OBSERVATIONAL STUDY PROTOCOL

Study Title:	Comparing Weight Gain on F/TAF and Placebo Using DISCOVER and iPrEx Study Data
Short Title:	iPrEx-DISCOVER Weight Change Study
Marketing Authorization Holder:	**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.
HMA-EMA RWD Catalogues No:	To be completed
Clinical Trials.gov Identifier:	Study not registered
Indication:	Pre-Exposure Prophylaxis of HIV-1 Infection
Active Substance:	Emtricitabine/Tenofovir Alafenamide (F/TAF) Emtricitabine/Tenofovir Disoproxil Fumarate (FTC/TDF)
Medicinal Product:	Descovy® (F/TAF) Truvada® (FTC/TDF)

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
Procedure Number:	To be completed
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
Protocol ID:	GS-US-311-7562
Protocol Version: Date:	Original: 05 February 2025
Author/Contact Information:	PPD
MAH Contact Person:	MAH.Gilead@gilead.com

Gilead EU Qualified Person Responsible for Pharmacovigilance:	Name: Dr Anne-Ruth van Troostenburg de Bruyn Telephone: +49 (0) 89 8998 90181 Email: EUQPPV@gilead.com

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TABLE OF CONTENTS

LIST OF IN-TEXT TABLES

LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

ADaM	Analysis Data Model
AE	adverse event
ALT	alanine aminotransferase
anti-HB	hepatitis B surface antibody
anti-HBc	hepatitis B core antibody
ART	antiretroviral therapy
ARV	antiretroviral
AST	aspartate aminotransferase
ATT	average treatment effect for the treated
eGFR	estimated glomerular filtration rate
EMA	European Medicines Agency
EU	European Union
FDC	fixed-dose combination
F/TAF	emtricitabine/tenofovir alafenamide (coformulated; Descovy®)
FTC/TDF	emtricitabine/tenofovir disoproxil fumarate (coformulated; Truvada®)
GPP	Good Pharmacoepidemiology Practices
Gilead	Gilead Sciences/Gilead Sciences, Inc.
GVP	Good Pharmacovigilance Practices
HBV	hepatitis B virus
HCV	hepatitis C virus
HIV	human immunodeficiency virus
HIV-1	human immunodeficiency virus type 1
HMA	Heads of Medicines Agencies
ID	identification
IEC	independent ethics committee
IgM	immunoglobulin M
IL	interleukin
IRB	institutional review board
ITT	intent to treat
MAH	marketing authorization holder
MSM	men who have sex with men
PAS	post-authorization study
PASS	post-authorization safety study
PrEP	pre-exposure prophylaxis
PWH	people with HIV
PWoH	people without HIV
Q	quarter
QPPV	qualified person for pharmacovigilance

RWD	real world data
SMD	standardized mean difference
STI	sexually transmitted infection
Sr	senior
TGW	transgender women
UK	United Kingdom
US	United States

PROTOCOL SYNOPSIS

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
Short Title:	iPrEx-DISCOVER Weight Change Study
HMA-EMA RWD Catalogues No:	To be completed
ClinicalTrials.gov Identifier:	Study not registered
Study Sites Planned:	Not applicable as this study will not collect data from study sites.
Rationale and Background:	People with HIV (PWH) often experience weight gain both upon first initiating antiretroviral (ARV) treatment regimens for HIV, and over the course of their treatment experience beyond the first year of treatment. There is concern that outlier weight gain may result in emergent obesity-related comorbidities, such as cardiovascular events, diabetes, and hypertension. This concern is not limited to PWH, as there are observed global increases in the prevalence of obesity and obesity-related metabolic outcomes among the general populations (ie, including people without HIV [PWoH]). In this context, there are ongoing efforts to understand the role of specific ARV agents for HIV treatment and HIV prevention in weight change, and how weight change among those exposed to specific ARVs may or may not differ from weight change trajectories among PWoH with no exposure to ARVs. Emtricitabine/tenofovir alafenamide (coformulated; Descovy®) (F/TAF) and emtricitabine/tenofovir disoproxil fumarate (coformulated; Truvada®) (FTC/TDF) are 2 fixed-dose combinations (FDCs) used in the treatment and prevention of HIV. There are data which demonstrate the weight-suppressive

	effect of FTC/TDF; however, the role of F/TAF in weight change remains unclear. Prior real-world studies have demonstrated an association between use of F/TAF and weight gain, but the causative nature of this relationship remains unclear. Specifically, in prior studies the reversible weight-suppressive effects of FTC/TDF and efavirenz may have impacted observed weight gain attributed to subsequent F/TAF regimens after switching. In addition, these studies are all conducted in the context of an ongoing, global obesity epidemic, with an average annual weight gain of 0.5 to 1 kg in many countries, independent of HIV status or antiretroviral therapy (ART) exposure; background factors impacting study participants could be influencing observations, and attribution, of weight gain while on F/TAF, even if F/TAF has no direct impact on weight. There are limited data available comparing weight trajectories of individuals exposed to F/TAF with general, HIV-negative, ARV-naive populations. In the present study, we propose to leverage data from 2 Phase 3 clinical studies, iPrEx (Study COUS1040288: FTC/TDF versus placebo) and DISCOVER (Study GSUS4122055: F/TAF vs FTC/TDF) to compare F/TAF with placebo weight trajectories, using the common FTC/TDF groups as a negative control to assess the validity of the primary analysis results. The results of this study will provide a valuable understanding of the role of F/TAF in weight change both among PWH using F/TAF for treatment and PWoH using F/TAF for HIV prevention.
Research Question and Objectives:	The primary objective of this study is: • To compare weight change/trajectory distributions between F/TAF and placebo cohorts. The secondary objectives of this study are: • To compare outlier weight gain between F/TAF and placebo cohorts.

	• To describe incidence of weight-related comorbidities (ie, cardiovascular events, diabetes, and hypertension) in F/TAF, FTC/TDF and placebo cohorts.
Study Design:	This study will utilize existing data collected during 2 large Phase 3 clinical studies of FTC/TDF and F/TAF (iPrEx: 2007-2011 and DISCOVER: 2016-2019) to conduct an indirect comparison of F/TAF (DISCOVER) and placebo treatment groups (iPrEX), using the common FTC/TDF treatment groups as negative controls. The iPrEx study enrolled HIV seronegative adult men who have sex with men (MSM), at high risk for acquisition of HIV infection, in Brazil, Ecuador, Peru, South Africa, Thailand, and the United States (US). DISCOVER enrolled adult men and transgender women (TGW) who have sex with men, at high risk for acquisition of HIV infection in Austria, Canada, Denmark, France, Germany, Ireland, Italy, the Netherlands, Spain, the United Kingdom (UK), and the US.
Study Size:	The total sample size is 7533 participants pooled over both iPrEx and DISCOVER studies. Broken down by study, there are 2499 participants contributed from iPrEx and 5034 contributed from DISCOVER.
Study Population:	Both studies that will be used for this study recruited individuals not living with HIV, all of whom were adults aged at least 18 years, and with 1 or more behavioral risk factors for contracting HIV-1. All iPrEx study participants were born male, and were recruited from North and South America, South Africa, and Thailand. All DISCOVER study participants were born male or were TGW, and were recruited from North America, 8 European Union (EU) countries, and the UK. Study start and randomized-primary completion dates were as follows, iPrEx: June 2007 to February 2011; DISCOVER: September 2016 to January 2019.

