Australian Government
Department of Health
Therapeutic Goods Administration

AusPAR Attachment 2

Extract from the Clinical Evaluation Report for tenofovir disoproxil fumarate / emtricitabine

Proprietary Product Name: Truvada

Sponsor: Gilead Sciences Australia

First round report: 16 July 2015

Second round report: 4 December 2015

TGA Health Safety Regulation

About the Therapeutic Goods Administration (TGA)

- The Therapeutic Goods Administration (TGA) is part of the Australian Government Department of Health, and is responsible for regulating medicines and medical devices.
- The TGA administers the *Therapeutic Goods Act 1989* (the Act), applying a risk management approach designed to ensure therapeutic goods supplied in Australia meet acceptable standards of quality, safety and efficacy (performance), when necessary.
- The work of the TGA is based on applying scientific and clinical expertise to decision-making, to ensure that the benefits to consumers outweigh any risks associated with the use of medicines and medical devices.
- The TGA relies on the public, healthcare professionals and industry to report problems with medicines or medical devices. TGA investigates reports received by it to determine any necessary regulatory action.
- To report a problem with a medicine or medical device, please see the information on the TGA website <https://www.tga.gov.au>.

About the Extract from the Clinical Evaluation Report

- This document provides a more detailed evaluation of the clinical findings, extracted from the Clinical Evaluation Report (CER) prepared by the TGA. This extract does not include sections from the CER regarding product documentation or post market activities.
- The words [Information redacted], where they appear in this document, indicate that confidential information has been deleted.
- For the most recent Product Information (PI), please refer to the TGA website <https://www.tga.gov.au/product-information-pi>.

Contents

Common abbreviations

Abbreviation	Meaning
AE	adverse event
ALT	alanine aminotransferase
AST	aspartate aminotransferase
ART	antiretroviral therapy
ASHM	Australasian Society for HIV Medicine
BMD	bone mineral density
CASI	computer-assisted structured interview
CDC	Centre for Disease Control
CI	confidence interval
DAIDS	NIH Division of AIDS
DEXA	dual-energy X-ray absorptiometry
DSMB	Data Safety Monitoring Board
EAE	expedited adverse event
FDA	Food and Drug Administration (US)
FDC	fixed dose combination
FTC	emtricitabine
FTC/TDF	emtricitabine and tenofovir disoproxil fumarate (Truvada®)
GCP	Good Clinical Practice
GMSM	gay men who have sex with men
HBsAg+	hepatitis B surface antigen positive
HBV	hepatitis B virus
HIV-1	human immunodeficiency virus (type 1)
HR	hazard ratio
HSV-2	herpes simplex virus type 2

Abbreviation	Meaning
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
Index subject	HIV-1 infected subject in a serodiscordant heterosexual couple
iPrEx	Pre-exposure Prophylaxis Initiative (Study CO-US-104-0288)
IQR	interquartile range
ITT	intent to treat
LLN	lower limit of normal
MedDRA	Medical Dictionary for Regulatory Activities
mITT	modified intent to treat
MSM	men who have sex with men
N/A	not applicable
NIH	National Institute of Health (US)
NNDSS	Australian National Notifiable Disease Surveillance System
NRTI	nucleoside reverse transcriptase inhibitor
Partners PrEP	Partners Pre-exposure Prophylaxis Study (CO-US-104-0380)
Partner subject	HIV-1 uninfected subject in a serodiscordant heterosexual couple
PBMC	peripheral blood mononuclear cell
PCR	polymerase chain reaction
PEP	post-exposure prophylaxis
PK	pharmacokinetic
PrEP	pre-exposure prophylaxis
PSUR	periodic safety update report
PT	preferred term

Abbreviation	Meaning
REMS	Risk Evaluation and Mitigation Strategy
RNA	ribonucleic acid
SAE	serious adverse event
SD	standard deviation
SIV	simian immunodeficiency virus
SOC	system organ class
STD	sexually transmitted disease
TDF	tenofovir disoproxil fumarate
TFV-DP	tenofovir diphosphate
ULN	upper limit of normal
URAI	unprotected receptive anal intercourse
US	United States
WHO	World Health Organization

1. Introduction

This is a Category 1 submission to register Truvada for a pre-exposure prophylaxis indication (PrEP) and to make editorial changes to the current indication.

Truvada is a fixed dose combination tablet containing tenofovir disoproxil fumarate 300 mg and emtricitabine 200 mg. Tenofovir disoproxil fumarate and emtricitabine are nucleotide and nucleoside analogue reverse transcriptase inhibitors (NRTIs) approved for the treatment of HIV-1 infection in adults.

The approved indication for the treatment of HIV-1 infection is:

> *TRUVADA is indicated for the treatment of HIV infected adults over the age of 18 years, in combination with other antiretroviral agents. This indication is based on analyses of plasma HIV-1 RNA levels and CD4 cell counts in controlled studies of VIREAD and EMTRIVA in treatment-naïve and treatment-experienced adults.*

The proposed modification of the current indication removes the qualifier statement:

> *TRUVADA is indicated for the treatment of HIV infected adults over the age of 18 years, in combination with other antiretroviral agents.*

The proposed modification brings the indication into line with other Gilead HIV-1 products approved in Australia.

The proposed new indication for HIV-1 pre-exposure prophylaxis is:

> *'TRUVADA is indicated in combination with safer sex practices for pre-exposure prophylaxis (PrEP) to reduce the risk of sexually acquired HIV-1 in adults at high risk. This indication is based on clinical trials in men who have sex with men (MSM) at high risk for HIV-1 infection and in heterosexual sero-discordant couples.'*

2. Clinical rationale

Up to 3 million new cases of HIV are diagnosed worldwide each year. The prevalence of HIV-1 infection remains high despite widespread public health campaigns which promote the use of safer sex practices and condoms. Combination antiretroviral therapy (ART) can now effectively suppress viral replication and maintain good health for extended periods, and it has the potential to reduce transmission to uninfected sexual partners. The value of post-exposure prophylaxis (PEP) with ART has been established in macaque monkeys infected with SIV, with occupational exposure to HIV-1 in healthcare workers, and with mother to child transmission. However, until recently, prevention of infection following sexual exposure in humans has not been demonstrated in large controlled clinical studies.

Truvada is a fixed dose combination tablet of emtricitabine (FTC) and the pro-drug tenofovir disoproxil fumarate (TDF) given as a once daily tablet in combination with other agents for the treatment of HIV-1 infection. Studies in macaques have shown that the FTC/TDF combination prevents or delays viraemia better than either individual component when administered before or shortly after rectal inoculation with SIV.[1] Pre-exposure combined with post-exposure was also highly effective in preventing viral transmission in this animal model. NRTIs such as Truvada are potent but well tolerated with long half-lives enabling once daily dosage. They also achieve high concentrations in male and female genital tracts.

[1] Garcia-Lerma J, et al. Prevention of rectal SHIV transmission in macaques by daily or intermittent prophylaxis with emtricitabine and tenofovir. PLoS Medicine; February 2008

Truvada was approved by the FDA for PrEP in July 2012 following the publication of two significant controlled trials. Based on this approval, and efficacy in preventing mother to child transmission, the CDC amended its guidelines to include PrEP in May 2014. Currently tenofovir plus emtricitabine is the only HIV prophylactic treatment recommended by the WHO. The WHO guideline suggests that PrEP might be valuable for:

- couples wishing to conceive a child where one partner is HIV positive;
- people who are unable to insist on condom use, in particular victims of coercion or violence;
- high risk populations such as men who have sex with men (MSM), female partners of MSM, and IV drug users.

In 2013, there were 1236 new cases of HIV-1 infection reported in Australia with a cumulative total of 33,287 reports. Truvada is not approved for PrEP in Australia but demand is growing. The ASHM has updated the Melbourne Declaration in April 2015 to strongly support access to PrEP for at risk subjects in Australia. VicPrEP and QPrEP are on-going pilot clinical trials in at risk subjects sponsored by Monash University, Queensland Department of Health and the HIV Foundation of Queensland, respectively. The TORCH study sponsored by the Kirby Institute, University of New South Wales is a survey of gay men to assess the feasibility of PrEP in an Australian setting. Gilead has been lobbied by these and other academic, medical and patient advocacy groups to support a submission for tenofovir disoproxil fumarate plus emtricitabine for PrEP in Australia.

3. Contents of the clinical dossier

3.1. Scope of the clinical dossier

The submission contained the following clinical information:

- Two pivotal efficacy/safety studies:
  - Study CO-US-104-0288 (iPrEx Study)
  - Study CO-US-104-0380 (Partner PrEP Study)
- Integrated Summary of Efficacy, Integrated Summary of Safety, and safety update sNDA
- Interim reports of an ongoing prospective observational study of individuals who seroconvert while taking Truvada for PrEP (GS-US-276-0103)
- Truvada PSUR covering 3 April 2013 to 2 April 2014

In addition, the sponsor supplied the FDA approved product label, summaries of clinical efficacy and summaries of clinical safety.

3.2. Paediatric data

The submission did not include paediatric data.

3.3. Good clinical practice

The clinical studies were conducted in accordance with ICH GCP.

4. Pharmacokinetics

No new studies were submitted.

5. Pharmacodynamics

No new studies were submitted.

6. Dosage selection for the pivotal studies

The selected dosage was the same as that approved for the treatment of HIV-1 infection.

7. Clinical efficacy

7.1. Pivotal efficacy studies

7.1.1. Study CO-US-104-0288 (iPrEx)

7.1.1.1. Study design, objectives, locations and dates

This was a randomised, double-blind, placebo-controlled, Phase III study of the safety and efficacy of FTC/TDF for prophylaxis in seronegative MSM at high risk of acquiring HIV-1 infection. It was sponsored by the NIH and the National Institute of Allergy and Infectious Diseases, with co-funding from the Bill and Melinda Gates Foundation. Study drug was supplied by Gilead. It was conducted after appropriately constituted IEC approvals under supervision of the NIH DAIDS DSMB. It commenced in July 2007 at 11 centres in six countries (Peru, Ecuador, Brazil, the US, Thailand, and South Africa). It completed in May 2010 and the results were published in the same year (Grant, 2010). The primary efficacy objective was to determine if FTC/TDF reduced seroconversions compared with placebo in HIV-1-uninfected MSM. The primary safety objective was to compare the rates of AEs in subjects receiving FTC/TDF or placebo. A total of 3,000 subjects followed for approximately 48 weeks was planned to observe at least 85 seroconversions. However, the DSMB later reduced the number of enrolled subjects to 2,499 and enrolment was stopped in November 2009. The study was event driven with double-blind assessments continuing for an indefinite period until 85 seroconversions were identified. After completion of the double-blind period, subjects were offered open-label FTC/TDF. HIV-1 testing was performed for a further 8 weeks after the last dose of study drug to monitor late seroconversions.

After a screening period of up to 28 days, visits occurred every four weeks during which study drug was dispensed and compliance counselling was given. At each visit, a medical history was taken and rapid testing for HIV-1 antibodies was performed. Subjects who were HBV negative at baseline were offered vaccination and 94% accepted. Subjects were also counselled on risk reduction, including condom use and the diagnosis of STDs. Compliance was assessed at each visit by subject self-report, by tablet counts, and by comparing the number of tablets dispensed at each visit with the time interval between visits. For statistical analysis, unreturned bottles were assumed to have been either unused (lower estimate) or completely used (higher estimate).

Routine laboratory tests including haematology and clinical chemistry were performed at Weeks 4, 8, 12, 16, and 24; and every 12 weeks thereafter. Routine screening for the common STDs was performed every 24 weeks and sexual partners were offered treatment for infections transmitted by the study subjects. Subjects who reported unprotected sexual exposure to an HIV infected partner were offered post-exposure prophylaxis and treatment with the study drug

was temporarily suspended. At screening and every 12 weeks during the treatment period, a computer-assisted structured interview (CASI) assessed education level, self-identified sexual behaviour, and alcohol use. To assess the relationship between study drug levels and protective effect, TFV-DP drug levels in plasma and PBMCs were tested in a pre-specified subgroup of approximately 10% of the overall population.

In an optional sub-study of changes in bone mineral density, 500 subjects were planned at sites with access to the appropriate equipment. DEXA scans were performed at baseline, at all 24 week visits thereafter, at the visit when study drug was stopped, and 24 weeks after stopping the drug. Measurements of BMD were made at the lumbar spine and femur. Fat distribution was also assessed at a combination of skeletal and soft-tissue landmarks. A total of 503 subjects (247 FTC/TDF and 256 placebo) were recruited from 5 countries (Peru, Thailand, USA, South Africa, and Brazil).

7.1.1.2. Inclusion and exclusion criteria

The key inclusion criteria were: males aged 18 years or more; not infected with HIV-1; evidence of high risk for acquiring HIV-1 infection based on protocol defined behaviours; Karnofsky performance status ≥ 80; normal renal function at baseline (creatinine clearance ≥ 60 mL/min using the Cockcroft-Gault equation and serum creatinine within normal limits); negative or trace urine dipstick glucose and protein; adequate hepatic function; adequate haematologic function (ANC ≥ 1,500/mm^3, platelets >150,000/mm^3, and haemoglobin ≥ 10 g/dL); and signed informed consent in local language.

High risk behaviours included:

- No condom use during anal intercourse with an HIV-positive male partner or a male partner of unknown HIV status in the 6 months prior to study enrolment.
- Anal intercourse with > 3 male sexual partners (> 5 partners at some sites) in the 6 months prior to study enrolment.
- Exchanged money, gifts, shelter, or drugs for anal sex with a male partner in the 6 months prior to enrolment.
- Had sex with a male partner and was diagnosed with an STD in the 6 months prior to enrolment.
- Had sex with a HIV-infected male partner with whom condoms were not consistently used in the six months prior to enrolment.

The key exclusion criteria were: previously diagnosed active and serious infections, malignancies or other significant medical problems; acute HBV infection; indications for treatment of chronic HBV; clinical evidence of hepatic cirrhosis; history of pathological bone fracture not related to trauma; ongoing treatment with ART or any potentially nephrotoxic therapy; possibility of receiving an anti-HIV vaccine or ART during the blinded treatment period; active alcohol or drug use likely to hinder compliance with the study in the opinion of the investigator; and significant proteinuria or glycosuria at screening or baseline.

7.1.1.3. Study treatments

- Truvada tablets
- Matching placebo tablets

7.1.1.4. Efficacy variables and outcomes

The main efficacy variables were:

- Acquisition of HIV-1 infection (infection was confirmed using an HIV testing algorithm adjudicated by an independent HIV Events Committee).

- Identification of attitudinal and behavioural characteristics before and during treatment.
- Plasma and PBMC study drug levels used to assess compliance. Drug assays were performed centrally at the University of Colorado.

The primary efficacy outcome was to determine if FTC/TDF reduced the incidence of seroconversions compared with placebo.

Other efficacy outcomes included:

- To determine if previous exposure to FTC/TDF affected the clinical and virological course of subsequent HIV-1 infection.
- To correlate FTC/TDF prophylaxis success or failure with compliance, attitude and sexual behaviour patterns.
- To determine if hepatic viral flares occurred during or after FTC/TDF prophylaxis in HBV infected subjects.

7.1.1.5. Randomisation and blinding methods

Subjects were randomised 1:1 to receive either Truvada or matching placebo. The randomisation code was generated by the study biostatistician (University of California, San Francisco). Using this code, sequentially numbered study bottles were manufactured and provided in kits to last each participant 24 weeks. Study subjects at each site were assigned a bottle number in consecutive sequence. The active and placebo study medications were identical in appearance and none of the study staff or investigators had access to the randomisation code. Unblinding was permitted only at the discretion of the protocol chairs. Subjects who discontinued study drug or who acquired HIV were not unblinded at the time of the event. The DSMB assessed the data as Group A and Group B without knowledge of the treatment assignments.

7.1.1.6. Analysis populations

The safety analysis set (SAS) included all randomised subjects for whom study drug was dispensed. The modified intent-to-treat analysis (mITT) included all randomised subjects. Randomised subjects who did not have at least one follow-up visit and those with detectable HIV-RNA were censored at Baseline.

7.1.1.7. Sample size

The planned sample size assumed that 1,500 subjects in each group would result in 85 seroconversions. This was estimated to give at least 80% power with a 1-sided $\alpha = 0.05$ to reject a null hypothesis of efficacy of 30% or less if the true efficacy was > 60%. The study objective of at least 30% efficacy is the generally accepted threshold used in HIV studies.

7.1.1.8. Statistical methods

The primary analyses were performed by the iPrEx study team while some post hoc analyses were performed by Gilead. Continuous data were generated and summarised as mean, SD, minimum and maximum values. Categorical data were summarised using counts and percentages and missing data were not categorised in these summaries. The primary efficacy analysis was performed on the mITT population. The analysis used a log-rank test comparing the distributions of infection times in the treatment groups. The null hypothesis was zero efficacy with a 1-sided alternative hypothesis of positive efficacy. Significance for rejection of the null hypothesis was set at 0.025. The test for a minimum of 30% efficacy was a 1-sided Wald test. A Cox model stratified by study site was used to calculate hazard ratios. Although HIV testing was carried out throughout the study, the single endpoint was HIV-1 detection and correction for multiplicity was not required.

7.1.1.9. Participant flow

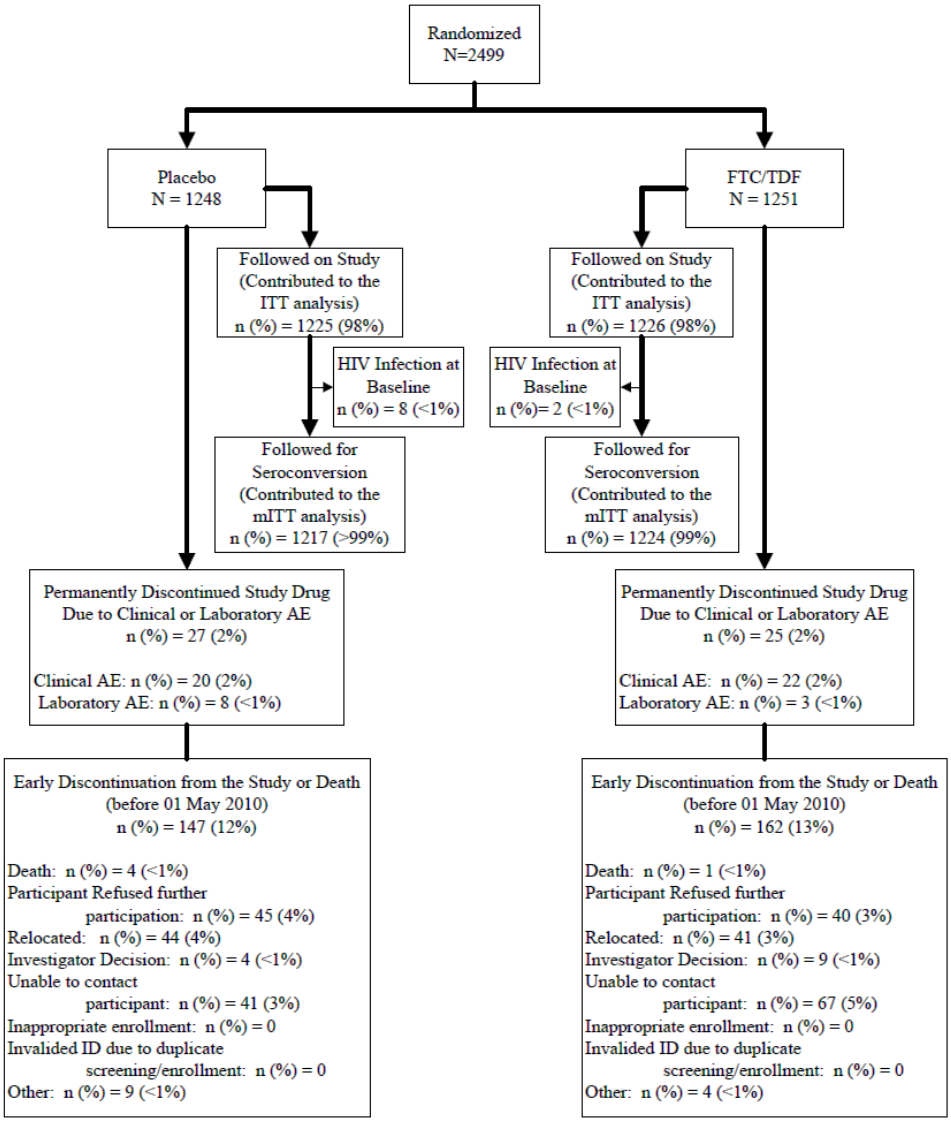
A total of 2,499 subjects were randomised (1,251 FTC/TDF, 1,248 placebo) and 98% in each group were followed and included in the ITT analysis. Total exposure to study drug was 4,237 person-years. At baseline, HIV infection was present in two subjects (< 1%) in the FTC/TDF group, and in 8 subjects (< 1%) of the placebo group. Discontinuations due to clinical or laboratory AEs occurred in 2% of each group. Discontinuations because of death, withdrawal, relocation, or other reasons occurred in 12% and 13% of the respective groups. Study drug was withdrawn after completion of follow-up; acquisition of HIV infection; unavailability for follow-up; dose-limiting toxicity; withdrawal of consent; or after taking excluded medications. Study drug was not withdrawn due to poor compliance. Additional details are shown in Figure 1. Approximately 90% of subjects attended each 12 week assessment visit. Most subjects reported that they did not know which treatment group they had been assigned to, and the minority of subjects who guessed were evenly distributed between the groups (see Table 1 below).

Table 1: Study CO-US-104-0288: Perceived group assignment at Week 12 by randomised treatment group (iPrEx analysis; randomised subjects)

Perceived Drug Assignment	Placebo (N=1248)	FTC/TDF (N=1251)	Total (N=2499)
Strongly Truvada	131 (11%)	154(13%)	285 (12%)
Somewhat Truvada	144 (12%)	124 (11%)	268 (11%)
Don't Know	719 (61%)	710 (61%)	1429 (61%)
Somewhat Placebo	86 (7%)	79 (7%)	165 (7%)
Strongly Placebo	29 (3%)	29 (3%)	58 (3%)
Decline to State	72 (6%)	74 (6%)	146 (6%)

Note: Perceived group assignment was recorded on a computer assisted structured interview at the Week 12 visit. The majority of subjects responded they did not know their randomization group. The responses were evenly distributed by group (p = 0.60 by Fisher exact test) indicating the integrity of the blinding. Analysis excludes 148 subjects (81 FTC/TDF, 67 placebo) with no Week 12 CASI results.

Figure 1: Study CO-US-104-0288: Disposition of study subjects (Gilead Analysis; randomised subjects)



7.1.1.10. Major protocol violations/deviations

Important protocol deviations were pre-defined as enrolment of an ineligible subject, incorrect study drug dispensed, or any subject who did not return for at least one on-treatment visit. The incidence of important deviations was generally low and comparable in each treatment group (see Table 2 below).

