxil fumarate for HIV prevention.

Methods This study is an ongoing, randomised, double-blind, multicentre, active-controlled, phase 3, non-inferiority trial done at 94 community, public health, and hospital-associated clinics located in regions of Europe and North America, where there is a high incidence of HIV or prevalence of people living with HIV, or both. We enrolled adult cisgender men who have sex with men and transgender women who have sex with men, both with a high risk of acquiring HIV on the basis of their self-reported sexual behaviour in the past 12 weeks or their recent history (within 24 weeks of enrolment) of bacterial sexually transmitted infections. Participants with current or previous use of PrEP with emtricitabine and tenofovir disoproxil fumarate were not excluded. We used a computer-generated random allocation sequence to randomly assign (1:1) participants to receive either emtricitabine (200 mg) and tenofovir alafenamide (25 mg) tablets daily, with matched placebo tablets (emtricitabine and tenofovir alafenamide group), or emtricitabine (200 mg) and tenofovir disoproxil fumarate (300 mg) tablets daily, with matched placebo tablets (emtricitabine and tenofovir disoproxil fumarate group). As such, all participants were given two tablets. The trial sponsor, investigators, participants, and the study staff who provided the study drugs, assessed the outcomes, and collected the data were masked to group assignment. The primary efficacy outcome was incident HIV infection, which was assessed when all participants had completed 48 weeks of follow-up and half of all participants had completed 96 weeks of follow-up. This full analysis set included all randomly assigned participants who had received at least one dose of the assigned study drug and had at least one post-baseline HIV test. Non-inferiority of emtricitabine and tenofovir alafenamide to emtricitabine and tenofovir disoproxil fumarate was established if the upper bound of the 95·003% CI of the HIV incidence rate ratio (IRR) was less than the prespecified non-inferiority margin of 1·62. We prespecified six secondary bone mineral density and renal biomarker safety endpoints to evaluate using the safety analysis set. This analysis set included all randomly assigned participants who had received at least one dose of the assigned study drug. This trial is registered with ClinicalTrials.gov, NCT02842086, and is no longer recruiting.

Findings Between Sept 13, 2016, and June 30, 2017, 5387 (92%) of 5857 participants were randomly assigned and received emtricitabine and tenofovir alafenamide (n=2694) or emtricitabine and tenofovir disoproxil fumarate (n=2693). At the time of the primary efficacy analysis (ie, when all participants had completed 48 weeks and 50% had completed 96 weeks) emtricitabine and tenofovir alafenamide was non-inferior to emtricitabine and tenofovir disoproxil fumarate for HIV prevention, as the upper limit of the 95% CI of the IRR, was less than the prespecified non-inferiority margin of 1·62 (IRR 0·47 [95% CI 0·19–1·15]). After 8756 person-years of follow-up, 22 participants were diagnosed with HIV, seven participants in the emtricitabine and tenofovir alafenamide group (0·16 infections per 100 person-years [95% CI 0·06–0·33]), and 15 participants in the emtricitabine and tenofovir disoproxil fumarate group (0·34 infections per 100 person-years [0·19–0·56]). Both regimens were well tolerated, with a low number of participants reporting adverse events that led to discontinuation of the study drug (36 [1%] of 2694 participants in the emtricitabine and tenofovir alafenamide group *vs* 49 [2%] of 2693 participants in the emtricitabine and tenofovir disoproxil fumarate group). Emtricitabine and tenofovir alafenamide was superior to emtricitabine and tenofovir disoproxil fumarate in all six prespecified bone mineral density and renal biomarker safety endpoints.

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Interpretation Daily emtricitabine and tenofovir alafenamide shows non-inferior efficacy to daily emtricitabine and tenofovir disoproxil fumarate for HIV prevention, and the number of adverse events for both regimens was low. Emtricitabine and tenofovir alafenamide had more favourable effects on bone mineral density and biomarkers of renal safety than emtricitabine and tenofovir disoproxil fumarate.

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Introduction

When taken as directed, pre-exposure prophylaxis (PrEP) with emtricitabine and tenofovir disoproxil fumarate is safe and highly effective in preventing HIV acquisition in diverse, at-risk populations with rare seroconversions or drug resistance.[1–11] Increasing population-level uptake of PrEP is associated with declining HIV incidence, particularly in jurisdictions with high access to health care, robust HIV prevention programmes, and where a high proportion of people with HIV are virologically suppressed.[12–17]

Tenofovir, a nucleotide reverse transcriptase inhibitor of HIV, inhibits viral replication in cells. Although tenofovir alafenamide and tenofovir disoproxil fumarate are both prodrugs of tenofovir, tenofovir alafenamide transports the active metabolite, tenofovir diphosphate, more rapidly into peripheral blood mononuclear cells (PBMCs) than tenofovir disoproxil fumarate, with at least four times higher concentrations, resulting in increased antiviral activity.[18] At 1–2 h after a single dose of tenofovir alafenamide, median tenofovir diphosphate concentrations exceed the 90% effective concentration (EC_{90}) associated with HIV prevention efficacy in PBMCs, whereas tenofovir disoproxil fumarate does not surpass this threshold until after 3 days of daily dosing.[19,20] Emtricitabine and tenofovir alafenamide has been shown to prevent rectal simian-human immunodeficiency virus in macaques.[21] In HIV and hepatitis B virus (HBV) treatment trials, tenofovir alafenamide was shown to be non-inferior to tenofovir disoproxil fumarate, and bone and renal safety biomarkers were significantly improved, which was most likely to have been caused by the 90% reduction in plasma tenofovir exposure with tenofovir alafenamide compared with tenofovir disoproxil fumarate.[22–31] Regimens that include emtricitabine and tenofovir alafenamide are recommended by HIV treatment guidelines.[32–34]

We did this active-controlled study to compare the efficacy and safety of emtricitabine and tenofovir

Research in context

Evidence before this study

We searched PubMed for clinical trials of HIV pre-exposure prophylaxis (PrEP) with tenofovir between database inception to Nov 3, 2019, using the title or abstract search term "HIV" AND ("prevention" OR "prophylaxis"). The search was limited to trials published in English. Our search yielded 174 articles published between 2007 and 2018, 16 of which reported efficacy outcomes. Oral emtricitabine and tenofovir disoproxil fumarate is highly effective for PrEP when adherence is adequate. The identified studies showed that emtricitabine and tenofovir disoproxil fumarate was well tolerated and safe, but was associated with modest and generally reversible declines in renal function and bone mineral density. A systematic review of nine trials of PrEP with emtricitabine and tenofovir disoproxil fumarate by the US Preventive Services Task Force confirmed the high efficacy of this drug combination and the strong positive association between adherence and efficacy, and showed that the use of this drug combination was associated with an increased risk of mild, generally reversible renal and gastrointestinal adverse events, but was not associated with an increased risk of fractures.

Added value of this study

The efficacy and safety of tenofovir alafenamide in HIV treatment has been well documented; however, the efficacy and safety of this drug in HIV prevention is unknown. To our knowledge, our study is the first active-controlled trial comparing a new regimen for PrEP (emtricitabine and tenofovir alafenamide) with the current standard-of-care regimen (emtricitabine and tenofovir disoproxil fumarate). Compared with emtricitabine and tenofovir disoproxil fumarate, we show that emtricitabine and tenofovir alafenamide has non-inferior efficacy and has more favourable effects on bone mineral density and biomarkers of renal safety when used as PrEP in HIV prevention. Therefore, the emtricitabine and tenofovir alafenamide combination shows similar effects when used for HIV prevention as it does for HIV treatment.

Implications of all the available evidence

The results of our study show that daily emtricitabine and tenofovir alafenamide is effective for HIV prevention and leads to favourable bone density and renal biomarker profiles in people without HIV, as it does in HIV treatment, when used as part of a complete HIV treatment regimen. These results establish emtricitabine and tenofovir alafenamide as an additional option for PrEP in cisgender men who have sex with men and transgender women who have sex with men, both at risk of acquiring HIV, particularly in those with risk factors for, or pre-existing, renal or bone disease. Whether PrEP with emtricitabine and tenofovir alafenamide shows efficacy in cisgender women who have sex with men is being investigated.

alafenamide with emtricitabine and tenofovir disoproxil fumarate for the prevention of HIV among cisgender men who have sex with men (MSM) and transgender women who have sex with men.

Methods

Study design

The DISCOVER study is an ongoing, randomised, double-blind, multicentre, active-controlled, phase 3, non-inferiority trial done at 94 community, public health and hospital-associated clinics, located in regions of Europe (Austria, Denmark, France, Germany, Ireland, Italy, Netherlands, Spain, and the UK) and North America (Canada and the USA). We chose study sites where HIV prevalence or incidence, or both, was high among cisgender MSM and transgender women who have sex with men. The study protocol was approved by the relevant ethics boards at each site and the study was done in compliance with Declaration of Helsinki, Good Clinical Practice Guidelines, Good Participatory Practice Guidelines,[35] and local regulatory requirements.