Main Eligibility Criteria:	Participants must meet all the following criteria to be eligible for inclusion in this study: 1. All inclusion criteria from the iPrEx and DISCOVER studies apply, except where superseded by the exclusion criteria listed below (TGW participants from DISCOVER, as there is no matching population in iPrEx). 2. Participants must have at least 1 record of measured body weight. Participants who meet *any* of the following criteria will be excluded from the study: 1. All exclusion criteria from the iPrEx and DISCOVER studies apply. 2. TGW recruited to the DISCOVER study.
Variables:	**Exposure** Treatment assigned at baseline randomization will be used regardless of discontinuation during follow up. For this study, there are 3 main exposures of interest: treatment with F/TAF, FTC/TDF, or placebo. **Weight outcomes** In both studies, participant body weight (in kg) was measured at baseline and at multiple visits up to 120 weeks after baseline. All available weight data measured on or following baseline will be used in this analysis with a limited exception: if participants had multiple distinct visit dates within the "baseline" window, only the chronologically last visit date prior to treatment will be retained. **Covariates** Available baseline demographics, clinical history, comorbidities, and other known factors prognostic for weight gain will be used. Participant comedications that may relate to weight change have been distilled from medication inventory files. If feasible, given recorded data, racial/ethnic group identity, and indicators of socioeconomic status like participant educational achievement may also be used as covariates.

Data Sources:	All data that will be used were collected as part of 2 Phase 3 randomized clinical studies. Data from both studies are owned by Gilead Sciences (Gilead). **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.
Data Analysis:	Observational research methodologies will be used to compare weight trajectories and probability of outlier weight gain (eg, ≥ 10% from baseline) between the cohorts of the F/TAF (DISCOVER) and placebo (iPrEx) treatment groups. Regression adjustment and layered propensity score-based weighting methods may be used to account for differences between populations and enrollment criteria for the 2 studies. For propensity score-based weighting, for example, the probability of being in the DISCOVER study based on a common set of baseline socio-demographic and clinical characteristics (propensity score) will be calculated for all included participants. Study participants for whom sufficient data are not available to allow regression adjustment or propensity score weighting will be excluded from the present analyses. DISCOVER and iPrEx had largely nonoverlapping geographies between the 2 study samples, which violates positivity assumptions (eg, participants from some countries would have probability zero of being recruited to DISCOVER) and could lead to biased inference if geography differentially impacts expected weight trajectories while on treatment. This study is designed to address this risk in 2 primary ways: (1)

	differences in weight trajectories between F/TAF and placebo will be first estimated in (overlapping) North American samples; additional geographies from iPrEx will then be added sequentially to increase statistical power, and point estimates will be monitored for internal consistency; (2) iPrEx and DISCOVER FTC/TDF treatment groups will be used as negative controls to assess the validity of the primary analysis results (we would expect no differences between iPrEx and DISCOVER). If point estimates are not consistent as geographies are added, or FTC/TDF groups are not comparable, inference with respect to the primary F/TAF versus placebo analyses will be limited.

PLANNED MILESTONES

Table 1. Planned Milestones

Milestone	Planned Date
Start of data collection	Q1 2025
End of data collection	Q2 2025
Registration in the HMA-EMA RWD catalogues	Q1 2025
Final report of study results	Q1 2026

EMA = European Medicines Agency; HMA = Heads of Medicines Agencies; Q = quarter; RWD = real world data

1. INTRODUCTION

1.1. Background

People with HIV (PWH) often experience weight gain both upon first initiating antiretroviral (ARV) treatment regimens for HIV, and over the course of their treatment experience beyond the first year of treatment. There is concern that outlier weight gain may result in emergent obesity-related comorbidities, such as cardiovascular events, diabetes, and hypertension {Mangili 2006, Sax 2020, Venter 2020}. Observed weight gain among PWH has been attributed to a return to health phenomena and societal norms that impact both PWH and people without HIV (PWoH) (eg, diet and exercise) {Mangili 2006, Sax 2020}. This concern is not limited to PWH, as there are observed global increases in the prevalence of obesity and obesity-related metabolic outcomes among the general populations (ie, PWoH). In this context, there are ongoing efforts to understand the role of specific ARV agents for HIV treatment and HIV prevention in weight change, and how weight change among those exposed to specific ARVs may or may not differ from weight change trajectories among PWoH with no exposure to ARVs.

Emtricitabine/tenofovir alafenamide (coformulated; Descovy®) (F/TAF) and emtricitabine/tenofovir disoproxil fumarate (coformulated; Truvada®) (FTC/TDF) are 2 fixed-dose combinations (FDCs) used in the treatment and prevention of HIV. There are data which demonstrate the weight-suppressive effect of FTC/TDF {Cahn 2019, Erlandson 2021, Mallon 2021}; however the role of F/TAF in weight change remains unclear {Erlandson 2021, Ogbuagu 2020}.

1.2. Rationale for the Study

Prior real-world studies have demonstrated an association between use of F/TAF and weight gain, but the causative nature of this relationship remains unclear. Findings from these studies are often based on data from treatment-experienced populations in which prior regimens and comparator regimens can impact observed weight trajectories while on F/TAF, making it difficult to determine whether the observed weight changes can be causally attributed to F/TAF use or to other confounding causal factors.

Specifically, in prior studies the reversible weight-suppressive effects of FTC/TDF and efavirenz may have impacted the observed weight gain attributed to subsequent F/TAF regimens after switching. Likewise in prior studies, using weight-suppressive regimens as comparators may have led to the appearance of weight gain on F/TAF even if F/TAF weight trajectories are in fact consistent with normal or expected weight gain, given an individual's age, sex, and region. Furthermore, there is an ongoing, global obesity epidemic, with an average annual weight gain of 0.5 to 1 kg in many countries, independent of HIV status or antiretroviral therapy (ART) exposure which could be influencing observations, and attribution, of weight gain while on F/TAF.

Interpretation of prior findings may be clarified by understanding whether F/TAF weight trajectories are consistent with weight gain that would be expected, or "normal," in the absence of F/TAF exposure, given increases in the prevalence of obesity globally; however, there are limited data available comparing weight trajectories of individuals exposed to F/TAF with general, HIV-negative, ARV-naive controls. The DISCOVER study (GS-US-412-2055) compared the efficacy of F/TAF at preventing HIV compared to FTC/TDF and collected key safety outcomes, including regular weight measurements on participants. Individuals on F/TAF gained more weight than individuals assigned to FTC/TDF after 96 weeks; however, no placebo group was included in the study, and it is not possible to determine if differences in weight change between FTC/TDF and F/TAF were due to the weight-suppressive nature of FTC/TDF or a causal impact of F/TAF on weight gain. The iPrEx study (CO-US-104-0288), a Phase 3 FTC/TDF efficacy study, also collected regular weight measures and included a placebo group; in this study, individuals assigned FTC/TDF lost more weight over the course of the study compared to placebo. Taken together, these studies suggest, informally, that the 2 FTC/TDF treatment groups have overlapping weight trajectories and that the F/TAF and placebo groups have overlapping weight trajectories–further suggesting that F/TAF is weight-neutral relative to a population not using ARVs, and that FTC/TDF treatment groups are both weight-suppressive; however, no formal comparison has been made between these studies. The sponsor is also unaware of any other studies that would allow for a formal, robust indirect comparison between F/TAF and placebo treatment groups, that could leverage a common FTC/TDF to bridge the studies.

In the present study, we propose to leverage data from the iPrEx and DISCOVER studies and propensity score methods to compare F/TAF with placebo weight trajectories. While the 2 studies were not contemporaneous and have divergent geographies, we will be able to leverage the common FTC/TDF treatment groups to serve as negative controls and allow for an assessment of potential bias from the indirect comparison of the 2 studies. Including global data from the two trials increases the statistical power and the transparency of the study. The results of this study will provide a valuable understanding of the role of F/TAF in weight changes in PWH using treatment and PWoH using prevention regimens that include F/TAF.

2. RESEARCH QUESTIONS AND OBJECTIVES

This study is designed to address the following primary and secondary research questions:

Primary:

- How do weight change trajectories/distributions compare between F/TAF and placebo cohorts?