Table 2: Study CO-US-104-0288: Summary of important protocol deviations as reported by sites (iPrEx analysis; randomised subjects)

	Placebo N = 1248	FTC/TDF N = 1251	Total N = 2499
Protocol Deviation	**n (%)**	**n (%)**	**n (%)**
Violation of Inclusion/Exclusion Criteria[a]	11 (1 %)	7 (< 1%)	18 (1%) [a]
Incorrect Dispensing of Study Drug	4 (< 1%)	0	4 (< 1%)
Never Returned for Study Visits	6 (< 1%)	9 (1%)	15 (1%)

a Includes violations determined to be valid upon review by the study sponsor and protocol chair.

7.1.1.11. Baseline data

With the exception of age, the baseline demographics were comparable in each group (see Table 3 below). The age range was 18 to 67 years but the mean age of the FTC/TDF group was marginally higher than that of the placebo group (27.5 years versus 26.8 years, p = 0.04). All subjects were genetically male although 1.2% reported female gender identity. The majority of subjects were Hispanic/Latino (72%), 18% were White, 9% were Black, and 5% were Asian. Most subjects consumed alcohol daily and 53% to 55% consumed ≥ 5 drinks daily. The incidence of high risk sexual behaviours and STDs diagnosed at screening were comparable in each group. A total of 12 subjects had chronic HBV infection at baseline and completed the blinded study period (6 FTC/TDF, 6 placebo). A further two HBV negative subjects in each group developed acute HBV infections during the study.

In the optional BMD sub-study which enrolled 503 subjects, 48% were of mixed race (mostly Hispanic or Latino), 20% were Asian, 18% were White, and 13% were Black. Mean BMI was 23.5 kg/m^2. A total of 48% were aged between 18 and 24 years (and likely to be still accruing bone mass). In this group, 37% had low BMD (T-score < -1) in the spine, and 16% had low BMD in the hip. Overall, the majority of subjects had a T-score ≥ 1 at baseline (85% FTC/TDF, 83% placebo).

Table 3: Study CO-US-104-0288: Demographics and Baseline characteristics (iPrEx analysis; randomised subjects)

Characteristic		Placebo (n=1,248)	FTC/TDF (n=1,251)
Demographic			
Age - no. (%)	**p = 0.04**		
18 – 24 years		662 (53)	591 (47)
25-29 years		241 (19)	274 (22)
30-39 years		224 (18)	249 (20)
≥ 40 years		121 (10)	137 (11)
Education Level - no. (%)	**p = 0.26**		
Less than Secondary		244 (20)	279 (22)
Completed Secondary		453 (36)	430 (34)
Post-Secondary		539 (43)	525 (42)
No Answer/Missing		12 (1)	17 (1)
Race/Ethnicity - no. (%)	**p = 0.40**		
Black/African American		97 (8)	117 (9)
White		208 (17)	223 (18)
Mixed/Other		878 (70)	849 (68)
Asian		65 (5)	62 (5)
Hispanic/Latino - no. (%)	p = 0.72	906 (73)	900 (72)
Number of Alcoholic Drinks (on Days When Alcohol was Consumed in the Past Month) - no. (%)	**p = 0.66**		
0 (in the past month)		184 (15)	206 (16)
1-4 per day		345 (28)	348 (28)
≥ 5 per day		687 (55)	666 (53)
Refused/Missing/Don't Know		32 (3)	31 (2)

Table 3 (continued). Study CO-US-104-0288: Demographics and Baseline characteristics (iPrEx analysis; randomised subjects)

Characteristic	Placebo (n=1,248)	FTC/TDF (n=1,251)
City, Country - no. (%) p = 1.0		
Lima, Peru	470 (38)	470 (38)
Iquitos, Peru	230 (18)	230 (18)
Guayaquil, Ecuador	150 (12)	150 (12)
Rio de Janeiro, Brazil	147 (12)	147 (12)
Sao Paulo, Brazil	37 (3)	39 (3)
San Francisco, United States	70 (6)	70 (6)
Boston, United States	44 (4)	43 (3)
Chiang Mai, Thailand	57 (5)	57 (5)
Cape Town, South Africa	43 (3)	45 (4)
Sexual Risk Factors at screening		
Number of Partners Last 12 Weeks - mean (SD) p = 0.51	18 (43)	18 (35)
URAI Last 12 Weeks – no. (%) p = 0.37	753 (60)	732 (59)
Unprotected Anal Intercourse with HIV+ / Unknown Status Partner Last 6 Months – no. (%) p = 0.34	1009 (81)	992 (79)
Involved in Transactional Sex Last 6 Months – no. (%) p = 0.84	510 (41)	517 (41)
Known HIV+ Partner Last 6 Months - no. (%) p = 0.22	32 (3)	23 (2)
Sexually Transmitted Infections diagnosed at screening		
Syphilis Seroreactivity - no. (%) p = 0.95	162/1239 (13)	164/1240 (13)
Serum Herpes Simplex Virus Type 2 Infection – no (%) p = 0.24	430/1243 (35)	458/1241 (37)
Urine Leukocyte Esterase Positive – no (%) p = 1.0	22 (2)	23 (2)

URAI = Unprotected receptive anal intercourse

7.1.1.12. Results for the primary efficacy outcome

HIV seroconversion was observed in 110 evaluable subjects, 10 of whom had HIV RNA detected in samples obtained at the enrolment visit. In the 100 subjects with treatment-emergent infection in the mITT population, 36 subjects were receiving FTC/TDF compared with 64 subjects in the placebo group (see Table 4). The relative risk reduction in favour of FTC/TDF was 44% (95% CI: 15%, 63%, p = 0.005).[2] In the ITT population, there was a comparable risk reduction (RR 47% (95% CI: 22%, 64%, p = 0.001)). The number of infections observed over time in the mITT population is shown in Figure 2 below. To capture infections acquired late in the treatment period, an analysis of seroconversions 8 weeks after the end of treatment was performed (see Table 5). In the mITT and ITT populations, the risk reductions were 43% (95% CI: 18%, 60%) and 46% (95% CI: 23%, 61%), respectively. In each analysis, the benefit in favour of FTC/TDF was statistically significant and clinically meaningful. However, as the lower bounds of the 95% CIs were less than 30%, the null hypothesis of efficacy could not be rejected.

[2] Efficacy measured as risk reduction equals 1 minus the HR.

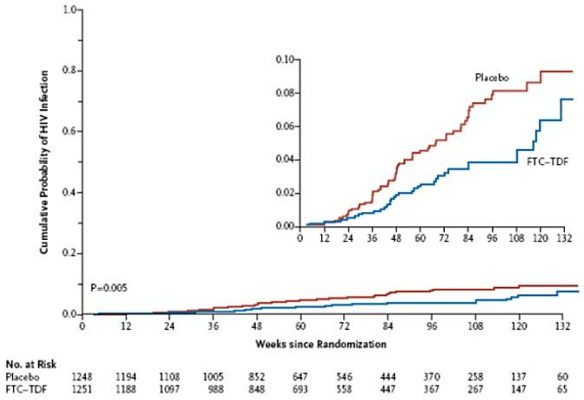
Table 4: Study CO-US-104-0288: Relative effectiveness: Primary analysis (iPrEx mITT and ITT analyses)

	Placebo	FTC/TDF	P-value[a]
mITT Analysis	(N = 1217)	(N = 1224)	
Subjects With Seroconversion Events	64	36	0.005[a]
Relative Effectiveness (2-sided 95% CI)	44% (15%, 63%)		
ITT Analysis	(N = 1225)	(N = 1226)	
Subjects With Seroconversion Events	72	38	0.001[a]
Relative Effectiveness (2-sided 95% CI)	47% (22%, 64%)		

a p-values by logrank test.

Note: the lower bound of the 1-sided 95% CI is 21% and 27% for the mITT and ITT analyses, respectively (Gilead analysis,

Figure 2: Study CO-US-104-0288: Kaplan-Meier estimates of time to HIV infection (iPrEx mITT analysis)



The cumulative probability of HIV acquisition is shown for the two study groups. The efficacy of pre-exposure prophylaxis with Truvada was 44%, as compared with placebo (p = 0.005). The inset graph shows a more detailed version of the overall graph up to a probability of 0.10.

Table 5: Study CO-US-104-0288: Relative effectiveness through the last dose of study drug (iPrEx mITT and ITT analyses)

	Placebo	FTC/TDF	P-value[a]
mITT Analysis	(N = 1217)	(N = 1224)	
Subjects With Seroconversion Events	83	48	0.002
Relative Effectiveness (2-sided 95% CI)	43% (18%, 60%)		
ITT Analysis	(N = 1225)	(N = 1226)	
Subjects With Seroconversion Events	91	50	< 0.001
Relative Effectiveness (2-sided 95% CI)	46% (23%, 61%)		

a p-value by logrank test.

Note: the lower bound of the 1-sided 95% CI is 23% and 27% for the mITT and ITT analyses, respectively (Gilead analysis,

Comment: Reported in the primary publication but not in the CSR, seroconversion rates were similar in both treatment groups during an undefined follow-up period after discontinuation of study drug at the end of the study (161 FTC/TDF versus 159 placebo) (see Clinical Questions).

7.1.1.13. Results for other efficacy outcomes

Compliance

Self-reported mean tablet use was lower in the FTC/TDF group compared with placebo at Week 4, (89% versus 92%, p < 0.001), and at Week 8 (93% versus 94%, p = 0.006). However, it was

the same (95%) in both groups thereafter. Approximately 6% of subjects at each visit did not report the number of tablets missed. At Week 4 and Week 8, 66% and 86% of tablet bottles, respectively, were returned. Based on tablet counts, usage increased during the first 8 weeks and remained stable at 89% to 95% at subsequent visits. However, based on tablet dispensation dates and quantities, the rate of tablet use decreased from 99% during the first year to 91% thereafter. A pre-defined analysis of efficacy was conducted based on self-reported tablet use, tablet counts, and dispensation records (< 50% daily use or ≥ 50% daily use). The risk reduction in the ≥ 50% usage group was 50% (95% CI: 18%, 70%) compared with 32% (95% CI: 41%, 67%) in the < 50% usage group. The difference between groups was not statistically significant (p = 0.48). However, in subjects who self-reported ≥ 90% tablet use, the rate reduction was 73% (95% CI: 41%, 88%) (see Table 6 below). This difference was statistically significant (p < 0.001) and the lower bound of the 95% CI exceeded the pre-defined 30% limit.

Table 6: Study CO-US-104-0288: Relative effectiveness: primary analysis by self-reported level of pill use (iPrEx mITT analysis)

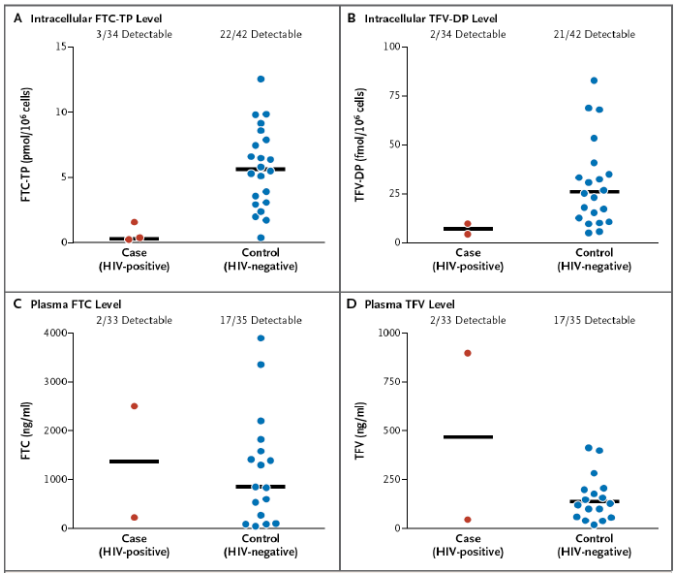
	Placebo	FTC/TDF	P-value[a]
Subjects Self-Reporting ≥ 50% Pill Use			
Subjects With Seroconversion Events	47 events	23 events	0.006[a]
Relative Effectiveness (2-sided 95% CI)	50% (18%, 70%)		
Subjects Self-Reporting ≥ 90% Pill Use			
Subjects With Seroconversion Events	30 events	8 events	< 0.001[a]
Relative Effectiveness (2-sided 95% CI)	73% (41%, 88)		

a p-values by Wald test from Cox model.

Comment: There appear to be minor inconsistencies between text and tables in the CSR (see Clinical Questions).

Based on TFV-DP PBMC levels, compliance was greater in subjects aged ≥ 25 years (46%) compared with those aged < 25 years (31%); and in subjects with a secondary education (42%) compared with those with less than secondary education. Compliance was greater in subjects aged ≥ 25 years, with higher education and URAI at screening (57%) compared with subjects without these attributes (29%).

Figure 3: Study CO-US-104-0288: Summary of the relationship between quantifiable levels of study drug components and HIV seroconversion events (iPrEx ITT analysis)



Levels of Study-Drug components in blood of subjects receiving FTC-TDF according to HIV status: Shown are intracellular levels (panels A and B) and plasma levels (panels C and D) of components of emtricitabine and tenofovir disoproxil fumarate (FTC-TDF), quantified in specimens obtained from subjects in the FTC-TDF group. FTC denotes emtricitabine triphosphate and TFV-DP tenofovir diphosphate. The horizontal lines in each panel indicate medians.

As shown in Figure 3 above, there was a close relationship between efficacy and quantifiable drug levels. The mean half-lives of FTC and TDF in plasma are 10 hours and 17 hours, respectively. However, the half-life of TFV-DP is 87 to 150 hours in PBMCs, and quantifiable levels may be detected up to 14 days after the last dose. Thus, subjects with no measurable plasma dug levels would have missed at least several days of study drug. Subjects with high plasma levels but no quantifiable TFV-DP PBMC drug levels were assumed to have taken no study drug for days or weeks and to have taken a dose just before attending a clinic visit. The risk of HIV infection was reduced by a factor of 12.9 (95% CI: 1.7, 99.3, $p < 0.001$) in the FTC/TDF group with quantifiable drug levels compared with placebo. The relative risk reduction was 92% (95% CI: 40%, 99%, $p < 0.001$). By correlating risk reduction with TFV-DP concentrations, it was estimated that four TDF doses per week conferred 97% efficacy (95% CI: 90%, 99.9%), and seven doses per week conferred 99% efficacy (95% CI: 97%, 99.9%).

Drug resistance

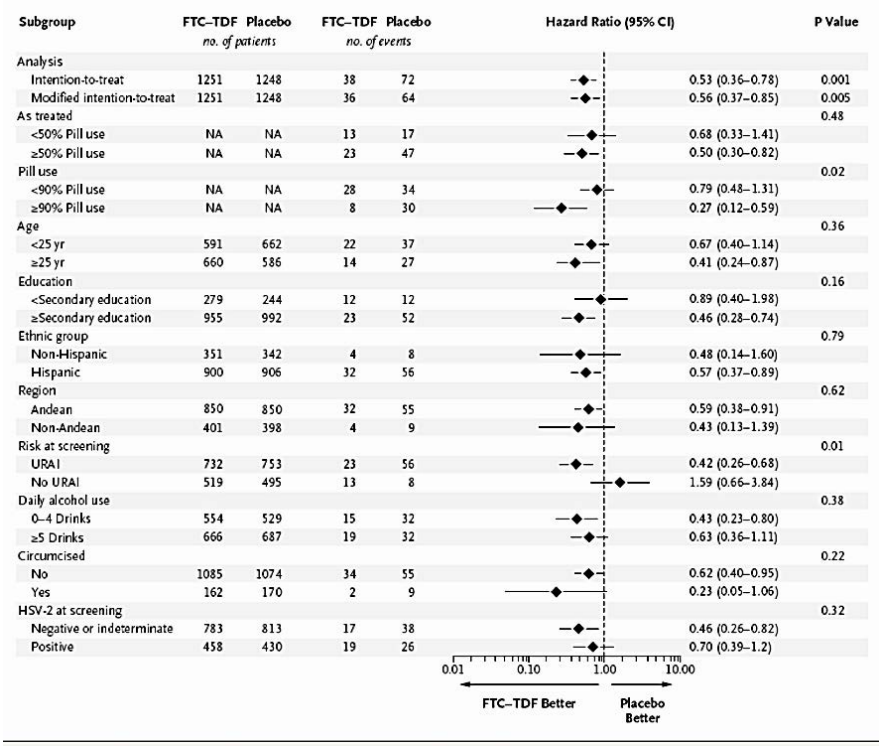
HIV RNA concentrations and CD4+ cell counts were comparable in subjects who seroconverted irrespective of their treatment group over the median 62.3 week exposure period. No drug resistant variants were detected in a post hoc analysis of subjects in the FTC/TDF group who seroconverted. FTC/TDF resistant variants in subjects who started treatment with pre-existing infection declined rapidly when treatment was discontinued.

Subgroup analyses

Pre-specified analyses were performed on subgroups defined by region (Andean/non-Andean), race, ethnicity, circumcision status, level of education, alcohol use, and age. In general, there was a treatment benefit in favour of the FTC/TDF group compared with placebo in all subgroups with the exception of subjects without a history of URAI (see Figure 4). Although there were no meaningful differences in relative risk reduction based on region, subject numbers in regions other than South America were too low to make meaningful comparisons (South American 2,070, Asia 114, Africa 88 and North America 227). The relative risk reduction in the URAI subgroup was 58% (95% CI: 32%, 74%, $p < 0.01$ compared with placebo) compared with -59%

(95% CI: -284%, 34%) in the non-URAI subgroup. Risk reduction rates were numerically higher in subjects aged ≥ 25 years (56%) compared with those aged < 25 years (28%); and in those with secondary or higher education (52%) compared with those without secondary education (12%). Relative risk reduction was highest (85%) in those aged ≥ 25 years, with a secondary education, and with a history of URAI compared with the group without these characteristics (23%).

Figure 4: Study CO-US-104-0288: Summary of subgroup analyses of the primary efficacy end point (iPrEx ITT analysis)



Subgroup	FTC–TDF (no. of patients)	Placebo (no. of patients)	FTC–TDF (no. of events)	Placebo (no. of events)	Hazard Ratio (95% CI)	P Value
Analysis						
Intention-to-treat	1251	1248	38	72	0.53 (0.36–0.78)	0.001
Modified intention-to-treat	1251	1248	36	64	0.56 (0.37–0.85)	0.005
As treated						0.48
<50% Pill use	NA	NA	13	17	0.68 (0.33–1.41)	
≥50% Pill use	NA	NA	23	47	0.50 (0.30–0.82)	
Pill use						0.02
<90% Pill use	NA	NA	28	34	0.79 (0.48–1.31)	
≥90% Pill use	NA	NA	8	30	0.27 (0.12–0.59)	
Age						0.36
<25 yr	591	662	22	37	0.67 (0.40–1.14)	
≥25 yr	660	586	14	27	0.41 (0.24–0.87)	
Education						0.16
<Secondary education	279	244	12	12	0.89 (0.40–1.98)	
≥Secondary education	955	992	23	52	0.46 (0.28–0.74)	
Ethnic group						0.79
Non-Hispanic	351	342	4	8	0.48 (0.14–1.60)	
Hispanic	900	906	32	56	0.57 (0.37–0.89)	
Region						0.62
Andean	850	850	32	55	0.59 (0.38–0.91)	
Non-Andean	401	398	4	9	0.43 (0.13–1.39)	
Risk at screening						0.01
URAI	732	753	23	56	0.42 (0.26–0.68)	
No URAI	519	495	13	8	1.59 (0.66–3.84)	
Daily alcohol use						0.38
0–4 Drinks	554	529	15	32	0.43 (0.23–0.80)	
≥5 Drinks	666	687	19	32	0.63 (0.36–1.11)	
Circumcised						0.22
No	1085	1074	34	55	0.62 (0.40–0.95)	
Yes	162	170	2	9	0.23 (0.05–1.06)	
HSV-2 at screening						0.32
Negative or indeterminate	783	813	17	38	0.46 (0.26–0.82)	
Positive	458	430	19	26	0.70 (0.39–1.2)	

HIV incidence among subjects receiving FTC-TDF, according to subgroup: The efficacy of FTC-TDF is 1 minus the hazard ratio. Hazard ratios of less than 1 indicate efficacy and 95% confidence intervals (shown by horizontal lines) that do not cross 1 indicate significant evidence of efficacy. All subgroup analyses were pre-specified except for testing for herpes simplex virus type 2 (HSV-2) at screening and pill use at the rate of 90%. P-values for the intention-to-treat and modified intention-to-treat analysis apply to the hypothesis of any evidence of efficacy; P-values for other comparisons refer to the hypothesis that efficacy differed between the two strata. NA = not applicable. URAI = unprotected receptive anal intercourse.

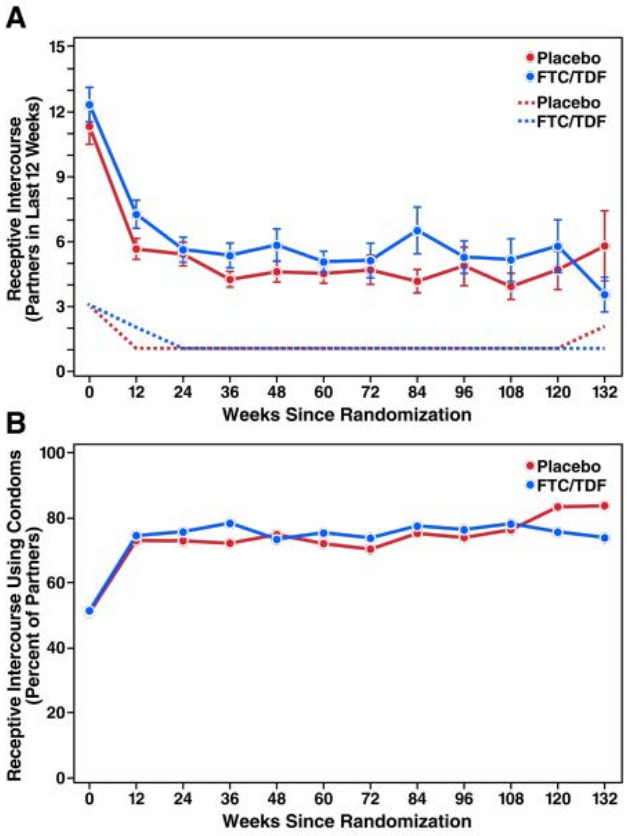
BMD sub-study

The results of the BMD sub-study are summarised in the section 'Clinical Safety; Laboratory Tests: Bone mineral density' below.

Changes in sexual practice

There were meaningful changes in sexual practice as shown in Figure 5 taken from the primary publication. In subjects engaging in receptive anal intercourse, the number of partners in the previous 12 weeks reduced by half for the duration of the study. Self-reported condom use increased in both study drug groups in the first 12 weeks of the study and the trend was sustained long-term.

Figure 5: Study CO-US-104-0288: Sexual practices by randomisation group



Partners with whom the participant had receptive anal sex in the previous 12 weeks (Panel A), and percentage of those partners using a condom (Panel B) by time on study and group. Solid lines represent means and dotted lines represent median numbers, and the error bars are the SE of the means.

