HIV-1 infection kinetics, drug resistance, and long-term safety of pre-exposure prophylaxis with emtricitabine plus tenofovir alafenamide (DISCOVER): week 144 open-label extension of a randomised, controlled, phase 3 trial

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Summary

Background Data characterising the long-term use and safety of emtricitabine plus tenofovir disoproxil fumarate as daily oral pre-exposure prophylaxis (PrEP) are scarce and there are uncertainties regarding the value of routine HIV-1 RNA testing during oral PrEP follow-up.

Methods The DISCOVER trial was a randomised, controlled, phase 3 trial in which cisgender men and transgender women aged 18 years and older with a high likelihood of acquiring HIV were recruited from 94 clinics in Europe and North America and randomly assigned to receive either emtricitabine plus tenofovir disoproxil fumarate (200/25 mg) tablets daily, with matched placebo tablets, or emtricitabine plus tenofovir alafenamide (200/300 mg) tablets daily, with matched placebo tablets, for at least 96 weeks. After completion of the trial, participants were offered enrolment in this 48-week open-label extension study of emtricitabine plus tenofovir alafenamide. In participants diagnosed with HIV during the randomised and open-label phases of the study, we characterised HIV-1 test results and measured HIV-1 RNA viral load retrospectively when available. Adherence based on tenofovir diphosphate concentrations in dried blood spots and genotypic resistance were assessed in participants diagnosed with HIV. Safety assessments included adverse events, laboratory parameters, and, in a subset of participants, bone mineral density. HIV-1 incidence in participants initially randomly assigned to receive emtricitabine plus tenofovir alafenamide was estimated using a Poisson distribution. Changes from baseline in safety endpoints were described in participants assigned to received emtricitabine plus tenofovir alafenamide and in those who switched from emtricitabine plus tenofovir disoproxil fumarate during the open-label phase. This trial is registered with ClinicalTrials.gov, NCT02842086, and is ongoing.

Findings Between Sept 13, 2016, and June 30, 2017, 5399 participants were enrolled and randomly assigned in DISCOVER. 2699 were assigned to receive emtricitabine plus tenofovir disoproxil fumarate and 2700 were assigned to receive emtricitabine plus tenofovir alafenamide, of whom 2693 and 2694, respectively, received at least one dose of study drug. 2115 (79%) assigned to emtricitabine plus tenofovir disoproxil fumarate switched to emtricitabine plus tenofovir alafenamide in the open-label phase, and 2070 (77%) continued with emtricitabine plus tenofovir alafenamide in the open-label phase. As of data cutoff (Dec 10, 2020), after 15 817 person-years of follow-up, 27 new HIV-1 diagnoses were observed across the total study period, with three occurring during the open-label phase. In participants who were initially assigned to emtricitabine plus tenofovir alafenamide, the incidence was 0·13 per 100 person-years (95% CI 0·061–0·23; ten of 2670). Stored plasma samples were available for 23 of 27 participants, including 22 with incident infection. In four (17%) of 23 participants, retrospective testing detected HIV-1 RNA before serological HIV-1 test positivity; one was a suspected baseline infection. Of the three incident cases, all three were non-adherent to PrEP and none developed drug resistance. Among participants taking emtricitabine plus tenofovir alafenamide for up to 144 weeks, markers of glomerular filtration and proximal renal tubule dysfunction (β2-microglobulin to creatinine ratio and retinol-binding protein to creatinine ratio) improved or remained stable at 144 weeks compared with baseline, bone mineral density in hip and lumbar spine increased or remained stable from baseline to week 144 (n=191), cholesterol and glucose concentrations remained stable, and median bodyweight increased by less than 1 kg per year. In participants who switched from emtricitabine plus tenofovir disoproxil fumarate during the open-label phase (2115 [79%] of 2693), markers of glomerular filtration and proximal renal tubule dysfunction improved or remained stable, bone mineral density increased, cholesterol concentrations increased, glucose concentrations were similar, and median bodyweight increased more compared with those who remained on emtricitabine and tenofovir alafenamide.

Interpretation Routine HIV-1 RNA testing for follow-up of individuals on daily oral PrEP provides modest additional clinical benefit. Long-term use of emtricitabine and tenofovir alafenamide as daily oral PrEP is safe and well tolerated and can be an especially appropriate choice for people with bone or renal morbidities.

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Introduction

Pre-exposure prophylaxis (PrEP) for prevention of HIV-1 infection with daily oral fixed-dose combination of emtricitabine plus tenofovir disoproxil fumarate or tenofovir alafenamide is safe, well tolerated, and highly effective.[1–3] The effectiveness of oral PrEP is dependent on adherence to maintain adequate drug concentrations during exposure events, and when adherence is suboptimal or oral PrEP is interrupted, HIV-1 infection can occur. Infection through transmission of drug-resistant virus in the setting of adequate adherence is possible but very rare.[4]

PrEP using the integrase strand-transfer inhibitor (INSTI) cabotegravir is also highly effective, showing significant superiority versus emtricitabine plus tenofovir disoproxil fumarate in the HPTN 083 and HPTN 084 studies.[5,6] Concerns about delayed detection of HIV-1 infection and development of drug resistance during PrEP with long-acting cabotegravir[7] have led to the recommendation by the US Centers for Disease Control and Prevention (CDC) that HIV-1 RNA testing be done at all routine follow-up visits for people receiving either oral or injectable PrEP.[8] However, the clinical value of RNA testing during oral PrEP is uncertain and is not recommended in guidelines from other public health agencies and organisations.[9,10]

Emtricitabine plus tenofovir disoproxil fumarate for PrEP is safe and highly tolerable, but some barriers to uptake have been described, including the potential for adverse events related to off-target effects of tenofovir in plasma in specific populations.[11,12] To address some of these limitations, tenofovir alafenamide was developed, which is associated with a 90% reduction in tenofovir concentrations in plasma compared with tenofovir disoproxil fumarate, and improved bone and renal safety among people with HIV undergoing antiretroviral therapy.[13] Nonetheless, data on long-term safety and efficacy are scarce for people

Research in context

Evidence before this study

We searched PubMed for English language publications from database inception up to Aug 9, 2023, using titles or abstract search terms "HIV-1" AND "emtricitabine" AND "tenofovir" AND "seroconversion" and, in a separate search, "HIV-1" AND "emtricitabine" AND "tenofovir" AND "prevention" OR "prophylaxis". The second search was limited to clinical trials. These searches identified 39 publications (published between 2008 and 2022) that described individuals newly diagnosed with HIV-1 infection while prescribed emtricitabine plus tenofovir for pre-exposure prophylaxis (PrEP). In these publications, most seroconversions occurred in individuals with suboptimal adherence to PrEP or with undiagnosed HIV-1 infection at the time of PrEP initiation. Drug resistance was reported to be uncommon in people who seroconverted while taking daily oral PrEP and was most likely to occur in those with undiagnosed HIV-1 infection at the time of PrEP initiation. A further search of PubMed for publications between database inception and Aug 9, 2023, using title or abstract search terms "HIV-1" AND "tenofovir alafenamide" AND "prevention" OR "prophylaxis" yielded 13 articles published between 2019 and 2023. In two articles, daily oral PrEP clinical trials and earlier results from the DISCOVER trial were reported. In these studies, emtricitabine plus tenofovir alafenamide had non-inferior efficacy compared with emtricitabine plus tenofovir disoproxil fumarate for HIV-1 prevention up to 96 weeks of blinded treatment. Additionally, emtricitabine plus tenofovir alafenamide was superior to emtricitabine plus tenofovir disoproxil fumarate in all six prespecified bone mineral density and renal biomarker parameters at weeks 48 and 96. More weight gain was seen among participants who received emtricitabine plus tenofovir alafenamide than among those who received emtricitabine plus tenofovir disoproxil fumarate, the latter of which is associated with weight suppression.

