# FINAL STUDY REPORT

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| **Study Title:** | A Prospective, Observational Study of Individuals Who Seroconvert While Taking Truvada® for Pre-Exposure Prophylaxis (PrEP) |
| **Indication:** | HIV Pre-Exposure Prophylaxis (PrEP) |
| **Sponsor:** | Gilead Sciences, Inc.<br>333 Lakeside Drive<br>Foster City, CA 94404<br>USA |
| **Study No.:** | GS-US-276-0103 |
| **Postmarketing Requirement (PMR) No:** | PMR 1906-2 |
| **IND No.:** | 108930 |
| **NDA No.:** | 021752/S-030 |
| **Clinical Trials.gov ID:** | NCT01902472 |
| **Gilead Study Director:** | Name: PPD<br>Telephone: PPD<br>Email: PPD |
| **Report Authors:** | Name: PPD<br>PPD |
| **Final Study Report Date:** | 20 March 2019 |
| **Previous Interim Report Dates:** | 15 September 2015<br>18 September 2014<br>20 September 2013 |

**CONFIDENTIAL AND PROPRIETARY INFORMATION**

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# 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 (NRTI) 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. Tenofovir Disoproxil Fumarate, an oral prodrug of tenofovir, is a nucleotide analog reverse transcriptase inhibitor (NtRTI). After absorption, TDF is rapidly converted to tenofovir (TFV), which 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 was first granted marketing approval by the United States (US) Food and Drug Administration (FDA) on 02 August 2004 for the treatment of HIV-1. Truvada tablets were first approved (centrally authorized) in the European Union (EU) on 21 February 2005, for the treatment of HIV-infected 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").

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) 1906-2

In connection with approval of the PrEP indication in the US, the following Post Marketing Requirement (PMR 1906-2) was agreed-upon by Gilead:

**Collect and analyze data from individuals who take Truvada® for a pre-exposure prophylaxis (PrEP) of sexually acquired HIV-1 infection and who seroconvert during follow-up. The following data should be collected and the following analyses conducted on data collected from a minimum of 150 seroconverters over a time period not to exceed 3 years:**

**A) Data regarding the presence or absence of signs and symptoms of acute HIV infection at study visit or since the last study visit when seroconversion is identified**

**B) Frequency of screening and screening method(s) used for evaluation of the seroconverter, and in general, at that enrollment site**

**C) Analyses of baseline samples from early seroconverters to evaluate HIV-1 RNA and the presence or absence of resistance**

**D) Resistance analyses of viral isolates from seroconverters that include population nucleotide sequence analysis followed by ultrasensitive testing (such as ultra-deep sequencing of proviral DNA or allele-specific PCR) if no resistance is identified by population sequencing**

The initial milestone dates were:

| | |
|---|---|
| Final Protocol Submission: | 10/2012 |
| Interim Report Submissions: | 09/2013, 09/2014, 09/2015 |
| Study Completion: | 03/2016 |
| Final Report Submission: | 09/2016 |

The original protocol was submitted to IND 108930 on 29 October 2012 (SN 0018). The interim reports were submitted to NDA 021752 on 20 September 2013 (SN 0485), 18 September 2014 (SN 0512), and 15 September 2015 (SN 0542).

## 1.2. Changes to PMR 1906-2

On 01 March 2016 (Reference ID 3894854), FDA acknowledged a request to extend the timelines due to estimated seroconversion rates being lower than expected based on previous clinical trials and slow uptake of PrEP in the US. The revised milestone dates for PMR 1906-2 were:

| | |
|---|---|
| Final Protocol Submission: | 10/2012 (completed) |
| Interim Report Submissions: | 09/2013, 09/2014, 09/2015 (completed) |
| Study Completion: | 06/2018 |
| Final Report Submission: | 09/2018 |

On 17 January 2019 (Reference ID 4377557), FDA acknowledged a request to extend the timelines in order to obtain individual-level data for the most recent cases of new HIV-1 infections. The revised milestone dates for PMR 1906-2 are:

| | |
|---|---|
| Study Completion: | 12/2018 |
| Final Report Submission: | 03/2019 |

# 2. INVESTIGATIONAL PLAN

## 2.1. Study Objectives

The objectives of this study are as follows:

- To evaluate data on the presence or absence of signs and symptoms of acute HIV infection prior to or at the time of seroconversion
- To assess the frequency of HIV-1 screening and screening method(s) used for evaluation of individuals taking Truvada for PrEP
- To evaluate the presence or absence of resistance at baseline and in uninfected individuals who seroconvert
- To describe resistance analyses of viral isolates from seroconverters, including population nucleotide sequence analysis and ultrasensitive testingTo assess the rate of seroconversion in subjects taking Truvada for PrEP

## 2.2. Study Design

This is an prospective, observational case series of HIV-1 negative individuals who participate in demonstration projects or clinical studies and take Truvada for PrEP. All subjects were enrolled and followed as described in the parent PrEP demonstration project or clinical study protocol until study completion, seroconversion, discontinued due to an adverse event, lost to follow-up or administrative censoring. Data from the different contributing studies were collected and pooled for analyses by Gilead.

The contributing studies provided clinical information on all subjects who seroconverted to HIV-1 positive. The contributing studies were requested to provide exposure data annually on all subjects receiving Truvada for PrEP.

Reports of individuals who did not participate in demonstration projects or clinical studies and seroconvert to HIV-1 positive during or after receiving Truvada for PrEP were included if the reports contain adequate data on exposure to Truvada and results of resistance testing. Individuals who did not participate in demonstration projects or clinical studies are not intended for inclusion in the seroconversion rate calculation analyses.

## 2.3. Changes in the Conduct of the Study or Planned Analysis

As noted in the response to FDA comments dated 04 February 2013 (Ref ID 3255449) submitted to IND 108930 on 04 March 2013 (SN 0023), Gilead has included data on seroconversion cases from US and other commercial sources (as reported by prescribers and/or identified by literature review). These data are presented separately from the data obtained from the demonstration projects or clinical studies and data on each individual who became HIV positive are also presented separately. Due to the fact that spontaneous and published case often lack person-time information (or duration of exposure information) these cases are not included in the seroconversion rate calculation analyses.

# 3. SUBJECT POPULATION

## 3.1. Number of Subjects and Subject Selection

The enrollment target was a minimum of 150 HIV-1 negative adults or adolescents (any sex/gender, including transgender) who developed new HIV-1 infection (i.e., seroconverted) while taking Truvada for PrEP.

## 3.2. Inclusion Criteria

To be eligible for inclusion in this data analysis, an individual must satisfy all of the following criteria:

- Evidence of new HIV-1 infection after initiating Truvada for PrEP
- Individuals may have received Truvada for PrEP from demonstration project or Truvada for PrEP clinical study or they may have received Truvada for PrEP as described in spontaneous or literature reports, always with accompanying results of resistance testing

## 3.3. Exclusion Criteria

- Spontaneous or literature report without results of resistance testing

# 4. STUDY PROCUDURES

## 4.1. Enrollment and Collection of Data

Subjects were consented and enrolled by the individual parent PrEP demonstration projects or as a part of the clinical studies in accordance with enrollment procedures that are described in those individual study protocols.

All subjects in parent PrEP demonstration projects or clinical studies who started treatment were followed until seroconversion, discontinued due to an adverse event, lost to follow-up or administrative censoring. These studies provided information on a regular basis of all the subjects that seroconverted during treatment.

For the subjects who seroconverted during participation in the parent PrEP studies, the following were collected, as available, during enrollment visit: confirmation of the HIV-1 negative status, risk behavior assessments, and baseline sample collection.

Documentation of signs and symptoms of acute infection, sexual risk for HIV-1 acquisition, and results of testing to confirm positive HIV-1 status at the seroconversion visit or since the last visit when the seroconversion occurred were collected, as available.

If a stored baseline sample was available and analyzed for viral resistance, the data were included in this report.

Results of resistance analyses of plasma HIV-1 were collected from the seroconversion visit when available. This includes population nucleotide sequence analysis, followed by ultrasensitive testing (such as deep sequencing or allele-specific PCR of either plasma or peripheral blood mononuclear cells) if no resistance was identified by population sequencing.

To preserve the confidentiality of all subjects in the parent studies, consented participants have been assigned a unique enrollment ID according to the PrEP demonstration project or PrEP clinical study protocol. The terms seroconversion and newly HIV-1 infection are used interchangeable throughout this report.

## 4.2. Criteria for Discontinuation of Follow Up

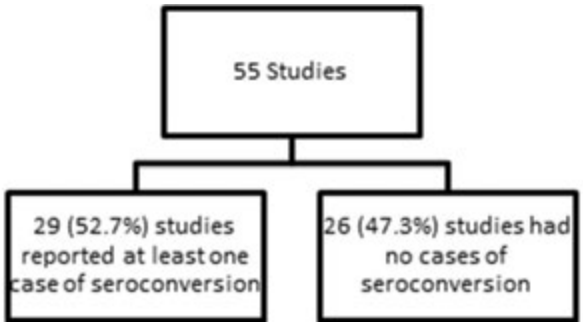
The decision to continue or discontinue Truvada belongs jointly to the subject and their investigators. In cases where subjects discontinued Truvada, they were followed according to the parent PrEP demonstration project or PrEP clinical study protocol.

# 5. OVERALL RESULTS

## 5.1. Demonstration Projects and Clinical Trials Reporting New HIV-1 Infections

Gilead requested data from 55 demonstration projects or studies during the course of this study. Data were requested for any individual who participated in one of these demonstration projects or studies and who developed a new HIV-1 infection (i.e., seroconverted). Twenty nine of the 55 (52.7%) studies provided data for at least one individual who developed a new HIV-1 infection. In 26 of the 55 (47.3%) studies, there were no reported cases of new HIV-1 infection through the 31 December 2018 data cut-off date.

**Figure 1. Studies That Reported New HIV-1 Infections (Seroconversions)**




Data were also requested for all individuals receiving daily dosing of Truvada for PrEP in the 55 demonstration projections or studies to calculate person-time exposure (Section 9). Forty six of the 55 (83.6%) studies provided exposure person-time data and 9 studies did not provide person-time data.

The 55 studies that provided data on new HIV-1 infections and/or data on person-time exposure are listed in Table 5-1.

**Table 5-1. Contributing Demonstration Projects and Clinical Studies**

| Study Number | Study Alias | Study Name | Contributed New HIV-1 Infection Cases | Contributed Person-Time Data |
|---|---|---|---|---|
| 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) | Yes | Yes |
| CO-US-164-0404 | iPrEX OLE | Open Label Extension of Active Daily Oral Truvada for HIV-1 Prevention Among Participants in the Trial "Chemoprophylaxis for HIV Prevention in Men"; a Phase 4 study with locations in the US, South Africa, Peru, Brazil, Ecuador, and Thailand | Yes | Yes |
| CO-US-164-0432 | DAIDS PrEP Demo | Implementation of HIV pre-exposure prophylaxis (PrEP): A Demonstration Project; a Phase 4 study to assess the uptake, acceptability, safety and feasibility of PrEP administered at sexually transmitted disease clinics and community health centers in the US | Yes | Yes |
| CO-US-164-0440 | IPERGAY | On Demand Antiretroviral Pre-Exposure Prophylaxis for HIV Infection in Men Who Have Sex with Men in France and Canada | Yes | No |
| CO-US-164-0441 | CDC PrEP Demo (SHIPP) | Sustainable Health Center Implementation PrEP Pilot Study (SHIPP Study); sites in the US to be determined | Yes | Yes |
| 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) | No* | Yes |
| CO-US-164-0451 | CDC Botswana PrEP OLE | Open Label Extension (OLE) of Active Daily Oral TDF/FTC for HIV-1 Prevention among former participants in the trial "Study of the Safety and Efficacy of Daily Oral Antiretroviral Use for the Prevention of HIV Infection in Heterosexually Active Young Adults in Botswana" (TDF 2) | No* | Yes |

| Study Number | Study Alias | Study Name | Contributed New HIV-1 Infection Cases | Contributed Person-Time Data |
|---|---|---|---|---|
| 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 | Yes | Yes |
| CO-US-164-0454 | PROUD | PRe-exposure Option for preventing HIV in the UK: an open-label randomisation to immediate or Deferred inclusion of Truvada as part of a comprehensive HIV prevention package | Yes | Yes |
| 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 | Yes | Yes |
| CO-US-164-0461 | CHAMPS | CHAMPS : Choices for Adolescent Methods of Prevention in South Africa | Yes | Yes |
| CO-US-164-0468 | Partner's PrEP Demo | An open-label, pilot demonstration and evaluation project of antiretroviral-based HIV-1 prevention among high-risk HIV-1 serodiscordant African couples; sites in Kenya and Uganda | Yes | Yes |
| CO-US-164-0471 | PrEPared & Strong | Pre-Exposure Prophylaxis for Black Men Who Have Sex With Men | No* | Yes |
| CO-US-164-0478 | ALERT | Active Linkage, Engagement and Retention to Reduce HIV; a Phase 4, randomized demonstration project to determine if the use of text-message based adherence intervention improves retention and adherence to PrEP compared to standard of care PrEP delivery; Locations in the US | Yes | Yes |

| Study Number | Study Alias | Study Name | Contributed New HIV-1 Infection Cases | Contributed Person-Time Data |
|---|---|---|---|---|
| CO-US-164-0480 | PATH – PrEP | Los Angeles Country HIV Combination Prevention Demonstration Project; A pilot demonstration project to operationalize pre-exposure prophylaxis as part of combination HIV prevention among MSM and transgender women in Los Angeles County | Yes | Yes |
| CO-US-164-0481 | Project PrEPare | Optimizing Antiretroviral-Based Prevention by enhancing PrEP Adherence in MSM | No* | Yes |
| IN-AU-164-0482 | VICPrEP/PRE:LUDE | The Australian PrEP Demonstration Project | Yes | No |
| 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 | Yes | Yes |
| CO-US-164-0488 | SEARCH | Sustainable East Africa Research in Community Health (SEARCH) | Yes | No |
| CO-US-164-1265 | SPARK | Intervention to Enhance PrEP Uptake and Adherence in a Community-Based Setting (SPARK) | No* | Yes |
| IN-CA-164-1261 | PREPARATORY-5 | A pilot study of daily TDF/FTC-based PrEP among high-risk Toronto MSM:The PREPARATORY-5 Study | No* | Yes |
| IN-AU-164-1888 | QPrEP | The Queensland Pre-Exposure Prophylaxis Demonstration Project | No* | Yes |
| CO-US-276-0108 | Brazilian PrEP | Brazilian Pre-Exposure Prophylaxys Demonstration Project | Yes | Yes |
| CO-US-276-0115 | PrEP in STD Clinics | Implementation of HIV Pre-Exposure Prophylaxis at Sexually Transmitted Diseases Clinics in Providence, Rhode Island and Jackson, Mississippi | Yes | Yes |
| CO-US-276-0117 | SAFER | Impact and Cost effectiveness of Safer Conception Strategies for HIV Prevention | No* | Yes |

| Study Number | Study Alias | Study Name | Contributed New HIV-1 Infection Cases | Contributed Person-Time Data |
|---|---|---|---|---|
| IN-US-276-0122 | Flash PrEP | Houston HIV-Pre-exposure Prophylaxis Demonstration Project | Yes | Yes |
| CO-US-276-0126 | SAPPH-Ire | Antiretrovirals for HIV Prevention and Treatment among Zimbabwean Sex Workers | Yes | No |
| GS-FR-276-1199 | French RTU | Temporary Recommendation For Use (RTU) of Truvada (Emtricitabine / Tenofovir DF FDC) For PreExposure Prophylaxis (PrEP) | Yes | No |
| IN-US-276-1262 | PrEPception | PrEPception: Expanding Assisted Reproduction Options for Serodiscordant Couples | No* | Yes |
| CO-US-276-1263 | Senegal FSW PrEP | A Demonstration Project of HIV PrEP with TDF/FTC among Female Sex Workers in Dakar, Senegal | No* | Yes |
| CO-US-276-1264 | 3Ps (Bekker/Celum) | A Pilot Prospective Cohort Evaluation of Uptake and Adherence to PrEP in Young South African Women | Yes | No |
| IN-US-276-1295 | FIGHT PrEP | PrEP with FTC/TDF to Prevent HIV-1 Acquisition in Young Adult MSM of Color | No* | Yes |
| CO-US-276-1317 | MP3 Kenya | Gender-specific combination HIV prevention for youth in high-burden settings: a pilot study | No* | Yes |
| CO-US-276-1318 | Benin PrEP/TasP | Early ART and PrEP for HIV prevention among female sex workers in Benin, West Africa | Yes | Yes |
| CO-US-276-1338 | CRUSH Demo | Connecting Resources for Urban Sexual Health (CRUSH Demonstration Project) | No* | Yes |
| IN-US-276-1340 | Women's PrEP Demo | PrEP to Prevent HIV Acquisition in US Women: A Demonstration Project | No* | Yes |
| CO-US-276-1510 | PrEP Demo in Kenya | Demonstrating the safety and effective delivery of daily oral PrEP as part of an HIV combination prevention intervention among young women at high HIV risk, FSW, and MSM in Kenya | Yes | No |

| Study Number | Study Alias | Study Name | Contributed New HIV-1 Infection Cases | Contributed Person-Time Data |
|---|---|---|---|---|
| CO-US-276-1639 | HERS/HPTN 082 | Evaluation of daily oral PrEP as a primary prevention strategy for young African women: A Vanguard Study | Yes | No |
| CO-US-276-1636 | S Africa TAPS Demo | Expanded use of ART for Treatment And Prevention for female Sex workers in South Africa | No* | Yes |
| CO-US-276-1691 | Nigeria PrEP | A Demonstration Project of Antiretroviral-based HIV-1 Prevention Among HIV-1 Serodiscordant Couples in Nigeria | No* | Yes |
| CO-US-276-1694 | Brazil Prevention | Combined use of HIV prevention methods and prophylaxis before and after consensual sexual exposure in Brazil: protocol for a pragmatic clinical trial at public healthcare clinics | No* | Yes |
| CO-US-276-1712 | AMPrEP | Biomedical Interventions for HIV Prevention in MSM in Amsterdam: a demonstration project | Yes | Yes |
| CO-US-276-1774 | POWER | Scaleable, efficient, effective delivery of PrEP and microbicides for young women in Kenya and South Africa | Yes | No |
| CO-US-276-1806 | MPYA | Next generation real-time monitoring to assess PrEP adherence for young women | No* | Yes |
| CO-US-276-1862 | Belgium PrEP | A demonstration project on HIV prevention with Pre-exposure Prophylaxis among men having sex with men in Belgium (Be-PrEP-ared) | No* | Yes |
| CO-US-276-1875 | Epi-PrEP | Feasibility of Short-Term PrEP Uptake for MSM with Episodic High-Risk for HIV (Epi-PrEP) | Yes | No |
| IN-US-276-1926 | Puerto Rican PrEP | Evaluating the Feasibility and Acceptability of Implementing a PrEP Program in PR-CoNCRA | No* | Yes |
| 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 | No* | Yes |

| Study Number | Study Alias | Study Name | Contributed New HIV-1 Infection Cases | Contributed Person-Time Data |
|---|---|---|---|---|
| CO-US-276-2003 | AEGIS | PrEP Adherence Enhancement Guided by iTAB and Drug Levels for Women (AEGIS) | No* | Yes |
| CO-US-276-2004 | Peru PrEP | A Demonstration Project of Implementation Feasibility for a Program of HIV Pre-Exposure Prophylaxis (PrEP) Among Men who have Sex with Men and Transgender Women: A PrEP Peru Study | No* | Yes |
| CO-US-276-2060 | SCIP | Pilot of an mHealth-enhanced, safer conception intervention to reduce HIV-1 risk among Kenyan HIV-1 serodiscordant couples | No* | Yes |
| CO-AU-276-2096 | EPIC NSW | Impact of the rapid expansion of pre-exposure prophylaxis (PrEP) on HIV incidence, in a setting with high testing and ART coverage, to achieve the virtual elimination of HIV transmission by 2020: a NSW HIV Strategy demonstration project | Yes | No |
| IN-US-276-2122 | ToT CCTG601 | HIV Pre-exposure Prophylaxis Linkage and Adherence in Men who have Sex with Men following Completion of a PrEP Demonstration Project | No* | Yes |
| CO-US-276-4263 | CFAR PrEP 2 | The Effect of Social Media Support and Financial Incentives on Adherence to HIV Pre-exposure Prophylaxis in young MSM of color in Washington, DC | No* | Yes |
| IN-US-276-4369 | EleMENt | Understanding substance use and incident HIV/STI among young black MSM | Yes | No |

* No new HIV-1 infections were reported from the study through 31 December 2018.

