21 July 2016
EMA/561440/2016
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Truvada

International non-proprietary name: emtricitabine / tenofovir disoproxil

Procedure No. EMEA/H/C/000594/II/0126

Note

Variation assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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List of abbreviations

AE	adverse event
ART	antiretroviral therapy
BMD	bone mineral density
CDC	Centers for Disease Control and Prevention
CI	confidence interval
CRF	case report form
CSR	clinical study report
DEXA	dual-energy x-ray absorptiometry
FHI	Female Health Initiative
FTC	emtricitabine, Emtriva®
FTC-TP	emtricitabine 5'-triphosphate
FTC/TDF	Truvada
GSI	Gilead Sciences, Incorporated
HBV	hepatitis B virus
HIV-1	human immunodeficiency virus type 1
HR	hazard ratio
iPrEx	Pre-exposure Prophylaxis Initiative (Study CO-US-104-0380)
ITT	intent-to-treat
MAA	Marketing Authorization Application
mITT	modified intent-to-treat
MSM	men who have sex with men
NDA	new drug application
NRTI	nucleoside reverse transcriptase inhibitor
NtRTI	nucleotide reverse transcriptase inhibitor
PBMC	peripheral-blood mononuclear cells
PEP	post-exposure prophylaxis of HIV-1 infection
PrEP	pre-exposure prophylaxis of HIV-1 infection
RE	relative effectiveness
RMP	Risk Management Plan
RNA	ribonucleic acid
SAE	serious adverse event

SAP	statistical analysis plan
SIV	simian immunodeficiency virus
STI	sexually transmitted infection
TDF	tenofovir disoproxil fumarate, tenofovir DF, Viread
TFV-DP	tenofovir diphosphate
UNAIDS	Joint United Nations Programme on HIV/AIDS
URAI	unprotected receptive anal intercourse

1. Background information on the procedure

1.1. Type II variation

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, Gilead Sciences International Ltd submitted to the European Medicines Agency on 13 January 2016 an application for a variation.

The following variation was requested:

Variation requested		**Type**	**Annexes affected**
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I and IIIB

Extension of the indication to add Pre-exposure prophylaxis (PrEP) in combination with safer sex practices to reduce the risk of sexually acquired HIV-1 in adults at high risk. As a consequence, sections 4.1, 4.2, 4.3, 4.4, 4.8, 4.9, 5.1, 5.2 and 5.3 of the SmPC are updated. The Package Leaflet is updated in accordance.

The requested variation proposed amendments to the Summary of Product Characteristics and Package Leaflet and to the Risk Management Plan (RMP).

Information on paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included an EMA Decision(s) P/0294/2015 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP P/0294/2015 was not yet completed as some measures were deferred.

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

Scientific advice

The MAH did not seek Scientific Advice at the CHMP regarding the PrEP indication. It should be noted that the MAH did not sponsor the studies that are reported in this assessment report to support the PrEP indication.

At a pre-submission meeting with the European Medicines Agency on 19 May 2015 it was explained that

the principal data source in the application to support the use of Truvada for PrEPs setting would be study CO-US-104-0288 (Chemoprophylaxis for HIV Prevention in Men; also known as the Pre-exposure Prophylaxis Initiative or iPrEx study). A second study (CO-US-104-0380; Parallel Comparison of Tenofovir and Emtricitabine/Tenofovir Pre-Exposure Prophylaxis to Prevent HIV-1 Acquisition within HIV-1 Discordant Couples; Partner's PrEP) would provide additional data in support of the application. Important data from some other clinical studies would be included where relevant, particularly to add to the safety information.

1.2. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP and the evaluation teams were:

Rapporteur: Greg Markey Co-Rapporteur: Pierre Demolis

Timetable	Actual dates
Submission date	13 January 2016
Start of procedure:	30 January 2016
CHMP Co-Rapporteur Assessment Report	29 March 2016
CHMP Rapporteur Assessment Report	18 February 2016
PRAC Rapporteur Assessment Report	1 April 2016
PRAC members comments	6 April 2016
Updated PRAC Rapporteur Assessment Report	8 April 2016
PRAC Outcome	14 April 2016
CHMP members comments	20 July 2016
Updated CHMP Rapporteur(s) (Joint) Assessment Report	21 April 2016
Request for supplementary information (RSI)	28 April 2016
CHMP Rapporteur Assessment Report	21 June 2016
PRAC Rapporteur Assessment Report	24 June 2016
PRAC members comments	29 June 2016
Updated PRAC Rapporteur Assessment Report	30 June 2016
PRAC Outcome	7 July 2016
CHMP members comments	11 July 2016
Updated CHMP Rapporteur Assessment Report	20 July 2016
Opinion	21 July 2016

2. Scientific discussion

2.1. Introduction

Problem statement

The Joint United Nations Programme on HIV/AIDS (UNAIDS) estimated that there were 2 million new HIV-1 infections in 2014, despite widespread knowledge of the protective benefits of abstinence, monogamy and condoms. In the EU/EEA, the ECDC reported that 29,381 diagnosed cases of HIV infection were newly reported in 2012, which equates with 5.8 per 100,000 persons. The principal interventions currently in use to prevent HIV-1 transmission in the EU are voluntary testing, risk counselling and the promotion of condoms. The effectiveness of these interventions has been variable and the prevalence of HIV-1 remains high even in settings with 100% condom promotion policies. In the absence of a pre-exposure vaccine, an important medical need exists for a novel approach to augment HIV-1 prevention services and reduce the spread of HIV.

Clinical studies to evaluate pre-exposure prophylaxis (PrEP) studies followed on from a demonstration that antiretroviral therapy (ART) could decrease HIV-1 seroconversion rates in animal models. ART was also found to decrease infection rates when applied to maternal-to-child transmission. Studies of the pathogenesis of early infection in primate models infected with simian immunodeficiency virus (SIV) suggested that systemic infection did not occur immediately, leaving a brief window of opportunity during which ART may modify or prevent viral replication at the site of infection, specifically in the initial target dendritic-like cells or lymph nodes.

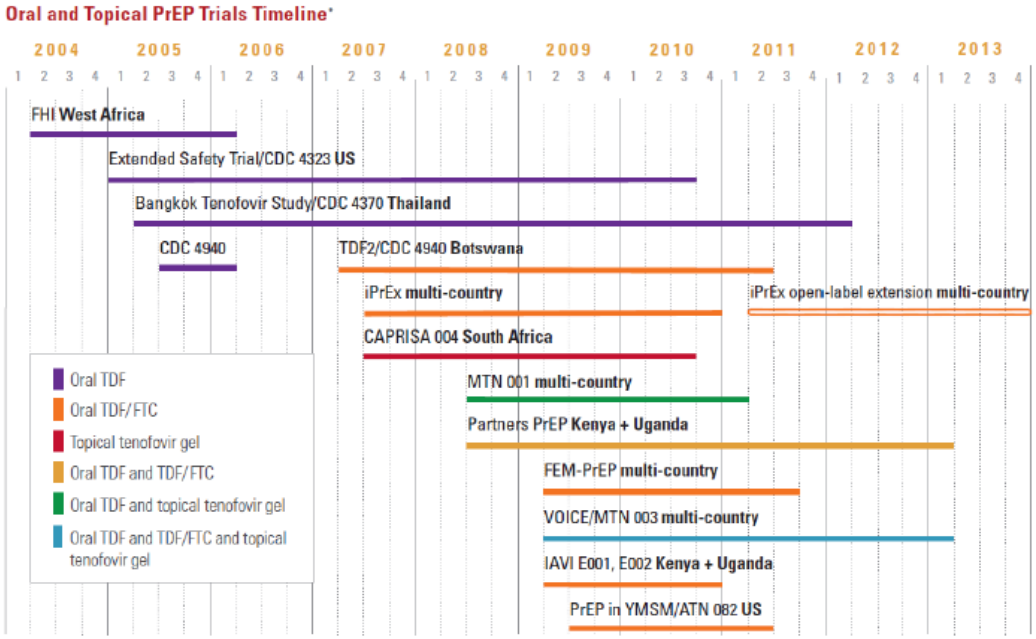
As a subpopulation, men who have sex with men (MSM) are disproportionately affected by the global HIV-1 epidemic with a rate of HIV-1 infection reported to be 19.3-fold higher than in the general population of adults of reproductive age based on a multinational meta-analysis of data from 38 low-to-middle income countries. Epidemiologic reports from high-income countries (e.g. US, Australia, Western EU) also indicate that MSM are disproportionately impacted. Recent trends showing high rates of HIV-1 infection among MSM in the US, particularly in younger or minority subpopulations, provide evidence of resurgence in the spread of HIV-1. European populations show a similar trend.

High risk for HIV-1 transmission is also inherent within stable, sexually active, HIV-1 discordant partnerships. In many settings, HIV-1 sero-discordant couples (in which one of the partners is infected with HIV-1 and the other is uninfected) comprise 50% of couples with at least one infected partner. HIV-1 discordant couples face unique challenges, including the desire to seek pregnancy. Thus, for stable, heterosexual, HIV-1 discordant partners, there is a critical public health need to identify simplified, non-contraceptive-based interventions that can prevent HIV-1 acquisition.

Clinical studies have evaluated tenofovir, either as a vaginal gel or as oral TDF or oral FTC/TDF for PrEP settings relevant to heterosexual HIV-1 transmission. Coitally-associated use of 1% tenofovir vaginal gel decreased the risk of HIV-1 acquisition among heterosexual women by 39%. Initial clinical data supporting oral TDF for HIV-1 PrEP were obtained from a Phase 2 US study in uninfected MSM and transgender women who have sex with men (CDC 4323) and from a Phase 2 study of TDF for HIV-1 PrEP in West African women (the FHI PrEP study). Studies with oral Truvada followed as summarised in the figure below. These included a study in heterosexually active adults in Botswana (CDC TDF2), which provided supportive evidence for the use of Truvada chemoprophylaxis.

In contrast, a study of oral FTC/TDF in African women at high-risk for HIV-1 infection was terminated early because there was an equal number of HIV-1 infections in the FTC/TDF and placebo groups (FEM-PrEP). Subsequently, the VOICE study was modified to eliminate the use of the oral TDF arm and

later terminated completely when planned reviews of study data concluded that the study would not be able to demonstrate that any of oral TDF or Truvada or TDF vaginal gel would be effective in preventing HIV in the women enrolled in the study. In both terminated studies the investigators concluded that lack of efficacy was due to poor adherence, which was supported by the plasma drug concentrations.



The EACS 2015 guidelines regarding PrEP are as follows:

PrEP can be used in adults at high-risk of acquiring HIV infection.

• Recommended in HIV-negative men who have sex with men (MSM) and transgender individuals who are inconsistent in their use of condoms with casual partners or with HIV-positive partners who are not on treatment. A recent STD or use of post-exposure prophylaxis may be markers of increased risk for HIV acquisition.

• May be considered in HIV-negative heterosexual women and men who are inconsistent in their use of condoms and likely to have HIV positive partners who are not on treatment.

While overall recommending a daily administration, the EACS guidelines state that for MSM with high-risk sexual behaviour, PrEP may be dosed 'on demand' (double dose of drug 2-24 hours before each sexual intercourse, followed by two single doses of drug, 24 and 48 hours after the first drug intake). If dosed 'on demand', the total dose per week should not exceed 7 tablets.

About the product

The rationale for development of Truvada for PrEP was based on nonclinical and clinical data, much of which was not generated by the MAH and some of which relates to TDF alone rather than Truvada. In addition, some of the data relate to daily prophylaxis (as proposed in this variation) and some to immediate pre- and post-exposure prophylaxis.

Controlled nonclinical studies in macaques showed that oral or subcutaneous treatment with TDF (with or without FTC) prevented or delayed the onset of viraemia when administered either before or shortly after rectal, vaginal or intravenous inoculation with SIV or HIV. Macaques that became infected while under treatment had a longer median time to infection or lower levels of viral DNA than untreated controls. Nonclinical studies regarding use of intermittent PrEP demonstrated that a pre-exposure dose combined with a post-exposure dose was highly protective.

The current application to add an indication for use of daily Truvada for PrEP is principally based on CO-US-104-0288 (iPrEx), which was conducted in MSM. A second study (CO-US-104-0380) in HIV-1 discordant couples (Partner's PrEP) provides additional supportive data. These were the two studies that were included in the FDA US application that led to approval of Truvada for PrEP. The data from CDC 4323 (see figure above) are considered supportive. Since approval of Truvada for PrEP in the US, two additional studies (Ipergay and PROUD; not shown in the figure above) reported on the use of Truvada for PrEP. The MAH does not have access to the databases for these studies. In publications, both studies reported an 86% reduction in HIV incidence among subjects who received Truvada as compared with those did not receive Truvada.

The Ipergay study (France/Canada) in high-risk MSM investigated Truvada as event-driven PrEP (dosing before and after sex). The PROUD study (UK) in MSM investigated daily Truvada. Both studies selected subjects who were highly sexually active and the HIV incidence in the control groups was higher than expected. Both studies were discontinued early due to overwhelming evidence of efficacy following review by separate external independent data review committees. Regardless of the Truvada PrEP dosing regimen used, the safety findings reported across both studies were consistent with its known profile as described in the SmPC.

Truvada is proposed to be suitable for PrEP based on QD dosing, a relatively long half-life, the large amount of data on safety and efficacy in HIV treatment and the infrequent selection of drug-resistant variants that have mutations associated with diminished capacity for replication.

Non-clinical and clinical data support use of FTC and TDF together for chemoprophylaxis based on increased activity and the barrier to drug resistance. The use of Truvada rather than TDF alone for HIV-1 prophylaxis is proposed to be supported by the comparison made in CO-US-104-0380.

The proposed new (additional) indication is as follows:

Pre-exposure prophylaxis (PrEP):

Truvada is indicated in combination with safer sex practices for pre-exposure prophylaxis to reduce the risk of sexually acquired HIV-1 infection in adults at high risk.