Secondary:

- How does outlier weight gain (≥ 5% or 10% from baseline) compare between F/TAF and placebo cohorts?
- What is the incidence of weight-related comorbidities in F/TAF ,FTC/TDF and placebo cohorts?

Primary hypothesis: The weight change/trajectories and outlier weight-gain distributions will be similar between F/TAF and placebo cohorts.

The primary objective of this study is:

- To compare weight change/trajectory distributions between F/TAF and placebo cohorts.

The secondary objectives of this study are:

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

3. RESEARCH METHODS

3.1. Study Design

This study will utilize existing data collected during 2 large Phase 3 clinical studies of FTC/TDF and F/TAF to conduct an indirect comparison of F/TAF (DISCOVER) and placebo treatment groups (iPrEX), using the common FTC/TDF treatment groups as negative controls. In brief, iPrEx-enrolled HIV-seronegative adult men who have sex with men (MSM), at high risk for acquisition of HIV infection, in Brazil, Ecuador, Peru, South Africa, Thailand, and the United States (US). DISCOVER enrolled adult men and transgender women (TGW) who have sex with men, at high risk for acquisition of HIV infection in Austria, Canada, Denmark, France, Germany, Ireland, Italy, the Netherlands, Spain, the United Kingdom (UK), and the US.

Observational research methodologies will be used to compare weight trajectories and probability of outlier weight gain (eg, 10% from baseline) between the cohorts of the F/TAF (DISCOVER) and placebo (iPrEx) treatment groups. In addition to standard regression adjustment, propensity score methods may be used to account for differences between populations and enrollment criteria for the 2 studies. For propensity score-based methods, the probability of being in the DISCOVER FTC/TDF group based on a common set of baseline socio-demographic and clinical characteristics (propensity score) may be calculated for all included participants. Study participants for whom sufficient data are not available to allow propensity score weighting will be excluded from the present analyses.

The largely nonoverlapping geographies between the iPrEx and DISCOVER studies could potentially confound results if not treated carefully. If geography differentially impacts expected weight trajectories while on treatment, positivity assumptions would be violated (eg, participants from some countries would have probability zero of being recruited to DISCOVER) and inference from the primary analyses could be biased. In addition to propensity score weighting, this study is designed to address this risk in 2 primary ways: (1) differences in weight trajectories between F/TAF and placebo will be first estimated in (overlapping) North American samples; additional geographies from iPrEx will then be added sequentially to increase statistical power, and point estimates will be monitored for internal consistency; (2) iPrEx and DISCOVER FTC/TDF treatment groups will be used as negative controls (we would expect no differences between iPrEx and DISCOVER) before the primary analysis. If point estimates are not consistent as geographies are added, or FTC/TDF groups are not comparable, inference with respect to the primary F/TAF versus placebo analyses will be limited.

3.2. Setting

Both studies that will be used for this study recruited individuals not living with HIV, all of whom were adults aged at least 18 years, and with 1 or more behavioral risk factors for contracting HIV-1. All iPrEx study participants were born male, and were recruited from North and South America, South Africa, and Thailand. All DISCOVER study participants were born male or were TGW, and were recruited from North America, 8 European Union (EU) countries, and the UK. Study start and randomized-primary completion dates were as follows, iPrEx:

June 2007 to February 2011; DISCOVER: September 2016 to January 2019. In Study GS-US-311-7049, the described analysis was performed with data limited to the following countries: Brazil, Ecuador, Peru, South Africa, Thailand, Canada, and the US. The current study will focus on a wider analysis with data from all the original DISCOVER countries involved. We assume that the weight change will act differently in TGW compared to other MSM due to hormone therapy. Given that there is no TGW population in placebo group from iPrEx, we will not include TGW from DISCOVER in the present analysis.

3.2.1. Inclusion Criteria

Participants must meet all the following criteria to be eligible for inclusion in this study:

1. All inclusion criteria from the iPrEx and DISCOVER studies apply (see Appendix 5), except where superseded by the exclusion criteria listed below.

2. Participants must have at least 1 record of measured body weight.

3.2.2. Exclusion Criteria

Patients who meet *any* of the following criteria will be excluded from the study:

1. All exclusion criteria from the iPrEx and DISCOVER studies apply (see Appendix 5).

2. TGW recruited to the DISCOVER study.

3.3. Variables

3.3.1. Exposure

Treatment assigned at baseline randomization will be used regardless of discontinuation during follow up. For this study, there are 3 main exposures of interest: F/TAF, FTC/TDF, or placebo. CCI [redacted]. In all cases, study drugs were administered orally, once daily. Formulations for F/TAF and FTC/TDF were 200/25 mg and 200/300 mg, respectively.

3.3.2. Weight Outcomes

In both studies, participant body weight (in kg) was measured at baseline and at multiple visits up to 120 weeks after baseline. All available weight data measured on or following baseline will be used in the analysis with a limited exception: if participants had multiple distinct visit dates within the "baseline" window, only the chronologically last visit date prior to treatment will be retained.

Table 2. Number of Participants With Available Weight Data at Windowed Study Visits for Each Study and Exposure Group

Study	Treatment Group	Weeks From Baseline											
		0	4	12	24	36	48	60	72	84	96	108	120
iPrEx	Placebo	1,248	–	460	983	260	866	113	625	81	395	49	235
	FTC/TDF	1,251	–	446	974	238	848	89	605	66	387	45	242
DISCOVER[a]	FTC/TDF	2507	2565	2540	2483	2453	2433	2440	2402	2339	2330	2271	2116
	F/TAF	2527	2613	2570	2485	2479	2453	2446	2367	2307	2308	2238	2089

F/TAF = emtricitabine/tenofovir alafenamide (coformulated; Descovy®); FTC/TDF = emtricitabine/tenofovir disoproxil fumarate (coformulated; Truvada®)

a Counts for the DISCOVER study include participants from North America and participants from General Data Protection Regulation-compliant European countries who consented to future use of their data.

3.3.3. Covariates

Available baseline demographics, clinical history, comorbidities, and other known factors prognostic for weight gain are summarized below. Participant comedications that may relate to weight change have been distilled from medication inventory files. If feasible, given recorded data, racial/ethnic group identity, and indicators of socioeconomic status like participant educational achievement may also be used as covariates. Baseline body mass index may be used as a derived covariate in place of baseline height and weight.

Table 3. Potential Baseline Covariates by Collection Type

Self Report	Investigator Report	Lab Assay
Education level	Blood pressure	ALT, AST
Participant age	Comedications[a]	Bilirubin
Racial/ethnic identity	Diabetes	eGFR
Sex at birth	Geographic location	Hemoglobin
Indicators of socioeconomic status	Participant height	Neutrophils
	Participant weight	Platelets
		Total blood glucose

ALT = alanine aminotransferase; AST = aspartate aminotransferase; eGFR = estimated glomerular filtration rate

a Also collected during the study observation period.

All of these variables are common to both studies.

3.4. Data Sources

All data that will be used were collected as part of 2 Phase 3 randomized clinical studies. Data from both studies are owned by Gilead Sciences (Gilead), and scale weight was assessed similarly across studies consistent with routine clinical practice.

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.

3.5. Data Management

Data are owned and managed by Gilead. This analysis will be conducted by Gilead. Data are already collected as part of the original clinical studies and will be de-identified; primary data collection is not part of this protocol. Data have been maintained in an analysis-ready format (following the Analysis Data Model, ADaM). Data are linked using unique participant identifier codes and dates of sample collection.