Participants

Study investigators enrolled adult cisgender MSM and transgender women who have sex with men, both with a high risk of acquiring HIV on the basis of their self-reported sexual behaviour within the past 12 weeks or their recent history (within 24 weeks of enrolment) of bacterial sexually transmitted infections (STIs). Active (outreach in person or via social media) and passive (fliers, advertisements, and radio spots) recruitment methods were customised for local cultural context and language by site. All recruitment materials were reviewed and approved by the trial sponsor and local ethics boards.

We included participants who tested negative for HIV by use of third-generation HIV antibody tests or fourth-generation HIV-1 antigen–antibody tests at screening and baseline, and who reported either condomless anal sex with at least two partners in the previous 12 weeks or having syphilis, rectal gonorrhoea, or rectal chlamydia in the previous 24 weeks. Previous or current use of emtricitabine and tenofovir disoproxil fumarate for PrEP was allowed. Individuals with any of the following conditions were excluded from participation: a suspected or known active serious infection (determination of serious was at the individual investigator's discretion); acute hepatitis A, B, or C infection, or chronic hepatitis B infection; a history of osteoporosis or fragility fractures; or impaired renal function, as defined by an estimated glomerular filtration rate by the Cockcroft-Gault formula ($eGFR_{CG}$) of less than 60 mL/min.

All participants provided written informed consent.

Randomisation and masking

Bracket Global (San Francisco, CA, USA), a provider of interactive web-voice response system, randomly assigned participants (1:1) using a computer-generated randomisation schedule with permuted blocks of four to receive once daily blinded tablets of either emtricitabine (200 mg) and tenofovir alafenamide (25 mg) or emtricitabine (200 mg) and tenofovir disoproxil fumarate (300 mg). Participants in both groups also received placebo tablets that were identical in appearance to the alternative study drug; therefore, all participants took two pills daily. The sponsor, investigators, participants, and study staff who provided the study drug, assessed outcomes, and collected data were masked to study drug assignment by use of the double-dummy method.

Procedures

Participants were screened for eligibility and randomly assigned to either group within 30 days. Post-baseline study visits were done at weeks 4 and 12, and then every 12 weeks thereafter. After week 96, participants were offered enrolment into the open-label phase, during which all participants received emtricitabine and tenofovir alafenamide and attended follow-up visits every 12 weeks for a further 48 weeks.

At the screening visit and all subsequent follow-up visits (at weeks 4 and 12, and then every 12 weeks thereafter), HIV testing was done by use of a rapid third-generation antibody test or fourth-generation antigen–antibody tests at the site. The tests were repeated by a central laboratory (Covance, Indianapolis, IN, USA) by use of third-generation HIV antibody test or a fourth-generation HIV antigen–antibody test, followed by a HIV-1/HIV-2 discrimination assay and HIV RNA qualitative test (if any of the previous rapid or central laboratory tests were positive). At baseline, HIV testing was done by use of the rapid third-generation antibody or fourth-generation antigen–antibody test. Plasma samples were not routinely collected at baseline unless participants had symptoms consistent with acute HIV infection and had a negative rapid HIV test result. Sites might have done other HIV tests according to local standard-of-care procedures (eg, qualitative HIV RNA analysis by GeneXpert; Cepheid, Sunnyvale, CA, USA). Genotypic HIV resistance testing was done in participants with HIV if they had a plasma concentration of at least 400 HIV-1 RNA copies per mL.

At all post-baseline visits, safety was assessed by physical examinations, laboratory tests (Covance Laboratories, Indianapolis, IN, USA), asking about concomitant drug use, and ascertaining adverse events, which were coded by use of the Medical Dictionary for Regulatory Activities (version 21.1). At screening and at each post-baseline visit, gonorrhoea and chlamydia nucleic acid amplification tests were done from rectal, pharyngeal, and urine specimens, and syphilis testing was done by local laboratories, in accordance with local guidelines.[36] Sites provided local standard-of-care risk reduction counselling, adherence counselling, and condoms and lubricant. Treatment for STIs and HIV post-exposure prophylaxis was offered as per local guidelines.

Adherence was assessed at all post-baseline visits by use of a computer-assisted self-interview for self-reporting and by pill count. In a randomly preselected subset of 536 (10%) participants, adherence was evaluated further by quantifying tenofovir diphosphate concentrations in dried blood spots (DBS) at the Colorado Antiviral Pharmacology Laboratory (Aurora, CO, USA; appendix p 6).[37] We also assessed tenofovir diphosphate concentrations in PBMCs in this subset of participants.

See Online for appendix

At baseline and every 48 weeks, we did dual energy x-ray absorptiometry (DXA) scans of the hip and lumbar spine in a subset of 383 participants (DXA substudy) who consented to participate and who were enrolled at sites with the capacity to do the scans (37 sites in seven countries). DXA scans were read and interpreted by a third party (BioClinica, Newtown, PA, USA) that was masked to the study groups.

Outcomes

The primary efficacy outcome was incident HIV infection, diagnosed by: (1) serological evidence of seroconversion (a reactive rapid or blood HIV antigen-antibody or antibody test, confirmed by the reactive blood HIV-1/HIV-2 differentiation assay); (2) virological evidence of HIV infection (a positive qualitative HIV-1 RNA test result or any detectable quantitative HIV RNA test result); or (3) evidence of acute HIV infection (a reactive p24 antigen test result or a positive qualitative or quantitative RNA test result, in the absence of reactive HIV antibody test results). A panel of physicians who were masked to the study groups independently reviewed the following data for all participants who acquired HIV to classify any as suspected baseline infections before unmasking: all local and study HIV testing data, including HIV RNA and genotyping test results; and seroconversion narratives from site staff interviews, which included the timing of risk events, with respect to study drug initiation.

We prespecified six secondary safety outcomes that have been associated with tenofovir exposure in previous studies[22–29] comparing tenofovir alafenamide with tenofovir disoproxil fumarate for HIV and HBV. These secondary safety outcomes, measured as percentage changes from baseline to week 48, included: (1) hip bone mineral density; (2) spine bone mineral density; (3) urine β_2-microglobulin to creatinine ratio; (4) retinol-binding protein to creatinine ratio; (5) changes in the distribution of urine protein to creatine ratio above the clinically significant threshold of 22·6 mg/mmol at 48 weeks[38]); and (6) change in serum creatinine from baseline.

Additional prespecified outcomes included the incidence of treatment-emergent adverse events; other laboratory abnormalities, including changes in blood lipids from baseline; changes in weight from baseline; adherence by self-reporting, pill counts, and DBS testing; tenofovir diphosphate concentrations in PBMCs; and HIV antiretroviral drug resistance in participants who acquired HIV infection.

Statistical analysis

We pooled data from three previous HIV prevention studies[1,3,4] of emtricitabine and tenofovir disoproxil fumarate versus placebo, yielding an expected HIV incidence of 1·44 infections per 100 person-years in the emtricitabine and tenofovir disoproxil fumarate group and an incidence rate ratio (IRR) between the placebo and emtricitabine and tenofovir disoproxil fumarate groups of 5·1 (95% CI 2·64–9·70). We derived 1·62, the square root of the lower bound of 2·64, as the non-inferiority margin to preserve at least 50% of the effect of emtricitabine and tenofovir disoproxil fumarate (see appendix pp 7–9). Assuming an average of 2 years of follow-up, we planned a sample size of 2500 participants in each arm to achieve 82·5% power to detect a margin of 1·62 for establishing non-inferiority of emtricitabine and tenofovir alafenamide to emtricitabine and tenofovir disoproxil fumarate, using a two-sided type 1 error of 5%.

The primary efficacy endpoint was analysed in the full analysis set, which included all participants who were randomly assigned, had received at least one dose of the study drug, and had at least one post-baseline HIV test. The primary efficacy endpoint was analysed when these participants had been followed up for a minimum of 48 weeks and when at least 50% of these participants had been followed up for 96 weeks. Follow-up time was calculated as the number of years since the baseline visit (ie, number of days divided by 365·25) and was censored at the last visit when HIV status was assessed. Participants who acquired HIV were censored at the time of their first visit with any reactive HIV test. As prespecified, we analysed the primary endpoint by baseline demographic characteristics. We also did two additional analyses of the primary endpoint: (1) a post-hoc sensitivity analysis, which excluded participants with suspected baseline infection; and (2) a prespecified analysis in the per-protocol analysis population, which excluded participants with suspected baseline infection and those with poor adherence (appendix p 9).

We did three planned interim analyses for an independent data and safety monitoring committee to review unblinded data when 50% of participants had completed 24 weeks, 48 weeks, and 72 weeks of follow-up. After each review, the committee concluded that continuation of the trial was warranted. An α penalty of 0·00001 was applied for each of the planned interim analyses. As a result, the significance level for the two-sided non-inferiority test for the primary endpoint was 0·04997, corresponding to a 95·003% CI (hereafter reported as 95% CI).

We used a generalised linear model with a Poisson distribution and logarithmic link, with the study arm as the main effect, to construct the point estimate of the HIV IRR and the associated 95% CI to establish non-inferiority (requiring an upper bound of <1·62).[39]

We assessed the association between adherence (tenofovir diphosphate concentrations in DBS) and efficacy in a nested case-control study using exact conditional logistic

regression; every incident HIV case was matched with five controls by study arm, diagnosis day, presence of a rectal STI, and geography.

