FINAL STUDY REPORT

Study Title:	Adherence, HIV-1 Infection, Resistance, and Renal and Skeletal Adverse Event in Individuals Taking Emtricitabine/Tenofovir Disoproxil Fumarate (FTC/TDF, Truvada®) for HIV Pre-Exposure Prophylaxis (PrEP): A Pooled Observational Study
Indication:	HIV Pre-Exposure Prophylaxis (PrEP)
Name of Drug:	Emtricitabine/Tenofovir Disoproxil Fumarate (FTC/TDF)
Active Substance:	Emtricitabine/tenofovir disoproxil fumarate 200 mg/300 mg film-coated tablets
Sponsor:	Gilead Sciences, Inc. 333 Lakeside Drive Foster City, CA 94404 USA
Study No.:	GS-US-276-0104
Postmarketing Requirement (PMR) No:	PMR 1906-3
IND No.:	108930
NDA No.:	021752/S-030
Clinical Trials.gov ID:	NCT01902472
Gilead Study Director:	Name: PPD Telephone: PPD Email: PPD
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Final Study Report Date:	27 April 2021

CONFIDENTIAL AND PROPRIETARY INFORMATION

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GLOSSARY OF ABBREVIATIONS AND DEFINITION OF TERMS

AE	adverse event
BLQ	below limit of quantification
BMD	bone mineral density
CDC	Center for Disease Control and Prevention
DBS	dried blood spot
EU	European Union
FDA	(United States) Food and Drug Administration
fmol	femtomole
FAS	Full Analysis Set
FTC	emtricitabine
FTC-TP	emtricitabine-triphosphate
FTC/TDF	emtricitabine/tenofovir disoproxil fumarate (Truvada®)
GLPS	Global Patient Safety
HIV, HIV-1	human immunodeficiency virus, human immunodeficiency virus type 1
IND	Investigational New Drug (Application)
iPrEx	Pre-exposure Prophylaxis Initiative (study)
LLoQ	lower limit of quantification
mL	milliliter
MSM	men who have sex with men
ng	nanograms
Parent protocol	original protocol of the PrEP demonstration project or clinical study that is providing data to this analysis
PBMC	peripheral blood mononuclear cells
PCR	polymerase chain reaction
PrEP	pre-exposure prophylaxis
PMR	Post Marketing Requirement
PR	protease
PWH	people with HIV
RBC	red blood cells
RMP	Risk Management Plan
RT	reverse transcriptase
sNDA	Supplemental New Drug Application
TDF	tenofovir disoproxil fumarate
TDR	transmitted drug resistance
TFV	tenofovir
TFV-DP	tenofovir-diphosphate
US, USA	United States, United States of America
wk	week

1. INTRODUCTION

Truvada® (FTC/TDF) is the brand name for the fixed-dose combination film-coated tablet that contains the active substances emtricitabine (FTC, Emtriva®) and tenofovir disoproxil fumarate (tenofovir DF, TDF, Viread®). Emtricitabine is a nucleoside HIV-1 reverse transcriptase inhibitor and a synthetic analog of the naturally occurring nucleoside, 2′-deoxycytidine, a pyrimidine nucleoside, which is structurally similar to lamivudine. Intracellularly, FTC is phosphorylated by cellular enzymes to form emtricitabine 5'-triphosphate (FTC-TP), the active metabolite. Emtricitabine is the active ingredient in Emtriva hard capsules and oral solution. TDF, an oral prodrug of tenofovir, is a nucleotide analog reverse transcriptase inhibitor, which rapidly converted to tenofovir (TFV) after absorption. TFV is metabolized intracellularly to the active metabolite, tenofovir diphosphate (TFV-DP). Tenofovir disoproxil (as fumarate) is the active ingredient in Viread film-coated tablets.

Truvada is commercially available in over 150 countries worldwide for the treatment of human immunodeficiency virus type 1 (HIV-1) -infected adults. Truvada received marketing approval by the United States (US) Food and Drug Administration (FDA) on 02 August 2004 for the treatment of HIV-1. Truvada was approved (centrally authorized) in the European Union (EU) on 21 February 2005, for the treatment of people with HIV (PWH) of adults over 18 years of age, in combination with other antiretroviral products.

Each Truvada tablet contains FTC and TDF at the same dosages as recommended for the individual components i.e., 200 mg of FTC, and 300 mg of TDF (equivalent to 245 mg tenofovir disoproxil). The recommended dosage of Truvada is one tablet once daily taken orally with or without food. The estimated patient-years of exposure to all TDF-containing products is more than 9 million, and the safety profiles of these products have been well characterized.

In 2011, a supplemental New Drug Application (NDA) 021752/S-030 was submitted to the FDA for use of Truvada in combination with safer sex practices for PrEP to reduce the risk of sexually acquired HIV-1 in adults at high risk. The principal data that supported the use of Truvada in this setting included a Phase 3 study, CO-US-104-0288, entitled "*Chemoprophylaxis for HIV Prevention in Men*" (also known as the Pre-exposure Prophylaxis Initiative or "iPrEx" study) and a second Phase 3 study, CO-US-104-0380, entitled "*Parallel Comparison of Tenofovir and Emtricitabine/Tenofovir Pre-Exposure Prophylaxis to Prevent HIV-1 Acquisition within HIV-1 Discordant Couples*" (also known as the "Partner's PrEP Study"). Truvada has been demonstrated to substantially reduce risk for HIV-1 acquisition among individuals with high adherence, that acquisition rate was reduced by 96% for four doses per week and 99% for daily dosing {Anderson 2012, Baeten 2012, Grant 2010}.

On 16 July 2012, FDA approved the use of Truvada in combination with safer sex practices for PrEP to reduce the risk of sexually acquired HIV-1 in adults at high risk. On 15 May 2018, FDA approved the use of Truvada in combination with safer sex practices for PrEP to reduce the risk of sexually acquired HIV-1 in at-risk adults and adolescents weighing at least 35 kg.

1.1. FDA Post Marketing Requirement (PMR) 1906-3

In connection with approval of the PrEP indication in the US, the following Post Marketing Requirement (PMR 1906-3) was agreed-upon by Gilead:

Conduct an analysis of data from ongoing and planned demonstration projects (trials) including at least 7,000 uninfected individuals taking Truvada® for a pre-exposure prophylaxis (PrEP) indication with the objective of examining the association between levels of adherence to the once-daily dosing regimen and risk of seroconversion, resistance development, and renal and skeletal adverse events. Levels of adherence should measure a gradient of adherence levels rather than the simple dichotomy of 'adherent' versus 'non-adherent' using any available data on drug levels as the measure of adherence. Seroconversion will be assessed every three months, and, upon each seroconversion, resistance testing should be performed. Assessment for renal and skeletal adverse events will be performed every three months, including evaluation of available laboratory data. Analyses will be performed by geographic region, including the United States.

The milestone dates were:

Original Protocol Submission:	11/2012
Original Study Completion:	04/2016
Original Final Report Submission:	12/2016

1.2. Changes to PMR 1906-3

On 01 March 2016 (Reference ID 3894854), FDA acknowledged a request to extend the timelines in order to obtain adherence data from more studies to have over 7,000 PrEP users. The revised milestone dates for PMR 1906-3 were:

Final Protocol Submission:	11/2012 (completed)
Study Completion:	04/2018
Final Report Submission:	04/2019

On 17 January 2019 (Reference ID 4377557), FDA acknowledged the request to extend the timeline to obtain data from additional ongoing studies. The revised milestone dates for PMR 1906-3 were:

Study Completion:	06/2020
Final Report Submission:	12/2020

On 18 November 2020, Gilead submitted a proposed revised milestone date to the FDA after the completion of adherence data collection for over 7,000 PrEP users from 21 studies. The proposed milestone timelines for PMR 1906-3 were:

Study Completion:	09/2020
Final Report Submission:	04/2021

This study is also intended to fulfill the Category 3 pharmacovigilance activity in the Truvada EU Risk Management Plan (RMP).

2. INVESTIGATIONAL PLAN

2.1. Study Objectives

The objectives of this study are as follows:

- To describe and assess the pattern of adherence of once-daily dosing regimen of Truvada for PrEP, which is measured by tenofovir-diphosphate (TFV-DP) in dried blood spot (DBS) or by TFV in plasma serum samples, in a target population of at least 7,000 individuals pooled from multiple global demonstration studies and clinical trials on PrEP.

- To evaluate the association between adherence level and the incidence of new HIV-1 infection.

- To assess the association between adherence level and the incidence of renal and skeletal adverse events, as well as with changes in renal function, measured by creatinine, and in bone mineral density (BMD), measured by dual energy X-ray absorptiometry (DEXA) scan, if enough data were provided.

- To describe resistance for individuals who developed new HIV-1 infections.

2.2. Study Design

This is an observational study of HIV-1 negative individuals who participated in demonstration projects or clinical studies and took daily Truvada for PrEP. All individuals were enrolled and followed as described in the parent PrEP demonstration project or clinical study protocol until study completion, HIV-1 infection, discontinuation due to an adverse event, lost to follow-up, or administrative censoring. The contributing studies were required to provide demographic and clinical information, PrEP adherence measurements of TFV-DP in DBS or of TFV in plasma, HIV-1 infection monitoring, follow-up information on renal or bone adverse events, and resistance testing results. Through October 2020, Gilead had collected data from 21 global PrEP demonstration projects and clinical studies for over 7,000 Truvada for PrEP users who had at least one measurement of adherence. Data from the different contributing studies were pooled for statistical analyses by Gilead.

3. STUDY POPULATION

3.1. Number of Participants and Participant Selection

The enrollment target was a minimum of 7,000 HIV-1 negative adults or adolescents (any sex/gender, including transgender) who had at least one measurement of adherence of TFV-DP in DBS or of TFV in plasma available while taking Truvada for PrEP.

3.2. Inclusion Criteria

To be eligible for study participation, an HIV-1 uninfected individual was required to satisfy the following criteria:

- Participant in a Truvada PrEP observational or clinical study.
- HIV-1 negative individual at the time of enrollment in a demonstration project or clinical study.
- Participants with at least one measurement of TFV-DP in DBS or TFV in plasma.

3.3. Exclusion Criteria

This observational study collected HIV-1 infection and resistance information along with renal or skeletal adverse events without intervention. In the pooled analysis, only available TFV-DP or TFV measurements were analyzed. Individuals with no TFV-DP or TFV measurements within 48 weeks after PrEP initiation, with HIV-1 infection tested positive before PrEP initiation date or before the first adherence measurement, and with PrEP initiation date later than PrEP end date were excluded. Adherence measurements with laboratory test date prior to the Truvada for PrEP initiation date, and with extreme values of TFV-DP in DBS over 4,000 femtomole/punch (fmol/punch) were excluded, based on communication with PPD from PPD, whose laboratory conducted all the tests for adherence of the individual studies.

4. STUDY PROCUDURES

4.1. Enrollment and Collection of Data

Individuals were consented and enrolled by the individual parent PrEP demonstration projects or the clinical studies in accordance with enrollment procedures as described in those individual study protocols. PrEP users in the demonstration projects or clinical studies were followed to collect PrEP adherence measurements, and were monitored for HIV-1 infection status, renal or bone adverse events, lost to follow-up, or administrative censoring.

For all individuals in the parent PrEP projects or studies, the following data were requested from the studies, as available, at the screening/baseline visit: participants' demographic characteristics (sex/gender, age, race/ethnicity, weight, height, and country), date of Truvada for PrEP initiation, medical history (specifically related to previous fractures or renal impairment), signs and symptoms of acute HIV-1 infection, and sexual risk for HIV-1 acquisition. Additionally, baseline HBsAg status and renal function status measured by creatinine were requested of individual projects or studies.

Follow-up visits were expected to occur on an average of every 3 months and corresponded to the parent PrEP project or clinical study visit schedule. TFV-DP in DBS concentrations in fmol/punch or TFV in plasma concentrations in ng/mL were collected at follow-up visits, at a frequency determined by the parent PrEP project or clinical study. Any protocol-defined renal adverse event or skeletal adverse event (bone fracture) reported by investigators, clinicians, or providers, as well as renal function measurements of creatinine and BMD measurements of DEXA scan, along with signs and symptoms of acute HIV-1 infection, and results of testing to confirm negative HIV-1 status, were extracted. Results of resistance analyses of were requested from the studies. Tests may include population nucleotide sequence analysis or allele-specific PCR of either plasma or peripheral blood mononuclear cells.

4.2. Criteria for Discontinuation of Follow Up

The decision to continue or discontinue Truvada belonged jointly to the individual and their investigators. Participants were followed according to the parent PrEP demonstration project or clinical study protocol.

4.3. Contributing Truvada for PrEP Studies

Gilead requested data from 21 demonstration projects or clinical trials of PrEP users from 20 countries. Data were requested for any individuals who participated in one of these demonstration projects or studies and provided measurements of adherence to PrEP. To assess the association between adherence and HIV-1 infection rates and renal/bone adverse events, each demonstration project or clinical study protocol pre-defined the frequency for clinic visits. Data collection for adverse events is described in Section 7. Contributing studies and the number of participants in each study are illustrated in Figure 4-1 and listed in Table 4-1.

A total of 10,577 PrEP users enrolled in the 21 studies, with 6,813 individuals providing at least one measurement of TFV-DP in DBS and 1,171 individuals providing at least one measurement of TFV in plasma (Figure 4-1). Of the 6,813 individuals with TFV-DP in DBS, 200 individuals were excluded due to the presence of one or more exclusion criteria shown in Section 3.3, which resulted in 6,613 (65.2% of all PrEP users) eligible individuals who comprised the DBS full analysis set (FAS). Of the 1,171 individuals with TFV in plasma, 442 individuals were excluded because they had additional valid TFV-DP measurement(s) and were included with TFV-DP adherence FAS. Of the remaining 729 individuals, 39 were excluded because the first TFV measurement was later than 48 weeks after PrEP initiation. The remaining 689 (6.5%) eligible individuals comprise the plasma FAS.

The total FAS (DBS and plasma) included 7,302 individuals who had at least one measurement of adherence from 20 countries. Median age at PrEP initiation was 30 years (minimum age 15, maximum 73, and interquartile range 24 – 38), 5,725 (78.4%) were male, 1,218 (16.7%) were female, and 350 (4.8%) were transgender. A total of 3,290 (45.1%) individuals were non-Hispanic White, 1,675 (22.9%) were Hispanic, 1,485 (20.3%) were non-Hispanic Black, and 288 (3.9%) were Asian.

Additionally, 1,116 adherence measurements from 518 individuals were excluded because the date of measurement collection was missing or was before Truvada for PrEP initiation date, and 52 TFV-DP measurements from 29 individuals were excluded because the value exceeded 4,000 fmol/punch.

