NONINTERVENTIONAL STUDY REPORT

Study Title:	Comparing Weight Gain on F/TAF and Placebo Using DISCOVER and iPrEx Study
Version Identifier:	1
Date of Last Version of the Final Study Report	27 March 2026
RWD Catalogues Number	EUPAS1000000509
ClinicalTrials.gov Identifier *(if applicable):*	NA
Active Substance:	Emtricitabine/Tenofovir Alafenamide (F/TAF) Emtricitabine/Tenofovir Disoproxil Fumarate (FTC/TDF)
Medicinal Product:	Descovy® (F/TAF) Truvada® (FTC/TDF)
Study No.:	GS-US-311-7562
Product Reference	**F/TAF:** Brazil: 1.0929.0007 Canada: 02454424 Europe (Austria, Denmark, France, Germany, the Netherlands, Ireland, Italy, Spain): EU/1/16/1099/003-004 South Africa: 51/20.2.8/0507 Thailand: 2C 15147/62 (NC) United Kingdom: PLGB 11972/0011 USA: NDA208215 **FTC/TDF:** Brazil: 1.0929.0004 Canada: 02274906 Ecuador: 4801-MEE-0819 Europe (Austria, Denmark, France, Germany, the Netherlands, Ireland, Italy, Spain): EU/1/04/305/001-003

	Peru: EE-09627 South Africa: 41/20.2.8/0171 Thailand: 2C 28/51(NC) United Kingdom: PLGB 11972/0022 USA: NDA021752
Marketing Authorization Holders	**F/TAF:** Brazil: Gilead Sciences Farmacêutica do Brasil Ltda Canada: Gilead Sciences Canada, Inc. Europe (Austria, Denmark, France, Germany, the Netherlands, Ireland, Italy, Spain): Gilead Sciences Ireland UC South Africa: Gilead Sciences South Africa (Pty) Ltd Thailand: DCH Auriga (Thailand) Limited United Kingdom: Gilead Sciences Ltd USA: Gilead Sciences, Inc. **FTC/TDF:** Brazil: Gilead Sciences Farmacêutica do Brasil Ltda Canada: Gilead Sciences Canada, Inc. Europe (Austria, Denmark, France, Germany, the Netherlands, Ireland, Italy, Spain): Gilead Sciences Ireland UC South Africa: Pharmacare Limited (South Africa) Thailand: DCH Auriga (Thailand) Limited United Kingdom: Gilead Sciences Ltd USA, Ecuador, Peru: Gilead Sciences, Inc.
MAH contact person	MAH.gilead@gilead.com
Joint PASS:	No
Research Question and Objectives	To compare weight change/trajectory distributions between F/TAF and placebo cohorts from the DISCOVER and iPrEx studies
Countries of Study	Austria, Brazil, Canada, Denmark, Ecuador, France, Germany, Ireland, Italy, the Netherlands, Peru, Spain, South Africa, Thailand, United Kingdom, United States
Author	Name: PPD

	Email:	PPD PPD
Gilead EU QPPV	Name:	PPD
	Telephone:	PPD
	Email:	EUQPPV@gilead.com

---

2. ABSTRACT

Study GS-US-311-7562
Gilead Sciences, Inc.
333 Lakeside Drive
Foster City, CA 94404 USA

Study title: Comparing Weight Gain on F/TAF and Placebo Using DISCOVER and iPrEx Study Data

Keywords: Emtricitabine/Tenofovir Alafenamide (F/TAF), pre-exposure prophylaxis (PrEP), weight change, people without HIV, placebo comparison

Rationale and background: The specific contribution of emtricitabine/tenofovir alafenamide (F/TAF) on weight remains unclear due to the presence of HIV-related factors, prior and/or concomitant use of other antiretroviral medications, and the use of weight-suppressive antiretroviral medications as comparators in previous studies. Data from pre-exposure prophylaxis (PrEP) trials in people without HIV provide a unique opportunity to evaluate weight change in the absence of HIV infection and combination antiretroviral therapy. By integrating data from the placebo-controlled iPrEx trial and the active-controlled DISCOVER trial using FTC/TDF as a bridge, this study aimed to compare weight trajectories between F/TAF and placebo and to assess whether F/TAF is associated with clinically meaningful weight change beyond background population trends.