The six prespecified secondary safety endpoints were adequately powered and tested in sequential order (as listed in the outcomes section). The type 1 error rate for the six endpoints was controlled by use of a fallback procedure.[40] We analysed the percentage change from baseline at 48 weeks in hip and spine bone mineral densities using ANOVA; the β_2-microglobulin to creatinine ratio and retinol-binding protein to creatinine ratio using the Van Elteren test; the urine protein to creatinine ratio category distribution using rank ANCOVA;[41] and the change from baseline in serum creatinine using ANCOVA.

We did prespecified subgroup analyses using the same method as was used for the overall DXA substudy. The percentage changes in hip and spine bone mineral densities by age group (≥18 years to <25 years *vs* ≥25 years) were analysed to evaluate the effect of the study drugs on people still rapidly accruing bone mass.[42,43] We also did prespecified subgroup analyses for participants who were taking emtricitabine and tenofovir disoproxil fumarate for PrEP at baseline to evaluate the effect of switching to emtricitabine and tenofovir alafenamide on bone mineral density and the renal biomarkers of tubular proteinuria (β_2-microglobulin to creatinine ratio and retinol-binding protein to creatinine ratio) and creatinine clearance ($eGFR_{CG}$).

We also analysed changes in weight (in kg) from baseline using ANCOVA and we analysed changes in $eGFR_{CG}$ from baseline using the Van Elteren test, stratifying by baseline emtricitabine and tenofovir disoproxil fumarate use. We compared changes in fasting lipid concentrations from baseline at 48 weeks using the two-sided Wilcoxon rank-sum test. Analyses of safety endpoints were based on observed data in the safety analysis population, with baseline use of emtricitabine and tenofovir disoproxil fumarate for PrEP as a stratification factor (fixed effect) when ANCOVA models included the baseline measure of the outcome as a covariate.

We used SAS version 9.4 for all analyses and PASS version 14 for the power calculation.

This study was done according to the trial protocol, without substantial deviations (appendix p 11), and is registered with ClinicalTrials.gov, NCT02842086.

Role of the funding source

Gilead Sciences funded the study, collected and analysed the data, interpreted the results in consultation with the other authors of the Article, and helped to write the report. All authors had access to the data. KHM, MD, SM, and DMB made the decision to submit the manuscript for publication.

Results

Between Sept 2, 2016, and June 30, 2017, 5857 individuals were screened, and 5399 were randomly assigned to either the emtricitabine and tenofovir alafenamide group (n=2700) or the emtricitabine and tenofovir disoproxil fumarate group (n=2699; figure 1). The full analysis set consisted of 5335 participants (2670 in the emtricitabine and tenofovir alafenamide group and 2665 in the emtricitabine and tenofovir disoproxil fumarate group). The safety analysis population consisted of 5387 participants (2694 in the emtricitabine and tenofovir alafenamide group and 2693 in the emtricitabine and tenofovir disoproxil fumarate group). Follow-up for the prespecified primary analysis was completed on Feb 22, 2019. Baseline demographic characteristics, clinical characteristics, and risk factors were well balanced between the two groups (table 1). The

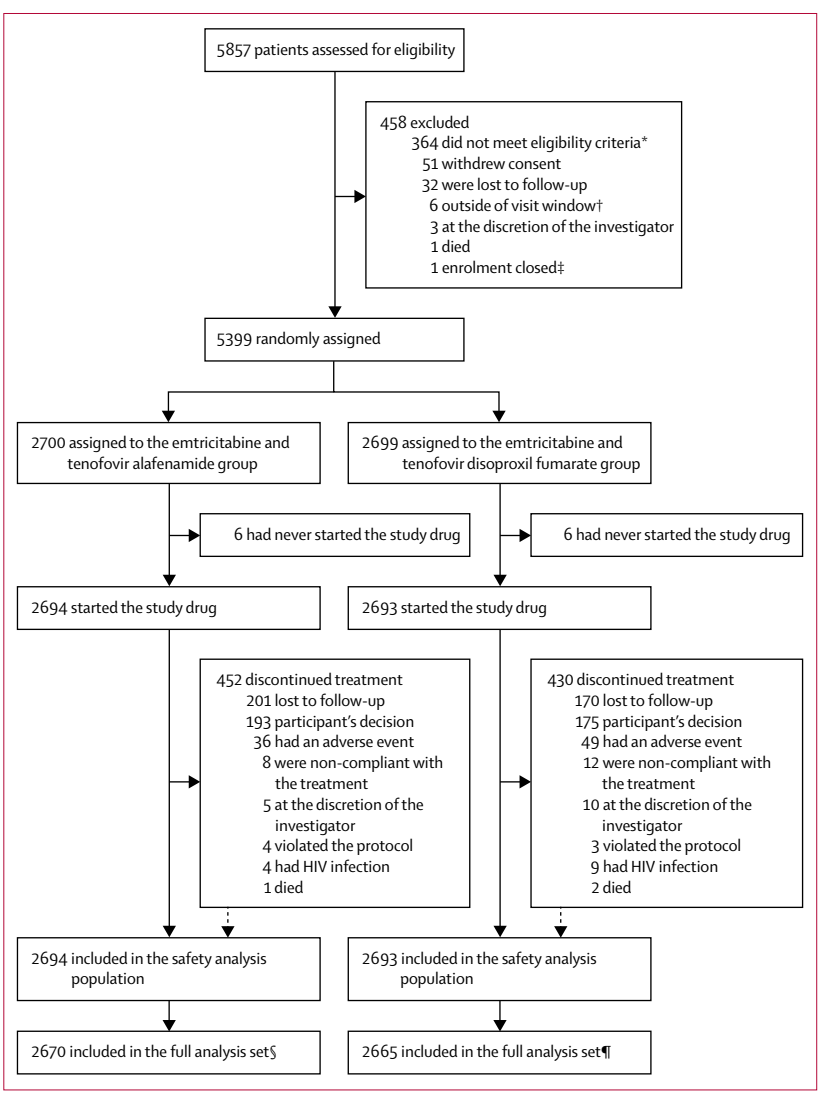

Figure 1: **Trial profile**

*49 (13·5%) of these participants were HIV positive at screening. †Refers to participants who returned for their baseline visit more than 30 days after their screening visit. ‡Enrolment to the study was closed before this participant could be randomly assigned, even though they had been screened. §24 participants were excluded for not having undergone a post-baseline HIV test. ¶28 participants were excluded for not having undergone a post-baseline HIV test.

	Emtricitabine and tenofovir alafenamide group (n=2694)	Emtricitabine and tenofovir disoproxil fumarate group (n=2693)
Demographics		
Age, years	34 (28–43)	34 (28–44)
Race*		
White	2264 (84%)	2247 (84%)
Black†	240 (9%)	234 (9%)
Asian	113 (4%)	120 (4%)
Other	74 (3%)	87 (3%)
Hispanic or Latinx ethnicity	635 (24%)	683 (25%)
Gender or sexual orientation		
Transgender women who have sex with men	45 (2%)	29 (1%)
Cisgender men who have sex with men	2649 (98%)	2664 (99%)
Sexual orientation		
Gay	2461 (92%)	2434 (91%)
Straight	21 (1%)	16 (1%)
Bisexual	171 (6%)	214 (8%)
Other	23 (1%)	13 (<1%)
Region		
USA	1591 (59%)	1629 (60%)
EU	912 (34%)	902 (33%)
Canada	191 (7%)	162 (6%)
Median body-mass index, kg/m²	25 (23–29)	25 (23–28)
Sexually transmitted infections by laboratory test at baseline visit		
Rectal gonorrhoea	123/2668 (5%)	113/2669 (4%)
Rectal chlamydia	199/2669 (7%)	189/2670 (7%)
Syphilis	7 (<1%)	4 (<1%)
Self-reported HIV risk factors		
Two or more of receptive condomless anal sex partners in the past 12 weeks‡	1616/2602 (62%)	1569/2597 (60%)
History of rectal gonorrhoea in the past 24 weeks	274 (10%)	262 (10%)
History of rectal chlamydia in the past 24 weeks	342 (13%)	333 (12%)
History of syphilis in the past 24 weeks	230 (9%)	263 (10%)
Recreational drug use in the past 12 weeks‡	1785/2680 (67%)	1786/2677 (67%)
Binge drinking‡§	618/2657 (23%)	599/2680 (22%)
Taking emtricitabine and tenofovir disoproxil fumarate for pre-exposure prophylaxis at baseline	465 (17%)	440 (16%)

Data are median (IQR), n (%), or n/N (%). *Denominator for race excludes eight participants with missing race data (three in the emtricitabine and tenofovir alafenamide group and five in the emtricitabine and tenofovir disoproxil fumarate group), as collection was not permitted. †Includes individuals who were mixed Black race. ‡As reported by use of a computer-assisted self interview. §Defined as the consumption of six or more drinks on one or more occasion occurring at least once per month.