Added value of this study

Open-label extension of the DISCOVER trial up to 144 weeks enables a comprehensive and detailed assessment of long-term PrEP use with emtricitabine plus tenofovir alafenamide, including HIV-1 seroconversions and safety of long-term use. These data support the safety and efficacy of long-term PrEP using emtricitabine plus tenofovir alafenamide and show no evidence of delayed HIV-1 seroconversion with its use as daily oral PrEP.

Implications of all the available evidence

Emtricitabine plus tenofovir disoproxil fumarate and emtricitabine plus tenofovir alafenamide have high efficacy for HIV prevention when taken with adequate adherence and are associated with a low risk of resistance development. Open-label extension of the DISCOVER trial showed the safety of long-term use of emtricitabine plus tenofovir alafenamide on the basis of stable or improving markers of renal function, bone density, and lipid metabolism. Increases in bodyweight were noted and similar to observations made in other HIV-1 prevention trials, including participants who received a placebo. Emtricitabine plus tenofovir alafenamide is a highly effective option for daily oral PrEP to prevent HIV in adult cisgender men and transgender women who have sex with men.

who would benefit from PrEP using emtricitabine plus tenofovir alafenamide.

DISCOVER[2,3] is a multinational, double-blind, randomised, controlled trial among adult cisgender men and transgender women who have sex with men. Emtricitabine plus tenofovir alafenamide showed non-inferior efficacy compared with emtricitabine plus tenofovir disoproxil for HIV prevention up to 96 weeks of blinded treatment. At the end of the 96-week randomised phase, participants were offered enrolment in a 48-week open-label extension study of emtricitabine plus tenofovir alafenamide. We used data from the randomised and open-label phases of DISCOVER to perform an in-depth analysis of HIV-1 seroconversion patterns (including PrEP adherence, resistance, and retrospective RNA testing) and to assess HIV incidence and long-term safety in participants receiving emtricitabine plus tenofovir alafenamide over 144 weeks of follow-up.

Methods

Study design and participants

Detailed methods and study procedures for the DISCOVER trial have been previously described.[2,3] Briefly, DISCOVER was a multinational, randomised, controlled, phase 3 trial run at 94 community, public health, and hospital-associated clinics in Europe and North America (principal investigators are listed in the appendix [pp 16–18]). Cisgender men and transgender women aged 18 years or older who have sex with men and who have a high likelihood of acquiring HIV were recruited and randomly assigned (1:1) to received either emtricitabine plus tenofovir alafenamide (200/25 mg) tablets daily, with matched placebo tablets (emtricitabine plus tenofovir alafenamide group), or emtricitabine plus tenofovir disoproxil fumarate (200/300 mg) tablets daily, with matched placebo tablets (emtricitabine plus tenofovir disoproxil fumarate group) for 96 weeks. The primary outcome was incident HIV infection. After completion of blinded treatment for at least 96 weeks, participants in both groups were offered enrolment in the open-label extension study of emtricitabine plus tenofovir alafenamide for PrEP. A graphical overview of the trial design is in the appendix (p 12).

See Online for appendix

This study was done in accordance with recognised international scientific and ethical standards, including but not limited to the International Council for Harmonisation guideline for Good Clinical Practice and the Declaration of Helsinki. The protocol and any amendments were approved by central or site-specific independent ethics committees or institutional review boards. All participants provided written informed consent. DISCOVER is registered with ClinicalTrials.gov, NCT02842086.

Procedures and interventions

After random assignment to treatment, participant visits occurred at weeks 4 and 12, and every 12 weeks thereafter. During the open-label phase, participants were seen every 12 weeks for 48 weeks. Participants were assessed for HIV-1 infection and safety at each visit. Additional information about HIV-1 infection and safety assessments is in the appendix (pp 3–4).

Tenofovir diphosphate concentrations were measured in dried blood spots (DBS), as previously described.[14,15] Tenofovir diphosphate concentrations in DBS reflect cumulative adherence (low, moderate, or high) over the preceding 8–12 weeks. High adherence was defined as 900 fmol or higher per two punches for emtricitabine plus tenofovir alafenamide and 700 fmol or higher per one punch for emtricitabine plus tenofovir disoproxil fumarate; moderate adherence was defined as 450 fmol to less than 900 fmol per two punches for emtricitabine plus tenofovir alafenamide and 350 fmol to less than 700 fmol per one punch for emtricitabine plus tenofovir disoproxil fumarate; and low adherence was defined as less than 450 fmol per two punches for emtricitabine plus tenofovir alafenamide and less than 350 fmol per one punch for emtricitabine plus tenofovir disoproxil fumarate. High adherence reflected an average of at least four doses per week in the past 8–12 weeks, moderate adherence reflected an average of two-to-three doses per week, and low adherence was indicative of less than two doses per week.[15,16]

Genotypic resistance testing was performed for all participants diagnosed with HIV infection and who had HIV-1 RNA concentration of more than 400 copies per mL using plasma samples (GenoSure MG, Monogram Biosciences, South San Francisco, CA, USA). Tenofovir and emtricitabine resistance-related mutations were as defined by the Monogram MG assay (Monogram Biosceinces).

Participants with suspected baseline HIV-1 infection were adjudicated by a panel of three physicians who independently reviewed HIV-1 testing data, medical history, self-reported sexual activity, recreational drug use, study drug adherence, study drug concentrations in DBS, and other information from the investigator and study staff. HIV diagnosis date was defined as the date of sample collection for the first laboratory evidence of HIV-1 infection in a participant with confirmed HIV-1 infection.

We assessed adverse events at each follow-up visit during the blinded and open-label phases of the study until 30 days after study drug discontinuation. Adverse events were coded using the Gilead Toxicity Grading Scale for Severity of Adverse Events and Laboratory Abnormalities (Antiviral Toxicity Grading Scale version April 1, 2015). Laboratory tests, including chemistry, haematology, and lipid profiles, were assessed using samples collected from study visits. For bone density analyses, a subset of 383 participants who consented were selected and assessed every 48 weeks during the blinded and open-label phases of the study. Scans were read and interpreted by a third party (BioClinica,

Newtown, PA, USA) who were masked to treatment assignments. Methods for laboratory and bone density analyses have been reported previously.[2]

Outcomes

Outcomes for this analysis were HIV-1 incidence, adherence, resistance, and safety. Incident HIV-1 infection was diagnosed by any of the following: (1) serological evidence of seroconversion (a reactive rapid or blood HIV-1 antigen–antibody or antibody test, confirmed by a reactive blood HIV-1/HIV-2 differentiation assay), (2) virological evidence of HIV-1 infection (a positive qualitative HIV-1 RNA test result or any detectable quantitative HIV-1 RNA test result), or (3) evidence of acute HIV-1 infection (a reactive p24 antigen test result or a positive qualitative or quantitative RNA test result, in the absence of reactive HIV-1 antibody test results).[2] We measured HIV-1 RNA viral load retrospectively for one or more visits before the HIV-1 diagnosis among participants with available banked plasma samples. We did genotypic resistance testing for all participants diagnosed with HIV-1 infection who had HIV-1 RNA concentrations of more than 400 copies per mL.

Safety was assessed by hip and spine bone mineral density, renal function, and metabolic parameters up to 144 weeks of follow-up. Safety analyses included six prespecified ranked safety outcomes that were previously assessed[2,3] for the study's week 48 and week 96 analyses: (1) hip and (2) spine bone mineral density; (3) urine β2-microglobulin to creatinine ratio; (4) retinol-binding protein to creatinine ratio; (5) urine protein to creatinine ratio above the clinically significant threshold of 22·6 mg/mmol at 144 weeks; and (6) change from baseline in serum creatinine concentration measured by estimated glomerular filtration rate (eGFR) with the Cockcroft-Gault formula. Other safety outcomes were incidence of treatment-emergent adverse events and laboratory abnormalities including changes from baseline in fasting lipids, fasting serum glucose, and bodyweight. Lipid measurements included total, LDL, and HDL cholesterol and triglycerides.