Comment: HIV prevalence in most Western countries is highest in men and transgender women who have sex with men. This was a large, double-blind, placebo-controlled study of HIV prophylaxis in MSM which was well designed and conducted with appropriate ethical and DSMB oversight. The study was conducted by the NIH with study drug supplied by Gilead who also provided a medical monitor and statistical support. The data and analyses provided in the CSR do not always meet the highest regulatory standards and several post hoc data analyses have been provided by the sponsor. Nonetheless, the overall quality of the CSR is acceptable and the conclusions can be considered robust.

The primary endpoint of HIV seroconversion was adjudicated and compliance with study drug was carefully monitored throughout. In the mITT group, there was a statistically significant and clinically meaningful relative risk reduction in subjects receiving FTC/TDF compared with placebo (RR 44% (95% CI: 15%, 63%, p = 0.005)). There was a comparable reduction (RR 47% (95% CI: 22%, 64%, p = < 0.001)) in the ITT group. However, the risk reductions did not exclude the null hypothesis as the lower bounds of the CI did not exceed 30%. With a median exposure to FTC/TDF of 62.3 weeks, the HIV infection rates in the respective groups were 4.2 and 2.4 per 100 person-years.

Efficacy rates were clearly driven by compliance with study drug. In subjects reporting ≥ 90% compliance, the relative risk reduction compared with placebo was 73% (95% CI: 41%, 88%, p<0.001). However, it is unclear how this reported compliance rate was calculated (see Clinical Questions). In subjects with quantifiable study drug levels, the relative risk reduction was an impressive 92%

(95% CI: 40%, 99%, p < 0.001). Relative risk reduction rates were also numerically higher in subjects aged ≥ 25 years, with secondary education, and with a history of URAI.

On an intent-to-treat basis, the overall efficacy result was statistically significant. However, the primary endpoint was not achieved, and the benefits of drug prophylaxis in a less intensively monitored population in real world conditions are likely to be even more marginal. Despite this caveat, efficacy rates were outstanding in compliant patients with quantifiable TFV-DP drug levels in PBMC. Efficacy rates were also notably higher in subjects with secondary education, and in those who were older (and presumably wiser). Overall, the study results are positive and support the use of pre-exposure prophylaxis in this population.

In summary, in this placebo-controlled study in MSM, there was a statistically significant 44% efficacy benefit in favour of FTC/TDF. This less than optimal efficacy rate was related almost entirely due to poor compliance in a relatively small proportion of the study population, mainly subjects with low educational levels. Much higher efficacy rates were achieved in more compliant subjects, and the benefits were associated with increased self-reported safer sex practices. With careful counselling and monitoring in the Australian context, FTC/TDF has the potential to reduce acquired HIV infections by up to 90% in MSM who are compliant with drug prophylaxis and safer sex practices.

7.1.2. Study C0-US-104-0380 (Partners PrEP)

7.1.2.1. Study design, objectives, locations and dates

This was a randomised, double-blind, placebo controlled, Phase III study of the safety and efficacy of PrEP with either TDF or FTC/TDF for prophylaxis in seronegative subjects in a known serodiscordant partnership (infected index subject and uninfected partner subject). It was sponsored by the University of Washington with funding from the Bill and Melinda Gates Foundation. The study drug was supplied by Gilead. It was conducted after appropriately constituted IEC approvals under the supervision of an independent DSMB. It commenced in June 2008 at nine centres in Kenya and Uganda. The study was stopped by the DSMB in July 2011 but continued treatment was offered to participants for an additional 12 months. The preliminary results were published in the same year.[3] The primary efficacy objective was to determine if oral PrEP with TDF or FTC/TDF reduced seroconversions compared with placebo in heterosexual HIV-discordant couples who were also using standard preventive measures. The primary safety objective was to assess the incidence of AEs in subjects receiving TDF or FTC/TDF compared with placebo. A total of 4,700 subjects were planned to be followed for 24 to 36 months (1,566 subjects in each group).

The study was event driven with assessments planned to continue until 191 seroconversions were identified. After two screening visits conducted within 56 days, partner subjects were randomised with visits scheduled every four weeks until seroconversion, or for the duration of the study. At each visit, study drug was dispensed and compliance counselling was given. Compliance was assessed at each visit by tablet counts, records of tablets dispensed, and a drug compliance questionnaire. Counselling was provided by clinicians and pharmacy staff at each visit and compliance aids such as weekly pill boxes were provided. A compliance sub-study in 1,147 subjects was performed at three Ugandan sites. Enrolled subjects had increased compliance monitoring including unannounced home visits at which tablet counts were performed. Additional counselling, motivational interviewing, and problem solving was provided if compliance fell below 80%.To further assess compliance with study drug, a nested

[3] Mujugira A, et al. Characteristics of HIV-1 serodiscordant couples enrolled in a clinical trial of antiretroviral pre-exposure prophylaxis for HIV-1 prevention: the Partners PrEP Study. PLoS One 2011; 6:e25828

case-cohort analysis of TFV-DP in plasma was performed. Plasma TFV-DP was measured in partner subjects in the active study drug groups who acquired HIV infection during the study. These samples were compared with randomly selected samples from 100 subjects in each active study drug group who did not acquire HIV infection.

Uninfected partner subjects were seen at monthly intervals, during which a medical history was taken. Rapid testing for HIV-1 antibodies[4] was performed and female partners had urine pregnancy testing. Women who became infected during the study stopped study drug while pregnant and breast feeding. Subjects were counselled on risk reduction, including condom use and the diagnosis of STDs. Routine laboratory tests including haematology and clinical chemistry were performed monthly at local laboratories. Routine screening for the common STDs was performed annually and treatment was provided as necessary. To assess the relationship between study drug levels and protective effect, plasma samples for measurement of PBMC drug levels were drawn at 6 monthly intervals and archived for testing at a central laboratory. In the event of HIV-1 seroconversion, study drug was stopped and the subjects were reviewed quarterly for 12 months. At each visit, medical history and physical examinations were performed. CD4+ counts and routine screening for STDs were also performed.

Index subjects were required to have documented but untreated HIV-1 infection with a CD4+ count of at least 250 cells/mm^3. They must not have qualified for ART under the national treatment guidelines of Kenya and Uganda. They were assessed every 3 months throughout the study. Medical histories and physical examinations were performed and treatment was provided for STDs. Samples for central laboratory analysis were taken at 6 monthly intervals and archived for a range of assessments including HIV-1 plasma viral load. No drug concentration measurements were conducted during the study. However, a case-cohort analysis of detectable plasma TDF was performed in subjects who seroconverted during the study compared subjects who did not seroconvert. No formal PK analyses were performed.

7.1.2.2. Inclusion and exclusion criteria

The main inclusion criteria for partner subjects were: aged 18 to 65 years inclusive; able and willing to give written informed consent; part of a sexually active heterosexual couple in a planned long-term relationship; HIV-1 uninfected based on negative HIV-1 rapid tests; adequate renal function with a creatinine clearance of at least 60 mL/min assessed by the Cockcroft-Gault formula, and a normal serum creatinine; adequate hepatic function with ALT not more than 1.5 x ULN and AST not more than 2 x ULN; adequate haematologic function with ANC > 1300/mm^3, platelets > 125,000/mm^3, and haemoglobin > 11 g/dL at screening; and not infected with hepatitis B. The main inclusion criteria for index subjects were: adults of legal age; able and willing to give written informed consent; part of a sexually active heterosexual couple in a planned long-term relationship; HIV-1 infected based on positive enzyme immunoassay; CD4+ cell count of at least 250 cells/mm^3; and no history of any clinical AIDS-defining diagnoses.

The main exclusion criteria for partner subjects were: current or planned pregnancy; current breast feeding; current enrolment in another HIV-1 vaccine or prevention study; urine dipstick glycosuria or proteinuria confirmed in repeat samples; active and serious infections; history of pathological bone fracture not related to trauma; receiving any ART; receiving other protocol-defined agents with nephrotoxic potential; and any other conditions considered significant by the investigator. The main exclusion criteria for index subjects were: current use of ART; and current enrolment in another HIV-1 treatment study.

Withdrawal criteria included: completion of all scheduled follow-up visits; acquisition of HIV-1 infection; subjects unavailable for further follow-up; drug-related toxicity; pregnancy in a

[4] A widely accepted HIV testing algorithm was used to standardise the identification and confirmation of HIV-1 infection. This included two HIV-1 rapid tests with confirmatory HIV antibody testing. The results were not centrally adjudicated.

female partner taking study drug; withdrawal of consent; termination by study chair or DSMB; initiation of excluded medications; and significant compliance issues likely to affect subject safety. Non-compliance with study drug was not of itself a withdrawal criterion.

7.1.2.3. Study drugs

The study drugs were provided in 30 tablet bottles by Gilead:

- Viread tablets with matching placebo tablets
- Truvada tablets with matching placebo tablets

7.1.2.4. Efficacy variables and outcomes

The main efficacy variables were:

- HIV-1 acquisition in partner subjects
- Compliance

The primary efficacy outcome was to measure the rates of HIV-1 acquisition in partner subjects receiving TDF or FTC/TDF compared with placebo.

Other efficacy outcomes included:

- To assess efficacy by gender of the partner subject
- To assess the effect of compliance on efficacy rates
- To assess plasma TDF in partner subjects who acquire HIV infection

7.1.2.5. Randomisation and blinding methods

Partner subjects in each couple were randomised 1:1:1 to receive one of the study medications using IVRS. The study medications were packaged in identical bottles and labelled in accordance with the randomisation schedule. Each subject was required to take two tablets once daily because TDF and FTC/TDF are dissimilar in appearance. Subjects randomised to TDF took one TDF tablet and one placebo FTC/TDF tablet; subjects randomised to the FTC/TDF group took one FTC/TDF tablet and one placebo TDF tablet; and subjects randomised to placebo took one placebo FTC/TDF tablet and one placebo TDF tablet. With the exception of the statistician and DSMB, all study staff and investigators remained blind to the assigned treatment.

7.1.2.6. Analysis populations

The ITT population included all randomised partner subjects who met the entry criteria. The safety analysis was performed using this population. The primary analysis was performed on the mITT population which excluded partner subjects deemed to be HIV positive at the time of randomisation. The subject numbers in each analysis set are shown in Table 7.

Table 7: Study CO-US-104-0388: Analysis sets (at time point 10 July 2011) in Partners PrEP Study

Analysis Set	TDF (N=1589)	FTC/TDF (N=1583)	Placebo (N=1586)	Total (N=4758)
Intent-to-Treat	1584	1579	1584	4747
Modified Intent-to-Treat	1572	1568	1568	4708

7.1.2.7. Sample size

Studies in macaque monkeys suggested a high protective rate with PrEP, but a conservative 60% target efficacy rate was set for the clinical study. This was assessed as the minimum rate

required to achieve a positive impact on public health practice when balanced against risks and costs. In line with current practice, a minimum efficacy rate of 30% was set to exclude the null hypothesis for each study drug with a type 1 error of 0.05. A loss to follow-up rate of 7% was assumed, based on previous HIV-1 studies. Based on these assumptions, 3,900 subjects (1,300 in each treatment group) would yield 191 HIV-1 seroconversions with 80% power to detect efficacy rates of between 57% and 60% for each active drug compared with placebo. However, following publication of another study of PrEP in serodiscordant heterosexual couples, the DSMB increased the sample size to 4,700 subjects (1,566 subjects in each group).

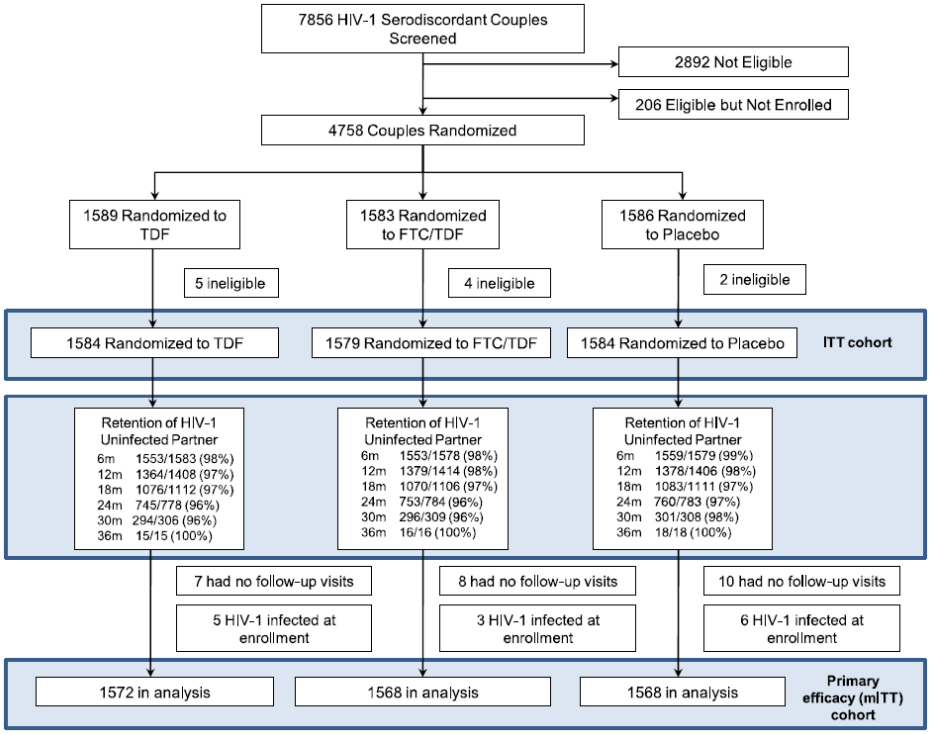
7.1.2.7.1. Statistical methods

A Cox proportional hazards model stratified by study site was used for the primary analysis. Two comparisons between each active drug and placebo were performed. The comparisons tested the null hypotheses of the hazard ratios being 1 or 0.7 (a 30% efficacy benefit). The significance level for rejection was set at a 2-sided $p = 0.05$ with $\alpha = 0.025$ for each comparison versus placebo. Although HIV testing was carried out throughout the study, the single endpoint of HIV-1 detection did not require correction for multiplicity. Similar analyses were conducted on pre-defined subgroup categories.

7.1.2.7.2. Participant flow

A total of 7,856 serodiscordant couples were screened, 4,758 couples were randomised, and 11 couples were withdrawn from the ITT group because of ineligibility. A total of 96% of partner subjects completed the follow-up period and were included in the mITT group. The subjects were followed-up for a median 23 months with a total exposure of 7,830 person-years. Additional details are shown in Figure 6.

Figure 6: Study CO-US-104-0380: Disposition of study subjects



7.1.2.8. Major protocol violations/deviations

Protocol deviations were not provided in the CSR. However, all partner subjects were included in the ITT or mITT groups.

7.1.2.9. Baseline data

The demographic characteristics for the partner and index subjects were comparable in each study drug group as shown in Table 8 and Table 9. The majority of partner subjects were male (61 to 64%) with a median age of 33 to 34 years and nearly all were married (97 to 98%). The median education duration was 7 years, and the majority received a monthly income (78 to 80%). With the exception of gender, the demographics of the index subjects were comparable. The median baseline CD4+ count was (491 to 499 cells/mm^3) and the median plasma HIV-1 RNA was 3.9 log10 copies/mL in each treatment group.

The couples had lived together for a median 7.0 to 7.1 years but their discordant HIV status was known for only a median 0.4 to 0.5 years. In the month before enrolment, sexual intercourse was reported on a median four occasions, and this was unprotected on 26 to 28% of occasions. STDs other than HIV were reported in 6 to 9% of partner and index subjects.

Table 8: Study CO-US-104-0380: Demographics and Baseline characteristics for partner and index subjects (ITT)

	TDF N=1584		FTC/TDF N=1579		Placebo N=1584	
	Partner Subject	Index Subject	Partner Subject	Index Subject	Partner Subject	Index Subject
Demographic Characteristics, n (%) or median (IQR)						
Gender						
Male	986 (62)	598 (38)	1013 (64)	566 (36)	963 (61)	621 (39)
Female	598 (38)	986 (62)	566 (36)	1013 (64)	621 (39)	963 (61)
Age, years	33 (28, 39)	32 (26, 39)	33 (28, 40)	32 (26, 39)	34 (28, 40)	33 (26, 39)
Age category						
18–24 years	184 (12)	268 (17)	177 (11)	287 (18)	172 (11)	273 (17)
25–34 years	721 (46)	657 (41)	690 (44)	636 (40)	688 (43)	629 (40)
35-44 years	480 (30)	474 (30)	498 (32)	460 (29)	513 (32)	509 (32)
≥45 years	199 (13)	185 (12)	214 (14)	196 (12)	211 (13)	173 (11)
Education, years	7 (4, 10)	7 (4, 9)	7 (4, 10)	7 (4, 9)	7 (4, 10)	7 (4, 9)
Monthly income, any (%)	1275 (80)	1069 (67)	1236 (78)	1052 (67)	1259 (79)	1079 (68)
Couple Characteristics, n (%) or median (IQR)						
Married to study partner	1543 (97)		1540 (98)		1552 (98)	
Years living with study partner	7.0 (3.0, 13.5)		7.1 (3.0, 14.0)		7.1 (3.0, 14.0)	
Living children in partnership	2 (1, 4)		2 (1, 4)		2 (1, 4)	
Couples without children	343 (22)		368 (23)		342 (22)	
Years aware of discordant status	0.5 (0.1, 2.0)		0.4 (0.1, 2.0)		0.4 (0.1, 2.0)	

Table 9: Study CO-US-104-0380: Clinical characteristics for partner and index subjects (ITT)

	TDF N=1584		FTC/TDF N=1579		Placebo N=1584	
	Partner Subject	Index Subject	Partner Subject	Index Subject	Partner Subject	Index Subject
Clinical Characteristics, n (%) or median (IQR)						
CD4 cell count/mm^3	.	491 (370, 661)	.	497 (380, 664)	.	499 (375, 663)
HIV-1 plasma RNA, log_{10}copies/mL	.	3.9 (3.2, 4.5)	.	3.9 (3.1, 4.5)	.	3.9 (3.2, 4.5)
Fully circumcised (men only)	533 (54)	198 (33)	540 (53)	177 (31)	509 (53)	202 (33)
Using contraception (women only) [a]	263 (44)	290 (29)	275 (49)	324 (32)	299 (48)	321 (33)
Pregnant (women only)	0 (0)	152 (15)	0 (0)	135 (13)	0 (0)	118 (12)
Curable sexually transmitted infection [b]	86 (6)	117 (8)	93 (6)	122 (8)	126 (8)	137 (9)
Herpes simplex virus type 2 seropositive [c]	835 (55)	.	814 (54)	.	875 (58)	.

Abbreviations: IQR = interquartile range; RNA = ribonucleic acid

a Any contraceptive use included: hormonal oral, injectable, and implantable contraceptives, intrauterine device, hysterectomy or bilateral tubal ligation. Overall, 83% of the female partner subjects and 85% of the female index subjects who used using contraception used a hormonal method.

b *Neisseria gonorrhoeae*, *Chlamydia trachomatis*, or *Trichomonas vaginalis*. Data were available from 98% of the partner subjects and 96% of the index subjects. *Trichomonas vaginalis* was the most common infection, accounting for 75% of the total infections detected. *Neisseria gonorrhoeae* and *Chlamydia trachomatis* testing were performed by APTIMA Combo 2 (Gen-Probe) or COBAS Amplicor (Roche Diagnostics), and *Trichomonas vaginalis* testing was performed by APTIMA TV TMA (Gen-Probe) or In Pouch TV (Biomed Diagnostics).

c Herpes simplex virus type 2 testing was performed using HerpeSelect-2 EIA (Focus Technologies). An index value of ≥ 3.5 was used to define a positive result.

7.1.2.10. Results for the primary efficacy outcome

When the study was stopped by the DSMB, 99 seroconversions had been reported. Of these, three were determined to be false positives and 14 were considered to be present at enrolment.

Overall, 82 infected subjects were included in the mITT group, representing 1.05 seroconversions per 100 person-years (95% CI: 0.83, 1.30). Seroconversion rates and hazard ratios in the mITT group are shown in Tables 10 and 11and Figure 7. In the TDF, FTC/TDF and placebo groups, 17, 13, and 52 subjects seroconverted with corresponding incidence rates of 0.65, 0.50, and 1.99 per person-years. The hazard ratios in the TDF, and FTC/TDF groups were 0.33 (95% CI: 0.19, 0.56), and 0.25 (95% CI: 0.13, 0.45), respectively. Efficacy rates in both active study drug groups were significantly different from placebo ($p < 0.0001$), but not from each other (HR 0.76 (95% CI: 0.37, 1.56)).[5] The hazard ratios indicated a 67% risk reduction (95% CI: 44%, 81%, $p = 0.0031$) for TDF compared with placebo, and a 75% risk reduction (95% CI: 55%, 87%, $p = 0.0004$) for FTC/TDF compared with placebo. The efficacy rates and Kaplan-Meier curves in the ITT were comparable to those in the mITT group (data not shown).

Table 10: CO-US-104-0380: HIV-1 sero incidence for partner subjects (mITT)

	TDF (N=1579)	FTC/TDF (N=1576)	Placebo (N=1578)	Total (N=4733)
Seroconversions, n	17	13	52	82
Person-years of follow-up	2604	2616	2607	7827
Incidence per 100 person-years	0.65	0.50	1.99	1.05
95% confidence interval	0.38, 1.05	0.27, 0.85	1.49, 2.62	0.83, 1.30

Table 11: CO-US-104-0380: Hazard ratio comparisons of HIV-1 infection risk (mITT)

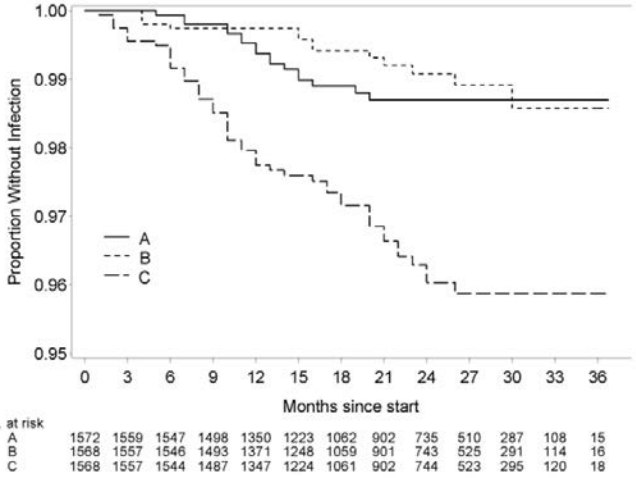
	Hazard Ratio (CI)	P-Value (0% efficacy, 30% efficacy) [a, b]
TDF compared with placebo	0.33 (0.19, 0.56)	< 0.0001, 0.0031
FTC/TDF compared with placebo	0.25 (0.13, 0.45)	< 0.0001, 0.0004
FTC/TDF compared with TDF	0.76 (0.37, 1.56)	0.2276, 0.5875

Abbreviation: CI = 95% confidence interval

a P-value using Cox's proportional hazards model for the active study drug relative to placebo.

b 0% efficacy represents the p-value for the evaluation of the hypothesis of any efficacy. 30% efficacy represents the p-value for the evaluation of the hypothesis of less than 30% efficacy (the premise for which the study was powered).