Table 1: **Baseline demographics and risk factors in the safety analysis population**

median age of participants was 34 years (IQR 28–43). Of the 5387 participants enrolled and treated, 876 (16%) were non-white, including 474 (9%) Black participants. 1318 (24%) of 5387 participants were of Hispanic or Latinx ethnicity. Most participants (4895 [91%] of 5357) self-identified as gay, 385 (7%) as bisexual, 41 (1%) as heterosexual, and 74 (1%) as transgender women. At baseline, participants had a normal median $eGFR_{CG}$ (123 mL/min [IQR 105–143] in the emtricitabine and tenofovir alafenamide group and 121 mL/min [104–142] in the emtricitabine and tenofovir disoproxil fumarate group) and most participants had a normal hip (284 [76%] of 375) and spine (272 [76%] of 378) bone mineral density, defined as a bone mineral density T-score from a male reference population of –1·0 or higher. 1247 (23%) of all 5387 participants had ever used tenofovir disoproxil fumarate for PrEP at baseline, whereas 905 (17%) participants reported using tenofovir disoproxil fumarate for PrEP.

At the time of the primary analysis, emtricitabine and tenofovir alafenamide was non-inferior to emtricitabine and tenofovir disoproxil fumarate for the prevention of HIV, as the upper limit of the 95% CI of the IRR was less than the prespecified non-inferiority margin of 1·62 (IRR 0·47 [95% CI 0·19–1·15]; figure 2). After 8756 person-years of follow-up, 22 participants were diagnosed with HIV, seven of whom were in the emtricitabine and tenofovir alafenamide group (0·16 infections per 100 person-years [95% CI 0·06–0·33]) and 15 of whom were in the emtricitabine and tenofovir disoproxil fumarate group (0·34 infections per 100 person-years [0·19–0·56]). One (0·04%) participant in the emtricitabine and tenofovir alafenamide group and four (0·15%) participants in the emtricitabine and tenofovir disoproxil fumarate group who tested negative for HIV at the screening visit, but who tested positive at week 4, were suspected to have acquired HIV infections before baseline (appendix p 13). All five of these participants had a negative rapid third-generation HIV antibody test at baseline. A sensitivity analysis of the primary endpoint excluding these five participants maintained non-inferiority of emtricitabine and tenofovir alafenamide to emtricitabine and tenofovir disoproxil fumarate (IRR 0·55 [95% CI 0·20–1·48]; appendix p 20). A per-protocol analysis of the primary endpoint excluding the five participants with suspected HIV at baseline and those with poor adherence (defined as as those who were off the study drug >16 days after discontinuation of emtricitabine and tenofovir alafenamide and >10 days after discontinuation of emtricitabine and tenofovir disoproxil fumarate) yielded an IRR of 0·400 (95% CI 0·078–2·064]; appendix p 20). Excluding these five participants with suspected baseline HIV infections, 15 (88%) of the remaining 17 participants had low (defined as taking an average of <2 doses per week) or undetectable tenofovir diphosphate concentrations in DBS on the day of HIV diagnosis (appendix p 21). Of the two remaining HIV-positive participants, one was in the emtricitabine and tenofovir alafenamide group and the other was in the emtricitabine and tenofovir disoproxil fumarate group. The participant in the emtricitabine and tenofovir alafenamide group decided to discontinue the study drug on day 49 (with no evidence of further dosing), had acute antiretroviral infection syndrome starting approximately on day 63, and tested positive for HIV on day 95, when the DBS analysis showed that the concentration of tenofovir diphosphate was 474 fmol per 10^6 cells, consistent with the participant taking two-to-three tablets per week.

The other participant in the emtricitabine and tenofovir disoproxil fumarate group did not have a DBS test on same day of the positive HIV test result (day 474); his adherence was imputed as four or more tablets per week, by carrying his previous DBS test result (a tenofovir diphosphate concentration of 803 fmol per 10^6 cells on day 425) forward. Both participants reported substance use with sex. The prespecified nested case-control study showed that a low DBS tenofovir diphosphate concentration (indicating <2 doses of the assigned drug per week) was the strongest predictor of an increased odds of HIV acquisition (p=0·00026 in the emtricitabine and tenofovir alafenamide group and p<0·0001 in the emtricitabine and tenofovir disoproxil fumarate group; appendix p 22), with similar results from the sensitivity analyses that excluded participants with suspected HIV infection at baseline. There were no differences in the distribution of time to HIV infection or the incidence of HIV between the two groups overall and after participants with suspected HIV infection at baseline were excluded (appendix p 23). No transgender women acquired HIV during the study period. The incidence of HIV was similar in both groups across demographic and risk behaviour subgroups (appendix p 24).

Emtricitabine and tenofovir alafenamide was superior to emtricitabine and tenofovir disoproxil fumarate in all six prespecified secondary safety endpoints (figure 3). In the bone mineral density subanalysis of 383 participants, those in the emtricitabine and tenofovir alafenamide group had stable hip bone mineral density (mean percentage change 0·18%) and an increase in mean spine bone mineral density (0·50%) from baseline to 48 weeks, whereas participants in the emtricitabine and tenofovir disoproxil fumarate group had decreased bone mineral density in the hip (–0·99%) and spine (–1·12%) at 48 weeks (figure 3A, B). At 48 weeks, a significant difference in the percentage change in hip bone mineral density (p<0·0001) and spine bone mineral density (p<0·0001) from baseline was observed between the two groups (figure 3A, B). Between baseline and 48 weeks, participants in the emtricitabine and tenofovir disoproxil fumarate group showed a 15·2% increase in the β_2-microglobulin to creatinine ratio and a 19·9% increase in the retinol-binding protein to creatinine ratio, whereas participants in the emtricitabine and tenofovir alafenamide group showed a 10·7% reduction in the β_2-microglobulin to creatinine ratio and a stable (0·2% increase) retinol-binding protein to creatinine ratio. At 48 weeks, a significant difference in the percentage change in β_2-microglobulin to creatinine ratio (p<0·0001) and retinol-binding protein to creatinine ratio (p<0·0001) from baseline was observed between the two groups (figure 3C, D). Significantly fewer participants in the emtricitabine and tenofovir alafenamide group (16 [1%] of 2694) had a study drug-emergent urine protein to creatinine ratio of more than 22·6 mg/mmol than in the emtricitabine and tenofovir disoproxil fumarate group (35 [2%] of 2693; p=0·005; figure 3E). Between baseline and 48 weeks, the total number of participants with a urine protein to creatinine ratio of more than 22·6 mg/mmol was constant at 25 in the tenofovir alafenamide group, and increased from 25 to 45 in the tenofovir disoproxil fumarate group (figure 3F). Between baseline and 48 weeks, participants in the emtricitabine and tenofovir alafenamide group had a median decrease in serum creatinine concentrations of 0·88 µmol/L and a median increase in $eGFR_{CG}$ of 1·8 mL/min, whereas participants in the emtricitabine and tenofovir disoproxil fumarate group had an increase in median creatinine concentration of 0·88 µmol/L and a decrease in $eGFR_{CG}$ of 2·3 mL/min (figure 3G, H). A significant difference in change from baseline at week 48 in serum creatinine concentrations (p<0·0001) and creatinine clearance (p<0·0001) was observed between the two groups (figure 3G, H).

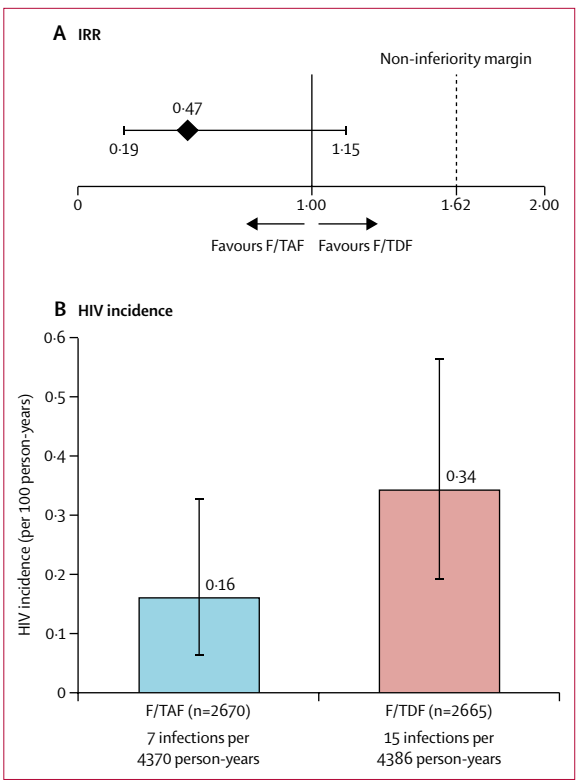

Figure 2: **HIV IRR and incidence on F/TAF versus F/TDF at the primary efficacy analysis**

IRR (F/TAF divided by F/TDF) of HIV (A) and incidence of HIV per 100 person-years (B) in the F/TAF and F/TDF groups. The primary efficacy analysis was done when participants had completed a minimum follow-up of 48 weeks and at least 50% of participants had completed 96 weeks of follow-up. Error bars represent 95% CIs. IRR=incidence rate ratio. F/TAF=emtricitabine and tenofovir alafenamide. F/TDF=emtricitabine and tenofovir disoproxil fumarate.