Statistical analysis

All statistical analyses for the blinded phase of the study were prespecified and previously reported.[2,3] This open-label phase was prespecified; however, retrospective HIV RNA-1 testing was done post hoc. For the current analysis, we assessed HIV-1 incidence and long-term safety outcomes by combining person-time during the randomised phase and 48-week open-label extension, allowing for at least 144 weeks of follow-up time on emtricitabine plus tenofovir alafenamide for participants who continued in the open-label extension phase. Within this subset, longitudinal measures (eg, laboratory parameters) were assessed for 144 weeks from the date of initial randomisation, irrespective of study phase. Cumulative measures (eg, HIV-1 infection and adverse events) included events documented up to the time when all participants had completed open-label week 48 or permanently discontinued the study. Participants who prematurely discontinued the study or who did not join the open-label extension were included in this analysis and censored at the time of discontinuation.

For in-depth analysis of participants who had HIV-1 seroconversion, we included all participants diagnosed with HIV-1 up to open-label week 48, irrespective of initial randomisation assignment. We characterised the timing of infection relative to study entry and study drug discontinuation, adherence, time from HIV-1 RNA detection to seropositivity, and antiretroviral resistance.

We calculated the point estimate of HIV-1 incidence in the participants who received emtricitabine plus tenofovir alafenamide on the basis of the Poisson distribution, and we calculated the exact 95% CI according to the method by Ulm.[17]

For all safety endpoints, we treated all missing data, loss to follow-up, and dropouts as missing completely at random. We calculated changes from baseline for each participant before group analysis. Statistical comparisons between study groups up to 96 weeks have been previously reported.[3] We compared differences in safety outcomes between participants who remained on emtricitabine plus tenofovir alafenamide and those who switched from emtricitabine plus tenofovir disoproxil fumarate in the open-label phase using Cochran–Mantel–Haenszel tests (for urine β2-microglobulin to creatinine ratio, retinol-binding protein to creatinine ratio, and eGFR), analysis of variance (hip and spine bone mineral density and bodyweight), or two-sided Wilcoxon rank sum tests (lipids and glucose). Changes in urine protein to creatinine ratio were reported descriptively.

We calculated the number of HIV-1 RNA tests that would have been needed in DISCOVER to detect each HIV-1 infection before seroconversion by dividing the total number of central laboratory HIV-1 antibody–antigen screening tests conducted during monitoring of participants on PrEP by the number of participants who were found to have detectable HIV-1 RNA before seroconversion.

All analyses were done in SAS version 9.4. p values of less than 0·05 were considered to be statistically significant.

Role of the funding source

The funder had a role in study design, data collection, data analysis, data interpretation, writing of the report, and in the decision to submit the paper for publication.

Results

Between Sept 13, 2016, and June 30, 2017, 5399 participants were enrolled and randomly assigned to treatment at baseline in DISCOVER (baseline demographic and clinical characteristics are shown in

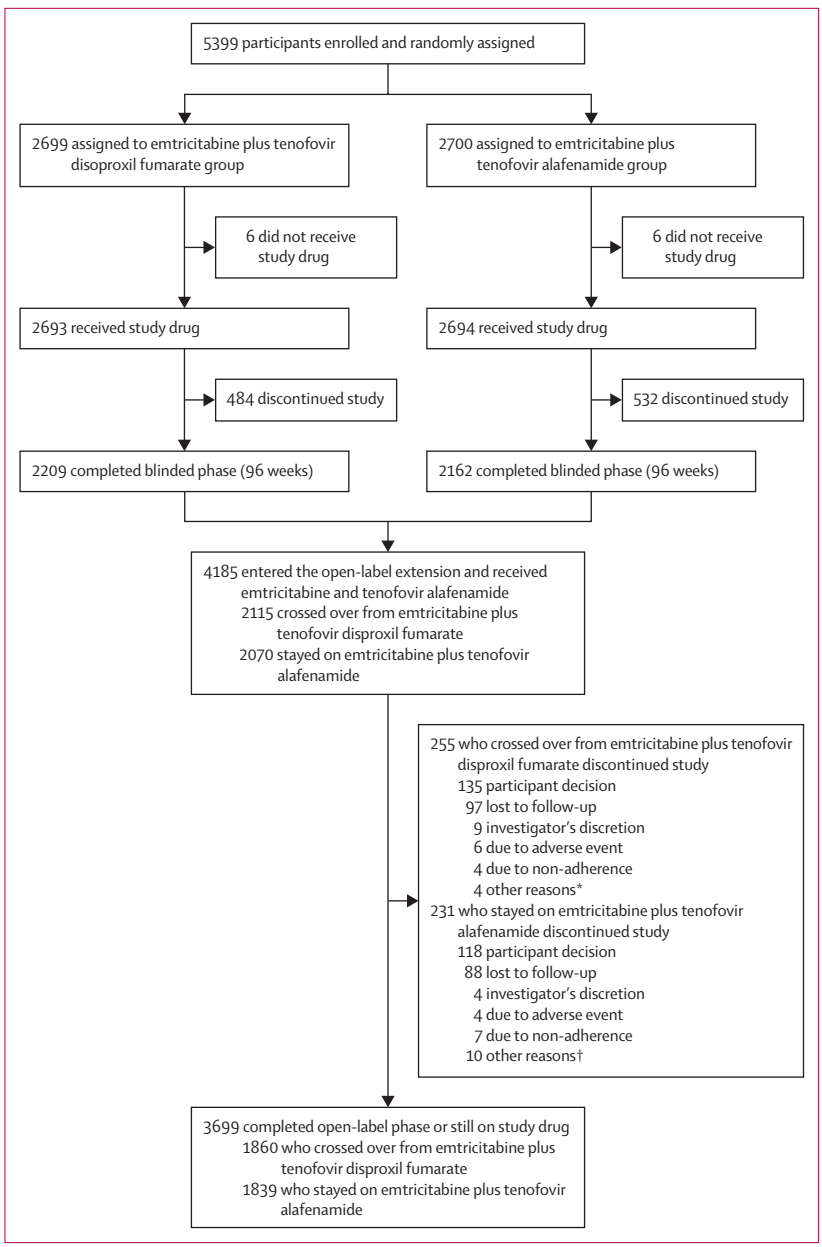


Figure 1: **Participant disposition up to week 144 of DISCOVER**
One participant who was randomly assigned to emtricitabine plus tenofovir alafenamide discontinued study drug due to a drug-related adverse event between the end of the blinded phase and week 48 of the open-label phase (diarrhoea). *Other reasons were death (n=1), protocol violations (n=2), and HIV-1 infection (n=1). †Other reasons were death (n=3), protocol violations (n=3), terminated by sponsor (n=1), and confirmed HIV-1 infection (n=3).

the appendix [p 6]). 2699 participants were assigned to receive emtricitabine plus tenofovir disoproxil fumarate and 2700 were assigned to receive emtricitabine plus tenofovir alafenamide, of whom 2693 and 2694, respectively, received at least one dose of study drug. Of 2694 participants who received at least one dose of emtricitabine plus tenofovir alafenamide, 2070 (77%) continued emtricitabine plus tenofovir alafenamide in the open-label phase, and of the 2693 participants who received at least one dose of emtricitabine plus tenofovir disoproxil fumarate, 2115 (79%) switched to emtricitabine plus tenofovir alafenamide in the open-label phase (figure 1). Demographic and behavioural characteristics were similar between participants initially assigned to emtricitabine plus tenofovir alafenamide and those who continued emtricitabine plus tenofovir alafenamide in the open-label extension (appendix p 6). As of data cutoff (Dec 10, 2020), 3699 (69%) participants were still on emtricitabine plus tenofovir alafenamide as of week 48 of the open-label phase (figure 1). Among participants with available data, rectal gonorrhoea or chlamydia was detected in 299 (11%) of 2648 participants at baseline and in 179 (9%) of 1963 over the course of 144 weeks of follow-up (appendix p 13).