2.2. Non-clinical aspects

2.2.1. Introduction

The MAH has not conducted any new nonclinical pharmacology, pharmacokinetic or toxicology studies to support the PrEP indication. No new non-clinical studies are required. An overview of the previously submitted pharmacology/virology, pharmacokinetics, and toxicology data with emtricitabine and tenofovir DF was provided along with more detailed discussion of the nonclinical bibliographic studies assessing the use of the combination for the prevention of HIV-1 infection. This was considered sufficient in support of this application.

Given that there are extensive clinical data with the combination of emtricitabine and tenofovir DF (Truvada) for the desired indication, only the nonclinical data assessing the use of the combination for the prevention of HIV-1 infection are discussed.

2.2.2. Pharmacology

A number of in-vivo studies were conducted to evaluate the use of FTC and/or TDF for pre- and post-exposure prophylaxis (see table below). These nonclinical studies investigated the use of oral FTC and TDF for pre-exposure prophylaxis of HIV-1 infection across multiple routes of transmission; including studies aimed at demonstrating that the addition of FTC to TDF administration increased protection from infection.

Oral studies (intended route of administration)

Non-human primates

Tenofovir disoproxil fumarate (TDF)

A series of studies was conducted in order to evaluate oral administration of low levels of SIV to infant rhesus macaques for 5 days to simulate transmission of HIV via breast milk (Van Rompay et al 2006, Van Rompay et al 2002). In the first of the relevant studies TDF at 10 mg/kg given to the animals for 7 days, starting from 1 day before to 1 day after the 5 days of inoculation. Five of 6 animals had no detectable viraemia and were re-inoculated at 4 weeks of age with oral SIV for 5 days and 10 mg/kg of TDF for 7 days. Three of the 5 animals remained uninfected.

Another group of macaques was similarly dosed, but treated continuously through the re-inoculation 4 weeks later for a total treatment period of 7 weeks. Five of 6 animals had no detectable viraemia 4 weeks after the first inoculation; 4 became infected after the second inoculation. Subsequent to this study, the pharmacokinetics associated with 10 mg/kg TDF over time was evaluated in healthy infant macaques. The levels of TFV in plasma were approximately 65% lower at 4 weeks of age than at 1 week of age, suggesting that the increased rate of infection at 4 weeks or greater of age may be related to suboptimal TFV levels.

Table 1. Summary of published *in vivo* prophylaxis efficacy in animal models

Abbreviated Journal Article Title/Reference	Test System / Route of Viral Inoculation	Test Article / Route of Administration
Antiretroviral Pre-Exposure Prophylaxis Prevents Vaginal Transmission Of HIV-1 {Denton et al 2008}	BLT mice / Intravaginal	FTC, TDF IP
Systemic Administration Of Antiretrovirals Prior To Exposure Prevents Rectal And Intravenous HIV-1 Transmission {Denton et al 2010}	BLT mice / Rectal, Intravenous	FTC, TDF IP
Early Initiation of Antiretroviral Therapy Can Functionally Control Productive HIV-1 Infection in Humanized-BLT Mice {Li et al }	BLT mice / IP	TDF, lamivudine / IP
1% TFV Gel Demonstrates Partial Protection from Vaginal HIV Infection {Denton et al 2011}	BLT mice / Intravaginal	TFV, Topical (vaginal) FTC, TFV, Topical (vaginal)
Prevention Of SIV Infection In Macaques By (*R*)-9-(2-Phosphonylmethoxypropyl)Adenine {Tsai et al 1995}	Juvenile rhesus macaques / IV	TFV SC
Two Doses Of PMPA Protect Newborn Macaques Against Oral SIV Infection {Van Rompay et al 1998}	Infant rhesus macaques / PO	TFV SC
Prophylactic And Therapeutic Benefits Of Short-Term PMPA Administration To Newborn Macaques Following Oral Inoculation With SIV {Van Rompay et al 2000}	Infant rhesus macaques / PO	TFV SC
Two Low Doses Of TFV Protect Newborn Macaques Against Oral Simian Immunodeficiency Virus Infection {Van Rompay et al 2001}	Infant rhesus macaques / PO	TFV SC
Efficacy Of Postexposure Prophylaxis After Intravaginal Exposure Of Pig-Tailed Macaques To A Human –Derived Retrovirus HIV Type 2 {Otten et al 2000}	Infant rhesus macaques / Intravaginal	TFV SC
Chemoprophylaxis With TDF Provided Partial Protection Against Infection With SHIV {Subbarao et al 2006}	Chinese rhesus macaques / Intrarectal	TDF PO
Prevention Of Rectal SHIV Transmission In Macaques By Daily Or Intermittent Prophylaxis With Emtricitabine And Tenofovir {Garcia-Lerma et al 2008}	Rhesus macaques / Intrarectal	FTC, TDF PO/SC
Intermittent Prophylaxis With Oral Truvada Protects Macaques From Rectal SHIV Infection {Garcia-Lerma JG 2010}	Rhesus macaques / Intrarectal	FTC, TDF PO
Efficacy of Intermittent Prophylaxis with TFV and FTC against Rectal SHIV Transmission {Garcia-Lerma et al 2010}	Rhesus macaques / Intrarectal	FTC, TDF PO
Complete Protection against Rectal Transmission of an FTC-resistant SHIV162p3$_{M84V}$ Mutant by Intermittent Prophylaxis with Truvada {Cong et al 2011b}	Rhesus macaques / Intrarectal	FTC, TDF PO
Topical Administration Of Low-Dose TDF To Protect Infant Macaques Against Multiple Oral Exposures Of Low Doses Of SIV {Van Rompay et al 2002}	Infant rhesus macaques / PO	TDF PO
Evaluation Of Oral TDF And Topical TFV, GS-7340 To Protect Infant Macaques Against SIV {Van Rompay et al 2006}	Infant rhesus macaques / PO	TDF PO
Complete Protection From Repeated Vaginal SHIV Exposures In Macaques By A Topical Gel {Parikh et al 2009}	Pig-tailed macaques / Intravaginal	FTC, TFV Topical (vaginal)
Prevention Of SIV Rectal Transmission And Priming Of T Cell Responses In Macaques After Local Pre-Exposure Application Of Tenofovir Gel {Cranage et al 2008}	Macaques / Intrarectal	TFV Topical (vaginal)
Repeated Vaginal SHIV Challenges in Macaques Receiving Oral or Topical Preexposure Prophylaxis Induce virus-Specific T-Cell Responses {Tsegaye et al }	Pig-tailed Macaques / Intravaginal	TDF +FTC/PO TFV gel / Topical (Vaginal) TFV intravaginal ring / Topical

Following these proof-of-principle studies, an intra-rectal repeat exposure model of HIV infection was developed. Non-traumatic rectal inoculation was conducted on anaesthetised macaques; animals remained recumbent for at least 15 minutes after inoculation. The intention was that all control animals were infected. The model used a challenge inoculum that is intended to more closely mimic the infection risk seen in the clinical setting. Multiple inoculations of virus have been used to mimic high-risk human exposures and evaluate protection against multiple transmission events in each animal.

One of the first studies to use this model evaluated Chinese rhesus macaques given 0 (control), 22 mg/kg TDF once daily or 22 mg/kg TDF orally once weekly for 36 weeks (4 animals per group) (Subbarao *et al*. 2006, Van Rompay *et al*. 2006).
All animals received weekly rectal inoculations of 3.8 × 105 of SHIV162p3 (10 TCID) either until they became infected or for 14 weeks. Plasma levels of TFV were measured 2 hours after oral TDF administration.
There was no difference in plasma TFV levels between treated groups and the mean and median TFV levels were 2003 ng/mL (SD ± 3521) and 499 ng/mL, respectively. Infection occurred after a median of 1.5 inoculations of the control animals. Infection was delayed in treated animals, occurring after 6 or 7 weeks in the daily or weekly treated TDF animals, respectively. One animal treated daily remained uninfected for the 36 week study duration. The low rate of complete protection (13%) may be have been due to the small group size, variable TFV plasma levels or the use of only one antiviral agent.

TDF, emtricitabine (FTC) / TDF or FTC / TFV (Tenofovir)

In another study daily and intermittent oral and SC administration of FTC and TDF in macaques inoculated with SHIV weekly for 14 weeks via rectal administration (Garcia-Lerma et al 2008) was examined. Each SHIV162p3 inoculation was 7.6 × 105 RNA copies (10× TCID50), within the range of HIV-1 RNA levels observed in semen (103-106 copies/mL) during acute infection in humans and higher than the levels (102-104 copies/mL) observed after primary viraemia. Animals were treated daily or intermittently. Daily treatment was initiated 7-9 days before the first virus inoculation. Treated animals that remained negative during the 14 weekly challenges were administered drug for an additional 28 days. Treated animals that became infected continued treatment to monitor plasma viraemia and drug resistance emergence.

Prior to the treatment phase, a single dose oral pharmacokinetic study was conducted in 6 macaques using FTC doses of between 12 and 48 mg/kg. An oral FTC dose of 20 mg/kg gave an AUC0-24 of 13.2 µg•h/mL, similar to that observed after a single 200 mg FTC dose in humans (AUC0-24 of 10 µg•h/mL). The PBMC intracellular concentrations of FTC triphosphate were also similar to that observed in clinical studies. As a result a dose of 20 mg/kg was selected as the FTC dose.

A single oral pharmacokinetic study was also conducted in 5 macaques using TDF doses between 15 and 46 mg/kg. Oral TDF doses of 20 and 24 mg/kg resulted in TFV AUC0-24 values of 3.2 and 3.4 µg•h/mL, respectively, similar to the TFV range observed in humans (2.1 to 3.2 µg•h/mL). The PBMC intracellular concentrations of TFV diphosphate were also similar to human levels. Therefore, a dose of 22 mg/kg was selected as the TDF dose.

The control group of 18 untreated animals became infected after a median of two rectal exposures. It was shown that the dual agent regimens were more efficacious than the single agent regimen.

Table 2. Daily or Intermittent Prophylaxis of Rhesus Macaques with Oral or Subcutaneous TDF, FTC, FTC/TDF or FTC/TFV

Untreated Controls (18)	NA	1 (6)	17 (94)	1 (n = 3), 2 (n = 6), 3 (n = 3) 4, 8, 10, 11, 12
Daily starting 7-9 days before inoculation (6)	PO FTC 20 mg/kg TDF 22 mg/kg	4 (67)	2 (33)	9, 12
Daily starting 7-9 days before inoculation (6)	SC FTC 20 mg/kg TFV 22 mg/kg	6 (100)	0 (0)	NA
Daily starting 7-9 days before inoculation (6)	SC FTC 20 mg/kg	2 (33)	4 (67)	5, 10, 12, 13
2 hours before and 24 hours after inoculation (6)	SC FTC 20 mg/kg TFV 22 mg/kg	6 (100)	0 (0)	NA

Garcia-Lerma et al, 2008

In the group that received daily FTC and TDF orally, four animals remained uninfected and infection was significantly delayed in the other two macaques (viraemia detected between exposures 9 and 12). All 12 macaques that received SC injections of FTC and TFV either daily or as a pre/post exposure regimen remained uninfected after 14 viral exposures. In the group that was given SC FTC only, two macaques did not become infected. Infection was significantly delayed in the other four animals (viraemia detected between exposures 5 and 13). The six treated animals with breakthrough infections had attenuated acute viraemia which may have helped to preserve immune function. Two macaques (one treated with FTC by SC; one treated with FTC and TDF, orally) had FTC resistant mutants emerge (M184V, M184I) but no TFV resistance developed.

A follow-up study was conducted that evaluated intermittent drug dosing modalities. It showed that orally administered FTC and TDF to rhesus macaque monkeys could prevent SHIV infection or reduce the early viraemia (Garcia-Lerma JG, 2010). Animals were inoculated with SHIV weekly for 14 weeks via rectal administration. Various dosing regimens using orally administered 20 mg/kg FTC and 22 mg/kg TDF were evaluated.

Table 3. Intermittent prophylaxis of rhesus Macaques with oral FTC/TDF

Time of Oral Drug[1] Administration Compared to Inoculation[2] (Group Size)	Number (%) Uninfected After 14 Challenges	Number (%) Infected After 14 Challenges	Time to Infection: # Challenges
Untreated Controls (9)	0 (0)	9 (100)	1 (n = 6), 3 (n = 2), 5 (n = 1)
1 day (22h) before and 2h after (6)	5 (83)	1 (17)	4
3 days before and 2h after (6)	5 (83)	1 (17)	2
7 days before and 2h after (6)	4 (67)	2 (33)	3, 14
2 hours before and 22 hours after (6)	3 (50)	3 (50)	2, 2, 9
2 and 26 hours after (6)	3 (50)	3 (50)	1, 2, 10
High dose (40 mg/kg FTC and 44 mg/kg TDF) 2 hr before and 24 hours after (6)	5 (83)	1 (17)	4

1 20 mg/kg FTC and 22 mg/kg TDF unless otherwise noted

2 Inoculations were via the intrarectal route, once weekly for 14 weeks

According to the MAH, all regimens provided a measure of protection from infection. In those treated animals that became infected, the mean peak viraemia was lower compared to the controls. Virus loads declined faster in infected animals during continued treatment. In the one animal that became infected after being administered the higher doses of FTC and TDF, plasma drug concentrations of FTC and TFV were consistently low. None of the animals that became infected had virus with detectable resistance. The limited plasma and rectal secretion pharmacokinetic data collected from satellite groups of animals given 20 mg/kg FTC orally and 22 mg/kg TDF were too variable to establish a clear association between protection and drug concentrations.

The efficacy of intermittent prophylaxis (pre- and post-exposure) of oral 20 mg/kg FTC and 22 mg/kg TDF was compared to the effectiveness of a single pre-exposure dose of oral 20 mg/kg FTC and 22 mg/kg TDF administered 3 days prior to virus challenge (Garcia-Lerma *et al*. 2010). Macaques (6/group) were inoculated with SHIV weekly for 14 weeks via rectal administration. This study also showed that oral administration of both FTC and TDF pre- and post-exposure significantly reduced the risk of infection. Despite the persistence of TFV-DP in PBMCs and high TFV-DP levels in rectal tissues, a single dose of FTC/TDF 3 days prior to exposure was not effective in preventing infection.