3.6. Study Size

The total sample size is 7533 participants pooled over both iPrEx and DISCOVER studies. Broken down by study, 2499 participants contributed from iPrEx and 5034 contributed from DISCOVER. Sample sizes for major study visits are shown in Table 2. Given the sample size, we estimate this design has 80% power to detect differences in average rate of weight change between groups of about 0.4 kg/year or more, and 90% power for differences of 0.5 kg/year or more. These minimum detectable effects are below what we would consider clinically meaningful.

Table 4. Sample Sizes in the iPrEx and DISCOVER Studies

iPrEx		***DISCOVER***	
Placebo	FTC/TDF	FTC/TDF	F/TAF
1248	1251	2507	2527

F/TAF = emtricitabine/tenofovir alafenamide (coformulated; Descovy®); FTC/TDF = emtricitabine/tenofovir disoproxil fumarate (coformulated; Truvada®)

3.7. Data Analysis

The goal of the proposed analysis is to engineer an F/TAF versus placebo contrast for the safety-related question of weight gain in people taking F/TAF for pre-exposure prophylaxis (PrEP). Due to current standards of care and the history of development of PrEP medications, this contrast is not available for any randomized controlled study and is currently only feasible through indirect comparison. In this study, we seek to approximate a randomized F/TAF versus placebo contrast by pooling together data from historical studies. The Gilead-sponsored DISCOVER study (Phase 3) compared the safety and efficacy of F/TAF versus FTC/TDF for

PrEP. Similarly, the older iPrEx study (also Phase 3) compared the safety and efficacy of FTC/TDF for PrEP versus placebo. Combining data from these studies would enable an F/TAF versus placebo contrast. The extent to which results of this analysis may be interpretable and transportable would then hinge critically on the study's ability to control for confounding factors in the 2 study samples. One advantage to using data from these studies in particular stems from the presence of the FTC/TDF treatment groups: a cross-study comparison of the 2 separate FTC/TDF treatment groups can in principle act as a negative control to assess the validity of the following primary analysis results.

In Section 3.7.3 we propose a method to model longitudinal changes in weight for participants in pooled iPrEx and DISCOVER study samples, and to promote a direct placebo versus F/TAF comparison therein. The iPrEx study sample was randomized (1:1) to placebo or FTC/TDF treatment groups, and the DISCOVER study sample was randomized (1:1) to FTC/TDF or F/TAF treatment groups. To support a comparison across nonrandomized treatment groups F/TAF and placebo treatment groups, 2 complementary approaches (layered covariate adjustment and study propensity-based weighting, see below) will be used to help mitigate potential confounding. As noted, FTC/TDF treatment groups from both samples will be retained to facilitate a conceptual negative control. Data from both studies will be pooled by defining comparable research-ready variables with harmonized definitions. A source study indicator variable for each participant will be retained in the pooled dataset. Baseline descriptive characteristics will be reported and stratified by study to characterize similarities and differences in the source study samples.

3.7.1. Covariate Adjustment

All analyses will be adjusted for study enrollment-related variables and baseline factors known to be prognostic for weight gain. Relevant baseline covariates may include participant age, blood-based markers of hepatic function (alanine aminotransferase [ALT] and bilirubin), blood pressure, height, medical history of diabetes, renal function (estimated glomerular filtration rate [eGFR]), and weight. Additional enrollment-related criteria that may be evaluated as potential covariates include other blood-based markers of hepatic function (aspartate aminotransferase [AST]), and hemoglobin, blood neutrophil and platelet concentrations, and either a group-level study indicator or a set of indicators for country of enrollment. If feasible, given recorded data, the analyses may also control for concurrent use of medications that may cause changes in weight, racial/ethnic group identity, and indicators of socioeconomic status like participant educational achievement. The selection of the covariates for adjustment will be determined by combining the team discussion of the close relevant factors of weight gain and data availability.

3.7.2. Study Propensity Score-Based Weighting

Models for propensity of study membership will be constructed using the same baseline covariates discussed above. Since we propose to combine data from 2 studies, study enrollment/membership is a binary category and a propensity of trial enrollment model can be estimated using logistic regression or similar method. Though they have numerous other uses, propensity scores are commonly taken to be probabilities of receiving a specific treatment, given covariates $\boldsymbol{x}$. Here, we have two separate source studies with two treatments randomly assigned

within each. If covariates did not relate to the treatment assignments in any way, we could justifiably treat data pooled from these studies as if they were part of a single, randomized trial. Propensity scores can be used in this context to weight individuals such that treatment assignments are approximately independent of $\boldsymbol{x}$ in the reweighted sample, approximating a single randomized study. Conceptually, since treatment assignments were made randomly and without complex stratification in each source study, we do not have to reweight for each specific treatment: the simpler target of reweighting for each study is sufficient. More formally, using the iPrEx placebo group as an example, the propensity score is $p(\text{Placebo, iPrEx} \mid \boldsymbol{x})$, and factors into the product $p(\text{Placebo} \mid \text{iPrEx}, \boldsymbol{x}) \times p(\text{iPrEx} \mid \boldsymbol{x}) = 0.5 \times p(\text{iPrEx} \mid \boldsymbol{x})$. Symmetrical arguments apply to the other three study-treatment pairs: the only quantity then left to estimate is $p(\text{iPrEx} \mid \boldsymbol{x})$, or conversely $p(\text{DISCOVER} \mid \boldsymbol{x}) = 1 - p(\text{iPrEx} \mid \boldsymbol{x})$.

Propensity score-based weighting will be applied to participant-level data to encourage distributional balance in potential baseline confounders in our group comparisons. Weighting will be used in conjunction with typical covariate adjustment to engineer "doubly robust" estimates of treatment effects. We may prefer to report the weighted estimates if they appear to have meaningfully smaller variance than estimates that are "only" covariate-adjusted in the typical manner; otherwise, weighted estimates may be reserved as a sensitivity check.

Overlap in the propensity score distributions will be examined across studies. If necessary, scores will be trimmed symmetrically to exclude participants with scores close to 0 or 1 (eg, to retain participants with estimated propensity scores in the interval [0.1, 0.9]). Weighted density plots will be examined for each covariate included in the propensity score model to assess approximate balance in the re-weighted sample. In addition, standardized mean differences (SMDs) will be calculated before and after weighting. Standardized mean differences within $\pm$ 0.10 may be interpreted as evidence of sufficient balance. If any variables have SMDs outside this range, their parameterization in the propensity score model will be reconsidered, and SMDs recalculated. Sensitivity analyses to explore the impact of data trimming and/or propensity score model specification will be considered to understand the potential impact of decisions described above.

3.7.3. Primary Analysis

The primary estimand of interest is the F/TAF versus placebo contrast for average longitudinal change in weight. This estimand will be targeted using a linear mixed model for participant weight controlling for potential baseline confounders noted in Section 3.7.4. In its most basic form, model structure will represent a flexible function of continuous time and that function's interaction with the 4 main treatment groups (placebo and FTC/TDF from iPrEx, and F/TAF and FTC/TDF from DISCOVER). Individual-level errors may be assumed autocorrelated in time. Models will be fit both with and without participant level propensity score-based weighting. For weighted models, bootstrap estimators will be used for the covariance of fixed effects. Fitted models will be validated using predictive simulation.

Model estimates will be summarized in terms of average longitudinal change in weight (kg) for the 2 study treatment groups in both respective studies. Taking the perspective that the creation of a synthetic placebo comparator for the DISCOVER F/TAF group is explored in this study, an

estimated longitudinal treatment effect difference curve will be summarized over DISCOVER participants that actually received F/TAF (ie, taken against the estimated counterfactual that these same participants had received placebo).

Due to inherent differences in the iPrEx and DISCOVER enrollment pools, we plan to model the data in stages:

1. Model only data collected from North American participants (US and Canada). Resulting sample sizes are given in the table below.