Up to open-label extension study week 48, there were 15 817 person-years of follow-up. A total of 27 participants were diagnosed with HIV-1 over at least 144 weeks of follow-up, of whom ten (37%) were initially assigned to emtricitabine plus tenofovir alafenamide and 17 (63%) were initially assigned to emtricitabine plus tenofovir disoproxil fumarate, including one who crossed over to emtricitabine plus tenofovir alafenamide in the open-label extension (figure 2). Of the 27 HIV infections that occured in the study up to the end of the 48-week open-label extension, 23 occurred up to week 96 of the blinded phase, one occurred between week 96 and the beginning of the open-label extension phase, and three occurred during the 48-week open-label extension phase. In participants who received emtricitabine plus tenofovir alafenamide for at least 144 weeks of follow-up, ten (<1%) of 2670 participants were diagnosed with HIV (incidence of 0·13 per 100 person-years [95% CI 0·061–0·23]). During the 48-week open-label extension period, two (<1%) of 2070 participants initially assigned to emtricitabine plus tenofovir alafenamide were diagnosed with HIV (0·093 per 100 person-years [95% CI 0·011–0·34]) and one (<1%) of 2115 participants initially assigned to emtricitabine plus tenofovir disoproxil fumarate was diagnosed with HIV (0·046 per 100 person-years [0·0012–0·25]).

Among the 27 participants who had an HIV diagnosis, five (19%) had suspected unrecognised baseline infection (one had been randomly assigned to emtricitabine plus tenofovir alafenamide and four had been assigned to emtricitabine plus tenofovir disoproxil fumarate). We classified the remaining 22 participants into three groups on the basis of the timing of study drug discontinuation and adherence: those who discontinued study drug at least 30 days before diagnosis (n=8), those who had a tenofovir diphosphate concentration in DBS consistent with low adherence preceding diagnosis or discontinued PrEP within 30 days of diagnosis (n=13), and those who had no DBS sample at diagnosis (n=1). Detailed HIV-1 testing results for all 27 participants are in the appendix (pp 7–10).

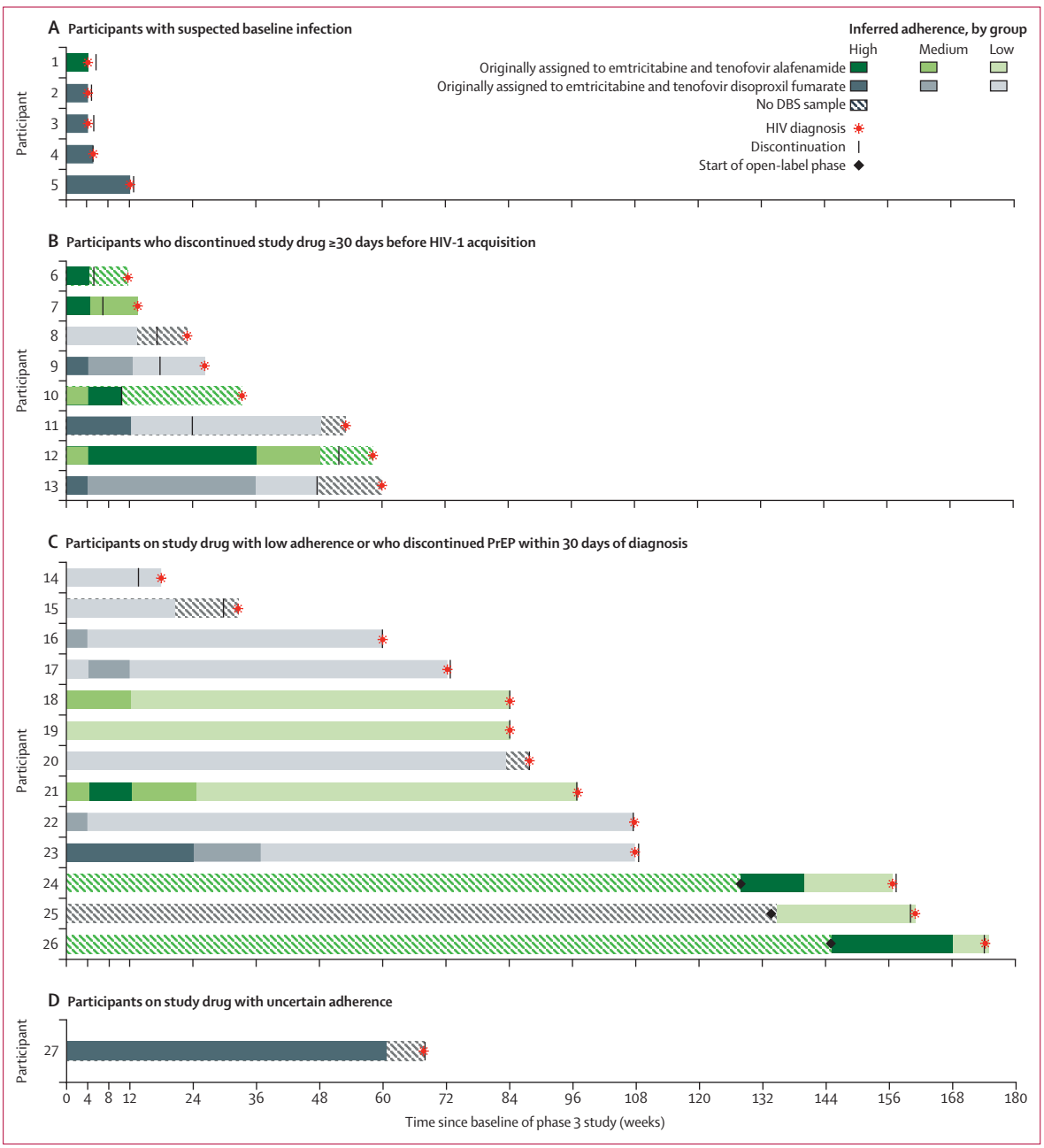


Figure 2: **Summary of PrEP adherence in participants who acquired HIV-1 infection (n=27), as measured by tenofovir diphosphate concentration in DBS**
Data are presented for participants with suspected baseline infections (A), participants who discontinued study drug ≥30 days before HIV-1 diagnosis (B), participants on study drug with low adherence or discontinued PrEP within 30 days of HIV-1 diagnosis (C), and for one participant with uncertain adherence (D). The bars are shaded with different intensities according to inferred adherence (in terms of doses taken per week) based on tenofovir diphosphate concentrations measured in DBS. DBS=dried blood spot. PrEP=pre-exposure prophylaxis.

Among the five participants who had suspected baseline HIV-1 infection, adherence based on tenofovir diphosphate concentrations in DBS was high (figure 2A). Four of these participants, all in the emtricitabine plus tenofovir disoproxil fumarate group, had virus with Met184Val or Met184Ile emtricitabine resistance-associated mutations in plasma samples collected at their HIV diagnosis study visit, and the fifth participant had a viral load too low to allow genotyping. Virus in two participants with Met184Val or Met184Ile mutations also had mutations associated with resistance to non-nucleoside reverse transcriptase inhibitors (Lys103Asn or Tyr188Leu).

Among the eight participants who were diagnosed with HIV-1 and had discontinued PrEP at least 30 days before

HIV-1 diagnosis, four (50%) had received emtricitabine plus tenofovir alafenamide and four (50%) had received emtricitabine plus tenofovir disoproxil fumarate. DBS samples were not collected at the time of diagnosis for six of these participants because they had discontinued PrEP. However, two of eight participants had low or moderate adherence at the time of study drug discontinuation (figure 2B). No tenofovir or emtricitabine resistance-associated mutations were identified in these eight participants.

13 participants were diagnosed with HIV-1 while on study drug (n=11) or less than 30 days after discontinuation (n=2; figure 2C). Five of these participants were in the emtricitabine plus tenofovir alafenamide group and eight were in the emtricitabine plus tenofovir disoproxil fumarate group, one of whom had switched to emtricitabine plus tenofovir alafenamide at the start of the open-label extension phase. Tenofovir diphosphate concentrations from DBS samples from all 13 participants indicated low adherence between 11 weeks and 104 weeks before diagnosis. Two participants (case numbers 15 and 20) did not have DBS samples collected at the time of HIV diagnosis but had consistently low adherence throughout their study participation. No tenofovir or emtricitabine resistance-associated mutations were detected by standard genotyping among participants in this group.