An additional study (Cong *et al*. 2011b) investigated whether FTC/TDF maintained prophylactic efficacy against an FTC-resistant virus containing the M184V mutation.
Similar to that seen in HIV-1 harbouring M184V, the SHIV162p3M184V isolate showed high level (> 100-fold) resistance to FTC and hyper-susceptibility (0.3-fold) to TFV compared to the wild type, SHIV162p3WT (Cong *et al*. 2011a). Due to reduced transmissibility, the dose of SHIV162p3M184V was increased 4-fold to 40 $TCID_{50}$ which was shown to infect 5/5 macaques after a median of three intra-rectal exposures.

Macaques were inoculated with the SHIV162p3M184V weekly for 14 weeks via rectal administration. Animals were given 20 mg/kg FTC and 22 mg/kg TDF orally. The antivirals were administered 3 days before and 2 hours after each inoculation, which can be compared to the efficacy (83% protected) after SHIV162p3WT inoculation using the same treatment regimen.

Table 4. Intermittent Prophylaxis of Rhesus Macaques with Oral FTC/TDF Against FTC-Resistant SHIV162p3M184V

Time of Oral Drug[1] Administration Compared to Inoculation[2] (Group Size)	Number (%) Uninfected After 14 Challenges	Number (%) Infected After 14 Challenges	Time to Infection: # Challenges
Untreated Controls (5)	0 (0)	5 (100)	2 (n=2), 3 (n=1), 7 (n=1), 11 (n=1)
3 days before and 2h after (5)	5 (100)	0 (0)	NA

1 20 mg/kg FTC and 22 mg/kg TDF

2 Inoculations were via the intrarectal route, once weekly for 14 weeks

FTC/TDF maintained prophylactic efficacy against an FTC-resistant SHIV162p3M184V isolate in macaques after 14 weekly inoculations and a 20-week follow-up period. The residual antiviral activity by FTC, the hyper susceptibility of the M184V mutants to TFV and/or the reduced viral fitness of the M184V mutants may have contributed to the prophylactic efficacy of FTC/TDF.

A macaque model was used to evaluate oral or topical pre-exposure prophylaxis via intravaginal inoculation (Teague *et al*. 2015). Macaques were inoculated with the SHIV162p3 virus weekly for up to 18 weeks via vaginal administration weekly for up to 18 weeks. Orally administered 20 mg/kg FTC and 22 mg/kg TDF was evaluated for prophylactic efficacy. The antivirals were administered 22 hours before and 2 hours after each inoculation, which can be compared to the efficacy (83% protected) after

SHIV162p3WT inoculation using the same treatment regimen. Five of the 6 exposed uninfected macaques developed virus-specific T cells that were detected up to 3 weeks after the last virus challenge.

Supportive data (other routes of administration)

Juvenile macaques were inoculated IV with a single high dose (10^3–10^5 $TCID_{50}$) of SIV/SHIV and given 20 or 30 mg/kg TFV subcutaneously (Tsai *et al*. 1995). Tenofovir was administered daily for 4 weeks starting either 48 hours before, 4 hours after or 24 hours after intravenous virus inoculation. Animals were monitored for up to 56 weeks. None of the 25 TFV-treated macaques became infected. In contrast, all 10 of the untreated animals became infected within 3 weeks post inoculation. The 30 mg/kg SC dose, however, provided very high plasma TFV concentrations in infant and juvenile macaques (AUCs > 45 µg•h/mL; 15 fold higher than TFV after oral TDF clinical exposure) which resulted in renal toxicity with chronic administration (Van Rompay, 2008).

Humanised mice (BLT mice) were given 3.5 mg FTC and 5.2 mg TDF daily for 7 days via intraperitoneal injection. Viral exposure via vaginal (Denton *et al*. 2008), rectal (Denton *et al*. 2010), or intravenous (Denton *et al*. 2010) HIV-1 administration occurred 3 hours after the third FTC/TDF dose. The administration of FTC and TDF in combination prevented rectal (n = 9), vaginal (n = 8) and intravenous (n = 5) HIV-1 infection in all treated animals based on the lack of HIV-1 DNA in blood and tissues. In the absence of treatment, 88 to 100% of the mice had evidence of infection.
BLT mice were administered the 1% TFV gel used in a clinical studies once vaginally 4 hours before and once 4 hours after vaginal viral (HIV-1JR-CSF) exposure (Denton *et al*. 2011). Protection from vaginal HIV-1 exposure transmission occurred in 7/8 mice after 7 weeks. Additionally, BLT mice were administered 28 µM of FTC and 16.5 µM of TDF once vaginally 4 hours before vaginal viral exposure (Denton *et al*. 2011). The combination of vaginal FTC/TDF protected 8 of 9 BLT mice from vaginal HIV-1 infection.

2.2.3. Pharmacokinetics

There are extensive clinical PK and toxicokinetic (TK) data with the combination of emtricitabine and tenofovir DF (Truvada) and there has been vast human exposure. Thus, non-clinical PK and TK data are superseded and will not be discussed in this report.

2.2.4. Toxicology

Due to extensive clinical usage non-clinical toxicology data will not be discussed in this report.

2.2.5. Eco toxicity / environmental risk assessment

The MAH has not provided an updated ERA as the potential use of Truvada in adult patients for pre-exposure prophylaxis (PrEP) is not considered to significantly impact the overall predicted volume of use to increase by more than 10%. As detailed in the ERAs for other emtricitabine (FTC) and tenofovir DF containing regimens, the highest RQ is for TDF in fish (0.0009), therefore an increase in use for Truvada of 1111 times would be needed to pose an unacceptable risk.
It is acknowledged that an increase of 10% has no impact on the outcome of the environmental risk assessment; however the MAH is requested to revisit the environmental risk assessment in view of the evolution of the global exposure data within the PSURs. As a consequence the MAH should revisit the RMP in case of major increase of the global exposure in the PSURs subsequent to approval of the PrEP indication.

2.2.6. Conclusion on the non-clinical aspects

The MAH has provided an adequate non-clinical overview that appropriately focused on the non-clinical prophylaxis studies. These were mainly carried in out in NHPs. Although results were variable (probably due to small animal numbers) on the whole these studies demonstrated efficacy for prophylactic admiration. Sections 4.6 and 5.3 of the SmPC are in line with the product literature for the approved product for HIV-1 treatment and are appropriate.

The CHMP acknowledged that an increase of 10% has no impact on the outcome of the environmental risk assessment; however the MAH is requested to revisit the environmental risk assessment in view of the evolution of the global exposure data within the PSURs. In addition, the MAH should also revisit the RMP in case of major increase of the global exposure in the PSURs subsequent to approval of the PrEP indication.

2.2.7. Discussion on non-clinical aspects

The CHMP considered that the submitted non-clinical are satisfactory and dta are adequately reflected in Sections 4.6 and 5.3 of the SmPC. The MAH is requested to revisit the environmental risk assessment in view of the evolution of the global exposure data within the PSURs.

2.3. Clinical aspects

2.3.1. Introduction

GCP

The two major and the supportive clinical trials were not sponsored by the MAH. The clinical expert does not provide a statement to the effect that the trials were performed in accordance with GCP. However, the two main studies in this application dossier were conducted under an IND and the CSRs contain detailed statements regarding compliance with ICH GCP requirements.

The MAH provided a separate statement of compliance regarding studies conducted outside of the EU.

2.3.2. Pharmacokinetics

Food effect study GS-US-236-0105

Study title: A Phase 1 Study to Determine the Effect of Food on the Pharmacokinetics of Elvitegravir, Emtricitabine, Tenofovir DF plus Pharmacoenhancer GS-9350 Fixed-Dose Combination Tablet

GS-US-236-0105 evaluated the effect of food (fasted, light and high-fat meal) on the PK of EVG, COBI, FTC and TFV when the F1 formulation of the QUAD STR (EVG 150 mg, COBI 150 mg, FTC 200 mg, TDF 300 mg) was administered once daily for 15 days. The AUC TFV increased by about 23-25% in the fed state regardless of the type of meal. Cmax increased by 20% after a light meal vs. fasted administration but such a difference was not observed after a high fat/high calorie meal.

Table 5. Study GS-US-236-0105: Statistical Comparison of Selected TFV Pharmacokinetic Parameters (PK Analysis Set)

Treatment Condition N=24	TFV PK Parameters[a]		
	C_{max} (ng/mL)	AUC_{inf} (ng•h/mL)	AUC_{last} (ng•h/mL)
HC/HF Meal GLSM	319.39	3083.60	2724.93
Light Meal GLSM	370.76	3094.48	2726.58
Fasted GLSM	308.90	2505.63	2178.74
HC/HF Meal vs. Fasted GLSM ratio (90% CI), %	103.39 (89.38, 119.60)	123.07 (117.08, 129.36)	125.07 (119.09, 131.35)
Light Meal vs. Fasted GLSM ratio (90% CI), %	120.02 (103.76, 138.84)	123.50 (117.50, 129.81)	125.14 (119.16, 131.42)
HC/HF Meal vs. Light Meal GLSM ratio (90% CI), %	86.14 (74.47, 99.65)	99.65 (94.80, 104.74)	99.94 (95.16, 104.95)

CI: confidence interval, GLSM: geometric least squares mean, HC: high calorie, HF: high fat
GLSMs were obtained using a mixed-effects model

Based on these data and on the wide range of plasma concentrations documented in patients who have received TDF in various combinations in clinical trials for treatment of HIV-1 the CHMP considers that there is no good reason to persist with demanding that Truvada is given with food. A statement that: It is preferable that Truvada is taken with food and has been added in section 4.2 of the SmPC and adequately reflected in the PL.

There were no new additional data except for those used to document the level of adherence in clinical trials.

2.3.3. Pharmacodynamics

There are no new data since the efficacy of TFV and FTC within regimens for treatment of HIV-1 is well established.

2.3.4. PK/PD modelling

Aspects of the relationship between plasma levels and protection against acquisition of HIV-1 are described by study in the section on efficacy.

2.3.5. Discussion on clinical pharmacology

For these well-established agents no further clinical pharmacology studies are required. There are some published data of relevance to the use of Truvada for PrEP. For example, Patterson et al. (2011) studied the concentrations of TFV, FTC, and their active metabolites in mucosal tissues, genital secretions, and blood plasma after a single oral dose of Truvada in 8 men and 7 women using an ultrasensitive assay and reported that TFV and TFV-DP concentrations were 100-fold higher in rectal tissue compared to vaginal and cervical tissues. Cottrell et al. (2016) developed a PK/PD model based on mucosal tissue concentrations of TFV, FTC and the phosphorylated active metabolites and competing endogenous nucleotides (dATP, dCTP) in 47 healthy women. Colorectal TFV-DP was 10 times higher vs. the female

genital tract while endogenous nucleotides were 7-11 times lower. The model predicted ≥98% of the population would achieve protective mucosal tissue exposure by the third daily dose of Truvada. A minimum adherence of 6/7 doses/week was required to protect in the female genital tract while 2/7 doses/week was required for colorectal tissue, indicating that adherence is even more important for efficacy in women than men.

2.3.6. Conclusions on clinical pharmacology

Please refer to the clinical efficacy section for the description of the relationship between detecting plasma TFV and/or intracellular TFV-DP and protection against HIV-1 acquisition.

2.4. Clinical efficacy

2.4.1. Dose response studies

There were no clinical dose response studies to support selection of the dose for PrEP. The dose of TDF/FTC approved for treatment of HIV-1 has been used for PrEP.

2.4.2. Main studies

MSM study – iPrEx (CO-US-104-0288)

The sponsor of this study was NIAID. The MAH provided study drug and matching placebo.

The interim study report (CSR) covers data from the blinded treatment phase up to the data cut used for the study primary efficacy endpoint (through 01 May 2010) and for 8 weeks after the final blinded study drug dose. A second final CSR provides the data up to 01 November 2010.

Methods

This study was designed to evaluate whether daily emtricitabine (FTC) and tenofovir disoproxil fumarate (TDF) (FTC/TDF; Truvada) has an acceptable safety profile and decreases the incidence of HIV-1 in uninfected men who have sex with men (MSM) who are receiving standard prevention interventions.

This was a randomised, double-blind, placebo-controlled study with a duration that was event driven, i.e. it was to continue until at least 85 seroconversion events had occurred. The blinded treatment phase was followed by an open-label, single-arm FTC/TDF dosing phase that initiated in 2011 following the implementation of Protocol Version 5.

Objectives

The primary objectives of the blinded treatment phase were:

- To determine if daily oral FTC/TDF was associated with comparable rates of adverse events (AEs) compared with placebo among HIV-1-uninfected MSM
- To determine if daily oral FTC/TDF reduced HIV-1 incidence among HIV-1-uninfected MSM

The secondary objectives of the blinded treatment phase were:

- To determine if hepatic viral flares occurred in subjects who are hepatitis B surface antigen positive (HBsAg+) during and after FTC/TDF chemoprophylaxis
- To determine if significant changes in bone mineral density, body fat distribution or fasting lipids occurred during and after FTC/TDF chemoprophylaxis
- To determine if prior exposure to FTC/TDF chemoprophylaxis affected the course of HIV-1 infection, as predicted by plasma RNA level, CD4 T-cell counts, drug resistance assays and other clinical, virological or immunological parameters
- To identify attitudinal and behavioural correlates of chemoprophylaxis failure or success, including frequency and type of sexual exposure and patterns of adherence. Risk behaviour on- and off-study drug was compared. The prevalence of sexually transmitted infections (STIs) was used as one index of sexual risk.

