Title Page

Title: **Longer-term safety and efficacy of emtricitabine and tenofovir alafenamide versus emtricitabine and tenofovir disoproxil fumarate for HIV-1 Pre-exposure Prophylaxis: Week 96 results from a randomized, double-blind, placebo-controlled phase 3 trial**

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Key Words: Antiretroviral Agents, Tenofovir, HIV Infections, Bone Density, Proteinuria

Word Count:

Structured Summary

Current word count: 303

Background: In DISCOVER, a multinational randomized controlled trial, emtricitabine and tenofovir alafenamide compared with emtricitabine and tenofovir disoproxil fumarate demonstrated noninferior efficacy for HIV prevention and improved bone mineral density and renal safety biomarkers at week 48. Here, we report outcomes analysed after all participants had completed 96 weeks of follow up.

Methods: This study is an ongoing, randomised, double-blind, multicentre, active-controlled, phase 3, noninferiority trial done at 94 community, public health, and hospital-associated clinics located in regions of Europe and North America. Adult cisgender men and transgender women who have sex with men with a high risk of acquiring HIV were randomly assigned (1:1) to either of two study arms of this noninferiority trial registered with ClinicalTrials.gov, NCT02842086. Incidence of HIV-1 infection per 100-person years (PY) was assessed, when the last participant had completed 96 weeks of follow up.

Findings: 5,387 participants were randomly assigned to receive emtricitabine and tenofovir alafenamide (n=2,694) or emtricitabine and tenofovir disoproxil fumarate (n=2,693), contributing 10,081 person-years (PY) of follow-up. There were eight HIV infections in emtricitabine and tenofovir alafenamide users (0·16 infections/100 PY [95% CI 0·07–0·31]), and 15 in emtricitabine and tenofovir disoproxil fumarate users (0·30 infections/100 PY [0·17–0·49]). Emtricitabine and tenofovir alafenamide maintained its noninferiority to emtricitabine and tenofovir disoproxil fumarate for HIV prevention, as the upper limit of the 95% CI of the infection rate ratio (IRR) was less than the prespecified noninferiority margin of 1·62 (IRR 0·54

[95% CI 0·23–1·26]). Approximately 78% to 82% of participants reported taking study medication more than 95% of the time across all study visits. Rates of sexually transmitted infections remained high and similar across arms (21 per 100 PYs for rectal gonorrhea and 28 per 100 PY for rectal chlamydia). Emtricitabine and tenofovir alafenamide continued to demonstrate superiority over emtricitabine and tenofovir disoproxil fumarate in all but one of the six prespecified bone mineral density and renal biomarkers. There was more weight gain among emtricitabine and tenofovir alafenamide users (median weight gain 1·7 kg vs. 0·5 kg, p<0·0001)

Interpretation: Emtricitabine and tenofovir alafenamide is safe and effective for longer-term PrEP in cisgender men and transgender women who have sex with men.

Funding: Gilead Sciences, Inc.

Research in Context

Evidence before this study

We searched PubMed for clinical trials assessing the use of tenofovir prodrugs for HIV pre-exposure prophylaxis (PrEP) from database inception to August 14, 2020, using the title or abstract search terms "HIV" AND ("prevention" OR "prophylaxis"). We restricted the search to trials in humans and those published in English. The search yielded 187 articles published between 2007 and 2019. Thirty-two of these reported safety outcomes, including findings from 14 trials. These studies showed that oral PrEP with emtricitabine and tenofovir disoproxil fumarate is well tolerated and generally safe but associated with mild and mostly reversible adverse events: In pooled analyses of data from 12 placebo-controlled trials, oral PrEP with emtricitabine and tenofovir disoproxil fumarate was associated with increased risk for gastrointestinal and renal adverse events, and for study withdrawal due to adverse events. Three trials also linked emtricitabine and tenofovir disoproxil fumarate to declines in bone mineral density.

Added value of this study

The safety of emtricitabine and tenofovir alafenamide for HIV treatment has been widely described. There is also emerging evidence showing its favorable short-term safety over tenofovir disoproxil fumarate, the current standard of care, when used for HIV prevention. However, longer use of this drug in HIV-uninfected individuals has not been previously assessed. To our knowledge, this is the first trial to compare safety outcomes of emtricitabine and tenofovir alafenamide to emtricitabine and tenofovir disoproxil fumarate for PrEP over a longer period (at least 96 weeks of follow up). We show that longer-term data continue to

demonstrate greater renal and bone safety for emtricitabine and tenofovir alafenamide compared to emtricitabine and tenofovir disoproxil fumarate

Implications of all the available evidence

This study supports longer-term use of emtricitabine and tenofovir alafenamide as PrEP in cisgender men and transgender women who have sex with men.

Main text (4525/4500 words)

Introduction

HIV infection remains a global pandemic in spite of significant advances in prevention and treatment with over 1.7 million new infections occurring in 2018 alone.[1] About 70,000 new cases occur each year in the United States and Europe, with men who have sex with men (MSM), primarily younger individuals (<30 years of age), transgender women and minority communities disproportionately acquiring HIV infection.[2] Pre-exposure prophylaxis (PrEP) is an effective tool for the prevention of HIV-1 infection among all risks groups[3-5] and, where uptake is high, leads to significantly decreased community incidence of HIV-1.[6] However, utilization of the first approved PrEP medication, emtricitabine and tenofovir disoproxil fumarate oral combination regimen, continues to lag behind need.[7] Barriers to uptake include risk misperception by high risk groups, insufficient provider knowledge and willingness to prescribe PrEP, limited access to prevention health services disproportionally experienced by the most vulnerable groups, stigma and concern for side effects.[8-10] These barriers have limited the real world effectiveness of PrEP and additional PrEP options are needed to expand coverage among those who could most benefit from it.

While emtricitabine and tenofovir disoproxil fumarate is generally well tolerated, there are well-documented clinical concerns around the long-term toxicities associated with the tenofovir pro-drug component. These include significant decreases in bone mineral density (BMD) that occur over time as well as proximal renal tubular dysfunction, rarely manifesting as Fanconi syndrome.[11] Thus, it is contraindicated for use in individuals with moderate renal impairment (creatinine clearance <60 mL/min) and best avoided for those with osteoporosis or osteopenia.[12]

These toxicities limit the use of tenofovir disoproxil fumarate-based PrEP for people at risk of HIV. To overcome these concerns, tenofovir alafenamide, another tenofovir pro-drug with a different pharmacokinetic profile was developed. Tenofovir alafenamide has been associated with less renal and bone toxicity [13,14] in people living with HIV.

DISCOVER, a multinational, randomized, active-controlled phase 3 trial, evaluated the safety and efficacy of fixed dose combinations of emtricitabine and tenofovir alafenamide versus emtricitabine and tenofovir disoproxil fumarate for HIV-1 prevention among high risk adult cisgender men and transgender women (TGW).[15] The primary analysis, when 100% completed 48 weeks of follow up and 50% of participants completed 96 weeks, found emtricitabine and tenofovir alafenamide to be noninferior to emtricitabine and tenofovir disoproxil fumarate for HIV prevention, which provided the basis for its approval by the US Food and Drug Administration (FDA), in October 2019, for prevention of sexual transmission of HIV in adults and adolescents, with the exception of those who are at risk of HIV-1 through receptive vaginal intercourse (a population not studied). In addition, emtricitabine and tenofovir alafenamide showed more favorable bone and renal safety outcomes than emtricitabine and tenofovir disoproxil fumarate and may be dosed in individuals with creatinine clearance as low as 30 mL per min, or 15 mL per min if on hemodialysis.

Longer term (96-week) secondary efficacy and safety outcomes of emtricitabine and tenofovir alafenamide for HIV PrEP are presented here.

Methods

Study design and participants

Detailed methods have been previously published.[15] Briefly, study investigators enrolled adult cisgender men and TGW who have sex with men at high risk of HIV acquisition as determined by self-reported sexual behavior or recent sexually transmitted infections. Prior use of emtricitabine and tenofovir disoproxil fumarate for PrEP was allowed. Full eligibility criteria are provided in the Supplementary Materials.

This study was undertaken in accordance with the Declaration of Helsinki and were approved by central or site-specific review boards or ethics committees. All participants provided written informed consent.

Randomisation and masking

We randomly assigned participants 1:1 to receive tablets of emtricitabine and tenofovir alafenamide (200/25 mg) or emtricitabine and tenofovir disoproxil fumarate (200/300 mg) and matched placebo, once daily (double-dummy method). The sponsor, all investigators, participants, and study staff providing study drug, assessing outcomes, and collecting data were masked to study drug assignment. A computer-generated random 1:1 allocation sequence (block size=4) was created and implemented by Bracket (San Francisco, US).

Procedures

Participants were screened for eligibility and randomised within 30 days. Post-baseline study visits occurred at weeks 4, 12, and every 12 weeks thereafter. After week 96, participants were offered enrolment into the open-label phase during which all participants receive emtricitabine and tenofovir alafenamide and are seen every 12 weeks through at least an additional 48 weeks.

At screening and each post-baseline visit, gonorrhea and chlamydia nucleic acid amplification testing were performed from rectal, pharyngeal, and urine specimens; syphilis testing was performed by local laboratories in accordance with local guidelines.[16] Adherence was assessed by dry blood spot, self-report and pill count through the primary endpoint and thereafter by self-report and by pill count. In a subset of 383 participants who consented, dual energy x-ray absorptiometry (DXA) scans of the hip and lumbar spine was performed. DXA scans were read and interpreted by a blinded third party (BioClinica, Newtown, PA, US).

Outcomes

Outcomes for this secondary analysis were assessed when the last participant had completed 96 weeks of follow up. Incident HIV infection was diagnosed by any of the following: 1) serologic evidence of seroconversion (reactive rapid or blood HIV Ag/Ab or Ab test, confirmed by the reactive blood HIV-1/HIV-2 differentiation assay), or 2) virologic evidence of HIV infection (positive qualitative HIV-1 RNA test or any detectable quantitative HIV RNA test), or 3) evidence of acute HIV infection (reactive p24 Ag or positive qualitative or quantitative RNA, in the absence of reactive HIV Ab results).

Six secondary safety outcomes that have been associated with tenofovir exposure in HIV and HBV treatment were prespecified.[13,17-23] These secondary safety outcomes were percentage changes from baseline to week 96 in hip and spine bone mineral density (BMD), urine beta-2 microglobulin: creatinine ratio (β2M:Cr), retinol-binding protein: creatinine ratio (RBP:Cr), clinically significant elevation in urine protein to creatinine ratio (UPCR) (>22·6 mg/mmol vs ≤22·6 mg/mmol[25]), and change from baseline in serum creatinine (SCr) measured by eGFR.