Figure 4-1. Studies that Provided Information for PrEP Users

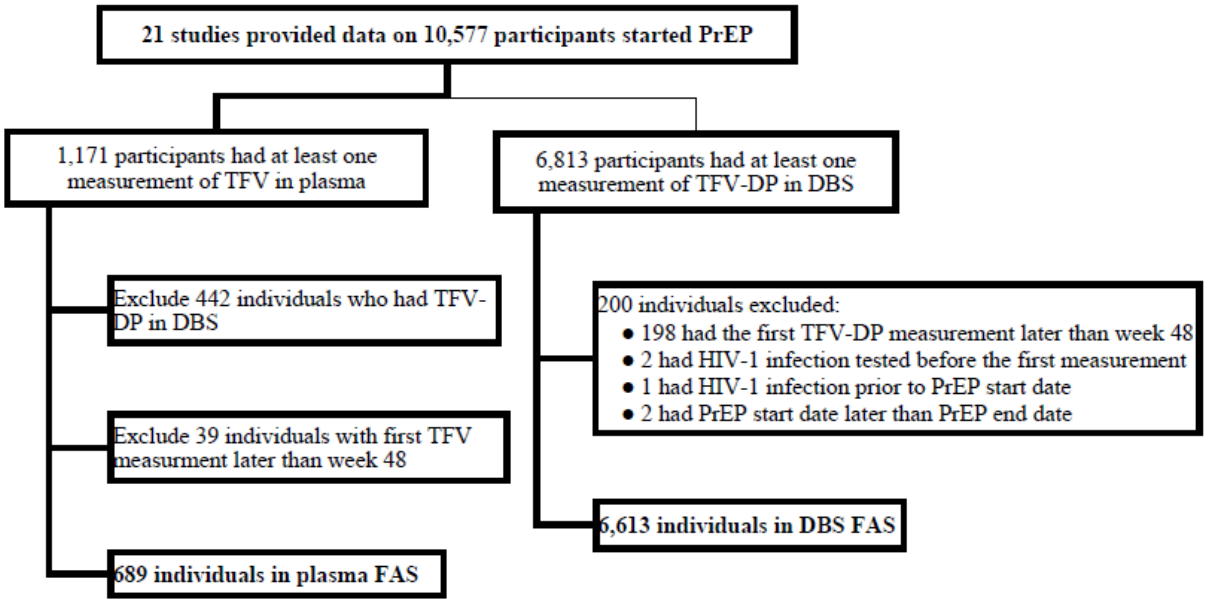


Table 4-1. Contributing Demonstration Projects and Clinical Studies

Study Number	Study Alias	Study Title	Number of Participants in the Study[1]	Number of Participants in the FAS[2]	Country[3]	Region
CO-US-164-0403	HPTN 067/ADAPT	A Phase II, Randomized, Open-Label, Pharmacokinetic and Behavioral Study of the Use of Intermittent Oral Emtricitabine/Tenofovir Disoproxil Fumarate Pre-Exposure Prophylaxis (Alternative Dosing to Augment PrEP pill-Taking ADAPT)	178	176	THA (N=60) USA (N=59) ZAF (N=59)	Africa (N=59) Asia (N=60) North America (N=59)
CO-US-164-0404	iPrEX OLE	Open label extension of Chemoprophylaxis for HIV Prevention in Men (iPrEx)	1225	1206	BRA (N=192) ECU (N=153) PER (N=562) THA (N=54) USA (N=224) ZAF (N=40)	Africa (N=40) Asia (N=54) North America (N=224) South America (N=907)
CO-US-164-0432	DAIDS PrEP Demo	Implementation of HIV pre-exposure prophylaxis (PrEP): A Demonstration Project	557	456	USA (N=557)	North America (N=557)
CO-US-164-0441	MAS of PrEP Demo (SHIPP)	Medication Adherence Sub-study (MAS) of the Sustainable Health Center Implementation PrEP Pilot Study (SHIPP Study)	1241	1038	USA (N=1241)	North America (N=1241)
CO-US-164-0450	EPIC PrEP	A Randomized Trial of Prepmate, a PrEP Adherence Intervention for young MSM in the US: Enhancing PrEP in Communities (EPIC)	121	115	USA (N=121)	North America (N=121)
CO-US-164-0452	Project PrEPare (ATN 110)	An Open Label Demonstration Project of Pre-Exposure Prophylaxis Use among YMSM in the United States; a Phase 2 study with locations in the US aimed to obtain additional data on the safety of TVD and to evaluate patterns of use, rates of adherence and patterns of sexual risk behavior among YMSM	184	176	USA (N=184)	North America (N=184)
CO-US-164-0455	PROJECT PrEPare (ATN 113)	An Open Label Demonstration Project and Phase II Safety Study of Pre-Exposure Prophylaxis use among 15- to 17-year-old Men Who Have Sex with Men in the United States	67	67	USA (N=67)	North America (N=67)
CO-US-164-0468	Partners Demonstration Project	An open-label, pilot demonstration and evaluation project of antiretroviral-based HIV-1 prevention among high-risk HIV-1 serodiscordant African couples	985	328	KEN (N=593) UGA (N=392)	Africa (N=985)
CO-US-164-0478	ALERT	A multicenter, randomized study of text messaging to improve adherence to PrEP in risky MSM (TAPIR)	398	357	USA (N=398)	North America (N=398)
CO-US-164-0480	PATH – PrEP	A Pilot Demonstration Project to Operationalize PrEP as part of Combination HIV Prevention Among MSM and Transgender Women in LA County (PATH-PrEP)	301	280	USA (N=301)	North America (N=301)
CO-US-164-0483	HPTN 073	Pre-Exposure Prophylaxis (PrEP) Initiation and Adherence among Black Men who have Sex with Men (BMSM) in Three U.S. Cities; a study to assess the initiation, acceptability, safety and feasibility of PrEP for Black MSM in three U.S. cities utilizing client-centered care coordination (C4) models	178	169	USA (N=178)	North America (N=178)

Study Number	Study Alias	Study Title	Number of Participants in the Study[1]	Number of Participants in the FAS[2]	Country[3]	Region
CO-US-164-1265	SPARK	Intervention to Enhance PrEP Uptake and Adherence in a Community-Based Setting (SPARK)	300	296	USA (N=300)	North America (N=300)
CO-US-276-0108	Brazilian PrEP	Brazilian Pre-Exposure Prophylaxis Demonstration Project	700	665	BRA (N=700)	South America (N=700)
CO-US-276-1264	3Ps (Bekker/Celum)	A Pilot Prospective Cohort Evaluation of Uptake and Adherence to PrEP in Young South African Women	200	182	ZAF (N=200)	Africa (N=200)
CO-US-276-1318	Benin PrEP/TasP	Early ART and PrEP for HIV prevention among female sex workers in Benin, West Africa	256	219	BEN (N=256)	Africa (N=256)
CO-US-276-1639	HPTN 082	Evaluation of daily oral PrEP as a primary prevention strategy for young African women: A Vanguard Study	427	412	ZAF (N=282) ZWE (N=145)	Africa (N=427)
CO-US-276-1712	AMPrEP	Biomedical Interventions for HIV Prevention in MSM in Amsterdam: a demonstration project	376	324	NLD (N=376)	Europe (N=376)
CO-US-276-1976	CRUSH Women	A Demonstration Project Examining Interest in and Uptake of HIV Pre-exposure Prophylaxis with Truvada® Among Women attending Community Health Clinics in Oakland	30	18	USA (N=30)	North America (N=30)
CO-US-276-2003	AEGIS	PrEP Adherence Enhancement Guided by iTAB and Drug Levels for Women (AEGIS)	135	118	USA (N=135)	North America (N=135)
CO-US-412-2055	DISCOVER	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	2693	678	AUT (N=42) CAN (N=162) DEU (N=183) DNK (N=104) ESP (N=195) FRA (N=14) GBR (N=265) IRL (N=38) ITA (N=21) NLD (N=40) USA (N=1629)	Europe (N=902) North America (N=1791)
IN-US-276-1262	PrEPception	PrEPception: Expanding Assisted Reproduction Options for Serodiscordant Couples	25	23	USA (N= 25)	North America (N=25)

1 Number includes all individuals with at least one non-missing PrEP start date.
2 The full analysis set (FAS) includes all individuals who had at least one measurement of TFV-DP in DBS or TFV in plasma within 48 weeks of treatment initiation. Exclusion criteria reference to Section 3.3.
3 AUT = Austria; BEN = Benin; BRA = Brazil; CAN = Canada; DEU = Germany; DNK = Denmark; ECU = Ecuador; ESP = Spain; FRA = France; GBR = Great Britain; IRL = Ireland; ITA = Italy; KEN = Kenya; NLD = Netherlands; PER = Peru; THA = Thailand; UGA = Uganda; USA = United States of America; ZAF = South Africa; ZWE = Zimbabwe.

5. ADHERENCE

5.1. Adherence Measurements

The presence of TFV-DP in red blood cells (RBCs) suggests that DBS, which contain millions of RBCs, is a suitable matrix for TFV-DP testing. TFV-DP was measured in DBS using a technique that approximately 25 µl of blood was spotted, and a 3-mm diameter disk was punched from the blood spot. Dried TFV/FTC in plasma and TFV-DP/FTC-TP in peripheral blood mononuclear cells (PBMCs) and RBCs were quantified by liquid chromatography/tandem mass spectrometry (LC-MS/MS) methods. Details for quantifying adherence were described previously {Bushman 2011, Castillo-Mancilla 2013}. Adherence concentrations were reported in fmol/punch. Plasma was collected after centrifugation of blood collections and analyzed for TFV via liquid chromatography/tandem mass spectrometry, and TFV was reported in ng/mL. TFV-DP has a 17-day half-life in RBCs that allows consistent measurement of long-term adherence to treatment, while TFV in plasma has a shorter half-life of approximately 14 hours, which does not accumulate appreciably with multiple doses, and better reflects adherence at the time of the measurement (i.e., whether a dose was recently ingested) {Castillo-Mancilla 2016, Louissaint 2013}.

Separate statistical analyses were conducted with TFV-DP in DBS and with TFV in plasma serum measurements as the primary adherence endpoint. Among all studies, 56 individuals in HPTN082 and 386 individuals in HPTN067 had both TFV-DP in DBS and TFV in plasma. Only DBS adherence was analyzed for these individuals. The remaining individuals in the FAS had adherence measurements of either DBS or plasma.

For concentrations identified as below the limit of quantification (BLQ), the measurement-specific lower limit of quantification (LLoQ) was identified if provided by the study. Otherwise, a value of 25 fmol/punch was assigned to TFV-DP measurements, and 0.31 ng/mL was assigned to TFV measurements, also based on communication with PPD from the PPD . Measurements with BLQ were assumed to have concentrations equal to the LLoQ to avoid underestimation of TFV-DP/TFV levels.

Among the 7,302 individuals in the FAS, 6,224 (85.2%) participants had more than one TFV-DP (5,771 among 6,613 in the DBS FAS) or TFV (453 among 689 in the plasma DBS) measurements during the 96 weeks of follow-up. A summary of the 19 studies that provided information on TFV-DP in DBS are shown in Table 5-1 and the 4 studies with information of TFV in plasma are shown in Table 5-2.

Table 5-1. Full Analysis Set (FAS) of Demonstration Projects and Clinical Studies with TFV-DP Measured Adherence in DBS

Study Number	Study Alias	N[1]	Gender[2]	Age Range	Adherence Measurements				New HIV-1 Infections[5]	Individuals with Adverse Events[6]
					Lab measurement date[3]	Ave. N of measurements per individual	TFV-DP Range (fmol/punch)[4]	TFV-DP Mean (fmol/punch)		
CO-US-164-0403	HPTN 067/ADAPT	56	M, T	18-58	2013-07-26-2014-11-19	3	BLQ-3032.0	477.1	0	2 FRX 12 RAE
CO-US-164-0404	iPrEX OLE	1206	M, T	19-70	2011-07-12-2013-11-22	3	2.5-3964.0	580.4	28	13 FRX 11 RAE
CO-US-164-0432	DAIDS PrEP Demo	456	M, T, O	18-66	2012-10-22-2015-01-27	3	2.5-3841.6	1139.3	2	8 FRX 9 RAE
CO-US-164-0441	MAS of PrEP Demo (SHIPP)	1038	F, M, T, O	18-69	2014-12-19-2018-04-02	3	BLQ-3997.0	1212.9	2	NA
CO-US-164-0450	EPIC PrEP	115	F, M, T, O	17-29	2015-04-29-2016-12-19	3	12.5-2903.3	1073.8	0	2 FRX
CO-US-164-0452	Project PrEPare (ATN 110)	176	M	18-23	2013-02-05-2014-08-21	5	1.3-3171.5	673.9	5	5 FRX 1 RAE
CO-US-164-0455	PROJECT PrEPare (ATN 113)	67	M	15-18	2013-08-27-2015-09-10	5	BLQ-2770.9	595.6	3	NA
CO-US-164-0478	ALERT	357	M, T	19-64	2013-05-22-2016-02-09	2	BLQ-3682.7	1216.5	2	NA
CO-US-164-0480	PATH – PrEP	280	M, T	20-69	2013-07-19-2016-05-26	4	BLQ-3961.3	1162.3	1	2 FRX 161 RAE
CO-US-164-0483	HPTN 073	169	M	19-68	2013-10-10-2015-09-22	3	BLQ-3537.0	632.3	4	2 FRX 9 RAE
CO-US-164-1265	SPARK	296	M, T	18-63	2014-04-10-2016-10-11	4	BLQ-3742.8	1255.6	0	NA
CO-US-276-0108	Brazilian PrEP	665	M, T	18-67	2014-07-01-2020-02-04	3	BLQ-3283.8	886.9	2	2 FRX 1 RAE
CO-US-276-1264	3Ps (Bekker/Celum)	182	F	16-25	2017-06-23-2018-05-08	3	17.0-3000.0	716.1	0	1 RAE
CO-US-276-1639	HERS/HPTN 082	390	F	16-25	2017-01-10-2018-10-25	3	BLQ-3032.0	318.0	4	1 FRX 187 RAE

Study Number	Study Alias	N[1]	Gender[2]	Age Range	Adherence Measurements				New HIV-1 Infections[5]	Individuals with Adverse Events[6]
					Lab measurement date[3]	Ave. N of measurements per individual	TFV-DP Range (fmol/punch)[4]	TFV-DP Mean (fmol/punch)		
CO-US-276-1712	AMPrEP	324	M, T	19-73	2016-02-29-2018-07-19	2	BLQ-3507.0	1158.0	2	2 FRX 27 RAE
CO-US-276-1976	CRUSH Women	18	F, T	22-69	2016-08-10-2017-08-21	2	BLQ-2449.0	797.7	0	NA
CO-US-276-2003	AEGIS	118	F	19-67	2016-07-08-2019-09-25	4	24.0-3341.9	852.7	0	61 RAE
CO-US-412-2055	DISCOVER	678	M, T	18-71	2016-10-04-2019-09-16	5	BLQ-3976.0	1234.0	14	11 FRX 76 RAE
IN-US-276-1262	PrEPception	23	F	21-47	2014-09-11-2016-08-04	1	106.4-1711.1	882.2	0	NA

1 The number in the FAS with at least one valid TFV-DP measurement in DBS.
2 F=Female, M=Male, O=Other or Unknown, T=Transgender.
3 Date collection date when valid TFV-DP measurements were reported.
4 BLQ = below the limit of quantitation.
5 HIV-1 infection counts limited to those reported within 0-96 weeks of treatment initiation.
6 FRX = Bone Fracture, RAE = Renal AE; Count of distinct individuals for which information on at least one bone or renal adverse events occurring within 96 weeks after treatment initiation was reported by the individual study.