## 5.2. Frequency of Screening for New HIV-1 Infections

Each demonstration project or clinical study protocol pre-defined the frequency for clinic visits and monitoring for new HIV-1 infections. A summary of the frequency of clinic visits and the test methods used is in Table 5-2. This information was obtained from the protocol for each study. The test methodology reflects the different time periods when the studies were planned and initiated, and regional variations.

**Table 5-2. Frequency of Monitoring for Seroconversion and Test Methods for Active Projects or Studies**

| Study Number | Study Alias | Monitoring Frequency for Seroconversion |
|---|---|---|
| CO-US-164-0403 | HPTN 067/ADAPT | Screening, Baseline and week 0, 4, 6, 10, 14, 18, 22, 30, 34. Test GenAptima HIV RNA test/ Rapid test |
| CO-US-164-0404 | iPrEX OLE | Months 0, 1, 2, 3, 6, 9, 12, 15, and 18 (US sites – Oraquick & STAT-PAK rapid antibody tests; Non-US sites – Determine & Bioline rapid antibody tests) |
| CO-US-164-0432 | DAIDS PrEP Demo | Months 0, 1, 3, 6, 9, and 12 (Abbott ARCHITECT HIV Ag/Ab Combo Assay) |
| CO-US-164-0440 | IPERGAY | Pre-enrollment, D0, Months 1, 2, 4, 6, 8, 10, 12, 24, 36 (Combined latest generation antigen and antibody at each visit and Plasma HIV RNA) |
| CO-US-164-0441 | CDC PrEP Demo (SHIPP) | Months 0 (EIA antibody test not specified or rapid fingerstick blood test), 3, 6, 9, 12, 15, 18, 21, and 24 (test method not specified) |
| CO-US-164-0451 | CDC Botswana PrEP OLE | Months 0, 3, 6, 9, 12 (Rapid test Unigold and Determine) |
| CO-US-164-0452 | Project PrEPare (ATN 110) | Months 0, 1, 2, 3, 6, 9, and 12 (Rapid test not specified) Months 4, 5, 7, 8, 10, and 11 (Antibody test no specified) |
| CO-US-164-0454 | PROUD | Months 0, 1, 2, 3, 6, 9, and 12 (Rapid test not specified) |
| CO-US-164-0455 | PROJECT PrEPare (ATN 113) | Screening, Baseline, Weeks 0, 4, 8, 12, 24, 36, 48 (FDA approved rapid assay and HIV home testing kit) |
| CO-US-164-0461 | CHAMPS | Screening, enrollment, Week, 4, 8, 12, 24, 36, 48 and 52 (Rapid test not specified) |
| CO-US-164-0468 | Partner's PrEP Demo | Months 0, 1, 3, 6, 9, 12, 15, 18, 21, and 24 (test not specified – 3rd or 4th generation EIA depending on study site) |
| CO-US-164-0471 | PrEPared & Strong | Months 0,1,3.6,9 and 12 ( 4th generation HIV antibody test) |
| CO-US-164-0478 | ALERT | Months 0, 1, 3, and then every 3 months until end of study (Rapid test not specified) |
| CO-US-164-0480 | PATH – PrEP | Day -14/-7 (Screening), Months 0, 1, 2, 3, 6, 9, and 12 (Rapid test not specified) |

| Study Number | Study Alias | Monitoring Frequency for Seroconversion |
|---|---|---|
| CO-US-164-0481 | Project PrEPare | Months 0, 1, 2, 3, 6<br>(HIV antibody by commercially available FDA approved EIA, Western blot) |
| IN-AU-164-0482 | VICPrEP/PRE:LUDE | Screening, Month 3, 6, 9, 12 (Rapid test unspecified) |
| CO-US-164-0483 | HPTN 073 | Day ≤ -45<br>(Screening), Months 0, 1, 2, 3, 6, 9, and 12 (Oraquick, Multispot HIV-1/2) |
| CO-US-164-0488 | SEARCH | Phase 2 PrEP. Baseline, Week 4, 12, every 12 weeks through 144 weeks. (Rapid test per country policy) |
| IN-CA-164-1261 | PREPARATORY-5 | Months 0, 1, 3, 6, 9, 12 (ELISA and Western Blot) |
| CO-US-164-1265 | SPARK | Months 0, 3, 6, 9, 12<br>(Rapid HIV testing OraQuick ADVANCE Rapid HIV-1/2 or the Clearview Complete HIV 1/2) |
| IN-AU-164-1888 | QPrEP | Months 0, 1, 2, 5, 8, 11, 12, and 13 (test not specified) |
| CO-US-276-0108 | Brazilian PrEP | Screening, Baseline, and Months 0, 1, 3, 6, 9, and 12<br>(test method not specified) |
| CO-US-276-0126 | SAPPH-Ire | Months 0, 3, 6, 9, and 12<br>(Rapid Immunoassay Determine HIV-1/2) |
| CO-US-276-0115 | PrEP in STD Clinics | Months 0, 1, 3, 6, 9, and 12 (test not specified) |
| CO-US-276-0117 | SAFER | Screening, Months 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14<br>(HIV Rapid test based on Zimbabwe guidelines) |
| IN-US-276-0122 | Flash PrEP | Eligibility screening, Months 1, 2, 5, 8, 11 \<br>(Rapid HIV testing not specific) |
| CO-US-276-0126 | SAPPH-Ire | Months 0, 3, 6, 9, 12 (Determine and Unigold) |
| GS-FR-276-1199 | French RTU | Per country guidelines |
| IN-US-276-1262 | PrEPception | Months 3 & 6 post each cycle. (Rapid test not specific) |
| CO-US-276-1263 | Senegal FSW PrEP | Screening, Month,1, 3, 6, 9, 12<br>(Antibody/antigen 4th generation) |
| CO-US-276-1264 | 3Ps (Bekker/Celum) | Screening, Enrollment, Month 1, 2, 3, 6, 9, Exit<br>(Rapid test not specified; ELISA) |
| IN-US-276-1295 | FIGHT PrEP | Screening, week 4, 8 (rapid test not specified); Premedication visit, Week 12, 24, 36, 48 (HIV RNA) |
| CO-US-276-1317 | MP3 Kenya | Months 0, 1, 2, 3, 4, 5, 6, 9, 12 (rapid testing not specific) |
| CO-US-276-1318 | Benin PrEP/TasP | Recruitment, Month 3, 6 ,9, 12, 15, 18, 21, 24<br>(SD Bioline HIV/Syphilis Duo Test) |
| CO-US-276-1338 | CRUSH Demo | Screening, Month 1, 3, 6, 9, and 12<br>( nucleic acid testing not specific) |
| IN-US-276-1340 | Women's PrEP Demo | Months 0, 1, 3, 4, 6 ( 4th generation and RNA) |
| CO-US-276-1510 | PrEP Demo in Kenya | Screening, Month 1, 3, 6, 9, 12 (test not specified) |
| CO-US-276-1639 | HERS/HPTN 082 | Enrollment, Weeks 4, 8, 13, 26, 39, 52 (test not specified) |

| Study Number | Study Alias | Monitoring Frequency for Seroconversion |
|---|---|---|
| CO-US-276-1636 | S Africa TAPS Demo | Months 0, 1, 3, 6, 9, 12, 15, 18, 21, 24 (Rapid test not specified) |
| CO-US-276-1691 | Nigeria PrEP | Months 0, 1, 3, 6, 9, 12, 15, 18 (Rapid test not specified) |
| CO-US-276-1694 | Brazil Prevention | Months 0, 3, 6, 12, 18, 24 (Western blot and negative anti-HIV test) |
| CO-US-276-1712 | AMPrEP | Screening, enrolment, Month 1, 3, then every 3 months through 48 months (4th Generation ELISA) |
| CO-US-276-1774 | POWER | Enrollment, Prep initiation visit, Month 1, 3, every 3 months through 36 months (test per national policy) |
| CO-US-276-1806 | MPYA | Screening, Months 0,1, 3, 6, 9, 12, 15, 18, 21, 24 (Test not specified) |
| CO-US-276-1862 | Belgium PrEP | Month 0, 1, 3, 6, 9, 12, 15 (HIV antigen/antibody rapid test not specified) |
| CO-US-276-1875 | Epi-PrEP | Day 0, Month1, 3 (4th generation ELISA) |
| IN-US-276-1926 | Puerto Rican PrEP | Months 0, 1, 3, 6, 9, 12 (4th generation antibody/antigen test) |
| CO-US-276-1976 | CRUSH Women | Months 0, 2, 3, 6, 9, 12, 15, 18, 21, 24 (4th generation rapid test) |
| CO-US-276-2003 | AEGIS | Months 0, 1, 3, 6, 9, 12 (ELISA, 4th gen and viral load) |
| CO-US-276-2004 | Peru PrEP | None, Participants are tested and prescribed PrEP by their primary care providers. |
| CO-US-276-2060 | SCIP | Months 0, 1, 3, 4, 5, pregnancy 6,9,12, (HIV-1 testing algorithms for Kenya) |
| CO-AU-276-2096 | EPIC NSW | Screening/enrollment/baseline, Month 1, 3, quarterly thereafter (HIV antibody test not specified) |
| IN-US-276-2122 | ToT CCTG601 | Months 6, 12 (Rapid HIV test) |
| CO-US-276-4263 | CFAR PrEP 2 | Months 0, 3, 6, 9, 12 (4th generation test not specified) |
| IN-US-276-4369 | EleMENt | Eligibility, Initiation, Month 3, quarterly through 24 months (Determine 4th generation antigen/antibody) |

## 5.3. Reported Cases of New HIV-1 Infection

All demonstration projects or clinical studies were asked to report details on new HIV-1 infections that occurred while an individual was taking Truvada for PrEP or during post-treatment follow-up periods. A total of 172 new HIV-1 infection cases are included in this report: 159 were reported from 29 demonstration projects or clinical studies through the 31 December 2018 data cut-off date for this report (Table 5-3); and 13 new HIV-1 infection cases from spontaneous reports or published literature are included.

**Table 5-3. Sources of Reported Cases of New HIV-1 Infection**

| Study Number / Source | Study Alias | Cases of New HIV-1 Infections N (%*) |
|---|---|---|
| CO-US-164-0403 | HPTN 067/ADAPT | 10 (5.8%) |
| CO-US-164-0404 | iPrEX OLE | 28 (16.3%) |
| CO-US-164-0432 | DAIDS PrEP Demo | 5 (2.9%) |
| CO-US-164-0440 | IPERGAY | 3 (1.7%) |
| CO-US-164-0441 | CDC PrEP Demo (SHIPP) | 12 (7.0%) |
| CO-US-164-0452 | Project PrEPare (ATN 110) | 10 (5.8%) |
| CO-US-164-0454 | PROUD | 12 (7.0%) |
| CO-US-164-0455 | PROJECT PrEPare (ATN 113) | 3 (1.7%) |
| CO-US-164-0461 | CHAMPS | 1 (0.6%) |
| CO-US-164-0468 | Partner's PrEP Demo | 17 (9.9%) |
| CO-US-164-0478 | ALERT | 2 (1.2%) |
| CO-US-164-0480 | PATH – PrEP | 1 (0.6%) |
| IN-AU-164-0482 | VICPrEP/PRE:LUDE | 1 (0.6%) |
| CO-US-164-0483 | HPTN 073 | 5 (2.9%) |
| CO-US-164-0488 | SEARCH | 13 (7.6%) |
| CO-US-276-0108 | Brazilian PrEP | 6 (3.5%) |
| CO-US-276-0126 | SAPPH-Ire | 2 (1.2%) |
| CO-US-276-0115 | PrEP in STD Clinics | 1 (0.6%) |
| IN-US-276-0122 | Flash PrEP | 1 (0.6%) |
| GS-FR-276-1199 | French RTU | 4 (2.3%) |
| CO-US-276-1264 | 3Ps (Bekker/Celum) | 1 (0.6%) |
| CO-US-276-1318 | Benin PrEP/TasP | 2 (1.2%) |
| CO-US-276-1510 | PrEP Demo in Kenya | 3 (1.7%) |
| CO-US-276-1639 | HERS/HPTN 082 | 4 (2.3%) |
| CO-US-276-1712 | AMPrEP | 2 (1.2%) |
| CO-US-276-1774 | POWER | 2 (1.2%) |
| CO-US-276-1875 | Epi-PrEP | 1 (0.6%) |
| CO-AU-276-2096 | EPIC NSW | 3 (1.7%) |
| IN-US-276-4369 | EleMENt | 4 (2.3%) |
| Spontaneous / Literature | - | 13 (7.6%) |
| Total | - | 172 |

* Percent each study with seroconverters contributed to the total of 172 new HIV-1 infections

### 5.3.1. Cases of New HIV-1 Infection

The demographics and baseline characteristics of subjects who developed new HIV-1 infection reported from demonstration projects or clinical studies and from spontaneous and literature sources are summarized in Table 5-4.

**Table 5-4. Demographics and Baseline Characteristics of Subjects with Reported Seroconversion**

| Subgroup | Cases of New HIV-1 Infections N (%) |
|---|---|
| Gender | |
| Male | 131 (76.2%) |
| Female | 39 (22.7%) |
| Transgender | 2 (1.2%) |
| Age (Years) | |
| Mean ± Standard Deviation | 26.9 ± 8.29 |
| Median (Interquartile Range [IQR]) | 25 (21 – 31) |
| Minimum − Maximum | 17 – 56 |
| Male Age (Years) | |
| Mean ± Standard Deviation | 27.1 ± 8.0 |
| Median (IQR) | 25 (22 – 31) |
| Minimum − Maximum | 17 – 56 |
| Male Age Group (Years) | |
| ≤ 24 | 55 (42.0%) |
| 25 – 34 | 70 (53.4%) |
| Unknown/Missing | 6 (4.6%) |
| Female Age (Years) | |
| Mean ± Standard Deviation | 26.2 ± 9.0 |
| Median (IQR) | 22 (19 – 31) |
| Minimum − Maximum | 17 – 56 |
| Female Age Group (Years) | |
| ≤ 24 | 22 (56.4%) |
| 25 – 34 | 17 (43.6%) |
| Unknown/Missing | 0 |
| Country | |
| USA | 54 (31.2%) |
| Ex-USA | 118 (68.6%) |

| Subgroup | Cases of New HIV-1 Infections N (%) |
|---|---|
| Country Name | |
| Australia | 4 (2.3%) |
| Benin | 1 (0.6%) |
| Brazil | 8 (4.6%) |
| Canada | 5 (2.9%) |
| Ecuador | 3 (1.7%) |
| El Salvador | 1 (0.6%) |
| France | 7 (4.1%) |
| Kenya | 6 (3.5%) |
| The Netherlands | 2 (1.2%) |
| Peru | 18 (10.5%) |
| South Africa | 17 (9.9%) |
| Thailand | 4 (2.3%) |
| Togo | 1 (0.6%) |
| Uganda | 27 (15.7%) |
| United Kingdom | 12 (7.0%) |
| United States | 54 (31.2%) |
| Zimbabwe | 2 (1.2%) |
| Transmission Risk | |
| MSM | 121 (70.4%) |
| Heterosexual | 50 (29.1%) |
| Bisexual | 1 (0.6%) |
| Race/Ethnicity | |
| White | 27 (15.7%) |
| Black | 88 (51.2%) |
| Hispanic | 5 (2.9%) |
| Asian | 4 (2.3%) |
| Mixed or Other | 23 (13.4%) |
| Unknown / Not Reported | 25 (14.5%) |
| Timing of New HIV-1 Infection | |
| Infection suspected before initiating PrEP | 25 (14.5%) |
| Infection after initiating PrEP | 97 (56.4%) |
| Infection > 30 days after PrEP discontinuation | 50 (29.1%) |

# 6. ANALYSIS OF HIV-1 INFECTIONS BEFORE INITATING PREP

## 6.1. Subject Characteristics

Twenty five individuals had HIV infection prior to the initiation of Truvada for PrEP, as judged by the study team from the parent studies, and their characteristics are listed in Table 6-1. Twenty four of the individuals participated in a demonstration project or clinical trial and one individual was reported as a spontaneous literature report. Seventeen individuals were male and were from Australia, France, Kenya, Thailand, Uganda or the United States. Thirteen males had an HIV risk due to MSM and 4 had an HIV risk due to heterosexual sex. Eight individuals were female and from South Africa or Uganda and had HIV risk due to heterosexual sex. Ages were available for 24 of the individuals (missing for 1) and ranged from 19 – 50 years of age. The mean age was 27.9 (standard deviation [SD] ± 8.27) years and the median age was 25 (IQR: 22 - 31) years.

**Table 6-1. Characteristics of Individuals Infected with HIV Before Initiating PrEP**

| Study ID / Patient ID / Case Number | Age / Gender | Country | Race or Ethnicity | HIV Risk |
|---|---|---|---|---|
| CO-US-164-0403 PPD | 31 years /Female | PPD | | Heterosexual |
| CO-US-164-0403 PPD | 19 years / Male | | | MSM |
| CO-US-164-0403 PPD | 22 years / Male | | | MSM |
| GS-FR-276-1199 PPD | 32 years/ Male | | | MSM |
| CO-US-164-0432 PPD | 50 years/ Male | | | MSM |
| CO-US-164-0432 PPD | 27 years/Male | | | MSM |
| CO-US-164-0432 PPD | 22 years/ Male | | | MSM |
| CO-US-164-0441 PPD | Not Reported/ Male | | | MSM |
| CO-US-164-0468 PPD | 27 years/ Male | | | Heterosexual |
| CO-US-164-0468 PPD | 26 years/ Male | | | Heterosexual |
| CO-US-164-0468 PPD | 25 years/ Male | | | Heterosexual |

| Study ID / Patient ID / Case Number | Age / Gender | Country | Race or Ethnicity | HIV Risk |
|---|---|---|---|---|
| CO-US-164-0468 PPD | 22 years/ Male | PPD | | Heterosexual |
| CO-US-164-0468 PPD | 24 years/ Female | | | Heterosexual |
| CO-US-164-0468 PPD | 28 years/ Male | | | Heterosexual |
| CO-US-164-0468 PPD | 20 years/ Female | | | Heterosexual |
| CO-US-164-0468 PPD | 19 years/ Female | | | Heterosexual |
| CO-US-164-0468 PPD | 33 years/ Female | | | Heterosexual |
| CO-US-164-0468 PPD | 25 years/ Female | | | Heterosexual |
| CO-US-164-0468 PPD | 47 years/ Male | | | Heterosexual |
| CO-US-164-0468 PPD | 25 years/ Male | | | Heterosexual |
| CO-US-164-0468 PPD | 24 years/ Female | | | Heterosexual |
| CO-US-164-0468 PPD | 25 years/ Male | | | Heterosexual |
| CO-US-164-0482 VPA-C-PPD | 31 years/ Male | | | MSM |
| CO-US-276-1264 PPD | 22 years/ Female | | | Heterosexual |
| Spontaneous PPD | 43 years/ Male | | | MSM |

MSM = men who have sex with men.
Not Reported= Data requested but not provided

## 6.2. Exposure for Truvada for PrEP

Three of the individuals with HIV infection participated in the CO-US-164-0403 HPTN 067/ADAPT study which had an initial direct observed treatment (DOT) phase during which the individuals received once weekly dosing of Truvada for PrEP. The subjects had received 4 weekly doses and PrEP was discontinued after documentation of the HIV infection. One individual in the GS-FR-276-1199 RTU study in France was prescribed Truvada for PrEP on a non-continuous dosing regimen (IPERGAY regimen is assumed). The other individuals had initiated Truvada for PrEP on daily dosing regimen and discontinued after the HIV infection was documented. Exposure to Truvada for PrEP ranged from 1 – 851 days. Table 6-2 provides lists the Truvada for PrEP exposure for each individual.