We did prespecified subgroup analyses of key secondary safety endpoints. In an analysis of bone mineral density stratified by age, younger participants (ie, those aged ≥18 years to <25 years) in the emtricitabine and tenofovir alafenamide group had stable bone mineral density, as did

older participants (ie, those aged ≥25 years). By contrast, younger participants in the emtricitabine and tenofovir disoproxil fumarate group had greater declines in bone mineral density (–2·2% at the hip and –2·4% at the spine; p<0·0001 for both) than those observed in participants older than 25 years on emtricitabine and tenofovir disoproxil fumarate (–0·9% at the hip and –1·0% at the spine; p<0·0001 for both; appendix p 25). Percentage changes in bone mineral density from baseline at week 48 in participants who were not taking emtricitabine and tenofovir disoproxil fumarate at baseline were similar to the overall DXA substudy (appendix p 26). Participants who were taking emtricitabine and tenofovir disoproxil fumarate at baseline and switched to emtricitabine and tenofovir alafenamide after they were randomly assigned had declines in tubular proteinuria (a median percentage change in β_2-microglobulin to creatinine ratio from baseline at 48 weeks of –27·1% and a median percentage change in retinol-binding protein to creatinine ratio from baseline at 48 weeks of –8·6%). By contrast, participants who continued to take emtricitabine and tenofovir disoproxil fumarate maintained a stable β_2-microglobulin to creatinine ratio (median percentage change from baseline to 48 weeks of –5·1%) and had an increased retinol-binding protein to creatinine ratio (median percentage change from baseline to 48 weeks of 11·36%; appendix p 27). The median percentage change in β_2-microglobulin to creatinine ratio (p<0·0001) and the retinol-binding protein to creatinine ratio (p<0·0001) between baseline and 48 weeks were significantly different between the two groups, regardless of whether participants were taking emtricitabine and tenofovir disoproxil fumarate at baseline. The magnitude of differences between groups among participants who were emtricitabine and tenofovir disoproxil fumarate-naive at baseline (appendix p 27) were similar to the overall safety analysis population (figure 3C, D). Participants who switched from emtricitabine and tenofovir disoproxil fumarate to emtricitabine and tenofovir alafenamide had a 3·9 mL/min increase in $eGFR_{CG}$ at 48 weeks, whereas those who continued emtricitabine and tenofovir disoproxil fumarate had stable $eGFR_{CG}$ (–0·6%; p<0·0001; appendix p 28).

Over a median exposure of 86 weeks, participants in both groups had similar numbers of adverse events (table 2). Most adverse events were grade 1 (mild) or

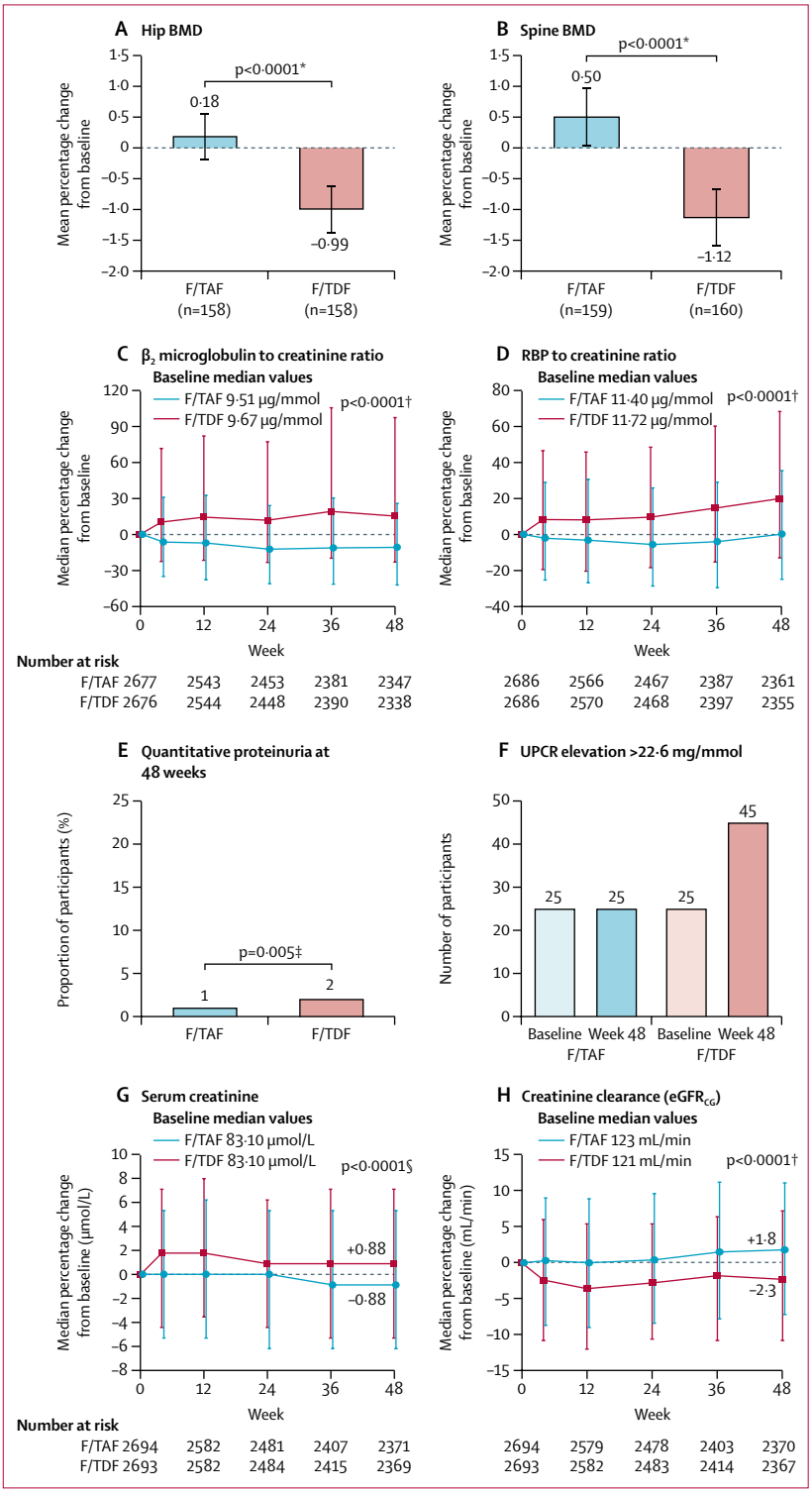

Figure 3: **Prespecified secondary endpoints**
Hip BMD (A), spine BMD (B), β_2-microglobulin to creatinine ratio (C), RBP to creatinine ratio (D), development of quantitative proteinuria (UPCR >22·6 mg/mmol) at 48 weeks among participants with UPCR ≤22·6 mg/mmol (E), participants with UPCR elevation of >22·6 mg/mmol (F), serum creatinine (G), and creatinine clearance ($eGFR_{CG}$). Data are mean (95% CI) or median (IQR). F/TAF=emtricitabine and tenofovir alafenamide. F/TDF=emtricitabine and tenofovir disoproxil fumarate. BMD=bone mineral density. RBP=retinol-binding protein. UPCR=urine protein to creatinine ratio. $eGFR_{CG}$=estimated glomerular filtration rate by Cockcroft-Gault. *ANOVA model with baseline F/TDF for pre-exposure prophylaxis and treatment as fixed effects. †Van Elteren test stratified by baseline F/TDF for pre-exposure prophylaxis to compare the two treatment groups. ‡Rank ANCOVA adjusting for baseline category. §ANCOVA model including baseline F/TDF for pre-exposure prophylaxis and treatment as fixed effects and baseline serum creatinine as a covariate.

grade 2 (moderate) in severity, and the most common (ie, ≥10% of adverse events) were bacterial STIs. The incidence of bacterial STIs was similar in the two study groups (rectal gonorrhoea, 22 infections per 100 person-years in the emtricitabine and tenofovir alafenamide group *vs* 21 infections per 100 person-years in the emtricitabine and tenofovir disoproxil fumarate group, p=0·2791; rectal chlamydia, 28 infections per 100 person-years in the emtricitabine and tenofovir alafenamide group *vs* 28 infections per 100 person-years in the emtricitabine and tenofovir disoproxil fumarate group, p=0·5381; and syphilis, ten infections per 100 person-years in the emtricitabine and tenofovir alafenamide group *vs* ten infections per 100 person-years in the emtricitabine and tenofovir disoproxil fumarate group, p=0·227). The most common adverse events in both groups that the investigator considered to be associated with the study drug were primarily gastrointestinal (appendix p 14). The prevalence of diarrhoea (135 [5%] of 2694 participants in the emtricitabine and tenofovir alafenamide group and 160 [6%] of 2693 participants in the emtricitabine and tenofovir disoproxil fumarate group) and nausea (114 [4%] of 2694 participants in the emtricitabine and tenofovir alafenamide group and 125 [5%] of 2693 participants in the emtricitabine and tenofovir disoproxil fumarate group) was highest during week 4, with declines in the prevalence of both adverse effects starting by week 8. The prevalence of diarrhoea and nausea was similar between the two groups (appendix p 29).