Table 5-2. Full Analysis Set (FAS) of Demonstration Projects and Clinical Studies with TFV Measured Adherence in Plasma

Study Number	Study Alias	N[1]	Gender[2]	Age Range	Adherence Measurements				New HIV-1 Infection[5]	Adverse Events[6]
					Lab measurement date[3]	Ave. Number of measurements per individual	TFV Range (ng/mL)[4]	TFV Mean (ng/mL)		
CO-US-164-0403	HPTN 067/ADAPT	120	F, M, T	18-58	2011-11-24-2014-02-19	2.89	BLQ-476.0	73.9	0	15 RAE
CO-US-164-0468	Partners Demo	328	F, M	18-64	2012-11-29-2016-05-30	2.95	0.3-836.0	66.7	15	1 FRX
CO-US-276-1318	Benin PrEPTasP	219	F	18-59	2014-10-16-2016-12-30	2.64	BLQ-484.0	46.2	0	NA
CO-US-276-1639	HPTN082	22	F	18-25	2016-11-16-2018-10-18	2.23	BLQ-290.0	24.3	0	NA

1 The number in the FAS with valid TFV measurement in plasma.
2 F=Female, M=Male, T=Transgender.
3 Date where valid TFV measurements were reported.
4 BLQ = below the limit of quantitation.
5 HIV-1 infection counts limited to those reported within 0-96 weeks of treatment initiation.
6 FRX = Bone Fracture, RAE = Renal AE; Count of distinct patients for which information on at least one bone or renal adverse events occurring within 96 weeks after treatment initiation was reported by the individual study.

5.2. Weighted Average of Adherence

The TFV-DP level in DBS provides a dynamic range that characterizes levels of cumulative dosing of PrEP in the preceding 4 to 8 weeks, which presumably includes the time of exposure to HIV-1 for individuals taking PrEP who were newly infected with HIV-1. A weighted average for the adherence calculations was therefore developed for TFV-DP in order to prioritize adherence measurements collected near the time of a new HIV-1 infection. For individuals who did not acquire an HIV-1 infection, the formula was simplified to the arithmetic mean. Applying this weighting formula allows prioritization of measurements in close proximity to HIV-1 infection events but otherwise equal or approach a standard arithmetic mean in calculation. Specifically, for every 4 weeks increment away from the HIV-1 infection (i.e., $\frac{t_i}{4\ weeks}$, where t_i is the distance in weeks from the event for measurement i) measurement i's weight (w_i) was decreased by 50% (i.e., $w_i = 50\%^{\left(\frac{t_i}{4\ weeks}\right)}$), resulting in the following formula:

$$average\ adherence = \frac{\sum_{i=1}^{n}\left(x_i * 50\%^{\left(\frac{t_i}{4\ weeks}\right)}\right)}{\sum_{i=1}^{n} 50\%^{\left(\frac{t_i}{4\ weeks}\right)}}$$

where $t_1 ... t_n$ represent the time in weeks from measurement i to the HIV-1 infection for the individual's n^{th} available measurements. For those who did not acquire an HIV-1 infection event, $t_1 ... t_n = 0$, the formula simplifies to the arithmetic mean, which is reflective of the fact that all measurements over time are likely of equal importance for those individuals.

For the relatively small sample size (n = 689) in the plasma FAS of this study, a low number of new HIV-1 infection cases (n = 15) was reported. The formula simplifies to the arithmetic mean under this scenario: the weighted mean of TFV measurements in plasma for all individuals in the plasma FAS within 96 weeks is 60.6 ng/mL (standard deviation 62.6), and the arithmetic mean is 60.7 ng/mL (standard deviation 62.5). The minimal difference aligns with expectations and provides a reasonable approach for application of the weighted average for both the TFV-DP and TFV measurements.

The calculated weighted average value (a numeric value) of TFV-DP in DBS or TFV in plasma concentrations were used to estimate the dose equivalent of Truvada for PrEP in tablets/week as the group for level of adherence:

- <2 (<350 fmol/punch of TFV-DP), 2-3 (350-<700 fmol/punch), 4-6 (700-<1,250 fmol/punch), and ≥7 (≥1,250 fmol/punch) tablets per week for TFV-DP in DBS, a dose equivalence groups consistent with the categorization derived previously {Grant 2014}.

- ≤10 ng/mL, >10-≤40 ng/mL, and >40 ng/mL for TFV measured in plasma. Level of adherence groups were consistent with the categorization derived in previous studies, which suggested over 80% protective effect of >40 ng/mL for TFV {Anderson 2011, Donnell 2014}. Both 0.31 ng/mL or the 10 ng/mL threshold has been used to define detectable tenofovir in plasma in individual studies that provided data, ≤10 ng/mL was used in this study.

A sensitivity analysis was conducted to evaluate incidence rates of new HIV-1 infection by adherence level defined with the weighted average as described above, and compared to either the arithmetic mean of all TFV-DP in DBS measurements, or the most recent TFV-DP in DBS measurement before new HIV-1 infection or study end date.

5.3. Evaluation of Adherence

The distribution of participants' new HIV-1 infection status, demographic factors, and baseline characteristics of Truvada for PrEP users by adherence level are shown in Table 5-3 for TFV-DP in DBS and in Table 5-5 for TFV in plasma.

Logistic regression was conducted for the association between demographic factors and baseline characteristics of Truvada users and adherence level to obtain the odds ratio (ORs) and corresponding 95% confidence interval (CI) of adherence with ≥700 fmol/punch (versus <700 fmol/punch) as reference in DBS measurements (Table 5-4).

5.3.1. Association Between Individual Characteristics and Adherence by TFV-DP in DBS

Of 6,613 participants with adherence based on TFV-DP in DBS, 21.1%, 14.2%, 35.7%, and 29.1% took <2, 2−3, 4−6, and ≥7 tablets of Truvada for PrEP per week, respectively (Table 5-3). In the DBS FAS, the median age at PrEP initiation was 30 years (minimum 15, maximum 73, interquartile range 24 - 38), with 21.8% of the individuals age 18-23 years, and 26.1% age 24-29 years. Approximately 40% of PrEP users under age 24 had lower adherence of <2 tablets/week (wk), and individuals in higher adherence increased with age. For example, 37.5% of individuals aged 30-34 years, 45.9% of those aged 35-44, and 56.9% of individuals ≥55 years had an average adherence of daily dosing (≥7 tablets/week), compared with only 9.0% of users age 15-18 years and 12.5% of users age 18-23 years adhere with daily dosing.

A total of 5,449 (82.4%) PrEP users were male, 806 (12.2%) were female, and 349 (5.3%) were transgender. Among transgender individuals, 316 were male to female transgender, 2 were female to male, and 32 did not provide this information. Among male PrEP users, 37.9% and 33.0% had average adherence to 4−6 tables/week and ≥7 tablets/week, respectively, while the corresponding numbers in female users were 23.6% and 9.4%. A total of 2,662 (40.3%) individuals were non-Hispanic White, 1,675 (25.3%) were Hispanic, and 1,485 (22.5%) were non-Hispanic Black. Adherence levels were higher in participants enrolled in studies conducted in North America (39.3% at 4−6 tablets/week and 36.1% at ≥7 tablets/week) and Europe (37.0% at 4-6 tablets/week and 51.9% at ≥7 tablets/week) compared to participants in Africa and in Asia. Homosexual contact was reported for 4,703 (71.1%) participants, 460 (7.0%) had heterosexual contact only, and 73 (1.1%) had serodiscordant partners. Among individuals reported homosexual contact only, 19.1%, 13.2%, 37.7%, and 30.0% had average adherence of <2, 2−3, 4−6, and ≥7 tablets per week, while ~80% of individuals who had heterosexual contact only had low adherence of <4 tablets/week.

In the logistic regression (Table 5-4), older age was significantly associated with higher odds of adhering at ≥4 tablets/week, the established protective dosage of Truvada PrEP. Participants enrolled in a study in Africa, Asian, or South America were significantly less likely to adhere at ≥4 tablets/week than participants enrolled in North America, the OR and corresponding 95% CI were 0.11 (0.09, 0.14), 0.28 (0.16, 0.48), and 0.26 (0.23, 0.30), respectively, while participants enrolled in a study in Europe were more likely to adhere at higher level with OR (95% CI) of 2.59 (2.02, 3.32). Hispanic and non-Hispanic Black individuals were lower in adherence compared with non-Hispanic White PrEP users, with OR (95% CI) for adhering at ≥4 tablets/week was 0.21 (0.18, 0.24) and 0.14 (0.12, 0.16) respectively. Normal or overweight individuals at baseline were more likely to adhere than underweight individuals. Individuals who had homosexual contact or serodiscordant partners were ~8 times more likely to have higher adherence than users who had heterosexual contact only. Females or individuals who tested positive on hepatitis B immunity were less likely to adhere compared to males and those with no hepatitis B immunity. No statistically significant association was observed between adherence and a history of bone fracture or renal disease and possible signs or symptoms of acute HIV-1 infection.

Table 5-3. Level of Adherence Measured by TFV-DP in DBS in the Pooled Study

	All	<350 (<2 tablets/wk)[1]	350-<700 (2-3 tablets/wk)[1]	700-<1,250 (4-<7 tablets/wk)[1]	1,250+ (≥7 tablets/wk)[1]
All [2]	6,613	1,394 (21.1%)	937 (14.2%)	2,358 (35.7%)	1,924 (29.1%)
New HIV-1 Infection [3]					
No	6,544 (99.0%)	1,335 (20.4%)	934 (14.3%)	2,352 (35.9%)	1,923 (29.4%)
Yes	69 (1.0%)	59 (85.5%)	3 (4.3%)	6 (8.7%)	1 (1.4%)
Age at PrEP Initiation (Years)					
15-<18	145 (2.2%)	52 (35.9%)	37 (25.5%)	43 (29.7%)	13 (9.0%)
18-<24	1,443 (21.8%)	573 (39.7%)	291 (20.2%)	399 (27.7%)	180 (12.5%)
24-<30	1,726 (26.1%)	375 (21.7%)	244 (14.1%)	648 (37.5%)	459 (26.6%)
30-<35	1,050 (15.9%)	137 (13.0%)	143 (13.6%)	445 (42.4%)	325 (31.0%)
35-<45	1,269 (19.2%)	161 (12.7%)	141 (11.1%)	491 (38.7%)	476 (37.5%)
45-<55	706 (10.7%)	63 (8.9%)	60 (8.5%)	259 (36.7%)	324 (45.9%)
≥55	255 (3.9%)	24 (9.4%)	18 (7.1%)	68 (26.7%)	145 (56.9%)
Missing	19 (0.3%)	9 (47.4%)	3 (15.8%)	5 (26.3%)	2 (10.5%)
Sex					
Male	5,449 (82.4%)	909 (16.7%)	674 (12.4%)	2,067 (37.9%)	1,799 (33.0%)
Female	806 (12.2%)	352 (43.7%)	188 (23.3%)	190 (23.6%)	76 (9.4%)
Transgender	349 (5.3%)	131 (37.5%)	74 (21.2%)	99 (28.4%)	45 (12.9%)
Other/Missing	9 (0.1%)	2 (22.2%)	1 (11.1%)	2 (22.2%)	4 (44.4%)
Race/ethnicity					
Non-Hispanic White	2,662 (40.3%)	186 (7.0%)	248 (9.3%)	1,085 (40.8%)	1,143 (42.9%)
Hispanic	1,675 (25.3%)	560 (33.4%)	242 (14.4%)	506 (30.2%)	367 (21.9%)
Non-Hispanic Black	1,485 (22.5%)	540 (36.4%)	333 (22.4%)	439 (29.6%)	173 (11.6%)
Asian	228 (3.4%)	30 (13.2%)	15 (6.6%)	75 (32.9%)	108 (47.4%)
Other/Missing	563 (8.5%)	78 (13.9%)	99 (17.6%)	253 (44.9%)	133 (23.6%)
Region					
North America	3,694 (55.9%)	461 (12.5%)	447 (12.1%)	1,451 (39.3%)	1,335 (36.1%)
South America	1,556 (23.5%)	565 (36.3%)	296 (19.0%)	514 (33.0%)	181 (11.6%)
Europe	698 (10.6%)	34 (4.9%)	44 (6.3%)	258 (37.0%)	362 (51.9%)
Africa	611 (9.2%)	313 (51.2%)	142 (23.2%)	122 (20.0%)	34 (5.6%)
Asia	54 (0.8%)	21 (38.9%)	8 (14.8%)	13 (24.1%)	12 (22.2%)

	All	<350 (<2 tablets/wk)[1]	350-<700 (2-3 tablets/wk)[1]	700-<1,250 (4-<7 tablets/wk)[1]	1,250+ (≥7 tablets/wk)[1]
BMI					
Underweight (<18.5)	93 (1.4%)	34 (36.6%)	17 (18.3%)	22 (23.7%)	20 (21.5%)
Normal (18.5-<25)	1,778 (26.9%)	501 (28.2%)	258 (14.5%)	570 (32.1%)	449 (25.3%)
Overweight (≥25)	1,785 (27.0%)	476 (26.7%)	310 (17.4%)	613 (34.3%)	386 (21.6%)
Other/Missing	2,957 (44.7%)	383 (13.0%)	352 (11.9%)	1,153 (39.0%)	1,069 (36.2%)
HIV Infection Risk					
Homosexual	4,703 (71.1%)	896 (19.1%)	622 (13.2%)	1,772 (37.7%)	1,413 (30.0%)
Heterosexual	460 (7.0%)	288 (62.6%)	83 (18.0%)	68 (14.8%)	21 (4.6%)
Serodiscordant partners	73 (1.1%)	10 (13.7%)	16 (21.9%)	30 (41.1%)	17 (23.3%)
Both homosexual and heterosexual contact	31 (0.5%)	6 (19.4%)	7 (22.6%)	11 (35.5%)	7 (22.6%)
Other/Missing	1,346 (20.4%)	194 (14.4%)	209 (15.5%)	477 (35.4%)	466 (34.6%)
Clinical Characteristics before Initiating PrEP					
History of Bone Fracture					
No	6,431 (97.2%)	1,350 (21.0%)	909 (14.1%)	2,299 (35.7%)	1,873 (29.1%)
Yes	182 (2.8%)	44 (24.2%)	28 (15.4%)	59 (32.4%)	51 (28.0%)
History of Renal Disease					
No	6,596 (99.7%)	1,393 (21.1%)	933 (14.1%)	2,350 (35.6%)	1,920 (29.1%)
Yes	17 (0.3%)	1 (5.9%)	4 (23.5%)	8 (47.1%)	4 (23.5%)
Possible Signs or Symptoms of Acute HIV Infection					
No	6,405 (96.9%)	1,360 (21.2%)	901 (14.1%)	2,287 (35.7%)	1,857 (29.0%)
Yes	208 (3.1%)	34 (16.3%)	36 (17.3%)	71 (34.1%)	67 (32.2%)
Hepatitis B Infected					
Negative	4,465 (67.5%)	995 (22.3%)	702 (15.7%)	1,645 (36.8%)	1,123 (25.2%)
Positive	15 (0.2%)	3 (20.0%)	3 (20.0%)	6 (40.0%)	3 (20.0%)
Not Collected/Missing	2,133 (32.3%)	396 (18.6%)	232 (10.9%)	707 (33.1%)	798 (37.4%)
Hepatitis B Immunity					
Negative	1,937 (29.3%)	646 (33.4%)	324 (16.7%)	598 (30.9%)	369 (19.1%)
Positive	1,083 (16.4%)	197 (18.2%)	166 (15.3%)	446 (41.2%)	274 (25.3%)
Not Collected/Missing	3,593 (54.3%)	551 (15.3%)	447 (12.4%)	1,314 (36.6%)	1,281 (35.7%)

1 Adherence calculations and categorization included valid TFV-DP measurements taken up to 96 weeks after treatment initiation; wk = week.
2 Percentages in the 'All' column are column percentages. All other percentages displayed are row percentages.
3 HIV-1 infection counts limited to those reported within 0-96 weeks of treatment initiation.