Additional outcomes included incidence of treatment-emergent adverse events; other laboratory abnormalities, including changes from baseline in lipids, fasting glucose and weight; adherence

by self-report and pill count; tenofovir-diphosphate concentrations in peripheral blood mononuclear cells (PBMCs), and HIV antiretroviral drug resistance associated mutations in those who acquired HIV infection.

Statistical analysis

All statistical methods used for this update were prespecified and previously reported.[15] Briefly, this trial was designed to enroll a sample size of 2,500 participants in each arm with 82·5% power to detect a margin of 1·62 for establishing noninferiority of emtricitabine and tenofovir alafenamide to emtricitabine and tenofovir disoproxil fumarate, using a 2-sided Type 1 error rate of 5%. Participants who acquired HIV were censored at the time of first visit with any reactive HIV test. For this study, the incidence of HIV-1 infection per 100-person years (PY) was assessed when the last participant had completed 96 weeks of follow up. A post-hoc sensitivity analysis excluding participants with suspected baseline infection was also conducted. Follow-up time was calculated up to the last post-baseline HIV test (first confirmed post-baseline HIV-1 positive result for those diagnosed with HIV-1 during the study).

For efficacy analysis, a generalized linear model with a Poisson distribution and logarithmic link with the study arm as the main effect was used to construct the point estimate of HIV incidence rate ratio and the associated 95% CI to establish noninferiority (requiring upper bound <1·62) was used.[25]

For safety analysis, six prespecified week 96 secondary endpoints were analyzed: percentage change from baseline in hip and spine BMD using analysis of variance; β2M:Cr and RBP:Cr using Van Elteren test; UPCR category distribution using rank analysis of covariance;[26] and the change from baseline in serum creatinine using analysis of covariance.

Prespecified subgroup analyses were conducted, using the same method as for the overall population, of percentage changes in hip and spine BMD by age group (≥18 to <25 versus ≥25 years) to evaluate the impact on persons still accruing bone to peak bone mass.[27,28] We also conducted prespecified subgroup analyses based on use of emtricitabine and tenofovir disoproxil fumarate for PrEP at baseline to evaluate the impact of switching to emtricitabine and tenofovir alafenamide on bone mineral density and the renal biomarkers of tubular proteinuria (β2M:Cr, RBP:Cr) and creatinine clearance ($eGFR_{CG}$). Lastly, we examined the impact of age (≥50 years) and baseline creatinine clearance (60 to ≤90 mL/min) on renal safety by evaluating change from baseline of β2M:Cr, RBP:Cr, and $eGFR_{CG}$ at week 96.

Weight changes (kg) from baseline were analysed using analysis of covariance and change from baseline in $eGFR_{CG}$ was assessed using the Van Elteren test, stratifying by baseline emtricitabine and tenofovir disoproxil fumarate use. Changes from baseline in fasting lipid values were compared using the 2-sided Wilcoxon rank sum test. Analyses of safety endpoints were based on observed data in the safety analysis set with baseline emtricitabine and tenofovir disoproxil fumarate for PrEP as a stratification factor (fixed effect) when analysis of covariance models included the baseline measure of the outcome as a covariate. For all safety endpoints, missing data, lost to follow-up, and dropouts were treated as missing at random.

All analyses were performed in SAS® version 9·4 (SAS Institute Inc., Cary, NC, US) and PASS® version 14 for power calculation.

This study was conducted according to protocol and is registered with ClinicalTrials.gov, number NCT02842086.

Role of the funding source

Gilead Sciences funded the study, collected and analyzed the data, interpreted the results in consultation with the other authors of the paper, and helped write the report. OO, DP, LCS, KH, DMA, DW, RG, GW, JMB, GK, and CDS enrolled participants, reviewed and interpreted analyses of data, and edited and/or approved the draft manuscript. RE, and LZ designed the study. YS, RE, LZ, and SC analyzed the data, which were reviewed and interpreted by AK, CC, MD, and DAB. The first draft was written by OO and AK. All authors contributed to edits of the final manuscript. OO, MD, and DAB made the decision to submit the manuscript for publication. All authors had access to the data and are responsible for data integrity and completeness.

Results

Between September 13, 2016 and June 30, 2017, we screened 5,857 individuals and randomised 5,399 (2,700 to emtricitabine and tenofovir alafenamide and 2,699 to emtricitabine and tenofovir disoproxil fumarate) (Figure 1). The follow-up for the current prespecified secondary analysis was completed on April 26, 2019. Baseline demographic, clinical, and risk factor characteristics were balanced between arms and reported previously[15] and presented in Appendix Table 1.

After 10,081 PY of follow-up, 23 participants were diagnosed with HIV, eight on emtricitabine and tenofovir alafenamide (HIV incidence rate: 0·16/100 PY, 95% exact CI: [0·07, 0·31]), and 15 on emtricitabine and tenofovir disoproxil fumarate (HIV incidence rate 0·34/100 PY, 95% exact CI: [0·17, 0·49]). Emtricitabine and tenofovir alafenamide was noninferior to emtricitabine and tenofovir disoproxil fumarate for the prevention of HIV at week 96, as the point estimate and upper limit of the 95% confidence interval of the incidence rate ratio (IRR), 0·54 (95% CI: [0·23, 1·26]), were below the pre-specified noninferiority margin of 1·62 (Figure 2). Excluding five participants who were suspected to have acquired HIV infection prior to baseline; the IRR was 0·64 (95·003% CI [0·25, 1·65]). No HIV infections were observed in TGW. The solitary new HIV infection that was diagnosed between weeks 48 and 96 in the emtricitabine and tenofovir alafenamide arm was at a week 96 visit. The participant's dried blood spot (DBS) tenofovir diphosphate levels were below the limit of quantification at weeks 48, 60, 72, 84 and 96.

Viral RNA could be amplified for genotypic testing in 20 of the 23 incident HIV infection cases. Four of 20 had emtricitabine resistance detected (M184V/I); all of whom were in the emtricitabine and tenofovir disoproxil fumarate arm and all of whom were suspected to have been infected prior to study enrollment. No participants had genotypic mutations detected conferring resistance to tenofovir.

As evaluated by self-report and pill count, participants continued to have high adherence to study drugs with no differences between arms through week 96. Approximately 78% to 82% of participants reported taking study medication more than 95% of the time across all study visits (Appendix Figure 1). Median pill count adherence at week 96 was 98% in both study arms. As previously reported, objective adherence was measured by DBS through the primary endpoint; at each visit 84% to 96% of participants had tenofovir diphosphate concentrations consistent with taking ≥4 tablets per week.[16]

Participants had high rates of bacterial STIs through 96 weeks of follow up. The incidence of STIs was similar between arms (emtricitabine and tenofovir alafenamide versus emtricitabine and tenofovir disoproxil fumarate): rectal gonorrhea, 21 per 100 PY versus 20 per 100 PY; rectal chlamydia, 27 per 100 PY versus 27 per 100 PY; and syphilis, 10 per 100 PY versus 9 per 100 PY.

Across the six prespecified secondary safety endpoints, emtricitabine and tenofovir alafenamide continued to be superior to emtricitabine and tenofovir disoproxil fumarate at week 96 for all safety assessments, with the exception of study drug-emergent urine to protein creatinine ratio of more than 22.6 mg per mmol (Figure 3). In the BMD substudy (n=383; see Appendix Table 2 for baseline characteristics, which did not differ between groups), participants on emtricitabine and tenofovir alafenamide continued to have increases in BMD at the hip and spine while those on emtricitabine and tenofovir disoproxil fumarate continued to have declines in spine BMD with stable hip BMD ($p<0{\cdot}0001$ between groups at both sites at weeks 48 and 96, with the magnitude of the difference increasing between the two time points) (Figure 3, panel A). For participants ≥25 years, there were significant differences in BMD trajectories with increased BMD in both hip and spine for emtricitabine and tenofovir alafenamide users and decreased BMD for

emtricitabine and tenofovir disoproxil fumarate users at the same sites (Appendix Figure 2). Similar trajectories were noted in younger participants (i.e. those ≥18 to <25 years), who experienced greater magnitude of increases and decreases in BMD in the emtricitabine and tenofovir alafenamide group and emtricitabine and tenofovir disoproxil fumarate group respectively. Results were similar to those observed in the overall population although there were small numbers of participants within that age group (n=25). Appendix Figure 3 presents BMD data stratified by fixed percentage increases and decreases in BMD with >5% decrease and 7% decrease in BMD considered significant changes for spine and hip respectively[12] over the 96-week study period. Focusing on participants with the greatest magnitude of changes over time, for spine measurements, only 4% on emtricitabine and tenofovir alafenamide had > 5% decrease in BMD as compared to 16% on emtricitabine and tenofovir disoproxil fumarate (p<0·0001). At the hip, 1% of participants on emtricitabine and tenofovir disoproxil fumarate and none of those on emtricitabine and tenofovir alafenamide experienced > 7% decrease in BMD (p=0·16).

At week 96, participants on emtricitabine and tenofovir alafenamide had a decline from baseline in β2M:Cr and stable RBP:Cr, while those on emtricitabine and tenofovir disoproxil fumarate had increases in both; between group differences for both markers were significant at all observed timepoints between weeks 4 and 96 (p<0·0001) (Figure 3, panel B). Although between group differences in study drug-emergent urine to protein creatinine ratio of more than 22.6 mg per mmol were observed to be significant at week 48 (16 participants [0·7%] emtricitabine and tenofovir alafenamide, 35 [1·5%] emtricitabine and tenofovir disoproxil fumarate, p=0.005), no differences were noted at week 96 (p=0.22) (Figure 3, panel C).

Significant differences were noted for median changes from baseline in serum creatinine and creatinine clearance ($eGFR_{CG}$) for all most timepoints between weeks 4 to 96 (Figure 3, panel

D). For those on emtricitabine and tenofovir alafenamide, creatinine clearance increased, with median change from baseline at week 96 of 3·7 mL per min while those on emtricitabine and tenofovir disoproxil fumarate had median change in creatinine clearance of -0·4 mL per min ($p<0·0001$). For individuals ≥50 years at baseline, there were significant declines in eGFR (-2·9 mL/min) at week 96 with emtricitabine and tenofovir disoproxil fumarate compared to an increase of 0.8 mL/min with emtricitabine and tenofovir alafenamide (Appendix Figure 4). Similarly, this age group had increased biomarkers of proximal tubular injury only with emtricitabine and tenofovir disoproxil fumarate at week 96, and the magnitude of increase was greater than that observed in participants <50 years. Those with moderate renal impairment (eGFR 60 to<90 mL/min) at study entry were observed to have an increase in eGFR (4·7 mL/min) if on emtricitabine and tenofovir alafenamide and compared to an increase of 1.0 mL/min) if on emtricitabine and tenofovir disoproxil fumarate (Appendix Figure 5).