**Table 6-2. Exposure for Truvada for PrEP for Individuals Infected with HIV Before Initiating PrEP**

| Study ID / Patient ID / Case Number | PrEP Start Date / PrEP Stop Date* | PrEP Duration of Exposure (days) | PrEP Dosing | Date of HIV Infection Documented | Adherence |
|---|---|---|---|---|---|
| CO-US-164-0403 PPD | PPD | 4 doses | 4 Weekly Doses | Week 4 | Week 4: Plasma TFV 0.4 ng/mL; TFV-DP 8.4 fmol/$10^6$ cells |
| CO-US-164-0403 PPD | | 4 doses | 4 Weekly Doses | PPD | Week 4: Plasma TFV not measured |
| CO-US-164-0403 PPD | | 4 doses | 4 Weekly Doses | | Week 4: Plasma TFV not measured; TFV-DP 6.6 fmol/$10^6$ cells |
| GS-FR-276-1199 PPD | | Not Reported | Non-continuous dosing | | Not Reported |
| CO-US-164-0432 PPD | | 7 | Daily | | Not Reported |
| CO-US-164-0432 PPD | | 7 | Daily | | Not Reported |
| CO-US-164-0432 PPD | | 14 | Daily | | Not Reported |
| CO-US-164-0441 PPD | | 21 | Daily | | Not Reported |
| CO-US-164-0468 PPD | | 1 | Daily | | Plasma on HIV diagnosis date: TFV=BQL |
| CO-US-164-0468 PPD | | 167 | Daily | | Plasma on HIV diagnosis date: TFV=BQL |
| CO-US-164-0468 PPD | | 170 | Daily | | Plasma on HIV diagnosis date: TFV-DP = 54.5 fmol/punch |
| CO-US-164-0468 PPD | | 170 | Daily | | Plasma on HIV diagnosis date: TFV-DP = 124 fmol/punch |
| CO-US-164-0468 PPD | | 29 | Daily | | Plasma on HIV diagnosis date: TFV-DP = 47.5 fmol/punch |

| Study ID / Patient ID / Case Number | PrEP Start Date / PrEP Stop Date* | PrEP Duration of Exposure (days) | PrEP Dosing | Date of HIV Infection Documented | Adherence |
|---|---|---|---|---|---|
| CO-US-164-0468 PPD | PPD | 28 | Daily | PPD | Plasma on HIV diagnosis date: TFV-DP = 74.6 fmol/punch |
| CO-US-164-0468 PPD | | 59 | Daily | | Plasma on HIV diagnosis date: TFV-DP = BLQ |
| CO-US-164-0468 PPD | | 170 | Daily | | Plasma on HIV diagnosis date: TFV-DP = BLQ |
| CO-US-164-0468 PPD | | 29 | Daily | | Plasma on HIV diagnosis date: TFV-DP = 54.4 fmol/punch |
| CO-US-164-0468 PPD | | 851 | Daily | | Plasma on HIV diagnosis date: TFV-DP = 40.7 fmol/punch |
| CO-US-164-0468 PPD | | 431 | Daily | | Plasma on HIV diagnosis date: TFV=BQL |
| CO-US-164-0468 PPD | | 1 | Daily | | Plasma on HIV diagnosis date: TFV=BQL |
| CO-US-164-0468 PPD | | 83 | Daily | | Plasma on HIV diagnosis date: TFV-DP = 78.4 fmol/punch |
| CO-US-164-0468 PPD | | 27 | Daily | | Plasma on HIV diagnosis date: TFV-DP = 90 fmol/punch |
| CO-US-164-0482 PPD | | 35 | Daily | | Site reported good adherence |
| CO-US-276-1264 PPD | | 34 | Daily | | DBS on HIV diagnosis date: TFV-DP = 339 fmol/punch |
| Spontaneous PPD | | 25 | Not Reported | | Not Reported |

* MM/DD/YYYY date format.
DBS=Dried Blood Spot
Not Reported= Data requested but not provided

## 6.3. Signs and Symptoms of HIV Infection and Resistance Testing

Table 6-3 provides details on the HIV tests that were done at screening, if any signs or symptoms of HIV infection were reported, the mutations that were reported from resistance testing, and a brief summary. In most cases, the screening testing failed to detect the HIV infection. In one case, the patient is believed to have become infected with HIV after screening and prior to initiating PrEP. Symptoms of the HIV infection were reported in 7 cases. The reported signs or symptoms were consistent with the established pattern of the acute retroviral syndrome and included fatigue, headache, lethargy, muscle weakness or pain, rash, fever, rash, flu-like symptoms, and abdominal pain. No signs or symptoms occurred in 15 individuals and no data were reported in 3 individuals. Resistance testing was performed in 21 of the 25 cases. In one case, the viral load was insufficient for testing; in another case sampling could not be amplified. The K65R mutation was detected in 2 individuals and M184V was detected in 10 individuals.

**Table 6-3. Signs and Symptoms of HIV Infection and HIV Testing Results for Individuals Infected with HIV Before Initiating PrEP**

| Study ID / Patient ID / Case Number | HIV Test at Screening | Signs or Symptoms at HIV Infection | Mutations | Comments |
|---|---|---|---|---|
| CO-US-164-0403 PPD | Rapid (2), 3rd generation tests | Not Reported | K65R (24.7%) | Had an acute HIV infection at enrollment that was not detected by 3rd generation rapid testing. Diagnosed at week 4 DOT phase (took 4 doses, none administered at W4 due to positive rapid test) {Sivay 2017} |
| CO-US-164-0403 PPD | Rapid (2), 3rd generation tests | Not Reported | M184I (3.5%), E138K (35.1%) | Had an acute HIV infection at enrollment that was not detected by 3rd generation rapid testing. Diagnosed at week 4 DOT phase (took 4 doses, none administered at W4 due to positive rapid test) {Sivay 2017} |
| CO-US-164-0403 PPD | Rapid (2), 3rd generation tests | Not Reported | No Mutations | Had an acute HIV infection at enrollment that was not detected by 3rd generation rapid testing. Diagnosed at week 4 DOT phase (took 4 doses, none administered at W4 due to positive rapid test) {Sivay 2017} |
| GS-FR-276-1199 PPD | 4th generation (ELISA) | No | No for all types, except not reported for Wild Type | HIV infection occurred 2 days prior to baseline PrEP visit |
| CO-US-164-0432 PPD | Rapid, 4th Generation | No | N/A | Viral load was insufficient to perform resistance testing in a second participant (120 copies/mL) {Liu 2016} |
| CO-US-164-0432 PPD | Rapid, 4th Generation | No | Wild Type, K65, K70, M184V/I | FTC resistance detected mixed with wild type (M184MI) one week after enrollment, which was not present at enrollment, suggesting acquired resistance; this participant was switch to combination antiretroviral therapy (TDF/FTC/darunavir/ritonavir/raltegravir) and has remained virologically suppressed {Liu 2016} |
| CO-US-164-0432 PPD | Rapid, 4th Generation | Yes - Fatigue, headache | No Mutations | No evidence of HIV resistance on standard or ultrasensitive minor variant testing, although testing was performed 6 weeks after PrEP discontinuation {Liu 2016} |
| CO-US-164-0441 PPD | 4th generation | Yes - Lethargy | N/A | HIV infection occurred 6 days prior to starting PrEP, and testing results available 9 days after starting PrEP. Resistance test not completed. |

| Study ID / Patient ID / Case Number | HIV Test at Screening | Signs or Symptoms at HIV Infection | Mutations | Comments |
|---|---|---|---|---|
| CO-US-164-0468 PPD | Rapid (2), Western Blot | Yes, Abdominal pain | No Mutations | Enrollment samples were quantified for HIV RNA after PrEP was initiated |
| CO-US-164-0468 PPD | Rapid (2), Western Blot | Yes - Fever, rash | No Mutations | Enrollment samples were quantified for HIV RNA after PrEP was initiated |
| CO-US-164-0468 PPD | Rapid (2), Western Blot | No | M184V | Enrollment samples were quantified for HIV RNA after PrEP was initiated |
| CO-US-164-0468 PPD | Rapid (2), Western Blot | No | K70, T69N, Y181C, K219Q, M184 | Enrollment samples were quantified for HIV RNA after PrEP was initiated |
| CO-US-164-0468 PPD | Rapid (2), Western Blot | Yes - fatigue, muscle weakness or pain | M184MV | Enrollment samples were quantified for HIV RNA after PrEP was initiated |
| CO-US-164-0468 PPD | Rapid (2), Western Blot | No | M184IMV | Enrollment samples were quantified for HIV RNA after PrEP was initiated |
| CO-US-164-0468 PPD | Rapid (2), Western Blot | No | E138A | Enrollment samples were quantified for HIV RNA after PrEP was initiated |
| CO-US-164-0468 PPD | Rapid (2), Western Blot | No | No Mutations | Enrollment samples were quantified for HIV RNA after PrEP was initiated |
| CO-US-164-0468 PPD | Rapid (2), Western Blot | No | Not Done – Sample could not be amplified | Enrollment samples were quantified for HIV RNA after PrEP was initiated |
| CO-US-164-0468 PPD | Rapid (2), Western Blot | No | No Mutations | Enrollment samples were quantified for HIV RNA after PrEP was initiated |
| CO-US-164-0468 PPD | Rapid (2), Western Blot | No | K201, E138G, V179D | Enrollment samples were quantified for HIV RNA after PrEP was initiated |
| CO-US-164-0468 PPD | Rapid (2), Western Blot | No | K20I, K103N, L210W, T215D | Enrollment samples were quantified for HIV RNA after PrEP was initiated |
| CO-US-164-0468 PPD | Rapid (2), Western Blot | No | M184V | Enrollment samples were quantified for HIV RNA after PrEP was initiated |
| CO-US-164-0468 PPD | Rapid (2), Western Blot | Yes - Rash | No Mutations | Enrollment samples were quantified for HIV RNA after PrEP was initiated |
| CO-US-164-0482 PPD | Rapid, AB test, Western Blot | Not Reported | K20R, V21I, A71V, D123E, E169K, D177E, M184IMV, G196E, V245E | Believed to have been HIV infected 2 days prior to baseline PrEP evaluation visit and did not report HIV exposure. He delayed starting PrEP until 16 days after HIV exposure |
| CO-US-276-1264 PPD | 4th generation | No | M184V/I | Plasma Genotype Resistance testing, Infected at enrollment |
| Spontaneous PPD | 4th generation | Yes - Flu-like illness | M184V/I | HIV testing results were negative, patient had flu-like illness the next day and waited to start PrEP until he felt better. HIV testing results were positive at next clinic visit |

Not Reported= Data requested but not provided

## 6.4. Selected Case Summaries by Study or Source

### 6.4.1. CO-US-164-0403 HPTN 067/ADAPT

Three participants in the HPTN 067/ADAPT study were acutely infected at enrollment {Sivay 2017}. The HIV testing that was performed at enrollment consisted of two 3rd generation HIV rapid tests and the tests failed to detect the HIV infection. The individuals received four weekly doses of Truvada during the directly observed therapy phase of the study. At Week 4, an HIV rapid test was reactive and a qualitative HIV RNA assay was positive and the HIV infection was detected. Retrospective testing revealed the individuals were HIV infected at enrollment. Resistance testing from Week 4 for individual #1 revealed K65R mutations in 24.7% of sequences and in individual #2 M184I and E138K were detected in 3.5% and 35.1% of sequences, respectively. No resistance was detected in individual #3. The investigators concluded that the very limited exposure to PrEP was sufficient to induce resistance.

### 6.4.2. CO-US-164-0432 DAIDS PrEP Demo

Three individuals who participated in the DAIDS PrEP Demonstration study in the US were acutely infected at enrollment {Liu 2016}. Participant #PPD started Truvada for PrEP on PPD after negative HIV testing at enrollment with a Rapid HIV test and a 4th generation HIV Ag/Ab test. The individual stopped PrEP one week later on PPD after HIV was detected in enrollment samples with Clearview Complete and CMIA 4th generation testing. There were no signs/symptoms at the time of HIV infection reported. Viral load was insufficient to perform resistance testing (120 copies/mL), and the individual maintained virologic suppression with antiretroviral therapy.

Participant #PPD started Truvada for PrEP on PPD after negative HIV testing at enrollment with a Rapid HIV test and a 4th generation HIV Ag/Ab test. The individual stopped PrEP one week later on PPD after HIV was detected in enrollment samples with Clearview STAT-Pack and CMIA 4th generation testing. There were no signs/symptoms at the time HIV infection was reported. Resistance testing detected FTC resistance (M184MI) mixed with wild type one week after enrollment, which was not present at enrollment, suggesting acquired resistance; this participant was switched to combination antiretroviral therapy (TDF/FTC/darunavir/ritonavir/raltegravir) and has remained virologically suppressed.

Participant #PPD started Truvada for PrEP on PPD after negative HIV testing at enrollment with a Rapid HIV test and a 4th generation HIV Ag/Ab test. The individual stopped PrEP 2 weeks later on PPD after a positive qualitative RNA test result HIV was detected in enrollment samples and were confirmed by quantitative HIV RNA findings. Symptoms of fatigue and headache at the time of HIV infection were reported. No evidence of HIV resistance on standard or ultrasensitive minor variant testing was detected, although testing was performed 6 weeks after PrEP discontinuation.

### 6.4.3. CO-US-164-0441 CDC PrEP Demo (SHIPP)

Participant #PPD PPD contacted another institution that was participating in CO-US-164-0441. The individual had a negative 4th generation test on PPD and received a prescription for Truvada for PrEP. At that visit, the individual reported lethargy but no other signs of acute HIV infection. PPD PPD . The individual returned to the clinic on PPD and requested a prescription for a 60 day supply of Truvada PPD A 4th generation test was repeated and the results were consistent with an acute HIV infection (p24 Ag+, Ab-, RNA +). Pre-exposure prophylaxis was subsequently discontinued.

### 6.4.4. CO-US-164-0468 Partner's Demonstration Project

There were a total of 14 individuals that were reported by the site to be infected at enrollment [Heffron 2018]. Patient PPD was not included in the report as the site reported the participant never initiated PrEP.

### 6.4.5. IN-AU-164-0482 VicPrEP

One individual acquired HIV infection 2 days prior to their baseline PrEP evaluation visit on PPD . The individual did not report HIV exposure. Truvada for PrEP was dispensed and the individual delayed initiating PrEP until 16 days (PPD ) after HIV exposure. No signs/symptoms were reported. The HIV infection was documented on PPD . Genotype resistance testing revealed M184IMV, I15V, K20R, V21I, E35D, M36I, R41K, I62V, L63C, 469Y, A71V, I72T, I93L, D123E, E169K, D177E, G196E, and V245E.

### 6.4.6. GS-FR-276-1199 French RTU

One individual in the French Temporary Recommendation for Use (RTU) study started Truvada for PrEP on PPD on a non-continuous (on demand) dosing schedule. At baseline, a 4th generation test was negative but no viral load or Western Blot test was performed. Results of PCR RNA viral load (800 000 copies/mL) from retesting a baseline sample confirmed the individual was infected with HIV. It is believed that the individual became infected 3 weeks prior to starting PrEP. No signs/symptoms were noted at time of HIV infection. Truvada for PrEP was discontinued onPPD . Genotype resistance testing was performed on a sample from PPD ; no mutations were reported and showed susceptibility to FTC/TFV.

### 6.4.7. CO-US-276-1264 3Ps

One participant in the 3Ps study in PPD was infected at enrollment. Individual #PPD started Truvada for PrEP on PPD after negative HIV test results at enrollment from a 4th generation test. Repeat testing at Week 4 with 4th generation test was positive and Truvada was stopped on PPD . No signs/symptoms were noted at time of HIV infection. Genotype testing for a sample collected PPD revealed MI84MV resistance mutations for FTC. The virus was susceptible to TFV. The other polymorphisms noted were E6D, V35K, T39E, S48T, V60I, K122E, K173A, Q174K, T200A, Q207S, R211K, F214L, V241I, V245Q, A272S, K281R, E291D, V292I, I293V, Q334N, and G335D.

### 6.4.8. Spontaneous Case PPD

A spontaneous literature case describes an individual who had negative pre-treatment HIV testing results (4th generation) {Desrosiers 2017}. The reason why PrEP was prescribed was that the individual had partners known to be from a high HIV prevalence area or social network. The patient did not practice safe sex before the reported HIV seroconversion. It was unknown how frequently the patient's HIV status was tested. It was unknown if the patient's HBV status was confirmed before starting Truvada. Truvada was prescribed once daily on PPD with negative HIV test but the patient developed flu-like illness the next day and did not initiate PrEP until mid-December when they felt better. According to the author this was likely seroconversion illness. The patient was adherent to Truvada PrEP as prescribed. Stop date of Truvada was on PPD. After the seroconversion genotype was performed which showed M184 mutation, the patient started on Triumeq® and Viread.

On 01 November 2017, upon further medical review, the event of 'Lack of effect' was removed from the case as authors identified acute retroviral syndrome during the period before the patient initiated Truvada for PrEP.

# 7. ANALYSIS OF HIV-1 INFECTIONS AFTER INITATION OF TRUVADA FOR PREP

## 7.1. Subject Characteristics

Ninety seven (97) cases of new HIV-1 infections were reported for individuals who had been prescribed Truvada for PrEP, of which 88 (90.7%) were participating in a demonstration project or clinical study and 9 (9.3%) were spontaneous cases reported in the literature or at a scientific meeting. The study identification, the individual's age and gender, the country, the individual's race/ethnicity, and HIV-1 risk factor are listed in Table 7-1.

The gender of the cases included 71 (73.2%) male, 24 (24.7%) females, and 2 (2.0%) transgender. Age data were available for 92 individuals and missing for 5 individuals. The mean age (± SD) was 26.5 (± 7.64) years and the median age was 25 (IQR: 21 – 30) years. For males, the median age was 25 years (range 17 – 50 years). For females, the median age was 22 years (range 17 - 56 years). For transgender, the one individual for whom the age was reported was 19 years. The country with the most cases was the United States (28, 28.9%). The other leading countries included 15 (15.5%) from Peru, 13 (13.4%) from South Africa, 12 (12.4%) from Uganda, 8 (8.3%) from Brazil and 4 (4.1%) from Kenya. The sexual risk factors for the cases included MSM (70, 72.1%), heterosexual (26, 26.8%), and bisexual (1, 1%).