Table 5-4. Odds Ratio (OR) and 95% Confidence Interval (CI) for Adherence of 700+ fmol/punch vs. <700 fmol/punch (reference) in DBS

	<700 fmol/punch (n)	700+ fmol/punch (n)	OR (95% CI)
Age at PrEP Initiation (Year)			
15-<18	89	56	Reference
18-<24	869	579	1.07 (0.75, 1.51)
24-<30	620	1,107	2.84 (2.01, 4.03)
30-<35	280	770	4.37 (3.05, 6.27)
35-<45	302	967	5.09 (3.56, 7.28)
45-<55	123	583	7.53 (5.12, 11.09)
≥55	42	213	8.06 (5.04, 12.90)
Sex			
Male	1,583	3,866	Reference
Female	546	266	0.20 (0.17, 0.24)
Transgender	205	144	0.29 (0.23, 0.36)
Race/ethnicity			
Non-Hispanic White	434	2,228	Reference
Asian	45	183	0.79 (0.56, 1.12)
Hispanic	802	873	0.21 (0.18, 0.24)
Non-Hispanic Black	879	612	0.14 (0.12, 0.16)
Region			
North America	908	2,786	Reference
Africa	461	156	0.11 (0.09, 0.14)
Asia	29	25	0.28 (0.16, 0.48)
Europe	78	620	2.59 (2.02, 3.32)
South America	861	695	0.26 (0.23, 0.30)
HIV-1 Infection Risk			
Heterosexual	377	89	Reference
Both homosexual contact and heterosexual contact	13	18	5.77 (2.73, 12.22)
Homosexual	1,518	3,185	8.75 (6.89, 11.11)
Serodiscordant partners unidentified sexual contact	26	47	7.54 (4.43, 12.83)
History of Bone Fracture			
No	2,265	4,172	Reference
Yes	72	110	0.83 (0.61, 1.12)
History of Renal Disease			
No	2,332	4,270	Reference
Yes	5	12	1.31 (0.46, 3.72)
Signs or Symptoms of Acute HIV Infection at Baseline			
No	2,267	4,144	Reference
Yes	70	138	1.07 (0.80, 1.44)

5.3.2. Association Between Individual Characteristics and Adherence by Plasma Measurements

Among 689 PrEP users who had TFV measurements in plasma only (Table 5-5), the median age at PrEP initiation was 30 years (minimum 18, maximum 64, interquartile range 25 - 27), 91.9% were from studies in Africa, 59.8% were female, and 29.0% had serodiscordant partners. Most participants (56.3%) had an average adherence of ≥40 ng/ml, while 15.1%, 11.8, and 16.8% had average adherence ≤0.31 ng/mL, >0.31-<10 ng/mL, and 10-<40 ng/mL, respectively.

Table 5-5. Level of Adherence Measured by TFV in Plasma in the Pooled Study

	All	≤0.31 ng/mL [1]	>0.31-<10 ng/mL [1]	10-<40 ng/mL[1]	≥40 ng/mL[1]
All [2]	689	104 (15.1%)	81 (11.8%)	116 (16.8%)	388 (56.3%)
New HIV-1 Infection [3]					
No	674 (97.8%)	103 (15.3%)	75 (11.1%)	115 (17.1%)	381 (56.5%)
Yes	15 (2.2%)	1 (6.7%)	6 (40.0%)	1 (6.7%)	7 (46.7%)
Age at PrEP Initiation (Years)					
18-<24	145 (21.0%)	37 (25.5%)	18 (12.4%)	22 (15.2%)	68 (46.9%)
24-<30	188 (27.3%)	29 (15.4%)	22 (11.7%)	31 (16.5%)	106 (56.4%)
30-<35	138 (20.0%)	16 (11.6%)	19 (13.8%)	23 (16.7%)	80 (58.0%)
35-<45	154 (22.4%)	15 (9.7%)	16 (10.4%)	31 (20.1%)	92 (59.7%)
45-<55	59 (8.6%)	7 (11.9%)	6 (10.2%)	9 (15.3%)	37 (62.7%)
≥55	5 (0.7%)	0	0	0	5 (100.0%)
Sex					
Male	276 (40.1%)	25 (9.1%)	25 (9.1%)	38 (13.8%)	188 (68.1%)
Female	412 (59.8%)	79 (19.2%)	56 (13.6%)	77 (18.7%)	200 (48.5%)
Transgender	1 (0.1%)	0	0	1 (100.0%)	0
Race/ethnicity					
Non-Hispanic Black	628 (91.1%)	103 (16.4%)	76 (12.1%)	101 (16.1%)	348 (55.4%)
Asian	60 (8.7%)	1 (1.7%)	5 (8.3%)	15 (25.0%)	39 (65.0%)
Other/Missing	1 (0.1%)	0	0	0	1 (100.0%)
Region					
Africa	628 (91.1%)	102 (16.2%)	76 (12.1%)	101 (16.1%)	349 (55.6%)
Asia	60 (8.7%)	1 (1.7%)	5 (8.3%)	15 (25.0%)	39 (65.0%)
North America	1 (0.1%)	1 (100.0%)	0	0	0
BMI					
Underweight (<18.5)	23 (3.3%)	7 (30.4%)	1 (4.3%)	1 (4.3%)	14 (60.9%)
Normal (18.5-<25)	299 (43.4%)	41 (13.7%)	32 (10.7%)	43 (14.4%)	183 (61.2%)

	All	≤0.31 ng/mL [1]	>0.31-<10 ng/mL [1]	10-<40 ng/mL[1]	≥40 ng/mL[1]
Overweight (≥25)	243 (35.3%)	52 (21.4%)	32 (13.2%)	43 (17.7%)	116 (47.7%)
Other/Missing	124 (18.0%)	4 (3.2%)	16 (12.9%)	29 (23.4%)	75 (60.5%)
HIV-1 Infection Risk					
Serodiscordant partners	328 (29.0%)	38 (11.6%)	28 (8.5%)	39 (11.9%)	223 (68.0%)
Heterosexual	241 (35.0%)	63 (26.1%)	37 (15.4%)	49 (20.3%)	92 (38.2%)
Other/Missing	120 (17.4%)	3 (2.5%)	16 (13.3%)	28 (23.3%)	73 (60.8%)
Clinical Characteristics before Initiating PrEP					
History of Bone Fracture					
No	685 (99.4%)	104 (15.2%)	81 (11.8%)	116 (16.9%)	384 (56.1%)
Yes	4 (0.6%)	0	0	0	4 (100.0%)
History of Renal Disease					
No	689 (100.0%)	104 (15.1%)	81 (11.8%)	116 (16.8%)	388 (56.3%)
Yes	0	0	0	0	0
Possible Signs or Symptoms of Acute HIV Infection					
No	654 (94.9%)	103 (15.7%)	75 (11.5%)	111 (17.0%)	365 (55.8%)
Yes	35 (5.1%)	1 (2.9%)	6 (17.1%)	5 (14.3%)	23 (65.7%)
Hepatitis B Infected					
Negative	667 (96.8%)	92 (13.8%)	79 (11.8%)	114 (17.1%)	382 (57.3%)
Positive	0	0	0	0	0
Not Collected/Missing	22 (3.2%)	12 (54.5%)	2 (9.1%)	2 (9.1%)	6 (27.3%)
Hepatitis B Immunity					
Negative	332 (48.2%)	53 (16.0%)	51 (15.4%)	74 (22.3%)	154 (46.4%)
Positive	7 (1.0%)	1 (14.3%)	0	1 (14.3%)	5 (71.4%)
Not Collected/Missing	350 (50.8%)	50 (14.3%)	30 (8.6%)	41 (11.7%)	229 (65.4%)

1 Adherence calculations and categorization included valid TFV measurements taken up to 96 weeks after treatment initiation.
2 Percentages in the 'All' column are column percentages. All other percentages displayed are row percentages.
3 HIV-1 infection counts limited to those reported within 0-96 weeks of treatment initiation.

5.3.3. Adherence Over Time

The pattern of adherence of individuals in the pooled study during follow up from 0-96 weeks is shown in Figure 5-1:

A) the proportion of PrEP users by adherence level measured in TFV-DP in DBS;

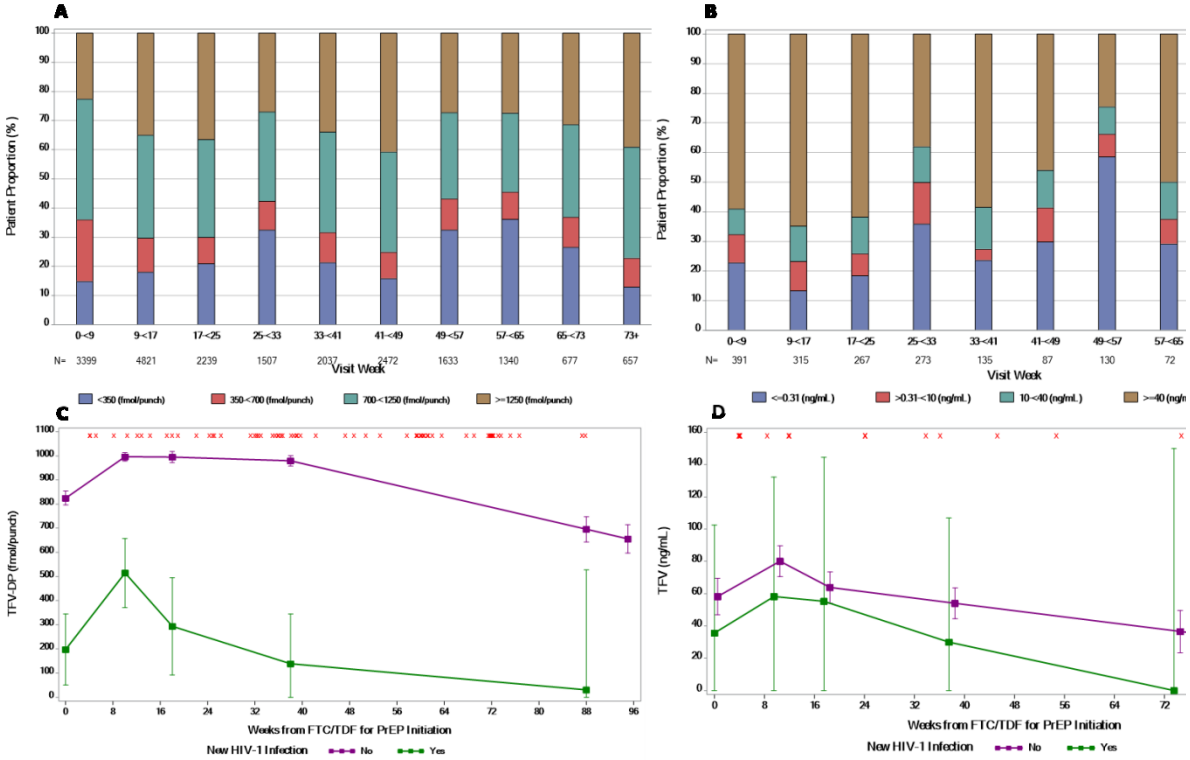
B) the proportion of PrEP users by adherence level measured in TFV in plasma;

C) the least-squares means of concentration of TFV-DP in DBS by visit week for PrEP users who had and who had no HIV-1 infections;

D) the least-squares means of concentration of TFV in plasma by visit week for PrEP users who had and who had no HIV-1 infections.

The proportion of users by adherence level was consistent during the course of study follow up measured by TFV-DP in DBS, and slightly decreased in those with a high adherence level after 48 weeks when measured by TFV in plasma (Figure 5-1A and Figure 5-1B). The least-squares means and the corresponding CI were obtained from piecewise linear (spline) mixed modeling HIV-1 infection status, visit time, and HIV-1 infection status and time interaction as predictors with by-subject time included as a random effect. Figure 5-1C shows that adherence based on TFV-DP measured in DBS was higher among users who had no new HIV-1 infections than users who tested positive for a new HIV-1 infection. TFV-DP in DBS decreased slightly after week 40 for individuals who had no new infections, while TFV-DP in DBS decreased at a higher rate after week 8 for those who had new HIV-1 infections. The least-squares means of TFV in plasma were not significantly different between users who had or did not have a new HIV-1 infection as indicated by the overlapping CI shown in Figure 5-1D.