Over a median exposure of 120 weeks, no new safety signals were detected. Similar rates of adverse events were observed between study arms (Table 1). Most adverse events were Grade 1 (mild) or 2 (moderate) in severity, and the most common (≥10%) were bacterial sexually transmitted infections (STIs).

Incidence of adverse events leading to premature study drug discontinuation was low and similar between arms: 2% (40 of 2694 participants) on emtricitabine and tenofovir alafenamide arm and 2% (51 of 2693) on emtricitabine and tenofovir disoproxil fumarate (Table 1). Incidence of serious adverse events was also similar between groups (8%, [n=202] emtricitabine and tenofovir alafenamide vs 7% (n=186) emtricitabine and tenofovir disoproxil fumarate; serious adverse events considered by the investigator to be related to study drug were rare (n=3 emtricitabine and tenofovir alafenamide, n=5 emtricitabine and tenofovir disoproxil fumarate). Study drug-related

adverse events occurred in 21% of participants on emtricitabine and tenofovir alafenamide and 24% of those on emtricitabine and tenofovir disoproxil fumarate (Appendix Table 3). Study drug-related renal events occurred in 18 participants on emtricitabine and tenofovir alafenamide and 36 participants on emtricitabine and tenofovir disoproxil fumarate.

Renal adverse events leading to discontinuation were rare; two with emtricitabine and tenofovir alafenamide and six with emtricitabine and tenofovir disoproxil fumarate users (Appendix Table 4). Only one case of Fanconi syndrome in an individual on emtricitabine and tenofovir disoproxil fumarate was previously reported[16] and no new cases occurred since the primary analysis. In each study group, 60 participants had fracture events (Appendix Table 5); of these, one on emtricitabine and tenofovir alafenamide and two on emtricitabine and tenofovir disoproxil fumarate were nontraumatic (pathologic) (Appendix Table 6). Nine percent of participants in each arm had grade ≥3 laboratory abnormalities (Table 1).

At baseline, the median body mass index (BMI) was 25.3 kg/m^2 and approximately 50% of participants were overweight or obese (BMI >25 kg/m^2, Appendix Table 1). At week 96, median increases from baseline in weight were 1.7 kg for participants on emtricitabine and tenofovir alafenamide arm and 0.5 kg for participants on emtricitabine and tenofovir disoproxil fumarate ($p<0·0001$) (Figure 4, panel A). Appendix Figure 6 shows the distribution of change from baseline in body weight at week 96.

Further analyses showed that between-group differences in median lipid fraction changes from baseline were in fasting total cholesterol (-0·08 mmol/L in emtricitabine and tenofovir alafenamide, -0·36 mmol/L in emtricitabine and tenofovir disoproxil fumarate), low density lipoprotein (LDL) cholesterol (-0·05 mmol/L in emtricitabine and tenofovir alafenamide, -0·18

mmol/L in emtricitabine and tenofovir disoproxil fumarate), and high density lipoprotein (HDL) cholesterol (-0·03 mmol/L in emtricitabine and tenofovir alafenamide, -0·10 mmol/L in emtricitabine and tenofovir disoproxil fumarate), ($p<0·0001$ for all) (Figure 4, panel B). There was no difference in change from baseline total cholesterol to HDL ratio at week 96 between arms (0·1 for emtricitabine and tenofovir alafenamide versus 0·0 for emtricitabine and tenofovir disoproxil fumarate, $p=0·18$).

Discussion

This multinational randomized active-controlled study, evaluating the efficacy and safety of emtricitabine and tenofovir alafenamide for HIV-1 prevention among high risk cisgender men and TGW who have sex with men, showed that there were numerically less HIV infections in emtricitabine and tenofovir alafenamide arm (eight vs 15 infections, incidence rate of 0.16 vs 0·34) which was statistically non-inferior to emtricitabine and tenofovir disoproxil fumarate, with an incidence rate ratio of 0·54 (95% CI 0·23-1·26). Key factors that contributed to the observed high levels of protection in both treatment groups (99·7% in the emtricitabine and tenofovir alafenamide arm and :99·4% in the emtricitabine and tenofovir disoproxil fumarate arm remained HIV-free at 96 weeks) were high rates of adherence to study medication, a well-known determinant of PrEP efficacy[29] as well as good tolerability with low rates of study drug discontinuations, which were numerically lower in the tenofovir alafenamide arm..

Medication adherence is known to be the primary correlate of PrEP efficacy, and the CDC estimates that emtricitabine and tenofovir disoproxil fumarate for PrEP is 99% effective when taken consistently.[30] In DISCOVER, tenofovir diphosphate levels were monitored in DBS, allowing an objective longitudinal assessment of study drug adherence. By DBS, 84-93% of participants were highly adherent in both study arms,[15] providing the most likely explanation for the low HIV incidence rates observed (0·16 and 0·30 per 100 PY for emtricitabine and tenofovir alafenamide and emtricitabine and tenofovir disoproxil fumarate, respectively). In contrast, the HPTN 083 study comparing long-acting cabotegravir to emtricitabine and tenofovir disoproxil fumarate reported emtricitabine and tenofovir disoproxil fumarate adherence rates of 67% to 82% by DBS, and an HIV incidence rate of 0·41 and 1·22 per 100 PY for cabotegravir and emtricitabine and tenofovir disoproxil fumarate, respectively.[31] This difference in adherence-

efficacy outcomes between DISCOVER and HPTN 083 further highlights the importance of considering adherence propensity both in individual participants and in clinical trial design. It is worth noting that DISCOVER participants were at high risk for HIV acquisition as shown be the high incidence of bacterial STIs through 96 weeks of follow-up. Further comparison of the differences between studies is of importance once full details of HPTN 083 are available.

Cisgender women were not included in the study. However, mechanism of protection and pharmacokinetics of emtricitabine and tenofovir alafenamide are not expected to differ [32] and additional studies are planned to evaluate its efficacy in cisgender women who are at risk for HIV through vaginal intercourse.

No HIV infections were observed in TGW; the efficacy of PrEP in TGW is likely due to high intracellular PBMC concentrations of tenofovir diphosphate and emtricitabine-triphosphate that were observed, including in those taking gender-affirming hormones, as previously reported.[15] Notably, intracellular levels of tenofovir diphosphate and emtricitabine-triphosphate were similar between TGW on gender-affirming hormones and MSM. Furthermore, pharmacokinetic studies have demonstrated no impact of emtricitabine and either tenofovir disoproxil fumarate[33] or tenofovir alafenamide[34] on ethinyl estradiol exposures. In addition, no effect on follicle-stimulating hormones, luteinizing hormones, nor on progesterone levels was observed in women taking emtricitabine and tenofovir alafenamide with hormonal contraceptives.[35] Accordingly, no effect on gender-affirming hormones is expected.

Both study drugs were well tolerated with low rates of discontinuation overall (2% in each arm) The most common adverse events were STIs, which were evenly distributed between study arms but not related to study drug. Drug-related serious adverse events occurred in only 0·1% and

0·2% of participants on emtricitabine and tenofovir alafenamide and emtricitabine and tenofovir disoproxil fumarate, respectively.

The DISCOVER study, unlike studies in people living with HIV, allowed for single variable safety evaluation of tenofovir alafenamide versus tenofovir disoproxil fumarate in individuals without HIV infection. Overall, declines in BMD occurred in participants who received emtricitabine and tenofovir disoproxil fumarate, which were significantly different compared to increases observed in those on emtricitabine and tenofovir alafenamide. The small number of participants aged ≥18 to <25 years with BMD data (n=24) limited assessment of statistical significance in this age group that was yet to achieve peak bone mass (shown to occur between 25 and 35 years).[36] Nonetheless, between-group trajectories of BMD for this age group were notably similar to those observed in participants ≥25 years. Differences persisted even after adjusting for prior tenofovir disoproxil fumarate use. These BMD trajectories are consistent with observations in studies comparing safety outcomes between tenofovir alafenamide and tenofovir disoproxil fumarate in people living with HIV.[13] These findings validate concerns with the long-term use of emtricitabine and tenofovir disoproxil fumarate among HIV-negative adolescents building up to peak bone mass and for older individuals, who are losing bone mass and may already have osteopenia or osteoporosis. That said, pathologic fractures were rare in the study.

Also, there were significant declines in estimated glomerular filtration rates (eGFR) in those receiving emtricitabine and tenofovir disoproxil fumarate compared to emtricitabine and tenofovir alafenamide. These differences were accentuated in older individuals ≥50 years and in those with moderate renal impairment at baseline, where emtricitabine and tenofovir alafenamide users had gains in eGFR. Changes in biomarkers of proximal tubular dysfunction (retinol binding protein and beta-microglobulin) noted with emtricitabine and tenofovir disoproxil fumarate alone

are most likely related to plasma concentrations of tenofovir (90% higher than in tenofovir alafenamide users[37]), and though exact mechanisms have yet to be fully elucidated, tubular mitochondrial damage has been found to occur.[38] Long-term clinical implications of these subclinical changes are unknown, but the potential for persistence or progression of the observed changes over time raise concern particularly for individuals whose renal function is already compromised or who have medical conditions or take medications that affect renal function.

Body weight and metabolic parameters were also assessed. Over the 96-week study period, participants on emtricitabine and tenofovir alafenamide gained a median of 1·7 kg compared to 0·5k g with emtricitabine and tenofovir disoproxil fumarate, a 1·2 kg difference. The low weight gain in the emtricitabine and tenofovir disoproxil fumarate may be due to the known weight-suppressive effect associated with tenofovir disoproxil fumarate use observed in the iPrEX PrEP trial[39] and more recently in the HPTN 083 PrEP trial.[31] On the other hand, weight gain in emtricitabine and tenofovir alafenamide arm (approximately 0.85 kg per year) mirrors weight gain noted in placebo arm of the iPrEX PrEP trial,[39] the placebo arm of HPTN 077,[40] and among community-dwelling young adults in a study on the association between diet and subsequent weight gain,[41] thereby suggesting a normal trajectory of weight gain over time.

Lipid parameters differed between groups with steeper declines in total cholesterol, HDL and LDL levels in those on emtricitabine and tenofovir disoproxil fumarate consistent with its known lipid-lowering effect[42] but total cholesterol:HDL ratios were similar in both study groups. Initiation of lipid-modifying agents was higher with tenofovir alafenamide when considering the full cohort but was similar between arms in a sensitivity analysis excluding participants who were taking emtricitabine and tenofovir disoproxil fumarate PrEP at baseline. These findings suggest that the increase in lipid-modifying agent initiation with emtricitabine and tenofovir

alafenamide was driven by the removal of the lipid-lowering effect of emtricitabine and tenofovir disoproxil fumarate. Fasting glucose levels were similar across groups.