Selection of subjects

Eligible subjects were adult males not infected with HIV-1 who had:

- Evidence of high risk for acquiring HIV-1 infection including any of the following:
    - Did not use a condom during anal intercourse with an HIV-positive male partner or a male partner of unknown HIV-1 status in the 6 months prior to study entry
    - Anal intercourse with > 5 male sex partners in the 6 months prior to study entry
    - Exchanged money, gifts, shelter or drugs for anal sex with a male partner in the 6 months prior to study entry
    - Had sex with a male partner and was diagnosed with an STI in the 6 months prior to study entry or at screening
    - Had sex with an HIV-infected male partner with whom condoms were not consistently used in the 6 months prior to study entry
- Provided a street address of residence for themselves and one personal contact who knew their whereabouts during the study period
- Ambulatory performance status ≥ 80 on the Karnofsky performance scale
- CrCLCG ≥ 60 mL/min and serum creatinine ≤ 1.2 within 28 days of enrolment
- Urine dipstick with a negative or trace results for glucose and protein within 28 days of enrolment
- Total bilirubin ≤ 1.5 mg/dL and ALT and AST ≤ 2 x ULN
- ANC ≥ 1,500/mm3; platelets > 150,000/mm3 and Hb ≥ 10 g/dL within 28 days of enrolment

Important exclusion criteria were:

- Previously diagnosed active and serious infections
- Active clinically significant medical problems, including cardiac disease, pulmonary disease or diabetes requiring hypoglycaemic medication
- Previously diagnosed malignancy expected to require further treatment
- Acute hepatitis B infection (anti-HBc positive, anti-HBs negative, and anti-HBc IgM positive
- Presence of treatment indications for hepatitis B based on local practice standards
- Clinical signs of hepatic cirrhosis
- History of pathological bone fractures not related to trauma
- Ongoing therapy with any ART, interferon (alpha, beta, or gamma) or interleukin therapy, aminoglycosides, amphotericin B, cidofovir, systemic chemotherapeutic agents, other agents with significant nephrotoxic potential, other agents that may inhibit or compete for elimination via active renal tubular secretion, ongoing diuretic therapy
- Active alcohol or drug use considered sufficient to hinder compliance with study procedures

Randomisation and treatment

The planned sample size was approximately 3000 subjects (1500 subjects per treatment group; see below). Subjects were randomized in a 1:1 ratio to receive either FTC/TDF tablets (Truvada) or matched placebo tablets and were to remain on study drug until the target number of seroconversion events was identified and the last enrolled subject completed 48 weeks of treatment. All subjects were instructed to take their assigned tablets once daily without regard to meals.
Randomisation was locally administered and was stratified by site. The randomisation schedule was developed the Division of Biostatistics at the University of California, San Francisco, using permuted blocks that randomly linked blinded study drug with study numbers. He was not involved in data management or statistical analysis of the study.
Each block consisted of 20 randomised treatment assignments, equally divided into 10 FTC/TDF and 10 placebo. Extra numbers were given a random assignment, to be used as reserve. Based on enrolment, study drugs were shipped to sites in these blocks during the study, and sites were instructed to dispense study drug consecutively by using the lowest kit number first (this process was known to be generally followed).
This system maintained treatment balance within sites and also allowed for a dynamic allocation of drug across sites to accommodate changes in accrual plans.
Subjects were to be unblinded to their drug only at the close of the trial. Subjects who developed HIV infections or discontinued study early were not unblinded at the time of the event. The DSMB was provided with the unblinded product coding information with study reports upon their request. However, the routine work of the DSMB was carried out according to randomisation codes (Group A versus B) and without knowledge of treatment.

Adherence

Blinded study medication was dispensed at baseline and at each study visit. Pill use was monitored by subject self-report during an interview, by clinic-based pill counts at visits when pills were either dispensed or suspended, and by comparing the number of pills dispensed at each visit with the time interval between visits (dispensation adherence). All subjects were instructed to return unused study medication in the original container at each post baseline study visit. Estimates of pill use by pill count assumed that no pills were taken from unreturned bottles (lower estimate) or that all pills were taken from unreturned bottles (higher estimate). The higher estimate was used in the as treated analysis.

At all on-treatment visits, subjects received counselling encouraging daily pill use, including the importance of taking the pill every day. An interactive, client-centred, motivational interviewing based approach for study pill use was implemented for all subjects starting between November 2009 and February 2010. This approach separated adherence assessment from counselling, to address social desirability bias in adherence reporting and to focus explicitly on barriers and facilitators of pill use, regardless of subjects' reported level of use.
Drug concentration measurements were conducted in plasma and peripheral blood mononuclear cells in subjects with documented 2 matched uninfected case controls.

- Plasma samples for possible assessments of FTC/TDF concentrations were collected from all subjects at baseline, every 12 weeks during the period of study drug administration, at the seroconversion visit, at the end-of-study visit and at every post study-drug follow-up visit.
- PBMC samples for possible assessments of FTC/TDF concentration were collected from all subjects at baseline, every 24 weeks during the period of study drug administration, at the seroconversion visit, at the end-of-study visit and at every post study-drug follow-up visit.

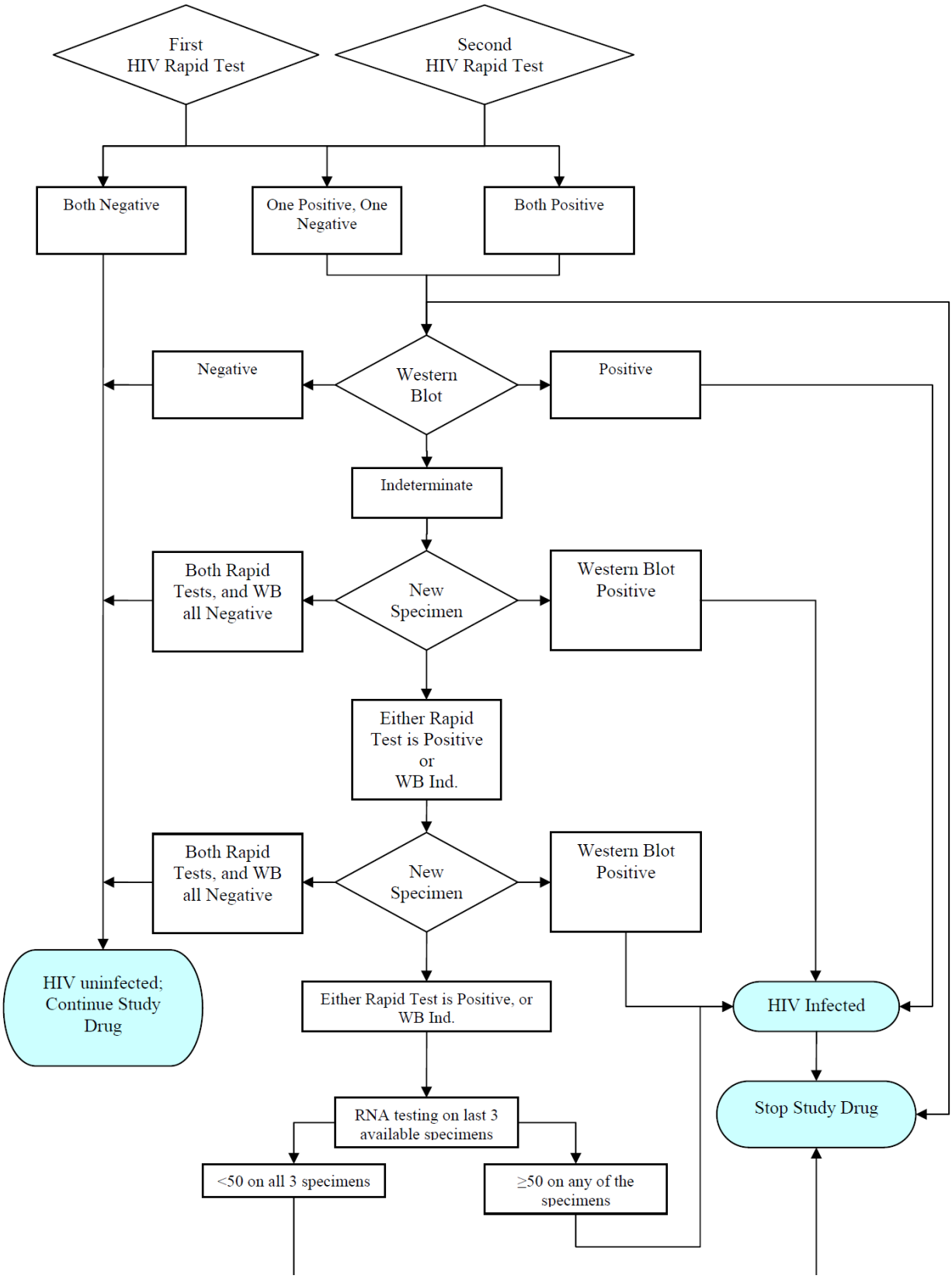
At the University of Colorado plasma TFV and FTC concentrations were assayed with a validated LC-MS-MS method that had a quantification range 10 to 1500 ng/mL for both agents. Intracellular TFV-DP and FTC-TP were assayed with a validated LC-MS-MS procedure using viably cryopreserved PBMCs. The quantifiable range for TFV-DP was 2.5 to 2000 fmol/sample and that for FTC was 0.10 to 200 pmol/sample. Results were adjusted for cell viability and reported as fmol or pmol per million viable cells. Both assay methods had been reviewed by the DAIDS CPQA.

Case detection

An HIV testing algorithm was developed to standardise the process, as shown in Figure 1.

The algorithm provided a means by which pre-existing HIV infections could be identified after enrolment, supporting the validity of the ITT analysis because any seroconversion identified during the study could be retrospectively "started" at the time of study entry if it was the result of pre-study infections. Further, an HIV Events Committee was established to review all events and to adjudicate any events that could not be confirmed through the algorithm.

Figure 1. HIV Testing Algorithm During Follow-Up



Other study procedures

Standard safety monitoring was performed, including assessment of AEs, clinical laboratory tests, and periodic physical examinations. Assessments of BMD and bone biochemical markers were performed in a subset.

Statistical approaches

The planned sample size of 3000 subjects (1500 per group) was estimated to produce the minimum target of 85 incident HIV infection events considered sufficient to yield a power of at least 80% with a 1-sided $\alpha = 0.05$ to reject a null hypothesis of efficacy of 30% or less if the true efficacy were 60% or more.

- The all randomised analysis set was used for safety analyses.
- The ITT analyses censored at baseline those who did not have at least 1 on-study HIV assessment.
- The mITT analysis set was used for the primary efficacy analysis and included all available data. Those who were not followed and those who had detectable HIV-RNA in their enrolment sample were censored at baseline.
- The secondary efficacy analysis set was used for the as-treated analysis. This used a time-dependent covariate indication as to whether the subject was known to fall below the pre-specified level of study-drug adherence (50%) based on records of study drug dispensation, pill-use calculation on the basis of study-drug dispensation and returns or subjects' self-report. For the as-treated analysis, pills from unreturned bottles were assumed to have been taken, and late visits were included in the analysis if the last dispensation allowed pill use on 50% or more of days.

Adjustments for multiple comparisons were not required because the primary efficacy endpoint of HIV-1 seroconversion was analysed at the primary analysis time point for the first time.

The MAH calculated $CrCL_{CG}$. The iPrEx team calculated treatment adherence.

The primary analysis of efficacy was based on the incidence of HIV infection (as defined in the algorithm shown above) in the mITT analysis set. For cases in which subject infection status could not be resolved by the algorithm because of unavailable specimens, the HIV Events Committee adjudicated whether there was sufficient evidence to conclude that HIV infection occurred.
Testing proceeded sequentially, starting with the sample immediately preceding the positive sample. If a prior HIV RNA test gave a value that was ≥ LL of its dynamic range, the date of that test was considered the date of HIV infection. If all prior tests gave values < LL of the dynamic range or if no prior plasma sample was available, the date of first evidence of HIV infection was considered the date of the first reactive HIV antibody test. Some subjects required additional testing to verify their HIV status and 3 additional visits could be required to satisfy the requirements of the algorithm. The date of first evidence of HIV infection was defined as the date of the first reactive HIV test or date of first positive HIV RNA test, whichever was earlier. Subjects who did not test antibody positive were censored at the time of their last negative antibody test.
A Cox model stratified by study site using the Efron method for ties was fit to estimate β, the log hazard ratio comparing the observed infection incidence in subjects randomized to receive FTC/TDF to the corresponding incidence observed in subjects assigned to placebo. The estimate was stratified by study

site. The efficacy measure was the *relative effectiveness* (RE), which was identical to the measure "vaccine efficacy" used in HIV vaccine studies. The RE was defined as 100 x (1-exp[β]). The estimated RE was reported with Wald-based 95% confidence intervals (CIs).

Two hypotheses were tested:

- The test of any efficacy was based on a log-rank test comparing the distributions of infection times between treatment groups. The null hypothesis was zero efficacy with a 1-sided alternative hypothesis of positive efficacy. The significance level for rejection of the null hypothesis was set at 0.025.
- The test of at least 30% efficacy consisted of a 1-sided Wald test of H0: RE = 0.30 (β = -.356) versus H1: RE > 0.30 (β < -.356). This test was equivalent to calculating a 1-sided 0.05 level Wald-based CI and refuting 30% efficacy if the upper bound of the CI was β <-.356.

Because there was a theoretical possibility that study treatment masked rather than prevented infection, an additional sensitivity analysis was planned (to be conducted at the end of the study) using methods described above that included all HIV results up to 8 weeks after the blinded study treatment period, even if the subject did not have HIV RNA detected in their last plasma sample taken while on study drug. The 8-week window was specified to provide for a sufficient duration of time in which to capture treatment-emergent HIV infections that occurred during the study period that were not detectable using HIV rapid testing through the last on-treatment study visit and confirmatory testing according to the HIV testing algorithm. This assessment was conducted in addition to the seroconversion assessment performed at end of study drug dosing (defined as the monthly visit following the date that the last 30-day supply was dispensed; the "8-weeks-post-stop" time point was 8 weeks after the end of study drug dosing.
Similar methods used for the mITT analysis were utilized to perform an ITT analysis. The p-value from the ITT analysis is valid for comparing treatment groups as the procedure for determining the time of seroconversion, as specified by the follow-up HIV testing algorithm includes retrospective testing if seroconversion occurs within the first 12 weeks after randomisation and study drug dispensation. Thus, the ITT analysis considers all HIV infections (including those determined to be at baseline) as seroconversion events.
An assessment of the assumption of proportional hazards was performed using the test and graphical methods of Grambsch and Therneau and no evidence of non-proportionality was evident through the 1 May 2010 cut off (p = 0.48).