Figure 5-1. Adherence Level of PrEP Users in the Pooled Study by Time of Follow up



Note: for Figure C and D, 'x' on the Figure represents visit week when a new HIV-1 infection was detected. Fit lines shown on the Figure for those with HIV-1 infection was plotted only until the visit week of last infection occurrence around 88 weeks

6. ASSOCIATION BETWEEN ADHERENCE AND NEW HIV-1 INFECTION RATE

A total of 89 of the 7,302 individuals in the FAS acquired HIV-1 infection after PrEP initiation. Multiple projects or clinical studies either had missing end of study dates or did not provide quality or reliable data for study specific treatment end information. As a conservative strategy, the date used for the calculation of the end of person-time was defined as date of HIV-1 infection, last TFV-DP or TFV measurement, or the study cut-off of 96 weeks, whichever occurred first. Person-time for individuals with new HIV-1 infections was calculated as (HIV-1 infection date – PrEP initiation date + 1)/365.25. For individuals who did not acquired an HIV-1 infection during the study, person-time was calculated as (last adherence measurement date within 96 weeks after Truvada for PrEP initiation – Truvada for PrEP initiation date + 1)/365.25. Person-time at risk was included in the Poisson regression model as an offset.

To compare the impact of the last adherence measurement date for person-time calculation on the findings for new HIV-1 infection rate, a sensitivity analysis was conducted using the last documented visit date, known treatment end date, or HIV-1 infection date of the individual, whichever occurred first, as the end date for person-time.

6.1. Incidence Rates of HIV-1 Infections by Adherence Measured in DBS

Sixty-nine of 6,613 individuals in the DBS FAS were diagnosed with an HIV-1infection, with a median PrEP exposure of 0.82 years and an incidence rate (IR) =1.163 per 100 person-years exposure (95% CI 0.919, 1.473; Table 6-1). Among all individuals who had new HIV-1 infections, 59 (85.5%), 3 (4.3%), 6 (8.7%), and 1 (1.4%) had an average adherence of <2, 2−3, 4−6, and ≥7 Truvada tablets/week, respectively, the IRs (95% CI) of a new infection were 5.199 (4.028, 6.710), 0.380 (0.123, 1.179), 0.276 (0.124, 0.614), and 0.055 (0.008, 0.387) per 100 person-years for individuals who took <2, 2−3, 4−6, and ≥7 Truvada tablets/week, respectively.

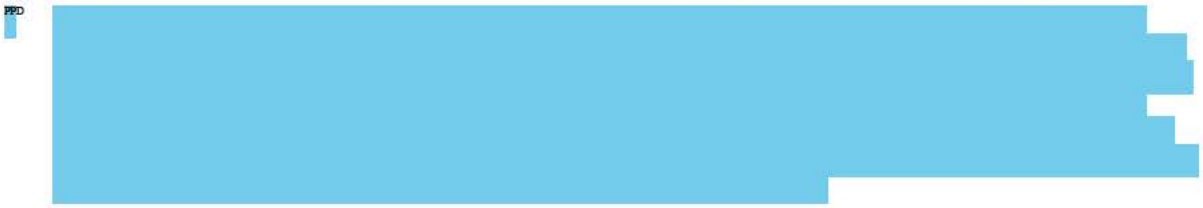
Among 5,449 male participants, the overall IR (95% CI) of HIV-1 infection was 1.249 (0.976, 1.599) per 100 patient-years, and were 7.362 (5.639, 9.612), 0.329 (0.082, 1.315), 0.305 (0.137, 0.680), and 0.058 (0.008, 0.408) per 100 person-years for individuals who took <2, 2−3, 4−6, and ≥7 Truvada for PrEP tablets/week, respectively. Four of 806 female participants had new HIV-1 infections with an IR (95% CI) of 0.710 (0.266, 1.891), of which 3 (75%) had adherence of <2 tablets/week and 1 (25%) had 2-3 tables/week. Two of 349 transgender participants had new HIV-1 infections, IR (95% CI) of 0.633 (0.158, 2.531), both had low adherence level (<2 tablets/week). As adherence increased with age, the IRs (95% CI) of a new HIV-1 infection were 4.830 (1.813, 12.870), 1.522 (1.174, 1.974), and 0.383 (0.192, 0.767) per 100 person-years for participants aged 15-<18, 18-<35, and ≥35 years at PrEP initiation, respectively. Three of 698 European participants had new HIV-1 infections, with an overall IR (95% CI) of 0.424 (0.137, 1.316) per 100 person-years.

The incidence rate ratios (IRR) and corresponding 95% CI comparing IRs for individuals with <2 and 2−3 tablets/week versus those adhere to ≥4 tablets/week Truvada for PrEP tablets/week as reference were 29.763 (13.596, 65.156) and 2.177 (0.563, 8.420), respectively (data not shown on table).

Table 6-1. Incidence Rates (95% Confidence Intervals) for New HIV-1 Infection by Adherence Level Measured by TFV-DP Concentrations in DBS in the Pooled Study, Followed up to 96 Weeks after PrEP Initiation

	HIV-1 infected		Non-HIV-1 infected		Incidence rate per 100 person-year (95% CI)
	N (Column %)	Mean person-year	N (Column %)	Mean person-year	
All (N=6,613)	69	0.82	6,544	0.90	1.163 (0.919, 1.473)
<350 (<2 tablets/wk)	59 (85.5%)	0.88	1,335 (20.4%)	0.81	5.199 (4.028, 6.710)
350-<700 (2-3 tablets/wk)	3 (4.3%)	0.75	934 (14.3%)	0.84	0.380 (0.123, 1.179)
700-<1,250 (4-6 tablets/wk)	6 (8.7%)	0.32	2,352 (35.9%)	0.92	0.276 (0.124, 0.614)
≥1,250 (≥7 tablets/wk)	1 (1.4%)	0.67	1,923 (29.4%)	0.95	0.055 (0.008, 0.387)
Male (N=5,449)	63	0.83	5,386	0.93	1.249 (0.976, 1.599)
<350 (<2 tablets/wk)	54 (85.7%)	0.88	855 (15.9%)	0.80	7.362 (5.639, 9.612)
350-<700 (2-3 tablets/wk)	2 (3.2%)	0.91	672 (12.5%)	0.90	0.329 (0.082, 1.315)
700-<1,250 (4-6 tablets/wk)	6 (9.5%)	0.32	2,061 (38.3%)	0.95	0.305 (0.137, 0.680)
≥1,250 (≥7 tablets/wk)	1 (1.6%)	0.67	1,798 (33.4%)	0.97	0.058 (0.008, 0.408)
Female (N=806)	4	0.53	802	0.70	0.710 (0.266, 1.891)
<350 (<2 tablets/wk)	3 (75.0%)	0.56	349 (43.5%)	0.82	1.043 (0.336, 3.234)
350-<700 (2-3 tablets/wk)	1 (25.0%)	0.42	187 (23.3%)	0.59	0.901 (0.127, 6.399)
700-<1,250 (4-6 tablets/wk)	0	NA	190 (23.7%)	0.61	NA
≥1,250 (≥7 tablets/wk)	0	NA	76 (9.5%)	0.65	NA
Transgender (N=349)	2	1.26	347	0.90	0.633 (0.158, 2.531)
<350 (<2 tablets/wk)	2	1.26	129 (37.2%)	0.85	1.782 (0.446, 7.125)
350-<700 (2-3 tablets/wk)	0	NA	74 (21.3%)	0.94	NA
700-<1,250 (4-6 tablets/wk)	0	NA	99 (28.5%)	0.94	NA
≥1,250 (≥7 tablets/wk)	0	NA	45 (13%)	0.92	NA
Age at PrEP Initiation 15-<18 years (N=145)	4	0.80	141	0.56	4.830 (1.813, 12.870)
<350 (<2 tablets/wk)	4	0.80	48 (34%)	0.71	10.754 (4.036, 28.652)
350-<700 (2-3 tablets/wk)	0	NA	37 (26.2%)	0.55	NA
700-<1,250 (4-6 tablets/wk)	0	NA	43 (30.5%)	0.48	NA
≥1,250 (≥7 tablets/wk)	0	NA	13 (9.2%)	0.34	NA

	HIV-1 infected		Non-HIV-1 infected		Incidence rate per 100 person-year (95% CI)
	N (Column %)	Mean person-year	N (Column %)	Mean person-year	
Age at PrEP Initiation 18-<35 years (N=4,219)	57	0.81	4,162	0.89	1.522 (1.174, 1.974)
<350 (<2 tablets/wk)	48 (84.2%)	0.88	1,037 (24.9%)	0.83	5.289 (3.986, 7.018)
350-<700 (2-3 tablets/wk)	3 (5.3%)	0.75	675 (16.2%)	0.84	0.527 (0.170, 1.634)
700-<1,250 (4-6 tablets/wk)	6 (10.5%)	0.32	1,486 (35.7%)	0.91	0.442 (0.199, 0.984)
≥1,250 (≥7 tablets/wk)	0	NA	964 (23.2%)	0.94	NA
Age at PrEP Initiation ≥35 years (N=2,230)	8	0.88	2,222	0.94	0.383 (0.192, 0.767)
<350 (<2 tablets/wk)	7 (87.5%)	0.91	241 (10.8%)	0.73	3.840 (1.831, 8.054)
350-<700 (2-3 tablets/wk)	0	NA	219 (9.9%)	0.90	NA
700-<1,250 (4-6 tablets/wk)	0	NA	818 (36.8%)	0.97	NA
≥1,250 (≥7 tablets/wk)	1 (12.5%)	0.67	944 (42.5%)	0.97	0.109 (0.015, 0.776)
Europe (N=698)	3	0.44	695	1.02	0.424 (0.137, 1.316)
<350 (<2 tablets/wk)	2 (66.7%)	0.33	32 (4.6%)	0.90	6.808 (1.703, 27.221)
350-<700 (2-3 tablets/wk)	0	NA	44 (6.3%)	0.98	NA
700-<1,250 (4-6 tablets/wk)	0	NA	258 (37.1%)	1.05	NA
≥1,250 (≥7 tablets/wk)	1 (33.3%)	0.67	361 (51.9%)	1.00	0.276 (0.039, 1.958)



6.2. Incidence Rates of HIV-1 Infections by Adherence Measured in Plasma

Table 6-2 shows the incidence of HIV-1 infection by adherence measured with TFV in plasma. Person-time for individuals with new HIV-1 infections was calculated as (HIV-1 infection date – PrEP initiation date + 1)/365.25. For individuals who had no new HIV-1 infection, person-time was calculated as (last measurement date of TFV in plasma within 96 weeks after Truvada for PrEP initiation – Truvada for PrEP initiation date + 1)/365.25.

Fifteen of 689 individuals with available adherence measurements of TFV in plasma tested HIV-1 positive, with an IR = 3.088 per 100 person-years exposure (95% CI 1.862, 5.123). Among all individuals who had new HIV-1 infections, 7 (1.0%), 1 (0.1%), and 7 (1.0%) had an average TFV of <10 ng/ml, 10-<40 ng/ml, and ≥40 ng/ml. The IRs (95% CI) of HIV-1 infection were 5.443 (2.595, 11.417), 1.039 (0.146, 7.374), and 2.684 (1.279, 5.629) per 100 person-years, for <10 ng/ml, 10-<40 ng/ml, and ≥40 ng/ml, respectively.

Table 6-2. Incidence Rates (95% Confidence Intervals) for New HIV-1 Infection by Adherence Level Measured by TFV Concentrations in Plasma in the Pooled Study, Followed up to 96 and 48 Weeks after PrEP Initiation

	HIV-1 infected		Non-HIV-1 infected		
	N (Column %)	Mean person-year	N (Column %)	Mean person-year	Incidence rate per 100 person-year (95% CI)
96 Weeks Follow Up (N=689)	15	0.46	674	0.71	3.088 (1.862, 5.123)
<10 ng/ml	7 (46.7%)	0.58	178 (26.4%)	0.70	5.443 (2.595, 11.417)
10-<40 ng/ml	1 (6.7%)	1.43	115 (17.1%)	0.82	1.039 (0.146, 7.374)
≥40 ng/ml	7 (46.7%) [1]	0.21	381 (56.5%)	0.68	2.684 (1.279, 5.629)

1 All 7 individuals who had high level of adherence tested with TFV in plasma were from Partner's Demonstration Project, 6 of the individuals had only one measurement of TFV which was the visit that HIV-1 infection was reported, and the TFV measurement was over the protective threshold of 40 ng/mL. The other individual measured BLQ for TFV in month 1, 3, and measured 54.5 ng/mL on the visit that HIV-1 infection was reported.

6.3. Sensitivity Analyses

Two sensitivity analyses examined the incidence rates of new HIV-1 infection by adherence level were conducted using:

1) the weighted average of adherence compared with the arithmetic means and the last measurement to define the level of adherence (Appendix Table 1);

2) the last date of measurement compared with the last date of visit in the calculation of person-time (Appendix Table 2).

Slight differences in IRs were detected, although IRs in both sensitivity analyses were generally lower than the reported IR findings. For example, the IR (95% CI) of new HIV-1 infection was 4.359 (3.294, 5.767) for the <2 tablets/week group using the arithmetic means and 3.581 (2.780, 4.611) using the most recent DBS measurement, compared with 5.199 (4.028, 6.710) based on the weighted average method. Similarly, when the analysis was limited to the 5,466 participants who had the last visit date within 96 weeks of follow up, the IR (95% CI) calculated using the last visit date was 0.867 (0.685, 1.097), compared with the IR using the last DBS measurement date that was 1.407 (1.111, 1.781). Findings from the two sensitivity analyses suggested that the reported IRs for evaluating the association between adherence to Truvada for PrEP and HIV-1 infection rates were conservative and underestimated the protective effect of Truvada.

Fourteen of the 21 study (which included 3,374 out of 7,302 individuals) had protocol defined follow-up to 1 year or study end after 48-week visit. A sensitivity analysis on HIV-1 infection rate limiting adherence measurements and new HIV-1 infections to within 48 weeks after Truvada initiation was conducted (Appendix Table 3). In the DBS FAS, 35 new HIV-1 infections, with a median Truvada exposure of 0.45 years, were identified within 48 weeks after PrEP initiation (IR [95% CI] = 1.020 [0.733, 1.421]), and the IRs (95% CI) of HIV-1 infection were 4.641 (3.204, 6.722), 0.235 (0.033, 1.671), 0.390 (0.162, 0.938), and 0.089 (0.013, 0.633) per 100 person-years for participants who took <2, 2−3, 4−6, and ≥7 Truvada tablets/week, respectively. In the plasma FAS within 48 weeks of follow up, 13 new HIV-1 infections were identified with an IR (95% CI) of 4.167 (2.420, 7.177).

7. ASSOCIATION BETWEEN ADHERENCE AND RENAL AND BONE SAFETY

Fifteen demonstration projects or clinical studies provided information on provider-reported renal or bone adverse events (AEs) or creatinine lab measurements. Sub-cohorts of the renal adverse events analysis included all participants in the FAS for studies where AE information was received within 96 weeks after initiation of Truvada for PrEP. Participants were counted only once regardless of multiple reported AEs.