This study's strengths included its large sample size and objective measures of adherence. Some of its limitations include the fact that the high level of adherence observed in this clinical trial may not be achievable in real-world settings. As a result, real-world effectiveness of both PrEP regimens may be lower than was observed here. Another limitation was that, because blood was not drawn at the baseline visit, we could not confirm whether the five participants who tested positive for HIV-1 at week 4 had acquired HIV before randomisation or while they were taking the study drug. As such, we considered these cases to be suspected HIV acquisitions between screening and baseline. Long-term clinical implications of changes in renal biomarkers and lipid parameters and BMD trajectories are unknown. Longer-term data will be required to determine their clinical relevance. The relatively low number of TGW and ethnic/racial minorities enrolled in the study limits the generalizability of study findings. Similarly, these findings cannot be generalized to individuals whose risk for HIV is through receptive vaginal or frontal sex or by injection drug use.

In conclusion, in this large multinational randomized controlled trial at 96 weeks, emtricitabine and tenofovir alafenamide remained noninferior to emtricitabine and tenofovir disoproxil fumarate for prevention of HIV-1 infection and resulted in more favorable bone and renal safety outcomes.

Notes

Contributors

OO, DP, LCS, KH, DMA, DW, RG, GW, JMB, GK, and CDS enrolled participants, reviewed and interpreted analyses of data. YS and RE designed the study. YS, RE, and SC analyzed the data, which were reviewed and interpreted by AK, CC, MD, and DAB. The first draft was written by OO and AK. All authors provided edits and approved the final manuscript and 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

DP has received research grants and/or honoraria for advisories and/or conferences from Viiv, Gilead, Janssen and MSD. CDS reports grants and personal fees from Gilead Sciences, during the conduct of the study; personal fees from AbbVie, grants and personal fees from Janssen-Cilag, grants and personal fees from MSD, grants and personal fees from ViiV Healthcare/GSK, outside the submitted work. YS, RE, SC, AK, CC, MD, and DMB are employees of Gilead and shareholders of Gilead stock. Other disclosures are forthcoming.

Data sharing

Gilead shares anonymized Individual Patient Data upon request or as required by law and/or regulation with qualified external researchers. Approval of such requests is at Gilead's discretion and is dependent on the nature of the request, the merit of the research proposed, the availability of the data, and the intended use of the data. Data requests should be sent to datarequest@gilead.com.

Acknowledgements

We thank the individuals who participated in this trial and their families, the principal investigators (Supplementary Materials) and their staff and the Gilead study staff. We also thank Dr. Sophia Majeed (Gilead Sciences) for the insightful review and editorial support. We thank Sarah Tse (BioSciences) for preparing the figures and Anna Kido and David McNeel (both of Gilead Sciences) for providing editorial assistance. Parts of this study have been presented at the virtual Conference on Retroviruses and Opportunistic Infections (CROI), March 10, 2020.

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Tables and Figures

Table 1. Overall summary of safety

n (%)	Emtricitabine and tenofovir alafenamide (N=2694)	Emtricitabine and tenofovir disoproxil fumarate (N=2693)
Participants experiencing any AE	2,523 (94)	2,521 (94)
Discontinuation of study drug due to AE	40 (2)	51 (2)
Serious adverse events*	202 (8)	186 (7)
Serious AEs considered related to study drug†	3 (<1)	5 (<1)
Deaths‡	3 (<1)	2 (<1)
Common adverse events (≥10% in either arm)		
Rectal chlamydia	890 (33)	902 (34)
Oropharyngeal gonorrhea	871 (32)	838 (31)
Rectal gonorrhea	805 (30)	797 (30)
Exposure to communicable disease	554 (21)	548 (20)
Diarrhea	480 (18)	453 (17)
Syphilis	413 (15)	392 (15)
Nasopharyngitis	399 (15)	402 (15)
Upper respiratory tract infection	402 (15)	346 (14)
Urethral chlamydia	346 (13)	314 (12)
Urethral gonorrhea	259 (10)	255 (10)
Grade 3 or 4 laboratory abnormality (≥1% in either arm)		
Any	246 (9)	240 (9)
AST (increased)	73 (3)	60 (2)
LDL (Fasting, Increased)	57 (2)	20 (1)
ALT (increased)	47 (2)	44 (2)
Amylase (Increased)	38 (1)	54 (2)
Urine Glucose (Glycosuria)	28 (1)	39 (2)
GGT (increased)	28 (1)	13 (1)
Neutrophils (decreased)	24 (1)	9 (<1)
Total cholesterol (fasting, hypercholesterolemia)	22 (1)	4 (<1)
Triglycerides (fasting, increased)	15 (1)	6 (<1)
Serum Glucose (fasting, hyperglycemia)	14 (1)	22 (1)

Urine RBC (hematuria, quantitative or dipstick)	13 (1)	13 (1)

ALT, alanine aminotransferase; AST, aspartate aminotransferase; GGT, gamma-glutamyl transferase; LDL, low-density lipoprotein cholesterol.

*In the tenofovir alafenamide arm, the most common (n≥5) serious adverse events included appendicitis (n=9, 0·3%); suicidal ideation (n=8, 0·3%); cellulitis, acute kidney injury (each n=7, 0.3%); hepatitis A (n=6, 0.2%); and pneumonia, depression, and suicide attempt (each n=5, 0.2%). In the tenofovir disoproxil fumarate arm, these included atrial fibrillation (n=7, 0.3%); and appendicitis and cellulitis (each n=5, 0.2%)

†In the tenofovir alafenamide arm, serious adverse events considered related to study drug included nephrotic syndrome (n=1), chest pain and loss of consciousness (n=1), and agranulocytosis and pyrexia in the same participant (n=1). In the tenofovir disoproxil fumarate arm, serious adverse events considered related to study drug included acute kidney injury (n=2), migraine (n=1), pneumonia (n=1), urinary calculus (n=1), and renal tubular necrosis (n=1).

‡In the tenofovir alafenamide arm, reasons for death included traffic accident, amphetamine intoxication, and fatal drug overdose. unknown. In the tenofovir disoproxil fumarate arm, these included unknown (n=2) and metastatic squamous cell carcinoma.

Figure 1. Study participant disposition through week 96

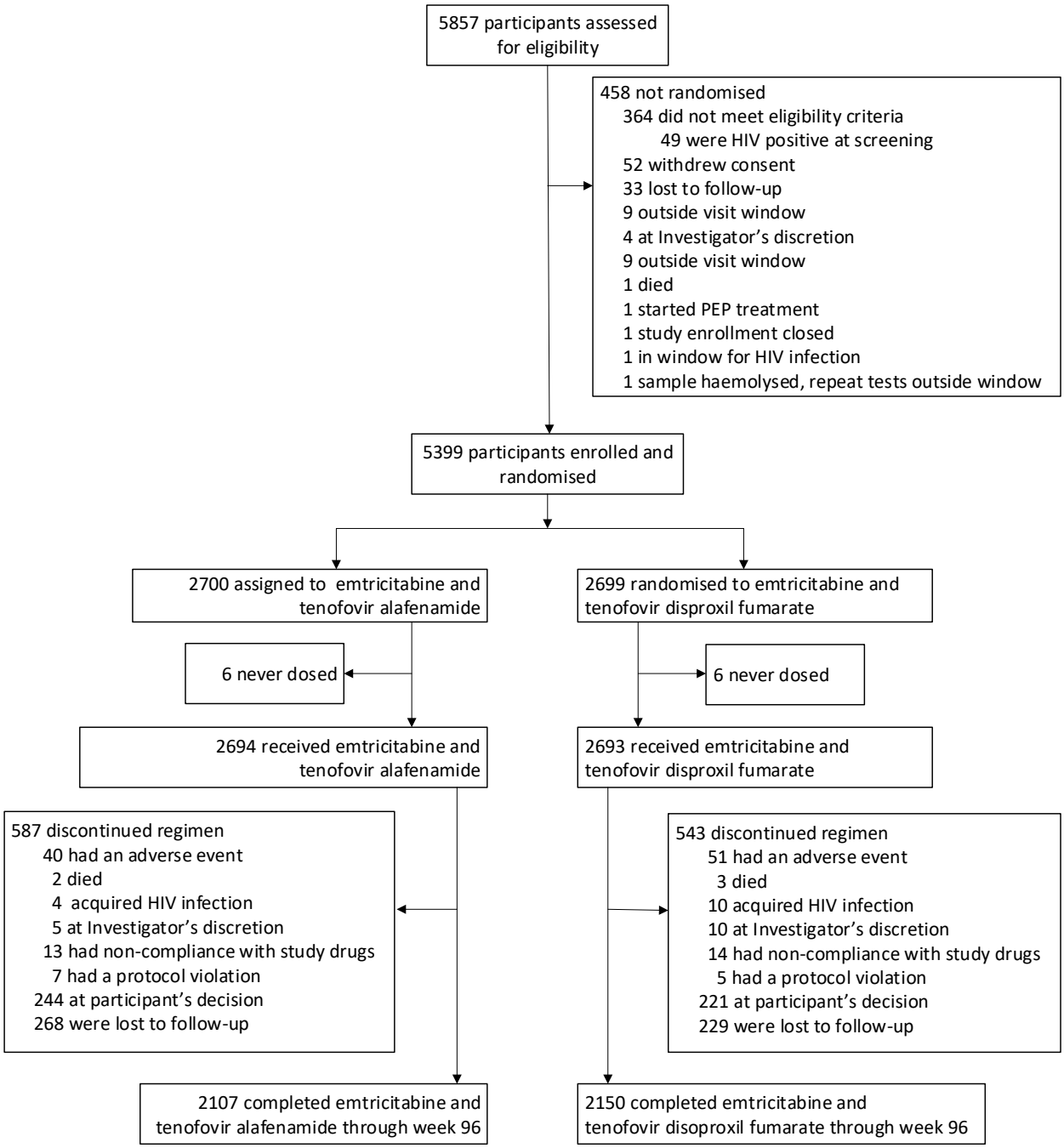
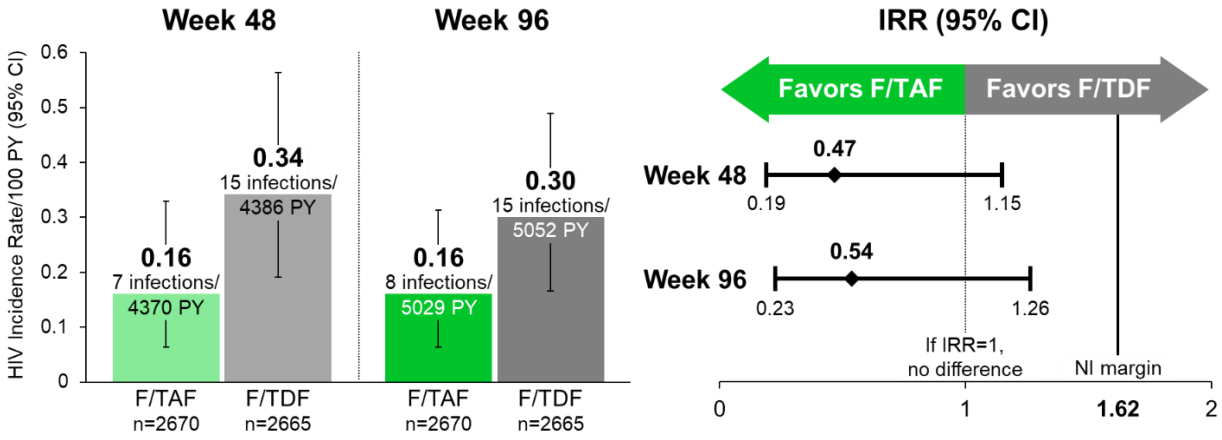