Secondary Efficacy Endpoint

Among subjects who acquired HIV-1 infection during the study, additional testing was performed to assess the proportion of subjects with mutant HIV-1 strains. Formal comparisons between the 2 populations were based on Fisher's exact test. The relative risk of occurrence of a resistant virus and the associated exact 95% CI also was calculated.

Interim analysis and DSMB

The DSMB met at least yearly according to the NIH/DAIDS multinational DSMB schedule of meeting dates. The DSMB examined safety data, and was provided with information about subject safety including abnormal labs, signs and symptoms and social harms. The rates of these were compared between the randomisation groups (group A versus group B) to allow continued blinding of the DSMB using Chi-squared and/or log-rank tests. The treatment groups that were linked to the randomisation codes were available in a sealed envelope to the DSMB, and were to be opened at the discretion of the DSMB. In addition, listings and tabulations of all study AEs were updated and provided for DSMB review.

The Protocol Safety Review Team examined toxicities and conferred with the principal investigator and study statistician. Based on the results of the safety reviews, the officer could call for an emergency meeting of the DSMB to review the safety data. No statistical bounds for recommending a study hold based on safety were specified.

Results – iPrEx interim analysis

This report includes data for the primary study analysis in the database as of 20 August 2010, which comprised study visits completed through 01 May 2010. Available follow-up seroconversion results for the end of treatment and through 8-week period after the last dose of study drug are also provided up to the cut-off of 21 November 2010. No study drug was dispensed after 31 July 2010.

Conduct of the study

The study was conducted at 11 study sites in 6 countries. Protocol oversight was co-chaired by the Gladstone Institute of Virology and Immunology (San Francisco) and the Investigaciones Medicas en Salud (Lima).

Table 6. Randomization Totals by Study Site

Site	Subjects Randomized
Rio de Janeiro, Brazil (Praça Onze)	94
Sao Paulo, Brazil (USP)	76
Rio de Janeiro, Brazil (FIOCRUZ)	200
Lima, Peru (Impacta)	440
Lima, Peru (INMENSA)	500
Iquitos, Peru (ACSA)	460
Guayaquil, Ecuador (Equidad)	300
San Francisco, USA (SFDPH)	140
Boston, USA (Fenway)	87
Cape Town, South Africa (DTHF)	88
Chiang Mai, Thailand (RIHES)	114

Enrolment started with Version 3 of the protocol. Prior to enrolling the first participant, a decision was made to expand the study to allow observation of at least 85 seroconversion events. The expanded protocol projected that 3000 persons followed for at least 48 weeks would be needed to observe the targeted 85 events. In November 2009, the DAIDS multinational DSMB concluded that the fewer than 3000 would be sufficient to generate the required number of events and enrolment was closed on 17 December 2009 at 2499 persons. Without access to interim findings, NIH decided that visits through 01 May 2010 would comprise the primary analysis of safety and efficacy.
An additional amendment (Protocol Version 5, implemented March 2011) provided for the termination of placebo administration and initiation of or extension of FTC/TDF. Version 5 was intended for implementation only if FTC/TDF was found to be superior to placebo based on the primary study analysis or other studies of chemoprophylaxis.

Important protocol deviations were defined as enrolment of an ineligible subject, dispensation of incorrect study medication, or any subject who never returned for an on-study visit. There were valid protocol violations in 37 subjects (16 [1%] FTC/TDF and 21 [2%] placebo). The 4 events of incorrect study drug dispensation occurred in the placebo group and in all cases the subjects received placebo as assigned. Most protocol violations were considered to be minor deviations that did not affect the quality of the data. Relevant protocol deviations were proportionally distributed between treatment groups and no subject violated more than 1 eligibility criterion.

Population studied

Subject disposition is shown in Table 7. Of the 2499 randomised subjects 12-13% per group had discontinued for some reason up to the May 01 2010 cut-off point.

Attendance at the quarterly study visits was high (~ 90% at each time point). There were no significant trends in study visit completion rates over time. Overall, subjects were followed for assessment of HIV-seroconversion for 3324 person-years with variable duration of observation. The median (Q1, Q3) duration of exposure was 62.3 (36.9, 100.3) weeks (FTC/TDF 62.3 weeks and placebo 62.2 weeks).

Table 7. CO-US-104-0288: Disposition of Subjects (Gilead Analysis; Randomized Subjects)

Subject Disposition	Placebo N = 1248 n (%)	FTC/TDF N = 1251 n (%)	Total N = 2499 n (%)
Randomized[a]	1248 (100%)	1251 (100%)	2499 (100%)
Followed On Study (ITT analysis)[b]	1225 (98%)	1226 (98%)	2451 (98%)
HIV Infected at Baseline	8 (< 1%)	2 (< 1%)	10 (< 1%)
Followed for Seroconversion (mITT analysis)[c]	1217 (> 99%)	1224 (> 99%)	2441 (> 99%)
Discontinued Study Drugs due to clinical AE or laboratory event[d]	27 (2%)	25 (2%)	52 (2%)
Discontinued Study Drugs due to clinical AE	20 (2%)	22 (2%)	42 (2%)
Discontinued Study Drugs due to laboratory event[d]	8 (<1%)	3 (<1%)	11 (<1%)
Early Study Discontinuation Through 01 May 2010[e]	147 (12%)	162 (13%)	309 (12%)
Reason for Discontinuation[e]			
Death	4 (< 1%)	1 (< 1%)	5 (< 1%)
Participant Refused Further Participation	45 (4%)	40 (3%)	85 (3%)
Participant Relocated, No Further Follow-up Planned	44 (4%)	41 (3%)	85 (3%)
Investigator's Discretion	4 (< 1%)	9 (< 1%)	13 (< 1%)
Unable to Contact Participant	41 (3%)	67 (5%)	108 (4%)
Other category [delete if not applicable]	9 (< 1%)	4 (< 1%)	13 (< 1%)

a Subjects randomized and received at least 1 dispensation (ie, bottle) of study drug; all subjects were included in safety analyses (eg, AEs, SAEs)

b Contributing to the Intent-to-Treat (ITT) analyses for iPrEx and Gilead efficacy evaluations

c Contributing to the modified Intent-to-Treat (mITT) analyses for iPrEx and Gilead efficacy evaluations

d Information derived from the study medication interruption log (SMIL) CRF.

e Includes all study terminations up to 01 May 2010.

Most subjects reported that they did not know their randomisation group at Week 12, and those who guessed they were assigned to placebo or FTC/TDF were evenly distributed.

Table 8. CO-US-104-0288: Perceived Group Assignment At Week 12 By Randomized Treatment Group (iPrEx Analysis; Randomized 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.

The age ranged from 18 to 67 years with means of 27.5 years FTC/TDF and 26.8 years placebo. No notable differences between treatment groups were observed in demographics and baseline characteristics. Among hepatitis B virus (HBV) susceptible subjects at screening, 94% accepted vaccination. Thirteen subjects with chronic HBV infection detected at screening were enrolled in the study and 3 additional acute HBV infections were detected as AEs after enrolment when elevated liver transaminases were observed (2 in the FTC/TDF group). These events resolved to immunity against HBV.

Treatment adherence

There were 21 subjects who temporarily stopped study medication to receive post exposure treatment (8 FTC/TDF group and 13 placebo; p = 0.28).

Self-reported pill use was lower in the FTC/TDF group at Week 4 (mean 89% vs. 92%; p < 0.001) and Week 8 (93% vs. 94%; p = 0.006) but was comparable thereafter (mean 95% in both groups). At each visit ~ 6% did not report numbers of pills missed.

Pill use estimated by pill count increased over the first 8 weeks, then remained stable at a median of 89% (lower estimate) to 95% (upper estimate). According to pill dispensations and quantities, overall pill use decreased from 99% to 91% over the first year, a trend that contrasts with pill counts and self-reports, in which pill use increased. Mean (SD) adherence by self-reported pill counts through the last visit preceding 01 May 2010 was 88.7% (18.1%) for FTC/TDF and 89.6% (17.6%) for placebo.

In a post hoc assessment of the correlation between subject-reported adherence from the entire study cohort (n = approximately 2045) and objective exposure based on drug concentrations using LC/MS/MS testing of PBMC samples from a representative subgroup (179 samples obtained at Week 24 from the FTC/TDF group), low or missing self-reported adherence was predictive of no quantifiable TFV-DP or FTC-TP exposure but high reported adherence was poorly predictive of TFV-DP or FTC-TP drug exposure. Among the samples tested, the detection rate for TFV-DP or FTC-TP was 97% for subjects from US sites compared with 50% for non-US-based subjects (p < 0.0001). The detection rate for TFV-DP or FTC-TP was 73% for those aged ≥ 25 years vs. 44% for those aged < 25 years (p < 0.001).

Primary analysis

HIV rapid testing was performed at 39,613 visits, among which there were false reactive tests for 3 subjects at 7 visits; each subject had multiple negative tests afterward. HIV seroconversion was observed in 110 persons, of whom 10 had plasma HIV RNA subsequently detected in specimens obtained at the enrolment visit. The other 100 HIV-infected subjects had < 40 copies/mL plasma HIV RNA before seroconversion and were distributed as shown below

Table 9. 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)	0.005[a]
Subjects With Seroconversion Events	64	36	
Relative Effectiveness (2-sided 95% CI)	44% (15%, 63%)		
ITT Analysis	(N = 1225)	(N = 1226)	0.001[a]
Subjects With Seroconversion Events	72	38	
Relative Effectiveness (2-sided 95% CI)	47% (22%, 64%)		

a p-values by logrank test.

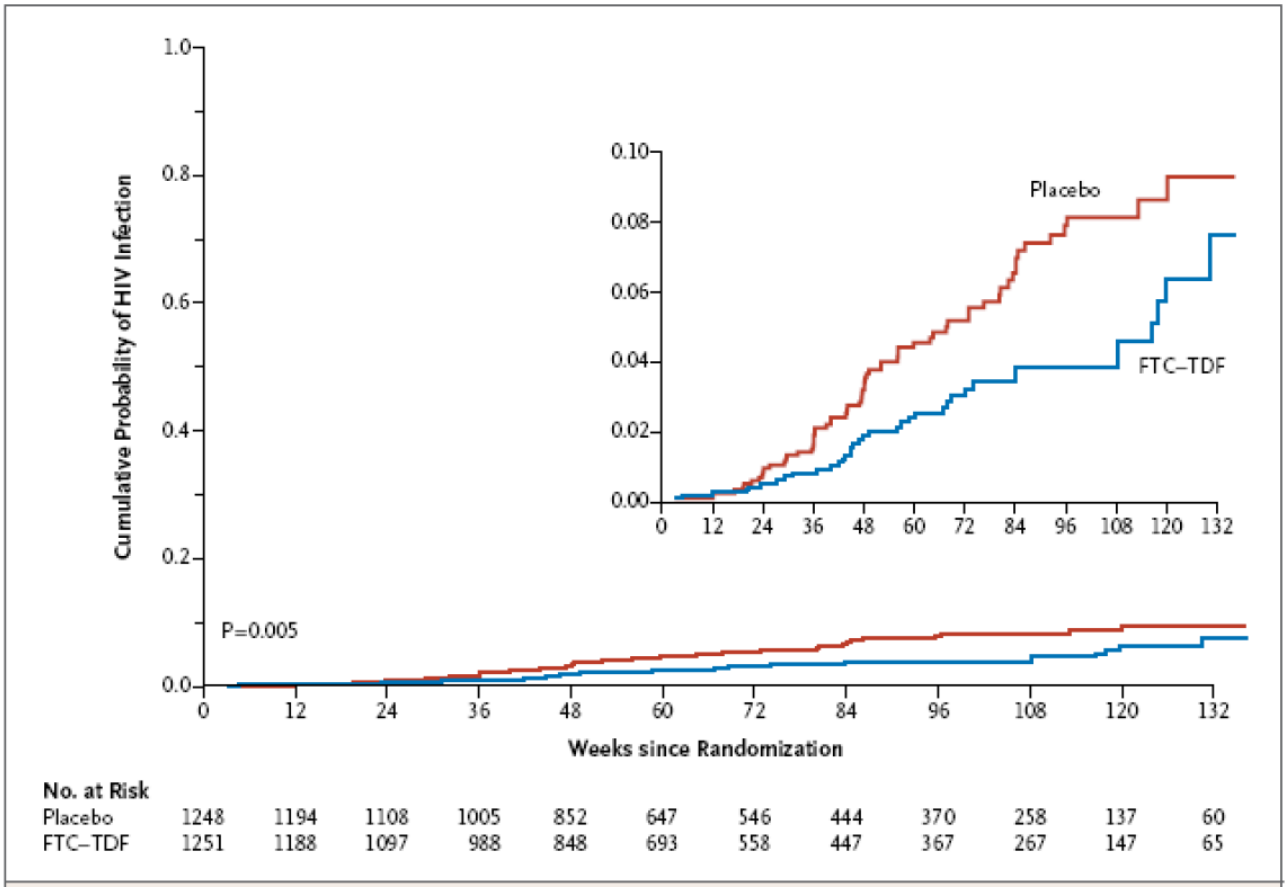
Note: the lower bound of the 1-sided 95% CI is 21% and 27% for the mITT and ITT analyses, respectively (Gilead analysis)

The iPrEx and MAH analyses gave lower bounds of the 95% CI above zero but below 30% for the mITT and ITT datasets. After adjustment for the difference in age between the 2 groups, the efficacy was 43% (95% CI: 14% to 62%).

There was no evidence of loss of efficacy with longer duration of follow-up, with minimal impact on the p-value for testing the null hypothesis of any efficacy.

Figure 2 is taken from the initial publication and excludes some events reported after acceptance of the manuscript.

Figure 2. 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 groups. The efficacy of pre-exposure prophylaxis with emtricitabine and tenofovir disoproxil fumarate (FTC-TDF) was 44 %, as compared with placebo (P-0.005). The inset graph shows a more detailed version of overall graph up to a probability of 0.10.