Studies that reported more than one case included 24 cases from CO-US-164-0404 (iPrEX OLE), 11 cases from CO-US-164-0488 (SEARCH), 9 cases from CO-US-164-0441 (SHIPP), 7 cases from CO-US-164-0403 (HPTN 067), 6 cases from CO-US-276-0108 (Brazilian PrEP), 4 cases each from CO-US-276-1639 (HERS/HPTN 082), CO-US-164-0452 (ATN 110), and CO-US-164-0483 (HPTN 073), 3 cases from CO-US-276-1510 (PrEP Demo in Kenya), 2 cases each from CO-US-164-0468 (Partner's PrEP Demo), CO-US-164-0440 (iPERGAY), CO-US-164-0454 (PROUD), CO-US-164-0468 (Partners PrEP), and CO-US-276-1712 (AMPrEP). Eight studies reported only 1 case each.

**Table 7-1. Characteristics of Individuals who Developed New HIV-1 Infections after Initiation of Truvada for PrEP**

| Study ID / Patient ID / Case Number | Age / Gender | Country | Race or Ethnicity | HIV Risk* |
|---|---|---|---|---|
| CO-US-164-0403 PPD | 21 years/ Female | PPD | | Heterosexual |
| CO-US-164-0403 PPD | 30 years/ Male | | | MSM |
| CO-US-164-0403 PPD | 20 years/ Male | | | MSM |
| CO-US-164-0403 PPD | 21 years/ Female | | | Heterosexual |
| CO-US-164-0403 PPD | 19 years/ Female | | | Heterosexual |
| CO-US-164-0403 PPD | 21 years/ Female | | | Heterosexual |
| CO-US-164-0403 PPD | 21 years/ Female | | | Heterosexual |
| CO-US-164-0404 PPD | 29 years/ Male | | | MSM |
| CO-US-164-0404 PPD | 34 years/ Male | | | MSM |
| CO-US-164-0404 PPD | 37 years/ Male | | | MSM |
| CO-US-164-0404 PPD | 31 years/ Male | | | MSM |
| CO-US-164-0404 PPD | 25 years/ Male | | | MSM |
| CO-US-164-0404 PPD | 25 years/ Male | | | MSM |
| CO-US-164-0404 PPD | 27 years/ Male | | | MSM |
| CO-US-164-0404 PPD | 22 years/ Male | | | MSM |
| CO-US-164-0404 PPD | 26 years/ Male | | | MSM |
| CO-US-164-0404 PPD | 24 years/ Male | | | MSM |
| CO-US-164-0404 PPD | 33 years/ Male | | | MSM |
| CO-US-164-0404 PPD | 37 years/ Male | | | MSM |

| Study ID / Patient ID / Case Number | Age / Gender | Country | Race or Ethnicity | HIV Risk* |
|---|---|---|---|---|
| CO-US-164-0404 PPD | 26 years/ Male | PPD | | MSM |
| CO-US-164-0404 PPD | 26 years/ Male | | | MSM |
| CO-US-164-0404 PPD | 22 years/ Male | | | MSM |
| CO-US-164-0404 PPD | 31 years/ Male | | | MSM |
| CO-US-164-0404 PPD | 21 years/ Male | | | MSM |
| CO-US-164-0404 PPD | 24 years/ Male | | | MSM |
| CO-US-164-0404 PPD | 22 years/ Male | | | MSM |
| CO-US-164-0404 PPD | 30 years/ Male | | | MSM |
| CO-US-164-0404 PPD | 20 years/ Male | | | MSM |
| CO-US-164-0404 PPD | 19 years/ Male | | | MSM |
| CO-US-164-0404 PPD | 20 years/ Male | | | MSM |
| CO-US-164-0404 PPD | 26 years/ Male | | | MSM |
| CO-US-164-0432 PPD | 45 years/ Male | | | MSM |
| CO-US-164-0440 PP | Not Reported/Male | | | MSM |
| CO-US-164-0440 PP | Not Reported/Male | | | MSM |
| CO-US-164-0441 PPD | 22 years/ Male | | | MSM |
| CO-US-164-0441 PPD | 28 years/ Male | | | MSM |
| CO-US-164-0441 PPD | 19 years/ Male | | | MSM |
| CO-US-164-0441 PPD | 19 years/ Transgender Female | | | MSM |
| CO-US-164-0441 PPD | Not Reported/ Transgender Female | | | MSM |
| CO-US-164-0441 PPD | Not Reported/ Male | | | MSM |

| Study ID / Patient ID / Case Number | Age / Gender | Country | Race or Ethnicity | HIV Risk* |
|---|---|---|---|---|
| CO-US-164-0441 PPD | 28 years/ Male | PPD | | MSM |
| CO-US-164-0441 PPD | 24 years/ Male | | | MSM |
| CO-US-164-0441 PPD | 33 years/ Male | | | MSM |
| CO-US-164-0452 PPD | 18 years/ Male | | | MSM |
| CO-US-164-0452 PPD | 20 years/ Male | | | MSM |
| CO-US-164-0452 PPD | 21 years/ Male | | | MSM |
| CO-US-164-0452 PPD | 20 years/ Male | | | MSM |
| CO-US-164-0454 PPD | 27 years/ Male | | | MSM |
| CO-US-164-0454 PPD | 24 years/ Male | | | MSM |
| CO-US-164-0455 PPD | PPD years/ Male | | | MSM |
| CO-US-164-0468 PPD | 30 years/ Female | | | Heterosexual |
| CO-US-164-0468 PPD | 26 years/ Female | | | Heterosexual |
| CO-US-164-0478 PPD | 39 years/ Male | | | MSM |
| CO-US-164-0483 PPD | 26 years/ Male | | | MSM |
| CO-US-164-0483 PPD | 19 years/ Male | | | MSM |
| CO-US-164-0483 PPD | 23 years/ Male | | | MSM |
| CO-US-164-0483 PPD | 23 years/ Male | | | MSM |
| CO-US-164-0488 PPD | 36 years/ Female | | | Heterosexual |
| CO-US-164-0488 PPD | 32 years/ Female | | | Heterosexual |
| CO-US-164-0488 PPD | 27 years/ Female | | | Heterosexual |

| Study ID / Patient ID / Case Number | Age / Gender | Country | Race or Ethnicity | HIV Risk* |
|---|---|---|---|---|
| CO-US-164-0488 PPD | 22 years/ Female | PPD | | Heterosexual |
| CO-US-164-0488 PPD | 56 years/ Female | | | Heterosexual |
| CO-US-164-0488 PPD | 27 years/ Female | | | Heterosexual |
| CO-US-164-0488 PPD | 22 years/ Male | | | Heterosexual |
| CO-US-164-0488 PPD | 21 years/ Male | | | Heterosexual |
| CO-US-164-0488 PPD | 41 years/ Female | | | Heterosexual |
| CO-US-164-0488 PPD | 35 years/ Female | | | Heterosexual |
| CO-US-164-0488 PPD | 21 years/ Female | | | Heterosexual |
| CO-US-276-0108 PPD | 25 years/ Male | | | MSM |
| CO-US-276-0108 PPD | 27 years/ Male | | | MSM |
| CO-US-276-0108 PPD | 25 years/ Male | | | MSM |
| CO-US-276-0108 PPD | 27 years/ Male | | | MSM |
| CO-US-276-0108 PPD | 24 years/ Male | | | Bisexual |
| CO-US-276-0108 PPD | 20 years/ Male | | | MSM |
| CO-US-276-0115 PPD | 24 years/ Male | | | MSM |
| CO-US-276-0126 PPD | 49 years/ Female | | | Heterosexual |
| CO-US-276-1199/U83119 PPD | 31 years/ Male | | | MSM |
| CO-US-276-1510 PPD | 32 years/ Male | | | MSM |

| Study ID / Patient ID / Case Number | Age / Gender | Country | Race or Ethnicity | HIV Risk* |
|---|---|---|---|---|
| CO-US-276-1510 PPD | PPD years/ Female | PPD | | Heterosexual |
| CO-US-276-1510 PPD | 32 years/ Female | | | Heterosexual |
| CO-US-276-1639 PPD | 19 years/ Female | | | Heterosexual |
| CO-US-276-1639 PPD | 18 years/ Female | | | Heterosexual |
| CO-US-276-1639 PPD | 18 years/ Female | | | Heterosexual |
| CO-US-276-1639 PPD | 18 years/ Female | | | Heterosexual |
| CO-US-276-1712 PPD | 50 years/ Male | | | MSM |
| CO-US-276-1712 PPD | 24 years/ Male | | | MSM |
| CO-US-276-1774 PPD | 22 Years/ Female | | | Heterosexual |
| CO-US-276-4369 PPD | 27 years/ Male | | | MSM |
| Literature PPD Author: Knox {Knox 2017} | 43 years/ Male | | | MSM |
| Literature PPD Author: Pilarski {Pilarski 2017} | 42 years/ Male | | | MSM |
| Literature PPD Author: Thaden {Thaden 2018} | 34 years/ Male | | | MSM |
| Literature PPD Author: Markowitz {Markowitz 2017} | 26 years/ Male | | | MSM |
| Literature PPD Author: Zucker {Zucker 2018} | 31 years/ Male | | | MSM |
| Literature PPD Author: Volk {Volk 2018} | 23 years/ Male | | | MSM |
| Literature PPD Author: Cohen {Cohen 2018} | 21 years/ Male | | | MSM |

| Study ID / Patient ID / Case Number | Age / Gender | Country | Race or Ethnicity | HIV Risk* |
|---|---|---|---|---|
| Literature<br>Author: Colby<br>{Colby 2018} | 28 years/ Male | PPD | | MSM |
| Spontaneous<br>PPD | 21 years/ Male | | | MSM |

* HIV risk factors were not collected for individuals who did not seroconvert
MSM = men who have sex with men.
Not Reported= Data requested but not provided

## 7.2. Estimated Time on Truvada for PrEP

The estimated time on Truvada for PrEP based upon the reported start and stop dates are listed in Table 7-2. The reported prescribed dosing regimen, the date of suspected HIV infection or date of HIV diagnosis, and the number of days from first prescription for PrEP and suspected HIV infection or date of HIV diagnosis are also listed. The median number of days for which the individual was prescribed Truvada for PrEP was 2 (range 5 – 944) days. The median number of days between when Truvada for PrEP was prescribed and the HIV infection was 274 (range 22 – 944) days. Two individuals were receiving weekly doses of Truvada as part of the study, 8 individuals were on intermittent dosing regimens, and the remaining 90 individuals were prescribed Truvada for PrEP on a daily regimen.

**Table 7-2. Estimated Exposure to Truvada for PrEP for Individuals who Developed New HIV-1 Infections after Initiation of Truvada for PrEP**

| Study ID / Patient ID / Case Number | PrEP Start Date / PrEP Stop Date | Estimated Time on PrEP (Days) | PrEP Dosing | Date of HIV Infection or HIV Diagnosis | Days from PrEP Start to HIV Infection |
|---|---|---|---|---|---|
| CO-US-164-0403 PPD | PPD | 60 | Weekly | PPD | Not Reported |
| CO-US-164-0403 PPD | | 22 | Weekly | | Not Reported |
| CO-US-164-0403 PPD | | 57 | Daily | | 5756 |
| CO-US-164-0403 PPD | | 109 | Intermittent | | 119 |
| CO-US-164-0403 PPD | | 33 | Intermittent | | 33 |
| CO-US-164-0403 PPD | | 153 | Intermittent | | 153 |
| CO-US-164-0403 PPD | | 75 | Intermittent | | 105 |
| CO-US-164-0404 PPD | | 417 | Daily | | 417 |
| CO-US-164-0404 PPD | | 507 | Daily | | 507 |
| CO-US-164-0404 PPD | | 35 | Daily | | 57 |
| CO-US-164-0404 PPD | | 505 | Daily | | 505 |
| CO-US-164-0404 PPD | | 506 | Daily | | 506 |
| CO-US-164-0404 PPD | | 428 | Daily | | 428 |
| CO-US-164-0404 PPD | | 423 | Daily | | 423 |
| CO-US-164-0404 PPD | | 429 | Daily | | 429 |
| CO-US-164-0404 PPD | | 612 | Daily | | 612 |
| CO-US-164-0404 PPD | | 170 | Daily | | 170 |

| Study ID / Patient ID / Case Number | PrEP Start Date / PrEP Stop Date | Estimated Time on PrEP (Days) | PrEP Dosing | Date of HIV Infection or HIV Diagnosis | Days from PrEP Start to HIV Infection |
|---|---|---|---|---|---|
| CO-US-164-0404 PPD | PPD | 526 | Daily | PPD | 526 |
| CO-US-164-0404 PPD | | 537 | Daily | | 537 |
| CO-US-164-0404 PPD | | 504 | Daily | | 504 |
| CO-US-164-0404 PPD | | 248 | Daily | | 248 |
| CO-US-164-0404 PPD | | 421 | Daily | | 421 |
| CO-US-164-0404 PPD | | 502 | Daily | | 502 |
| CO-US-164-0404 PPD | | 483 | Daily | | 483 |
| CO-US-164-0404 PPD | | 252 | Daily | | 252 |
| CO-US-164-0404 PPD | | 174 | Daily | | 174 |
| CO-US-164-0404 PPD | | 273 | Daily | | 273 |
| CO-US-164-0404 PPD | | 199 | Daily | | 199 |
| CO-US-164-0404 PPD | | 257 | Daily | | 257 |
| CO-US-164-0404 PPD | | 384 | Daily | | 384 |
| CO-US-164-0404 PPD | | 477 | Daily | | 477 |
| CO-US-164-0432 PPD | | 133 | Daily | | 133 |
| CO-US-164-0440 PPI | | Not Reported | Intermittent | | Not Reported |
| CO-US-164-0440 PPI | | Not Reported | Intermittent | | Not Reported |
| CO-US-164-0441 PPD | | 496 | Daily | | 508 |
| CO-US-164-0441 PPD | | 161 | Daily | | 161 |

| Study ID / Patient ID / Case Number | PrEP Start Date / PrEP Stop Date | Estimated Time on PrEP (Days) | PrEP Dosing | Date of HIV Infection or HIV Diagnosis | Days from PrEP Start to HIV Infection |
|---|---|---|---|---|---|
| CO-US-164-0441 PPD | PPD | 83 | Daily | PPD | 83 |
| CO-US-164-0441 PPD | | 688 | Daily | | 688 |
| CO-US-164-0441 PPD | | 141 | Daily | | 141 |
| CO-US-164-0441 PPD | | 97 | Daily | | 93 |
| CO-US-164-0441 PPD | | 153 | Daily | | 159 |
| CO-US-164-0441 PPD | | 84 | Daily | | 84 |
| CO-US-164-0441 PPD | | 59 | Daily | | 59 |
| CO-US-164-0452 PPD | | 330 | Daily | | 341 |
| CO-US-164-0452 PPD | | 229 | Daily | | 232 |
| CO-US-164-0452 PPD | | 5 | Daily | | 29 |
| CO-US-164-0452 PPD | | 296 | Daily | | 296 |
| CO-US-164-0454 PPD | | 945 | Daily | | 945 |
| CO-US-164-0454 PPD | | 37 | Daily | | 37 |
| CO-US-164-0455 PPD | | 225 | Daily | | 226 |
| CO-US-164-0468 PPD | | 84 | Daily | | 84 |
| CO-US-164-0468 PPD | | 453 | Daily | | 453 |
| CO-US-164-0478 PPD | | 240 | Daily | | 240 |
| CO-US-164-0483 PPD | | 355 | Daily | | Not Reported |

| Study ID / Patient ID / Case Number | PrEP Start Date / PrEP Stop Date | Estimated Time on PrEP (Days) | PrEP Dosing | Date of HIV Infection or HIV Diagnosis | Days from PrEP Start to HIV Infection |
|---|---|---|---|---|---|
| CO-US-164-0483 PPD | PPD | 21 | Daily | PPD | 14 |
| CO-US-164-0483 PPD | | 225 | Daily | | 225 |
| CO-US-164-0483 PPD | | 247 | Daily | | 247 |
| CO-US-164-0488 PPD | | 171 | Daily | | 171 |
| CO-US-164-0488 PPD | | 200 | Daily | | 220 |
| CO-US-164-0488 PPD | | 283 | Daily | | 283 |
| CO-US-164-0488 PPD | | 422 | Daily | | 422 |
| CO-US-164-0488 PPD | | 413 | Daily | | 413 |
| CO-US-164-0488 PPD | | 444 | Daily | | 444 |
| CO-US-164-0488 PPD | | 211 | Daily | | 211 |
| CO-US-164-0488 PPD | | 395 | Daily | | 395 |
| CO-US-164-0488 PPD | | 147 | Daily | | 147 |
| CO-US-164-0488 PPD | | 184 | Daily | | 184 |
| CO-US-164-0488 PPD | | 120 | Daily | | 120 |
| CO-US-276-0108 PPD | | 484 | Daily | | 484 |
| CO-US-276-0108 PPD | | 701 | Daily | | 703 |
| CO-US-276-0108 PPD | | 176 | Daily | | 176 |

| Study ID / Patient ID / Case Number | PrEP Start Date / PrEP Stop Date | Estimated Time on PrEP (Days) | PrEP Dosing | Date of HIV Infection or HIV Diagnosis | Days from PrEP Start to HIV Infection |
|---|---|---|---|---|---|
| CO-US-276-0108 PPD | PPD | 509 | Daily | PPD | 502 |
| CO-US-276-0108 PPD | | 267 | Daily | | 267 |
| CO-US-276-0108 PPD | | 232 | Daily | | 190 |
| CO-US-276-0115 PPD | | 106 | Daily | | 106 |
| CO-US-276-0126 PPD | | 30 | Daily | | 30 |
| CO-US-276-1199 PPD | | 26 | Intermittent | | 26 |
| CO-US-276-1510 PPD | | 79 | Daily | | 79 |
| CO-US-276-1510 PPD | | 128 | Daily | | 128 |
| CO-US-276-1510 PPD | | 23 | Daily | | 53 |
| CO-US-276-1639 PPD | | 155 | Daily | | 154 |
| CO-US-276-1639 PPD | | 290 | Daily | | 270 |
| CO-US-276-1639 PPD | | 274 | Daily | | 275 |
| CO-US-276-1639 PPD | | 74 | Daily | | 74 |
| CO-US-276-1712 PPD | | 245 | Daily | | 239 |
| CO-US-276-1712 PPD | | 100 | Daily | | 99 |
| CO-US-276-1774 PPD | | 22 | Daily | | 22 |
| CO-US-276-4369 PPD | | 105 | Daily | | 93 |

| Study ID / Patient ID / Case Number | PrEP Start Date / PrEP Stop Date | Estimated Time on PrEP (Days) | PrEP Dosing | Date of HIV Infection or HIV Diagnosis | Days from PrEP Start to HIV Infection |
|---|---|---|---|---|---|
| Literature PPD {Knox 2017} | PPD | 753 | Daily | PPD | 753 |
| Literature PPD {Pilarski 2017} | | 203 | Daily | | 203 |
| Literature PPD {Thaden 2018} | | 440 | Daily | | 432 |
| Literature PPD Author: {Markowitz 2017} | | 147 | Daily | | 124 |
| Literature PPD {Zucker 2018} | | 29 | Daily | | 29 |
| Literature PPD {Volk 2018} | | 276 | Intermittent (only took single doses pre/post sex) | | 276 |
| Literature PPD {Cohen 2018} | | 395 | Daily | | 395 |
| Literature Author: Colby {Colby 2018} | | 62 | Daily | | 62 |
| Spontaneous PPD | | 417 | Daily | | 417 |

Not Reported= Data requested but not provided

## 7.3. Signs/Symptoms of HIV-1 Infection, Adherence Comments, and Resistance Testing in Individuals who Developed New HIV-1 Infections after Initiation of Truvada for PrEP

The signs or symptoms of HIV infection reported, whether a dried blood spot (DBS) test was done, adherence comments, and the mutations reported from the results of the resistance testing are listed in Table 7-3. Twenty seven (27, 27.8%) of the individuals reported signs or symptoms of acute HIV infection. The reported signs or symptoms included abdominal pain, bone pain, cough, dysphagia, dysuria, fatigue, fever, headache, lymphadenopathy, malaise, muscle weakness or pain (myalgia), nasal congestion, nasal obstruction, pyrexia, oropharyngeal pain, rash, rhinorrhea, sore throat, stress, vomiting, and/or weight loss.