2. Extend the model to include data from outside of North America (Austria, Brazil, Denmark, Ecuador, France, Germany, Ireland, Italy, the Netherlands, Peru, Spain, South Africa, Thailand and UK) and evaluate stability of model estimates in the extended sample. The main motivation to do this is to increase usage of iPrEx data, particularly with respect to the placebo group.

Comparing the 2, an analysis with only North American participants, while more highly controlled, may lose power to detect treatment effects on weight due to the limited sample size enrolled in iPrEx in this stratum. If effect estimates remain relatively stable as the balance of data from iPrEx is "added back" in stage 2, it may suggest that country of enrollment does not strongly confound results. This would lead us to prefer inference from the "extended" model indicated in stage 2. If on the other hand estimates appear highly variable, we may default to inference from the more controlled analysis indicated in stage 1. "Relatively stable" and "highly variable" may be determined for example by testing classical equivalence null hypotheses. In any case, we may develop a bias-variance tradeoff analysis to guide preference of model and data.

Table 5. Sample Sizes Limited to Data From North American Participants (Baseline only)

iPrEx		***DISCOVER***	
Placebo	TDF/FTC	FTC/TDF	F/TAF
114	113	1791	1782

F/TAF = emtricitabine/tenofovir alafenamide (coformulated; Descovy®); FTC/TDF = emtricitabine/tenofovir disoproxil fumarate (coformulated; Truvada®); FTC = emtricitabine (Emtriva®); TDF = tenofovir disoproxil fumarate (Viread®)

Preliminary feasibility assessment suggested that the size of the iPrEx placebo group is a key determinant of analytical power in this setting and so it is generally advantageous to incorporate as much of these data as possible.

3.7.4. Secondary Analyses

There is some concern that PrEP medications may shift the shape of the distribution of weight change over time. For example, one hypothesis could conceivably be that exposure to F/TAF may skew the distribution of weight change such that a higher proportion of treated participants eventually experience a large change in weight relative to placebo. While the primary analysis models longitudinal shifts in the center of the distribution of weight change given treatment, it

may or may not be sensitive to effects on higher order moments such as skewness. While the rough plausibility of these types of hypotheses can be evaluated by examining grouped residuals plots from the primary analysis, standard software for linear mixed effects models assumes residual variance, skewness, etc, are constant (ie, regardless of treatment). To complement the primary analysis and help provide a general fail-safe option, a secondary plan is outlined below.

For the secondary analysis, the main estimands of interest are,

1. Model-based summaries of the distribution of percent weight change given starting weight, treatment, etc, and

2. Longitudinally varying odds ratios participants experience increased weight gain given different treatments (F/TAF versus placebo).

Both of these targets can be estimated efficiently using standard semiparametric "proportional odds" regression models for longitudinal ordinal data. Specifically, for the second estimand, dichotomized weight-gain outcomes with defined thresholds at 5% and 10% (from baseline) will be assessed as surrogates for outlier weight gain; specific thresholds will also be re-assessed based on empiric weight change distributions observed for the primary analyses. This family of models introduces additional parameters to estimate the shape of the distribution of the response variable. As in logistic regression, proportional odds model coefficients can be interpreted directly as log odds ratios (logistic regression is a special case of proportional odds). The main difference between this approach and the linear mixed model strategy described in Section 3.7.3 is that here longitudinal weight outcomes will be treated as ordinal variates rather than continuous. In this analysis, covariates will remain the same, as will the overall strategy of modeling the data in stages, both with and without propensity score-based adjustment.

The hypothesis that treatment changes the shape of the distribution of weights over time can be encoded by relaxing the proportional odds assumption on time and the interaction between time and treatment. Practically, relaxing proportional odds entails augmenting the model with additional parameters. In trade, the ability to formally test hypotheses about the relationship between treatment and the shape of the conditional distribution of participant weights will be obtained.

Hypotheses about specific weight quantiles may also be assessed using the primary analysis model (if the primary model fits the data well it implies a model for *all* weight change quantiles) and/or quantile regression methods. Analyses of this type may be considered to supplement proportional odds regression results, or as a possible alternative in the event of technical numerical issues arising from model optimization.

Other Differences Between the Primary and Secondary Analyses

Unlike linear-family models, proportional odds models do not have an error term to absorb lack of fit. This property can render proportional odds models sensitive to misspecification and can sometimes pose other technical difficulties. For example, in Section 3.7.3 "individual-level errors will be assumed autocorrelated in time..." There is no natural equivalent to modeling

outcome autocorrelation in the standard proportional odds framework. If necessary, (functions of) time-lagged outcomes may be included as covariates in the secondary analysis to approximate this type of structure.

Also, as noted, proportional odds models encode the entire shape of the outcome distribution through a series of additional (constrained) parameters. In this context, if there are K unique values of the weight outcome, the model will use $K - 1$ parameters just to encode this shape. While this construction affords the model substantial flexibility, it can also create significant computational overhead when K is large. If necessary, this complexity may be limited by rounding (eg, to the nearest kilogram) or otherwise binning the weight outcomes to reduce the number of unique values. The meaning of "large" K is software dependent, but generally K up to about 1000 is still manageable, while beyond may become unwieldy.

3.7.5. Other Analyses

3.7.5.1. Sensitivity Analyses: Study Drug Adherence

Study drug compliance, defined as the proportion of pills taken between the first and last dispense dates, was recorded for both studies. Since it could be argued that a participant with zero overall adherence effectively self-selects into a placebo-like regimen, (functions of) participants' compliance rate may be used in place of treatment group indicators. When placebo is used as the reference, this strategy effectively considers zero-compliance treated participants as if they had been assigned placebo.

For example, define a binary indicator Z_i such that $Z_i = 1$ denotes that participant i was enrolled in the DISCOVER study and subsequently randomized to F/TAF treatment ($Z_i = 0$ otherwise). Also let $\bar{C}_i$ denote the ith participant's overall study-average adherence proportion ($0 \leq \bar{C}_i \leq 1$). Using Z_i at face value to estimate an effect of F/TAF would reflect an intent-to-treat (ITT) analysis. Alternatively, a new variable, $Z_i^* = Z_i \times \bar{C}_i$, may be defined to denote the ith participant's overall compliance with DISCOVER F/TAF and use this variable (or a function thereof) in place Z_i in the analysis. If necessary, explicit comparisons between ITT analyses and models using Z_i^* can be developed, for example, with generalized cross validation. If the non-adherence sensitivity analysis results differ markedly from the intent-to-treat-type analysis, we will prefer the non-adherence result.

3.7.5.2. Feasibility Analysis

An informal power simulation based on the actual sample sizes and observation schedules from the iPrEx and DISCOVER studies has been conducted to discern what effect sizes may be reasonably discoverable with the intended analysis. Per simulation results, group differences in rate of weight change around 0.4 (kg/year) or larger are detectable with approximately 80% power.

3.7.5.3. Missing Data Assessment

Mixed models accommodate missing data naturally and efficiently when the missingness mechanism is random given the observed outcome and covariates {Fitzmaurice 2011}. As with many longitudinal studies, iPrEx and DISCOVER incurred some sample attrition. Three hundred-nine individuals enrolled in iPrEx and 570 in DISCOVER withdrew or were withdrawn, died during follow up, or were otherwise lost to contact during the study observation period. Common reasons given for participant discontinuation across the 2 studies will be catalogued. Potential correlates of common reasons will be evaluated as possible covariates in the analysis.

3.7.5.4. Incidence of Weight-Related Comorbidities

Incidence of weight-related comorbidities like diabetes mellitus, hypertension, and cardiovascular diseases is also of general interest. Though not the main focus of this study, incident weight-related comorbidities may help contextualize any findings generated through the primary and secondary analyses. Basic summaries of recorded incidence of each of the above comorbidities will be provided. For these analyses, participants with recorded medical history of the comorbidity on or prior to their baseline visit will be excluded; for all other participants, incidence of the comorbidity will be derived from adverse event (AE) records or calculated from the vital signs. Summaries will include raw counts and proportions of participants in each study treatment group that developed the comorbidity.