Figure 2. HIV incidence and infection rate ratio at weeks 48 and 96



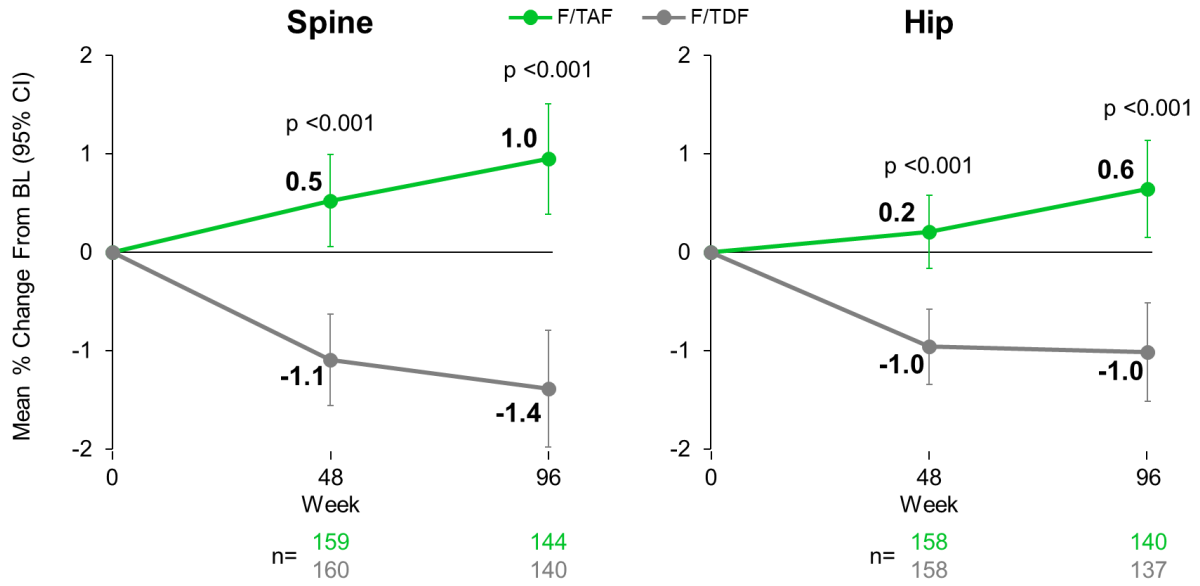
Incidence of HIV PER 100 person-years in the F/TAF and F/TDF groups and IRR (F/TAF divided by F/TDF).

Error bars represent 95% CIs. IRR=incidence rate ratio.

F/TAF=emtricitabine and tenofovir alafenamide. F/TDF=emtricitabine and tenofovir disoproxil fumarate.

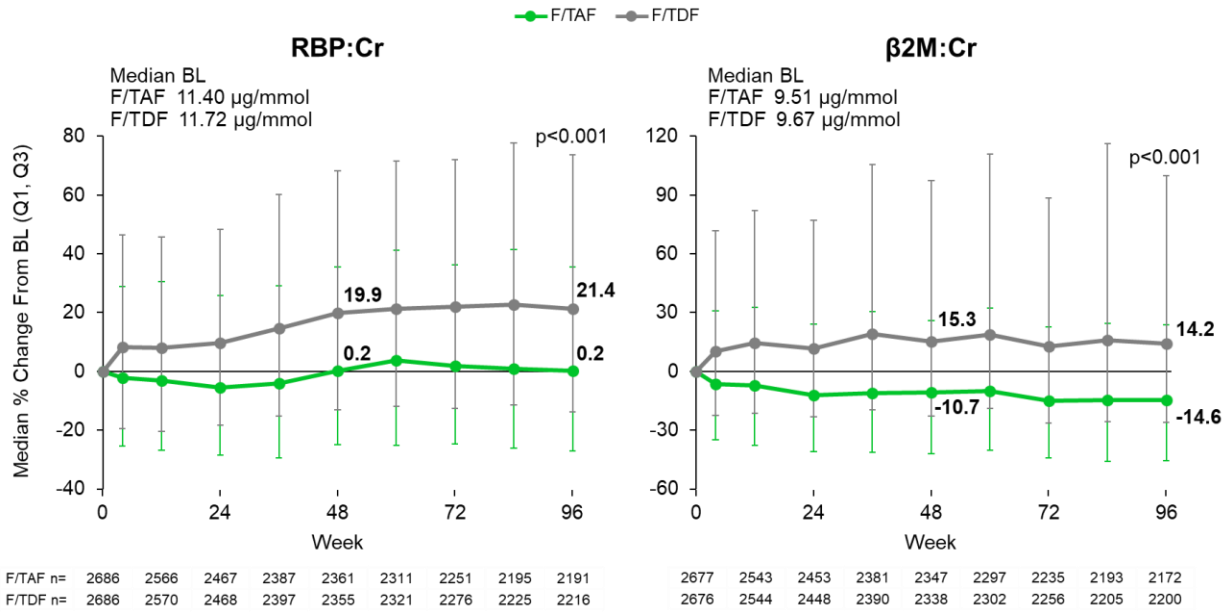
Figure 3. Safety endpoints at week 96

(A) Bone Mineral Density



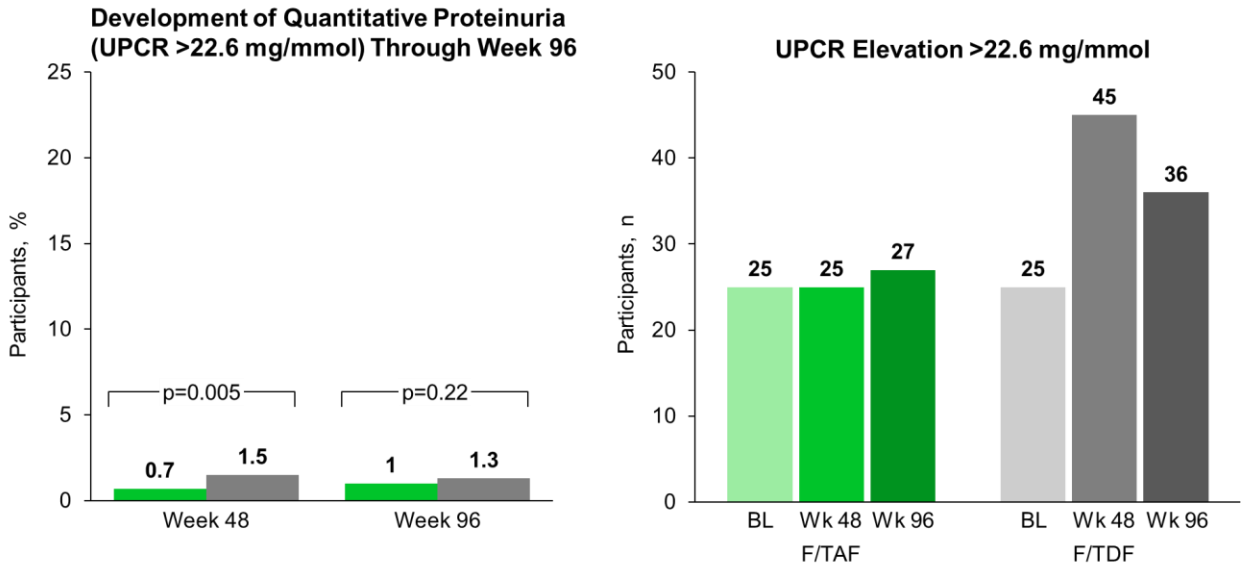
*p-values from analysis of variance model with BL F/TDF for PrEP and study arm as fixed effects

(B) Proximal Tubular Proteinuria

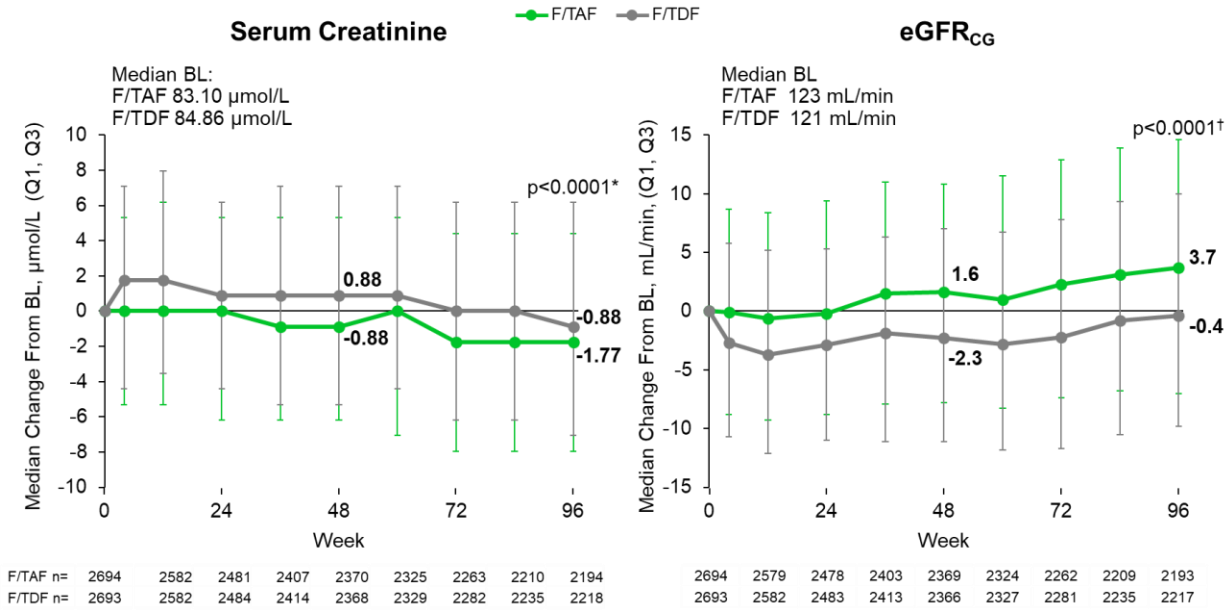


*p-values from Van Elteren test stratified by BL F/TDF for PrEP to compare 2 study arms.