At end of treatment and 8 weeks post-treatment Truvada demonstrated a reduced rate of HIV-1 infection relative to placebo in the mITT and ITT analysis sets. As observed in the analysis at the primary time point, the null hypothesis of efficacy of 30% or less could not be rejected based on the iPrEx or MAH's analyses.

Table 10. 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)	0.002
Subjects With Seroconversion Events	83	48	
Relative Effectiveness (2-sided 95% CI)	43% (18%, 60%)		
ITT Analysis	(N = 1225)	(N = 1226)	< 0.001
Subjects With Seroconversion Events	91	50	
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)

Table 11. CO-US-104-0288: Relative Effectiveness Through 8 Weeks After 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	85	52	0.004
Relative Effectiveness (2-sided 95% CI)	39% (14%, 57%)		
ITT Analysis	(N = 1225)	(N = 1226)	
Subjects With Seroconversion Events	93	54	0.001
Relative Effectiveness (2-sided 95% CI)	43% (20%, 59%)		

a p-value by logrank test.

Note: the lower bound of the 1-sided 95% CI is 19% and 24% for the mITT and ITT analyses, respectively (Gilead analysis)

Secondary efficacy endpoints

HIV RNA concentrations and CD4+ T-cell counts in those with seroconversion were similar over time (through Week 60, the last time point available) between treatment groups.

Among the 10 subjects in whom plasma HIV-1 RNA was subsequently detected in specimens obtained at enrolment 2/2 in the FTC/TDF group and 1/8 in the placebo group had FTC-resistant virus. FTC resistance waned rapidly after FTC/TDF was discontinued. No TDF-resistant virus was observed in either treatment group. Five of the 10 had symptoms of an acute viral syndrome at enrolment, 2 had symptoms 1 week later, 1 had an anal sore and 2 had leukopenia at enrolment.

Among the subjects with HIV-1 seroconversion in the primary analysis, no FTC or TDF resistance was detected. In a post hoc assessment using drug-resistance assays based on allele-specific PCT (LLQ 0.5%) sensitive for the detection of minor sequence variants (RT K65R, K70E, M184V and M184I), no minor drug resistant variants were detected among subjects in the FTC/TDF group.

After discontinuation of study drug, seroconversion rates were similar among 320 subjects (161 FTC/TDF, 159 placebo through the 01 May 2010 cut-off; p = 0.42). These 320 subjects had a total of 1173 visits for HIV-1 testing after the discontinuation of a study drug (642 FTC/TDF, 531 placebo) through the 01 May 2010 cut-off. During this timeframe, 5 had seroconversion (2 FTC/TDF).

Other analyses of efficacy

As with the mITT and ITT analyses, efficacy of < 30% could not be ruled out in the pre-specified as-treated analysis at 50% pill use (p = 0.09). However, among subjects who reported a high degree (≥ 90%) of adherence the null hypothesis was rejected.

Table 12. CO-US-104-0288: Relative Effectiveness: Primary Analysis, by Self-reported Level of Pill Use (iPrEx mITT Analysis)

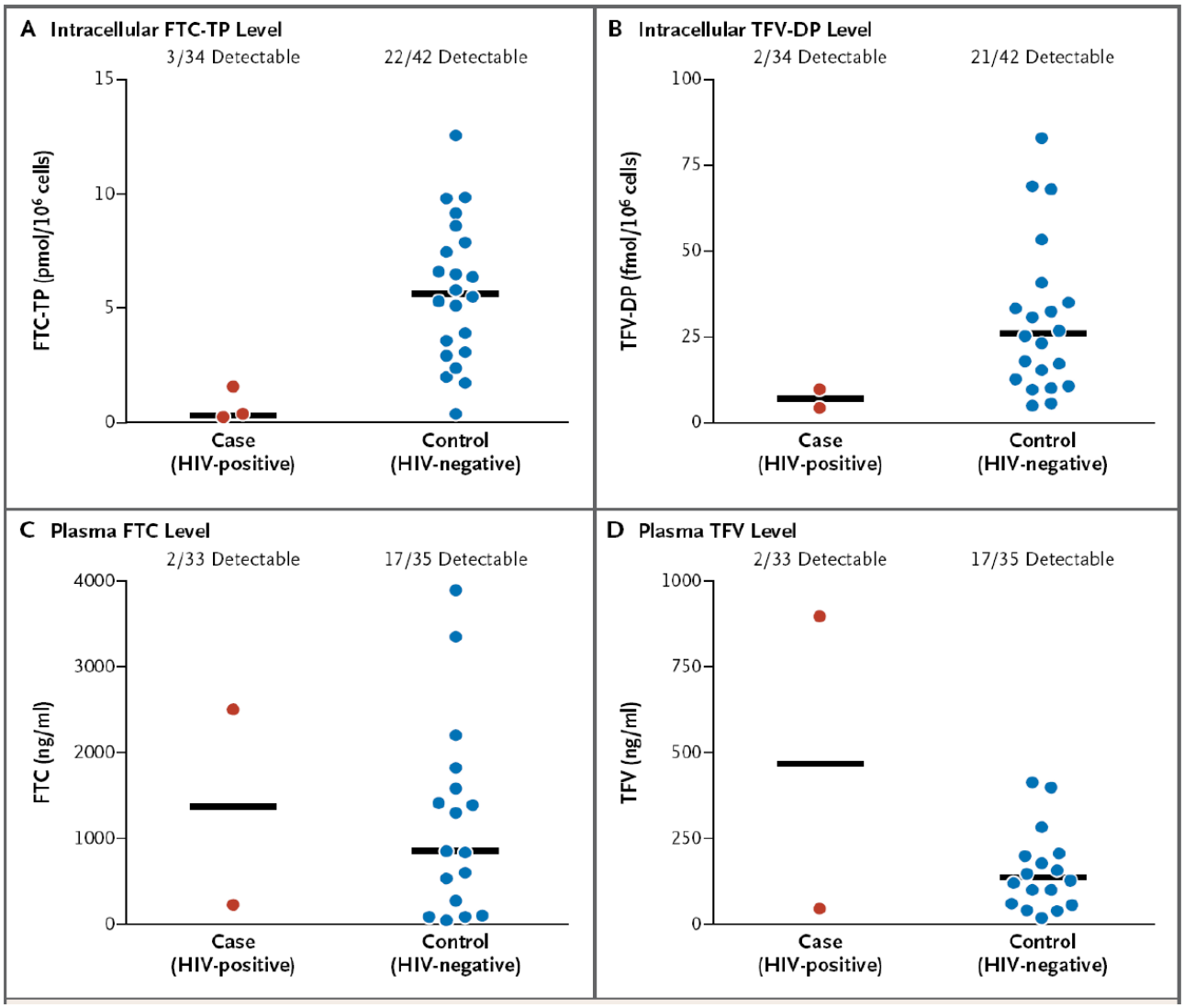
	Placebo	FTC/TDF	P-value[a]
Subjects self-reporting ≥50% pill use	47 events	23 events	0.006[a]
Subjects with seroconversion			
Relative effectiveness (2-sided 95% CI)	50% (18%, 70%)		
Subjects self-reporting ≥50% pill use	30 events	8 events	< 0.001a
Subjects with seroconversion			
Relative effectiveness (2-sided 95% CI)	73% (41%,88)		

a p-values by Wald test from Cox model.

Further support for the correlation between adherence and treatment effect was derived from pre-specified evaluations of HIV-1 seroconversion rates by plasma TFV or intracellular TFV=DP levels. Subjects without quantifiable PBMC TFV-DP but with high TFV plasma levels were assumed to have missed several days/weeks but to have taken study drug just prior to the study visit.

Figure 3 demonstrates a high correlation between quantifiable intracellular TFV-DP and FTC-TP or plasma FTC and TFV concentrations and reductions in HIV-1 infection with FTC/TDF vs. placebo and vs. subjects with no quantifiable concentrations. In the FTC/TDF group, the odds of HIV-1 infection was reduced by a factor of 12.9 (95% CI: 1.7 to 99.3; $p < 0.001$) for those with quantifiable concentrations. This finding corresponds to a relative reduction in HIV risk of 92% (95% CI: 40% to 99%; $p < 0.001$) in subjects with quantifiable levels. After adjusting for unprotected receptive anal intercourse (URAI) the effect persisted, with a 95% relative risk reduction (95% CI: 70% to 99%; $p < 0.001$) in subjects with quantifiable levels compared with those without quantifiable levels.

Figure 3. CO-US-104-0288: Summary of the Relation Between Quantifiable Levels of Study Drug Components and HIV Seroconversion Events (iPrEx ITT Analysis)



Shown are intracellular (Panel A and B) levels and plasma levels (Panel C and D) form the components of emtricitabine and tenofovir disoproxil fumarate (FTC-TDF) quantified from specimens obtained from subjects in the FTC-TDF group. FTC-TP denotes emtricitabine triphosphate and TFV-DP, tenofovir diphosphate. Horizontal lines in each panel indicate medians.

Efficacy by geographic region showed a consistent effect of FTC/TDF (p = 0.99 by city) but some geographic subgroups had small sample sizes. Randomisation was stratified by study site and specific results for relative risk reduction at the local (city) level ranged from 2% to 100%.

Table 13. CO-US-104-0288: Relative Effectiveness by Site Location (City) Subgroup (iPrEx mITT Analyses)

	Placebo Number of Seroconversion Events (%)	FTC/TDF Number of Seroconversion Events (%)	Relative Risk Reduction	P-value[a]
City				0.99
Lima	N = 470 34 (7%)	N = 470 17 (4%)	52% (95% CI: 14%, 73%)	
Iquitos	N = 230 8 (3%)	N = 230 7 (3%)	11% (95% CI: -144%, 68%)	
Rio de Janiero	N = 147 3 (2%)	N = 147 1 (1%)	67% (95% CI: -220%, 97%)	
Sao Paulo	N = 37 1 (3%)	N = 39 0 (0%)	100% (95% CI: NA, 100%)	
Chiang Mai	N = 57 1 (2%)	N = 57 1 (2%)	2% (95% CI: -1465%, 94%)	
Guayaquil	N = 150 13 (9%)	N = 150 8 (5%)	31% (95% CI: -66%, 72%)	
Cape Town	N = 43 2 (5%)	N = 45 1 (2%)	56% (95% CI: -383%, 96%)	
San Francisco	N = 70 1 (1%)	N = 70 1 (1%)	3% (95% CI: -1457%, 94%)	
Boston	N = 44 1 (2%)	N = 43 0 (0%)	100% (95% CI: NA, 100%)	

a p-value by logrank test and refer to hypothesis of any evidence of a subgroup effect.

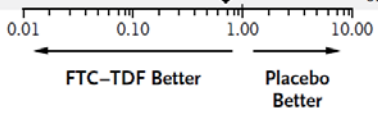
N = Number of subjects enrolled, by city and treatment group; percentages based on subject incidence per number enrolled per city per treatment group.

Efficacy in subgroups

The figure below summarises the findings. In particular, efficacy was higher among subjects who reported at screening that they had previously had URAI (58%; 95% CI: 32% to 74%) than among those who did not (-59%; 95% CI: -284% to 34%). There was no significant between-group difference in protection on the basis of other subgroups analysed.

Table 14. CO-US-104-0288: Summary of Subgroup Analyses of the Primary Efficacy Endpoint (iPrEx ITT Analysis)

Subgroup	FTC–TDF	Placebo	FTC–TDF	Placebo	Hazard Ratio (95% CI)	P Value
	no. of patients		*no. of events*			
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)	



The efficacy of emtricitabine and tenofovir disoproxil fumarate (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 prespecified 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 analysis and the 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 denotes not applicable, and URAI unprotected receptive anal intercourse.

Results – iPrEx final CSR

The addendum includes cumulative efficacy data through 21 November 2010 (double-blind primary analysis plus data through the end of the double-blind treatment period). This is referred to as the complete double-blind analysis. After 31 July 2010 subjects were asked to return any unused study medication and to present to the clinic for 2 more monthly visits to monitor HIV-1 seroconversion.

Between 01 May 2010 and 21 November 2010 an additional 304 subjects (149 FTC/TDF, 155 placebo) had discontinued from the study, giving a total of 613 discontinuations.

Table 15. CO-US-104-0288: Disposition of Subjects (Gilead Analysis; Randomized Subjects)

Subject Disposition	Placebo N = 1248 n (%)	FTC/TDF N = 1251 n (%)	Total N = 2499 n (%)
Randomized[a]	1248 (100)	1251 (100)	2499 (100)
Followed on study[b]	1226 (98)	1226 (98)	2452 (98)
HIV Infected at Baseline	8 (< 1)	2 (<1)	10 (<1)
Followed for seroconversion (mITT analysis)[c]	1218 (>99)	1224 (<99)	2442 (>99)
Discontinued study drugs due to clinical AE or laboratory event[d]	51 (4)	48 (4)	99 (4)
Discontinued Study Drugs due to clinical AE	42 (3)	41 (3)	83 (3)
Discontinued Study Drugs due to laboratory event[d]	9 (< 1)	7 (< 1)	16 (< 1)
Early Study Discontinuation Through 21 November 2010[e]	302 (24)	311 (25)	613 (25)
Reason for Discontinuation[e]			
Death	7 (< 1)	2 (< 1)	9 (< 1)
Participant Refused Further Participation	80 (6)	67 (5)	147 (6)
Participant Relocated, No Further Follow-up Planned	81 (6)	77 (6)	158 (6)
Investigator's Discretion	22 (2)	31 (2)	53 (2)
Unable to Contact Participant	92 (7)	115 (9)	207 (8)
Other category	20 (2)	19 (2)	39 (2)

a Subjects randomized and received at least 1 dispensation (ie, bottle) of study drug; all subjects were included in safety analyses (eg, AEs, SAEs)

b Refers to randomized subjects who had at least 1 follow up HIV test on study drug. The percentage of subjects followed for seroconversion and infected at baseline is calculated relative to the number followed.

c Contributing to the modified Intent-to-Treat (mITT) analyses for iPrEx and Gilead efficacy evaluations

d Information derived from the study medication interruption log (SMIL) CRF. Percentages are calculated relative to the number of subjects randomized.

e Includes all study terminations up through 21 November 2010. Deaths, however, were recorded regardless of when they occurred during the study. Eight subjects died as of 21 November 2010 and 1 subject died on 02 January 2011 from a thermal burn. The number of subjects who had an early discontinuation includes those subjects who had a termination date or death date recorded on the Study Termination CRF. Percentages are calculated relative to the number of subjects randomized.