Dried blood spot (DBS) tests were collected in 61 (62.9%) individuals and results were available for 52 (53.6%) of individuals who developed an HIV infection. Nine individuals in study CO-US-164-0441 (SHIPP) had DBS collected but the study has not reported the results. The DBS tests were collected either at the clinic visit when the HIV infection was diagnosed or shortly before or after the HIV infection. A tenofovir diphosphate (FTV-DP) concentration > 700 fmol per punch is consistent with taking at least 4 Truvada tablets per week and is considered adequate adherence. Four of the 52 (7.7%) of the individuals had TFV-DP concentrations > 700 fmol per punch and were considered adherent. Good adherence was reported for 2 individuals who had DBS tests taken but no results were reported. Two individuals were reported to have good adherence but did not have DBS samples taken. In total 8 of the 52 (15.4%) were considered adherent to PrEP dosing.

**Table 7-3. Signs/Symptoms of HIV Infection, Adherence, and Resistance Testing in Individuals who Developed New HIV-1 Infections after Initiation of Truvada for PrEP**

| Study ID / Patient ID / Case Number | Signs or Symptoms at HIV Infection | DBS | Adherence Comments | Mutations |
|---|---|---|---|---|
| CO-US-164-0403 PPD | Not Reported | No | Acquired infection during DOT phase Diagnosed at Week 5 W4 Plasma TFV-DP = 8.5 fmol/$10^6$ cells W5 TFV-DP = 2.6 fmol/$10^6$ cells W6 TFV-DP = 2.7 fmol/$10^6$ cells | No Mutations |
| CO-US-164-0403 PPD | Not Reported | No | Acquired infection during DOT phase W4 Plasma FTC = 0.8 fmol/$10^6$ cellsW6 TFV-DP = 6.3 fmol/$10^6$ cells | No Mutations |
| CO-US-164-0403 PPD | Yes - headache | No | Drug detected in only 1 plasma and one plasma sample collected | K103N |
| CO-US-164-0403 PPD | No | No | Drug detected in 2 out of 4 plasma samples, low levels in PBMCs; considered not adherent | No Mutations |

| Study ID / Patient ID / Case Number | Signs or Symptoms at HIV Infection | DBS | Adherence Comments | Mutations |
|---|---|---|---|---|
| CO-US-164-0403 PPD | No | No | Adherence was intermittent. Took dose every 3–4 days first six weeks, then 2 pills/wk next 2 weeks irregularly. Took pill 4 days before acute infection visit after no pills for 7 days. | K65R, M184I |
| CO-US-164-0403 PPD | No | No | Drug detected in 1 out of 7 plasma and 2 out of 3 PBMC samples. Infrequent use/low adherence - 42% of assigned doses. | No Mutations |
| CO-US-164-0403 PPD | No | No | Drug detected in 2 out of 4 plasma and 1 out of 2 PBMC samples, infrequent use/low adherence - 67% of assigned doses. | No Mutations |
| CO-US-164-0404 PPD | Not Reported | Yes | DBS on HIV diagnosis date: TFV-DP = BLQ | PRK20R, PRM36I |
| CO-US-164-0404 PPD | Not Reported | Yes | DBS on HIV diagnosis date: TFV-DP = 416 | PRM36I |
| CO-US-164-0404 PPD | Not Reported | Yes | DBS on HIV diagnosis date: TFV-DP = BLQ | No Mutations |
| CO-US-164-0404 PPD | Not Reported | Yes | DBS on HIV diagnosis date: TFV-DP = BLQ | PRM36I, PRA71V |
| CO-US-164-0404 PPD | Not Reported | Yes | DBS on HIV diagnosis date: TFV-DP = BLQ | RTV90I |
| CO-US-164-0404 PPD | Not Reported | Yes | DBS on HIV diagnosis date: TFV-DP = 49.9 | No Mutations |
| CO-US-164-0404 PPD | Not Reported | Yes | DBS on HIV diagnosis date: TFV-DP = 77.2 | PRK20M, PRM3VI |
| CO-US-164-0404 PPD | Yes - headache | Yes | DBS on HIV diagnosis date: TFV-DP = BLQ | RTE138A |
| CO-US-164-0404 PPD | Not Reported | Yes | DBS on HIV diagnosis date: TFV-DP = BLQ | No Mutations |
| CO-US-164-0404 PPD | Not Reported | Yes | DBS on HIV diagnosis date: TFV-DP = BLQ | PRL10V |
| CO-US-164-0404 PPD | Yes – fever, headache | Yes | DBS 9 days before HIV diagnosis date: TFV-DP = BLQ | K65, M184, K70, K103N |
| CO-US-164-0404 PPD | Yes - fever | Yes | DBS on HIV diagnosis date: TFV-DP = BLQ | RTK103N |
| CO-US-164-0404 PPD | Not Reported | Yes | DBS on HIV diagnosis date: TFV-DP = 110 | PRM36I |
| CO-US-164-0404 PPD | Not Reported | Yes | DBS on HIV diagnosis date: TFV-DP = 219 | PRM36I |

| Study ID / Patient ID / Case Number | Signs or Symptoms at HIV Infection | DBS | Adherence Comments | Mutations |
|---|---|---|---|---|
| CO-US-164-0404 PPD | Not Reported | Yes | DBS on HIV diagnosis date: TFV-DP = 160 | M184 |
| CO-US-164-0404 PPD | Not Reported | Yes | DBS on HIV diagnosis date: TFV-DP = BLQ | PRM36I |
| CO-US-164-0404 PPD | Not Reported | Yes | DBS on HIV diagnosis date: TFV-DP is 44.5 | K65, M184, K70, PRM36I, PRA71V |
| CO-US-164-0404 PPD | Not Reported | Yes | DBS on HIV diagnosis date: TFV-DP is BLQ | No Mutations |
| CO-US-164-0404 PPD | Not Reported | Yes | DBS on HIV diagnosis date: TFV-DP is 104 | PRM36I |
| CO-US-164-0404 PPD | Not Reported | Yes | DBS on HIV diagnosis date: TFV-DP is BLQ | RTK101Q, RTV179D, PRL10I |
| CO-US-164-0404 PPD | Not Reported | Yes | DBS on HIV diagnosis date: TFV-DP is BLQ | PRM36I, PRT74S |
| CO-US-164-0404 PPD | Not Reported | Yes | DBS on HIV diagnosis date: TFV-DP is BLQ | PRK20R, PRM36I |
| CO-US-164-0404 PPD | Not Reported | Yes | DBS on HIV diagnosis date: TFV-DP is 50.8 | PRK20R, PRM36I |
| CO-US-164-0404 PPD | No | Yes | DBS on HIV diagnosis date: TFV-DP is 55.3 | PRM36I |
| CO-US-164-0432 PPD | Not Reported | Yes | DBS on HIV diagnosis date: TFV-DP is 36.4. This participant reported last taking PrEP 37 days before seroconversion and had TFV-DP levels of < 2 doses/wk at his seroconversion and all prior visits. | K103N |
| CO-US-164-0440 PPD | Not Reported | No | Subject returned 60 out of 60 tablets - not adherent. | No Mutations |
| CO-US-164-0440 PPD | Yes - Not Reported | No | Subject returned 58 out of 60 tablets - not adherent | No Mutations |
| CO-US-164-0441 PPD | No | Yes - Not Reported | Has been off and on by self-report. The last reported use was approximately 2 weeks prior to HIV diagnosis. | No Mutations |
| CO-US-164-0441 PPD | No | Yes - Not Reported | Not Reported | Not Reported |
| CO-US-164-0441 PPD | Yes -Not Reported | Yes - Not Reported | Not Reported | Not Reported |
| CO-US-164-0441 PPD | No | Yes - Not Reported | Not Reported | Not Reported |

| Study ID / Patient ID / Case Number | Signs or Symptoms at HIV Infection | DBS | Adherence Comments | Mutations |
|---|---|---|---|---|
| CO-US-164-0441 PPD | Yes - rash beginning 3 months prior to diagnosis, cold symptoms 6 weeks prior to diagnosis | Yes - Not Reported | Not Reported | V179D, E35D, A71V |
| CO-US-164-0441 PPD | Yes – cough, congestion, night sweats, difficulty sleeping for 2 weeks | Yes - Not Reported | Not Reported | M184V/I, L10I, E35D, D60E, A71T |
| CO-US-164-0441 PPD | None reported at time of seroconversion, EHR documents visit to another clinic on PPD. Patient presented with flu-like symptoms, but not tested | Yes - Not Reported | Not Reported | M184 |
| CO-US-164-0441 PPD | No | Yes - Not Reported | Not Reported | Not Reported |
| CO-US-164-0441 PPD | No | Yes - Not Reported | Reported taking TDF/FTC on day of diagnosis but staff impression was that he may not have been consistently adherent. | Not Reported |
| CO-US-164-0452 PPD | Yes - Stress | Yes | DBS 9 days before HIV diagnosis: TFV-DP = 48 fmol/punch | Not Done, inability for amplification |
| CO-US-164-0452 PPD | No | Yes | DBS on HIV diagnosis date: TFV-DP is 12.5 fmol/punch | No Mutations |
| CO-US-164-0452 PPD | Yes - nasal congestion, rhinorrhea, oropharyngeal pain, nasal obstruction | Yes | DBS on HIV diagnosis date: TFV-DP = 12.5 fmol/punch | R211K, L63P, H69Q, V77I |
| CO-US-164-0452 PPD | Yes - pyrexia, dysphagia, malaise | Yes | DBS 3 days before HIV diagnosis: TFV-DP = 12.5 fmol/punch | L210F, R211K, E35D, L63P, V771 |
| CO-US-164-0454 PPD | No | No | - | Not Done, inability for amplification |
| CO-US-164-0454 PPD | Not Reported | No | - | M184 |
| CO-US-164-0455 PPD | Not Reported | Yes | The investigator reported that the DBS analysis was consistent with taking fewer than a mean of 2 doses per week at the likely time of HIV acquisition. | T69N |
| CO-US-164-0468 PPD | Yes - diffuse macular / pamaculopapular/morbiliform rash, enlarged cervical lymph node, fever, fatigue, sore throat, rash, in, vomiting, bone pain | No | Plasma on HIV diagnosis date: TFV-DP = BLQ. | No Mutations |
| CO-US-164-0468 PPD | No | No | Plasma on HIV diagnosis date: TFV-DP = 54.4 fmol/punch | Not Done – Sample could not be amplified |

| Study ID / Patient ID / Case Number | Signs or Symptoms at HIV Infection | DBS | Adherence Comments | Mutations |
|---|---|---|---|---|
| CO-US-164-0468 PPD | No | No | Plasma on HIV diagnosis date: TFV-DP = 40.7 fmol/punch | No Mutations |
| CO-US-164-0468 PPD | Yes - headache, vomiting | No | Plasma on HIV diagnosis date: TFV-DP = BLQ | No Mutations |
| CO-US-164-0478 PPD | Yes - weight loss | Yes | Individual reported discontinuing drug prior to seroconversion | M184, K103N, A71T, Other minor mutations |
| CO-US-164-0483 PPD | Not Reported | Yes | DBS on day after HIV diagnosis: TFV-DP = BLQ | A71T |
| CO-US-164-0483 PPD | Yes - 1 week history of headache, rhinorrhea, and cough. | Yes | DBS completed 3 wks after HIV infection TFV-DF = 351 fmol/punch | T97Aa (98.6%), E157Q (99.11%), Resistant to drugs EVG and RAL |
| CO-US-164-0483 PPD | Not Reported | Yes | Approx 4 months before HIV infection, DBS TFV-DP = 278 fmol/punch. At visit 6.0 (26 week visit) 13/JAN/15. The DBS results for both FTC-TP and TFV-DP were BLQ. | Q146L (5.2%) |
| CO-US-164-0483 PPD | Not Reported | Yes | 52 days prior to seroconversion date DBS = 138 fmol/punch | K65R (2.5%), K103N (99.0%), resistant to drugs TDF, DDI, ABC, D4T, FTC, 3TC, EFV, NVP |
| CO-US-164-0488 PPD | Yes - Intermittent fever, Lymphadenopathy | No | Subject reported intermittent poor adherence prior to HIV infection | Site plans to perform resistance testing on available samples in the coming months |
| CO-US-164-0488 PPD | No | No | Subject reported poor adherence prior to HIV infection | Site plans to perform resistance testing on available samples in the coming months |

| Study ID / Patient ID / Case Number | Signs or Symptoms at HIV Infection | DBS | Adherence Comments | Mutations |
|---|---|---|---|---|
| CO-US-164-0488 PPD | No | No | Subject reported missing PrEP for a period of 2 weeks during which she engaged with a new sexual partner. | Site plans to perform resistance testing on available samples in the coming months |
| CO-US-164-0488 PPD | No | No | Subject reported poor adherence starting in late 2017; Husband is HIV+ and unsuppressed. | No Mutations |
| CO-US-164-0488 PPD | No | No | Subject moved away and off PrEP after 1st month and off PrEP for approx 1 year. Subject tested HIV+ on return to study. | No Mutations |
| CO-US-164-0488 PPD | No | No | Subject lost to follow-up shortly after enrollment for approx. 1 year; has partner of unknown HIV status. | No Mutations |
| CO-US-164-0488 PPD | No | No | Not Reported | No Mutations |
| CO-US-164-0488 PPD | No | No | Not Reported | Site plans to perform resistance testing on available samples in the coming months |
| CO-US-164-0488 PPD | No | No | Subject reported poor adherence in last weeks, missed pills for 2 weeks prior to seroconversion. | Site plans to perform resistance testing on available samples in the coming months |
| CO-US-164-0488 PPD | No | No | Subject reported she lost medications and had multiple partners prior to seroconversion | Site plans to perform resistance testing on available samples in the coming months |

| Study ID / Patient ID / Case Number | Signs or Symptoms at HIV Infection | DBS | Adherence Comments | Mutations |
|---|---|---|---|---|
| CO-US-164-0488 PPD | No | No | Patient reported she stopped PrEP 12 weeks prior to seroconversion, suspected husband infidelity. | Site plans to perform resistance testing on available samples in the coming months |
| CO-US-276-0108 PPD | No | Yes | DBS 3 month before HIV infection: TFV-DP = BLQ | 41L, 67N, 211K, 215V, 219E, 333E, 190A, 35I, 40D, 49R, 68G, 135T, 162N, 173Q, 178V, 200I, 214L, 218E, 228H, 272P, 294T, 297K, 332?, 324P, 329L, 334H |
| CO-US-276-0108 PPD | Yes - fever, myalgia | Yes | DBS completed 120 days after HIV infection, TFV-DP = BLQ. | E35D, L63A, S162C, P176S, T200A, R211K, E248D, A272P, K277R, V292I, I293V, E297Q, I326V, Q334L |
| CO-US-276-0108 PPD | Yes - fever | Yes | DBS one month before HIV infection: TFV-DP = BLQ. | 41L, 67N, 211K, 215V, 219E, 333E, 190A, 35I, 40D, 49R, 68G, 135T, 162N, 173Q, 178V, 200I, 214L, 218E, 228H, 272P, 294T, 297K, 332, 324P, 329L, 334H |
| CO-US-276-0108 PPD | Yes - cervical adenopathy | Yes | DBS completed 224 days after HIV infection, TFV-DP = 191 fmol/punch. | No Mutations |
| CO-US-276-0108 PPD | Yes - fever, cervical adenopathy | Yes | DBS completed 465 days after HIV infection, TFV-DP = BLQ. | 63P |
| CO-US-276-0108 PPD | No | Yes | DBS results pending analysis | No, Inability for amplification |

| Study ID / Patient ID / Case Number | Signs or Symptoms at HIV Infection | DBS | Adherence Comments | Mutations |
|---|---|---|---|---|
| CO-US-276-0115 PPD | No | Yes | The site reported that the patient's drug concentrations were consistent with daily dosing, values not reported | D67N, K10SR, M184V, T215S, K219Q, L10I, P9T, K11R, V60I, K102E, E122K, 5162C, Q207N, L214F, L228H, E248V, K249Q, G333E, VSI, E35D, S37E, D60E, L63P, I72M, I93L |
| CO-US-276-0126 PPD | No | Yes | DBS results pending analysis | No samples available for testing |
| CO-US-276-1199 PPD | Not Reported | No | The infection date was estimated 6 to 9 days after initiation of Truvada when the subject had multiple unprotected homosexual experiences with psychoactive drug consumption during sex. According to the physician, the subject was adherent the prescribed regimen and had no concomitant treatment. Plasma 1 day after HIV diagnosis: TFV = 77 ng/mL. The adherence to Truvada was qualified as "good". | M184V/1, 101, 15V, 69K, 891 |
| CO-US-276-1510 PPD | No | No | MEMS cap data shows the participant took Truvada on 38 days and missed 40 days | No samples available for testing |
| CO-US-276-1510 PPD | No | No | MEMS cap data shows the participant took Truvada on 69 days and missed 58 days | No samples available for testing |
| CO-US-276-1510 PPD | No | No | MEMS cap data shows the participant took Truvada on 17 days and missed 6 days | No samples available for testing |
| CO-US-276-1639 PPD | No | Yes | DBS Week 13: 559 fmol/ punch, Week 26: 243 fmol/ punch | No Mutations |
| CO-US-276-1639 PPD | No | Yes | DBS Week 13: 145 fmol/punch, Week 26: 74 fmol/ punch | K101E, K103N, E138A, G190A |

| Study ID / Patient ID / Case Number | Signs or Symptoms at HIV Infection | DBS | Adherence Comments | Mutations |
|---|---|---|---|---|
| CO-US-276-1639 PPD | No | Yes | DBS Week 13: 263 fmol/punch, Week 26: BLQ | No Mutations |
| CO-US-276-1639 PPD | No | Yes | DBS Week 13: BLQ | No Mutations |
| CO-US-276-1712 PPD | Yes – fever, dysuria | Yes | DBS at time of HIV diagnosis: TFV-DP = 2258 fmol/punch. Despite good adherence, infected with Wild Type HIV. | No Mutations |
| CO-US-276-1712 PPD | Yes – fever, dysuria, malaise, headache, facial erythematous maculae | No | Lost to follow-up, when HIV was detected he told the site he stopped PrEP 3 months before infection | No Mutations |
| CO-US-276-1774 PPD | No | No | - | K20R, V35T, T39G, S48T, V60I, K122E, D123S, S162A, Q174R, D177E, G196E, T200A, Q207E, R211K, V245Q, D250E, A272P, K275R, K277R, E291D, V292I, I293V, Q334D, G335N, R356K, M357V, R358K, G359T, A360T, K366R, A376S, T377M, T386I, K390R, A400T, E404D, A437V, M184V, K103N, M184 |