(C) Proximal Tubular Proteinuria



(D) Serum creatinine and creatinine clearance ($eGFR_{CG}$)

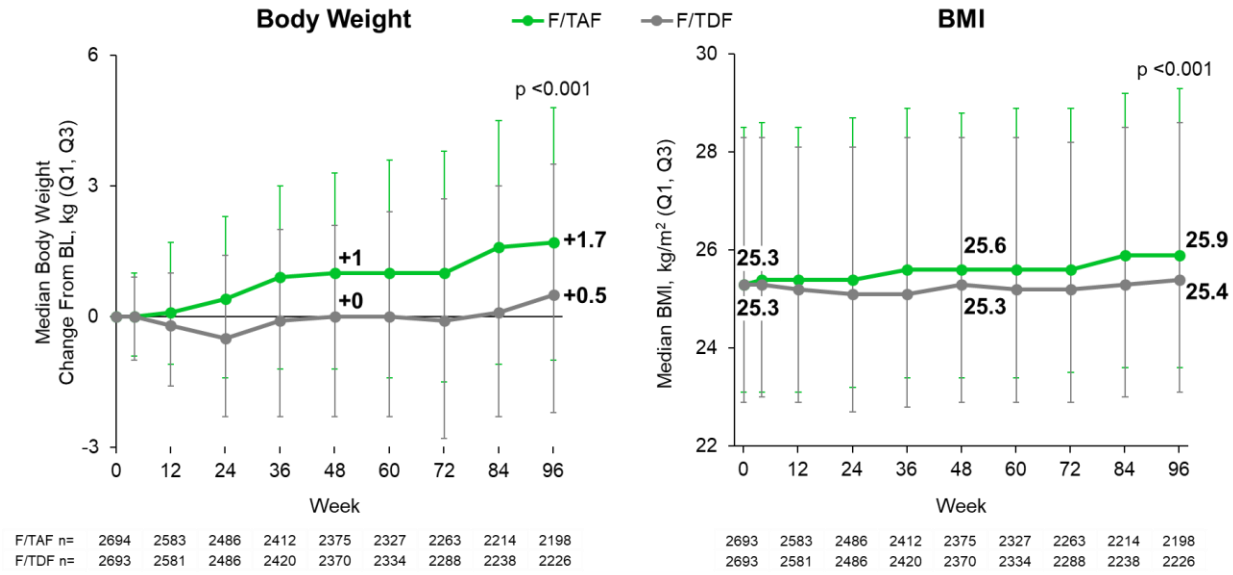


*p-value from ANOVA model including BL F/TDF for PrEP and treatment as fixed effects; †p-value from Van Elteren test stratified by BL F/TDF for PrEP to compare 2 study arms.

F/TAF=emtricitabine and tenofovir alafenamide, F/TDF=emtricitabine and tenofovir disoproxil fumarate, RBP:Cr Retinol-binding Protein to Creatinine ratio, UPCR=urine protein to creatinine ratio, β2M:Cr= urine beta-2 microglobulin: creatine ratio, $eGFR_{CG}$=estimated glomerular filtration rate by Cockcroft-Gault. BL=Baseline

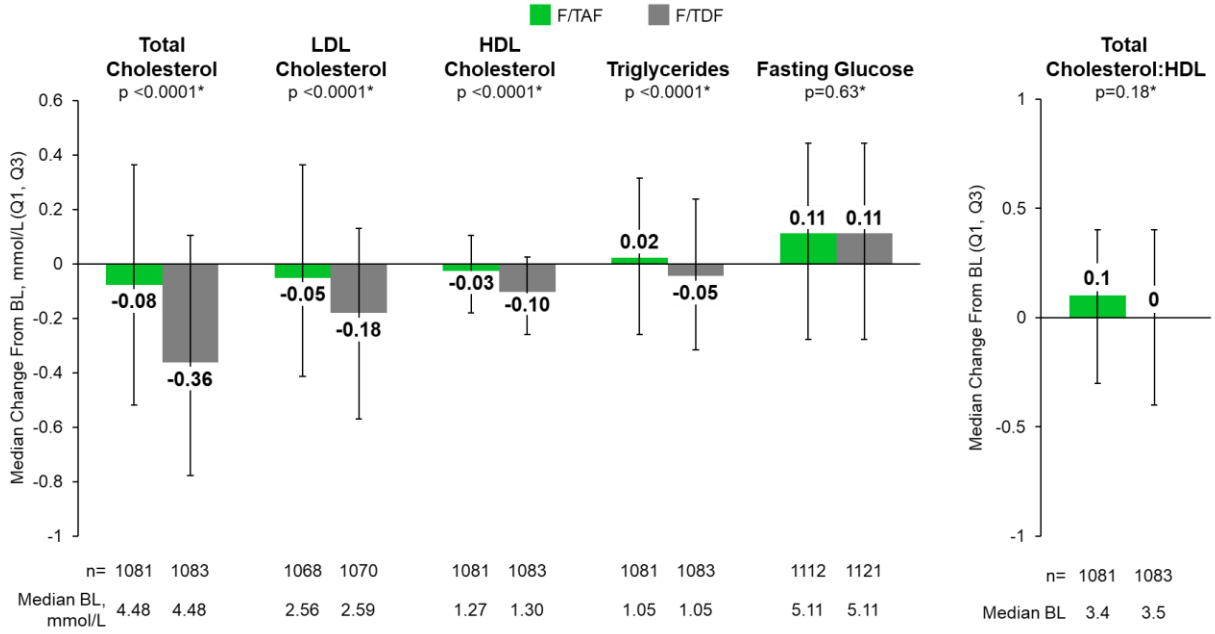
Figure 4. Lipids and body weight at week 96

(A) Body weight and BMI



p-values for changes from baseline from analysis of covariance model including BL F/TDF for PrEP and study arm as fixed effects and BL body weight or body mass index (BMI) as a covariate.

(B) Fasting Lipids and glucose



*p-values from 2-sided Wilcoxon rank sum test to compare 2 study arms.

F/TAF=emtricitabine and tenofovir alafenamide. F/TDF=emtricitabine and tenofovir disoproxil fumarate. BMI=Body Mass Index, BL=Baseline

Supplementary Materials

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Supplemental Methods

Eligibility Criteria

Inclusion Criteria

Participants must be at high risk of sexual acquisition of HIV and meet *all* of the following inclusion criteria to be eligible for participation in this study.

1) HIV-1 negative status

2) MSM or TGW (male at birth) who have at least one of the following:

   a) condomless anal intercourse with at least two unique male partners in the past 12 weeks (partners must be either HIV-infected or of unknown HIV status)

   b) documented history of syphilis in the past 24 weeks

   c) documented history of rectal gonorrhea or chlamydia in the past 24 weeks

3) Age ≥ 18 years

4) Estimated GFR ≥ 60 mL/min according to the Cockcroft-Gault formula for creatinine clearance:

$$\frac{(140 - \text{age in years}) \times (\text{wt in kg})}{72 \times (\text{serum creatinine in mg/dL})} = CL_{cr}\ (\text{mL/min})$$

5) Adequate liver and hematologic function:

   - AST and ALT ≤ 2.5 × upper limit of normal (ULN); and total bilirubin ≤ 1.5 mg/dL, or normal direct bilirubin

   - Absolute neutrophil count ≥ 1000/mm^3; platelets ≥ 75,000/mm^3; hemoglobin ≥ 10 g/dL

6) Willing and able to comply with study procedures

Exclusion Criteria

Participants who meet *any* of the following exclusion criteria are not to be enrolled in this study.

1) Known hypersensitivity to the IMP, the metabolites, or formulation excipient.

2) Have a suspected or known active, serious infection(s)

3) Acute viral hepatitis A, B or C or evidence of chronic hepatitis B infection. Subjects found to be susceptible to HBV infection should be referred for HBV vaccination. Subjects found to be positive for HCV at screening must not have active infection or must have completed treatment and achieved a sustained virologic response.

4) Need for continued use of any contraindicated concomitant medications

5) Have an implanted defibrillator or pacemaker

6) Have a history of osteoporosis or bone fragility fractures

7) Current alcohol or substance abuse judged by the Investigator to be problematic such that it potentially interferes with subject study compliance

8) Grade 3 or Grade 4 proteinuria or glycosuria that is unexplained or not clinically manageable.

9) Any other clinical condition or prior therapy that, in the opinion of the Investigator, would make the subject unsuitable for the study or unable to comply with dosing requirements

10) Have received investigational agents for the treatment or prevention of HIV-1 infection in the 30 days prior to screening

11) Participation in any other clinical trial (including observational trials) without prior approval from the sponsor is prohibited while participating in this trial

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.

Resistance Testing

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.

Self-reported Adherence

Adherence was assessed at all post-baseline visits by use of a computer-assisted self-interview for self-reporting and by pill count.

Appendix Table 1. Baseline demographic and risk factors

	Emtricitabine and tenofovir alafenamide (N=2694)	Emtricitabine and tenofovir disoproxil fumarate (N=2693)
Demographics		
Median age, years (IQR)	34 (28, 43)	34 (28, 44)
Race, n (%)		
White	2264 (84)	2247 (84)
Black*	240 (9)	234 (9)
Asian	113 (4)	120 (5)
Hispanic or Latinx ethnicity, n (%)	635 (24)	683 (25)
Gender/sexual orientation		
Transgender women, n (%)	45 (2)	29 (1)
Cisgender MSM	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, n (%)		
United States	1591 (59)	1629 (60)
European Union	912 (34)	902 (33)
Canada	191 (7)	162 (6)
Median body mass index, kg/m^2 (Q1, Q3)	25.3 (23, 29)	25.3 (23, 28)
Medical history (%)		
Hypertension	282 (11)	298 (11)
Diabetes mellitus	79 (3)	89 (3)
STIs by laboratory test at the baseline visit		
Rectal gonorrhea	123/2668 (5)	113/2669 (4)
Rectal chlamydia	199/2669 (7)	189/2670 (7)
Syphilis	7 (<1)	4 (<1)
HIV risk factors by CASI, n (%)		
≥2 condomless anal sex (receptive), past 12 weeks	1660 (62)	1628 (60)
Rectal gonorrhea, past 24 weeks	274 (10)	262 (10)
Rectal chlamydia, past 24 weeks	342 (13)	333 (12)

Syphilis, past 24 weeks	230 (9)	263 (10)
Recreational drug use, past 12 weeks	1785 (67)	1786 (67)
Binge drinking‡	618 (23)	599 (22)
Taking emtricitabine and tenofovir disoproxil fumarate for PrEP at baseline	465 (17)	440 (16)

β2M:Cr, urine beta-2 microglobulin: creatine ratio; BMD, bone mineral density; $eGFR_{CG}$, estimated glomerular filtration rate calculated using the Cockcroft-Gault equation; IQR, interquartile range; PrEP, pre-exposure prophylaxis; RBP:Cr, urine retinol-binding protein: creatinine ratio; CASI, computer-assisted self-interview.