Figure 7: Study CO-US-104-0380: Kaplan-Meier curves of HIV-1 Survival (mITT)



Abbreviations: A = TDF; B = FTC/TDF, C = Placebo

7.1.2.11. Results for other efficacy outcomes

Compliance

Study medication was dispensed at 100% of visits to the eligible subjects (96%) (see Table 12 below). The most common reasons for not dispensing drug were pregnancy (30%), possible

[5] Efficacy measured as risk reduction equals 1 minus the HR.

seroconversion (22%), and subject refusal. Renal toxicity (10%) and other AEs were responsible for not dispensing study drugs in the remaining subjects. Monthly tablet counts were available for 99% of the overall population. Overall, 98% of the dispensed bottles were returned and 97% of the dispensed study tablets were counted as taken. Partner subjects reported missing at least one dose of study drug at 15% of visits but only 4% of subjects reported missing two consecutive doses. Overall, compliance in each study drug group was estimated to be at least 90% at the 87% of visits it was estimated. In the compliance sub-study of 1,147 subjects, HIV-1 infections were acquired by 14 subjects, all of which were in the placebo group (efficacy 100% (95% CI: 87%, 100%, p < 0.001)).

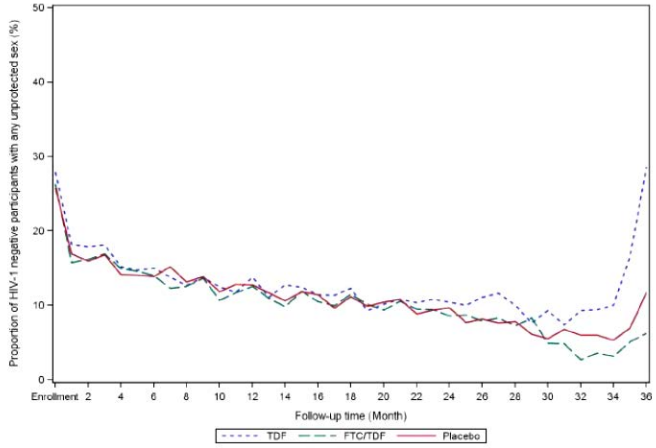
Table 12: CO-US-104-0380: Study Drug Dispensing by Group

	TDF	FTC/TDF	Placebo	Total
Follow-up visits attended				
Total participants, n	1577	1571	1574	4722
Total visits attended, n	32,835	33,110	33,059	99,004
Visits eligible to receive study drug, n (%)	31,347 (95)	32,020 (97)	31,882 (96)	95,249 (96)
Visits study drug dispensed, n (%)	31,224 (100)	31,913 (100)	31,754 (100)	94,891 (100)
Study drug withheld				
Total subjects, n	278	249	281	808
Total interruptions, n	320	294	322	936
Reasons for study drug being withheld, n (%)				
Possible seroconversion	66 (21)	49 (17)	87 (27)	202 (22)
Renal toxicity	30 (9)	36 (12)	25 (8)	91 (10)
Adverse event other than renal toxicity	28 (9)	44 (15)	31 (10)	103 (11)
Subject refused	44 (14)	60 (20)	45 (14)	149 (16)
Subject pregnant	110 (34)	79 (27)	96 (30)	285 (30)
Subject was breastfeeding	2 (1)	1 (0)	2 (1)	5 (1)
Investigator: adherence/procedures	2 (1)	0 (0)	0 (0)	2 (0)
Investigator: safety	1 (0)	5 (2)	1 (0)	7 (1)
Other	39 (12)	30 (10)	41 (13)	110 (12)

Changes in sexual behaviour

During the study follow-up period, there was a reduction in the proportion of partner subjects having sex without condoms from 27% at baseline to 13% at 12 months, and 9% at 24 months (see Figure 8). The results were comparable in each treatment group. The proportion of partner subjects who reported having sex with an outside partner in any previous month increased from 9% (13% men, 0.4% women) at baseline to 30% (42% men, 9% women) during the study.

Figure 8: Study CO-US-104-0380: Proportion of HIV-1 Partner subjects reporting any sex with the index subjects unprotected by condoms during the prior month



Subgroup analyses

HR rates were analysed in partner subject subgroups defined by gender, age, circumcision status, country, and reported frequency of unprotected sex in the month before enrolment. Index subjects were analysed according to HIV-1 plasma viral load and CD4+ count. A summary of the number and incidence of seroconversions in each group is shown in Table 13 and the corresponding hazard ratios are shown in Table 14. Overall, there was a benefit for both active study drugs compared with placebo in all subgroups. Differences within subgroups were observed but the low number of seroconversions in each subgroup did not allow meaningful comparisons.

Table 13: Study CO-US-104-0380: Summary of number and incidence of seroconversions by subgroup (mITT)

	TDF (N=1579)			FTC/TDF (N=1576)			Placebo (N=1578)		
	n Sero. (n Total)	PY	Incidence (CI)	n Sero. (n Total)	PY	Incidence (CI)	n Sero. (n Total)	PY	Incidence (CI)
Gender									
Female	8 (595)	994	0.81 (0.35, 1.59)	9 (566)	943	0.95 (0.44, 1.81)	28 (619)	996	2.81 (1.87, 4.06)
Male	9 (984)	1610	0.56 (0.26, 1.06)	4 (1010)	1673	0.24 (0.07, 0.61)	24 (959)	1611	1.49 (0.96, 2.22)
Circumcision (male only)									
Yes	6 (542)	859	0.70 (0.26, 1.52)	3 (543)	870	0.34 (0.07, 1.01)	13 (512)	854	1.52 (0.81, 2.60)
No	3 (440)	749	0.40 (0.08, 1.17)	1 (467)	804	0.12 (0.00, 0.69)	11 (447)	757	1.45 (0.73, 2.60)
Viral load (Index Partner at Enrollment)									
< 50,000 copies/mL	13 (1277)	2117	0.61 (0.33, 1.05)	9 (1279)	2136	0.42 (0.19, 0.80)	32 (1263)	2118	1.51 (1.03, 2.13)
≥ 50,000 copies/mL	4 (269)	447	0.90 (0.24, 2.29)	4 (271)	445	0.90 (0.25, 2.30)	18 (289)	458	3.93 (2.33, 6.21)
Country									
Kenya	7 (699)	1145	0.61 (0.25, 1.26)	7 (697)	1160	0.60 (0.24, 1.24)	22 (694)	1158	1.90 (1.19, 2.88)
Uganda	10 (880)	1459	0.69 (0.33, 1.26)	6 (879)	1457	0.41 (0.15, 0.90)	30 (884)	1449	2.07 (1.40, 2.96)
Age									
18–24 years	3 (184)	280	1.07 (0.22, 3.13)	6 (177)	257	2.34 (0.86, 5.09)	10 (170)	248	4.04 (1.94, 7.42)
≥ 25 years	14 (1395)	2324	0.60 (0.33, 1.01)	7 (1399)	2360	0.30 (0.12, 0.61)	42 (1408)	2359	1.78 (1.28, 2.41)
Unprotected sex									
Yes	3 (441)	659	0.46 (0.09, 1.33)	5 (415)	640	0.78 (0.25, 1.83)	22 (408)	611	3.60 (2.26, 5.45)
No	14 (1138)	1945	0.72 (0.39, 1.21)	8 (1161)	1977	0.40 (0.18, 0.80)	30 (1170)	1996	1.50 (1.01, 2.15)
CD4 (Index Partner at Enrollment)									
250–349 count/mm^3	8 (312)	512	1.56 (0.68, 3.08)	4 (297)	515	0.78 (0.21, 1.99)	10 (299)	512	1.95 (0.94, 3.59)
≥ 350 count/mm^3	9 (1267)	2092	0.43 (0.20, 0.82)	9 (1279)	2101	0.43 (0.20, 0.81)	42 (1279)	2095	2.01 (1.45, 2.71)

Abbreviations: CI = 95% confidence interval, PY = person-years, Incidence = incidence per 100 person-years, Sero = seroconversions

Table 14: Study CO-US-104-0380: Hazard ratio comparisons of hiv-1 infection risk by subgroup (mITT)

	Hazard Ratio (CI)		P-Value
Gender	**Female**	**Male**	
TDF compared with placebo	0.29 (0.13, 0.63)	0.37 (0.17, 0.80)	0.65
FTC/TDF compared with placebo	0.34 (0.16, 0.72)	0.16 (0.06, 0.46)	0.24
FTC/TDF compared with TDF	1.18 (0.45, 3.06)	0.43 (0.13, 1.39)	0.18
Circumcision (male only)	**Yes**	**No**	
TDF compared with placebo	0.46 (0.17, 1.20)	0.28 (0.08, 1.00)	0.54
FTC/TDF compared with placebo	0.22 (0.06, 0.79)	0.09 (0.01, 0.68)	0.42
FTC/TDF compared with TDF	0.49 (0.12, 1.97)	0.31 (0.03, 3.01)	0.73
Country	**Kenya**	**Uganda**	
TDF compared with placebo	0.32 (0.14, 0.74)	0.33 (0.16, 0.68)	0.94
FTC/TDF compared with placebo	0.31 (0.13, 0.74)	0.20 (0.08, 0.48)	0.46
FTC/TDF compared with TDF	0.99 (0.35, 2.82)	0.60 (0.22, 1.64)	0.50
Age	**18–24 years**	**≥ 25 years**	
TDF compared with placebo	0.28 (0.08, 1.01)	0.34 (0.18, 0.61)	0.79
FTC/TDF compared with placebo	0.59 (0.21, 1.61)	0.17 (0.07, 0.37)	0.06
FTC/TDF compared with TDF	2.12 (0.53, 8.48)	0.49 (0.20, 1.22)	0.08
Unprotected sex	**No**	**Yes**	
TDF compared with placebo	0.47 (0.25, 0.89)	0.13 (0.04, 0.44)	0.05
FTC/TDF compared with placebo	0.27 (0.12, 0.58)	0.22 (0.08, 0.58)	0.77
FTC/TDF compared with TDF	0.56 (0.24, 1.35)	1.68 (0.40, 7.02)	0.19
Viral load (index partner at Enrollment)	**< 50,000 copies/mL**	**≥ 50,000 copies/mL**	
TDF compared with placebo	0.40 (0.21, 0.76)	0.23 (0.08, 0.69)	0.39
FTC/TDF compared with placebo	0.28 (0.13, 0.58)	0.23 (0.08, 0.68)	0.79
FTC/TDF compared with TDF	0.69 (0.29, 1.61)	0.99 (0.25, 3.96)	0.66
CD4 cell count (index partner at Enrollment)	**250–349 count/mm^3**	**≥ 350 count/mm^3**	
TDF compared with placebo	0.79 (0.31, 2.01)	0.21 (0.10, 0.44)	0.03
FTC/TDF compared with placebo	0.39 (0.12, 1.26)	0.21 (0.10, 0.44)	0.39
FTC/TDF compared with TDF	0.50 (0.15, 1.65)	0.99 (0.39, 2.50)	0.36

Abbreviation: CI = 95% confidence interval

Note: Efficacy (risk reduction) is 1 minus the HR. P-values for heterogeneity of effect.

PK/PD assessment

Plasma TDF was measured in 17 partner subjects who acquired HIV infection in the TDF group, and in 12/13 infected subjects in the FTC/TDF group. These samples were compared with samples from 200 randomly selected subjects (100 in each active study drug group) who did not acquire HIV infection. In the infected subjects, detectable TFV-DP levels were present in 35.3% of the TDF group and 25.0% of the FTC/TDF group. In the sample of uninfected subjects, TFV-DP was detected in 83.1% of the TDF group, and in 80.6% of the FTC/TDF group. For partner subjects in the TDF group, the presence of detectable TFV-DP was associated with an 86% reduction in the risk of acquiring HIV infection (95% CI: 67%, 95%, $p < 0.001$) compared with subjects with no detectable levels. The reduction in risk in the FTC/TDF group with detectable TFV-DP levels was 90% (95% CI: 56%, 98%, $p = 0.002$) (see Table 15 below).

Table 15: CO-US-104-0380: Detection of tenofovir in plasma and hiv-1 prophylactic effects

	Number/ Total Samples (%) with Tenofovir Detected		Risk Estimate for HIV-1 Protection: Detection versus No Detection of Tenofovir	
	Case	Cohort	Hazard Ratio (95% CI)	p-value
TDF group	6/17 (35.3)	363/437 (83.1)	0.14 (0.05, 0.33)	<0.001
FTC/TDF group	3/12 (25.0)	375/465 (80.6)	0.10 (0.02, 0.44)	0.002

Drug resistance

Drug resistance was assessed in 95.8% of the 96 subjects who seroconverted during the study (see Table 16 below) in subjects who acquired HIV-1 infection after enrolment, only one resistant mutation was observed in a subject receiving FTC/TDF. The duration of persistence was not recorded.

Table 16: Study CO-US-104-0380: Primary study resistance mutations

Reverse transcriptase mutation conferring resistance, n/N (%)	TDF	FTC/TDF	Placebo
K65R confers resistance to TDF			
Overall	1/20 (5.0)	0/15 (0.0)	0/57 (0.0)
Among subjects retrospectively found to be HIV-1 infected at enrollment	1/5 (20.0)	0/3 (0.0)	0/6 (0.0)
Among subjects who acquired HIV-1 infection after enrollment	0/15 (0.0)	0/12 (0.0)	0/51 (0.0)
K70E confers resistance to TDF			
Overall	0/20 (0.0)	0/15 (0.0)	0/57 (0.0)
Among subjects retrospectively found to be HIV-1 infected at enrollment	0/5 (0.0)	0/3 (0.0)	0/6 (0.0)
Among subjects who acquired HIV-1 infection after enrollment	0/15 (0.0)	0/12 (0.0)	0/51 (0.0)
M184I confers resistance to FTC			
Overall	0/20 (0.0)	0/15 (0.0)	0/57 (0.0)
Among subjects retrospectively found to be HIV-1 infected at enrollment	0/5 (0.0)	0/3 (0.0)	0/6 (0.0)
Among subjects who acquired HIV-1 infection after enrollment	0/15 (0.0)	0/12 (0.0)	0/51 (0.0)
M184V confers resistance to FTC			
Overall	0/20 (0.0)	1/15 (6.7)	0/57 (0.0)
Among subjects retrospectively found to be HIV-1 infected at enrollment	0/5 (0.0)	1/3 (33.3)	0/6 (0.0)
Among subjects who acquired HIV-1 infection after enrollment	0/15 (0.0)	0/12 (0.0)	0/51 (0.0)
K65N confers resistance to TDF			
Overall	1/20 (5.0)	0/15 (0.0)	0/57 (0.0)
Among subjects retrospectively found to be HIV-1 infected at enrollment	0/5 (0.0)	0/3 (0.0)	0/6 (0.0)
Among subjects who acquired HIV-1 infection after enrollment	1/15 (6.7)	0/12 (0.0)	0/51 (0.0)
K70R confers low-level resistance to several NRTIs (including potentially TDF)			
Overall	1/20 (5.0)	0/15 (0.0)	0/57 (0.0)
Among subjects retrospectively found to be HIV-1 infected at enrollment	1/5 (20.0)	0/3 (0.0)	0/6 (0.0)
Among subjects who acquired HIV-1 infection after enrollment	0/15 (0.0)	0/12 (0.0)	0/51 (0.0)
T215C confers low-level resistance to several NRTIs (including potentially TDF)			
Overall	0/20 (0.0)	0/15 (0.0)	1/57 (1.8)
Among subjects retrospectively found to be HIV-1 infected at enrollment	0/5 (0.0)	0/3 (0.0)	0/6 (0.0)
Among subjects who acquired HIV-1 infection after enrollment	0/15 (0.0)	0/12 (0.0)	1/51 (2.0)
K103N or V106A confer resistance to NNRTIs			
Overall	2/20 (10.0)	1/15 (6.7)	1/57 (1.8)
Among subjects retrospectively found to be HIV-1 infected at enrollment	0/5 (0.0)	0/3 (0.0)	0/6 (0.0)
Among subjects who acquired HIV-1 infection after enrollment	2/15 (13.3)	1/12 (8.3)	1/51 (2.0)

Pregnancies

The number of pregnancies occurring during the study and the pregnancy outcomes are summarised in the laboratory tests section of clinical efficacy later in this document.

Comment: This was a large, double-blind, placebo-controlled study of PrEP in HIV-1 discordant heterosexual couples. It was well designed and conducted with appropriate ethical and DSMB oversight. The primary endpoint of HIV seroconversion used a widely accepted diagnostic algorithm and events were monitored by the DSMB. Compliance with study drug and safer sex measures were emphasised at each visit and carefully monitored throughout. Rapid HIV-1 testing and pregnancy testing were performed monthly. The study was conducted in East Africa in a population of

married couples; most were employed and most had at least seven years of education.

In the mITT group, there were statistically significant and clinically meaningful relative risk reductions in subjects receiving TDF (67% (95% CI: 44%, 81%, p = 0.0031)) or FTC/TDF (75% (95% CI: 55%, 87%, p = 0.0004)). The risk reductions in both active study drug groups excluded the null hypothesis as the lower bounds of the CI exceeded 30%. In the TDF, FTC/TDF and placebo groups, the HIV infection rates in the respective groups were 0.65, 0.50, and 1.99 per 100 person-years. Efficacy in subgroups was comparable with the overall population, including gender. However, the numbers of infections in each subgroup were too small to make meaningful comparisons.

As in iPrEx, efficacy rates were driven largely by compliance with study drug. Overall, compliance with study drug was approximately 90% based on self-reporting and tablet counts. The relationship between efficacy and compliance with study drug was also assessed in a nested case-cohort analysis. In subjects who acquired HIV infection, detectable TDF levels were found in only 35.3% and 25% of subjects in the TDF and FTC/TDF groups, respectively. In contrast, in a sample of uninfected partner subjects, detectable TDF levels were found in 83.1% and 80.6% of the respective groups. Detectable TDF levels were associated with an 86% risk reduction in the TDF group, and a 90% reduction in the FTC/TDF group.

Although the difference was not statistically significant, FTC/TDF was numerically superior to TDF. The protective effect of FTC/TDF for PrEP was statistically significant, highly clinically meaningful, and clearly related to drug compliance. Condom use increased during the study. However, there was some evidence of sexual disinhibition with a marked increase in the number of outside partners in each study group.

7.2. Other efficacy studies

No other efficacy studies were submitted.

7.3. Analyses performed across trials (pooled analyses and meta-analyses)

No pooled efficacy analyses were performed.

7.4. Evaluator's conclusions on clinical efficacy for the indication

Truvada is indicated in combination with safer sex practices for pre-exposure prophylaxis (PrEP) to reduce the risk of sexually acquired HIV-1 in adults at high risk. This indication is based on clinical trials in men who have sex with men (MSM) at high risk for HIV-1 infection and in heterosexual serodiscordant couples.

Two pivotal studies have been submitted to support the proposed indication. In the double-blind, placebo-controlled iPrEx Study, 2,499 HIV-uninfected MSM were randomised and received FTC/TDF or placebo for a median of 62 weeks. In the mITT population, HIV-1 seroconversions were reported in 2.9% of the FTC/TDF group compared with 5.3% of subjects receiving placebo. There was a 44% relative risk reduction for the FTC/TDF group compared with placebo. This benefit in favour of FTC/TDF in the mITT population was statistically significant (p = 0.005) although it did not exclude the null hypothesis of 30% efficacy or less (95% CI: 15%, 63%). There was a clear relationship between efficacy and compliance with drug therapy. In subjects with ≥ 50% self-reported compliance, the relative risk reduction was 50%

(95% CI: 18%, 70%, p = 0.006). In subjects with ≥ 90% self-reported compliance, the relative risk reduction was 73% (95% CI: 41%, 88%). In subjects with detectable TFV-DP drug levels, the relative risk reduction was 92% (95% CI: 40%, 99%).

In the double-blind, placebo-controlled Partners PrEP study, 4,758 heterosexual, HIV-discordant couples received either TDF, FTC/TDF or placebo for a median of 23 months. Post-randomisation HIV-1 infections were reported in 17, 13, and 52 partner subjects in the respective study drug groups, representing incidence rates of 0.65, 0.50, and 1.99 per 100 person-years. TDF and FTC/TDF were significantly more effective than placebo ($p < 0.0001$) but not different from each other. In the TDF group, there was a 67% reduction in the risk of HIV-1 acquisition (95% CI: 44%, 81%), and in the FTC/TDF group there was a 75% reduction (95% CI: 55%, 87%). Based on tablet counts, 97% of study medication was taken although 15% of subjects reported missing at least one dose of study medication in the preceding month. Compared with subjects with undetectable TFV-DP levels, subjects with detectable levels had a 90% reduction in the risk of HIV-1 acquisition (95% CI: 56%, 98%, p = 0.002). Sex without condom use decreased from 27% overall at baseline to 13% and 9% at 12 and 24 months, respectively.

Both pivotal studies enrolled large subject numbers in the different populations at risk. In both studies the primary endpoint of HIV-1 seroconversion was confirmed by repeat testing and adjudication. Both studies used a double-blind, placebo-controlled design and both studies confirmed highly significant reductions in the risk of HIV-1 acquisition compared with placebo. Compliance with study drug was carefully monitored in both studies by tablet counts, self-reported estimates, and plasma TFV-DP levels. Efficacy was directly related to compliance in both studies, and approximately 90% risk reduction for HIV-1 acquisition was observed in subjects with detectable TFV-DP levels.

Subject numbers in subgroups were too low to permit statistical analysis, although efficacy rates were comparable with the overall populations in both studies. There were no meaningful gender differences in the Partner PrEP study. Continuous counselling was provided and condom use increased in both studies. This was probably a factor in the observation that risk reduction was highest in older and more educated subjects. Drug resistance to FTC/TDF was not observed in subjects who acquired HIV-1 infection during the iPrEx Study, and it was observed in only one subject in the Partners PrEP Study. In both studies, resistant strains were detected in subjects with pre-existing infection. However, the resistant variants declined during the follow-up period when the study drugs were discontinued.

The studies were conducted largely in South American and East African populations with lower educational and healthcare standards compared with Australia. However, the overall efficacy rates were outstanding in patients who complied with drug and safer sex practices. There is no reason to expect less in the Australian context with appropriate counselling and monitoring.