One participant (case number 27) had a positive HIV diagnosis at week 68 while on study drug (figure 2D). At week 60, tenofovir diphosphate concentrations in their DBS sampled indicated high adherence. A DBS sample was not collected at the time of diagnosis and, therefore, adherence leading up to HIV infection is unknown. Virus from this participant had no detectable tenofovir or emtricitabine resistance-associated mutations.

23 (85%) of 27 participants diagnosed with HIV had stored plasma samples for at least one visit before their HIV diagnosis, including all incident cases, allowing quantitative HIV-1 RNA concentration assessment. Stored samples from the day 1 visit were not available for four of the participants who had suspected baseline HIV-1 infection. Four (17%) of 23 participants had detectable HIV-1 RNA at the visit before their HIV-1 diagnosis, based on seroconversion (figure 3). No HIV-1 RNA was detected after retrospective testing of stored plasma samples from the visit before the HIV diagnosis in the remaining 19 (83%) participants with available samples.

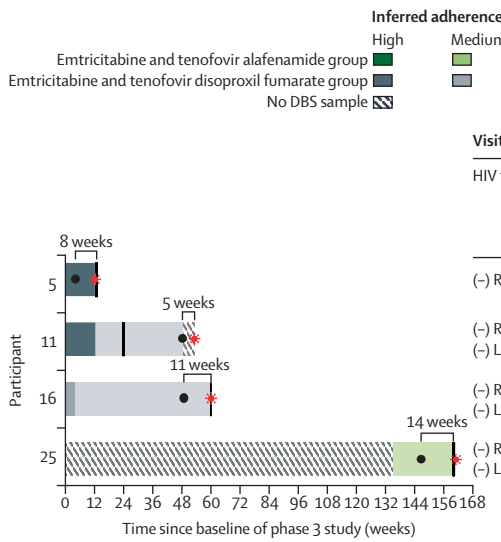
One participant (case number 5, who was assigned to emtricitabine plus tenofovir disoproxil fumarate) had a suspected baseline HIV-1 infection. The diagnosis of HIV-1 infection was made on day 85 on the basis of a positive rapid fourth generation test and a viral load of 407 copies per mL. On day 29, this participant had a negative rapid fourth generation test and laboratory-based HIV-1 testing was not performed. However, retrospective testing of stored plasma from day 29 showed a viral load of 1150 copies per mL.

The second participant (case number 11, who was assigned to emtricitabine plus tenofovir disoproxil fumarate) discontinued PrEP more than 5 months before their HIV diagnosis on day 372 (week 53), which was made on the basis of a positive rapid fourth generation test and a viral load of 8610 copies per mL. At the visit before their HIV diagnosis, on day 338 (week 48), rapid unknown generation and laboratory fourth generation test results were negative. Retrospective viral load testing of the day 338 sample revealed an HIV-1 RNA concentration of 220 000 copies per mL, and additional retrospective testing from day 254 (week 36) was negative for HIV-1 RNA. Tenofovir diphosphate concentrations from the DBS samples collected at both timepoints were below the limits of quantification.

The third participant (case number 16, who was assigned to emtricitabine plus tenofovir disoproxil fumarate) was diagnosed on day 420 (week 60) on the basis of positive results from both rapid and laboratory fourth generation tests and a viral load of 5340 copies per mL. At the visit before HIV diagnosis, on day 342 (week 48), retrospective testing showed the participant had a viral load of 332 copies per mL and negative results on rapid unknown generation and laboratory fourth generation tests. HIV-1 RNA was not detected in further retrospective testing of stored plasma from day 250 (week 36). Tenofovir diphosphate concentration in the DBS sample from day 342 was 69 fmol per punch, consistent with an average adherence of only approximately one dose every 2 weeks over the preceding 8–12 weeks.

The fourth participant (case number 25, who was initially assigned to the emtricitabine plus tenofovir disoproxil fumarate group but switched to emtricitabine plus tenofovir alafenamide at the start of the open-label extension phase, 134 weeks after randomisation) was diagnosed on day 1127 (open-label study day 191). At the visit before HIV diagnosis, on day 1027 (open-label day 91), retrospective testing showed the participant had a viral load of 257 copies per mL and negative results on rapid unknown generation and laboratory fourth generation tests. HIV-1 RNA was not detected by further retrospective testing of stored plasma from day 937 (open-label day 1). Tenofovir diphosphate was not detectable in the DBS sample on day 1027 or at the time of diagnosis.

From study initiation up to week 48 of the open-label extension, 77 873 central laboratory HIV-1 screening tests (third generation antibody or fourth generation antibody–antigen tests) were performed. Among these tests, we identified four instances when central laboratory serological HIV-1 screening was negative but quantitative HIV-1 RNA testing was positive. On the basis of these observations, an estimated 19 468 quantitative HIV-1 RNA tests would have been needed to make a single



Visit before HIV diagnosis			HIV diagnosis visit			
HIV test	HIV-1 RNA (copies per mL)	Tenofovir diphosphate (fmol per punch)	HIV test	HIV-1 RNA (copies per mL)	Tenofovir diphosphate (fmol per punch)	Resistance
(–) Rapid, 4th generation	1150	804	(+) Rapid, 4th generation	407	725	Met184Val
(–) Rapid, unknown generation (–) Laboratory, 4th generation	220 000	BLQ	(+) Rapid, 4th generation	8610	3·1	None
(–) Rapid, unknown generation (–) Laboratory, 4th generation	332	69	(+) Rapid, 4th generation (+) Laboratory, 4th generation	5340	212	None
(–) Rapid, unknown generation (–) Laboratory, 4th generation	257	BLQ	(+) Rapid, 3rd generation (+) Laboratory, 4th generation	ND	BLQ	None

Figure 3: **Summary of adherence and retrospective HIV-1 RNA testing data in participants who had detectable HIV-1 RNA before HIV-1 diagnosis (n=4)**
BLQ=below limit of quantification. DBS=dried blood spot. ND=not detected.

earlier diagnosis of incident HIV-1 infection compared with serological testing alone.

Among participants who were randomly assigned to and received at least one dose of emtricitabine plus tenofovir alafenamide (n=2694), at week 144, the median percentage change from baseline in the β2-microglobulin to creatinine ratio was –21% (IQR –51 to 18) and the median change from baseline in the retinol-binding protein to creatinine ratio was –1·3% (–28 to 36; figure 4A, B). The median change from baseline in serum creatinine concentration was –0·02 mg/dL (IQR –0·090 to 0·060) and median change from baseline in eGFR was 2·2 mL/min (IQR –8 to 13; figure 4C, D). The proportion of participants who had a urine protein to creatinine ratio of more than 22·6 mg/mmol after 48, 96, or 144 weeks of emtricitabine plus tenofovir alafenamide was 0·7% (16 of 2334), 1·0% (21 of 2155), and 0·5% (ten of 1895), respectively (table 1). During the open-label phase, decreases in β2-microglobulin and retinol-binding protein to creatinine ratio and an increase in eGFR were observed in participants who switched from emtricitabine plus tenofovir disoproxil fumarate to emtricitabine plus tenofovir alafenamide compared with those who remained on emtricitabine plus tenofovir alafenamide (appendix p 14).

In the subgroup of participants taking emtricitabine plus tenofovir alafenamide who had dual-energy x-ray absorptiometry scans (n=191), the median change from baseline in hip and spine bone mineral density was an increase of 0·54% for hip and 1·02% for spine bone mineral density at week 144 (table 1). During the open-label phase, hip and spine bone mineral density increased in participants who switched from emtricitabine plus tenofovir disoproxil fumarate to emtricitabine plus tenofovir alafenamide compared with those who remained on emtricitabine plus tenofovir alafenamide (appendix pp 14– 15).