Overall, median (Q1, Q3) adherence by self-reported pill counts through the last visit preceding 21 November 2010 was 94.4% for the FTC/TDF group and 94.8% for the placebo group.

The ITT analytic approach utilized by UCSF considered all seroconversion events up to the first visit after 01 August 2010 as part of the End of Treatment analysis. The cut-off date for the End of Treatment + 8 Weeks analysis is 21 November 2010. Similar trends in relative risk reduction to those observed for the primary analysis were observed, as shown in Table 16.

Table 16. CO-US-104-0288: Relative Risk Reduction Through the End of Treatment and Through the End of Treatment Plus 8 Weeks, (iPrEx mITT and ITT Analyses)

Complete Double-blind Analysis[a]										Primary Analysis[c]
Overall	N		Patient Years		No. Events		Hazard Ratio (95% CI)	Relative Risk Reduction (%) (95% CI)	P-value[b]	Relative Risk Reduction (%) (95% CI)
Analyses	FTC/TDF	Placebo	FTC/TDF	Placebo	FTC/TDF	Placebo				
End of Treatment										
mITT	1251	1248	2124	2113	48	83	0.577 (0.404, 0.824)	42 (18, 60)	0.0020	44 (15, 63)
ITT	1251	1248	2124	2113	50	91	0.548 (0.388, 0.774)	45 (23, 61)	0.0005	47 (22, 64)
mITT Age Adjusted	1251	1248	2124	2113	48	83	0.590 (0.413, 0.843)	41 (16, 59)	0.0037	43 (14, 62)
End of Treatment + 8 Weeks										
mITT	1251	1248	2125	2113	52	85	0.607 (0.430, 0.858)	39 (14, 57)	0.0042	39 (14, 57)
ITT	1251	1248	2125	2113	54	93	0.576 (0.412, 0.806)	42 (19, 59)	0.0011	43 (20, 59)

Note: Efficacy (relative risk reduction) is 1 minus the hazard ratio; values < 1 indicate efficacy, and intervals that do not cross 1 indicate significant evidence of efficacy. P-values for the MITT and ITT analysis apply to the hypothesis of any evidence of efficacy.

a For the End of Treatment, the data cutoff is the first visit after 31 July 2010 (the last study drug dispensation date). For the End of Treatment + 8 Weeks, the data cutoff date is 21 November 2010.

b P-values by logrank test.

c Data collected for the primary double-blind analysis, which included data through 01 May 2010

Between 21 November 2010 and 28 February 2011, 4 participants in the DEXA sub-study additionally tested positive for HIV infection at their DEXA 24-week post-stop study drug scan. The iPrEx endpoint committee adjudicated 3 as events (one in the FTC/TDF group). The HIV test result from the fourth subject (FTC/TDF group) was considered to be a false positive but the case was awaiting further testing and final adjudication by the endpoint committee. These 3 adjudicated seroconversion events were not included in the complete double-blind analysis but they were included in the database provided to the US FDA.

The MAH performed sensitivity analyses of relative risk reduction that only included data from subjects while on treatment during the double-blind period (data through the last dose of study drug; mITT analysis set). For the On-Treatment analysis, the cut-off was therefore the last dose of study drug. For the On-Treatment + 8 Weeks analysis, the cut-off was the last dose of study drug plus 56 days. Results for the On-Treatment and On-Treatment + 8 Weeks analyses of relative risk reduction were consistent with the corresponding mITT analyses performed by the UCSF statistical team.

Updated analyses in the addendum include the plasma or intracellular FTC/TDF levels in the nested case-control study. The original design included all with HIV seroconversion regardless of treatment assignment. Each subject with HIV seroconversion was matched by site and weeks since enrolment to two controls (one from the FTC/TDF arm and one from the placebo arm). In September 2010 the study chair, at the request of the protocol pharmacologist, who had no knowledge of or access to the data, approved the discontinuation of all testing on placebo-treated subjects with seroconversion and their corresponding controls. The FTC/TDF-treated subjects with seroconversion and their corresponding controls were included in the updated design, which included testing plasma and PBMCs in specimens obtained closest to the time of infection. Each FTC/TDF-treated subject with seroconversion was matched (by site and weeks since enrolment) with 2 random controls and 1 control who reported URAI in a period that covered the specimen date for the control.

Table 17. CO-US-104-0288: Relative Risk Reduction by Plasma or Intracellular FTC/TDF Levels – Matched Case-Control Analysis of FTC/TDF Subjects, (iPrEx mITT and ITT Analyses)

Complete Double-blind Analysis[a]					Primary Analysis[b]
Cohort	Drug Detected	Drug Not Detected	Odds Ratio[c] (95% CI)	Relative Risk Reduction (%) (95% CI)	Relative Risk Reduction (%) (95% CI)
Cases (HIV+)	4 (8)	44 (92%)	15.84 (3.68, 68, 24)	94 (78, 99)	92 (40, 99)
Active-Arm Matched Control (HIV-)	63 (44%)	81 (56%)	—	—	—

a Data from the double-blind treatment period and data from the 8-week follow-up period immediately following the end of treatment through 21 November 2010

b Data collected for the primary double-blind analysis, which included data through 01 May 2010

c Odds ratio calculated from a condition logistic regression with strata defined by matched sets of cases and controls.

The relative risks by subgroup for the updated and primary analyses are shown in Table 18. Only URAI had a significant effect although several other factors were associated with numerically higher adherence rates and risk reduction.

The report states that post hoc analyses to assess efficacy by adherence measures (pill counts and drug concentrations [plus matched controls]) through 8 weeks after the last dose of study drug had not been completed at the time of the CSR but will be reported in a subsequent CSR once the data cleaning and analysis has been completed.

Table 18. CO-US-104-0288: Relative Risk Reduction by Subgroups, (iPrEx mITT Analysis)

Subgroup	Complete Double-blind Analysis[a] N		Patient Years		No. Events					Primary Analysis[b]
Analyses	FTC/TDF	Placebo	FTC/TDF	Placebo	FTC/TDF	Placebo	Hazard Ratio (95% CI)	Relative Risk Reduction (%) (95% CI)	P-value	Relative Risk Reduction (%) (95% CI)
50% Adherence									0.1283	
Adherence < 50%			557	516	20	22	0.840 (0.459, 1.540)	16 (–54, 54)		32 (–41, 67)
Adherence ≥ 50%			1567	1598	28	61	0.469 (0.300, 0.733)	53 (27, 70)		50 (18, 70)
90% Adherence									0.0426	
Adherence < 90%			1189	1163	37	49	0.745 (0.486, 1.141)	26 (–14, 51)		21 (–31, 52)
Adherence ≥ 90%			935	950	11	34	0.325 (0.164, 0.640)	68 (36, 84)		73 (41, 88)
Age									0.1757	
Under 25	592	662	979	1108	30	47	0.724 (0.458, 1.145)	28 (–15, 54)		28 (–14, 54)
25 or Older	659	586	1145	1005	18	36	0.438 (0.248, 0.771)	56 (23, 75)		56 (23, 75)
Ethnicity									0.6444	
Non Hispanic/ Latino	351	343	413	405	7	14	0.475 (0.191, 1.178)	52 (–18, 81)		53 (–17, 81)
Hispanic/ Latino	900	905	1710	1708	41	69	0.599 (0.407, 0.883)	40 (12, 59)		40 (12, 59)
Education[c]									0.1642	
Less than Secondary	279	244	463	403	16	16	0.858 (0.429, 1.718)	14 (–72, 57)		14 (–72, 57)
Secondary or Higher	955	992	1629	1682	31	67	0.481 (0.314, 0.737)	52 (26, 69)		52 (26, 69)
URAI									0.0349	
Reported no URAI	519	495	796	791	14	11	1.246 (0.565, 2.750)	–25 (–175, 44)		–24 (–174, 44)
Reported URAI	732	753	1328	1322	34	72	0.477 (0.317, 0.718)	52 (28, 68)		52 (28, 68)
HSV									0.3398	
Negative/ Indeterminate	789	817	1259	1304	24	50	0.491 (0.302, 0.800)	51 (20, 70)		51 (20, 70)
Positive	461	431	864	810	24	33	0.697 (0.411, 1.180)	30 (–18, 59)		30 (–18, 59)

Circumcision									0.097	
Not Circumcised	1085	1073	1882	1864	46	71	0.643 (0.444, 0.933)	36 (7, 56)		36 (7, 56)
Circumcised	162	171	237	246	2	12	0.174 (0.039, 0.779)	83 (22, 96)		83 (23, 96)
Perceived Treatment at Week 12									0.5974	
Placebo	108	115	196	201	3	10	0.314 (0.086, 1.143)	69 (–14, 91)		NA
Truvada	278	275	482	464	12	18	0.677 (0.326, 1.408)	32 (–41, 67)		NA
Don't Know	738	748	1336	1342	28	49	0.564 (0.355, 0.898)	44 (10, 65)		NA
Transactional Sex									0.3454	
No Exchange	734	738	1177	1181	24	49	0.493 (0.302, 0.804)	51 (20, 70)		51 (14, 72)
Exchange	517	510	946	933	24	34	0.696 (0.413, 1.175)	30 (–17, 59)		34 (–21, 63)
Drinking During Past Month[c]									0.8126	
0-4 Drinks	554	529	914	867	22	39	0.522 (0.309, 0.882)	48 (12, 69)		48 (12, 69)
≥ 5 Drinks	666	687	1144	1179	24	44	0.570 (0.347, 0.938)	43 (6, 65)		43 (6, 65)
Identify Female									1	
Yes	15	14	26	24	0	0	NA	NA		NA
No	1226	1232	2084	2088	47	83	0.568 (0.397, 0.813)	43 (19, 60)		45 (17, 64)
Identify Trans									0.1696	
Trans	163	162	283	280	10	10	1.017 (0.422, 2.450)	–2 (–145, 58)		–5 (–166, 58)
Not Trans	1088	1086	1841	1833	38	73	0.518 (0.350, 0.767)	48 (23, 65)		51 (23, 69)

Note: Efficacy is 1 minus the hazard ratio; values < 1 indicate efficacy, and intervals that do not cross 1 indicate significant evidence of efficacy. P values refer to the null hypothesis that efficacy differed in the 2 strata.

a Data from the double-blind treatment period and data from the 8-week follow-up period immediately following the end of treatment through 21 November 2010

b Data collected for the primary double-blind analysis, which included data through 01 May 2010

c Data derived from computer-assisted structured interview (CASI) questionnaire

Other outcome measures

To assess whether participation in the study impacted attitudinal and behavioural correlates that could impact failure or success of chemoprophylaxis the study included pre-specified evaluations of sexual practices and an assessment of the prevalence of STIs. The number of sexual partners with whom respondents had receptive anal intercourse decreased after study enrolment, and the percentage of those partners who used a condom increased with similar results in each treatment group at each time point. No significant between-group differences were found in the incidence of syphilis (p = 0.49), gonorrhoea (p = 0.74), chlamydia (p = 0.43), genital warts (p = 0.53) or genital ulcers (p = 0.62) during follow-up.

iPrEx Open Label Extension (Grant et al., Lancet ID 2014)

In this open label cohort study 1526/1678 eligible subjects were MSM who had previously been enrolled in iPrEx and avoided acquisition of HIV-1. Other subjects came from two other studies in men and transgender women who have sex with men.

Participants were told their randomised assignment in the prior study before enrolment at which time they were offered daily Truvada. Subjects were followed in the same way irrespective of whether they chose to take PrEP. Visits were at weeks 4, 8, 12, 24, 36, 48, 60 and 72 and subjects could start PrEP at any visit up to 48 weeks, after which they were followed up to 72 weeks on study (off or on PrEP). Counselling was provided. Drug concentrations were assessed in plasma at one visit during the first 12 weeks after receiving PrEP and analysed in case-cohort design. Subjects were tested for HIV antibodies at all visits and for STIs every 24 weeks or if they had symptoms. HIV incidence on and off PrEP was assessed using a Poisson model (with a robust SE), enabling comparison between randomised and open-label periods.