For the statistical analysis of the incidence rates for renal or bone AEs, person-time at risk was defined as (date of first renal or bone AE – Truvada for PrEP initiation date + 1)/365.25 for those with a renal or bone AE, and [(date of new HIV-1 infection, last TFV-DP or TFV measurement within the FAS, whichever occurred first – Truvada for PrEP initiation date + 1)/365.25] for those without a renal or bone AE. Person-time at risk was included in the Poisson regression model as an offset.

7.1. Renal Adverse Events

A total of 5,169 and 5,890 participants in the FAS had available information on reported renal AE or creatinine measurements, respectively. Demographic characteristics, history of renal disease, and adherence level in the 2 sub-cohorts by reported renal AE and by laboratory measured creatinine ever exceeding 1.3 mg/dL as a threshold are shown in Table 7-1.

A total of 571 (11.0%) participants were reported by the individual study to have one or more renal AE. Mean age at the reported renal AE was 31.5 years (minimum 16.5 years and maximum 71.0 years), and mean age at reported renal AE by adherence level was 23.0, 26.5, 33.9, and 41.3, respectively, for individuals who took <2, 2−3, 4−6, and ≥7 Truvada for PrEP tablets/week.

Additionally, among the 5,890 participants who had at least one laboratory measurement of creatinine during follow up visits, 421 (7.1%) individuals had ever been tested creatinine over 1.3 mg/dL (a total of 807 creatinine elevated test events) within 96 weeks after initiation of Truvada for PrEP, for whom 153 (36.3% of the 421 individuals) had sustainable elevation with more than one creatinine tests over 1.3 mg/dL.

Older participants were more likely to have elevated creatinine events, with ~13% of those aged 45 years or older compared to <6% in individuals under age 24. Non-Hispanic Black individuals had higher reported renal AE (18.2% compared to 11.0% in non-Hispanic White individuals), but AE detected on creatinine measurements over 1.3 mg/dL was higher for non-Hispanic White (9.6%) than non-Hispanic Black participants (7.8%). A total of 17 participants had prior history of renal disease prior to the initiation of PrEP, and they were more likely to develop renal AE or have elevated creatinine levels after PrEP initiation. Events of creatinine over 1.3 mg/dL occurred more frequently with increased adherence levels. Elevated creatinine levels over 1.3 mg/dL were reported for 1.9%, 5.6%, 7.2%, and 10.4% of participants who took an average of <2, 2-3, 4-6, and ≥7 tablets per week, respectively.

Table 7-1. Provider-Reported and Lab-Monitored Renal Adverse Events in the Sub-Cohort where Renal AE Data is Available within 96 Weeks of Follow Up

	Provider-Reported Renal AE			Creatinine over 1.3 mg/dl		
	Total N in Cohort	N (% of total in cohort)	Events	Total N in Cohort	N (% of total in cohort)	Events
All	5,169	571 (11.0%)	796	5,890	421 (7.1%)	807
Age at PrEP initiation (years)						
15-<18	82	13 (15.9%)	14	89	1 (1.1%)	1
18-<24	1,289	176 (13.7%)	213	1,251	27 (2.2%)	30
24-<30	1,245	99 (8%)	130	1,487	86 (5.8%)	160
30-<35	812	68 (8.4%)	97	998	82 (8.2%)	161
35-<45	997	109 (10.9%)	175	1,202	107 (8.9%)	186
45-<55	535	75 (14%)	119	634	86 (13.6%)	183
≥55	192	29 (15.1%)	46	212	28 (13.2%)	78
Other/Missing	17	2 (11.8%)	2	17	4 (23.5%)	8
Sex						
Male	3,977	308 (7.7%)	430	4,743	351 (7.4%)	712
Female	882	263 (29.8%)	366	890	66 (7.4%)	91
Transgender	308	0	0	252	4 (1.6%)	4
Other/Missing	2	0	0	5	0	0
Race/ethnicity						
Non-Hispanic White	1,829	202 (11%)	303	2,167	207 (9.6%)	433
Non-Hispanic Black	1,429	260 (18.2%)	335	1,527	119 (7.8%)	200
Hispanic	1,264	75 (5.9%)	100	1,483	54 (3.6%)	115
Asian	207	8 (3.9%)	13	235	10 (4.3%)	10
Other/Missing	440	26 (5.9%)	45	478	31 (6.5%)	49
History of Renal Disease						
No	5,152	564 (10.9%)	782	5,873	411 (7.0%)	763
Yes	17	7 (41.2%)	14	17	10 (58.8%)	44
TFV-DP concentration in DBS						
<350 (<2 tablets/wk)	1,235	165 (13.4%)	208	1,213	23 (1.9%)	37
350-<700 (2-3 tablets/wk)	738	68 (9.2%)	90	728	41 (5.6%)	83
700-<1,250 (4-6 tablets/wk)	1,577	173 (11%)	257	1,855	133 (7.2%)	253
≥1,250 (≥7 tablets/wk)	1,149	150 (13.1%)	224	1,445	151 (10.4%)	330
TFV concentration in Plasma	470	15 (3.2%)	17	649	73 (11.2%)	104
≤0.31 ng/ml	53	1 (1.9%)	1	92	9 (9.8%)	14
>0.31 - <10 ng/ml	46	2 (4.3%)	2	73	9 (12.3%)	12
10-<40 ng/ml	69	4 (5.8%)	3	113	20 (17.7%)	24
≥40 ng/ml	302	8 (2.6%)	10	371	35 (9.4%)	54

7.2. Incidence Rates of Renal Adverse Events Provided in the Pooled Study

The IRs and IRRs for provider-reported renal AEs by adherence level are shown in Table 7-2. A total of 4,699 (71.1%) participants in the DBS FAS had available renal AE information, with renal AE reported in 556 (11.8%) participants. Of 470 (68.2%) participants in the plasma FAS and had available renal AE information, renal AE was reported in 15 (3.2%) participants.

The overall renal AE IR (95% CI) in all 5,169 individuals with available renal data was 13.595 (12.524, 14.757) per 100 person-years [14.203 (13.070, 15.434) among the 4,699 participants with DBS adherence, and 5.256 (3.169, 8.718) for the 470 participants with plasma adherence]. The IR (95% CI) by adherence level measured in DBS was 16.993 (14.588, 19.794), 11.598 (9.144, 14.709), 12.947 (11.155, 15.028), and 14.689 (12.517, 17.239), respectively, for participants who took <2, 2−3, 4−6, and ≥7 Truvada for PrEP tablets/week. IRRs comparing the rate of renal AEs for participants who took <2, 2−3, or 4−6 tablets/week to those who took ≥7 tablets/week did not suggest statistically significant differences.

Table 7-2. Incidence Rates and Incidence Rate Ratios (95% Confidence Interval, CI) for Provider-Reported Renal Adverse Events (AEs) within 96 Weeks of Follow Up

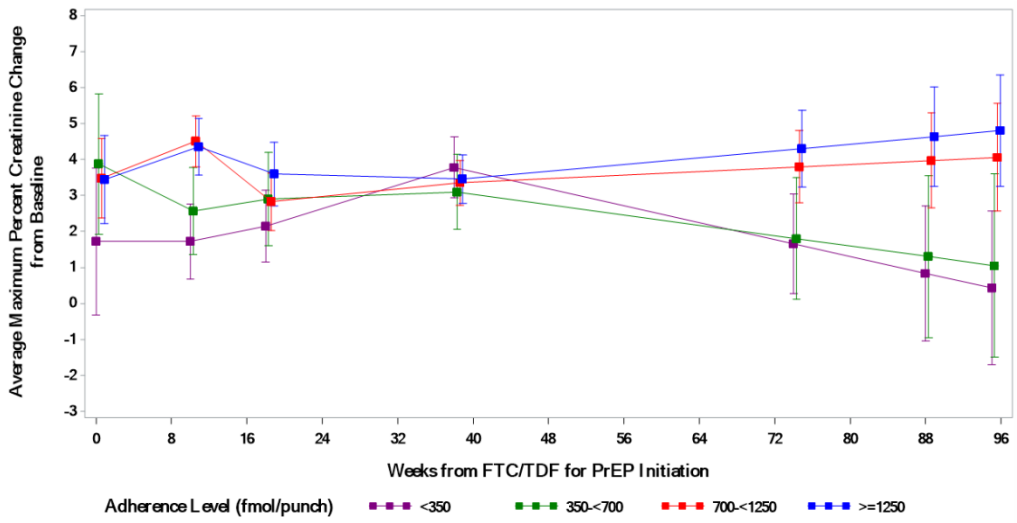
Adherence	Renal AE reported		No reported renal AE		Incidence rate per 100 person-year (95% CI)	Incidence Rate Ratio (95% CI) N (Column %)
	N (Column %)	Mean person-year	N (Column %)	Mean person-year		
TFV-DP in DBS (N=4,699)	556	0.47	4,143	0.88	14.203 (13.070, 15.434)	
<350 (<2 tablets/wk)	165 (29.7%)	0.61	1,070 (25.8%)	0.81	16.993 (14.588, 19.794)	1.157 (0.927, 1.443)
350-<700 (2-3 tablets/wk)	68 (12.2%)	0.49	670 (16.2%)	0.83	11.598 (9.144, 14.709)	0.790 (0.593, 1.051)
700-<1,250 (4-6 tablets/wk)	173 (31.1%)	0.36	1,404 (33.9%)	0.91	12.947 (11.155, 15.028)	0.881 (0.708, 1.097)
≥1,250 (≥7 tablets/wk)	150 (27.0%)	0.43	999 (24.1%)	0.96	14.689 (12.517, 17.239)	Reference
TFV in Plasma (N=470)	15	0.3	455	0.62	5.256 (3.169, 8.718)	
≤0.31 ng/mL	1 (6.7%)	0.24	52 (11.4%)	0.5	3.833 (0.540, 27.208)	0.894 (0.112, 7.144)
>0.31-<10ng/mL	2 (13.3%)	0.38	44 (9.7%)	0.52	8.533 (2.134, 34.118)	1.989 (0.422, 9.368)
10-<40 ng/mL	4 (26.7%)	0.29	65 (14.3%)	0.74	8.105 (3.042, 21.595)	1.890 (0.569, 6.275)
≥40 ng/mL	8 (53.3%)	0.3	294 (64.6%)	0.63	4.289 (2.145, 8.577)	Reference

7.3. Change in Creatinine by Adherence Level

In the FAS, 5,890 participants had creatinine measurements (an average of 6 measurements per participant in the DBS FAS and 4 in the plasma FAS) within 96 weeks after initiation of Truvada for PrEP. Baseline creatinine was obtained from the laboratory measurement of the last non-missing value prior to PrEP initiation and was assigned as a visit week of 0. Least-squared means of the percent change of follow-up visit creatinine value from the week 0 value [(creatinine in follow up visit - baseline creatinine)/baseline creatinine %] was obtained from piecewise linear mixed modeling with adherence level, visit week, and the adherence level and visit week interaction as predictors, and with by-subject time included as a random effect. The least-squared means by visit week are plotted in Figure 7-1.

For participants with a higher adherence level (≥700 fmol/punch, ≥4 tablets/week), creatinine increased faster than that in participants with a lower adherence level (<700 fmol/punch, ≤3 tablets/week) to around week 8 after PrEP initiation. The differences in percent creatinine change by adherence level diminished after week 8 and almost no differences were detected around week 40. The magnitude of creatinine increase was higher for individuals with high adherence from week 72 to week 96. In particular, the least-squared means of percent change from baseline was 1.72%, 2.83%, 4.30%, and 4.17% for participants who took <2, 2−3, 4−6, and ≥7 Truvada for PrEP tablets/week at week 8, and similarly, was 0.37%, 1.02%, 4.08%, and 4.83% at week 96 by adherence level.

Figure 7-1. Least Squared Means of Creatinine Percent Change from Baseline by Visit Week and Adherence Level



7.4. Bone Adverse Events

In the FAS, 4,985 participants had available information on provider-reported bone fractures. Of these, 51 (1.0%) had a reported bone AE, with 44 (86.3%) of these reported as a traumatic bone fracture, and the remaining 7 cases with unknown nature of the fracture. The mean age at bone fracture was 35.6 years (minimum 19.5 years and maximum 59.0 years). Individual demographic characteristics, history of bone disease, and adherence levels in the sub-cohort by reported bone AEs are shown in Table 7-3.

Older participants had slightly more bone AEs than younger participants, with <1% in individuals under age 45 and ~2% in those 45 years and above. A total of 186 individuals had a history of bone fracture, and 5 (2.7%) of these PrEP users had bone fracture after taking PrEP, compared to 1.0% PrEP users without history of bone fracture and had bone fracture after PrEP initiation. Bone AEs were reported in 1.3%, 0.9%, 0.9%, and 1.3% of participants who took <2, 2-3, 4-6, and ≥ 7 tablets per week, respectively.

Table 7-3. Provider-Reported Bone Adverse Events (AEs) in the Sub-Cohort where Bone AE Data is Available (96 Weeks Follow Up)

	Provider-Reported Bone AE		
	Total N in Cohort	**N (% of total in cohort)**	**N of Events**
All	4,985	51 (1.0%)	61
Age at PrEP Initiation (years)			
15-<18	28	0	0
18-<24	1,212	12 (1.0%)	14
24-<30	1,290	10 (0.8%)	14
30-<35	794	6 (0.8%)	6
35-<45	958	10 (1.0%)	10
45-<55	508	8 (1.6%)	11
≥55	178	4 (2.2%)	4
Other/Missing	17	1 (5.9%)	2
Sex			
Male	4,087	49 (1.2%)	59
Female	584	1 (0.2%)	1
Transgender	309	0	0
Other/Missing	5	1 (20.0%)	1
Race/ethnicity			
Non-Hispanic White	1,834	29 (1.6%)	37
Non-Hispanic Black	1,234	10 (0.8%)	12
Hispanic	1,272	10 (0.8%)	10
Asian	215	2 (0.9%)	2
Other/Missing	430	0	0
History of Bone Fracture			
No	4,799	46 (1.0%)	50
Yes	186	5 (2.7%)	11
TFV-DP Concentration in DBS			
<350 (<2 tablets/wk)	1,180	15 (1.3%)	18
350-<700 (2-3 tablets/wk)	659	6 (0.9%)	6
700-<1,250 (4-6 tablets/wk)	1,534	14 (0.9%)	14
≥1,250 (≥7 tablets/wk)	1,142	15 (1.3%)	22
TFV Concentration in Plasma	470	1 (0.2%)	
<10 ng/mL	99	0	0
10-<40 ng/mL	69	0	0
≥40 ng/mL	302	1 (0.3%)	1

7.5. Incidence Rates of Bone Adverse Events Provided in the Pooled Study

The IRs and IRRs for provider-reported renal AE by adherence are shown in Table 7-4. A total of 4,515 (68.3%) participants in the DBS FAS had available bone AE information, with bone fracture reported in 50 (1.1%) participants. Similarly, 470 individuals in the plasma FAS had bone AE data, and 1 individual had a reported bone AE.