Research objectives:

The primary objective of this study was:

- To compare trajectories of weight change between F/TAF and placebo

The secondary objectives of this study were:

- To compare outlier weight gain between F/TAF and placebo
- To describe incidence of weight-related comorbidities (i.e., cardiovascular events, diabetes, and hypertension) in F/TAF, FTC/TDF and placebo

Setting: The two trials used for this study enrolled individuals not living with HIV who were aged ≥18 years and had one or more behavioral risk factors for HIV-1 acquisition. All iPrEx participants were assigned male at birth and were recruited from North and South America, South Africa, and Thailand. DISCOVER enrolled participants assigned male at birth or transgender women, and were recruited from North America, eight European Union (EU) countries, and the UK.

Study design: This study utilized existing data collected during two large phase 3 randomized clinical trials of FTC/TDF and F/TAF to compare longitudinal weight change between F/TAF (DISCOVER) and placebo treatment groups (iPrEX). The details of study design were shown in Figure 1.

Study size: The pooled study population included 7,533 participants across iPrEx and DISCOVER: 2,499 from iPrEx (1,248 receiving placebo and 1,251 receiving FTC/TDF) and 5,034 from DISCOVER (2,507 receiving FTC/TDF and 2,527 receiving F/TAF).

Data sources: All data were collected as part of two Phase 3 randomized clinical studies.

iPrEx (Study CO-US-104-0288; NCT00458393)

Emtricitabine/Tenofovir Disoproxil Fumarate for HIV Prevention in Men

DISCOVER (Study GS-US-412-2055; NCT02842086)

A Phase 3, Randomized, Double-blind Study to Evaluate the Safety and Efficacy of Emtricitabine and Tenofovir Alafenamide (F/TAF) Fixed-Dose Combination Once Daily for Pre Exposure Prophylaxis in Men and Transgender Women Who Have Sex With Men and Are At Risk of HIV-1 Infection.

Variables:

- **Exposure**

Exposure assigned at baseline randomization was used in the analysis regardless of discontinuation during follow-up. There were three main exposures of interest: F/TAF, FTC/TDF, and placebo. The FTC/TDF groups from two trials were pooled and presented as a single group. Study drug adherence, defined as the proportion of pills taken between the first and last dispense dates, was recorded for both trials.

- **Weight Outcomes**

Body weight was measured at baseline and at multiple follow-up visits up to 120 weeks (every 4 weeks in iPrEx and at Weeks 4, 12, and every 12 weeks thereafter in DISCOVER). All available post-baseline weight measurements were included. When individuals had multiple baseline-window visits, only the last measurement before receiving FTC/TDF, F/TAF, or placebo was used.

- **Weight-related Comorbidities**

Weight-related comorbidities, including cardiovascular events, diabetes and hypertension, were derived from adverse event (AE) records.

- **Covariates**

Available baseline demographics, clinical history, comorbidities, and other known factors prognostic for weight change are summarized in Table 1. Individual comedications that may relate to weight change were extracted from medication inventory files.

Statistical methods: To compare mean weight changes between individuals assigned to F/TAF and placebo over time, we used linear mixed models adjusting for potential confounders. Data from the two FTC/TDF groups were pooled and analyzed as a single group to facilitate an overall estimate of average TDF-associated weight change.

To investigate whether F/TAF selectively caused excessive weight change in only a small fraction of individuals or otherwise shifted the shape of the distribution of weight change over time relative to placebo, we compared top percentiles of weight change at Week 48 between individuals assigned to F/TAF and placebo using quantile regression adjusted by the same set of covariates as the linear mixed model. To adjust for differential patterns of missing information between the source studies, we estimated the probability of having complete data at Week 48 with logistic regression and weighted each individual by the inverse probability in the quantile regression model.