In all participants who received one dose of emtricitabine plus tenofovir alafenamide (n=2694), most adverse events were grade 1 (mild) or 2 (moderate) in severity, and the most common adverse event was a bacterial sexually transmitted infection (table 2). There were seven deaths over at least 144 weeks of follow-up. Reasons for death were cardiac arrest, traffic accident, amphetamine intoxication, suspected suicide, homicide, fatal drug overdose, and progressive vasodilatory shock with metabolic acidosis and multisystem dysfunction after crystal methamphetamine injection. No deaths were related to study drug. Over a median exposure of 51 weeks (IQR 48–60) in the open-label study, no new safety signals were observed.

At week 144, median changes from baseline in total cholesterol, LDL, HDL, total cholesterol to HDL ratio, triglycerides, and glucose were 3 mg/dL (IQR –14 to 21), 3 mg/dL (IQR –12 to 16), –1 mg/dL (IQR –7 to 4), 0·13 (IQR –0·32 to 0·60), 5 mg/dL (IQR –19 to 32), and 2 mg/dL (IQR –4 to 9), respectively (figure 4F). Lipid-modifying medications were used by 113 (4%) of 2694 participants on emtricitabine plus tenofovir alafenamide at baseline and an additional 61 (2%) participants had initiated lipid-modifying therapy by week 144. Participants who switched from emtricitabine plus tenofovir disoproxil fumarate to emtricitabine plus tenofovir alafenamide in the open-label phase showed an increase in median fasting total cholesterol, LDL, HDL, total cholesterol to HDL ratio, and triglycerides compared with those who remained on emtricitabine plus tenofovir alafenamide (appendix p 11), resulting in similar overall cholesterol concentrations compared with those who were initially assigned to emtricitabine plus tenofovir

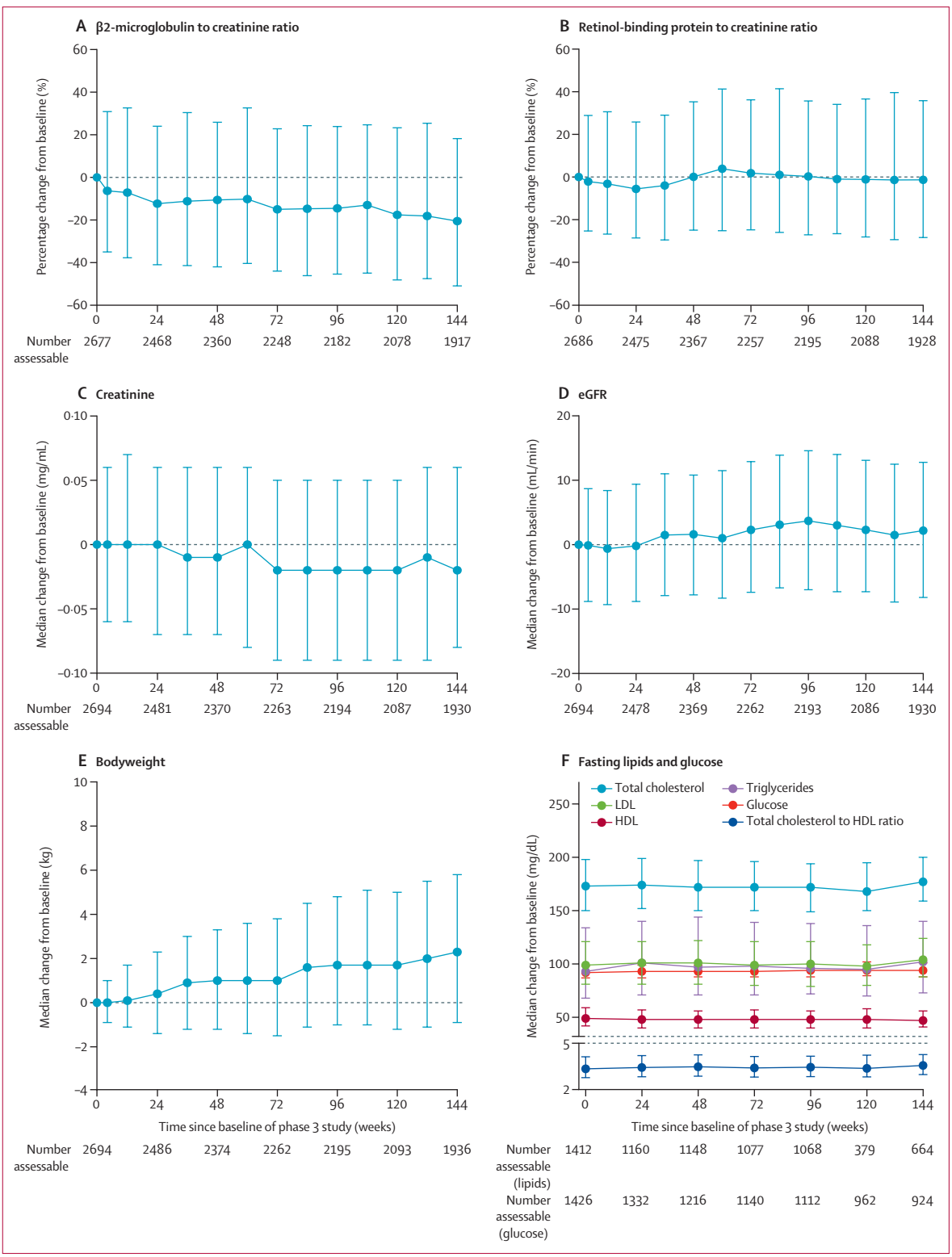


Figure 4: **Safety outcomes after up to 144 weeks of emtricitabine plus tenofovir alafenamide (n=2694)**
(A) β2-microglobulin to creatinine ratio. (B) Retinol-binding protein to creatinine ratio. (C) Serum creatinine. (D) eGFR. (E) Bodyweight. (F) Fasting serum lipids and glucose. Data are median change estimates, with error bars showing IQR. In panel F, the number of results for lipids (all variables shown except glucose) is the minimum across each variable (there was no more than 2·1% difference for any value shown between variables). eGFR=estimated glomerular filtration rate.

alafenamide and remained on it during the open-label extension. Glucose concentrations were similar across all participants, regardless of initial treatment assignment (appendix p 11).

Median bodyweight was 80·7 kg (IQR 72·0 to 91·0) at baseline. Among participants who received emtricitabine plus tenofovir alafenamide for up to 144 weeks, participants gained a median of 2·3 kg (IQR –0·90 to 5·8) of bodyweight from baseline, which equates to a median annualised increase in bodyweight of 0·83 kg per year (figure 4E). At week 48 of the open-label phase, participants who switched from emtricitabine plus tenofovir disoproxil fumarate had a median bodyweight gain of 2·0 kg (IQR –0·30 to 4·6) compared with 1·2 kg (–1·2 to 3·7) in those who remained on emtricitabine plus tenofovir alafenamide (appendix p 11).

	Proteinuria		Bone mineral density*	
	Total†	New cases *vs* baseline‡	Hip	Spine
Baseline	25/2687 (0·9%)	..	..	..
Week 48	25/2361 (1·1%)	16/2334 (0·7%)	0·22% (–0·15 to 0·59)	0·51% (0·046 to 0·98)
Week 96	27/2181 (1·2%)	21/2155 (1·0%)	0·55% (0·07 to 1·03)	0·85% (0·28 to 1·41)
Week 144	15/1919 (0·8%)	10/1895 (0·5%)	0·54% (–0·11 to 1·19)	1·02% (0·40 to 1·63)

Data are n/N (%) or median percentage change from baseline (95% CI). Proteinuria was defined as a UPCR of more than 22·6 mg/mmol. UPCR=urine protein to creatinine ratio. *Dual x-ray absorptiometry was done in 191 participants who received emtricitabine and tenofovir alafenamide. †Where n is the number of participants with UPCR >22·6 mg/mmol at each timepoint (including those with no baseline value) and N is the number with available UPCR data. ‡Where n is the number of participants with UPCR <22·6 mg/mmol at baseline and UPCR >22·6 mg/mmol at the indicated timepoint and N is the number with available UPCR data at both timepoints.