8. Clinical safety

8.1. Studies providing evaluable safety data

The following studies and information sources provided evaluable safety data:

- Two pivotal efficacy studies:
  - Study C0-US-104-0288 (iPrEx)
  - Study CO-US-104-0380 (Partners PrEP)
- Interim analyses of two post-marketing safety studies:

- GS-US-276-0101
- GS-US-276-0103

- Latest Periodic Benefit Risk Evaluation Report of TRUVADA (3 April 2013 to 2 April 2014)

8.2. Pivotal efficacy studies

In the pivotal efficacy studies, the following safety data were collected:

- General adverse events (AEs) were assessed and reported by Gilead in accordance with ICH guidelines using MedDRA SOC and PT terminology.
- AE severity was assigned by the investigator using the Graded DAIDS Grading Table
- Expedited adverse events (EAEs) included all SAEs, all Grade 3 AEs, foetal loss, any medical event required to treat any of the above criteria, any Grade 2 creatinine elevation, and all bone fractures.
- AEs related to renal function abnormalities were assessed by measurements of serum creatinine and creatinine clearance using the Cockcroft-Gault equation.
- Bone mineral density was assessed by DEXA
- Laboratory tests, including HIV-1 RNA testing were performed at local laboratories.

8.2.1.1. Pivotal studies that assessed safety as a primary outcome

No studies were submitted.

8.2.1.2. Dose-response and non-pivotal efficacy studies

No studies were submitted.

8.2.1.3. Other studies evaluable for safety only

GS-US-276-0101 and GS-US-276-0103

8.2.1.4. Published studies with summary data provided by the sponsors

Study CDC 4323, FHI PrEP, CDC TDF2, and FEM PrEP.

8.2.1.5. Clinical pharmacology studies

No studies were submitted.

8.2.1.6. Pivotal studies that assessed safety as a primary outcome

No studies were submitted.

8.2.2. Other studies that assessed safety

The following studies are summarised from preliminary published data (see references). Gilead has not been provided with the CSRs or raw data.

8.2.2.1. Study CDC 4323

Methodology

Study CDC 4323 (CO-US-104-0277) was a Phase II, randomised, double-blind, placebo-controlled trial of daily TDF in HIV-1 negative MSM conducted at three centres in the

US.[6] The primary endpoint was safety. A total of 400 subjects were randomised 1:1:1:1 to receive immediate or delayed TDF 300 mg or placebo. Subjects randomised to delayed chemoprophylaxis received study drug after a 9 month interval. Seroconversions, compliance and patterns of sexual behaviour were assessed every 3 months for 24 months. Subjects with confirmed HIV-1 infection discontinued study drug but continued with safety observations for up to 12 months. In the TDF and placebo groups, most subjects were White (81% versus 73%) with an overall mean age of approximately 38 years. A total of 50% of subjects in each group had a College education. A BMD sub-study was performed in 200 subjects (100 TDF and 100 placebo).

Results

AEs were reported in 91% of subjects and the severity was mild or moderate in 97% of subjects. The frequencies of commonly reported AEs, severe AEs and SAEs were comparable in both groups. However, nausea was reported more commonly in the TDF group (11% versus 6%). There was one death (in the TDF group) related to an opiate and ethanol overdose. Grade 1 and 2 serum creatinine elevations were reported in 1% of both groups, but there were no events of Grade 3 or higher in either group. Grade 2 Hypophosphataemia (2.0 to 2.4 mg/dL) was reported in 17% and 13% of the respective groups, and Grade 3 or 4 events were reported in ≤3% of both groups. Discontinuations were comparable in both groups (16% versus 19%). Back pain was more likely in the TDF group (13%) compared with the placebo group (6%, p = 0.04), but these events were not associated with documented fractures. Fractures and the results of the BMD study are summarised in the 'bone mineral density' section found under 'Clinical safety: laboratory tests' later in this document.

Seven HIV-1 seroconversions were reported during the study period, four on placebo and three in subjects in the delayed group who had not yet received study drug. Compliance and changes in sexual behaviour were monitored but the data has not yet been published.

Comment: In this US population of MSM, TDF was generally well tolerated and no new safety signals were detected. Nausea, Hypophosphataemia and BMD loss were reported more commonly in the TDF group. Although it was not an endpoint, HIV-1 seroconversion was not reported in any of the TDF group compared with seven events in subjects not receiving active drug.

8.2.2.2. Study FHI PrEP

Methodology

FHI PrEP was a randomised, double-blind, placebo-controlled, Phase II study of the acceptability of TDF PrEP among women at high risk for HIV.[7] It was conducted by Family Health International in Ghana, Cameroon, and Nigeria. A total of 936 HIV-1 negative women were randomised 1:1 to receive TDF 300 mg or placebo and then followed at monthly intervals for 12 months. At each visit, counselling and free male condoms were provided. Tablet counts, questionnaires and qualitative interviews were conducted at each visit to assess compliance and the participants' perceptions of the program. HIV-1 testing was conducted at baseline and monthly thereafter but HIV-1 acquisition rates were not reported.

[6] Grohskopf L, et al. Preliminary analysis of biomedical data from the Phase II clinical safety trial of tenofovir disoproxil fumarate (TDF) for pre-exposure prophylaxis (PrEP) among U.S. men who have sex with men (MSM) [Oral presentation]. XVIII International AIDS Conference; 2010 July 18-23; Vienna, Austria.

[7] Peterson L, et al. Tenofovir disoproxil fumarate for prevention of HIV infection in women: a phase 2, double-blind, randomised, placebo-controlled trial. PLoS Clin Trials 2007; 2(5):e27

Results

Self-reported compliance was consistently > 82% throughout the study period but overall compliance was estimated to be 69%. The most common reasons for non-compliance were pregnancy and missed or late clinic visits. AEs were reported in 75% of the TDF group and 72% in the placebo group. The most commonly reported AEs were malaria, vaginal candidiasis, and urinary tract infections with comparable frequency in each group. In a sub-study of 400 Ghanaian women, 31% of women reported adverse events at the first monthly visit, most commonly GI disturbances, fatigue, and dizziness in the TDF group. A total of 17 subjects reported 22 SAEs but none were considered drug related. One subject died in each group (complications of abortion and anaemia, respectively) but neither was considered drug related. Laboratory abnormalities were reported with similar frequency in both groups. A single Grade 3 reduction was reported in the TDF group (< 1.0%). Grade 1 creatinine elevations were reported in 4% of each group but no events greater than Grade 1 was reported. There were no meaningful differences in AST/ALT increases between groups in the 23 TDF-treated HBsAg positive subjects when they discontinued treatment. No Grade 3 or 4 abnormalities were reported in the TDF group compared with 1% in the placebo group. Condom use increased from 52% at baseline to > 90% throughout the 12 month study period. The mean number of sexual partners in the previous month decreased from 21 at screening to 14 during the follow-up period.

Comment: In a population of West African women, TDF was well tolerated although GI disturbances, fatigue, and dizziness were reported commonly in the first month of the study. There was comparable renal and hepatic safety in subjects irrespective of HBsAg status. Sexual behaviours changed with increased condom use and a reduction in the number of sexual partners.

8.2.2.3. Study CDC TDF2

Methodology

CDC TDF2 was a double-blind, placebo-controlled, Phase III study conducted in sexually active, male and female Botswanans at high risk.[8] A total of 1200 subjects received FTC/TDF or placebo for a median 1.1 years with testing for HIV-1 seroconversion every month. Approximately 45% of subjects were female and the majority of the overall population were unmarried (94%). Counselling was provided at each visit and compliance was assessed by self-reports, tablet counts, and TFV-DP drug levels.

Results

Compliance assessed by tablet counts was approximately 84% in both groups, and approximately 90% in subjects who seroconverted. AEs were reported in 91% of the FTC/TDF group compared with 88% of the placebo group (p = 0.003). AEs occurring more commonly in the FTC/TDF group included nausea (19% versus 7%, p < 0.0001), vomiting (11% versus 7%, p = 0.008), and dizziness (15% versus 11%, p = 0.03). SAEs were reported in 10% and 11% of the respective groups. Six deaths were reported during the study (0.3% versus 0.7%) but none were considered drug related. There were no meaningful differences in abnormal laboratory values between the groups, including Hypophosphataemia and elevated creatinine values. Overall self-reported compliance was approximately 84% Other planned analyses include drug level testing, changes in BMD, and changes in risk behaviour over time.

HIV-1 seroconversion occurred in 9 subjects in the FTC/TDF group compared with 24 subjects in the placebo group. The rate reduction was 62.6% (95% CI: 21.5%, 83.4%, p = 0.013).

[8] Thigpen MC, et al. Daily oral antiretroviral use for the prevention of HIV infection in heterosexually active young adults in Botswana: results from the TDF2 study. (Oral Presentation). 6th IAS Conference on HIV Pathogenesis, Treatment and Prevention; 2011 July 17-20; Rome, Italy.

Comment: This was a large, placebo-controlled study in sexually active men and women in Botswana. Although the primary endpoint was safety, there was a clinically and statistically significant reduction in the rate of HIV-1 acquisition in the group receiving FTC/TDF. FTC/TDF was generally well tolerated and no new safety signals were detected. Nausea, vomiting, and dizziness were more commonly reported in subjects given FTC/TDF.

8.2.2.4. Study FEM PrEP

FEM-PrEP was a randomised, double-blind, placebo controlled study of FTC/TDF compared with placebo in 2,056 African women followed for 52 weeks.[9] The study was stopped after a planned interim futility analysis showed no prospect of demonstrating a protective effect of FTC/TDF. The incidence rate of infections in the FTC/TDF group was 4.7/100 person-years compared with 5.0/100 person-years in the placebo group, with a hazard ratio of 0.94 (95% CI: 0.59, 1.52, p = 0.81). It was assumed that the lack of efficacy was related to poor compliance despite counselling. In the FTC/TDF group, TFV-DP was detected in fewer than 50% of infected subjects and uninfected matched controls.

Comment: In contrast to other published studies, FTC/TDF did not prevent HIV-1 acquisition in a large population of African women. Poor overall compliance was assumed to be the cause of the failure. The main value of the study is to show that successful PrEP depends totally on adequate drug compliance.

8.3. Patient exposure

In iPrEx, median exposure in the FTC/TDF group was 62.3 weeks. Subjects were followed for one day to 145 weeks with a total exposure of 3,324 person-years. In Partners PrEP, no formal analysis of exposure was performed. The median follow-up time was 23 months and 7,830 person-years of follow-up were reported.

8.4. Adverse events

8.4.1. All adverse events (irrespective of relationship to study treatment)

8.4.1.1. Pivotal studies

Study CO-US-104-0288/iPrEx

A summary of treatment-emergent AEs is shown in Table 17 (below). AEs were reported in 55% of the FTC/TDF group compared with 56% of the placebo group. Most AEs were mild or moderate, and Grade 3 or 4 events were reported in only 9% of each group. The most common AEs reported by SOC were infections and infestations (36% versus 36%), and gastrointestinal disorders (13% versus 12%). The most common AEs by reported by PT were pharyngitis (6% versus 6%), urethritis (4% versus 5%), and depression (3% versus 5%). AEs reported with an incidence ≥ 2% with a higher incidence in the FTC/TDF group compared with placebo were headache (4% versus 3%), syphilis (4% versus 3%), abdominal pain (2% versus 1%), and nausea (2% versus < 1%).

[9] Van Damme L, et al. FEM-PrEP: randomised, double-blinded, placebo-controlled trial of oral FTC/TDF (Truvada®) as Pre-Exposure Prophylaxis (PrEP) among high risk women (Abstract). Presented at: 19th Conference on Retroviruses and Opportunistic Infections (CROI); 2012 March 5-8; Seattle, WA.

Table 17: Study CO-US-104-0288: Overall summary of treatment-emergent adverse events (Gilead Analysis; randomized subjects)

Adverse Event Category, n (%)[a]	Placebo (N=1248)	FTC/TDF (N=1251)
Any Clinical AE	705 (56%)	693 (55%)
Study Drug-Related Clinical AE	59 (5%)	77 (6%)
Grade 3 or 4 Clinical AE	112 (9%)	111 (9%)
Grade 3 or 4 Study Drug-Related Clinical AE	4 (< 1%)	3 (< 1%)
Grade 2, 3, or 4 Clinical AE	704 (56%)	683 (55%)
Clinical AE That Caused Permanent Discontinuation of Study Drug	20 (2%)	22 (2%)
Laboratory Toxicity That Caused Permanent Discontinuation of Study Drug	5 (< 1%)	3 (< 1%)
Any Clinical SAE	51 (4%)	48 (4%)
Any Laboratory SAE	12 (< 1%)	11 (< 1%)
Study Drug-Related Clinical SAE	2 (< 1%)	1 (< 1%)
Death[a]	4 (< 1%)	1 (< 1%)

a Treatment-emergent AEs were defined as AEs occurring on or after the first dose dispense date and on or before the last dose date + 30 days through 01 May 2010; results for death comprise all reported events, including 1 event in the placebo group (Subject 9116736) who died > 30 days after the last dose of study drug. Two additional AEs with fatal outcomes (1 fatal event of hepatobiliary failure and 1 fatal motor vehicle accident in the FTC/TDF group) were reported in the database through 20 May 2010 with onset dates after the 01 May 2010 cutoff.

Study CO-US-104-0380/Partners PrEP

A summary of treatment-emergent AEs is shown in Table 18. AEs were reported in 85%, 86%, and 85% of the TDF, FTC/TDF and placebo groups, respectively. Overall, the most common AEs reported by SOC were investigations (72%), Infections and infestations (43%), and Gastrointestinal disorders (10%), with no meaningful differences between the groups. The most frequent AEs reported by PT are shown in Table 19. Decreased neutrophil counts were reported in 37% of the placebo group compared with 38% of subjects in the TDF group, and 44% in the FTC/TDF group. With this exception, there were no notable differences between the study groups. Non-serious AEs were not tabulated according to severity in the CSR.

Table 18: Study CO-US-104-0380: Overall summary of adverse events for partner subjects (ITT)

	TDF (N=1584)	FTC/TDF (N=1579)	Placebo (N=1584)	Total (N=4747)
Any adverse event, n (%) [a]	1350 (85)	1362 (86)	1350 (85)	4062 (86)
Subjects with safety-related study drug interruptions, n (%) [a]	56 (4)	71 (4)	53 (3)	180 (4)
Total time off study drug for safety reasons, years	14.7	18.1	14.4	47.3
Any expedited adverse events, n (%) [a]	354 (22)	375 (24)	343 (22)	1072 (23)
Any serious adverse events, n (%) [a]	118 (7)	115 (7)	118 (7)	351 (7)
Total number of serious adverse events, n	148	142	141	431
Probably related, n (%) [b, c]	1 (1)	1 (1)	0 (0)	2 (0)
Possibly related, n (%) [b, c]	12 (8)	17 (12)	19 (13)	48 (11)
Probably not related, n (%) [b, c]	60 (41)	50 (35)	42 (30)	152 (35)
Not related, n (%) [b, c]	75 (51)	74 (52)	80 (57)	229 (53)
Grade 5/death, n (%) [b]	8 (5)	8 (6)	9 (6)	25 (6)
Grade 4/life-threatening, n (%) [b]	39 (26)	52 (37)	45 (32)	136 (32)
Congenital anomaly, n (%) [b]	5 (3)	3 (2)	1 (1)	9 (2)
Grade 3, 2, or 1, n (%) [b]	96 (65)	79 (56)	86 (61)	261 (61)

a Percentage based on the number of partner subjects.

b Percentage based on the number of serious adverse events.

c Assessments of treatment-relatedness were performed by the investigators. The coordinating center's safety monitor assessed all serious adverse events, on behalf of the study sponsor, with the exception of 2 events in the placebo group, as probably not related or not related. The 2 events that were assessed as possibly related by the site investigators and the safety monitor were both Grade 4 increases in ALT and AST, unaccompanied by clinical symptoms/signs. In both cases, the Grade 4 measurement did not confirm on repeat testing, performed within 7 days of the initial measurement; both repeat counts were within normal limits. Study medication was briefly withheld and then resumed in both cases. A subsequent Grade 3 or 4 adverse event did not occur in relation to these laboratory assessments.

Table 19: Study CO-US-104-0380: Adverse events reported for at least 3% of the partner subjects in any treatment group (ITT)

MedDRA Preferred Term, n (%)	TDF (N=1584)	FTC/TDF (N=1579)	Placebo (N=1584)	Total (N=4747)
Neutrophil count decreased	599 (38)	691 (44)	582 (37)	1872 (39)
Blood phosphorus decreased	440 (28)	461 (29)	473 (30)	1374 (29)
Malaria	302 (19)	284 (18)	306 (19)	892 (19)
Haemoglobin decreased	260 (16)	231 (15)	232 (15)	723 (15)
Platelet count decreased	190 (12)	190 (12)	177 (11)	557 (12)
Upper respiratory tract infection	125 (8)	159 (10)	142 (9)	426 (9)
Blood bicarbonate decreased	123 (8)	118 (7)	135 (9)	376 (8)
Respiratory tract infection	108 (7)	91 (6)	115 (7)	314 (7)
Urinary tract infection	109 (7)	86 (5)	103 (7)	298 (6)
Aspartate aminotransferase increased	94 (6)	104 (7)	97 (6)	295 (6)
Blood creatinine increased	76 (5)	107 (7)	86 (5)	269 (6)
Alanine aminotransferase increased	91 (6)	89 (6)	75 (5)	255 (5)
White blood cell count decreased	50 (3)	71 (4)	64 (4)	185 (4)
Blood bilirubin increased	56 (4)	50 (3)	63 (4)	169 (4)
Pelvic inflammatory disease	62 (4)	48 (3)	55 (3)	165 (3)
Diarrhoea	48 (3)	38 (2)	39 (2)	125 (3)
Proteinuria	40 (3)	36 (2)	34 (2)	110 (2)

Abbreviation: MedDRA = Medical Dictionary for Regulatory Activities

Note: Percentages based on numbers of partner subjects reporting individual events.

8.5. Treatment-related adverse events (adverse drug reactions)

8.5.1. Pivotal studies

Study CO-US-104-0288/iPrEx

ADRs were reported in 6% of the FTC/TDF group compared with 5% in the placebo group. The most common events were headache, upper abdominal pain and diarrhoea, but there were no meaningful differences between the groups.

Study CO-US-104-0380/Partners PrEP

ADRs were not reported in the CSR.

8.6. Deaths and other serious adverse events

8.6.1. Pivotal studies

Study CO-US-104-0288/iPrEx

Five deaths (< 1%) were reported but none were considered drug related by the investigator. The cause of death was unknown in one case, and the other four cases were related to trauma. The incidence and pattern of SAEs were comparable (4% in each group). The most common events were suicide and depression in both groups but SAEs were reported by PT in no more than 1% of subjects. Serious laboratory toxicities were also comparable in the FTC/TDF (< 1%) and placebo groups (< 1%). The number of events in subgroups was too small to make meaningful comparisons.

Study CO-US-104-0380/Partners PrEP

A total of 25 deaths were recorded in the TDF (n = 8), FTC/TDF (n = 8), and placebo groups (n = 9) (see Table 20 below). Two deaths in the FTC/TDF group (pulmonary embolus and influenza) were considered drug related by the investigator but not by the study monitor. Overall, SAEs were reported in 7% of partner subjects, mostly Grade 1-3 in severity, and comparable in each group. Few SAEs were considered drug related and the incidence of ADRs was comparable in each study drug group (TDF 13/1584, FTC/TDF 18/1579, and placebo 19/1584).

Table 20: Study CO-US-104-0380: Listing of partner subjects deaths by study drug group (ITT)

Subject Number	Serious Adverse Event Term [a]	Site Causality [b]	CC Causality [c]
TDF			
[redacted]	Gastroenteritis shigella	Not related	Probably not related
	Fall	Not related	Not related
	Alcohol poisoning	Probably not related	Not related
	Alcohol poisoning	Probably not related	Not related
	Road traffic accident	Not related	Not related
	Oesophageal carcinoma	Not related	Not related
	Lung abscess	Not related	Not related
	Acute abdomen	Not related	Probably not related
FTC/TDF			
[redacted]	Gun shot wound	Not related	Not related
	Poisoning	Not related	Probably not related
	Pulmonary tuberculosis	Probably not related	Probably not related
	Road traffic accident	Not related	Not related
	Road traffic accident	Not related	Not related
	Gastroenteritis	Not related	Not related
	Pulmonary embolism	Possibly related	Probably not related
	Influenza like illness	Possibly related	Probably not related
Placebo			
[redacted]	Road traffic accident	Not related	Not related
	Haematemesis	Probably not related	Probably not related
	Febrile infection	Probably not related	Probably not related
	Electrocution	Not related	Not related
	Completed suicide	Probably not related	Not related
	Road traffic accident	Not related	Not related
	Road traffic accident	Not related	Not related
	Hypotension	Probably not related	Probably not related
	Diabetic complication	Probably not related	Probably not related

Abbreviation: CC = coordinating center

a Serious adverse event term assigned using the Medical Dictionary for Regulatory Activities.

b Relationship to study drug (causality) assigned by the investigator.

c Relationship to study drug (causality) assigned by the coordinating center's safety monitor.

Subject identifiers have been redacted from Table 20.

8.7. Discontinuation due to adverse events

8.7.1. Pivotal studies

Study CO-US-104-0288/iPrEx

Overall, discontinuations due to clinical or laboratory AEs were reported in 2% of patients with no meaningful differences between groups.

Study CO-US-104-0380/Partners PrEP

Overall, there were only six AEs (0.1%) leading to discontinuation. All were minor increases in serum creatinine.

8.8. Laboratory tests

Study CO-US-104-0288/iPrEx

The number of subjects with graded laboratory AEs, including those related to hepatic, renal, and haematological function is shown in Table 21 below.

Study CO-US-104-0380/Partners PrEP

The number of subjects with treatment-emergent laboratory AEs related to hepatic and haematological function is shown in Table 22.