In the sensitivity analysis, we repeated the primary analyses after excluding individuals with suboptimal adherence to their assigned study drug.

Incidence of adverse events related to weight (cardiovascular events, diabetes and hypertension) were reported for each source study.

Results: A total of 7,533 participants with at least one recorded body-weight measurement were included across the two studies, comprising 2,499 participants from iPrEx and 5,034 from DISCOVER. Across both studies, 3,758 participants received FTC/TDF (1,251 in iPrEx and 2,507 in DISCOVER), 2,527 received F/TAF (DISCOVER), and 1,248 participants received placebo (iPrEx).

Participants in DISCOVER, compared with iPrEx participants, were generally: more likely to be self-identified White, older, had higher baseline BMI, and had more use of medications associated with weight increase. A larger proportion of iPrEx participants were Hispanic/Latine and identified as transgender compared with DISCOVER. Mean levels of alanine aminotransferase levels, estimated glomerular filtration rate, and non-fasting blood glucose levels were similar across trials. Countries of enrollment varied substantially, with 57% of iPrEx participants enrolled in Peru and 64% of DISCOVER participants enrolled in the US.

In participants without prior use of FTC/TDF, adjusted mean weight change was not significantly different between participants receiving F/TAF versus those receiving the placebo at any point during follow-up (overall P = 0.65). Estimated mean difference in weight change between F/TAF without prior FTC/TDF and placebo was less than 0.2 kg over follow-up time, with the largest gap occurring around Week 48 (i.e., mean difference in kg [95% CI]: 0.18 [–0.12–0.47]). On average, treatment-naïve participants receiving FTC/TDF had a statistically significant decrease in body weight compared with those receiving the placebo (on average 0.8 kg below placebo over time, overall P <0.001) (Figure 3a). For participants who switched from FTC/TDF at baseline to F/TAF, mean weight change was higher versus those assigned F/TAF with no prior F/TDF (on average 0.7 kg above treatment-naïve F/TAF over time, overall P = 0.02).

In our study, individual variance in weight in the placebo group was much larger than the estimated weight change attributable to F/TAF, suggesting any differences between F/TAF and placebo appeared to be negligible compared with the normal variation in weight.

The proportion of individuals experiencing extreme increases or decreases in mean body weight over 48 weeks were comparable between participants receiving placebo and F/TAF without prior FTC/TDF.

The counts of cardiovascular, diabetes and hypertension adverse events that occurred during iPrEx/DISCOVER were below the threshold required for analysis.

Adjusted mean weight change remained consistent when individuals with ≤90% adherence to assigned study drug were excluded from the analysis (35% and 18% of participants in iPrEx and DISCOVER, respectively). Results of the predictive simulation of the model fit showed a good fit to the data

Discussion: This analysis represents the first comparison of longitudinal weight changes associated with F/TAF versus placebo among people without HIV, leveraging data from two Phase 3 randomized, double-blind PrEP studies.

Across all analyses, no statistically or clinically meaningful differences in adjusted mean weight change were observed between PrEP naïve individuals receiving F/TAF and those receiving placebo. Estimated differences in weight change between F/TAF and placebo remained small over follow-up (i.e., less than 0.2 kg) and were negligible relative to normal inter-individual variability in weight. This suggests that any observed differences attributable to F/TAF are minimal and that background physiological weight changes likely play a larger role.

Although residual confounding related to differences in study period, geography, and population characteristics cannot be fully excluded, the use of rigorously collected clinical trial data among PWoH, and adjustment of prespecified confounders, supports the internal validity of the findings. Overall, the results of this analysis suggest that the effect of F/TAF on weight change in PWoH is minimal and provides important insight relevant to PWH.

Conclusion: Leveraging data from two large, randomized, double-blind Phase 3 PrEP studies in PWoH, we observe no statistically or clinically meaningful differences in mean weight change between individuals receiving F/TAF and those receiving placebo. Observed weight changes with F/TAF were small relative to normal inter-individual variability and consistent with background physiological weight trends.