The overall bone AE IR (95% CI) in the pooled study was 1.161 (0.882, 1.528) per 100 person-years [1.219 (0.924, 1.608) for the 4,515 participants in DBS FAS, and 0.345 (0.049, 2.451) for the 470 participants in plasma FAS]. The IR (95% CI) by adherence level measured in DBS was 1.507 (0.908, 2.500), 1.016 (0.457, 2.262), 0.980 (0.581, 1.655), and 1.377 (0.830, 2.284), respectively, for participants who took <2, 2−3, 4−6, and ≥7 Truvada for PrEP tablets/week. Individuals who had bone fractures with low adherence (<2 tablets/week) were likely to be young individuals with traumatic fractures (mean age 28.9 years for those <2 tablets/week, compared with a mean age of 38.0 years for individuals with high adherence). IRRs of bone AE for participants who took <2, 2−3, or 4−6 tablets/week compared to those who took ≥7 tablets/week did not suggest statistically significant differences.

Table 7-4. Incidence Rates and Incidence Rate Ratios (95% Confidence Interval) for Provider-Reported Bone Adverse Events (AEs) within 96 Weeks Follow Up

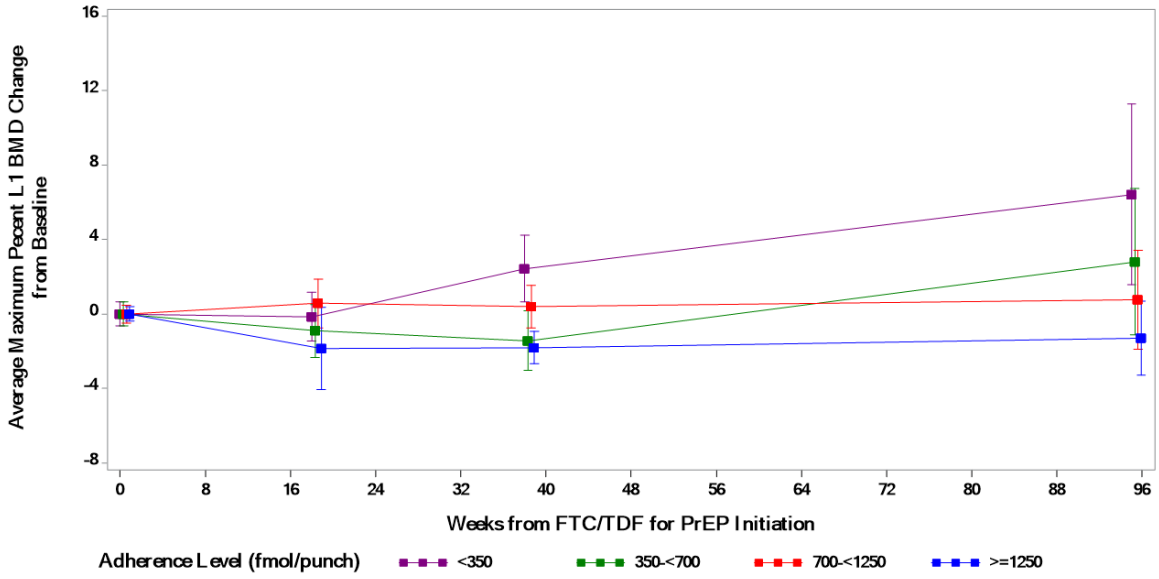
Adherence	Reported bone AE		No reported bone AE		Incidence rate per 100 person-year (95% CI)	Incidence Rate Ratio (95% CI)
	N (Column %)	Mean person-year	N (Column%)	Mean person-year		
TFV-DP in DBS (N=4,515)	50	0.46	4,465	0.91	1.219 (0.924, 1.608)	
<350 (<2 tablets/ wk)	15 (30.0%)	0.35	1,165 (26.1%)	0.85	1.507 (0.908, 2.500)	1.094 (0.535, 2.238)
350-<700 (2-3 tablets/wk)	6 (12.0%)	0.41	653 (14.6%)	0.9	1.016 (0.457, 2.262)	0.738 (0.286, 1.902)
700-<1,250 (4-6 tablets/wk)	14 (28.0%)	0.55	1,520 (34.0%)	0.93	0.980 (0.581, 1.655)	0.712 (0.344, 1.475)
≥1,250 (≥7 tablets/wk)	15 (30.o%)	0.5	1,127 (25.2%)	0.96	1.377 (0.830, 2.284)	Reference
TFV in Plasma (N=470)	1	0.93	469	0.62	0.345 (0.049, 2.451)	

7.6. Change in Bone Mineral Density by Adherence Level

Two studies with a total of 155 participants in the FAS provided BMD measured by DEXA: DISCOVER (n in FAS = 678; n in FAS with DEXA = 88) and ATN113 (n in FAS = 67; n in FAS with DEXA = 67). Of those, 139 participants (n = 82 from DISCOVER and n = 57 from ATN113) had at least one baseline and one follow-up BMD measurement of L1, L2, L3, L4, or Ward's within 96 weeks after initiation of Truvada for PrEP. Least-squared means of the percent change of follow-up visit of BMD value of lumbar vertebrae L1 from the week 0 value [(BMD in follow up visit - baseline BMD)/baseline BMD %] was obtained from piecewise linear mixed modeling with adherence level, visit week, and the adherence level and visit week interaction as predictors, and with by-subject time included as a random effect. The least-squared means by visit week are plotted in Figure 7-2.

Individuals that adhered to the highest level of Truvada for PrEP (≥7 tablets/week) had BMD decrease in week 24, 48, and 96, no change or slight increase of BMD were observed for individuals who had lower adherence. The least-squared means of L1 BMD percent change was 0.6%, -1.1%, 0.5%, and -1.9%, respectively, for participants who took <2, 2−3, 4−6, and ≥7 Truvada for PrEP tablets/week at week 24, 3.1%, -0.7%, 0.5%, and -1.7% at week 48, and 6.5%, 2.9%, 0.8%, and -1.3% at week 96. A similar trend was observed for L2, L3, L4 BMD change.

Figure 7-2. Least Squared Means of Bone Mineral Density Percent Change from Baseline by Visit Week and Adherence Level



8. RESISTANCE

Resistance in PrEP generally occurs by three mechanisms. The most common pathway to emergent resistance is the unrecognized baseline infection, indicating when an undiagnosed participant infected with HIV-1 is allowed to start the PrEP agent may lead to resistance {Gibas 2019}. Another mechanism that can lead to PrEP failure is when resistance mutations are already present on the viral strain infecting the participant which is referred to as transmitted drug resistance (TDR). The third way resistance is due to inadequate adherence when individuals becomes infected during low periods of adherence but continues to take study drug and resistance emerges. Known protease (PR) or reverse transcriptase (RT) resistance mutations, defined and reported according to the definitions of the International AIDS Society, as well as additional PR/RT resistance mutations reported in the literature, were show in Appendix Table 4.

In the FAS of this study, resistance analysis results were available from 6 studies (out of 13 studies that reported cases of new HIV-1 infection) which include 47 (56.0%) of the total 84 eligible HIV-1 infection cases with adherence measurements. All available resistance tests results were collected at the time of HIV-1 diagnosis. Table 8-1 provides details on the reported resistance test mutations, the weighted average of adherence level, the last measurement of adherence level at the time of the new HIV-1 infection, and signs and symptoms for HIV-1 infection for each individual.

Signs or symptoms were reported in 9 (19.1% out of 47) individuals which included fatigue, fever, rash, and sore throat, and one case had reported abdominal pain, nausea, vomiting, blood phosphorus decreased, malaise, dysphagia, pyrexia. In the remaining 38 (80.9%) individuals, signs or symptoms were not present, or information was not provided.

The primary resistance mutations for TFV are K65R/N and K70E, and the primary resistance mutation for FTC is M184V/I. It is likely that individuals in this study acquired resistance due to a combination of the three mechanisms.

- The K65R mutation was detected in 2 (4.3%) individuals and M184V/I resistance to FTC was detected in 9 (19.1%) individuals. Both participants (CO-US-164-0432/PPD and CO-US-164-0432/PPD) with PPD also had PPD present as well as other PPD .
- One participant with PPD (CO-US-164-0468/PPD) had significant PPD , also suggesting PPD.
- Three of the 9 participants (CO-US-164-0468/PPD , CO-US-164-0468/PPD , and CO-US-164-0468/5PPD) had only the PPD present at diagnosis with evidence of PPD and a short time period between PPD , which could suggest PPD .
- Three of the 9 participants with PPD PPD present and had evidence of PPD suggesting PPD while on study drug although PPD .

Among them, CO-US-164-0404/PPD and CO-US-164-0480/PPD had an average TFV-DP in DBS adherence of PPD fmol/punch and PPD fmol/punch, respectively, and TFV-DP of the last measurement on PPD of PPD fmol/punch and PPD fmol/punch, respectively, indicating PPD . While CO-US-164-0468/PPD had TFV in plasma PPD on the visit PPD , the last TFV measurement PPD as the individual had 2 previous TFV measurements of PPD, suggesting PPD .

- Other common resistance mutations included the NNRTI resistance mutation K103N (4 individuals, 8.5%), the PI resistance mutations M36I (10 individuals, 21.3%), A71V/T (7 individuals, 14.9%), and K20R (3 individuals, 6.4%) which all would have been due to TDR. No mutations were detected in 12 (25.5%) individuals.


PPD


PPD


PPD

9. SUMMARY

This is the final report for Study GS-US-276-0104, an observational study of 7,302 individuals pooled from demonstration projects and clinical studies globally to assess the association between objectively measured Truvada for PrEP adherence and the rate of new HIV-1 infection as well as renal and bone adverse events and resistance among individuals taking Truvada for PrEP. This study fulfills PMR 1906-3 established in the NDA 021752/S-030 approval letter dated 16 July 2012, as well as the Truvada EU RMP Category 3 PV activity. By October 2020, 21 studies from 20 countries provided data for 10,577 PrEP users. Of these, 7,302 individuals had at least one measurement of adherence were included in this analysis. The median age at PrEP initiation was 30 years (interquartile range 24 – 38), 5,725 (78.4%) were male, 1,218 (16.7%) were female, and 350 (4.8%) were transgender. Adherence level was measured by TFV-DP in DBS in 6,613 (90.6%) individuals, and 689 (9.4%) had adherence measured by TFV in plasma.

Adherence

In the pooled study, most participants had more than one TFV-DP or TFV measurements during the 96 weeks of follow up. A weighted average of adherence was developed to evaluate the gradient of adherence to the equivalent weekly dosage. Of the 6,613 participants with adherence determined by TFV-DP in DBS, 21.1%, 14.2%, 35.7%, and 29.1% took <2, 2−3, 4−6, and ≥7 tablets of Truvada PrEP per week. PrEP adherence increased with age, and individuals who were male, had homosexual contact, or were enrolled in a study in Europe had high adherence, while adherence were relatively low for Hispanic and non-Hispanic Black individuals or for participants enrolled in a study in Africa, Asian, or South America.

HIV-1 Infection after PrEP Initiation

A total of 84 (1.2%) individuals tested positive for HIV-1 infection after PrEP initiation, 69 had TFV-DP measurement in DBS and 15 with TFV in plasma. Overall, adherence level was consistent over the 96 weeks of the study period, yet individuals who had new HIV-1 infections had significantly lower levels of adherence over time compared to participants who were not infected.

The majority (85.5%) of the 69 individuals with TFV-DP in DBS had low adherence levels of under 2 tablets/week. The overall IR (95% CI) for a new HIV-1 infection among PrEP users who had TFV-DP in DBS was 1.163 (0.919, 1.473) per 100 person-years within 96 weeks of follow up, and the IRs of HIV-1 infection decreased with higher levels of adherence. The IR (95% CI) for HIV-1 infection was 1.249 (0.976, 1.599) for males, 0.710 (0.266, 1.891) for females, and 0.633 (0.158, 2.531) for transgender individuals. As adherence increased with age, the IRs of new HIV-1 infection decreased in older participants. Three of 698 European participants had new HIV-1 infections, with an overall IR of 0.424 (95% CI 0.137, 1.316).

In the separate analysis using TFV adherence in plasma, 15 of 689 individuals had a new HIV-1 infection, with an IR of 3.088 per 100 person-years exposure. Several individuals had measured ≥40 ng/mL on the visit that HIV-1 infection was reported. As TFV adherence reflect short-term adherence, it was possible that the individuals were infected prior to the visit.

Renal Adverse Events

A total of 5,169 and 5,890 participants in the FAS had information on provider-reported renal AEs or laboratory measured creatinine, respectively. Of these, 571 (11.0%) participants were reported to have renal AE(s), and 421 (7.1%) had been tested creatinine over 1.3 mg/dL after Truvada for PrEP initiated. The overall renal AE IR (95% CI) in the pooled study was 13.595 (12.524, 14.757) per 100 person-years. While no significant increase of IR for reported renal AE was observed with increased level of adherence, events of creatinine over 1.3 mg/dl increased substantially in individuals with high adherence. When looking at the dynamic measurement of creatinine over time, participants with high adherence had more rapid increases in creatinine than those who had low level of adherence after PrEP initiation.

Bone Adverse Events

In the FAS, 4,985 participants had information on provider-reported bone fracture, and 51 (1.0%) of these had a reported bone AE, majority were traumatic fractures. Bone AEs were reported for 1.3%, 0.9%, 0.9% and 1.3% of participants who took <2, 2-3, 4-6, and ≥7 tablets per week, respectively. The overall bone AE IR (95% CI) in the pooled study was 1.161 (0.882, 1.528) per 100 person-years. There was no substantial increase of bone AE IR in participants with elevated adherence level. The IRRs of bone AEs for participants who took <2, 2−3, or 4−6 tablets/week compared to those who took ≥7 tablets/week did not suggest any statistically significant differences. BMD decreased after PrEP initiation for individuals who adhered at the highest level, but insignificant change was observed for those at lower adherence levels.

Resistance

The results of resistance testing in the FAS were available for 47 of the 84 new HIV-1 infection cases. Nine individuals had resistance to Truvada for PrEP, all of them (19.1%) had the M184V/I FTC mutation and 2 (4.3%) individuals additionally had the K65R TFV mutation. The 2 participants with both K65R and M184V mutations and 1 other participant with M184V also had several other unrelated resistance mutations present suggesting TDR. Three of the 9 participants with M184V had high levels of TFV in plasma and failed soon after initiation of PrEP which could suggest undiagnosed baseline infection and the resistance emerged while on study. The final 3 participants had only M184V present, with information on level of TFV-DP or TFV suggesting infection with suboptimal adherence and then emergence of M184V, although TDR cannot be ruled out. Other mutations found in the study, including the PR mutations (M36I,A71V, K20R, and A71T), were considered secondary PR or TDR mutations and did not contribute to the PrEP failure. While none of the three mechanisms of resistance can be conclusive, this data suggests TDR may play a role in the resistance observed. Overall, widespread failure of PrEP due to resistance has not been shown to be a large concern with PrEP.