Table 21: CO-US-104-0288: Number of subjects with graded laboratory abnormalities (Data up to 01 May 2010; iPrEx Analysis)

AE	Maximum Severity Grade[b]	FTC/TDF N = 1251	Placebo N = 1248	P-value[a]
Absolute neutrophil count	Overall	26	28	0.76
	1	20	24	
	2	5	2	
	3	1	1	
	4	0	1	
Total hemoglobin (low)	Overall	54	60	0.52
	1	42	49	
	2	9	8	
	3	3	3	
	4	0	0	
Platelet count (low)	Overall	12	6	0.16
	1	7	4	
	2	3	2	
	3	2	0	
	4	0	0	
Sodium (low)	Overall	102	96	0.61
	1	99	91	
	2	1	2	
	3	1	1	
	4	1	2	
Sodium (high)	Overall	212	220	0.61
	1	207	214	
	2	3	5	
	3	1	1	
	4	1	0	
Potassium (low)	Overall	35	32	0.70
	1	35	32	
	2	0	0	
	3	0	0	
	4	0	0	
Potassium (high)	Overall	36	28	0.31
	1	33	23	
	2	3	2	
	3	0	0	
	4	0	3	

Table 21 (continued): CO-US-104-0288: Number of subjects with graded laboratory abnormalities (Data up to 01 May 2010; iPrEx Analysis)

AE	Maximum Severity Grade[b]	FTC/TDF N = 1251	Placebo N = 1248	P-value[a]
Alkaline phosphatase	Overall	53	48	
	1	50	47	
	2	3	1	0.62
	3	0	0	
	4	0	0	
Alanine aminotransferase	Overall	212	225	
	1	149	161	
	2	47	47	0.54
	3	12	13	
	4	4	4	
Aspartate aminotranferase	Overall	178	194	
	1	138	147	
	2	25	31	0.40
	3	11	13	
	4	4	3	
Total bilirubin	Overall	158	162	
	1	115	101	
	2	38	52	0.84
	3	4	9	
	4	1	0	
Amylase	Overall	93	96	
	1	73	74	
	2	15	16	0.85
	3	4	5	
	4	1	1	
Glucose (high)	Overall	247	276	
	1	218	232	
	2	29	41	0.20
	3	0	3	
	4	0	0	
Creatinine (high)	Overall	25	14	
	1	22	12	
	2	3	1	0.08
	3	0	1	
	4	0	0	
Phosphorus	Overall	171	165	
	1	74	84	
	2	86	74	0.66
	3	11	7	
	4	0	0	
CO_2/bicarbonate	Overall	116	107	
	1	115	106	
	2	1	1	0.47
	3	0	0	
	4	0	0	
Leukocyte count (low)	Overall	3	6	
	1	2	5	
	2	1	1	0.32
	3	0	0	
	4	0	0	

a Log-rank test for time to onset of first laboratory abnormality

b Grading based on DAIDS criteria (website: http://rsc.tech-res.com/safetyandpharmacovigilance/ "Table for Grading the Severity of Adult and Pediatric Adverse Events") with the exception of Grade 1 for serum creatinine, for which Grade 1 will be defined as the maximum of a) DAIDS criteria, b) 1.5 times the baseline value, or c) a creatinine clearance of < 50 mL/min.

Table 22: CO-US-104-0380: Percentage of highest achieved post baseline laboratory toxicity grades (ITT-Partners PrEP) Randomized Subjects

	Total Leukocyte Count	Absolute Neutrophils	Total Hemoglobin	Platelet Count	Bicarbonate	Total Bilirubin	AST	ALT
TDF (N=1584)								
Grade 1	6 (0.4)	114 (7.2)	46 (2.9)	31 (2.0)	3 (0.2)	13 (0.8)	17 (1.1)	11 (0.7)
Grade 2	0 (0.0)	82 (5.2)	34 (2.1)	22 (1.4)	4 (0.3)	3 (0.2)	9 (0.6)	7 (0.4)
Grade 3	0 (0.0)	37 (2.3)	24 (1.5)	8 (0.5)	0 (0.0)	0 (0.0)	5 (0.3)	2 (0.1)
Grade 4	0 (0.0)	5 (0.3)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	4 (0.3)	3 (0.2)
Total	6 (0.4)	238 (15.0)	104 (6.6)	62 (3.9)	7 (0.4)	16 (1.0)	35 (2.2)	23 (1.5)
FTC/TDF (N=1579)								
Grade 1	9 (0.6)	119 (7.5)	43 (2.7)	23 (1.5)	1 (0.1)	8 (0.5)	13 (0.8)	17 (1.1)
Grade 2	1 (0.1)	101 (6.4)	22 (1.4)	23 (1.5)	2 (0.1)	4 (0.3)	11 (0.7)	5 (0.3)
Grade 3	0 (0.0)	52 (3.3)	15 (0.9)	2 (0.1)	0 (0.0)	0 (0.0)	5 (0.3)	1 (0.1)
Grade 4	0 (0.0)	9 (0.6)	4 (0.3)	3 (0.2)	0 (0.0)	1 (0.1)	1 (0.1)	2 (0.1)
Total	10 (0.6)	281 (17.8)	84 (5.3)	51 (3.2)	3 (0.2)	13 (0.8)	30 (1.9)	25 (1.6)
Placebo (N=1584)								
Grade 1	10 (0.6)	105 (6.6)	27 (1.7)	27 (1.7)	2 (0.1)	15 (0.9)	17 (1.1)	11 (0.7)
Grade 2	1 (0.1)	75 (4.7)	32 (2.0)	26 (1.6)	4 (0.3)	2 (0.1)	8 (0.5)	5 (0.3)
Grade 3	0 (0.0)	28 (1.8)	18 (1.1)	2 (0.1)	0 (0.0)	0 (0.0)	2 (0.1)	1 (0.1)
Grade 4	0 (0.0)	1 (0.1)	1 (0.1)	4 (0.3)	0 (0.0)	0 (0.0)	2 (0.1)	2 (0.1)
Total	11 (0.7)	209 (13.2)	78 (4.9)	59 (3.7)	6 (0.4)	17 (1.1)	29 (1.8)	19 (1.2)
Total (N=4747)								
Grade 1	25 (0.5)	338 (7.1)	116 (2.4)	81 (1.7)	6 (0.1)	36 (0.8)	47 (1.0)	39 (0.8)
Grade 2	2 (0.0)	258 (5.4)	88 (1.9)	71 (1.5)	10 (0.2)	9 (0.2)	28 (0.6)	17 (0.4)
Grade 3	0 (0.0)	117 (2.5)	57 (1.2)	12 (0.3)	0 (0.0)	0 (0.0)	12 (0.3)	4 (0.1)
Grade 4	0 (0.0)	15 (0.3)	5 (0.1)	8 (0.2)	0 (0.0)	1 (0.0)	7 (0.1)	7 (0.1)
Total	27 (0.6)	728 (15.3)	266 (5.6)	172 (3.6)	16 (0.3)	46 (1.0)	94 (2.0)	67 (1.4)

Abbreviations: ALT = alanine aminotransferase; AST = aspartate transaminase

8.8.1. Liver function

Study CO-US-104-0288/iPrEx

The incidence of LFT abnormalities was comparable in each group. Grade 4 ALT abnormalities were recorded in only four subjects (< 0.01%) in each group. No hepatic flares were observed in the 12 subjects with chronic HBV infection at baseline, or in the four subjects who acquired acute HBV infection during the double-blind period.

Study CO-US-104-0380/Partners PrEP

No more than 2% of any study group experienced AEs related to ALT and AST abnormalities. Only two subjects in the FTC/TDF group experienced a Grade 4 ALT elevation.

8.8.2. Kidney function

Study CO-US-104-0288/iPrEx

AEs related to increases in creatinine levels were more common in the FTC/TDF group (0.02%) compared with placebo (< 0.01%, p < 0.08). However, nearly all events were mild to moderate in severity and no Grade 3 or 4 events were reported in the FTC/TDF group. Median creatinine values remained similar to baseline throughout the study, and there were no meaningful trends in either group. There were no meaningful changes or trends in creatinine clearance in either group throughout the study.

Study CO-US-104-0380/Partners PrEP

Changes in serum creatinine are shown in Table 23. AEs related to raised serum creatinine levels were reported in < 1.0% of subjects in each group. Only one subject (receiving TDF) had a Grade 2 elevation, and there were no Grade 3 or 4 elevations.

Table 23: CO-US-104-0380: Post-baseline creatinine and phosphorus laboratory toxicities (ITT)

	TDF (N=1575)	FTC/TDF (N=1570)	Placebo (N=1573)	Total (N=4718)
Maximum postbaseline toxicity grade, n (%)				
Grade 1	320 (20)	341 (22)	355 (23)	1016 (22)
Grade 2	90 (6)	83 (5)	82 (5)	255 (5)
Grade 3	11 (< 1)	11 (< 1)	9 (< 1)	31 (< 1)
Grade 4	0 (0)	1 (< 1)	0 (0)	1 (< 1)
Creatinine, n (%)				
Grade 1	3 (< 1)	6 (< 1)	4 (< 1)	13 (< 1)
Grade 2	1 (< 1)	0 (0)	0 (0)	1 (< 1)
Grade 3	0 (0)	0 (0)	0 (0)	0 (0)
Grade 4	0 (0)	0 (0)	0 (0)	0 (0)
Phosphorus, n (%)				
Grade 1	321 (20)	337 (21)	351 (22)	1009 (21)
Grade 2	89 (6)	83 (5)	82 (5)	254 (5)
Grade 3	11 (< 1)	11 (< 1)	9 (< 1)	31 (< 1)
Grade 4	0 (0)	1 (< 1)	0 (0)	1 (< 1)

Note: Partner subjects were counted once at the maximum postbaseline severity for each laboratory test. The denominator for the percentages is the number of subjects in the ITT cohort with at least one postbaseline laboratory test(s). All grades recorded in the table represent treatment-emergent laboratory abnormalities, which were defined as values that increased at least one toxicity grade postbaseline. Relevant baseline laboratory data were not missing for any subjects.

Creatinine was graded based on the following: Grade 0 (< 1.5 mg/dL), Grade 1 (1.5–2.0 mg/dL), Grade 2 (2.0–3.0 mg/dL), Grade 3 (3.0–6.0 mg/dL), and Grade 4 (> 6.0 mg/dL).

Phosphorus was graded based on the following: Grade 1 (lower limit of normal–1.0 mg/dL), Grade 2 (1.5–2.0 mg/dL), Grade 3 (1.0–1.5 mg/dL), and Grade 4 (< 1.0 mg/dL).

Note, for sites in Kampala, Mbale, and Tororo, the lower limit of normal was 2.5 mg/dL. For sites in Eldoret, Kabwohe, Kisumu, Nairobi, and Thika, the lower limit of normal was 0.81 mmol/L.

8.8.3. Other clinical chemistry

Study CO-US-104-0288/iPrEx

With the exception of serum phosphate, there were no meaningful changes or trends in either drug group relating to other clinical chemistry variables. AEs relating to decreased serum phosphate were reported in 13.7% of the FTC/TDF group compared with 13.2% in the placebo group. There were no Grade 4 AEs but Grade 3 events were reported in 0.9% and 0.6% of the respective groups.

Study CO-US-104-0380/Partners PrEP

AEs related to clinical chemistry abnormalities were reported in no more than 4% of each treatment group. With the exception of serum phosphate AEs, there were no meaningful changes in other clinical chemistries. AEs related to decreased serum phosphate were reported in 6.6% of the overall population with no meaningful differences between the study drug groups.

8.8.4. Haematology

Study CO-US-104-0288/iPrEx

AEs relating to haematological variables were uncommon in both treatment groups (< 0.1%). Only six Grade 3 events and no Grade 4 events were reported in the FTC/TDF group.

Study CO-US-104-0380/Partners PrEP

Overall, AEs relating to neutrophils, haemoglobin and platelets were reported in 15.3%, 5.6%, and 3.6% of partner subjects. Compared with placebo, low neutrophils and low haemoglobin

were reported marginally more frequently in the FTC/TDF group (7.5% versus 6.6%) and (2.7% versus 1.7%), respectively.

8.8.5. Electrocardiograph

ECGs were not recorded in either pivotal study.

8.8.6. Vital signs

Study CO-US-104-0288/iPrEx

There were no clinically significant changes or trends in vital signs throughout the study.

Study CO-US-104-0380/Partners PrEP

No vital sign findings were summarised in the CSRs. Significant abnormalities were captured as AEs.

8.8.7. Pregnancies

Study CO-US-104-0380/Partners PrEP

A total of 1,785 female partners were randomised, and pregnancies were reported in 18%, 13%, and 14% of subjects in the TDF, FTC/TDF, and placebo groups, respectively as summarised in Table 24.

Pregnancy outcomes are summarised in Table 25. Of the 288 pregnancies reported, 62% were completed, 51% resulted in a live birth, and 49% of pregnancies were lost. Five deaths were reported in newborns within 3 months of delivery but none were considered drug related (see Table 26). Pregnancy outcomes were comparable in each study drug group.

Table 24: Study CO-US-104-0380: Summary of pregnancies in partner subjects (ITT)

	TDF	FTC/TDF	Placebo	Total
Total eligible female partner subjects enrolled, n	598	566	621	1785
Female subjects reporting a pregnancy, n (%)	105 (18)	74 (13)	88 (14)	267 (15)
Pregnancies reported, n	112	80	96	288
Incidence of pregnancy per 100 female partner subject-years	11.9	8.8	10.0	10.3
95% confidence interval	9.8, 14.4	7.0, 10.9	8.1, 12.3	9.1, 11.5

Table 25: Study CO-US-104-0380: Summary of pregnancy outcomes in partner subjects (ITT)

	TDF	FTC/TDF	Placebo	Total
Pregnancies reported, n	112	80	96	288
Pregnancies completed, n (%) [a]	70 (63)	54 (68)	54 (56)	178 (62)
Live births, n (%) [b]	42 (60)	23 (43)	25 (46)	90 (51)
Loss of pregnancy, n (%) [b]	28 (40)	31 (57)	29 (54)	88 (49)
Spontaneous abortion, n	21	28	21	70
Loss at < 20 weeks gestation, n	18	27	20	65
Loss at 20–36 weeks gestation, n	1	1	0	2
Loss at ≥ 37 weeks gestation, n	0	0	1	1
Gestation age at loss unknown, n	2	0	0	2
Induced abortion, n	7	3	8	18

a Percentage based on the number of pregnancies reported.

b Percentage based on the number of pregnancies completed.

Table 26: Study CO-US-104-0380: Expedited adverse events for newborns of partner subjects (ITT)

Study Drug	Partner Subject Number	Visit	Preferred Term	Status	Date of Death
TDF		3 Month	Diarrhoea	Death	
FTC/TDF		1 Month	Bronchopneumonia	Death	
FTC/TDF		1 Month	Sepsis	Death	
Placebo		1 Month	Sepsis neonatal	Death	
Placebo		3 Month	Malaria	Death	

Note: Preferred term based assigned using the Medical Dictionary for Regulatory Activities.

Note: Greyed out information redacted for patient confidentiality reasons.

Comment: As pointed out in the CSR, medical abortion is illegal in Kenya and Uganda and an unknown number of spontaneous abortions may actually have been induced. There was no evidence of increased adverse pregnancy outcomes in the FTC/TDF group compared with placebo. In general, the pregnancy outcomes are reassuring but follow-up appears to have been somewhat limited in scope. In particular, exposure and the incidence of birth defects do not appear to have been reported (see Clinical Questions below). Differing standards of antenatal care and social factors make it difficult to interpret these pregnancy data in the Australian context.

8.8.8. AEs of special interest

With the exception of EAEs (see Clinical efficacy: pivotal efficacy studies above) there were no pre-defined AEs of interest in the pivotal studies. However, post hoc analyses of AEs of interest were conducted in relation to EAEs, gastrointestinal events identified in the FTC/TDF product information (diarrhoea, nausea, and weight loss), and renal events related to proximal tubular dysfunction with TDF.

Study CO-US-104-0288/iPrEx

Treatment-emergent gastrointestinal AEs are shown in Table 27 (below):

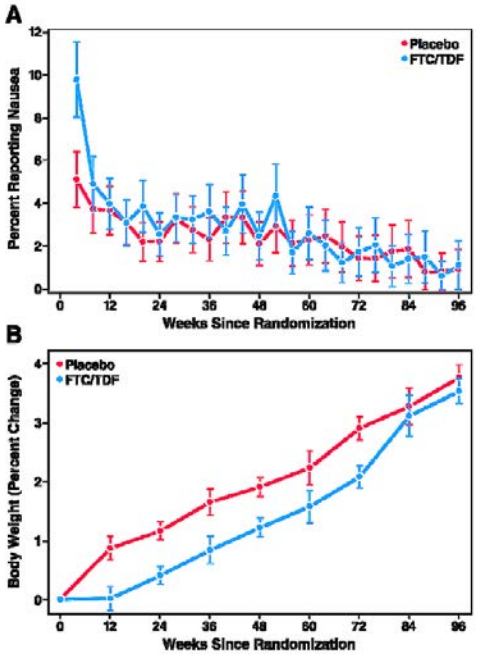
Table 27: Study CO-US-104-0288: Incidence of treatment-emergent clinical AEs for key events identified in the FTC/TDF CCDS - CSI (Gilead Analysis; Randomized Subjects)

AEs by Preferred Term, n (%)[a]	Placebo (N=1248)	FTC/TDF (N=1251)
Diarrhea	47 (4%)	43 (3%)
Vomiting	2 (< 1%)	3 (< 1%)
Nausea	7 (< 1%)	19 (2%)
Flatulence	10 (< 1%)	14 (1%)
Weight decreased	14 (1%)	27 (2%)
Dizziness	2 (< 1%)	4 (< 1%)

a AEs are coded using MedDRA Version 10 Preferred Terms and SOC classifications. Treatment-emergent AEs were defined as AEs occurring on or after the first dose dispense date and on or before the last dose date + 30 days through 01 May 2010.

Overall, the incidence of GI events was low but, with the exception of diarrhoea, there were more events in the FTC/TDF group compared with placebo, notably nausea (2% versus 1%) and decreased body weight (2% versus 1%). As shown in Figure 9 below, increased rates of nausea and body weight reduction in the FTC/TDF group occurred during the initial phase of the study with resolution thereafter.

Figure 9: CO-US-104-0288: Nausea and weight change by randomization Group (data up to 01 May 2010 iPrEx analysis; randomized subjects)



Changes in serum creatinine and creatinine clearance are summarised in the 'Clinical safety: laboratory tests – renal function' section above. AEs related to renal function were reported less frequently in the FTC/TDF group compared with placebo (3% versus 4%), and no SAEs were reported.

At the end of the double-blind study period, 36 subjects reported bone fractures. Fractures were more common in the FTC/TDF group (n=21, 2%) compared with the placebo group (n=15, 1%). All were traumatic, none appeared pathological, and none were considered drug related. There were no reports of delayed healing in subjects with follow-up information available. Decreased serum phosphate was not identified as an AE of interest in this study but there were no apparent differences between groups.

Study CO-US-104-0380/Partners PrEP

Diarrhoea was reported in 2% to 3% of subjects. SAEs were reported in only three subjects and none were considered drug related. Only one subject reported nausea in the FTC/TDF group and this was non-serious. Decreased body weight was reported in 9, 4, and 6 subjects in the TDF, FTC/TDF, and placebo groups, respectively. A single Grade 4 event was related to pulmonary tuberculosis.

Changes in serum creatinine and creatinine clearance are summarised in the 'Clinical safety: laboratory tests – renal function' section above. Increased serum creatinine (nearly all Grade 1) was reported in 5%, 7%, and 5% of partner subjects in the TDF, FTC/TDF, and placebo groups, respectively. Decreased serum phosphate was observed in 28%, 29%, and 30% of the respective groups. These decreases were reported as an EAE in 6% to 7% of each group. Most events were Grade 2 (Grade 1 events were not reported as AEs), and no confirmed events were Grade 4. Bone fractures were reported in 0.7% of the overall population with comparable frequency in each study drug group (< 1%). Nearly all of the fractures were related to direct trauma and no fracture SAEs were considered to be drug related.

8.8.9. Bone mineral density

Study CO-US-104-0288/iPrEx

Mean percentage changes in BMD from baseline in the hip and spine are shown in Table 27 below. At Week 24, there were modest but highly significant percentage decreases in BMD in the FTC/TDF group compared with placebo (total hip: p = 0.0004, spine: p = 0.0007). The decreases in BMD ranged from approximately 0.5% to 1% but no further reductions were apparent at subsequent visits to Week 96. Total hip osteopaenia (defined as a T-score of -1.0 to -2.5) at any post-baseline visit was reported in 19% of the FTC/TDF group compared with 18% in the placebo group. No subjects in either group had a marked reduction in BMD (> 7.0% at ≥ 2 consecutive visits). A decrease of ≥ 5% in BMD in the spine was reported in 14% of the FTC/TDF group compared with 6% of the placebo group. Marked decreases (> 5% at ≥ 2 consecutive visits) were observed in 3% and 2% of the respective groups. Increases in body fat were observed in both treatment groups with minor smaller increases in the FTC/TDF group.

Table 27: CO-US-104-0288: Least Square Mean (Standard Error) percentage change in BMD from Baseline to on-study drug visit (Data from the iPrEx study team) (iPrEx analysis; subjects who participated in the DEXA sub-study)

	Placebo		FTC/TDF		% Difference FTC/TDF-Placebo	
	n	LS Mean (SE) % Change	n	LS Mean (SE) % Change	LS Mean (95% CI)	p-value
Total Hip						
Week 24	211	0.29 (0.12)	207	−0.34 (0.13)	−0.63 (−0.98 to −0.28)	0.0004
Week 48	167	0.72 (0.18)	162	−0.22 (0.18)	−0.94 (−1.45 to −0.43)	0.0003
Week 72	112	0.41 (0.23)	105	−0.07 (0.24)	−0.48 (−1.14 to 0.19)	0.1588
Week 96	56	−0.24 (0.32)	55	−0.77 (0.32)	−0.53 (−1.42 to 0.36)	0.2401
Spine						
Week 24	211	0.32 (0.19)	210	−0.60 (0.19)	−0.92 (−1.45 to −0.39)	0.0007
Week 48	168	0.10 (0.23)	165	−0.51 (0.23)	−0.61 (−1.24 to 0.02)	0.0581
Week 72	112	0.24 (0.28)	107	−0.91 (0.28)	−1.15 (−1.93 to −0.38)	0.0037
Week 96	56	−0.08 (0.44)	55	−1.09 (0.45)	−1.01 (−2.25 to 0.22)	0.108
Trochanter						
Week 24	211	0.06 (0.18)	207	−0.47 (0.18)	−0.53 (−1.03 to −0.03)	0.0367
Week 48	167	0.37 (0.27)	162	−0.48 (0.27)	−0.85 (−1.60 to −0.10)	0.026
Week 72	111	0.04 (0.32)	105	−0.93 (0.33)	−0.97 (−1.87 to −0.07)	0.0348
Week 96	56	−0.18 (0.40)	55	−1.06 (0.40)	−0.88 (−2.00 to 0.23)	0.1184
Femoral Neck						
Week 24	211	0.29 (0.21)	207	0.01 (0.21)	−0.28 (−0.86 to 0.30)	0.3492
Week 48	167	0.35 (0.29)	162	−0.54 (0.29)	−0.89 (−1.69 to −0.08)	0.0311
Week 72	112	−0.04 (0.39)	105	−0.38 (0.40)	−0.34 (−1.43 to 0.75)	0.5411
Week 96	56	0.10 (0.44)	55	−0.25 (0.45)	−0.34 (−1.57 to 0.89)	0.5846

LS = least square

Note: This table was generated by the UCSF statistical team and has not been published.

Note: The analysis excludes scans after seroconversion and includes data from scan performed up to the last dose of study drug.

Note: The LS means (SE) of % change from baseline are from a repeated measures model regressing on treatment by week. The n is the number of subjects with evaluable scans at the visit.

Study CO-US-104-0380/Partners PrEP

No BMD assessments were made.