The incidence of adverse events that led to premature discontinuation of the study drug was similarly low between the two groups (36 [1%] of 2694 participants in the emtricitabine and tenofovir alafenamide group compared with 49 [2%] of 2693 participants in the emtricitabine and tenofovir disoproxil fumarate group; table 2). Serious adverse events occurred in 169 (6%) individuals in the emtricitabine and tenofovir alafenamide group and 138 (5%) participants in the emtricitabine and tenofovir disoproxil fumarate group. Serious adverse events that the investigator considered to be associated with the study drug were rare (n=3 in the emtricitabine and tenofovir alafenamide group and n=5 in the emtricitabine and tenofovir disoproxil fumarate group). Renal adverse events occurred in 263 (10%) participants in the emtricitabine and tenofovir alafenamide group and 266 (10%) of participants in the emtricitabine and tenofovir disoproxil fumarate group; study drug-related renal events occurred in 14 (0·5%) participants in the emtricitabine and tenofovir alafenamide group and 26 (1%) participants in the emtricitabine and tenofovir disoproxil fumarate group (appendix p 15). Renal adverse events leading to discontinuation were rare (n=2 in the emtricitabine and tenofovir alafenamide group and n=6 in the emtricitabine and tenofovir disoproxil fumarate group; appendix p 16). There were no cases of proximal renal tubulopathy or Fanconi syndrome among participants in the emtricitabine and tenofovir alafenamide group. In the emtricitabine and tenofovir disoproxil fumarate group there was one case of Fanconi syndrome in a 49-year-old participant who had no reported medical conditions, including no renal comorbidities or renal risk factors. This participant did not report receiving any concomitant medications associated with renal toxicity during the study. From baseline, he showed an early and persistent increase in tubular proteinuria, accompanied by a decline in $eGFR_{CG}$ and an increasing urine protein to creatinine ratio, preceding the clinical identification of grade 3 Fanconi syndrome on study day 421 (appendix p 30). In both groups, 53 participants had fracture events (appendix p 17); of these, one event in the emtricitabine and tenofovir alafenamide group and two events in the

	Emtricitabine and tenofovir alafenamide group (n=2694)	Emtricitabine and tenofovir disoproxil fumarate group (n=2693)
Participants with any adverse event	2498 (93%)	2494 (93%)
Discontinuation of study drug because of adverse event	36 (1%)	49 (2%)
Serious adverse event*	169 (6%)	138 (5%)
Treatment-related serious adverse event†	545 (20%)	630 (23%)
Death‡	1 (0·04%)	1 (0·04%)
Common adverse events (≥10% in either group)		
Rectal chlamydia	770 (29%)	792 (29%)
Oropharyngeal gonorrhoea	740 (27%)	722 (27%)
Rectal gonorrhoea	693 (26%)	671 (25%)
Exposure to a communicable disease	465 (17%)	441 (16%)
Diarrhoea	430 (16%)	422 (16%)
Nasopharyngitis	350 (13%)	355 (13%)
Upper respiratory tract infection	356 (13%)	310 (12%)
Syphilis	342 (13%)	321 (12%)
Urethral chlamydia	280 (10%)	259 (10%)
Grade 3 or 4 laboratory abnormality (≥1% in either group)		
Any	196 (7%)	206 (8%)
Increased alanine aminotransferase§	39 (1%)	40 (2%)
Increased amylase§	34 (1%)	46 (2%)
Increased aspartate aminotransferase§	63 (2%)	51 (2%)
Hyperglycaemia, fasting§	12 (<1%)	17 (1%)
Increased LDL, fasting§	51 (2%)	18 (1%)
Glycosuria§	19 (1%)	32 (1%)

Data are n (%). *The most common serious adverse events in the emtricitabine and tenofovir alafenamide group were appendicitis (n=8, 0·3%), suicidal ideation (n=7), acute kidney injury (n=5), hepatitis A (n=5), cellulitis (n=4), pneumonia (n=4), depression (n=4), suicide attempt (n=4), and road traffic accident (n=4); the most common serious adverse events in the emtricitabine tenofovir disoproxil fumarate group were appendicitis (n=9), suicidal ideation (n=5), cellulitis (n=4), pneumonia (n=4), atrial fibrillation (n=4), chest pain (n=4), anal abscess (n=3), and diverticulitis (n=3). †Serious adverse events considered to be associated with emtricitabine tenofovir alafenamide included nephrotic syndrome (n=1), chest pain and loss of consciousness (n=1), and agranulocytosis and pyrexia in the same participant (n=1); serious adverse events considered to be associated with emtricitabine tenofovir disoproxil fumarate included acute kidney injury (n=2), migraine (n=1), pneumonia (n=1), urinary calculus (n=1), and renal tubular necrosis (n=1). ‡Reasons for death included one traffic accident in the emtricitabine and tenofovir alafenamide group, and one unknown cause in the emtricitabine and tenofovir disoproxil fumarate group. §Threshold values for the defined concentrations are in the appendix (p 10).

Table 2: **Adverse events and laboratory abnormalities in the safety analysis population over a median of 86 weeks of follow-up**

emtricitabine and tenofovir disoproxil fumarate group were non-traumatic (ie, pathological; appendix p 18). Grade 3 or above laboratory abnormalities occurred at a low frequency (ie, 2% or lower) in both groups (table 2).

Over half of participants (2876 [54%] of 5387) were overweight (defined by a body-mass index of >25 kg/m²) at baseline (table 1). Participants in the emtricitabine and tenofovir disoproxil fumarate group lost weight in the first 24 weeks and returned to baseline weight at week 48 (mean change in bodyweight between baseline and 48 weeks was –0·1 kg), whereas those in the emtricitabine and tenofovir alafenamide group had a mean increase in bodyweight of 1·1 kg at week 48. Participants in the emtricitabine and tenofovir alafenamide group had a significantly greater mean change in bodyweight between baseline and 48 weeks than did those in the emtricitabine and tenofovir disoproxil fumarate group (p<0·0001; appendix p 31). Median changes from baseline to week 48 in total cholesterol concentrations (–0·03 mmol/L in the emtricitabine and tenofovir alafenamide group *vs* –0·28 mmol/L in the emtricitabine and tenofovir disoproxil fumarate group; p<0·0001), LDL concentrations (0·03 mmol/L in the emtricitabine and tenofovir alafenamide group *vs* –0·18 mmol/L in the emtricitabine and tenofovir disoproxil fumarate group; p<0·0001), and HDL concentrations (–0·05 mmol/L in the emtricitabine and tenofovir alafenamide group *vs* –0·13 mmol/L in the emtricitabine and tenofovir disoproxil fumarate group; p<0·0001) were significantly different between the two groups. The median change in the total cholesterol to HDL ratio between baseline and 48 weeks was not significant between the two groups (0·1 in the emtricitabine and tenofovir alafenamide group *vs* 0·1 in the emtricitabine and tenofovir disoproxil fumarate group; p=0·73; appendix p 32).

There were no differences in adherence between the two groups by self-report, pill count, and DBS analysis. Between 96–98% of participants reported taking the study drug more than 80% of the time across all study visits (appendix p 33). Median pill count adherence was 98% (IQR 93·4–99·8) in the emtricitabine and tenofovir alafenamide group and 98% (93·5–99·9) in the emtricitabine and tenofovir disoproxil fumarate group. Objective adherence, as measured by DBS analysis in a subset of participants at each visit, showed that 84–96% of these participants had tenofovir diphosphate concentrations consistent with taking four or more tablets per week (appendix p 33).

Trough tenofovir diphosphate concentrations in PBMCs at 4 weeks were 6·3 times higher in the emtricitabine and tenofovir alafenamide group (n=158) than in the emtricitabine and tenofovir disoproxil fumarate group (n=151; geometric least square percentage mean ratio 631 [90% CI 514–773]); 155 (98%) of 158 participants in the emtricitabine and tenofovir alafenamide group and 102 (68%) of 151 participants in the emtricitabine and tenofovir disoproxil fumarate group had trough tenofovir diphosphate concentrations above the EC_{90} (40 fmol per 10^6 cells; p<0·0001; appendix p 34). On steady state dosing of study drugs, the median duration of time above the EC_{90} after the last dose received was 16 days in the emtricitabine and tenofovir alafenamide group compared with 10 days in the emtricitabine and tenofovir disoproxil fumarate group (appendix p 35). In 17 transgender women in the emtricitabine and tenofovir alafenamide group who reported taking high-dose gender-affirming hormone therapy, trough tenofovir diphosphate concentrations and emtricitabine-triphosphate concentrations in PBMCs at week 4 were similar to those observed in MSM, and were above the EC_{90} (appendix p 36).

Viral RNA could be amplified for genotypic resistance testing in 19 (86%) of the 22 participants who were infected with HIV. Emtricitabine resistance (M184V or M184I reverse transcriptase mutations, or both) was detected in four (21%) of these 19 participants; all four participants were in the emtricitabine and tenofovir disoproxil fumarate group and were all suspected to have been infected before baseline. No participants had genotypic mutations detected that were consistent with resistance to tenofovir (appendix p 19).