*Includes mixed black race; †n=383 for BMD substudy; ‡≥6 drinks on ≥1 occasion, at least monthly.

Appendix Table 2. DXA Substudy - Baseline Demographics

		Total		BMD Substudy	
		DVY n=2694	TVD n=2693	DVY n=194	TVD n=189
Median age, y (range)		34 (18–76)	34 (18–72)	38 (19–74)	36 (19–72)
Race, %	White	84	84	84	88
	Black/mixed black	9	9	11	7
	Asian	4	5	4	3
Hispanic or Latinx ethnicity, %		24	25	19	22
Transgender women, %		2	1	1	<1
≥2 condomless anal sex (receptive) partners, past 12 wk, %		60	58	61	59
Rectal gonorrhea, past 24 wk, %		10	10	9	8
Rectal chlamydia, past 24 wk, %		13	12	14	6
Syphilis, past 24 wk, %		9	10	10	8
Recreational drug use, past 12 wk, %		67	67	68	65
Binge drinking,[a] %		23	22	17	15
Taking TVD for PrEP at baseline, %		17	16	13	14

a. ≥6 drinks on one occasion, at least monthly.

Appendix Table 3. Common Study Drug-Related Adverse Events (≥1% in Either Arm)

Participants, n (%)	Emtricitabine and tenofovir alafenamide (N=2694)	Emtricitabine and tenofovir disoproxil fumarate (N=2693)
Study drug-related AEs	564 (21)	654 (24)
Diarrhoea	136 (5)	161 (6)
Nausea	116 (4)	127 (5)
Headache	60 (2)	57 (2)
Fatigue	46 (2)	70 (3)
Abdominal pain	26 (1)	35 (1)
Flatulence	22 (1)	33 (1)
Renal*	18 (1)	36 (1)
Abdominal discomfort	18 (1)	30 (1)

* Include: Increased blood creatinine, decreased urine protein to creatinine ratio, decreased glomerular eGFR, and increased urine protein to albumin ratio.

Appendix Table 4. Renal Discontinuation Cases

Emtricitabine and tenofovir alafenamide (N=2694)					Emtricitabine and tenofovir disoproxil fumarate (N=2693)				
AE	**Grade**	**Related**	**Age Range, y**	**Contributing Factors**	**AE**	**Grade**	**Related**	**Age Range, y**	**Contributing Factors**
Acute kidney injury	1	No	40–49	Myocardial infarction, contrast nephropathy	Fanconi syndrome	3	Yes	40–49	None identified
Acute kidney injury	2	Yes	30–39	Hypertension, FSGS on renal biopsy	Renal impairment	1	Yes	40–49	None identified
					Acute kidney injury	2	Yes	40–49	None identified
					Glomerular proteinuria	2	Yes	60–69	Hypertension
					Acute kidney injury	2	Yes	60–69	History of kidney disease, hypertension, NSAID use
					Renal impairment	2	Yes	60–69	Baseline kidney disease, NSAID use
					Renal impairment	2	Yes	50-59	None identified

FSGS, focal segmental glomerulosclerosis; NSAID, nonsteroidal anti-inflammatory drugs

Appendix Table 5. Fracture Adverse Events at week 96

Participants, n (%)	Emtricitabine and tenofovir alafenamide (N=2694)	Emtricitabine and tenofovir disoproxil fumarate (N=2693)
Fracture adverse events	60 (2)	60 (2)
Nontraumatic fracture (pathologic)	1 (<0·1)	2 (<0·1)
Common fracture adverse events		
Lower extremity	34 (1)	19 (1)
Upper extremity	20 (<1)	25 (1)
Rib	5 (<1)	8 (<1)

Appendix Table 6. Nontraumatic Fracture Cases at week 96

Age Range, y	Study Drug	Fracture Site	Grade	Related	DXA	Possible Contributing Factors
60–69	Emtricitabine and tenofovir alafenamide	Cervical (facet joint)	1	No	N/A	Proton pump inhibitor use*
50–59	Emtricitabine and tenofovir disoproxil fumarate	Metatarsal	1	No	N/A	Osteoporosis†
70–79	Emtricitabine and tenofovir disoproxil fumarate	Shoulder	2	No	N/A	None‡

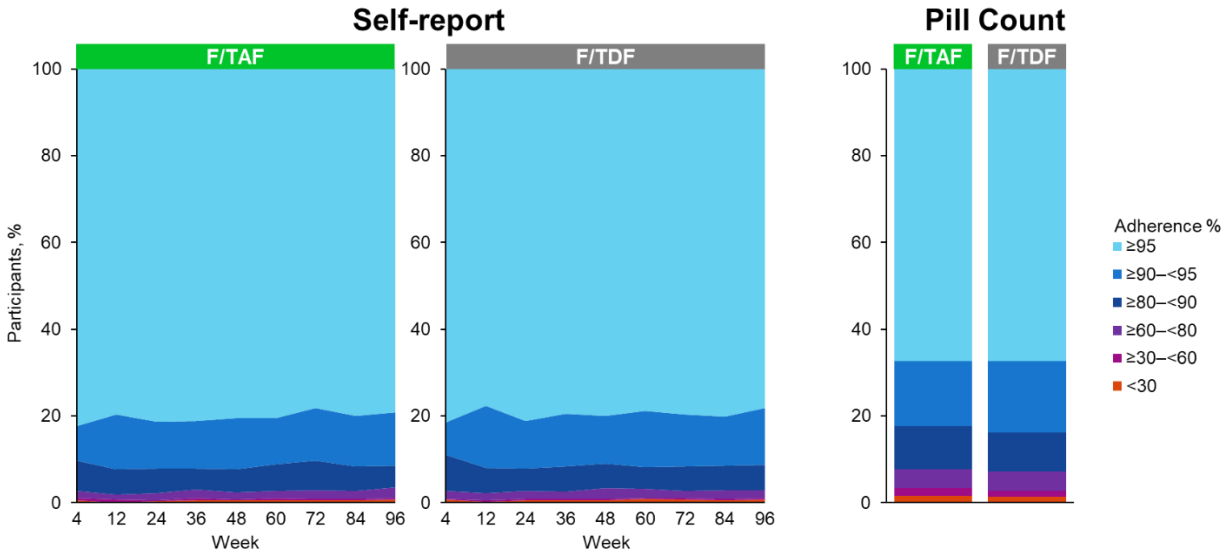
*Other medical conditions included gastroesophageal reflux disease, history of transient ischemic attack, hyperlipidemia, and Sjogren's syndrome.

†Investigator-reported AE of osteoporosis after fracture AE (not study drug related); other medical conditions included hypothyroidism and hyperlipidemia.

‡Other medical conditions included osteoarthritis, hypertension, hyperlipidemia, and type 2 diabetes mellitus.

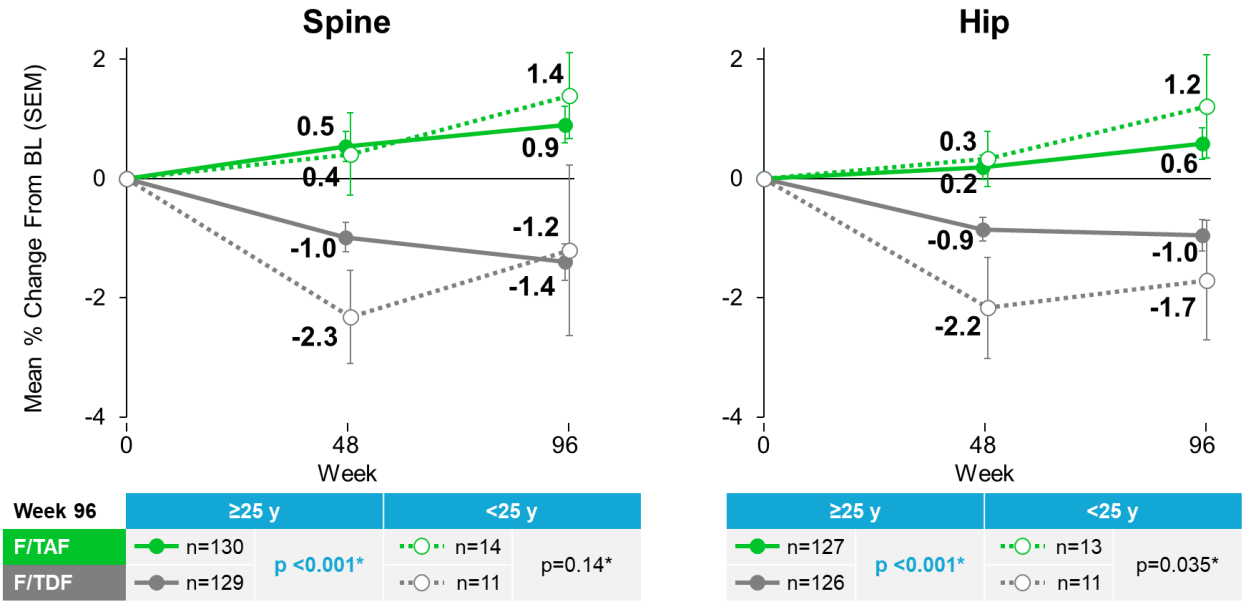
N/A, not available.

Appendix Figure 1. Adherence by self-report and pill count



F/TAF=emtricitabine and tenofovir alafenamide, F/TDF=emtricitabine and tenofovir disoproxil fumarate

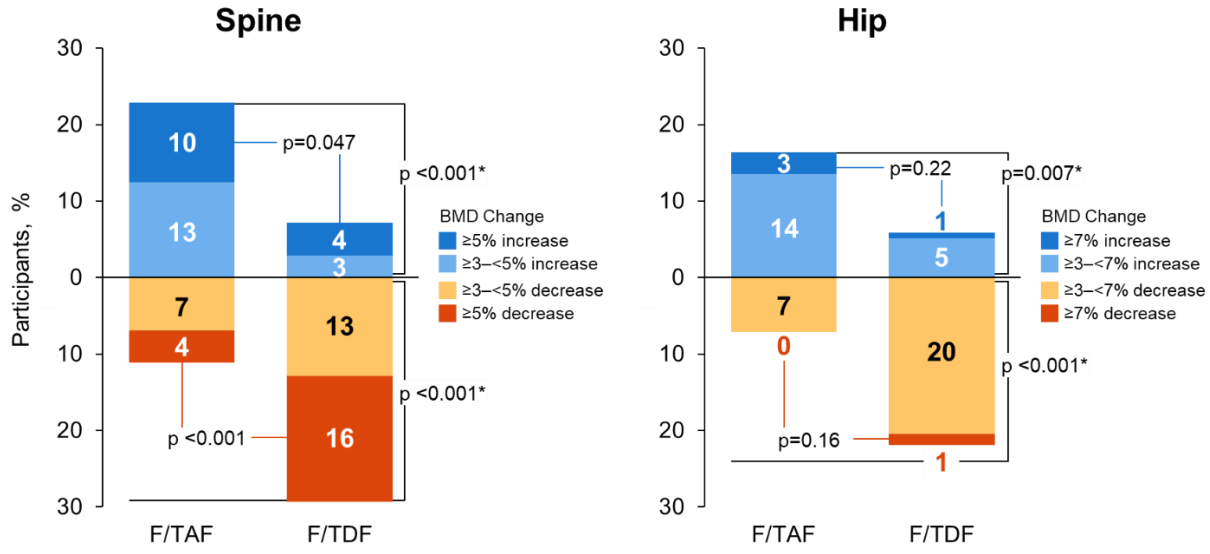
Appendix Figure 2. Bone Mineral Density changes in participants by age categories at week 96



*p-values from analysis of variance model with BL F/TDF for PrEP and study arm as fixed effects. SEM, standard error of mean.