Table 1: **Quantitative proteinuria and bone mineral density, in participants who received up to 144 weeks of emtricitabine and tenofovir alafenamide (n=2694)**

Discussion

In DISCOVER, we found that, over 144 weeks, HIV-1 incidence was low and adherence was generally low among those who had incident infections. During this time, emtricitabine plus tenofovir alafenamide maintained a favourable safety profile, with improvements in renal and bone markers observed among those who switched from emtricitabine plus tenofovir disoproxil fumarate to emtricitabine plus tenofovir alafenamide at week 96.

Minimal changes in lipid concentrations were observed over 144 weeks in participants who remained on tenofovir alafenamide for the course of the study, while lipids, including total cholesterol, LDL, and HDL, increased in those who switched to tenofovir alafenamide from tenofovir disoproxil fumarate in the open-label extension. Incidence of HIV-1 infection in study participants receiving emtricitabine plus tenofovir alafenamide as PrEP for at least 144 weeks (0·13 per 100 person-years) was low despite evidence of high rates of condomless sex, as indicated by the ongoing relatively high incidence of bacterial sexually transmitted infections in study participants. Among participants with available data, HIV-1 infections were largely observed only in those who had either stopped study drug or who had suboptimal adherence, as measured by tenofovir diphosphate concentrations (one participant had unknown adherence around the time of diagnosis). These observations are consistent with the well described association between oral PrEP efficacy and adherence.[2,3,18] The characterisation of adherence, resistance, and patterns of diagnostic test results in individuals who acquired HIV while on PrEP with emtricitabine plus tenofovir disoproxil fumarate is also consistent with other studies.[19–25] Importantly, these data demonstrate the continued low incidence of HIV-1 infection after nearly 3 years of use of emtricitabine plus tenofovir alafenamide.

HIV-1 RNA was retrospectively detected before HIV-1 diagnosis on the basis of antibody testing in four of 23 participants with archived samples available, including three participants with incident infections; none of the incident cases developed antiretroviral resistance. Therefore, in DISCOVER, an estimated 19 468 routine HIV-1 RNA tests would have been required to detect one incident HIV-1 infection not detected by serological screening and would not have prevented any cases of drug resistance. These findings are in contrast with clinical trials of injectable cabotegravir for PrEP,[7] in which delays in serological HIV-1 diagnosis occurred in participants taking cabotegravir as intended. Delays in HIV-1 diagnosis observed in cabotegravir for PrEP were probably caused by suppression of HIV-1 replication by cabotegravir, a finding that was the impetus for the inclusion of RNA testing in CDC HIV prevention guidelines.[7] However, in DISCOVER, the only participants diagnosed with HIV (with samples available for viral load testing) who had detectable HIV-1 RNA before serological diagnosis were not actively taking PrEP or were not optimally adherent. Therefore, delay in diagnosis attributable to oral PrEP is unlikely to underlie these cases. We acknowledge that real-world oral PrEP use might differ from that in a clinical trial setting; however, our observation that routine HIV-1 RNA testing would have offered modest additional diagnostic benefit in DISCOVER is relevant for consideration in daily oral PrEP clinical practice.

Viral resistance was detected at the time of HIV-1 diagnosis in four of the five participants with suspected baseline infection and all had virus bearing Met184Val or Met184Ile mutations. Detection of emtricitabine resistance in HIV-1 frequently occurs in PrEP recipients who are likely to have been infected before PrEP initiation, which reinforces the concept that exposure to incompletely suppressive antiretroviral therapy (ie, two reverse transcriptase inhibitors without a third drug from a different class) risks the emergence of antiretroviral drug resistance. Because plasma samples were not collected at baseline in DISCOVER, we do not know whether participants with resistance were infected with a resistant strain of HIV-1 or whether the virus acquired resistance while they were on study drug. The presence of

	Total population
Any treatment-emergent adverse event	2544 (94%)
Any grade 3 or 4 treatment-emergent adverse event	67 (3%)
Discontinuation of study drug due to adverse event	43 (2%)
Serious adverse events*	257 (10%)
Serious adverse events related to study drug†	3 (<1%)
Deaths‡	7 (<1%)
Common treatment-emergent adverse events§	
Anal chlamydia infection	1030 (38%)
Oropharyngeal gonococcal infection	997 (37%)
Proctitis gonococcal	921 (34%)
Exposure to communicable disease	647 (24%)
Diarrhoea	522 (19%)
Syphilis	494 (18%)
Nasopharyngitis	468 (17%)
Upper respiratory tract infection	456 (17%)
Urethritis chlamydial	394 (15%)
Urethritis gonococcal	295 (11%)
Grade 3 or 4 laboratory abnormalities¶	
Any	385 (14%)
Increased aspartate aminotransferase	83 (3%)
Increased LDL while fasting	70 (3%)
Increased alanine aminotransferase	54 (2%)
Increased amylase	49 (3%)
Urine glucose (glycosuria)	37 (1%)
Increased γ-glutamyl transferase	34 (1%)
Increased lipase	32 (1%)
Decreased neutrophil count	31 (1%)
Total cholesterol while fasting (hypercholesterolaemia)	27 (1%)
Serum glucose non-fasting (hyperglycaemia)	24 (1%)

*The most common (n≥5) serious adverse events included appendicitis (17 [<1%]); suicidal ideation (9 [<1%]); cellulitis and suicide attempt (each 8 [<1%]); acute kidney injury (7 [<1%]); hepatitis A (6 [<1%]); and pneumonia and depression (each 5 [<1%]). †Serious adverse events considered related to study drug were nephrotic syndrome (1 [<1%]), chest pain and loss of consciousness (1 [<1%]), and agranulocytosis and pyrexia in the same participant (1 [<1%]). ‡Reasons for death were cardiac arrest, traffic accident, amphetamine intoxication, suspected suicide, homicide, fatal drug overdose, and progressive vasodilatory shock with metabolic acidosis and multisystem dysfunction after crystal methamphetamine injection (each 1 [<1%]). §Occurring in at least 10% of participants. ¶Occurring in at least 1% of participants.

Table 2: **Overall summary of safety in participants who received up to 144 weeks of emtricitabine and tenofovir alafenamide (n=2694)**

mutations (Lys103Asn or Tyr188Leu) associated with resistance to non-nucleoside reverse transcriptase inhibitors suggests the likelihood of transmitted resistance in at least two cases. Of the participants who acquired HIV-1 after discontinuing study treatment, none had viral resistance detected, a finding that is not unexpected given that selective pressure for resistance was minimal or non-existent. Most international HIV treatment guidelines recommend first-line antiretroviral regimens that are based on an INSTI. The effect of nucleoside reverse transcriptase inhibitor resistance, such as that conferred by Met184Val, on the efficacy of subsequent INSTI-based antiretroviral therapy is minimal.[26,27]

Emtricitabine plus tenofovir alafenamide was generally well tolerated during the 48-week open-label phase and the rate of study drug discontinuation was similar to that of the double-blinded phase.[2,3] Long-term follow-up of renal and bone biomarkers continued to demonstrate a favourable safety profile associated with long-term use of emtricitabine plus tenofovir alafenamide. Markers of glomerular filtration and proximal tubular dysfunction (ie, retinol-binding protein to creatinine ratio and β2-microglobulin to creatinine ratio) were stable or improved over 144 weeks of follow-up, indicating the absence of renal toxicity. In the subset of participants who were part of the bone density substudy, bone mineral density was stable or increased compared with week 96 data and remained increased compared with baseline, although the lower bound of the 95% CI for hip bone mineral density was less than zero. The improvement in bone mineral density and renal toxicity parameters compared with emtricitabine plus tenofovir disoproxil fumarate was previously reported[3] and is likely a result of lower plasma tenofovir concentrations that occur with tenofovir alafenamide than with tenofovir disproxil fumarate.[28] The ongoing absence of bone toxicity suggests that tenofovir alafenamide can be an appropriate choice for younger people who would benefit from PrEP and who might still be accruing bone mass, as well as those at high risk of, or already diagnosed with, low bone mineral density.