| Study ID / Patient ID / Case Number | Signs or Symptoms at HIV Infection | DBS | Adherence Comments | Mutations |
|---|---|---|---|---|
| CO-US-276-4369 PPD | No | Yes | Negative at baseline; PrEP start 40 days after baseline (negative); HIV NAT positive at 3m; unprotected anal intercourse with HIV+ partner but good adherence/protective levels; suspected infection at initiation or before achieving protection. At the time the participant tested positive, the DBS TFV level (2382 fmol /punch) was consistent with his taking 4 doses of TDF/FTC per week | M184 |
| Literature PPD {Knox 2017} | Yes - fever, abdominal pain | Yes | Plasma sample on day of diagnosis revealed a TFV concentration of 152 ng per milliliter, consistent with recent administration of the drug. DBS obtained on day 24 revealed TFV-DP concentration of 2297 fmol/punch consistent with daily dosing. | M41L, D67G, T69D, K70R, M184V, Y215E, Y181C, L10I, H51Y, E92Q |
| Literature PPD {Pilarski 2017} | No | No | No testing after starting PrEP as patient did not return to clinic until August 2016. Deep sequencing and tropism testing were attempted but failed due to low viral load. Pharmacy dispensing reports confirmed consistent TDF/FTC refill. Untimed drug level report confirmed presence of FTC. | E138A, Q58E, M184 |
| Literature PPD {Thaden 2018} | Yes – fevers, chills, myalgia | No | Plasma TFV (75 ng/ml) and FTC (281 ng/ml) levels were consistent with recent dosing. TFV and FTC levels in the hair were consistent with high adherence over the 3 months prior to infection. | K65R, K70T, K103N, M184V |
| Literature PPD {Markowitz 2017} | No | Yes | DBS obtained on day 35 revealed TFV-DP concentration of 1478 fmol/punch, consistent with daily dosing. | M184V, K103S, E138Q, Y188L, K65R, M184 |
| Literature PPD {Zucker 2018} | Yes – Nausea resolving 2 days prior to the seroconversion visit | No | No objective adherence data collected; self-reported 100% adherence | Not known, insufficient HIV infected cells or associated DNA to amplify. |

| Study ID / Patient ID / Case Number | Signs or Symptoms at HIV Infection | DBS | Adherence Comments | Mutations |
|---|---|---|---|---|
| Literature PPD {Volk 2018} | Yes – pruritic rash (also diagnosed with syphilis) | No | The site reported that 28 days later, the patient returned to the clinic, reporting 100% tenofovir-emtricitabine adherence. | M184V |
| Literature PPD Author: Cohen {Cohen 2018} | No | Yes | The site reported that the patient used pills given to him by his primary sexual partner, who had an FTC/TDF prescription for PrEP but was not using the medication consistently. DBS FTV-DP = 1012 fmol/punch (2 days after ART initiation) Per the physician, the patient was adherent to Truvada PrEP as prescribed, but missed on average less than 1 doses per week and missed an average of less than 4 doses per month | M184V, L74V, K103N, M184 |
| Literature Author: Colby {Colby 2018} | No | No | Hair samples taken 4 days after stop of PrEP indicated daily dosing of PrEP in the preceding 6 weeks The plasma sample taken 40 hours after the last PrEP dose had a TFV level of 25 ng/mL | M184, A98G, K103N |
| Spontaneous PPD | Yes – Swollen lymph nodes for 2 days | No | Patient was off PrEP for 2 weeks prior to seroconversion visit and had recently restarted daily dosing | M184 V/I, V32I, L33F, M46I, 147V |

BLQ-=Below Limit of Qualification
MEMs Cap is a device used to record when a participant opens a vial
Not Reported= Data requested but not provided

## 7.4. Selected Case Summaries by Study or Source

Additional details on the new HIV-1 infections for selected studies or literature reports are summarized below.

### 7.4.1. CO-US-164-0403 HPTN 067

In the HPTN 067 (CO-US-164-0403) study, two individuals developed HIV infection while taking part in the initial direct observed therapy phase of the study and were taking Truvada once per week. The TFV-DP plasma results were < 350 fmol per punch in both individuals.
Five individuals were prescribed Truvada on a daily regimen, all were considered non-adherent.

In 5 of the individuals no HIV-1 mutations were detected. One individual had K65 and M184 detected and another individual had K103N detected.

### 7.4.2. CO-US-164-0404 iPrEX OLE

In the iPrEX OLE study (CO-US-164-0404), the DBS results revealed non-adherence in all 25 individuals who developed new HIV infections. The TFV-DP DBS results were below the limit of quantification (BLQ) in 15 of the individuals, were < 350 fmol per punch in 9 individuals, and were 350 – 700 fmol per punch in one individual.

In 5 of the individuals no HIV-1 resistant mutations were detected. One individual had M184 detected. Minor mutations were detected in 17 of the individuals who developed HIV infection.

### 7.4.3. CO-US-164-0440 IPERGAY

In the IPERGAY study (CO-US-164-0440), both of the 2 individuals who developed HIV infection were reported as non-adherent with the prescribed Truvada for PrEP. Both individuals received 60 Truvada tablets and at follow-up clinic visits one returned all 60 of the tablets and one returned 58 of the 60 tablets.

In both of the individuals no HIV-1 mutations were detected.

### 7.4.4. CO-US-164-0441 CDC PrEP Demo (SHIPP)

In the SHIPP study (CO-US-164-0441), 3 individuals had no HIV-1 resistant mutations detected. In 2 of the individuals, M184V/I were detected. Minor mutations were detected in 1 individual and mutation results have not been reported for 3 individuals.

### 7.4.5. CO-US-164-0452 ATN 110

In the ATN 110 study (CO-US-164-0452), all 4 individuals had TFV-DP DBS results that were <350 fmol per punch, suggesting non-adherence at the time of the HIV infection.

Two of the individuals had no HIV-1 mutations and minor HIV-1 mutations were reported in 2 individuals.

### 7.4.6. CO-US-164-0468 Partner's Demo

In the Partner's Demo study (CO-US-164-0468), the DBS results revealed non-adherence in both individuals who developed new HIV infections. The TFV-DP DBS results were BLQ in 1 individual and were < 350 fmol per punch in the other individual.

In 2 of the individuals no HIV-1 mutations were detected.

### 7.4.7. CO-US-164-0488 SEARCH

In the SEARCH study (CO-US-164-0488), poor adherence with Truvada for PrEP was reported by 9 of the 11 individuals who developed HIV infection. The individuals reported various stories of missing PrEP doses. No adherence data were provided for the other 2 individuals.

Resistance testing is ongoing for this study; 4 individuals had resistance testing completed so far. Among the 4 individuals, no HIV-1 mutations were detected. Of the 11 individuals who seroconverted, only one was lost to follow up and did not initiate ART. The 10 individuals who were linked to ART all initiated TDF/3TC/EFV with no known treatment failures suggesting no resistance to these ARVs.

### 7.4.8. CO-US-276-0108 Brazilian PrEP

In the Brazilian PrEP study (CO-US-276-0108), the DBS results revealed non-adherence in all 5 individuals who developed new HIV infections. The TFV-DP DBS results were BLQ in 4 of the individuals, and were < 350 fmol per punch in the other individual.

Minor HIV-1 mutations were reported in 3 individuals.

### 7.4.9. CO-US-276-1510 PrEP Demo in Kenya

The PrEP Demo study in Kenya (CO-US-276-1510) did not collect DBS samples and instead monitored adherence with a medication event monitoring system (MEMS Cap).
Three individuals developed an HIV infection. MEMS Cap data revealed that individual PPD took Truvada on 38 of 78 total days. PPD took Truvada on 69 of 127 total days. PPD took Truvada on 17 of 23 days; it is unknown whether she initiated ART. Samples were not available for resistance testing, however PPD and PPD had no known treatment failures on TDF/3TC/EFV.CO-US-276-1712 AmPrEP

Subject PPD had good adherence with TFV-DP DBS concentrations of 2234 and 2258 fmol/punch at 6 months after start of Truvada for PrEP and at the time of HIV diagnosis {Hoornenborg 2017}. Tablet counts and daily diary information indicated adherence to the use of 7 tablets per week. Before starting and while taking PrEP the subject had over 140 anal sex partners (range 12 – 75 partners per month) with receptive anal sex without a condom including use of drugs during sex. The subject was diagnosed with new rectal gonorrhea infections at 3 and 6 months while on PrEP. About 8 months after starting PrEP, the subject became infected with wild-type HIV-1. No HIV viral mutations were detected. The likely cause of PrEP failure was the high-inoculum effect with multiple exposures and concomitant lymphogranuloma venereum infection.

### 7.4.10. Literature Cases

Knox et al., describes a case of a 43 year old male who was on PrEP for 753 days (approximately 24 months) {Knox 2017}. Plasma sample collected on the day of diagnosis revealed a TFV concentration of 152 ng/mL, consistent with recent administration of the drug. Dried blood spot obtained on Day 24 revealed TFV-DP concentration of 2297 fmol/punch, consistent with daily dosing. The authors suggest the likely cause of PrEP failure was infection with an HIV strain that was resistant to FTC and TDF. The major HIV mutations noted included K70R and M184V.

Pilarski et al. described a Latin American MSM who started PrEP in January 2016 following a negative HIV test {Pilarski 2017}. The patient continued to receive monthly refills but did not present for follow up testing until August 2016 at which time HIV infection was confirmed with the Recent Infection Testing Algorithm concluding the infection occurred within the past 5 months. They performed genotype testing and deep sequencing and discovered M184I, E138A, and Q58E mutations. A stored serum sample from the initial PrEP visit revealed a VL of 117 copies/mL. The authors concluded that the patient was infected prior to starting PrEP.

Thaden, et al., describes a case of a 34 year old white cisgender male who initiated TDF/FTC in February 2016 receiving a year of refills, following a negative HIV test in December 2015. He reported no sexual activity during the December to February period. He reported full adherence until May 2016; due to perceived lack of risk he did not take any tablets until July when he restarted. He did not present for any follow-up HIV testing after initiating PrEP in February 2016. In March 2017, after developing fever, chills, and myalgia, he received a negative influence test result at an urgent care clinic. He was diagnosed with HIV-1 the following month after presenting for assessment of anal condylomata. {Thaden 2018}. Hair and plasma samples were consistent with both recent dosing and high adherence during the 3 months prior. The authors suggest the likely cause of PrEP failure was infection with an HIV strain that was resistant to TDF and emtricitabine. The major HIV mutations noted included K65R and M184V.

Markowitz et al., describe a case of a 26 year old male who was on PrEP for 147 days (approximately 5 months) {Markowitz 2017}. The patient reported insertive and receptive condomless anal intercourse with their regular (virally suppressed) partner, and at 11 weeks and 5.5 weeks prior to the seroconversion visit, two additional partners of unknown HIV serostatus. Dried blood spot obtained on Day 35 revealed TFV-DP concentration of 1478 fmol/punch, consistent with daily dosing {Markowitz 2017}. The authors suggest the likely cause of PrEP failure was infection with an HIV strain that was resistant to FTC and TDF. The major HIV mutations revealed with genotype testing included K65R and M184V in addition to K103S, E138Q, and Y188L.

Zucker et al., describe a case of a 31 year old male who presented for PrEP consultation and had negative 3rd generation rapid and NAAT test results. The patient reported inconsistent condom use with multiple partners with known HIV positive status over the prior three months. Pre-exposure prophylaxis was initiated one week following PrEP assessment. The patient returned for follow up one month following PrEP and reported sustaining 100% adherence; HIV RNA qualitative testing at that visit was positive and virus was detected over the next two weeks with COBAS Quantitative and Qualitative tests. The patient reported having nausea which resolved two days prior to the visit. The virus could not be sufficiently amplified for successful archival genotype resistance testing, however the patient remains virally suppressed on EVG/COBI/FTC/TAF (Genvoya®) {Zucker 2018}.

Volk et al., reported a case of a 23 year old Hispanic male with a history of using injection drugs and sex exchange. The patient's sexual partner had a prescription for FTC/TDF for PrEP but did not take it consistently and so the partner provided the patient with extra tablets. The patient only took single tablets of FTC/TDF before and after some sexual encounters beginning in late 2015 through September 2016 when the patient presented to the emergency department and was diagnosed with rectal gonorrhea, secondary syphilis, and HIV (VL 47,980 copies/mL). The patient's initial genotype test revealed M184V and they initiated DRV with EVG/COBI/FTC/TAF. The patient remained detectable at 6 months (160 copies/mL) which was attributed to inconsistent adherence reported by the patient. Later genotype testing was not successful due to undetectable viral load. It is possible that this patient acquired FTC resistance due to suboptimal adherence and lack of clinical support {Volk 2018}.

Cohen et al., described a 21 year old Latino male who had sex with men, transgender women, and cisgender women. The patient initiated PrEP, receiving a prescription for 3 months of FTC/TDF, following negative rapid antibody and HIV RNA tests. Twelve months following PrEP initiation the patient was diagnosed with urethral gonorrhea. One month later the patient's prescription was renewed after a negative rapid antibody test result. At that visit the patient reported recent condomless receptive anal intercourse and using methamphetamine. Five days after the follow up visit, the patient's HIV RNA result was 559 copies/ mL and the patient was linked to care. When treatment was initiated, the patient's HIV RNA result was 1544 copies/mL Genotype testing revealed M184V which was consistent with the single-genome sequencing. Plasma, hair analyses, and DBS all indicated high adherence. The authors determined that the patient was infected with a strain resistant to FTC; one of the patient's partners also had the same mutations. The patient initiated treatment with TAF/FTC, DTG, RTV, and DRV {Cohen 2018}.

Colby et al., described a case of a 28 year old Thai male sex worker who reported condomless insertive and receptive anal intercourse as well as using methamphetamine, poppers, and alcohol after he initiated FTC/TDF for PrEP in March 2016 {Colby 2018}. At 5 weeks following PrEP initiation, antibody test results continued to be nonreactive. Three weeks later, the patient had a positive qualitative HIV-1 RNA result after another nonreactive antibody test. Quantitative HIV-1 RNA was determined to be 116,187 copies/mL four days later. Hair and plasma samples were consistent with high adherence. Genotype testing performed prior to ART initiation revealed M184V, A98G, and K103N mutations. The authors concluded it is unlikely the patient was infected at PrEP initiation but could not conclusively determine whether the NRTI resistance was transmitted or acquired.

# 8. ANALYSIS OF HIV-1 INFECTIONS AFTER DISCONTINUATION OF TRUVADA FOR PREP

## 8.1. Subject Characteristics

Fifty (50) cases of new HIV-1 infections were reported for individuals who discontinued Truvada for PrEP and continued to the followed by the studies and subsequently obtained new HIV-1 infections greater than 30 days after the last PrEP dose. The study identification, the individual's age and gender, the country, the individual's race/ethnicity, and HIV-1 risk factor are listed in Table 8-1.

Most of the cases were male (43, 86%). Age data was available for 49 individuals and missing for 1 individual. The mean age (± SD) was 27 (± 9.3) years and the median age (IQR) was 25 (20 – 31) years. The majority (30, 60%) of the cases were from outside of the US and included 10 cases from the United Kingdom, 2 cases from Uganda and South Africa, 3 cases each from Australia, Canada, France and Peru, and 1 case each from Benin, Kenya, Togo, and Zimbabwe. There were 20 cases (40%) from the United States. The risk factors for the cases included MSM (42, 84%) and heterosexual sex (8, 16%).

**Table 8-1. Subject Characteristics for New HIV-1 Infections after Discontinuation of Truvada for PrEP**

| Study ID / Patient ID / Case Number | Age / Gender | Country | Race or Ethnicity | HIV Risk |
|---|---|---|---|---|
| CO-US-164-0404 PPD | 34 years/ Male | PPD | | MSM |
| CO-US-164-0404 PPD | 25 years/ Male | | | MSM |
| CO-US-164-0404 PPD | 27 years/ Male | | | MSM |
| CO-US-164-0404 PPD | 49 years/ Male | | | MSM |
| CO-US-164-0432 PPD | 20 years/ Male | | | MSM |
| CO-US-164-0440 PPD | Unknown Age/ Male | | | MSM |
| CO-US-164-0441 PPD | 20 years/ Male | | | MSM |
| CO-US-164-0441 PPD | 31 years/ Male | | | MSM |
| CO-US-164-0452 PPD | 21 years/ Male | | | MSM |
| CO-US-164-0452 PPD | 19 years/ Male | | | MSM |
| CO-US-164-0452 PPD | 20 years/ Male | | | MSM |

| Study ID / Patient ID / Case Number | Age / Gender | Country | Race or Ethnicity | HIV Risk |
|---|---|---|---|---|
| CO-US-164-0452 PPD | 18 years/ Male | PPD | | MSM |
| CO-US-164-0452 PPD | 19 years/ Male | | | MSM |
| CO-US-164-0452 PPD | 19 years/ Male | | | MSM |
| CO-US-164-0454 PPD | 31 years/ Male | | | MSM |
| CO-US-164-0454 PPD | 22 years/ Male | | | MSM |
| CO-US-164-0454 PPD | 31 years/ Male | | | MSM |
| CO-US-164-0454 PPD | 26 years/ Male | | | MSM |
| CO-US-164-0454 PPD | 21 years/ Male | | | MSM |
| CO-US-164-0454 PPD | 34 years/ Male | | | MSM |
| CO-US-164-0454 PPD | 40 years/ Male | | | MSM |
| CO-US-164-0454 PPD | 32 years/ Male | | | MSM |
| CO-US-164-0454 PPD | 26 years/ Male | | | MSM |
| CO-US-164-0454 PPD | 29 years/ Male | | | MSM |
| CO-US-164-0455 PPD | PPD years/ Male | | | MSM |
| CO-US-164-0455 PPD | PPD years/ Male | | | MSM |
| CO-US-164-0461 PPD | 19 years/ Female | | | Heterosexual |
| CO-US-164-0468 PPD | 19 years/ Female | | | Heterosexual |
| CO-US-164-0478 PPD | 20 years/ Male | | | MSM |
| CO-US-164-0480 PPD | 20 years/ Male | | | MSM |
| CO-US-164-0483 PPD | 23 years/ Male | | | MSM |
| CO-US-164-0488 PPD | 50 years/ Male | | | Heterosexual |
| CO-US-164-0488 PPD | 19 years/ Female | | | Heterosexual |

| Study ID / Patient ID / Case Number | Age / Gender | Country | Race or Ethnicity | HIV Risk |
|---|---|---|---|---|
| CO-US-276-0122 PPD | 22 years/ Male | PPD | | MSM |
| CO-US-276-0126 PPD | 28 years/ Female | | | Heterosexual |
| CO-US-276-1199 PPD | 43 years/ Male | | | MSM |
| CO-US-276-1199 PPD | 45 years/ Male | | | MSM |
| CO-US-276-1318 PPD | 42 years/ Female | | | Heterosexual |
| CO-US-276-1318 PPD | 22 years/ Female | | | Heterosexual |
| CO-US-276-1774 PPD | 25 years/ Female | | | Heterosexual |
| CO-US-276-1875 PPD | 56 years/ Male | | | MSM |
| CO-US-276-2096 PPD | 26 years/ Male | | | MSM |
| CO-US-276-2096 PPD | 24 years/ Male | | | MSM |
| CO-US-276-2096 PPD | 22 years/ Male | | | MSM |
| CO-US-276-4369 PPD | 28 years/ Male | | | MSM |
| CO-US-276-4369 PPD | 20 years/ Male | | | MSM |
| CO-US-276-4369 PPD | 24 years/ Male | | | MSM |
| I'Actuel Montreal Cohort 1 | 27 years/ Male | | | MSM |
| I'Actuel Montreal Cohort 2 | 25 years/Male | | | MSM |
| I'Actuel Montreal Cohort 3 | 26 years/Male | | | MSM |

MSM = men who have sex with men.
Not Reported= Data requested but not provided

## 8.2. Exposure to Truvada for PrEP

The duration of PrEP exposure and the time from stopping PrEP to the new HIV-1 infection are listed in Table 8-2.