Study CDC 4323

In the BMD sub-study, 184 subjects had at least one DEXA scan after randomisation. Compared with placebo, there were significant net decreases in mean BMD of -1.1% in the femoral neck (95% CI: -0.4%, -1.9%, p = 0.004), and of -0.8% in the total hip (95% CI: -0.3%, -1.3%). There

was a net decrease of -0.7% in the lumbar spine but the difference was not statistically significant (95% CI: -0.1%, 1.5%). The BMD results were comparable after adjustment for baseline BMD, race, age, BMI, and renal function. Overall, 13% of subjects in the TDF group experienced ≥ 5% loss of BMD compared with 6% in the placebo group (p = 0.13). Hypogonadism or vitamin D deficiency was observed in four of the 27 subjects with severe osteopaenia. In the follow-up period, 10 fractures were reported (6 TDF, 4 placebo, p = 0.75) but all were related to trauma and not considered drug related. The probability of changes in spinal bone density in the TDF and placebo groups at 24 months is shown in Figures 10 and 11 (see below). The proportion of subjects experiencing bone loss of any severity was higher in the TDF group compared with placebo.

Figure 10: Study CDC 4323: Probability density of percent changes in bone density at 24 months at the total spine (L2 to L4) (Study CDC 4323 Dexa sub-study participants)

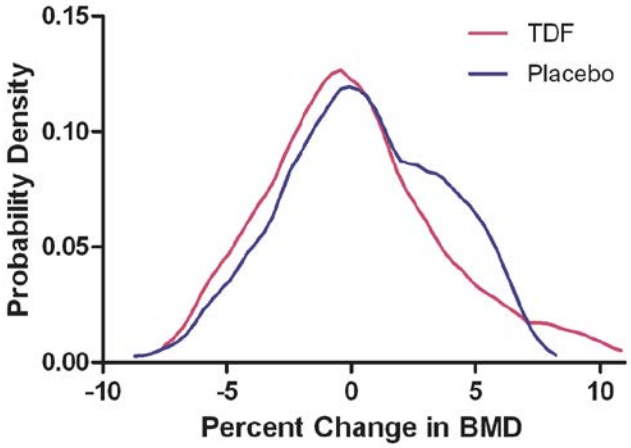
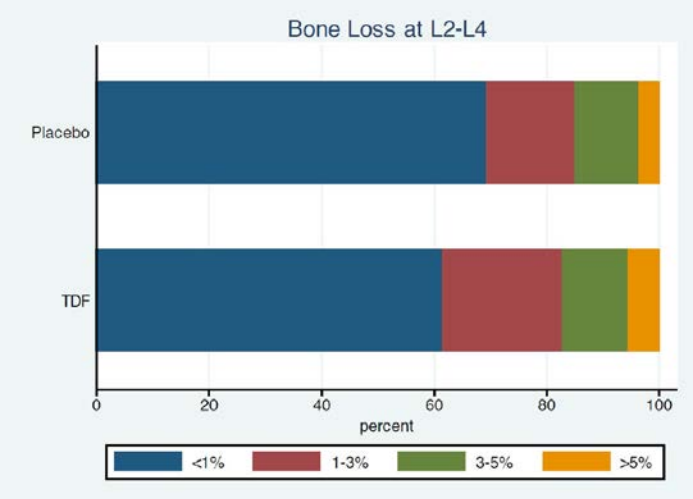


Figure 11: Study CDC 4323: Proportion of subjects experiencing bone loss at 24 Months compared to Baseline (Study CDC 4323 Dexa sub-study participants)



8.9. Post-marketing experience

Post-marketing safety has been assessed in:

1. Data from the Antiretroviral Pregnancy Registry, including an interim report from 1 January 2011 to 31 January 2014 (Study GS-US-276-0101).
2. An observational study of subject receiving Truvada for PrEP who seroconvert during follow-up (Study GS-US-276-0103).

3. The latest Periodic Benefit Risk Evaluation Report (PSUR/PBRER) for Truvada dated 3 April 2013 to 2 April 2014.
4. An updated summary of literature data since submission of the sNDA to 30 November 2014.
5. Additional reports submitted to the FDA after the sNDA with a cut-off date of 24 July 2013.

8.9.1. Study GS-US-276-0101

This is an ongoing 3 year, prospective, observational study of maternal and foetal outcomes in HIV-uninfected women receiving Truvada for PrEP before conceiving. The study was mandated by the FDA as a condition of approval. Data from evaluable subjects enrolled into the Antiretroviral Pregnancy Registry (APR) between 1 January 2011 and 31 January 2014 have been analysed in this interim report. Patients receiving any antiretroviral therapy are enrolled into the APR as soon as possible after pregnancy is confirmed. At the interim analysis cut-off point, 36 pregnant women with reported Truvada prescriptions were identified in the APR database. Of the 36 patients receiving Truvada, 35 were enrolled in the Partners PrEP study which mandated discontinuation of study drug. All pregnant women taking Truvada for PrEP were then matched 1:1 with a comparison group of other HIV-1-infected pregnant women receiving any other antiretroviral therapy identified in the APR. The process matched pregnancies as closely as possible based on gestation time, exposure to antiretroviral therapy, and other demographic variables. The study outcomes include birth defects and other reported pregnancy outcomes such as spontaneous abortions, induced abortions, stillbirths and live births.

Patient demographics in the Truvada and matched control groups are shown in Table 28 below. Of the 36 patients receiving Truvada for PrEP, the mean age was 30.0 years (range 22 to 40), most were from Africa (97.2%), most were Black (91.7%), and most were enrolled in a clinical study (97.2%). All patients were exposed during the first trimester and all but one patient discontinued Truvada during the pregnancy. The mean exposure to Truvada was 6.61 weeks (range 0.1 to 31.4). Exposure was 12.9 weeks in the single individual who continued treatment during her pregnancy. The incidence of birth defects was comparable in the Truvada and control groups as shown in Table 29. In the Truvada group, there was one birth defect in 19 live births with a prevalence rate of 0.05 (95% CI: 0.01 to 0.26). The birth defect (a 2 cm haemangioma and a 1 cm umbilical hernia in the same infant) was not considered drug related. The prevalence of adverse pregnancy outcomes is shown in Table 30. In the Truvada group, there were 17 events (11 spontaneous abortions, and 6 induced abortions) with a prevalence of 0.47 (95% CI: 0.30 to 0.65). In the matched control group, there were fewer events (4 spontaneous abortions, 2 induced abortions, and 2 stillbirths).

Table 28: Study GS-US-276-0101: Patient demographics and clinical characteristics at Baseline among Truvada for PrEP cases and matched HIV-infected controls

	Truvada for PrEP, HIV-			Any Treatment, HIV+ (N=36)	p-value*
	Discontinued (N=35)	Continued (N=1)	Total (N=36)		
Age (years)					
N	25	1	26	35	
Mean (95% CI)	29.6 (27.7-31.4)	40.0 (-)	30.0 (28.0-31.9)	30.1 (27.6-32.5)	0.95
Median (IQR)	29.0 (6.0)	40.0 (-)	29.5 (8.0)	31.0 (9.0)	
Minimum – Maximum	22.0 – 38.0	-	22.0-40.0	15.0-44.0	
Age Group (years)†					
≤19	0	0	0	5 (13.9%)	0.07
20-34	20 (57.1%)	0	20 (55.6%)	19 (52.8%)	
≥35	5 (14.3%)	1 (100%)	6 (16.7%)	11 (30.6%)	
Geographical Region					
Africa	34 (97.1%)	1 (100%)	35 (97.2%)	30 (83.3%)	0.05
United States	1 (2.9%)	0	1 (2.8%)	6 (16.7%)	
Race†					
White	0	0	0	0	0.05
Black	32 (91.4%)	1 (100%)	33 (91.7%)	22 (61.1%)	
Hispanic	0	0	0	2 (5.6%)	
Asian	1 (2.9%)	0	1 (2.8%)	0	
Other	2 (5.7%)	0	2 (5.6%)	7 (19.4%)	
Hepatitis B &/or C					
Yes	0	0	0	1 (2.8%)‡	0.31
No	35 (100%)	1 (100%)	36 (100%)	35 (97.2%)	
Last Menstrual Period (year)					
2011	20 (57.1%)	1 (100%)	21 (58.3%)	17 (47.2%)	0.28
2012	15 (42.9%)	0	15 (41.7%)	17 (47.2%)	
2013	0	0	0	2 (5.6%)	
Clinical Study Enrollment					
Yes	34 (97.1%)	1 (100%)	35 (97.2%)	30 (83.3%)	0.05
No	1 (2.9%)	0	1 (2.8%)	6 (16.7%)	
Prenatal Testing					
Yes	1 (2.9%)	1 (100%)	2 (5.6%)	14 (38.9%)	0.001
No	34 (97.1%)	0	34 (94.4%)	22 (61.1%)	
Trimester of Initial Exposure					
1st	35 (100.0%)	1 (100%)	36 (100.0%)	36 (100.0%)	0.99
2nd	0	0	0	0	
3rd	0	0	0	0	
Trimester of Enrollment†					
1st	19 (54.3%)	1 (100%)	20 (55.6%)	20 (55.6%)	0.05
2nd	0	0	0	6 (16.7%)	
3rd	0	0	0	1 (2.8%)	
Gestational Age at Presentation (weeks)					
N	19	1	20	27	
Mean (95% CI)	5.5 (4.4-6.6)	10.0 (-)	5.7 (4.5-6.9)	10.1 (7.2-13.0)	0.01
Median (IQR)	5.0 (3.0)	10.0 (-)	5.0 (3.0)	7.0 (10.0)	
Minimum – Maximum	2.0-11.0	-	2.0-11.0	0-33.0	
Days from LMP to Date of Notification					
N	35	1	36	36	
Mean (95% CI)	177 (136-218)	65 (-)	174 (133-214)	192 (132-251)	0.62
Median (IQR)	198 (254)	65 (-)	194 (251)	123 (217)	
Minimum – Maximum	8-354	-	8-354	-13-646	
Clinical Status at Pregnancy Start					
A. Asymptomatic, acute (1˚) HIV or PGL	0	0	0	29 (80.6%)	<0.0001
B. Symptomatic, not (A) or (C)	0	0	0	2 (5.6%)	
C. Other AIDS-indicator conditions &/or CD_4 <200 µL	0	0	0	5 (13.9%)	
D. HIV prophylaxis	35 (100%)	1 (100%)	36 (100%)	0	
CD_4 Cell Counts at Pregnancy Start (µL)†					
≥500	0	0	0	17 (47.2%)	-
200-499	0	0	0	11 (30.6%)	
<200	0	0	0	0	

* *P*-values are based on statistical tests comparing the overall Truvada for PrEP, HIV- (total) group and the controls (any treatment, HIV+) group. Independent *t*-tests were used for continuous variables and chi-square tests were used for categorical variables. Unpresented p-values (-) indicate that calculations were not possible.

† Percentages may not total to 100% due to unavailable/missing data.

‡ Single subject reported Hepatitis B virus infection.

Table 29: Study GS-US-276-0101: Prevalence of birth defects*

	Truvada for PrEP, HIV- (N=36)			Any Treatment, HIV+ (N=36)		
	Birth Defects (n)	Live Births (n)	Prevalence (95% CI)	Birth Defects (n)	Live Births (n)	Prevalence (95% CI)
Total	1	19	0.05 (0.01-0.26)	1	28	0.04 (0.01-0.18)
Age (years)						
≤19	0	0	-	0	5	0.00 (0.00-0.52)
20-34	1	11	0.09 (0.01-0.41)	0	14	0.00 (0.00-0.23)
≥35	0	0	-	1	8	0.13 (0.01-0.53)
Geographical Region						
Africa	1	18	0.06 (0.01-0.28)	1	24	0.04 (0.01-0.21)
United States	0	1	0.00 (0.00-0.98)	0	4	0.00 (0.00-0.60)
Clinical Study Enrollment						
Yes	1	18	0.06 (0.01-0.28)	1	24	0.04 (0.01-0.21)
No	0	1	0.00 (0.00-0.98)	0	4	0.00 (0.00-0.60)
Prenatal Testing						
Yes	0	1	0.00 (0.00-0.98)	1	11	0.09 (0.01-0.41)
No	1	18	0.06 (0.01-0.28)	0	17	0.00 (0.00-0.20)

* Prevalence estimates were based on the number of live births. Defects include those meeting the Centers for Disease Control and Prevention Criteria (CDC) definition only. Excludes reported defects in abortions < 20 weeks.

Table 30: Study GS-US-276-0101: Prevalence of adverse pregnancy outcomes (spontaneous abortions, induced abortions and stillbirths)

	Truvada for PrEP, HIV- (N=36)			Any Treatment, HIV+ (N=36)		
	Events (n)	Pregnancies (n)	Prevalence (95% CI)	Events (n)	Pregnancies (n)	Prevalence (95% CI)
Total Adverse Outcomes	17	36	0.47 (0.30-0.65)	8	36	0.22 (0.10-0.39)
Age (years)*						
≤19	0	0	-	0	5	0.00 (0.00-0.52)
20-34	9	20	0.45 (0.23-0.69)	5	19	0.26 (0.09-0.51)
≥35	6	6	1.00 (0.54-1.00)	3	11	0.27 (0.06-0.61)
Geographical Region						
Africa	17	35	0.49 (0.31-0.66)	6	30	0.20 (0.08-0.39)
United States	0	1	0.00 (0.00-0.98)	2	6	0.33 (0.04-0.78)
Clinical Study Enrollment						
Yes	17	35	0.49 (0.31-0.66)	6	30	0.20 (0.08-0.39)
No	0	1	0.00 (0.00-0.98)	2	6	0.33 (0.04-0.78)
Prenatal Testing						
Yes	1	2	0.50 (0.01-0.99)	3	14	0.21 (0.05-0.51)
No	16	34	0.47 (0.30-0.65)	5	22	0.23 (0.08-0.45)
Spontaneous Abortions	11	36	0.31 (0.16-0.48)	4	36	0.11 (0.03-0.26)
Age (years)*						
≤19	0	0	-	0	5	0.00 (0.00-0.52)
20-34	6	20	0.30 (0.12-0.54)	3	19	0.16 (0.03-0.40)
≥35	4	6	0.67 (0.22-0.96)	1	11	0.09 (0.01-0.41)
Geographical Region						
Africa	11	35	0.31 (0.17-0.49)	4	30	0.13 (0.04-0.31)
United States	0	1	0.00 (0.00-0.98)	0	6	0.00 (0.00-0.46)
Clinical Study Enrollment						
Yes	11	35	0.31 (0.17-0.49)	4	30	0.13 (0.04-0.31)
No	0	1	0.00 (0.00-0.98)	0	6	0.00 (0.00-0.46)
Prenatal Testing						
Yes	1	2	0.50 (0.01-0.99)	1	14	0.07 (0.01-0.34)
No	10	34	0.29 (0.15-0.48)	3	22	0.14 (0.03-0.35)
Induced Abortions	6	36	0.17 (0.06-0.33)	2	36	0.06 (0.01-0.19)
Age (years)*						
≤19	0	0	-	0	5	0.00 (0.00-0.52)
20-34	3	20	0.15 (0.03-0.38)	1	19	0.05 (0.01-0.26)
≥35	2	6	0.33 (0.04-0.78)	1	11	0.09 (0.01-0.41)
Geographical Region						
Africa	6	35	0.17 (0.07-0.34)	1	30	0.03 (0.01-0.17)
United States	0	1	0.00 (0.00-0.98)	1	6	0.17 (0.01-0.64)
Clinical Study Enrollment						
Yes	6	35	0.17 (0.07-0.34)	1	30	0.03 (0.01-0.17)
No	0	1	0.00 (0.00-0.98)	1	6	0.17 (0.01-0.64)
Prenatal Testing						
Yes	0	2	0.00 (0.00-0.84)	1	14	0.07 (0.01-0.34)
No	6	34	0.18 (0.07-0.35)	1	22	0.05 (0.01-0.23)
Stillbirths	0	36	0.00 (0.00-0.10)	2	36	0.06 (0.01-0.19)
Age (years)*						
≤19	0	0	-	0	5	0.00 (0.00-0.52)
20-34	0	20	0.00 (0.00-0.17)	1	19	0.05 (0.01-0.26)
≥35	0	6	0.00 (0.00-0.46)	1	11	0.09 (0.01-0.41)
Geographical Region						
Africa	0	35	0.00 (0.00-0.10)	1	30	0.03 (0.01-0.17)
United States	0	1	0.00 (0.00-0.98)	1	6	0.17 (0.01-0.64)
Clinical Study Enrollment						
Yes	0	35	0.00 (0.00-0.10)	1	30	0.03 (0.01-0.17)
No	0	1	0.00 (0.00-0.98)	1	6	0.17 (0.01-0.64)
Prenatal Testing						
Yes	0	2	0.00 (0.00-0.84)	1	14	0.07 (0.01-0.34)
No	0	34	0.00 (0.00-0.10)	1	22	0.05 (0.01-0.23)

* Events and pregnancies may not total to 100% due to unavailable/missing data.

Comment: Single birth defects were reported in both the Truvada group and the control group of women receiving other antiretroviral therapies. While reassuring, the value of this study to the current submission is limited at present as 35/36 pregnancies occurred in Partners PrEP. Because Partners PrEP and Study GS-US-276-0101 overlapped in time, the great majority of pregnancies in Partners PrEP were not eligible for inclusion in GS-US-276-0101. The details of all 288 pregnancy outcomes in Partners PrEP, including those occurring in the placebo control group, are summarised in the 'Clinical safety: laboratory tests – pregnancy outcomes' section. Data from the latest update from the APR are summarised under the 'Supplemental NDA safety update' section later in this document.

8.9.2. Study GS-US-276-0103

This is an ongoing, prospective, observational study of subjects who seroconvert while taking Truvada for PrEP. The study was mandated as a condition of approval by the FDA and this interim report is date 18 September 2014. The planned target is a minimum of 150 adult HIV-1 negative subjects who seroconvert while taking Truvada for PrEP. Data relating to signs and symptoms of infection, sexual risk factors, and viral resistance are being collected. As of 12 August 2014, 3,604 HIV-negative subjects have or will be enrolled in 15 demonstration projects or studies of Truvada for PrEP, not including the Partner PrEP study. Screening for acquisition HIV-1 has been performed using various test kits at various intervals defined by the protocols.

The baseline demographics and baseline characteristics of the 39 subjects who seroconverted are shown in Table 31. All were male with a mean age of 27.8 years. Most subjects were of

mixed or other race (51.3%), Black (25.6%), or White (15.4%). A total of 34 evaluable seroconversions have been reported in 2190 subjects with a total exposure to Truvada of 1,925 person-years, and an estimated seroconversion rate of 1.77 per 100 patient years. Resistance testing was performed in 14 cases at the cut-off date: all cases were wild type virus and no resistance mutations were identified.

Comment: The ongoing studies of Truvada for PrEP in this analysis are all sponsored by the NIH or US universities. At the cut-off date, no viral resistance has been demonstrated. While the resistance data are reassuring, the number of seroconversions is currently too low to draw valid conclusions.

Table 31: Study GS-US-276-0103: Demographics and Baseline characteristics

Subgroup	Cases of Seroconverters N (%)
Gender	
Male	39 (100%)
Female	0
Age (years)	(n=38)
Mean ± Standard Deviation	27.8 ± 8.2
Median	26
Interquartile range	9
Minimum - Maximum	18 – 50
Age Group (years)	
≤ 29	26 (66.7%)
30 – 39	8 (20.5%)
40 – 49	3 (7.7%)
≥ 50	1 (2.6%)
Unknown/Not Reported	1 (2.6%)
Country	
USA	12 (30.8%)
Ex-USA	27 (69.2%)
Country Name	
USA	12 (30.8%)
Brazil	2 (5.1%)
Ecuador	3 (7.7%)
Peru	18 (46.2%)
South Africa	3 (7.7%)
Thailand	1 (2.6%)
Transmission Risk	
MSM	39 (100%)
Race	
White	6 (15.4%)
Black	10 (25.6%)
Hispanic	1 (2.6%)
Asian	1 (2.6%)
Mixed or Other	20 (51.3%)
Unknown/Not Reported	1 (2.6%)

8.9.3. Truvada PSUR/PBRER (3 April 2013 to 2 April 2014)

Summary: Since it was first approved in 2004, the cumulative exposure to Truvada is estimated to be 3,032, 901 patient-tears, including 461,395 patient-years in the latest update period (5,814 in Australia and New Zealand) (see Table 32). During the period of the latest PSUR/PBRER, approximately 3,305 subjects received Truvada in HIV (n = 2,955) and HBV (n = 350) clinical trials. In addition, there were 56 ongoing collaborative clinical trials with a cumulative exposure of 20,559 subject-years. During the most recent observation period, no new potential safety signals have been detected and the risk-benefit profile of Truvada remains positive.

While no new safety signals have been detected, emerging data have resulted in updated warnings and precautions in the USPI. Established safety concerns include renal toxicity, loss of BMD, hepatic flares in HIV-1/HBV co-infected patients, pancreatitis, interaction with didanosine, lipodystrophy, and lactic acidosis and severe hepatomegaly with steatosis. A sNDA was submitted and approved by the FDA on 13 June 2013. This updated the USPI for products

containing TDF with label changes relating to BMD, muscle effects, and high dose NSAID use in patients with risk factors for renal dysfunction. No new safety signals were detected in relation to post-treatment flares in HIV-1/HBV co-infected patients; potential interactions with didanosine; pancreatitis; lactic acidosis and severe hepatomegaly with steatosis; or lipodystrophy.

Table 32: Truvada PSUR/PBRER: Estimated patient exposure to marketed Truvada (1 April 2013 to 31 March 2014 and cumulatively)

Geographic Area	Patient Exposure (patient-years) (rounded to nearest whole number)	
	01 April 2013 to 31 March 2014	Cumulative to 31 March 2014
USA	188,087	1,335,737
Europe		
France	39,926	282,858
Spain	27,693	204,242
Italy	26,240	176,605
UK & Ireland	26,478	169,143
Germany	25,923	138,263
European Distributor [a]	28,048	150,243
Portugal	10,073	58,687
Mid-Mediterranean & Middle East [b]	7,075	22,073
Turkey	2,550	8,844
Rest of World		
Latin America[c]	49,258	257,369
Africa[d]	123	58,906
Australia & New Zealand	5,814	35,492
Japan	10,517	50,192
Asia (excluding Japan)	3,194	28,198
Canada	10,395	56,048
Total [e]	461,395	3,032,901

Note: Sales figures are to the end of the month.
a Includes Austria, Benelux (Belgium, Netherlands, Luxemburg), European Distributor (Croatia, Cyprus, Czech Republic, Hungary, Israel, Poland, Russia, Slovenia, Slovak Republic), Nordics (Denmark, Sweden, Finland, Norway), Switzerland and East Europe.
b Includes Mid-Mediterranean (Greece) and Middle East (Egypt, Kuwait, Lebanon, Malta, Oman, Qatar, Saudi Arabia and United Arab Emirates).
c Includes Argentina, Barbados, Brazil, Chile, Colombia, Dominican Republic, Guatemala, Mexico, Netherlands Antilles, Trinidad and Tobago, Uruguay and Venezuela.
d Generic tenofovir DF available in this territory.
e Totals do not match figures in columns due to the effects of rounding of the values of each Geographic Area.