Discussion

The DISCOVER study, which was a large active-controlled, non-inferiority trial of PrEP, showed that daily emtricitabine and tenofovir alafenamide has non-inferior efficacy to daily emtricitabine and tenofovir disoproxil fumarate for HIV prevention. Both tenofovir prodrugs were well tolerated, with general safety profiles similar to those observed in previous trials[22–31] of HIV and HBV treatment; in particular, the emtricitabine and tenofovir alafenamide drug combination was found to have more favourable effects on bone mineral density and biomarkers of renal safety than emtricitabine and tenofovir disoproxil fumarate in our study. The number of serious adverse events and adverse events that led to drug discontinuation, including renal events, were similarly low in both groups. Non-traumatic fractures were rare in both groups. Emtricitabine and tenofovir alafenamide was associated with weight gain when compared with emtricitabine and tenofovir disoproxil fumarate (mean 1·2 kg difference in bodyweight change between groups at week 48).

The incidence of HIV infection in our study was among the lowest reported in randomised trials[1,3,4,44] of PrEP that have been done to date (0·16 infections per 100 person-years in the emtricitabine and tenofovir alafenamide group and 0·34 infections per 100 person-years in the emtricitabine and tenofovir disoproxil fumarate group). As adherence is directly associated with the efficacy of PrEP, the low incidence of HIV in both groups could have been attributable to the high adherence observed in both study groups.[20,36,45] All but two participants who acquired HIV infection post-baseline had low tenofovir concentrations by DBS

analysis, suggesting suboptimal or poor adherence. A per-protocol analysis, which excluded both the five participants who were infected with HIV at baseline and those who were non-adherent, yielded an IRR point estimate (0·40 [95% CI 0·08–2·06]) similar to that of the primary analysis (0·47 [0·19–1·15]), but which had a wider 95% CI than the primary analyses because the excluded participants (ie, number of HIV infections and follow-up time) reduced the power. The low incidence of HIV cannot be explained by low occurrence of risk behaviours, given the persistently high number of STIs acquired during the trial, including rectal gonorrhoea, which is directly associated with HIV incidence.[46] Similarly, the low incidence of HIV in our study cannot be fully explained by declining HIV incidence in the community. Despite the increasing prevalence of virological suppression among MSM living with HIV in communities where the DISCOVER trial was done, new HIV diagnoses among PrEP-eligible MSM who were not taking PrEP in many of the DISCOVER sites remained persistently high.[47] Low HIV incidence was observed in both study groups, in participants with ongoing risk sexual behaviours, and in communities where the HIV transmission among MSM remained high, strongly suggesting the high efficacy of both regimens in the context of high adherence.

Even though adherence to the study drug was similarly high in both groups, tenofovir diphosphate concentrations in PBMCs at week 4 was 6·3 times higher in the emtricitabine and tenofovir alafenamide group than in the emtricitabine and tenofovir disoproxil fumarate group, consistent with previous studies.[18,48] After the last dose, intracellular tenofovir diphosphate concentrations in the emtricitabine and tenofovir alafenamide group remained above the EC_{90} (consistent with protection against HIV infection) for 60% longer (median 16 days) than in the emtricitabine and tenofovir disoproxil fumarate group (median 10 days). Additionally, with the same level of adherence between groups, 155 (98%) of 158 participants in the emtricitabine and tenofovir alafenamide group had concentrations of intracellular tenofovir diphosphate above the EC_{90} compared with 102 (68%) of 151 participants in the emtricitabine and tenofovir disoproxil fumarate group.[19,20] These data could suggest that emtricitabine and tenofovir alafenamide might be more forgiving, maintaining protective concentrations if daily doses are missed. However, our trial was not sufficiently powered to assess this hypothesis, which deserves future investigation.

The DISCOVER trial is the largest single variable comparison of the safety of the two tenofovir prodrugs, and the results are not complicated by underlying HIV or HBV infection or confounded by the presence of other antiretroviral drugs, which can increase plasma tenofovir concentrations and have their own independent effects on safety. This trial found no difference in adverse events between the two study groups. All six prespecified bone density and renal biomarker secondary endpoints showed the statistical superiority of emtricitabine and tenofovir alafenamide over emtricitabine and tenofovir disoproxil fumarate after 48 weeks. We chose these endpoints because early changes in these biomarkers have been associated with meaningful differences in clinical bone and renal outcomes during 144 weeks of follow-up in previous HIV treatment trials (appendix p 37).[22–29] Compared with the emtricitabine and tenofovir disoproxil fumarate group, the improved bone density and renal biomarkers in the emtricitabine and tenofovir alafenamide group were attributable to the 90% lower plasma tenofovir concentrations, and the subsequent lower cumulative toxicity of tenofovir in bone and at the proximal renal tubules.

Participants in the emtricitabine and tenofovir alafenamide group had stable hip bone mineral density and increased spine bone mineral density at 48 weeks, whereas participants in the emtricitabine and tenofovir disoproxil fumarate group lost about 1% of their bone mineral density over 48 weeks. The median age of all participants was 34 years at baseline, and many participants had yet to achieve peak bone mass, which is a key determinant of fracture risk later in life.[49,50] Furthermore, subgroup analyses indicated that younger participants (aged ≥18 to <25 years) in the emtricitabine and tenofovir disoproxil fumarate group showed greater loss of bone mineral density (>2%) compared with older participants (aged >25 years), and that the increase in bone mineral density in the emtricitabine and tenofovir alafenamide group was not completely driven by participants switching from emtricitabine and tenofovir disoproxil fumarate to emtricitabine and tenofovir alafenamide. It is unknown whether the increase in bone mineral density in people taking tenofovir alafenamide compared with those taking tenofovir disoproxil fumarate will translate to a reduced fracture risk later in life. Previous or current tenofovir disoproxil fumarate treatment was identified as a strong independent risk factor for fracture in 11 820 people living with HIV in the EuroSIDA study cohort,[51] which included 86 118 person-years of follow-up, but no significant correlation was observed in a smaller case-control study.[52] Therefore, it is not clear whether the same fracture risk pertains to persons without HIV and who are not taking other antiretrovirals. There is a wide diversity in the duration of PrEP use, with trends changing as awareness and uptake increases; some individuals use daily prophylaxis for short periods during so-called seasons of risk, others use daily prophylaxis continuously for several years, and some individuals might use PrEP with event-based dosing, which has been recommended by some guidelines for MSM.[44,53–59] Long-term follow-up of people taking PrEP with an assessment of duration of tenofovir disoproxil fumarate exposure is needed to understand the effect of this treatment on long-term bone health, particularly in younger PrEP users who have not yet reached peak bone mass.

Tenofovir disoproxil fumarate has been associated with cumulative renal toxicity in previous HIV treatment and prevention trials,[22–29] with a systematic review by the US Preventative Services Task Force in 2019 pooling the results of nine trials of PrEP with emtricitabine and tenofovir disoproxil fumarate that showed a 54% increased risk of renal adverse events over placebo.[60] The magnitude of differences in biomarkers of renal function between the two tenofovir prodrugs in our trial are similar to those observed in other HIV treatment trials.[22–29] Although results of HIV treatment trials might not be directly applicable to people without HIV in trials on HIV prevention, several HIV treatment studies with longer-term follow-up than the current study have shown that these early, small biomarker differences manifest as an increase in the number of cases of proximal renal tubulopathy and renal adverse events, leading to discontinuation of the study drug (appendix p 37).[29] Moreover, the improvement in renal biomarkers at week 48 in participants switching from tenofovir disoproxil fumarate to tenofovir alafenamide in our study is consistent with the results of previous HIV treatment studies, in which participants switched from regimens containing tenofovir disoproxil fumarate to regimens containing tenofovir alafenamide.[29] In our study, no difference in the number of renal adverse events between the two treatment groups in our study was observed. In addition, no cases of Fanconi syndrome were reported in the emtricitabine and tenofovir alafenamide group, whereas one case of Fanconi syndrome was reported in the emtricitabine and tenofovir disoproxil fumarate group. The improved renal biomarker profile of emtricitabine and tenofovir alafenamide over tenofovir disoproxil fumarate suggests that less frequent creatinine monitoring might be safe for people with normal renal function and who do not have risk factors for renal disease. This hypothesis should be explored through implementation science research. Further study is needed to evaluate whether tenofovir alafenamide has less of an effect on renal function when compared with tenofovir disoproxil fumarate in people with kidney disease or other predisposing comorbidities (eg, diabetes or hypertension), who intend to take PrEP chronically, especially given that the duration of PrEP use is increasing.[54,55]

The weight and lipid changes observed in our trial are consistent with the well documented weight-suppressive and lipid-suppressive effects of tenofovir disoproxil fumarate.[22–29,61–65] In both the DISCOVER and the iPrEX trials,[62] participants who were given tenofovir disoproxil fumarate had initial weight loss after starting the study drug, followed by weight stability at week 48 (appendix p 31). The weight gain in the emtricitabine and tenofovir alafenamide group in our study is similar to that observed in the placebo groups of the iPrEX[62] and HPTN 077[66] trials of PrEP, and is consistent with annual weight gain in the general populations of the USA (0·5–1 kg/year) and western Europe.[67–69] By contrast with studies of PrEP, larger weight gains have been reported in participants taking tenofovir alafenamide in HIV treatment studies, especially when used in combination with integrase inhibitors (in contrast to protease inhibitors or efavirenz).[61,70] In our study, participants in the emtricitabine and tenofovir alafenamide group showed minimal changes in blood lipid concentrations, whereas those in the emtricitabine and tenofovir disoproxil fumarate group had proportional reductions in LDL and HDL cholesterol at week 48, similar to the results of the iPrEX trial.[62] Of note, no change in the total cholesterol to HDL ratio, which is an indicator of cardiovascular risk with a greater predictive value than individual cholesterol parameters, was observed in either group.[71–73] However, the clinical significance of the weight gain and changes in blood lipid profiles observed for tenofovir alafenamide compared with tenofovir disoproxil fumarate for PrEP is not known.