These individuals were reported to be taking PrEP for a median of 164 days (range: 1 - 656). After discontinuation, the median time to HIV-1 infection was 142 days (range: 31 - 945).

**Table 8-2. Exposure to Truvada for PrEP**

| Study ID / Patient ID / Case Number | PrEP Start Date / PrEP Stop Date* | PrEP Duration of Exposure (days) | PrEP Dosing | Date of HIV-1 Infection* | Time to HIV-1 Infection After Stopping PrEP (days) | Comments |
|---|---|---|---|---|---|---|
| CO-US-164-0404 PPD | PPD | 252 | Daily | PPD | 163 | - |
| CO-US-164-0404 PPD | | 86 | Daily | | 330 | - |
| CO-US-164-0404 PPD | | 264 | Daily | | 170 | - |
| CO-US-164-0404 PPD | | 34 | Daily | | 452 | DBS on HIV diagnosis date: TFV-DP is BLQ |
| CO-US-164-0432 PPD | | 334 | Daily | | 66 | The study reported this participant had TFV-DP levels consistent with daily dosing only at week 4, dropping to < 2 doses/wk or TFV-DP < BLQ thereafter. |
| CO-US-164-0440 PPD | | 153 | Intermittent | | 93 | Returned all Truvada tablets at PPD visit |
| CO-US-164-0441 PPD | | 137 | Daily | | 116 | - |
| CO-US-164-0441 PPD | | 228 | Daily | | 178 | - |
| CO-US-164-0452 PPD | | 33 | Daily | | 440 | Individual in the extension phase of study |
| CO-US-164-0452 PPD | | 330 | Daily | | 169 | Individual in the extension phase of study |
| CO-US-164-0452 PPD | | 330 | Daily | | 343 | Individual in the extension phase of study |

| Study ID / Patient ID / Case Number | PrEP Start Date / PrEP Stop Date* | PrEP Duration of Exposure (days) | PrEP Dosing | Date of HIV-1 Infection* | Time to HIV-1 Infection After Stopping PrEP (days) | Comments |
|---|---|---|---|---|---|---|
| CO-US-164-0452 PPD | PPD | 329 | Daily | PPD | 339 | Individual in the extension phase of study |
| CO-US-164-0452 PPD | | 338 | Daily | | 348 | Individual in the extension phase of study |
| CO-US-164-0452 PPD | | 487 | Daily | | 101 | Individual in the extension phase of study |
| CO-US-164-0454 PPD | | 183 | Daily | | 170 | - |
| CO-US-164-0454 PPD | | 656 | Daily | | 53 | - |
| CO-US-164-0454 PPD | | 275 | Daily | | 132 | - |
| CO-US-164-0454 PPD | | 15 | Daily | | 606 | - |
| CO-US-164-0454 PPD | | 1 | Daily | | 425 | - |
| CO-US-164-0454 PPD | | 463 | Daily | | 244 | - |
| CO-US-164-0454 PPD | | 359 | Daily | | 652 | - |
| CO-US-164-0454 PPD | | 84 | Daily | | 945 | - |
| CO-US-164-0454 PPD | | 545 | Daily | | 115 | - |
| CO-US-164-0454 PPD | | 41 | Daily | | 476 | - |

| Study ID / Patient ID / Case Number | PrEP Start Date / PrEP Stop Date* | PrEP Duration of Exposure (days) | PrEP Dosing | Date of HIV-1 Infection* | Time to HIV-1 Infection After Stopping PrEP (days) | Comments |
|---|---|---|---|---|---|---|
| CO-US-164-0455 PPD | PPD | 219 | Daily | PPD | 31 | Individual did not have detectable levels of TFV-DP in the sample that was drawn closest to the HIV-1 infection date. The individual was immediately linked to medical care and no antiviral drug resistance was detected. |
| CO-US-164-0455 PPD | | 343 | Daily | | 142 | Individual did not have detectable levels of TFV-DP in the sample that was drawn closest to the HIV-1 infection date. The individual was immediately linked to medical care and no antiviral drug resistance was detected. |
| CO-US-164-0461 PPD | | 166 | Daily | | 184 | - |
| CO-US-164-0468 PPD | | 251 | Daily | | 131 | - |
| CO-US-164-0478 PPD | | 89 | Daily | | 57 | "Both of the HIV seroconverters reported drug prior to seroconversion." {Moore 2018} |

| Study ID / Patient ID / Case Number | PrEP Start Date / PrEP Stop Date* | PrEP Duration of Exposure (days) | PrEP Dosing | Date of HIV-1 Infection* | Time to HIV-1 Infection After Stopping PrEP (days) | Comments |
|---|---|---|---|---|---|---|
| CO-US-164-0480 PPD | PPD | 252 | Daily | PPD | 66 | Participant attended study visits per protocol through week 24, then were lost to follow-up. Despite initially good adherence (weeks 4 and 12), his week 24 DBS specimen suggested adherence on average of fewer than 2 doses/week over the prior 4-8 weeks. |
| CO-US-164-0483 PPD | | 56 | Daily | | 266 | - |
| CO-US-164-0488 PPD | | 28 | Daily | | 307 | Patient stopped PrEP after 28 days, but continued intermittent study participation. After seroconversion was started on TDF/3TC/EFV for 1 month then lost to follow-up. |
| CO-US-164-0488 PPD | | 16 | Daily | | 141 | - |
| CO-US-276-0122 PPD | | 126 | Daily | | 91 | - |
| CO-US-276-0126 PPD | | 131 | Daily | | 65 | - |
| CO-US-276-1199 PPD | | 730 | Intermittent | | 40 | - |
| CO-US-276-1199 PPD | | 195 | Daily | | 106 | - |

| Study ID / Patient ID / Case Number | PrEP Start Date / PrEP Stop Date* | PrEP Duration of Exposure (days) | PrEP Dosing | Date of HIV-1 Infection* | Time to HIV-1 Infection After Stopping PrEP (days) | Comments |
|---|---|---|---|---|---|---|
| CO-US-276-1318 PPD | PPD | 273 | Daily | PPD | 300 | Study reported that she stopped being on PrEP quite a long time before her seroconversion |
| CO-US-276-1318 PPD | | 108 | Daily | | 324 | Patient stopped PrEP when she became pregnant. Seroconverted approximately 10 months later. |
| CO-US-276-1774 PPD | | 8 | Daily | | 91 | - |
| CO-US-276-1875 PPD | | 61 | Daily | | 35 | Wanted to continue PrEP but unable to make appointment with provider between PPD . Reported unprotected receptive anal intercourse ~20 days after last PrEP dose. Believes he was infected in PPD He had. 6 recent sex partners. |
| CO-US-276-2096 PPD | | 29 | Daily | | 381 | - |
| CO-US-276-2096 PPD | | 110 | Daily | | 343 | - |

| Study ID / Patient ID / Case Number | PrEP Start Date / PrEP Stop Date* | PrEP Duration of Exposure (days) | PrEP Dosing | Date of HIV-1 Infection* | Time to HIV-1 Infection After Stopping PrEP (days) | Comments |
|---|---|---|---|---|---|---|
| CO-US-276-2096 PPD | PPD (Started Truvada) PPD (Changed over to generic TDF/FTC stopped generic TDF/FTC in PPD | 351 | Daily | PPD | 60 | - |
| CO-US-276-4369 PPD | PPD | 127 | Daily | | 50 | - |
| CO-US-276-4369 PPD | | 156 | Daily | | 129 | - |
| CO-US-276-4369 PPD | | 159 | Daily | | 82 | - |
| I'Actuel Montreal Cohort #1 | Not Reported | 300 (10 Months) | Not Reported | Not Reported | 56 Days from PrEP stop to HIV detection | Individual stopped PrEP due to expiration of health card |
| I'Actuel Montreal Cohort #2 | Not Reported | 60 (2 Months) | Not Reported | Not Reported | 107 Days from PrEP stop to HIV detection | Individual stopped PrEP due to side effects including diarrhea |
| I'Actuel Montreal Cohort #3 | Not Reported | 360 (12 Months) | Not Reported | Not Reported | 117 Days from PrEP stop to HIV detection | Individual stopped PrEP due to personal decision |

* MM/DD/YYYY date format.
Not Reported= Data requested but not provided

## 8.3. Signs/Symptoms of HIV-1 Infection and Resistance Testing in Individuals who Developed New HIV-1 Infections after Discontinuation of Truvada for PrEP

Table 8-3 provides details on the reported signs and symptoms at the time of the new HIV-1 infection for each individual. Signs or symptoms were reported in 8 (16%) of individuals and included fatigue, fever, inflamed lymph nodes, night sweats, non-productive cough, rash, and sore throat. In 21 (42%) of the individuals, there were no signs or symptoms of an acute viral infection. In the remaining 21 (42%) individuals, the presence or absence of signs or symptoms were not provided or not specified.

The tests that were used to document the HIV-1 infection and resistance testing are reported for each individual in Table 8-3. HVI-1 resistance testing was completed in 37 (74%) of the individuals and mutations were reported in 12 (26.1%) of the 37 individuals. No mutations to tenofovir were reported in these individuals. Given the time between the last exposure to Truvada and the new HIV-1 infection, the mutations are representative of the HIV-1 strain that the individual became infected with.

**Table 8-3. Signs/Symptoms of HIV-1 Infection and Resistance Testing in Individuals who Developed New HIV-1 Infections after Discontinuation of Truvada for PrEP**

| Study ID / Patient ID / Case Number | Signs or Symptoms at HIV Infection | HIV Test at Seroconversion | HIV Resistance Testing Completed | Mutations | Comments |
|---|---|---|---|---|---|
| CO-US-164-0404 PPD | Not Reported | Not Reported- Protocol stated that Determine & Bioline rapid antibody tests were used | Yes | RTV118I, PRL10V, PRV11I, PRA71V | No TDF or FTC resistance. |
| CO-US-164-0404 PPD | Not Reported | Not Reported- Not Protocol stated that Determine & Bioline rapid antibody tests were used | Yes | PRA71T | - |
| CO-US-164-0404 PPD | Not Reported | Rapid | Yes | PRL10I, PRA71V | - |
| CO-US-164-0404 PPD | Not Reported | Not Reported- Not Protocol stated that Oraquick & STAT-PAK rapid antibody tests | Yes | No Mutations | - |
| CO-US-164-0432 PPD | Not Reported | Rapid, 4th generation | Yes | No Mutations | No evidence of TDF or FTC resistance on standard or ultrasensitive minor variant genotyping assays |
| CO-US-164-0440 PPD | Yes – Influenza symptoms | ELISA (Architect) HIV RNA (Cobas TaqMan) | Yes | No Mutations | - |
| CO-US-164-0441 PPD | Yes - Night sweats, fatigue | HIV RNA VL | Yes | No Mutations | - |
| CO-US-164-0441 PPD | No | 4th generation, Cascade RFLX on 02/26/2016 | No | Not Reported | - |
| CO-US-164-0452 PPD | Not Reported | FDA Approved Ab testing (details not provided) | Yes | K103N | - |
| CO-US-164-0452 PPD | Not Reported | FDA Approved Ab testing (details not provided) | Yes | No Mutations | - |

| Study ID / Patient ID / Case Number | Signs or Symptoms at HIV Infection | HIV Test at Seroconversion | HIV Resistance Testing Completed | Mutations | Comments |
|---|---|---|---|---|---|
| CO-US-164-0452 PPD | Not Reported | FDA Approved Ab testing (details not provided) | Yes | No Mutations | - |
| CO-US-164-0452 PPD | Not Reported | FDA Approved Ab testing (details not provided) | Yes | No Mutations | - |
| CO-US-164-0452 PPD | Not Reported | FDA Approved Ab testing (details not provided) | Yes | No Mutations | - |
| CO-US-164-0452 PPD | Not Reported | FDA Approved Ab testing (details not provided) | Yes | K103N | - |
| CO-US-164-0454 PPD | Yes - Not Reported | HIV antibody | Yes | No Mutations | Wild type |
| CO-US-164-0454 PPD | Not Reported | Not Provided | Yes | No Mutations | Wild type |
| CO-US-164-0454 PPD | Not Reported | HIV ag/ab, immunocomb | Yes | No Mutations | Wild type |
| CO-US-164-0454 PPD | Not Reported | Insti, Determine & serology | Yes | V106I | - |
| CO-US-164-0454 PPD | Not Reported | Not Reported | Yes | No Mutations | Individual was HIV reactive at 61 weeks and had been prescribed no study drug since the enrollment visit |
| CO-US-164-0454 PPD | Not Reported | 4th generation | Yes | No Mutations | Wild type |
| CO-US-164-0454 PPD | Not Reported | 4th generation | Yes | No Mutations | - |
| CO-US-164-0454 PPD | Not Reported | 4th generation | Yes | PI minor mutations | - |
| CO-US-164-0454 PPD | Not Reported | 4th generation | Yes | No Mutations | Wild type |

| Study ID / Patient ID / Case Number | Signs or Symptoms at HIV Infection | HIV Test at Seroconversion | HIV Resistance Testing Completed | Mutations | Comments |
|---|---|---|---|---|---|
| CO-US-164-0454<br>PPD | Not Reported | 4th generation | Yes | No Mutations | Wild Type |
| CO-US-164-0455<br>PPD | Not Reported | FDA Approved Ab testing (details not provided) | Yes | No Mutations | No antiviral drug resistance was detected. |
| CO-US-164-0455<br>PPD | Not Reported | FDA Approved Ab testing (details not provided) | Yes | No Mutations | |
| CO-US-164-0461<br>PPD | No | Determine Combo Rapid Test (antibody+antigen) Unigold Rapid Test (antibody) | No | - | Seroconversion sample lost by processing lab. Subsequent sample heamolysed and final sample sent when participant already on antiretroviral treatment and amplification failed as viral load <200 copies/ml |
| CO-US-164-0468<br>PPD | No | Rapid Test | Yes | No Mutations | - |
| CO-US-164-0478<br>PPD | No | Abbott Architect HIV Ag/Ab Combination | Yes | L101<br>M361 | Combinations of some nucleoside analog mutations causing resistance to any NRTI may enhance susceptibility to all approved NNRTIs in vitro, and efavirenz or etravirine in vivo. Polymorphisms in protease in non-B subtypes may trigger rules of unknown clinical implications. |
| CO-US-164-0480<br>PPD | Not Reported | Rapid | Yes | M184 | Participant attended study visits per protocol through week 24, and then lost to follow-up. Despite initially good adherence (weeks 4 and 12), his week 24 DBS specimen suggested adherence on average of fewer than 2 doses /week over the prior 4-8 weeks. |
| CO-US-164-0483<br>PPD | Not reported | Rapid, Elisa | Yes | M46I (2.7%) | - |
| CO-US-164-0488<br>PPD | No | Rapid antibody testing per country algorithm, HIV RNA | No | - | Site plans to perform resistance testing on available samples in the coming months |

| Study ID / Patient ID / Case Number | Signs or Symptoms at HIV Infection | HIV Test at Seroconversion | HIV Resistance Testing Completed | Mutations | Comments |
|---|---|---|---|---|---|
| CO-US-164-0488 PPD | No | Rapid | No | Not Reported | Site plans to perform resistance testing on available samples in the coming months |
| CO-US-276-0122 PPD | Yes - Inflamed lymph Notes | Multispot | Yes | E138K | - |
| CO-US-276-0126 PPD | No | Rapid, Antibody | No | - | - |
| CO-US-276-1199 PPD | No | HIV PCR RNA VL | Yes | No Mutations | - |
| CO-US-276-1199 PPD | No | Not Reported | Yes | No Mutations | - |
| CO-US-276-1318 PPD | No | ELISA (Murex HIV) confirmed by Rapid test (Bioline HIV Ag/Ab Combo) | No | - | - |
| CO-US-276-1318 PPD | No | ELISA (Murex HIX), Rapid | Yes | I13V, I15V, G16E, K201. E35D, M261, R41K, L63V, I64M, H69K, L89M, E13A, K20R, T27A. V35T, V601, V106I | - |
| CO-US-276-1774 PPD | No | 4th generation | Yes | No Mutations | - |
| CO-US-276-1875 PPD | Yes - Fever (100° F), body aches, body rash | 4th generation (ELISA) | Yes | R211K; E35D; M36I; L63P; I93L | - |
| CO-US-276-2096 PPD | Yes - Unwell for 5 days, cannot talk, non-productive cough, rash on palms of hands and on chest | 4th generation, antigen test- positive Western blot test- negative | Yes | No Mutations | - |

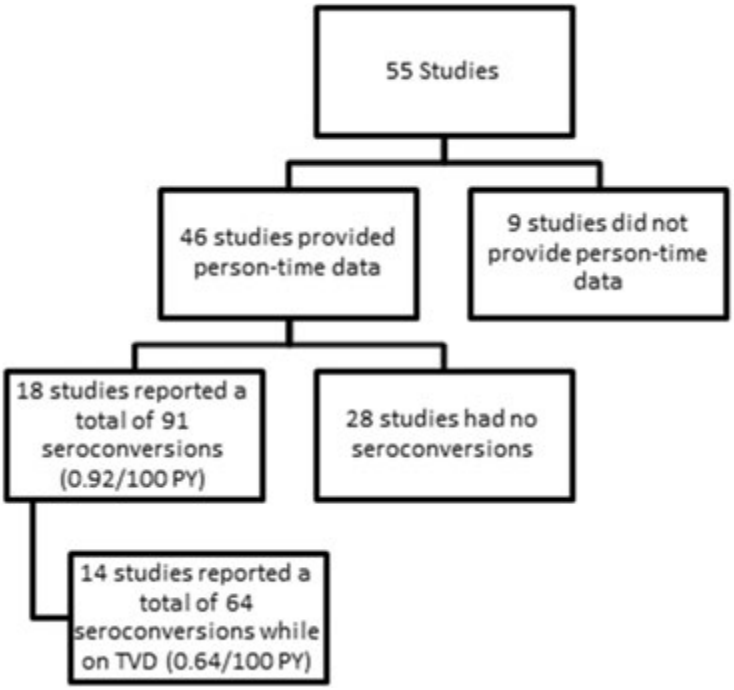
| Study ID / Patient ID / Case Number | Signs or Symptoms at HIV Infection | HIV Test at Seroconversion | HIV Resistance Testing Completed | Mutations | Comments |
|---|---|---|---|---|---|
| GS-US-276-2096 PPD | Yes - Fatigue | Western Blot | Yes | No Mutations | - |
| CO-US-276-2096 PPD | Yes - Sore throat with enlarged lymph node | Western Blot | Yes | No Mutations | - |
| CO-US-276-4369 PPD | No | Determine | No | - | - |
| CO-US-276-4369 PPD | No | Determine | No | - | - |
| CO-US-276-4369 PPD | No | Determine | No | - | - |
| I'Actuel Montreal Cohort 1 | Not Reported | Not Reported | Not Reported | Not Reported | Viral load at diagnosis: 247,000 copies/ml3<br>CD4 count at diagnosis: 699 cells/ml3 |
| I'Actuel Montreal Cohort 2 | Not Reported | Not Reported | Not Reported | Not Reported | Viral load at diagnosis: 103,000 copies/ml$^3$<br>CD4 count at diagnosis: 430 cells/ml$^3$ |
| I'Actuel Montreal Cohort 3 | Not Reported | Not Reported | Not Reported | Not Reported | Viral load at diagnosis: 65,885 copies/ml$^3$<br>CD4 count at diagnosis: 440 cells/ml$^3$ |

# 9. ANALYSIS OF INCIDENCE RATE OF NEW HIV-1 INFECTIONS

## 9.1. Incidence Rate of New HIV-1 Infections Overall

Patient-time exposure data for daily use of Truvada for PrEP was contributed by 46 demonstration projects or clinical studies using a cut-off date of 30 October 2017. In 18 of the 46 studies there were 91 cases of new HIV-1 infections that occurred at any time (i.e., before initiating PrEP, after initiating PrEP, and > 30 days after discontinuation). In 14 of the 46 studies, there were 64 cases of new HIV-1 infections that occurred while receiving Truvada for HIV-1 PrEP (i.e., before initiating PrEP and after initiating PrEP).