At the request of the FDA, Gilead provided an analysis of their Drug Safety and Public Health database for bone/muscle events (such as rhabdomyolysis, osteomalacia, muscular weakness, and myopathy) due to proximal renal tubulopathy/loss of BMD. In 11,786 TDF events in the database, PRT events were reported in 6.6% of cases and bone/muscle events were reported in 3.0% of cases. Only 23.9% of cases with a bone/muscle event also reported a PRT event, and only 10.9% of PRT cases also reported a bone/muscle event. Only 0.7% of all cases in the database reported both PRT and bone/muscle events. Cases which reported both PRT and NSAID use accounted for only 0.6% of all cases in the database. NSAIDs were used before a diagnosis of PRT in 4.3% of PRT cases, and high doses of NSAIDs were reported in 26.5% of these cases. All reported cases occurred in patients with risk factors for renal dysfunction. In patients with a diagnosis of PRT, only 17 cases with bone/muscle events and NSAID use were identified. A disproportionality analysis did not show an increased likelihood of PRT with NSAIDs and TDF. In addition, a multivariate analysis showed that NSAID use before or after a bone/muscle event did not increase the risk of PRT with or without exposure to TDF. In a separate Renal Tubulopathy Reversibility review, data from various sources indicated that PRT was reversible in 81% to 93% of cases following cessation of TDF. In cases that did not resolve, the outcomes were confounded by lack of prolonged follow-up and pre-disposing factors such as hypertension and diabetes.

A total of 51 cases relating to bone events were reported in the latest PSUR. Of these 20 events were related to osteopaenia/osteoporosis which improved during an 18 month observational study of DEXA following withdrawal of Truvada therapy. A total of 139 reports relating to renal toxicity were reported in the latest PSUR, corresponding to 2.5 events/10,000 patient-years exposure (see Table 33 below). This figure was comparable to that reported in the previous PSUR (2.2/10,000 patient-years). Six deaths were reported but all had other factors contributing to the fatalities.

Table 33: Truvada PSUR/PBRER: Renal cases by outcome (renal events with fatal outcome, reported as life-threatening or requiring dialysis)

	Number of Cases				
	Life-Threatening		Not Life-Threatening		
Outcome	Required Dialysis	No Dialysis	Required Dialysis	No Dialysis	Total (%) [a]
Fatal	0	1	1	4	6 (4.5%)
Not resolved	1	2	1	15	19 (21.3%)
Resolved	1	1	1	30	33 (38.2%)
Resolved with sequelae	0	0	1	1	2 (2.3%)
Resolving	0	1	4	24	29 (33.7%)
Unknown	0	3	2	45	50 (-)
Total	**2**	**8**	**10**	**119**	**139**

a Cases with an unknown outcome are excluded from the percentages. Percentages are rounded to 1 decimal place.

A summary of pregnancies reported in the APR to 31 July 2013 is also included in the latest PSUR/PBRER. A total of 201 birth defects have been recorded among 6,926 live births with a prevalence of 2.9 per 100 births among women exposed to Truvada in the first trimester (95% CI: 2.5, 3.3). This was comparable to the prevalence of 2.8 per 100 live births among women exposed in the second or third trimester [prevalence ratio 1.02 (95% CI: 0.85, 1.23)]. In women exposed to Truvada or any other antiretroviral drug in the APR, there does not appear to be an increased risk of birth defects when compared with those exposed to other drugs in population-based surveillance systems.

8.9.4. Supplemental NDA safety update

Gilead has provided a summary of new data reported since submission of the sNDA. The update is dated 16 March 2012. The main focus of the report was on newly reported bone fractures and new drug testing data in the iPrEx study; and new pregnancy outcomes and SAEs in the Partners PrEP study. In addition, a summary of new publications relevant to the PrEP indication was provided. CSRs to support the publications were not provided to Gilead.

8.9.4.1. iPrEx update

Updated data from the iPrEx study relating to TFV-DP drug testing and bone fractures are included in Sections *Pivotal efficacy studies; Study CO-US-104-0288 (iPrEx)* and *AEs of special interest; Pivotal studies*, respectively.

8.9.4.2. Partner PrEP update

Pregnancy outcome data in the Partner PrEP study are summarised in GS-US-276-0101 (see Section 8.6.1).

Pregnancies reported after submission of the sNDA are summarised in Section *Truvada PSUR/PBRER 3 April 2013 to 2 April 2014* as part of latest PSUR.

A total of 24 new SAEs have been reported in 20 subjects. One SAE was fatal (a cerebrovascular event) but it was not considered drug related. Non-fatal SAEs were related to an inguinal hernia birth defect, pain, pyrexia, pneumonia, malaria, back pain, spontaneous abortion, acute psychosis, and asthma.

A study drug compliance sub-study involving 1,147 subjects was conducted as part of the Partner PrEP study. The results are summarised in Section *Study C0-US-104-0380 (Partners PrEP)*.

8.9.4.3. Newly published studies

- CDC 4323 (CO-US-104-0277): a Phase II study of TDF for PrEP in a US MSM population
- FHI PrEP (GS-02-1020): a Phase II study of TDF for PrEP in West African women
- CDC Botswana/TDF2 (CO-US-104-0294): a Phase III study of FTC/TDF in heterosexual adults
- FEM PrEP (CO-US-164-0184): A Phase III study of FTC/TDF in high risk African women

These studies are summarised in above.

8.10. Safety issues with the potential for major regulatory impact

8.10.1. Liver toxicity

No hepatic toxicity was identified. No cases of hepatic viral flares were reported during or after treatment in subjects with acute or chronic HBV infection in the iPrEx or FHI PrEP studies.

8.10.2. Haematological toxicity

No haematological toxicities were identified.

8.10.3. Serious skin reactions

No serious issues were identified in the pivotal studies. In iPrEx, AEs related to skin disorders were reported in 4% of each study drug group. In Partners PrEP, AEs related to skin disorders were reported in 1% of the TDF, FTC/TDF, and placebo groups.

8.10.4. Cardiovascular safety

No issues were identified.

8.10.5. Unwanted immunological events

Not applicable.

8.10.6. Other safety issues

8.10.6.1. Safety in special populations

No additional data have been submitted.

8.10.6.2. Safety related to drug-drug interactions and other interactions

No new or updated information has been provided.

8.11. Evaluator's overall conclusions on clinical safety

Safety data to support the new proposed indication are derived primarily from two pivotal Phase III studies of FTC/TDF used for PrEP in two high risk populations, MSM and heterosexual HIV-1 discordant couples. Supportive data were provided from published studies of MSM in the US, and African women and heterosexual adults. Routine recording of AEs and laboratory abnormalities was performed and compared with data in the Gilead Core Data Sheet. In addition, AEs of interest were identified including renal dysfunction and changes in bone mineral density, both related to the known effects of TDF on the proximal renal tubule.

In the iPrEx study in 2,499 randomised MSM, FTC/TDF was well tolerated with a safety profile comparable to placebo. AEs of any severity were reported in 55% of the FTC/TDF group

compared with 56% in the placebo group (Gilead analysis). A similar incidence of Grade 3 or 4 AEs (9% versus 9%) and SAEs (4% versus 4%) were reported in the respective groups. Deaths occurred in < 0.1% of each group. Clinical and laboratory AEs leading to drug discontinuations were reported in 2% and < 0.1% of each group, respectively. The most commonly reported AEs by SOC were related to Infections and Infestations (36% in each group), and Psychiatric Disorders (8% versus 9%). The frequency of AEs related to gastric disturbances was similar in each group although nausea was more common in the group receiving FTC/TDF (2% versus < 1%). Bone fractures were reported in 1% of the FTC/TDF group compared with < 1% in the placebo group. However, all fractures were traumatic and none were considered drug related. Overall, serum creatinine elevations above ULN were reported more commonly in the FTC/TDF group (25 versus 14 subjects, p = 0.08) but no Grade 3 or 4 events were reported in the FTC/TDF group. Decreased serum phosphate levels were comparable in each group but Grade 3 elevations were more common in the FTC/TDF group (11 versus 7 subjects, p = 0.66).

In the Partner PrEP study, FTC/TDF and TDF were well tolerated with a safety profile comparable to placebo. AEs of any severity were reported in 86%, 85%, and 85% of the FTC/TDF, TDF, and placebo groups, respectively. Grade 4 events were reported in 37%, 26%, and 32% of the respective groups, and SAEs were reported in 7% of each group. Deaths were reported in 6%, 5%, and 6% of the respective groups. The most common AEs reported by PT in the overall population were decreased neutrophil count (39%), blood phosphorus decreased (29%), malaria (19%), haemoglobin decreased (15%), decreased platelet count (12%), and upper respiratory infections (9%). Diarrhoea was reported in 2% to 3% of the study drug groups but nausea was reported in < 1% of any group. Grade 1 or higher increases in serum creatinine were reported in < 1% of each group. Bone fractures occurred in < 1% of subjects in each study drug group. All were traumatic and not considered drug related.

In the overall populations, PrEP with FTC/TDF was well tolerated with a safety profile comparable to placebo. No obvious differences in subgroups (in particular gender) were identified although subject numbers in some categories were too small to identify possible differences. No new safety signals have been detected in the pivotal studies or supportive studies of PrEP using FTC/TDF or TDF alone. The rates of AEs, laboratory AEs, severe AEs, SAEs and deaths were generally similar in the active and placebo study groups. The overall data were also comparable with the known safety profile of Truvada used as treatment for HIV-1 infection.

AEs of interest were identified based on the known effects of Truvada. As expected, gastrointestinal adverse events (in particular nausea and vomiting) were more common in subjects receiving FTC/TDF compared with placebo. However, most events occurred in the first month and resolved with continued exposure.

Renal events associated with TDF renal tubulopathy were generally mild. Increased serum creatinine was reported more commonly in subjects receiving FTC/TDF but no Grade 3 or 4 events were reported and most elevations resolved with cessation of treatment. There was a low incidence of PRT associated with the use of TDF and NSAIDs, and most events occurred in subjects with predisposing renal risk factors.

Hypophosphataemia was also reported more commonly in subjects receiving FTC/TDF or TDF alone. Compared with placebo, there was a mean 0.5% to 1% loss of BMD in subjects receiving FTC/TDF over observation periods of 24 to 96 weeks. Most of the observed bone loss occurred in the first six months of drug administration but further minor progression was observed over the remaining period. Overall, changes in BMD were modest and there was no evidence of an increased rate of bone fractures in subjects receiving FTC/TDF. However, in the iPrEx study, BMD loss of ≥ 5% in the spine measured at any visit was observed in more subjects receiving FTC/TDF (14% versus 6%). This observation was confirmed in Study CDC4323 in which loss of BMD was higher in the FTC/TDF group (13% versus 6%). The subjects in these BMD substudies were male and no PrEP studies have been performed in women, or in women receiving depot medroxyprogesterone acetate. There was no evidence of an increased rate of bone fractures

with the use of FTC/TDF or TDF alone. However, more long-term data are required to exclude progressive and damaging bone loss following extended periods of chemoprophylaxis.

No hepatic viral flares during or after treatment with FTC/TDF or TDF were reported in subjects with chronic or acute HBV infection. However, subject numbers infected with HBV were low and the risk of potentially serious hepatic events cannot be discounted.

Pregnancy outcomes in the FTC/TDF and placebo groups were comparable with no unexpected increase in birth defects. The pregnancy and foetal outcome data were comparable to data from other ART drug registries.

Sexual disinhibition is a significant safety concern as PrEP alone will not prevent HIV-1 transmission in all cases. The perception that PrEP is a 'chemical condom' might lead to a reduction in safer sex practices and actually increase the risk of infections, particularly in subjects with poor drug compliance. However, opposite trends were apparent in the pivotal studies with increased self-reported condom use and a decrease in the number of sexual partners.

9. First round benefit-risk assessment

9.1. First round assessment of benefits

The benefits of Truvada in the proposed usage are:

- Reduced risk of HIV-1 infection in high risk MSM
- Reduced risk HIV-1 infection in sexually active, HIV-1 discordant partnerships
- Well tolerated with safety profile comparable to placebo
- Adverse events related to tenofovir disoproxil fumarate well understood and predictable
- Improved safer sex practices associated with counselling and close medical supervision

9.2. First round assessment of risks

The risks of Truvada in the proposed usage are:

- Reduced but still significant risk of acquiring HIV-1 infection
- Potential viral resistance in subjects with unrecognised HIV-1 infection
- Adverse events related to tenofovir disoproxil fumarate , in particular reduced bone mineral density
- Risk of post-treatment viral flares in subjects with HBV infection
- Efficacy dependent almost entirely on good drug compliance and safer sex practices
- Reduced efficacy if not closely supervised by experienced HIV healthcare providers
- The value of PrEP not yet fully evaluated in the Australian context.

9.3. First round assessment of benefit-risk balance

The benefit-risk balance of Truvada, given the proposed usage, is favourable.

There is a statistically significant and clinically meaningful benefit for Truvada in MSM and HIV-1 discordant couples. With appropriate counselling, education, and medical supervision of

selected and motivated individuals, efficacy rates of up to 90% are possible. However, as demonstrated in the FEM PrEP study in African women, chemoprophylaxis is virtually worthless unless compliance is encouraged and closely monitored. Cultural factors and the public health environment are important and PrEP has not yet been evaluated as part of an overall risk reduction strategy in the Australian context. However, PrEP has been endorsed by the ASHM and limited free access schemes are currently available in Queensland, New South Wales and Victoria.

The risks of chemoprophylaxis are generally recognised. ART requires triple therapy and the use of Truvada in infected individuals will inevitably lead to viral resistance. However, in practice and with frequent HIV-1 testing, the rate of viral resistance is low and it resolves when drug is discontinued. Discontinuation of therapy may lead to viral hepatic flares in HBV positive individuals. This does appear to be common although the number of subjects studied with HBV is limited. The adverse event profile of Truvada is characterised by gastrointestinal disturbance in some subjects in the first month of prophylaxis. Renal effects including increased serum creatinine and proteinuria are often observed but severe renal AEs are unusual. Modest reductions in bone mineral density can be expected. This appears to occur in the first year with lesser reductions thereafter. However, long-term studies of PrEP have not been performed, and DEXA studies in healthy females have not been conducted. The fear that PrEP might lead to reduced safer sex practices has not been observed in trials to date. With appropriate education and counselling, condom use may increase and the number of sexual partners may decrease.

10. First round recommendation regarding authorisation

Authorisation is recommended for the proposed new indications:

> *Truvada is indicated for the treatment of HIV infected adults over the age of 18 years, in combination with other antiretroviral agents.*

The proposed modification brings the indication into line with other Gilead HIV-1 products approved in Australia.

The proposed new indication for pre-exposure prophylaxis is:

> *Truvada is indicated in combination with safer sex practices for pre-exposure prophylaxis (PrEP) to reduce the risk of sexually acquired HIV-1 in adults at high risk. This indication is based on clinical trials in men who have sex with men (MSM) at high risk for HIV-1 infection and in heterosexual serodiscordant couples.*

11. Clinical questions

11.1. Additional expert input

Not required

11.2. Pharmacokinetics

None applicable

11.3. Pharmacodynamics

Not applicable.

11.4. Efficacy

1. Reported in the primary publication but not in the iPrEx CSR, seroconversion rates were similar in both treatment groups during an undefined follow-up period after discontinuation of study drug (161 FTC/TDF versus 159 placebo). Please provide the duration of this follow-up period, with a Kaplan-Meier plot if it is available.
2. In the iPrEx CSR, relative effectiveness in subjects with ≥ 50% tablet usage is reported as 50% (95% CI: 18%, 70%). In the text, it is stated that tablet usage was based on pill counts, self-report, and dispensation records. However, in the supporting table (see above Table 6. Study CO US 104 0288: Relative effectiveness: primary analysis by self-reported level of pill use (iPrEx mITT analysis)) relative effectiveness in the ≥ 50% usage group is identical but described as self-reported only. Please clarify this discrepancy. For the same table, please state which method of calculation was used to report relative effectiveness in the ≥ 90% usage group.
3. In the iPrEx CSR, the relative risk reduction after adjustment for high-risk sexual practice (specifically URAI) was stated to be 95% (95% CI: 70%, 99%) compared with placebo. However, it is not explained how this statistic was calculated. Please clarify.
4. Approximately 50% of MSM in the iPrEx study consumed ≥ 5 alcoholic drinks per day. Has an analysis been made of the influence of alcohol on compliance and efficacy rates? If not, can this be provided?
5. It appears that only 35/288 pregnancies occurring in Partners PrEP were reported in Study GS-US-276-0101. Please confirm that this was related to the overlapping timeframes of the two studies. Expedited AEs for newborns are reported in the Partners PrEP CSR. However, the incidence of birth defects does not appear to have been reported. Please provide these data if they are available. In addition, please confirm that all pregnant women had study drug withdrawn and provide exposure data if they are available.

11.5. Safety

No questions.

12. Second round evaluation of clinical data submitted in response to questions

In this section, the initial TGA questions following first round evaluation report are mentioned first followed by a summary of the sponsor's response and then the evaluator's comments on the response.

12.1. Efficacy

Question 1
Reported in the primary publication but not in the iPrEx CSR, seroconversion rates were similar in both treatment groups during an undefined follow-up period after discontinuation of study drug (161 FTC/TDF vs 159 placebo). Please provide the duration of this follow-up period, with a Kaplan-Meier plot if it is available.

12.1.1.1. Sponsor's response

A total of 161 subjects in the FTC/TDF group were followed for a total of 62.2 person years off drug. During this time, there were two HIV seroconversions at a rate of 3.2 per 100 patient

years. In the placebo group, 159 subjects were followed for a total of 49.2 person years. During this time, there were three HIV seroconversions at a rate of 6.1 per 100 person years. The log rank test is not significantly different with a hazard ratio of FTC/TDF to placebo of 0.48 (95% CI: 0.08, 2.9). A Kaplan-Meier plot cannot be easily calculated as the data include both temporary holds and permanent discontinuations of study drug.

12.1.1.2. Evaluator's response

The sponsor's response is satisfactory.

12.1.2. Question 2

In iPrEx CSR, relative effectiveness in subjects with ≥50% tablet usage is reported as 50% (95% CI: 18%, 70%). In the text, it is stated that tablet usage was based on pill counts, self-report, and dispensation records. However, in the supporting table (see Table 6 above) *Study CO US 104 0288: Relative effectiveness: primary analysis by self-reported level of pill use (iPrEx mITT analysis))*, relative effectiveness in the ≥50% usage group is identical but described as self-reported only. Please clarify this discrepancy. In the same, please state which method of calculation was used to report relative effectiveness in the ≥90% usage group.

12.1.2.1. Sponsor's response

Tablet usage calculations were based on a combination of pill counts, self-reports, and dispensation records in all instances. This included the data in the table in the CSR.

12.1.2.2. Evaluator's response

The sponsor's response is satisfactory.

12.1.3. Question 3

In the iPrEx CSR, the relative risk reduction after adjustment for high-risk sexual practice (that is, URAI) was stated to be 95% (95% CI: 70%, 99%) compared with placebo. However, it is not explained how this statistic was calculated. Please clarify.

12.1.3.1. Sponsor's response

This result was a per cent risk reduction as compared to those without detected drug. The analysis was performed using a conditional logistic model, based on a matched case-control analysis in which placebo subjects were matched to cases (HIV+). The presence of any quantifiable drug concentration in the specimen was considered "detectable" drug. The absence of any quantifiable drug was considered "undetectable" drug.

For HIV infected subjects, plasma and peripheral PBMC specimens were selected from the visit having the first laboratory evidence of HIV infection. HIV- controls were tested at the study week of seroconversion for their matched cases. The design was to match the sample at the seroconversion visit from all HIV+ seroconversion cases in both arms with a sample from one HIV- placebo participant and from another HIV- active arm participant. Matching was based on study week of the seroconversion visit, and study site. Given that the HIV infection cases were most likely exposed to HIV by unprotected sexual intercourse, HIV exposure in controls was enriched by selecting at random from among participants reporting URAI at the time of the specimen. If such specimens were not available, a control was selected at random. A maximum difference in study duration of 12 weeks was allowed in the matching.

12.1.3.2. Evaluator's response

The sponsor's response is satisfactory.

12.1.4. Question 4

Approximately 50% of MSM in the iPrEx study consumed ≥5 alcoholic drinks per day. Has an analysis been made of the influence of alcohol on compliance and efficacy rates? If not, can this be provided?

12.1.4.1. Sponsor's response

The iPrEX study team has updated the subgroup analysis of efficacy by alcohol use strata (reporting ≥5 or <5 drinks per day). The efficacy (by intention to treat) was 48% (95% CI: 12%, 61%) in those reporting <5 drinks per day and 43% (95% CI: 6%, 65%) in those reporting ≥5 drinks per day (p=0.81 for treatment by subgroup interaction).

12.1.4.2. Evaluator's response

The sponsor's response is satisfactory. The sponsor has not addressed the question of compliance; however, this is not important given the lack of interaction in the efficacy analysis.

12.1.5. Question 5

It appears that only 35/288 pregnancies occurring in Partners PrEP were reported in 0101. Please confirm that this was related to the overlapping timeframes of the two studies. Expedited AEs for newborns are reported in the Partners PrEP CSR. However, the incidence of birth defects does not appear to have been reported. Please provide these data if they are available. In addition, please confirm that all pregnant women had study drug withdrawn and provide exposure data if they are available.

12.1.5.1. Sponsor's response

A total of 288 pregnancies were reported in the Partners PrEP study. A total of 80 pregnancies, with 47 live births, and four birth defects (8.5%) were reported in the Truvada group. None of the defects were considered drug related by the investigator or sponsor. In the Partners PrEP study 34/35 pregnant women discontinued therapy during pregnancy as mandated by the protocol and prospectively reported to the APR. Exposure data are not available for these subjects. One woman continued therapy for 12.9 weeks after reporting the pregnancy. There were no birth defects or other adverse outcomes.

12.1.5.2. Evaluator's response

The sponsor's response is satisfactory.

12.1.6. Conclusion

The clinical evaluator deemed the responses and data submitted for the all the clinical questions as satisfactory.

Specifically to Question 4, 'Approximately 50% of MSM in the iPrEx study consumed ≥ 5 alcoholic drinks per day. Has an analysis been made of the influence of alcohol on compliance and efficacy rates? If not, can this be provided?' the evaluator felt the sponsor has not addressed the question of compliance; however, this is not important given the lack of interaction in the efficacy analysis.

12.2. Second round assessment of benefits

No new clinical information was submitted in response to questions. Accordingly, the benefits of Truvada are unchanged from those identified in the first round assessment of benefits.

12.3. Second round assessment of risks

No new clinical information was submitted in response to questions. Accordingly, the risks of Truvada are unchanged from those identified in the first round assessment of risks.

12.4. Second round assessment of benefit-risk balance

No new clinical information was submitted in response to questions. Accordingly, the benefit-risk balance of Truvada is unchanged from those identified in the first round assessment of benefit-risk balance.

13. Second round recommendation regarding authorisation

Unchanged from the first round recommendation regarding authorisation.

14. References

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