Our trial had several limitations. The sharply lower-than-expected number of HIV infections observed reduced the statistical power of the comparison between the two groups. However, non-inferiority of emtricitabine and tenofovir alafenamide to emtricitabine and tenofovir disoproxil fumarate was shown because of the imbalance in the number of infections between the two groups, which lowered the point estimate of the IRR to less than 1 and reduced the upper bound of the accompanying 95% CI. A key limitation of the active-controlled design is the absence of a concurrent non-PrEP control group. As a result, we cannot eliminate the possibility that the low number of HIV infections was because of a low risk of infection in the recruited population or because of a higher prevalence of virological suppression among people living with HIV who were partners of the recruited population. Various approaches, each with their own limitations, have attempted to estimate HIV incidence in such counterfactual populations of individuals who do not use PrEP (similar to those enrolled in our study) to provide context to the results of our active-controlled trial.[50,58,74]

Another important limitation of our study was that blood was not drawn at the baseline visit, which was designed to be minimally invasive. Five participants (one in the emtricitabine and tenofovir alafenamide group and four in the emtricitabine and tenofovir disoproxil fumarate group) who tested positive for HIV-1 at week 4 were suspected to have acquired HIV infection between screening and baseline. The absence of a stored plasma sample at baseline precluded the ability to distinguish whether these five participants acquired HIV before randomisation or while they were taking the study drug. Given the crucial importance of ensuring that participants are not infected with HIV at the time of PrEP initiation, in future clinical trials of PrEP, all participants who are not screened with a sensitive fourth-generation antigen–antibody test should have negative HIV-1 RNA test results before initiation of PrEP

or have plasma samples saved from the baseline visit for retrospective testing.

The DISCOVER trial did not achieve the desired inclusion of Black participants and transgender women. 60% of the study population (3220 of 5387 participants) were enrolled in the USA, with the remaining 40% (2167 of 5387) enrolled in Canada and Europe. Therefore, the results might not be generalisable to populations of MSM and transgender women in other locations. Even though 41% of new HIV infections in the USA are among Black individuals, only 474 (9%) of 5387 participants in our study were Black, representing 422 (13%) of 3220 participants enrolled in the USA and 52 (2%) of 2867 participants enrolled in Europe.[75] Similarly, only 74 (1%) of all 5387 participants were transgender women, despite the disproportionately high prevalence of HIV in this population (22–28%).[76,77] A subgroup analysis of Black (n=474) and Latinx (n=1318) participants showed that there were no significant differences in the efficacy or safety of PrEP in racial and ethnic subgroups when compared with non-Black or non-Latinx participants in either study group (appendix p 24). Among the few transgender women we enrolled, both adherence and STI acquisition were high, but none acquired HIV. Notably, transgender women receiving emtricitabine and tenofovir alafenamide together with high-dose gender-affirming hormones had similar distributions of intracellular tenofovir diphosphate concentrations in PBMCs as cisgender MSM. These results are consistent with phase 1 drug–drug interaction studies[78] showing the absence of an effect of oral contraceptive hormones on plasma exposure of tenofovir alafenamide, tenofovir, and emtricitabine, and no effect of tenofovir alafenamide, tenofovir, or emtricitabine on exposure of oral contraceptive hormones. Collectively, these data provide reassurance about the appropriateness of tenofovir-based PrEP for transgender women taking gender-affirming hormones. Lastly, the DISCOVER trial did not evaluate the efficacy of emtricitabine and tenofovir alafenamide for HIV prevention in individuals who have receptive vaginal or frontal sex, or in injection drug use, although the mechanism of protection and pharmacokinetics are not expected to differ in these settings. Additional studies are planned to evaluate the efficacy of emtricitabine and tenofovir alafenamide in these populations.

The DISCOVER study, which was a large active-controlled, non-inferiority trial of PrEP, showed that daily emtricitabine and tenofovir alafenamide has non-inferior efficacy to daily emtricitabine and tenofovir disoproxil fumarate for HIV prevention in cisgender MSM and transgender women who have sex with men, and has more favourable effects on bone mineral density and biomarkers of renal safety. Both emtricitabine and tenofovir alafenamide and emtricitabine and tenofovir disoproxil fumarate were safe and well tolerated. Daily emtricitabine and tenofovir alafenamide therefore offers a new option for HIV prevention in these populations.

Contributors

KHM, J-MM, MAT, PLA, KCM, JJDW, ED, HJ, RMG, PJR, CB, AC, PC, FAP, and CBH enrolled participants, and reviewed and interpreted the results of the data analyses. SM, RE, and LZ designed the study. PW, RE, LZ, AM, and CC analysed the data, which were reviewed and interpreted by PLA, SEC, MD, SM, and DMB. The first draft of the manuscript was written by KHM and MD. All authors edited the manuscript and approved the final version. KHM, MD, SM, and DMB made the decision to submit the manuscript for publication. All authors had access to the data and are responsible for data integrity and completeness.

Declaration of interests

KHM reports grants from Gilead Sciences and Merck, and reports fees for serving on their scientific advisory boards. J-MM has served on advisory boards for Gilead Sciences, Merck, and ViiV Healthcare, and reports grants from Gilead Sciences (in support of the French Agency for AIDS and Viral Hepatitis Research PrEP project). MAT reports research funding paid to the AIDS Research Consortium of Atlanta from BMS, CytoDyn, Cepheid, GlaxoSmithKline, Gilead Sciences, Merck Sharp & Dohme, Roche Laboratories, Taimed, and ViiV Healthcare. PLA reports grants and personal fees from Gilead Sciences during the conduct of the study, and reports grants from Gilead Sciences outside of the submitted work. KCM reports grants paid to Philadelphia FIGHT (Philadelphia, PA, USA) from Gilead Sciences during the conduct of the study. JJDW has served on advisory boards and speakers' bureaus for Gilead Sciences, ViiV Healthcare, and Merck, has previously been a consultant for AbbVie, and reports grants from Gilead Sciences during the conduct of the study. ED reports grants and personal fees from Gilead Sciences during the conduct of the study; grants and personal fees from Gilead Sciences for serving on advisory boards and speakers' bureaus; and personal fees from ViiV Healthcare, Janssen Pharmaceuticals, and Theratechnologies for serving on advisory boards, all outside the submitted work. HJ reports grants from Gilead Sciences and the US Military HIV Research Program during the conduct of the study; grants from ViiV Healthcare and Merck Sharp & Dohme for board membership; speaker fees from ViiV Healthcare, Janssen-Cilag, and Hormosan Pharma for speaker activities; and personal fees from Gilead Sciences, Janssen-Cilag, ViiV Healthcare, and Merck Sharp & Dohme for travel, accommodation, and meeting expenses. RMG reports unrestricted research funding from Gilead Sciences during the conduct of the study, and has served on scientific advisory boards for Gilead Sciences and Merck. PJR has served as a speaker for and owns stock in Gilead Sciences; has served as a consultant for Gilead Sciences, ViiV Healthcare, Merck, and AbbVie; and reports grants from Gilead Sciences, ViiV Healthcare, Merck, AbbVie, and Allergan. PW, RE, LZ, AM, CC, SEC, MD, SM, and DMB are employees of Gilead Sciences and hold stock interest in the company. CB reports grants from Gilead Sciences, Braintree, Novo Nordisk, ViiV Healthcare, CoLucid, SlieaGen, Shionogi, Sanofi, Daiichi Sankyo, and Theratechnologies; and personal fees from Gilead Sciences and Theratechnologies during the conduct of the study and outside the submitted work. AC has served on advisory boards; has provided staff training for Gilead Sciences and GlaxoSmithKline; and reports personal fees from Gilead Sciences, Janssen Pharmaceuticals, and GlaxoSmithKline outside of the submitted work. PC reports grants and non-financial support from Gilead Sciences; and fees from Janssen Pharmaceuticals, Merck, and ViiV Healthcare for serving on their scientific advisory boards. FAP reports grants from King's College Hospital during the conduct of the study and outside of the submitted work; grants from Gilead Sciences, ViiV Healthcare, Janssen Pharmaceuticals during the conduct of the study; and personal fees from Gilead Sciences, ViiV Healthcare, Janssen Pharmaceuticals, and Merck Sharp & Dohme outside of the submitted work. CBH reports grants from Gilead Sciences, Merck, and Janssen Pharmaceuticals during the conduct of the study and outside of the submitted work.

Data sharing

Gilead Sciences shares anonymised individual patient data with qualified external researchers on request, or as required by law or regulation, or both. Approval of such requests is at the discretion of

Gilead Sciences, and is dependent on the nature of the request, merit of the research proposed, availability of the data, and intended use of the data. Data requests should be sent to datarequest@gilead.com.

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