**Figure 2. Studies That Reported Person-Time Data and New HIV-1 Infections (Seroconversions)**




Data were provided for 10,609 individuals with a total exposure time to daily Truvada for PrEP of 9936.4 person-years. The overall rate of new HIV-1 infections for the 91 new cases of HIV-1 was 0.92 per 100 person-years (95% CI: 0.746 – 1.125).

A summary of the pooled analysis for the new HIV-1 infection rates by gender, region, race, age group, and exposure time on PrEP is presented in Table 9-1.

## Table 9-1. Results of Overall Pooled Analysis

| Subgroup | Number of Subjects | Number of New HIV-1 Infections | Total Person Years | Rate of New HIV-1 Infections (95% CI) |
|---|---|---|---|---|
| Total | 10609 | 91 | 9936.4 | 0.92 (0.75, 1.13) |
| Gender | | | | |
| Female | 2133 | 13 | 1114.0 | 1.17 (0.68, 2.01) |
| Male | 8047 | 77 | 8384.5 | 0.92 (0.74, 1.15) |
| Other | 14 | 0 | 14.5 | 0.00 |
| Transgender | 74 | 1 | 61.6 | 1.62 (0.23, 11.52) |
| Unknown/Missing | 341 | 0 | 361.8 | 0.00 |
| Region | | | | |
| Africa | 2937 | 19 | 1892.6 | 1.00 (0.64, 1.57) |
| Australia | 164 | 0 | 284.3 | 0.00 |
| Europe | 1044 | 9 | 1499.4 | 0.60 (0.31, 1.15) |
| Multi-Region | 1402 | 29 | 1612.8 | 1.80 (1.25, 2.59) |
| New Zealand | 103 | 0 | 28.9 | 0.00 |
| North America | 4028 | 28 | 3540.6 | 0.79 (0.55, 1.15) |
| South America | 931 | 6 | 1077.8 | 0.56 (0.25, 1.24) |
| Race | | | | |
| American Indian or Alaska Native | 21 | 0 | 14.9 | 0.00 |
| Asian | 312 | 1 | 276.3 | 0.36 (0.05, 2.57) |
| Black/African American | )4144 | 42 | 3046.5 | 1.38 (1.02, 1.87) |
| Latino | 479 | 1 | 426.3 | 0.23 (0.03, 1.67) |
| Middle Eastern | 8 | 0 | 5.7 | 0.00 |
| Mixed | 431 | 3 | 509.2 | 0.59 (0.19, 1.83 |
| Native Hawaiian or Pacific Islander | 38 | 0 | 22.8 | 0.00 |
| Other | 1101 | 24 | 1209.0 | 1.99 (1.33, 2.96) |
| Unknown/Missing | 913 | 3 | 850.0 | 0.35 (0.11, 1.09) |
| White | 3162 | 17 | 3575.8 | 0.48 (0.3, 0.77) |
| Age Group | | | | |
| 13 – 24 | 2607 | 47 | 1827.8 | 2.57 (1.93, 3.42) |
| 25 – 34 | 3767 | 34 | 3396.5 | 1.00 (0.72, 1.40) |
| 35 – 50 | 2616 | 6 | 2501.5 | 0.24 (0.11, 0.53) |
| > 50 | 588 | 1 | 576.9 | 0.17 (0.02, 1.22) |
| Unknown/Missing | 1031 | 3 | 1630.7 | 0.18 (0.06, 0.57) |

| Subgroup | Number of Subjects | Number of New HIV-1 Infections | Total Person Years | Rate of New HIV-1 Infections (95% CI) |
|---|---|---|---|---|
| Time on PrEP (months) | | | | |
| 0 – 1 | 664 | 6 | 9150.6 | 0.07 (0.03, 0.15) |
| 1 – 6 | 2731 | 29 | 9121.9 | 0.32 (0.22, 0.46) |
| 6 – 12 | 2976 | 30 | 8270.8 | 0.36 (0.25, 0.52) |
| >12 | 3640 | 24 | 5847 | 0.41 (0.28, 0.61) |
| Unknown/Missing | 598 | 2 | 785.8 | 0.25 (0.06, 1.02) |

## 9.2. Incidence Rate of New HIV-1 Infections While on Truvada for PrEP

Of the 91 cases of new HIV-1 infection that occurred at any time, 27 individuals developed new HIV-1 infections >30 days after the last dose and are removed from this analysis. There were 64 individuals developed new HIV-1 infections while taking Truvada for PrEP (i.e., before initiating PrEP and after initiating PrEP). For the 10,609 individuals, the total exposure time to daily Truvada for PrEP was 9936.4 person-years. The overall rate of new HIV-1 infections while taking Truvada for PrEP was 0.64 per 100 person-years (95% CI: 0.504 – 0.823).

A summary of the pooled analysis for the new HIV-1 infection rates by gender, region, race, age group, and exposure time on PrEP is presented in Table 9-2. This analysis was not powered or designed to compare different subgroups. For age, individuals in the 13 – 24 year old group had a higher rate of new HIV-1 infections (1.64 per 100 person-years; 95% CI 1.148, 2.347) relative to other age groups.

**Table 9-2. Results of Pooled Analysis While Taking Truvada for PrEP**

| Subgroup | Number of Subjects | Number of New HIV-1 Infections | Total Person Years | Rate of New HIV-1 Infections (95% CI) |
|---|---|---|---|---|
| Total | 10609 | 64 | 9936.4 | 0.64 (0.504, 0.823) |
| Gender | | | | |
| Female | 2133 | 9 | 1114.0 | 0.81 (0.420, 1.553) |
| Male | 8047 | 54 | 8384.5 | 0.64 (0.493, 0.841) |
| Other | 14 | 0 | 14.5 | 0.00 |
| Transgender | 74 | 1 | 61.6 | 1.62 (0.229, 11.519) |
| Unknown/Missing | 341 | 0 | 361.8 | 0.00 |
| Region | | | | |
| Africa | 2937 | 13 | 1892.6 | 0.69 (0.399, 1.183) |
| Australia | 164 | 0 | 284.3 | 0.00 |
| Europe | 1044 | 3 | 1499.4 | 0.20 (0.065, 0.620) |
| Multi-Region | 1402 | 26 | 1612.8 | 1.61 (1.098, 2.368) |
| New Zealand | 103 | 0 | 28.9 | 0.00 |
| North America | 4028 | 16 | 3540.6 | 0.45 (0.277, 0.738) |
| South America | 931 | 6 | 1077.8 | 0.56 (0.250, 1.239) |

| Subgroup | Number of Subjects | Number of New HIV-1 Infections | Total Person Years | Rate of New HIV-1 Infections (95% CI) |
|---|---|---|---|---|
| Race | | | | |
| American Indian or Alaska Native | 21 | 0 | 14.9 | 0.00 |
| Asian | 312 | 1 | 276.3 | 0.36 (0.051, 2.569) |
| Black/African American | 4144 | 28 | 3046.5 | 0.92 (0.0635, 1.331) |
| Latino | 479 | 0 | 426.3 | 0.00 |
| Middle Eastern | 8 | 0 | 5.7 | 0.00 |
| Mixed | 431 | 3 | 509.2 | 0.59 (0.190, 1.827) |
| Native Hawaiian or Pacific Islander | 38 | 0 | 22.8 | 0.00 |
| Other | 1101 | 19 | 1209.0 | 1.57 (1.002, 2.464) |
| Unknown/Missing | 913 | 0 | 850.0 | 0.00 |
| White | 3162 | 13 | 3575.8 | 0.36 (0.211, 0.626) |
| Age Group | | | | |
| 13 – 24 | 2607 | 30 | 1827.8 | 1.64 (1.148, 2.347) |
| 25 – 34 | 3767 | 26 | 3396.5 | 0.77 (0.521, 1.124) |
| 35 – 50 | 2616 | 4 | 2501.5 | 0.16 (0.060, 0.426) |
| > 50 | 588 | 1 | 576.9 | 0.17 (0.024, 1.224) |
| Unknown/Missing | 1031 | 3 | 1630.7 | 0.18 (0.059, 0.570) |
| Time on PrEP (months) | | | | |
| 0 – 1 | 664 | 5 | 9150.6 | 0.05 (0.023, 0.131) |
| 1 – 6 | 2731 | 21 | 9121.9 | 0.23 (0.150, 0.353) |
| 6 – 12 | 2976 | 17 | 8270.8 | 0.21 (0.128, 0.331) |
| >12 | 3640 | 19 | 5847 | 0.32 (0.207, 0.509) |
| Unknown/Missing | 598 | 2 | 785.8 | 0.25 (0.064, 1.018) |

# 10. SUMMARY

This is the final report for Study GS-US-276-0103, a prospective observational study of individuals who seroconvert while taking Truvada for PrEP. This study fulfills Postmarketing Requirement (PMR) 1906-2 established in the NDA 021752/S-030 approval letter dated 16 July 2012. The original request from 2012 was for a minimum of 150 individuals who developed new HIV-1 infections (i.e, seroconverters). Through 31 December 2018, data on 172 individuals who seroconverted were collected and included in this report. Unfortunately, despite multiple follow-up attempts and requests, not all studies provided all the requested data.

Data on individuals who were diagnosed with HIV-1 after initiating Truvada for PrEP were collected from demonstration projects and clinical studies, and eventually from spontaneous and literature cases. Data were requested from 55 demonstration projects or studies that were being conducted world-wide with Truvada for PrEP during the course of this study. Data were requested for any individual who participated in the study and developed a new HIV-1 infection (i.e., seroconverted). Twenty-nine of the 55 (52.7%) studies reported at least one individual who developed a new HIV-1 infection. In 26 of the 55 (47.3%) studies, there were no reported cases of new HIV-1 infection through the 31 December 2018 data cut-off.

The majority of the cases, 118 of 172 (68.6%) were from countries outside of the US. Males accounted for 131 (76.2%) of the 172 cases (most of the demonstration projects and clinical studies enrolled males). There were 39 (22.7%) females and all were from demonstration projects and clinical studies in Africa. Most females were from Uganda (17, 43.6%) or South Africa (14, 35.9%).

There were 25 (14.5%) individuals who had an HIV infection that was not detected prior to starting PrEP. Most of these were from the Partner's PrEP Demo (CO-US-164-0468). HIV RNA samples from baseline were quantified after individuals seroconverted after initiating PrEP.

Of the 25 individuals who had an HIV infection that was not detected prior to starting PrEP, resistance testing was done in 21 and revealed that 3 (14.3%) individuals had K65R or K70R mutations for tenofovir. These individuals were believed to have been infected with these mutant strains prior to initiating PrEP, however, development of the mutations while on PrEP cannot be ruled out. Follow-up information on one of the individuals revealed viral suppression after initiation of a TDF-containing treatment regimen. Resistance to emtricitabine with M184V/I mutations were detected in 10 (47.6%) individuals.

There were 97 individuals who developed an HIV infection after Truvada for HIV-1 PrEP was prescribed or within 30 days of the last reported PrEP dose. The two largest contributing studies were iPrEX-OLE (CO-US-164-0404) and the SEARCH study (CO-US-164-0188) which reported 24 (24.7%) and 11 (11.3%) of the cases, respectively. Only 28 (28.9%) of the cases were from the US.

Dried blood spot (DBS) tests were collected in 61 (62.9%) individuals and results were available for 52 (53.6%) of individuals who developed an HIV infection, and 4 of the 52 (7.7%) had TFV-DP concentrations > 700 fmol/punch and were considered adherent. Good adherence was reported for 2 individuals who had DBS tests taken but no results were reported. Two individuals were reported to have good adherence but did not have DBS samples taken. In total, 8 of the 52 (15.4%) were considered adherent to PrEP dosing. It is important to recognize that this only refers to individuals who developed new HIV-1 infections. Gilead study GS-US-276-0104 which was designed to support PMR-1906-3 will be assessing adherence in a target of 7000 individuals on Truvada for HIV-1 PrEP. The results from that study will better define adherence in the demonstration projects.

The results of resistance testing were available from 79 of the cases, and 6 (8%) individuals had K65R and/or K70R mutations for tenofovir. Two individuals had both K65R and K70R, 3 individuals had K65R, and one had K70R mutations. In two cases reported in the literature (PPD ), the authors reported that the individuals were considered to be adherent to PrEP dosing and were possibly infected with resistant strains. It was also possible that the individuals became infected during periods of lower adherence and subsequently developed resistance. Resistance to FTC with M184V/I mutations was detected in 20 (26.7%) individuals. The development of resistance after exposure to Truvada cannot be excluded although the individuals were likely infected with resistant strains.

Fifty individuals developed HIV-1 infection more than 30 days after discontinuation of Truvada for PrEP. These were reported as many of the demonstration projects/clinical studies continued to follow individuals after the study-defined dosing with Truvada for HIV-1 PrEP was over. The median time to HIV-1 infection after PrEP discontinuation was 142 days (range: 31 – 945). HIV-1 resistance testing was completed in 30 (60%) of the individuals and mutations were reported in 10 (30%) of the 30 individuals. No mutations to tenofovir were reported in these individuals. Given the time between the last exposure the Truvada and the new HIV-1 infection, the mutations are representative of the HIV-1 strain that the individual became infected with.

Forty six of the 55 (83.6%) studies provided exposure person-time data that allowed for calculation of the incident rate of new HIV-1 infections. There were a total of 10,609 individuals included with a total exposure time to daily Truvada for PrEP of 9936.4 person-years. In 14 of the 46 studies, there were 64 cases of new HIV-1 infections that occurred while receiving Truvada for HIV-1 PrEP (i.e., both before initiating PrEP and while taking PrEP or within 30 days of the last dose). The rate of new HIV-1 infections while taking Truvada for PrEP was 0.64 per 100 person-years (95% CI: 0.504 – 0.823).

In summary, study GS-US-276-0103 has collected the data required for PMR-1906-2 and reported on 172 individuals who developed new HIV-1 infections. Twenty five (14.5%) individuals were considered to be infected with HIV-1 prior to initiation of Truvada for HIV-1 PrEP and 97 (56.4%) individuals were infected with HIV-1 after initiation of Truvada for HIV-1 PrEP. Based on the DBS data, the majority of these 97 individuals were not compliant to the prescribed Truvada for HIV-1 PrEP regimen. Although K65R, K70R mutations were observed in 8% of individuals, the cases with sufficient information suggest that the individuals became infected with the resistant strains. Finally, 50 (29.1%) of individuals became infected with HIV-1 more than 30 days after discontinuation of Truvada for HIV-1 PrEP.

# 11. REFERENCES

Cohen SE, Sachdev D, Lee SA, Scheer S, Bacon O, Chen MJ, et al. Acquisition of tenofovir-susceptible, emtricitabine-resistant HIV despite high adherence to daily pre-exposure prophylaxis: a case report. The lancet. HIV 2018.

Colby DJ, Kroon E, Sacdalan C, Gandhi M, Grant RM, Phanuphak P, et al. Acquisition of Multidrug-Resistant Human Immunodeficiency Virus Type 1 Infection in a Patient Taking Preexposure Prophylaxis. Clin Infect Dis 2018;67 (6):962-4.

Desrosiers AA, Roberts AD, Simon GL. Preexposure Prophylaxis: A Cautionary Tale. AIDS 2017;31 (15):2177-8.

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.

Knox DC, Anderson PL, Harrigan PR, Tan DH. Multidrug-Resistant HIV-1 Infection despite Preexposure Prophylaxis. N Engl J Med 2017;376 (5):501-2.

Liu AY, Cohen SE, Vittinghoff E, Anderson PL, Doblecki-Lewis S, Bacon O, et al. Preexposure Prophylaxis for HIV Infection Integrated With Municipal- and Community-Based Sexual Health Services. JAMA internal medicine 2016;176 (1):75-84.

Markowitz M, Grossman H, Anderson PL, Grant R, Gandhi M, Horng H, et al. Newly Acquired Infection With Multidrug-Resistant HIV-1 in a Patient Adherent to Preexposure Prophylaxis. J Acquir Immune Defic Syndr 2017;76 (4):e104-e6.

Moore DJ, Jain S, Dube MP, Daar ES, Sun X, Young J, et al. Randomized Controlled Trial of Daily Text Messages to Support Adherence to Preexposure Prophylaxis in Individuals at Risk for Human Immunodeficiency Virus: The TAPIR Study. Clin Infect Dis 2018;66 (10):1566-72.

Pilarski R, Baril JG, Serhir B, Brenner B, Maxwell K, Harrigan R, et al. Delayed HIV Seroconversion Markers in a Patient Started on PrEP with TDF/FTC While in Eclipse Period [Abstract Number CC2/1]. 16th European Aids Conference (EACS); 2017 25-27 October; Milan, Italy.

Sivay MV, Li M, Piwowar-Manning E, Zhang Y, Hudelson SE, Marzinke MA, et al. Characterization of HIV Seroconverters in a TDF/FTC PrEP Study: HPTN 067/ADAPT. J Acquir Immune Defic Syndr 2017;75 (3):271-9.

Thaden JT, Gandhi M, Okochi H, Hurt CB, McKellar MS. Seroconversion on Preexposure Prophylaxis: A Case Report with Segmental Hair Analysis for Timed Adherence Determination [Author Manuscript]. AIDS 2018;32 (9):F1-F4.

Volk JE, Nguyen DP, Hare CB, Marcus JL. HIV Infection and Drug Resistance with Unsupervised Use of HIV Pre-Exposure Prophylaxis. AIDS Res Hum Retroviruses 2018;34 (4):329-30.

Zucker J, Carnevale C, Rai AJ, Gordon P, Sobieszczyk ME. Positive or Not, That Is the Question: HIV Testing for Individuals on Pre-exposure Prophylaxis. J Acquir Immune Defic Syndr 2018;78 (2):e11-e3.