F/TAF=emtricitabine and tenofovir alafenamide, F/TDF=emtricitabine and tenofovir disoproxil fumarate.

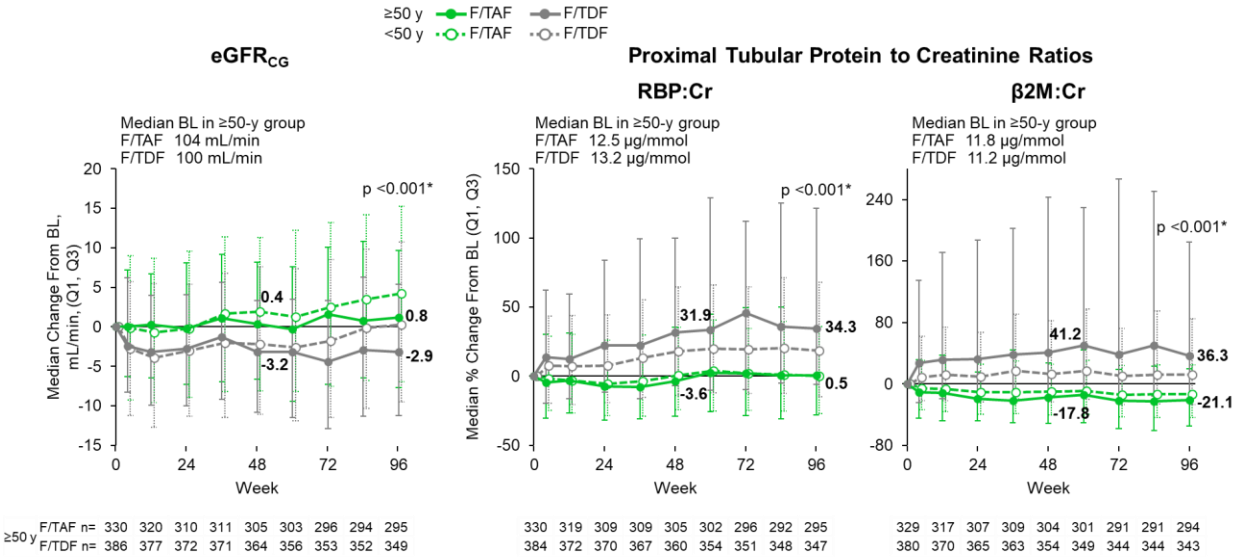
Appendix Figure 3. Categorical BMD Changes (By Percent Change) at Week 96



*p-values for ≥3% change include ≥5% change. All p-values based on dichotomized response from Cochran-Mantel-Haenszel test for nominal data (general association statistic) adjusting for BL F/TDF for PrEP.

F/TAF=emtricitabine and tenofovir alafenamide, F/TDF=emtricitabine and tenofovir disoproxil fumarate

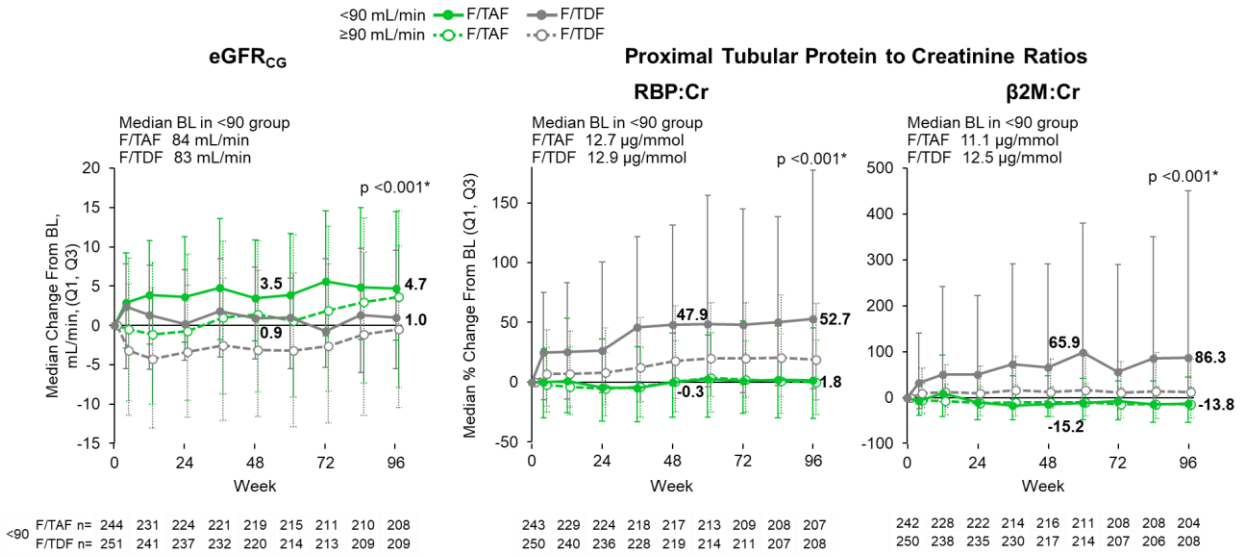
Appendix Figure 4. Renal safety for participants by age categories at week 96



*p-values from Van Elteren test stratified by BL F/TDF for PrEP to compare treatments within age group. Wk 48 and 96 values displayed for ≥50-y group.

F/TAF=emtricitabine and tenofovir alafenamide, F/TDF=emtricitabine and tenofovir disoproxil fumarate, RBP:Cr Retinol-binding Protein to Creatinine ratio, β2M:Cr= urine beta-2 microglobulin: creatine ratio, $eGFR_{CG}$=estimated glomerular filtration rate by Cockcroft-Gault. BL=Baseline

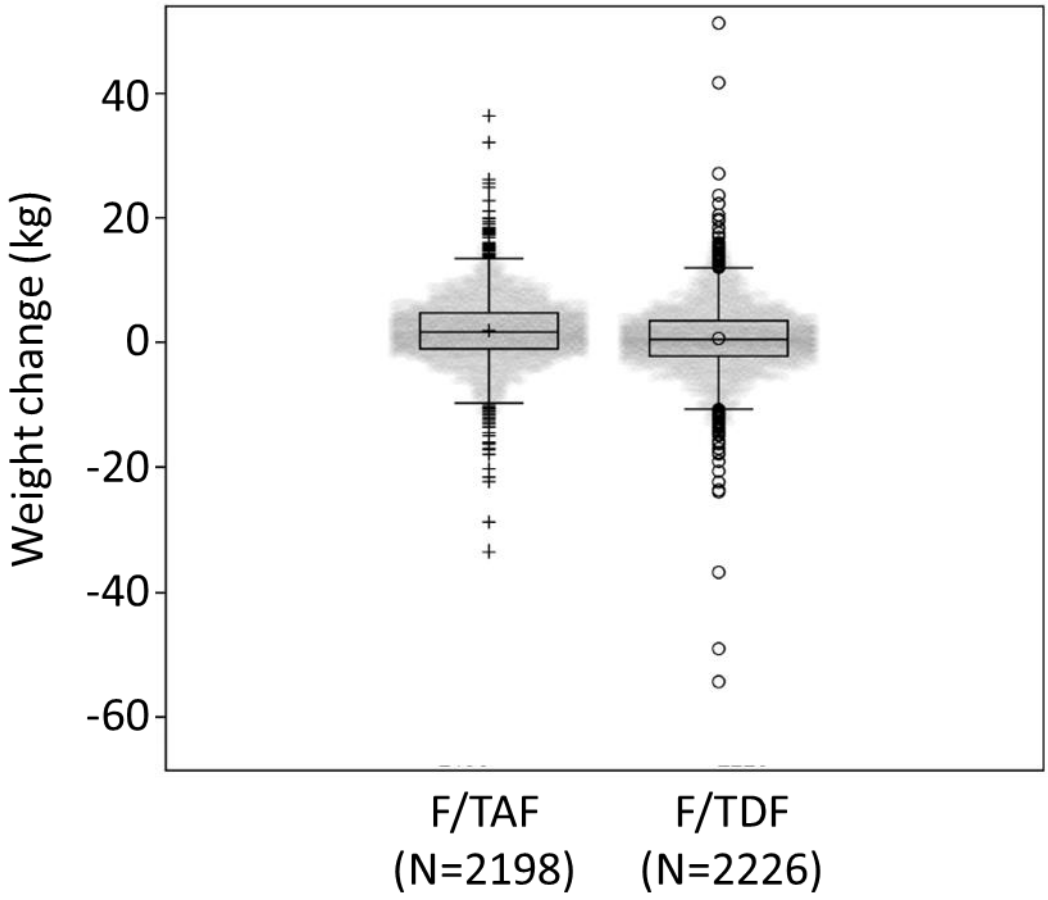
Appendix Figure 5. Renal safety for participants with BL eGFR 60– ≤90 mL/min versus BL eGFR >90 at week 96



*p-values from Van Elteren test stratified by BL F/TDF for PrEP to compare treatments within age group. Wk 48 and 96 values displayed for <90-mL/min group.

F/TAF=emtricitabine and tenofovir alafenamide, F/TDF=emtricitabine and tenofovir disoproxil fumarate, RBP:Cr Retinol-binding Protein to Creatinine ratio, β2M:Cr= urine beta-2 microglobulin: creatine ratio, $eGFR_{CG}$=estimated glomerular filtration rate by Cockcroft-Gault. BL=Baseline

Appendix Figure 6. Distribution of change from baseline in body weight at week 96



F/TAF=emtricitabine and tenofovir alafenamide, F/TDF=emtricitabine and tenofovir disoproxil fumarate