3.7.5.5. Assessment of Study Viability and Biased Inference

As detailed above, in addition to propensity score-based weighting, 2 primary approaches have been proposed to assess bias from the indirect comparison across largely nonoverlapping iPrEx and DISCOVER samples. (1) Point estimates and confidence bounds will first be calculated for overlapping F/TAF and placebo geographic samples (ie, North America). Additional geographies from iPrEx will then be added sequentially (stepwise) to increase statistical power. As part of this sequential process, point estimates will be monitored for internal consistency. Rough internal consistency can be assessed by verifying that model parameter estimates do not differ by more than 1 or 2 standard errors with the addition of data. Bias-variance tradeoff analyses can also be developed to assess how large any bias would have to be to overcome gains in efficiency due to increasing the size of the placebo group. (2) Primary analyses will also be summarized comparing FTC/TDF treatment groups across the 2 studies. We expect that FTC/TDF weight change distributions will be similar in both studies in the absence of bias. In this way, FTC/TDF treatment groups will serve as negative controls: significant differences in weight trajectories between FTC/TDF treatment groups across the 2 studies could indicate that propensity score weighting was not sufficient to create a balanced comparison between the F/TAF and placebo treatment groups.

3.7.5.6. Bias Assessment: Primary Results Inference and Reporting

The methodology for and results from both approaches to bias assessment of the indirect comparison will be reported in any communication or publication. If the potential for limited bias that could undermine study interpretation or inference from results is identified, the study

investigators will clearly describe the bias and potential impact on interpretation of results, including sensitivity analyses to quantify/bracket potential impact on results as appropriate or feasible (ie, describe which geographies are most impacting inconsistent results). If significant bias is suspected, the study team will consider reporting that the study was not viable, without providing point estimates or inference from the results. Finally, the study team would consider stopping the study early and not continuing with outlined analyses if the study is considered infeasible based on FTC/TDF negative control results, and/or inconsistency of the point estimates as new geographies are added.

3.8. Quality Control

After the initial pooling of the datasets, a validation process will be implemented to ensure data quality. Main study results will be independently verified by a second member of the study team to ensure accuracy in reporting.

3.9. Limitations of the Research Methods

The following limitations are expected:

- Study enrollment and observation periods occurred over completely disjoint years. The iPrEx study began in June of 2007 and its randomized-phase completion date was in February of 2011. The DISCOVER study begin in September of 2016 and its primary completion date was in January of 2019.
- The iPrEx and DISCOVER enrollments were drawn from distinct geographical regions, with the US being the only country of overlap. Geography may relate to a number of factors that could influence gross trends in weight (eg, cultural differences in diet; eg, see {Desbouys 2020} for a review). In light of this particular issue, a staged inclusion of iPrEx data has been proposed in Section 3.7.3.
- Race/ethnicity and correlates of socioeconomic status are known to be associated with body composition and body mass index {Heymsfield 2016, McLaren 2007}. This information, however, may be somewhat difficult to control for the comparison. Due to geographical differences in the enrolled study samples, racial/ethnic groups may be ill-defined in the pooled data. Similarly, educational achievement—a commonly used correlate of socioeconomic status—is only available for iPrEx participants from Ecuador or Peru; coding schemes for education level were somewhat different between the 2 studies.
- iPrEx and DISCOVER studies were designed to test the efficacy of FTC/TDF and F/TAF at preventing HIV and were not designed to answer the research questions posed in this study. As such, limited data on other behavioral factors such as diet and exercise will be available. Not including all published RCTs in the current project may limit the generalizability of the findings. We are also not aware of other data that would allow for the contrast being proposed in this study. Additionally, with the rigorous methods of confounding control and the use of negative controls, the results from this study would maintain internal validity. Considering the availability of data and logistical constraints, the evidence will be of significant value to the community.

A cross-study comparison of the 2 separate FTC/TDF treatment groups may act as a "negative control" and could help us survey the potential impact of any bias that may be due to the limitations noted above.

3.10. Other Aspects

This study will be conducted according to the Good Pharmacoepidemiology Practices (GPP) and in line with the relevant Modules of the Heads of Medicines Agencies (HMA) Good Pharmacovigilance Practices (GVP).

4. PROTECTION OF HUMAN SUBJECTS

4.1. Institutional Review Board (IRB) or Independent Ethics Committee (IEC) Review and Approval

Gilead will submit this protocol, to an independent ethics committee (IEC), as applicable. Before implementation, Gilead will submit to and receive documented approval from the IEC for any modifications made to the protocol.

4.2. Confidentiality

The patient identifiers in all data sources have been removed and the data will contain no patient identifiable fields.

4.3. Informed Consent

No informed consent will be obtained to participate in this secondary analysis of existing data; however, informed consent has been granted when original study data were collected, depending on the ethics approval procedures of the/each country. Only patients who consented to subsequent future data use in the original study will be used.

5. RESPONSIBILITY AND STUDY CONDUCT

5.1. Study Files and Retention of Records

As this concerns a study with a design based on secondary use of data, all analytical datasets will be maintained per records retention schedule and local regulations.

5.2. Access to Information for Audit and Inspections

This study, based on secondary use of existing data, will be conducted in-house; therefore, audits of external parties (eg, investigators) are not applicable and are covered by the original protocols.

5.3. Protocol Compliance

The study will be conducted according to this protocol.

6. MANAGEMENT AND REPORTING OF SAFETY INFORMATION

This observational study makes secondary use of data (ie, data previously collected for other purposes), therefore expedited collection and submission of suspected adverse reactions in the form of individual case safety reports is not required. Should any adverse events/reactions be collected for the study, they will be recorded and summarized in the interim safety analysis and in the final study report.

7. PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

7.1. Study Report and Publications

The results of this study will be submitted for publication. Authorship of study manuscripts and presentations at scientific conferences will follow the guidelines established by the International Committee of Medical Journal Editors (https://www.icmje.org/). Any final manuscript will be submitted to regulatory authorities within 2 weeks after first acceptance for publication.

Gilead will ensure that the final study report is submitted to respective regulatory authorities within 12 months from study completion unless otherwise required by local regulations.

8. REFERENCES

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9. APPENDICES

Appendix 1. List of Stand-Alone Documents

Number	Document Reference Number	Date	Title
1. None			

Appendix 2. ENCePP Checklist for Study Protocols

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

EU PAS Register® number:
Study reference number (if applicable):

Section 1: Milestones	**Yes**	**No**	**N/A**	**Section Number**
1.1 Does the protocol specify timelines for				
1.1.1 Start of data collection[1]	☒	☐	☐	Table 1
1.1.2 End of data collection[2]	☒	☐	☐	Table 1
1.1.3 Progress report(s)	☐	☐	☒	
1.1.4 Interim report(s)	☐	☐	☒	
1.1.5 Registration in the EU PAS Register®	☒	☐	☐	Table 1
1.1.6 Final report of study results.	☒	☐	☐	Table 1

Comments:

Secondary use of data

Section 2: Research question	**Yes**	**No**	**N/A**	**Section Number**
2.1 Does the formulation of the research question and objectives clearly explain:				
2.1.1 Why the study is conducted? (e.g. to address an important public health concern, a risk identified in the risk management plan, an emerging safety issue)	☒	☐	☐	1.2
2.1.2 The objective(s) of the study?	☒	☐	☐	2.0
2.1.3 The target population? (i.e. population or subgroup to whom the study results are intended to be generalised)	☒	☐	☐	3.2
2.1.4 Which hypothesis(-es) is (are) to be tested?	☒	☐	☐	2.0
2.1.5 If applicable, that there is no *a priori* hypothesis?	☐	☐	☒	

Comments:

[1] Date from which information on the first study is first recorded in the study dataset or, in the case of secondary use of data, the date from which data extraction starts.
[2] Date from which the analytical dataset is completely available.