Changes in lipid concentration were minimal over 144 weeks of follow-up in participants initially randomly assigned to emtricitabine plus tenofovir alafenamide. By contrast, previously published data from DISCOVER showed that participants who were randomly assigned to emtricitabine plus tenofovir disoproxil fumarate had decreases from baseline in cholesterol concentrations, with LDL and HDL being affected similarly.[2] In the present work, we found that participants who were initially assigned to emtricitabine plus tenofovir disoproxil fumarate and switched to emtricitabine plus tenofovir alafenamide in the open-label extension had increases in cholesterol concentrations, including HDL and LDL, resulting in absolute lipid concentrations similar to those who remained on tenofovir alafenamide in the open-label extension. These findings are most likely explained by the inherent lipid-suppressive effect of tenofovir disoproxil fumarate[29] affecting cholesterol concentrations during the randomised phase of the study and then reversed in the open-label extension. The clinical impact of these lipid effects is uncertain because LDL and HDL concentrations are similarly affected. During 144 weeks of follow-up, 61 (2%) of 2694 participants initiated lipid-modifying therapies, which is consistent with recent observational data.[30] Nevertheless, clinicians should be aware that increases in lipid concentrations might occur when switching to

emtricitabine plus tenofovir alafenamide from emtricitabine plus tenofovir disoproxil fumarate.

During 144 weeks of emtricitabine plus tenofovir alafenamide, participants gained a median of 2·3 kg of bodyweight from baseline, corresponding to a median annualised increase of 0·83 kg per year. This finding is consistent with observations after 96 weeks of follow-up in participants receiving emtricitabine plus tenofovir alafenamide, who gained a median of 1·7 kg (IQR –1·0 to 4·8), while participants receiving emtricitabine plus tenofovir disoproxil fumarate gained a median of 0·5 kg (–2·2 to 3·5).[3] Notably, the bodyweight gain observed in participants receiving emtricitabine plus tenofovir alafenamide is in line with that seen in the placebo groups of the iPrEX[31] and HPTN 077[32] trials, and the cabotegravir group in HPTN 083.[6] These increases in bodyweight are not unexpected given the average annual trends observed in the general population in the USA.[33] By contrast, tenofovir disoproxil fumarate has previously been associated with a weight-suppressive effect in the iPrEX[31] and HPTN 083[6] PrEP trials.

Although the large sample size and use of objective measures of adherence are strengths of this analysis, there are limitations that should be considered when interpreting the study findings. Because plasma samples were not collected at study baseline, laboratory testing to confirm baseline HIV-1 status in the five cases of suspected baseline infection could not be conducted. However, the adherence, resistance, and viral load data strongly suggest these participants had baseline HIV-1 infections. Clinical study settings might not reflect conditions of real-world behaviour using daily oral PrEP therapy and, as demonstrated in other trials, adherence and rates of infection can differ across populations. The clinical benefit of RNA testing, including the number of tests needed to facilitate earlier HIV diagnosis, might differ in populations with differing HIV-1 incidence rates. Individuals initiating PrEP in real-world settings might be less rigorous in presenting for routine monitoring than motivated participants in a clinical trial, which might lead to longer intervals of undetected infection among those who become infected. The open-label phase of the follow-up period resulted in the absence of an active comparator group, as well as the possibility of over-reporting of adverse events. Although retention in the open-label phase was high (1839 [89%] of 2070 participants assigned to emtricitabine plus tenofovir alafenamide who stayed on treatment until week 144), some retention bias in terms of study population characteristics might have occurred compared with the blinded phase. The study population consisted of adult cisgender men and transgender women who have sex with men, potentially limiting transferability of results to other relevant populations such as cisgender women, adolescent men who have sex with men, or people who inject drugs. The safety and efficacy of emtricitabine plus tenofovir alafenamide in cisgender adolescent girls and young women who could benefit from PrEP will be assessed as part of the PURPOSE 1 trial (NCT04994509).

In conclusion, among DISCOVER trial participants, HIV-1 acquisition was rare. Except in one participant who had incomplete data, those who acquired HIV-1 infection during study follow-up had either stopped PrEP weeks before becoming infected or had objective evidence of suboptimal adherence. We found no evidence of substantial delays in diagnosis attributable to oral PrEP when routine laboratory-based HIV-1 antigen–antibody testing was used, suggesting little additional diagnostic benefit of RNA testing during follow-up care in people taking daily oral PrEP. The almost 3-year follow-up period found no new safety findings in participants receiving emtricitabine plus tenofovir alafenamide as PrEP against HIV-1 infection, highlighting that the regimen is safe and well tolerated. These findings demonstrate the long-term safety of emtricitabine plus tenofovir alafenamide, that both this combination and emtricitabine plus tenofovir disoproxil fumarate are highly effective in those who take them as directed, and underscore the critical importance of supporting continued PrEP adherence.

Contributors

Conceptualisation: DAW, CDS, PJR, MR, CC, SC, MD, AK, and JMB. Data curation: CC, SC, JCH, YS, and AK. Data access and verification: DAW and CDS. Formal analysis: CC, SC, and YS. Enrolled participants and collected data: DAW, CDS, JF, CBH, SD-L, PJR, J-MM, CB, MR, AC, GC, CM, RMG, KMo, and KMa. Reviewing collected data and identifying samples for retrospective testing in this analysis: CC, SC, MD, and AK. Methodology: DAW, CC, SC, JCH, YS, and AK. Design of figures: CC. Writing of the original draft of the manuscript: DAW, CDS, CC, SC, JCH, MD, and AK. Reviewing and editing the manuscript: DAW, CDS, JF, CBH, SD-L, PJR, J-MM, AM, CB, MR, AC, GC, CC, SC, JCH, YS, MD, AK, JMB, RMG, KMo, and KMa. All authors had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Declaration of interests

DAW has received grants, consulting fees, and speaker honoraria from Gilead Sciences; grants from Merck; consulting fees and speaker honoraria from ViiV Healthcare; and consulting fees and speaker honoraria from Janssen Pharmaceuticals. CDS has received funding, grants, consulting fees, and non-financial support from Gilead Sciences; grants and speaker honoraria from AbbVie; grants and personal fees from Janssen-Cilag; grants and personal fees from MSD, ViiV Healthcare, BioNtech, and Eli Lilly; grants from Cepheid; grants, personal fees, and non-financial support from B Braun Melsungen; consulting fees from AstraZeneca; personal fees, non-financial support, and other support outside the submitted work from Apeiron Biologics; and personal fees from GSK, Formycon, Moderna, Molecular Partners, Novartis, Roche, Sobi, and Pfizer. JF, PJR, and RMG have received research funding from Gilead Sciences. CBH has received research grant support from Gilead Sciences. SD-L has received research grant support (paid to their institution) from Gilead Sciences and Merck. J-MM has received grants (paid to their institution) from Gilead Sciences and Merck; consulting fees from Gilead Sciences, Merck, and ViiV Healthcare; and payments for participation on an advisory board from AELIX Therapeutics. AM has received research funding (paid to their institution) from Gilead Sciences, ViiV Healthcare, Merck, GSK, AbbVie, and TaiMed Biologics; speaker honoraria from Gilead Sciences, ViiV Healthcare, and EMD Serono; and payments for participation on an advisory board from Gilead Sciences and ViiV Healthcare. CB has received funding and speaker honoraria from Gilead Sciences; speaker

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Data sharing

Gilead Sciences shares anonymised individual patient data upon request or as required by law or regulation with qualified external researchers based on submitted curriculum vitae and reflecting non-conflict of interest. The request proposal must also include a statistician. Approval of such requests is at Gilead Science'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.

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