Strengths and Limitations

This is the largest observation study to date that evaluates the objectively measured adherence for 7,000 Truvada for PrEP users globally. The strength of the pooled analysis includes enhanced statistical power, the opportunities of using standard measurements from the same laboratory to test adherence for PrEP across studies, and the ability to estimate study outcomes across sites, settings, and different populations with the adherence assessment. Limitations of the study included the variations in study procedures and variables definitions, uneven distribution of study population (e.g., most female participants were from studies in Africa), and missing information on key variables from individual studies (e.g., PrEP stop date, which was not available or largely missing from individual studies).

Conclusion

In summary, study GS-US-276-0104 has collected data required for PMR-1906-3 and the Truvada EU RMP, reported on the association between adherence to Truvada for PrEP and risk of new HIV-1 infection, resistance, and renal or skeletal AEs among 7,302 individuals who had at least one objective measurement of adherence. Approximately 64% of all participants adhere at protective level of Truvada for PrEP during study follow up, with a total of 84 individuals reported infected with HIV-1 after the initiation of Truvada for PrEP and 83% of these individuals did not adhere to the prescribed regimen. The incidence rate for new HIV-1 infection among PrEP users who had TFV-DP in DBS was 1.163 per 100 person-years in 96 weeks and decreased with increased level of adherence to Truvada for PrEP. A positive association was observed between laboratory measured creatinine and adherence level after PrEP initiation, yet there was insufficient evidence to establish a significant association between the gradient of adherence level and provider reported renal adverse events or bone fracture. Finally, M184V/I and K65R mutations were observed in several individuals who acquired new HIV-1 infection, which may suggest a combination of underlying mechanisms for PrEP resistance. Overall, widespread failure of PrEP due to resistance has not been shown to be a concern with PrEP use in this large, pooled study.

10. REFERENCES

Anderson PL, Glidden DV, Liu A, Buchbinder S, Lama JR, Guanira JV, et al. Emtricitabine-tenofovir concentrations and pre-exposure prophylaxis efficacy in men who have sex with men. Science translational medicine 2012;4 (151):151ra25.

Anderson PL, Kiser JJ, Gardner EM, Rower JE, Meditz A, Grant RM. Pharmacological considerations for tenofovir and emtricitabine to prevent HIV infection. J Antimicrob Chemother 2011;66 (2):240-50.

Baeten J, Donnell D, Ndase P, Mugo N, Campbell J, Wangisi J, et al. Antiretroviral prophylaxis for HIV prevention in heterosexual men and women. N Engl J Med 2012;367 (5):399-410.

Bushman LR, Kiser JJ, Rower JE, Klein B, Zheng J-H, Ray ML, et al. Determination of nucleoside analog mono-, di-, and tri-phosphates in cellular matrix by solid phase extraction and ultra-sensitive LC–MS/MS detection. J Pharm Biomed Anal 2011;56:390-401.

Castillo-Mancilla JR, Aquilante CL, Wempe MF, Smeaton LM, Firnhaber C, LaRosa AM, et al. Pharmacogenetics of unboosted atazanavir in HIV-infected individuals in resource-limited settings: a sub-study of the AIDS Clinical Trials Group (ACTG) PEARLS study (NWCS 342). J Antimicrob Chemother 2016;71 (6):1609-18.

Castillo-Mancilla JR, Zheng JH, Rower JE, Meditz A, Gardner EM, Predhomme J, et al. Tenofovir, emtricitabine, and tenofovir diphosphate in dried blood spots for determining recent and cumulative drug exposure. AIDS Res Hum Retroviruses 2013;29 (2):384-90.

Donnell D, Baeten JM, Bumpus NN, Brantley J, Bangsberg DR, Haberer JE, et al. HIV Protective Efficacy and Correlates of Tenofovir Blood Concentrations in a Clinical Trial of PrEP for HIV Prevention. J Acquir Immune Defic Syndr 2014;66 (3):340-8.

Gibas KM, van den Berg P, Powell VE, Krakower DS. Drug Resistance During HIV Pre-Exposure Prophylaxis. Drugs 2019;79:609-19.

Grant RM, Anderson PL, McMahan V, Liu A, Amico KR, Mehrotra M, et al. Uptake of pre-exposure prophylaxis, sexual practices, and HIV incidence in men and transgender women who have sex with men: a cohort study. Lancet Infect Dis 2014:1-10.

Grant RM, Lama JR, Anderson PL, McMahan V, Liu AY, Vargas L, et al. Preexposure Chemoprophylaxis for HIV Prevention in Men Who Have Sex with Men. N Engl J Med 2010;363 (27):2587-99.

Hoornenborg E, Prins M, Achterbergh RCA, Woittiez LR, Cornelissen M, Jurriaans S, et al. Acquisition of Wild-Type HIV-1 Infection in a Patient on Pre-Exposure Prophylaxis with High Intracellular Concentrations of Tenofovir Diphosphate: A Case Report. The lancet. HIV 2017:1-7.

Louissaint NA, Cao YJ, Skipper PL, Liberman RG, Tannenbaum SR, Nimmagadda S, et al. Single Dose Pharmacokinetics of Oral Tenofovir in Plasma, Peripheral Blood Mononuclear Cells, Colonic Tissue, and Vaginal Tissue. AIDS Res Hum Retroviruses 2013.

11. APPENDIX

Appendix Table 1. Sensitivity Analysis of New HIV-1 Infection Rates with Adherence Levels Assessed by the Weighted Average, Arithmetic Means, and the Most Recent Measurement

	New HIV-1 infected		Non-HIV-1 infected		Incidence rate per 100 person-year (95% CI)
	N (Column %)	Mean person-year	N (Column %)	Mean person-year	
Weighted Average (N=6,613)	69	0.82	6,544	0.90	1.163 (0.919, 1.473)
<350 (<2 tablets/wk)	59 (85.5%)	0.88	1,335 (20.4%)	0.81	5.199 (4.028, 6.710)
350-<700 (2-3 tablets/wk)	3 (4.3%)	0.75	934 (14.3%)	0.84	0.380 (0.123, 1.179)
700-<1,250 (4-6 tablets/wk)	6 (8.7%)	0.32	2,352 (35.9%)	0.92	0.276 (0.124, 0.614)
1,250+ (≥7 tablets/wk)	1 (1.4%)	0.67	1,923 (29.4%)	0.95	0.055 (0.008, 0.387)
Arithmetic Means (N=6,613)	69	0.82	6544	0.90	1.163 (0.919, 1.473)
<350 (<2 tablets/wk)	49 (71.0%)	0.87	1,334 (20.4%)	0.81	4.359 (3.294, 5.767)
350-<700 (2-3 tablets/wk)	10 (14.5%)	0.83	935 (14.3%)	0.84	1.255 (0.675, 2.333)
700-<1,250 (4-6 tablets/wk)	9 (13.0%)	0.54	2,352 (35.9%)	0.92	0.413 (0.215, 0.794)
1,250+ (≥7 tablets/wk)	1 (1.4.0%)	0.67	1,923 (29.4%)	0.95	0.055 (0.008, 0.387)
Most Recent (N=6,613)[1]	69	0.82	6544	0.90	1.163 (0.919, 1.473)
<350 (<2 tablets/wk)	60 (87%)	0.87	1,869 (28.6%)	0.87	3.581 (2.780, 4.611)
350-<700 (2-3 tablets/wk)	2 (2.9%)	0.90	742 (11.3%)	0.84	0.321 (0.080, 1.285)
700-<1,250 (4-6 tablets/wk)	6 (8.7%)	0.32	2,010 (30.7%)	0.91	0.329 (0.148, 0.732)
1,250+ (≥7 tablets/wk)	1 (1.4%)	0.67	1,923 (29.4%)	0.94	0.055 (0.008, 0.393)

1 Most recent measurement on or prior to the visit date of HIV-1 infection, discontinuation, or 96 weeks, whichever occurred first.

Appendix Table 2. Sensitivity Analysis of New HIV-1 Infection Rates by Adherence Level, using the Last DBS Measurement Date or the Last Visit Date as PrEP Stop Date in the Person-Time Calculation

	New HIV-1 infected		Non-HIV infected		Incidence rate per 100 person-year (95% CI)
	N (Column %)	Mean person-year	N (Column %)	Mean person-year	
Last DBS Date (N=5,466)[1]	69	0.82	5,397	0.90	1.407 (1.111, 1.781)
<350 (<2 tablets/ wk)	59 (85.5%)	0.88	1,067 (16.3%)	0.79	6.631 (5.137, 8.558)
350-<700 (2-3 tablets/wk)	3 (4.3%)	0.75	790 (12.1%)	0.84	0.452 (0.146, 1.401)
700-<1,250 (4-6 tablets/wk)	6 (8.7%)	0.32	1,935 (29.6%)	0.93	0.333 (0.149, 0.740)
1,250+ (≥7 tablets/wk)	1 (1.4%)	0.67	1,605 (24.5%)	0.96	0.065 (0.009, 0.459)
Last Visit Date (N=5,466)[1]	69	0.88	5,397	1.46	0.867 (0.685, 1.097)
<350 (<2 tablets/ wk)	49 (71.0%)	0.93	1,067 (19.8%)	1.10	4.819 (3.734, 6.220)
350-<700 (2-3 tablets/wk)	10 (14.5%)	1.01	970 (18%)	1.24	0.305 (0.098, 0.944)
700-<1,250 (4-6 tablets/wk)	9 (13.0%)	0.35	1,935 (35.9%)	1.52	0.204 (0.092, 0.453)
1,250+ (≥7 tablets/wk)	1 (1.4.0%)	0.67	1,605 (29.7%)	1.75	0.036 (0.005, 0.253)

1 Limited to participants who had the last visit date within 96 weeks of follow up.

Appendix Table 3. Incidence Rates (95% Confidence Intervals) for New HIV-1 Infection by Adherence Level Measured by TFV-DP Concentrations in DBS and TFV in Plasma in the Pooled Study, Limited to Followed up to 48 Weeks after PrEP Initiation

	HIV-1 infected		Non-HIV-1 infected		Incidence rate per 100 person-year (95% CI)
	N (Column %)	Mean person-year	N (Column %)	Mean person-year	
TFV-DP in DBS (N=6,613)	35	0.45	6578	0.52	1.020 (0.733, 1.421)
<350 (<2 tablets/wk)	28 (80%)	0.50	1296 (19.7%)	0.45	4.641 (3.204, 6.722)
350-<700 (2-3 tablets/wk)	1 (2.9%)	0.42	915 (13.9%)	0.46	0.235 (0.033, 1.671)
700-<1,250 (4-6 tablets/wk)	5 (14.3%)	0.16	2373 (36.1%)	0.54	0.390 (0.162, 0.938)
≥1,250 (≥7 tablets/wk)	1 (2.9%)	0.67	1994 (30.3%)	0.56	0.089 (0.013, 0.633)
TFV in Plasma (N=689)	13	0.35	676	0.45	4.167 (2.420, 7.177)
<10 ng/ml	6 (46.2%)	0.51	182 (26.9%)	0.39	8.191 (3.680, 18.233)
10-<40 ng/ml	0	0	108 (16%)	0.54	NA
≥40 ng/ml	7 (53.8%)	0.21	386 (57.1%)	0.46	3.882 (1.851, 8.143)

Appendix Table 4. Resistance Mutations by Antiretroviral Class

Drug Class	Resistance Mutations[1] Codon Mutations	
Nucleoside Reverse Transcriptase Inhibitors (NRTIs)	M41L, E44D, A62V, K65R/N, D67N, T69 insertion, T69D/N, K70E/R, L74V/I, V75I, F77L, Y115F, F116Y, V118I, Q151M, M184V/I, L210W, T215Y/F, K219E/Q/N/R	
Thymidine Analogue Mutations (TAMs)	M41L, D67N, K70R, L210W, T215Y/F[2], K219Q/N/E/R	
Nucleoside-Associated Mutations (NAMs)	TAMs plus E44D[3], K65R/N, T69D/N[3], K70E, L74V/I, Y115F, V118I[3], M184V/I	
Multi-NRTI Resistance Mutations	Q151M Complex : A62V, V75I, F77L, F116Y, Q151M	
Multi-NRTI Resistance Mutations	T69 Insertion Complex : T69S-SS, -SA, -SG, or others	
Nonnucleoside Reverse Transcriptase Inhibitors (NNRTIs)	V90I, A98G, L100I, K101E/H/P, K103N/S, V106M/A/I, V108I, E138A/G/K/Q/R, V179D/F/L/T, Y181C/I/V, Y188C/H/L, G190A/E/Q/S, H221Y, P225H, F227C, M230L/I	
Protease Inhibitors (PIs)	Primary D30N, V32I, L33F, M46I/L, I47V/A, G48V, I50V/L, I54M/L, Q58E, T74P, L76V, V82A/F/L/S/T, I84V, N88S, L90M	Secondary L10I/F/R/V/C, V11I, I13V, G16E, K20I/M/R/T/V, L24I, L33I/V, E34Q, E35G, M36I/L/V, K43T, F53L/Y, I54A/S/T/V, D60E, I62V, L63P, I64L/M/V, H69K, A71V/T/I/L, G73A/C/S/T, V77I, V82I, N83D, I85V, N88D, L89V, I93L/M
Entry Inhibitors	—	G36D/S, I37V, V38A/E/M, Q39R, Q40H, N42T, N43D
Integrase Strand Transfer Inhibitors (INSTIs)[4]	Primary T66I/A/K, E92Q/G/V, T97A, Y143R/H/C, S147G, Q148H/K/R, N155H/S	Secondary M50I, H51Y, L68V/I, V72A/N/T, L74M, Q95K/R, G118R, S119P/R/T, F121C/Y, A128T, E138K/A, G140A/C/S, P145S, Q146R/I/K/L/P, V151L/A, S153A/F/Y, E157K/Q, G163K/R, E170A, R263K

1 Adapted from the current International Antiviral Society-USA (IAS-USA) Guidelines lists with some modifications.
2 Reversion mutations at RT codon T215, including T215A/C/D/E/G/H/I/L/N/S/V have not been definitively shown to be associated with reduced response to either FTC or TDF.
3 E44D, T69D/N, and V118I mutations can be natural polymorphisms in RT and have not been shown to be associated with reduced response to either FTC or TDF.
4 Primary and secondary IN mutations observed in clinical studies of INSTIs