Section 3: Study design		**Yes**	**No**	**N/A**	**Section Number**
3.1	Is the study design described? (e.g. cohort, case-control, cross-sectional, other design)	☒	☐	☐	3.1
3.2	Does the protocol specify whether the study is based on primary, secondary or combined data collection?	☒	☐	☐	3.4
3.3	Does the protocol specify measures of occurrence? (e.g., rate, risk, prevalence)	☒	☐	☐	3.7.3
3.4	Does the protocol specify measure(s) of association? (e.g. risk, odds ratio, excess risk, rate ratio, hazard ratio, risk/rate difference, number needed to harm (NNH))	☒	☐	☐	3.7.3
3.5	Does the protocol describe the approach for the collection and reporting of adverse events/adverse reactions? (e.g. adverse events that will not be collected in case of primary data collection)	☐	☐	☒	6.0

Comments:

Secondary use of data

Section 4: Source and study populations		**Yes**	**No**	**N/A**	**Section Number**
4.1	Is the source population described?	☒	☐	☐	3.2
4.2	Is the planned study population defined in terms of:				
	4.2.1 Study time period	☒	☐	☐	3.2
	4.2.2 Age and sex	☒	☐	☐	3.3.3
	4.2.3 Country of origin	☒	☐	☐	3.2
	4.2.4 Disease/indication	☒	☐	☐	3.2
	4.2.5 Duration of follow-up	☒	☐	☐	3.3
4.3	Does the protocol define how the study population will be sampled from the source population? (e.g. event or inclusion/exclusion criteria)	☒	☐	☐	3.2.1, 3.2.2

Comments:

Section 5: Exposure definition and measurement		**Yes**	**No**	**N/A**	**Section Number**
5.1	Does the protocol describe how the study exposure is defined and measured? (e.g. operational details for defining and categorising exposure, measurement of dose and duration of drug exposure)	☒	☐	☐	3.3.1
5.2	Does the protocol address the validity of the exposure measurement? (e.g. precision, accuracy, use of validation sub-study)	☐	☐	☒	
5.3	Is exposure categorised according to time windows?	☒	☐	☐	3.3.1
5.4	Is intensity of exposure addressed? (e.g. dose, duration)	☒	☐	☐	3.7.5.1

Section 5: Exposure definition and measurement		**Yes**	**No**	**N/A**	**Section Number**
5.5	Is exposure categorised based on biological mechanism of action and taking into account the pharmacokinetics and pharmacodynamics of the drug?	☐	☒	☐	3.3.1
5.6	Is (are) (an) appropriate comparator(s) identified?	☒	☐	☐	3.7

Comments:

Secondary use of data

Section 6: Outcome definition and measurement		**Yes**	**No**	**N/A**	**Section Number**
6.1	Does the protocol specify the primary and secondary (if applicable) outcome(s) to be investigated?	☒	☐	☐	3.3.2, 3.7.5.4
6.2	Does the protocol describe how the outcomes are defined and measured?	☒	☐	☐	3.3.2
6.3	Does the protocol address the validity of outcome measurement? (e.g. precision, accuracy, sensitivity, specificity, positive predictive value, use of validation sub-study)	☐	☐	☒	
6.4	Does the protocol describe specific outcomes relevant for Health Technology Assessment? (e.g. HRQoL, QALYs, DALYS, health care services utilisation, burden of disease or treatment, compliance, disease management)	☐	☐	☒	

Comments:

Secondary use of data

Section 7: Bias		**Yes**	**No**	**N/A**	**Section Number**
7.1	Does the protocol address ways to measure confounding? (e.g. confounding by indication)	☒	☐	☐	3.7.1, 3.7.2, , 3.7.5
7.2	Does the protocol address selection bias? (e.g. healthy user/adherer bias)	☒	☐	☐	3.7.5.1, 3.7.5.3
7.3	Does the protocol address information bias? (e.g. misclassification of exposure and outcomes, time-related bias)	☒	☐	☐	3.7.5.1

Comments:

Section 8: Effect measure modification		**Yes**	**No**	**N/A**	**Section Number**
8.1	Does the protocol address effect modifiers? (e.g. collection of data on known effect modifiers, sub-group analyses, anticipated direction of effect)	☒	☐	☐	3.7

Comments:

Section 9: Data sources		**Yes**	**No**	**N/A**	**Section Number**
9.1	Does the protocol describe the data source(s) used in the study for the ascertainment of:				
	9.1.1 Exposure? (e.g. pharmacy dispensing, general practice prescribing, claims data, self-report, face-to-face interview)	☒	☐	☐	3.4
	9.1.2 Outcomes? (e.g. clinical records, laboratory markers or values, claims data, self-report, patient interview including scales and questionnaires, vital statistics)	☒	☐	☐	3.4
	9.1.3 Covariates and other characteristics?	☒	☐	☐	3.4
9.2	Does the protocol describe the information available from the data source(s) on:				
	9.2.1 Exposure? (e.g. date of dispensing, drug quantity, dose, number of days of supply prescription, daily dosage, prescriber)	☒	☐	☐	3.3.1
	9.2.2 Outcomes? (e.g. date of occurrence, multiple event, severity measures related to event)	☒	☐	☐	3.3.2
	9.2.3 Covariates and other characteristics? (e.g. age, sex, clinical and drug use history, co-morbidity, co-medications, lifestyle)	☒	☐	☐	3.3.3
9.3	Is a coding system described for:				
	9.3.1 Exposure? (e.g. WHO Drug Dictionary, Anatomical Therapeutic Chemical (ATC) Classification System)	☐	☐	☒	
	9.3.2 Outcomes? (e.g. International Classification of Diseases (ICD), Medical Dictionary for Regulatory Activities (MedDRA))	☐	☐	☒	
	9.3.3 Covariates and other characteristics?	☐	☐	☒	
9.4	Is a linkage method between data sources described? (e.g. based on a unique identifier or other)	☒	☐	☐	3.5

Comments:

Secondary use of data

Section 10: Analysis plan		**Yes**	**No**	**N/A**	**Section Number**
10.1	Are the statistical methods and the reason for their choice described?	☒	☐	☐	3.7.3
10.2	Is study size and/or statistical precision estimated?	☒	☐	☐	3.7.3
10.3	Are descriptive analyses included?	☒	☐	☐	3.7
10.4	Are stratified analyses included?	☒	☐	☐	3.7
10.5	Does the plan describe methods for analytic control of confounding?	☒	☐	☐	3.7.1, 3.7.2
10.6	Does the plan describe methods for analytic control of outcome misclassification?	☐	☐	☒	
10.7	Does the plan describe methods for handling missing data?	☒	☐	☐	3.7.5.3
10.8	Are relevant sensitivity analyses described?	☒	☐	☐	3.7.5

Comments:

Secondary use of data

Section 11: Data management and quality control		**Yes**	**No**	**N/A**	**Section Number**
11.1	Does the protocol provide information on data storage? (e.g. software and IT environment, database maintenance and anti-fraud protection, archiving)	☒	☐	☐	3.5
11.2	Are methods of quality assurance described?	☒	☐	☐	3.8
11.3	Is there a system in place for independent review of study results?	☒	☐	☐	3.8

Comments:

Secondary use of data

Section 12: Limitations		**Yes**	**No**	**N/A**	**Section Number**
12.1	Does the protocol discuss the impact on the study results of:				
	12.1.1 Selection bias?	☒	☐	☐	3.7.5.5, 3.7.5.6, 3.9
	12.1.2 Information bias?	☒	☐	☐	
	12.1.3 Residual/unmeasured confounding? (e.g. anticipated direction and magnitude of such biases, validation sub-study, use of validation and external data, analytical methods).	☒	☐	☐	
12.2	Does the protocol discuss study feasibility? (e.g. study size, anticipated exposure uptake, duration of follow-up in a cohort study, patient recruitment, precision of the estimates)	☒	☐	☐	3.7.3, 3.7.5.2

Comments:

Section 13: Ethical/data protection issues		**Yes**	**No**	**N/A**	**Section Number**
13.1	Have requirements of Ethics Committee/Institutional Review Board been described?	☒	☐	☐	4.1
13.2	Has any outcome of an ethical review procedure been addressed?	☒	☐	☐	4.1
13.3	Have data protection requirements been described?	☒	☐	☐	4.2

Comments:

Section 14: Amendments and deviations		**Yes**	**No**	**N/A**	**Section Number**
14.1	Does the protocol include a section to document amendments and deviations?	☒	☐	☐	Appendix 4

Comments:

Section 15: Plans for communication of study results		**Yes**	**No**	**N/A**	**Section Number**
15.1	Are plans described for communicating study results (e.g. to regulatory authorities)?	☒	☐	☐	7.1
15.2	Are plans described for disseminating study results externally, including publication?	☒	☐	☐	7.1

Comments:

Name of the main author of the protocol: Xiwen Huang

Date: dd/Month/year

Signature: *Signature captured electronically– refer to the last page of the protocol*

Appendix 3. Gilead Signature Page

Gilead Sciences, inc.

333 Lakeside Drive
Foster City, CA 94404
USA

COMPARING WEIGHT GAIN ON F/TAF AND PLACEBO USING DISCOVER AND IPREX STUDY DATA

ORIGINAL 05 FEBRUARY 2025

This protocol has been approved by Gilead Sciences, Inc. The following signatures document this approval.

PPD

Signature captured electronically–refer to the last page of the protocol

Gilead Sr Manager, Epidemiology, Real World Evidence Virology (Printed)
Author

Signature

Date captured electronically–refer to the last page of the protocol

Date

PPD

Signature captured electronically–refer to the last page of the protocol

Gilead EU QPPV (Printed)

Signature

Date captured electronically–refer to the last page of the protocol

Date

Appendix 4. Amendments and Updates

Table 6. Protocol Amendments and Updates

Amendment or Update Number	Date	Section of Study Protocol	Amendment or Update	Reason
None	-	-	-	-

Protocol modifications may only be made by Gilead Sciences, Inc.

Appendix 5. iPrEx and DISCOVER Study Inclusion/Exclusion Criteria

Inclusion Criteria

iPrEx:

1. Male sex (at birth)

2. Willing and able to provide written informed consent

3. Age having reached the local age of consent

4. Not living with HIV

Evidence of high risk for HIV infection including any of the following: 1) No condom use during anal intercourse with a male partner with HIV or a male partner of unknown HIV status during the last 6 months; (2) anal intercourse with more than 3 male sex partners during the last 6 months; (3) exchange of money, gifts, shelter, or drugs for anal sex with a male partner during the last 6 months; (4) sex with a male partner and sexual transmitted infection (STI) diagnosis during the last 6 months or at screening, or (5) sexual partner of a man not living with HIV with whom condoms are not consistently used in the last 6 months.

5. Able to provide a street address of residence for themselves and 1 personal contact who would know their whereabouts during the study period.

6. Ambulatory performance status ≥ 80 on the Karnofsky scale.

7. Adequate renal function (creatinine clearance ≥ 60 ml/min estimated by the Cockcroft Creatinine Clearance Formula AND serum creatinine ≤ the upper limit of normal) within 28 days of enrollment.

8. A urine dipstick with a negative or trace result for both glucose and protein within 28 days of enrollment.

9. Adequate hepatic function (total bilirubin and hepatic transaminases (alanine aminotransferase [ALT] and aspartate aminotransferase [AST]) ≤ 2 × upper limit of normal within 28 days of enrollment).

10. Adequate hematologic function (absolute neutrophil count ≥ 1,500/mm^3; platelets within normal limits; and hemoglobin ≥ 10 g/dL within 28 days of enrollment)

11. Ability to understand and local language for which an informed consent form has been approved by a local institutional review board (IRB) and registered with the study sponsor.

DISCOVER:

1. HIV-1 negative status
2. Men who have sex with mem (MSM) and transgender women (TGW) (male at birth) who have at least 1 of the following:
    a. Condomless anal intercourse with at least 2 unique male partners in the past 12 weeks (partners must be either living with HIV 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 glomerular filtration rate ≥ 60 mL/min according to the Cockcroft-Gault formula for creatinine clearance.
5. Adequate liver and hematologic function:
    a. Aspartate aminotransferase and ALT ≤ 2.5 × upper limit of normal and total bilirubin ≤ 1.5 mg/dL, or normal direct bilirubin.
    b. 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

iPrEx:

1. Previously diagnosed active and serious infections, including tuberculosis infection, osteomyelitis, or infections requiring parenteral antibiotic therapy; active clinically significant medical problems including heart disease (eg, symptoms of ischemia, congestive heart failure, arrhythmia), lung disease (steroid-dependent chronic obstructive pulmonary disease), diabetes requiring hypoglycemic medication, or previously diagnosed cancer expected to require further treatment.
2. Acute hepatitis B infection determined by the following hepatitis serological results: hepatitis B core antibody (anti-HBc) positive, hepatitis B surface antibody (anti-HBs) negative, and hepatitis B core antibody immunoglobulin M (IgM) (anti-HBc IgM) positive at the screening visit; or presence of treatment indications for hepatitis B based on local practice standards; or clinical signs of hepatic cirrhosis.
3. History of pathological bone fractures not related to trauma.

4. Receiving ongoing therapy with any of the following: antiretroviral therapy (ART), including nucleoside analogs, nonnucleoside reverse transcriptase inhibitors, protease inhibitors or investigational antiretroviral agents, interferon (alpha, beta, or gamma) or interleukin (eg, IL-2) therapy, aminoglycoside antibiotics, amphotericin B, cidofovir, systemic chemotherapeutic agents, other agents with significant nephrotoxic potential, other agents that may inhibit or compete for elimination via active renal tubular secretion (eg, probenecid), and/or other investigational agents;

5. Definitely or possibly received an anti-HIV vaccine while participating in a blinded clinical trial.

6. Concomitant participation in a clinical trial or cohort study other than substudies of this protocol. Co-enrollment in cohort studies and iPrEx requires written approval of both the protocol chair of the cohort study and the iPrEx protocol chair.

7. Active alcohol or drug use considered sufficient by the site physician to hinder compliance with any study procedures.

8. At enrollment, has any other condition that, based on the opinion of the investigator or designee, would preclude provision of informed consent; make participation in the study unsafe; complicate interpretation of study outcome data; or otherwise interfere with achieving the study objectives.

9. Sites may utilize additional criteria that restrict enrollment to a subset of people who meet the protocol-defined enrollment criteria.

DISCOVER:

1. Known hypersensitivity to the study drug, 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. Participants found to be susceptible to hepatitis B virus (HBV) infection should be referred for HBV vaccination. Participants found to be positive for hepatitis C virus (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 participant 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 participant 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 study (including observational studies) without prior approval from the sponsor is prohibited while participating in this study.

GS-US-311-7562_Observational Study Protocol_05Feb2025

ELECTRONIC SIGNATURES

Signed by	Meaning of Signature	Server Date (dd-MMM-yyyy hh:mm:ss)
PPD	QPPV eSigned	10-Feb-2025 06:23:00
PPD	Real-World Evidence eSigned	10-Feb-2025 15:32:19