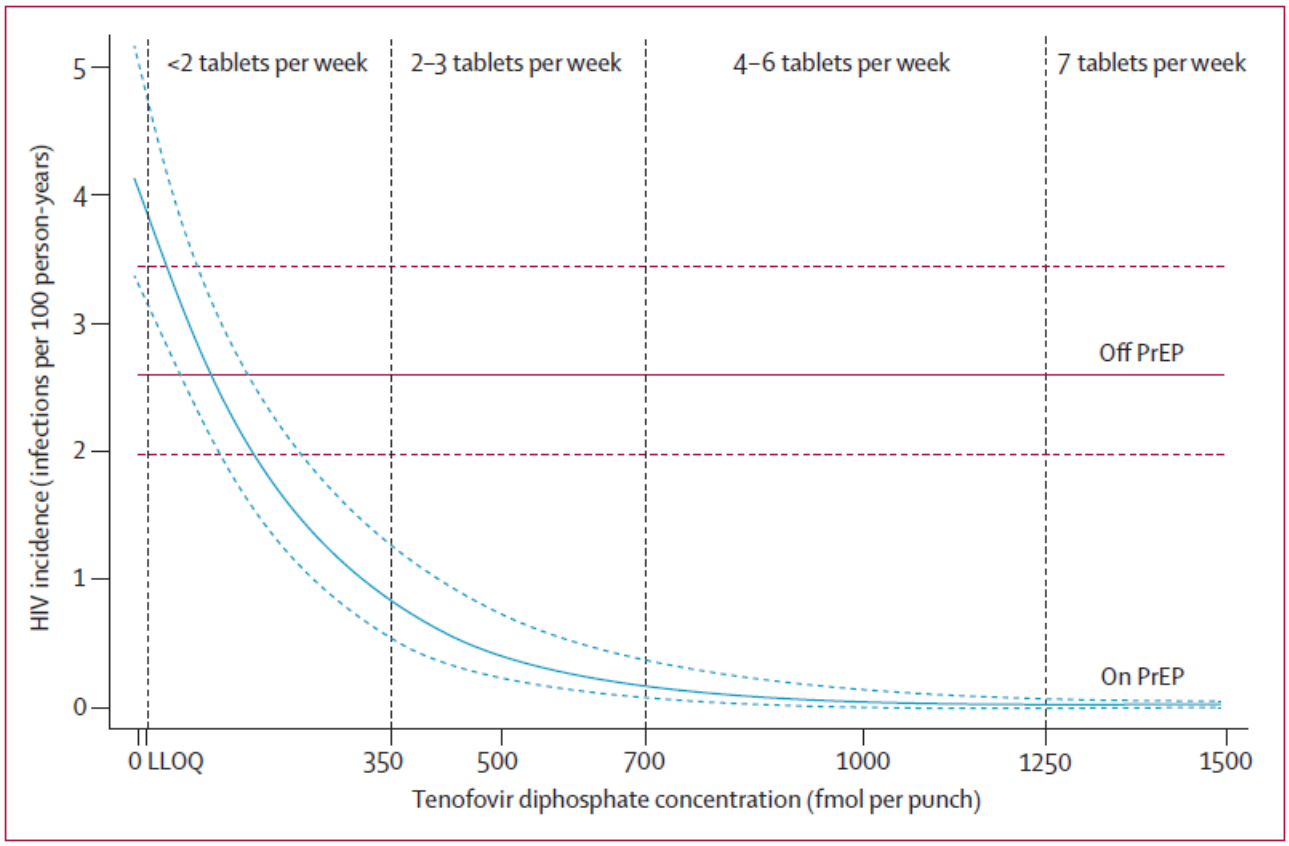
The study finally enrolled 1603 HIV-negative subjects of whom 1225 (76%) received PrEP. Uptake was higher in those reporting URAI (416/519 [81%] vs. 809/1084 [75%], p=0.003). Retention in the study was not associated with receipt of PrEP (945/1128 [84%] vs. 312/378 [83%], p=0.42). PrEP treatment was interrupted 380 times in 365 subjects due to reasons other than LTFU, end of study or HIV infection.

There were 41 subjects infected with HIV during the study, including 13 not receiving PrEP and 28 receiving PrEP. Of those receiving PrEP, HIV incidence was 1.8 infections per 100 p-y, compared with 2.6 infections per 100 p-y in those who concurrently did not choose PrEP (HR 0.51, 95% CI 0.26–1.01, adjusted for sexual behaviours). These rates compare with 3.9 infections per 100 p-y in the placebo group of the previous randomised phase in iPrEx (HR 0.49, 95% CI 0.31–0.77).

Considering only participants from iPrEx, the HIV incidence on PrEP was 53% (95% CI 26 to 70) lower than in the placebo group of the randomised phase (3.93 infections per 100 p-y) and 51% (95% CI 23 to 69) lower than during the gap between the randomised phase and the OLE (3.81 infections per 100 p-y).

Tenofovir diphosphate (TFV-DP) concentrations in dried blood spots were strongly associated with HIV incidence among those receiving PrEP. HIV incidence was 4.7 infections per 100 p-y if drug was not detected in dried blood spots, 2.3 infections per 100 p-y if concentrations suggested use of <2 tablets per week, 0.6 per 100 p-y for use of 2-3 tablets per week and zero for use of ≥ 4 tablets per week (p<0.0001).

Figure 4. Pre-exposure prophylaxis and HIV incidence



For those visits on PrEP, the incidence of HIV is estimated by exponential regression by tenofovir diphosphate in dried blood spots. The incidence for the concomitant off -PrEP group is depicted as a constant for reference. The dotted lines represent the estimate bounded by 1 SE. Dosing for each interval is estimated by pharmacokinetic modelling. LLOQ=lower limit of quantitation.

TFV-DP concentrations in dried blood spots were higher among subjects of older age, with more years of schooling, reporting URAI, with more sexual partners, a history of syphilis or herpes, any HIV-positive sexual partner or lower estimated CrCL. The effect of age was not explained by differences in estimated CrCL.

Table 19. Predictors of drug concentration in dried blood spot

	Adjusted OR (95% CI)	p value
Non-condom intercourse at entry		
None	Reference	
Non-condom insertive anal intercourse	1·06 (0·71–1·58)	0·78
Non-condom receptive anal intercourse	1·66 (1·37–2·02)	<0·0001
Male sexual partners in 3 months before entry		
0–1	Reference	
2–4	1·33 (1·09–1·62)	0·005
≥5	1·82 (1·42–2·33)	<0·0001
Known HIV-positive partner	1·44 (1·05–1·99)	0·03
Any sexually transmitted infection at enrolment in open-label extension	1·05 (0·85–1·30)	0·65
Transgender	0·72 (0·55–0·94)	0·02
Age at enrolment to open-label extension (years)		
18–24	Reference	
25–29	1·19 (0·92–1·55)	0·19
30–39	1·64 (1·26–2·15)	0·0002
≥40	3·29 (2·39–4·53)	<0·0001
Education		
Less than secondary	Reference	
Secondary	1·99 (1·59–2·48)	<0·0001
Post-secondary	1·93 (1·55–2·41)	<0·0001
Alcohol drinks per day (on days when drinking)		
<5	Reference	
≥5	0·81 (0·65–1·02)	0·07
Methamphetamine use in the 30 days before enrolment	0·78 (0·43–1·42)	0·42
Cocaine use in the 30 days before enrolment	1·07 (0·83–1·38)	0·6
Body-mass index (kg/m²)	1·00 (0·98–1·01)	0·57
Estimated creatinine clearance at entry (mL/min)	0·98 (0·98–0·99)	<0·0001

ORs adjusted for the other variables in the table, study site, and weeks on study. OR=odds ratio.

Plasma TFV was determined at one of weeks 4 (n=305), 8 (n=851) or 12 (n=33). In those who received PrEP TFV was detected in 71% but varied by study region (83% in the USA, 77% in Brazil, 63% in Peru, 62% in Ecuador, 68% in South Africa and 80% in Thailand. These proportions were similar to that in the first 8 weeks of the randomised phase of iPrEx trial (70%; 60% after weighing for sampling fraction). In 63 subjects who were tested during both phases of the iPrEx study, drug detection increased in Peru from 44% (28/63) in the randomised phase to 63% (40/63) in the OLE (p=0.02).

The authors concluded that PrEP uptake was high when made available free of charge by experienced providers. The effect of PrEP was increased by greater uptake and adherence during periods of higher risk. Drug concentrations in dried blood spots were strongly correlated with protective benefit.

People who more often engaged in risky sexual practices and who had sexually transmitted infections were more likely to join the study, more likely to choose PrEP, and more likely to have sustained protective levels of PrEP use. Such preferential use of PrEP during times of greater risk shows subject's capacity to recognise and respond appropriately to risks.

Discordant couples study – Partner's PrEP (CO-US-104-0380)

The sponsor of this study was the University of Washington, Seattle. The MAH provided study drug and matching placebo.
The CSR covers data from the blinded treatment phase up to the data cut used for the study primary efficacy endpoint (through 10 July 2011; data are reported up to 18 August 2011). On July 2010 the placebo group was discontinued but the active treatment groups remained blinded to assignment.

Methods

This was a multicentre, randomised, double-blind and placebo-controlled study to evaluate the safety and efficacy of PrEP with either TDF or FTC/TDF administered once daily. The study evaluated the prevention of HIV-1 acquisition among HIV-1 uninfected individuals within a known HIV-1 sero-discordant heterosexual partnership. The study was initiated in July 2008 and was conducted in Kenya (4 sites) and Uganda (5 sites). In this endpoint-driven study subjects were to be followed for a minimum of 24 months and a maximum of 36 months.

The primary objectives were:

- To determine if PrEP with TDF or FTC/TDF provides additional protection over standard measures against HIV-1 acquisition in uninfected persons within heterosexual HIV-1 discordant couples
- To assess the safety of TDF or FTC/TDF by comparing rates of AEs vs. placebo

The secondary objectives were:

1) Factors influencing efficacy

- To evaluate efficacy by frequency of sexual activity and HIV-1 viral load in the infected partner
- To assess efficacy by gender of the HIV-1 uninfected partner
- To measure the effect on efficacy of CD4 count of the HIV-1 infected partner and, for both partners, HSV-2 serostatus, STIs and male circumcision

2) Adherence

- To assess adherence and the effect of adherence on efficacy
- To evaluate the frequency of PrEP drug sharing between the HIV-1 uninfected and HIV-1 infected partners by drug assays

3) Risk compensation

- To characterise sexual behaviour change of HIV-1 uninfected individuals
- To compare risk behaviours among HIV-1 discordant couples previously enrolled in the Partners in Prevention study (which evaluated the efficacy of HSV-2 suppressive therapy when given to the HIV-1 infected partner for preventing HIV-1 transmission), by examining changes in sexual behaviours when the HIV-1 infected versus HIV-1 uninfected partner is receiving a study drug

4) Safety
To assess the effect of chemoprophylaxis on the rate of congenital abnormalities

5) Effect of PrEP on early HIV-1 disease
To assess the effect of study drug on plasma HIV-1 viral load and CD4 cell counts in the first 12 months after seroconversion and assess phenotypic antiretroviral drug resistance

Selection criteria

The study was conducted in heterosexual HIV-1 sero-discordant couples in which the uninfected partner could be male or female. Enrolment criteria were evaluated through study screening procedures. Eligible partners were enrolled within 56 days of screening and were followed at 4-week intervals for evidence of HIV-1 seroconversion, adherence to the study drug and clinical toxicity. Laboratory measures of safety were performed quarterly.

Partner subjects (HIV-1 Uninfected)

- Aged 18-65 years with negative HIV-1 rapid tests at screening and enrolment
- Part of a heterosexual couple in which one partner met the study eligibility criteria for index subjects (see below). The couple had to be sexually active (vaginal intercourse at least 6 times in prior 3 months with plans to remain in the relationship for the duration of the study period.
- $CrCL_{CG}$ ≥60 mL/min AND serum creatinine ≤1.3 mg/dL for men and 1.1 mg/dL for women
- Total bilirubin ≤1.5xULN AND ALT and AST <2xULN
- ANC >1300/mm^3, platelets >125,000/mm^3 and Hb >11 g/dL
- Negative hepatitis B surface antigen test
- Not pregnant or breastfeeding
- Other exclusion criteria were similar to those in the iPrEx study

Index Subjects (HIV-1 Infected)
As above except HIV-1 infected (positive EIA), CD4 cell count ≥250 cells/mm^3 and did not otherwise meet national guidelines for initiation of ART with no history of AIDS-defining diagnoses. Subjects were excluded if they were on ART.

Randomisation and treatment

The randomisation code was generated and maintained by the Protocol Biostatistician or designee. A block randomisation scheme using a block size of 30 was implemented. Blocks were assigned to sites and drug kits were shipped as needed to ensure reliability of the drug supply. Subjects received their identification numbers in sequential order as they entered the study at each site and were randomized to study kit in block order within each site using a telephonic system. Every 6 months, designated study staff members accessed the telephonic system to dispense an appropriate kit to each subject.
The HIV-1 uninfected partner within each couple was randomised (1:1:1) to TDF, FTC/TDF or placebo. Because TDF and FTC/TDF tablets are dissimilar each subject ingested two tablets daily (either one active and one placebo or two placebo).
At each monthly visit, the study staff assessed subject adherence through a structured interview and tablet count and provided adherence counselling to both partners. Adherence messaging was reinforced by counsellors, clinicians and pharmacy staff. Weekly pill boxes and other adherence aids were provided.
No formal pharmacokinetic endpoints were evaluated but a preliminary comparison was conducted of *detection of tenofovir* in plasma among a case-cohort sample of partner subjects who acquired HIV-1

relative to partner subjects who did not acquire HIV-1 during the study. No drug concentration measurements were conducted.

Blinding

None of the study staff or investigators had access to the randomisation schedule. At the MAH's facility packaging and QA staff members were unblinded to the bottle assignments. Programmers and statisticians at the sponsor were unblinded to provide QA review of the drug kit dispensing system and to prepare the DSMB reports.

Statistical methods

The study used a common placebo group for comparison to each of the active arms and aimed to demonstrate efficacy of each regimen separately vs. placebo. Concordant with Phase 3 study designs for HIV vaccines, the minimum level of efficacy was considered to be 30%. Therefore the null hypothesis of efficacy evaluated in this study was 30% (or less) for each active study drug with the standard Type I error rate of 0.05. It was further anticipated that the loss to follow-up rate would be approximately 18% (i.e. 7% per year) based on results of previous HIV-1 studies conducted with HIV-1 sero-discordant couples in East Africa.

Assuming that the true efficacy of TDF or FTC/TDF would be 60% and HIV-1 incidence rates in the placebo group would be between 3.2 and 4 per 100 person-years, calculations indicated that a sample size of 3900 HIV-1 uninfected subjects (1300 per group) would be expected to yield 191 HIV-1 seroconversion events, which would result in 80% power to detect an efficacy between 57% and 60% for each active study drug relative to placebo (against the null hypothesis of 30%). Under the same assumptions, 191 seroconversion events would provide 90% power to detect a true efficacy between 61% and 65%.

Once the study had initiated, after discussion with the DSMB, the estimated sample size was revised to 4700 HIV-1 uninfected subjects (1566 per group). This decision was based on new information from another PrEP study in discordant couples in which the HIV-1 incidence rate was 2.8 per 100 person-years in the placebo group.

The analysis sets were:

- ITT - all randomised partner subjects who met the entry criteria. The safety analysis was conducted in the ITT cohort
- mITT – this cohort was used for the primary efficacy analyses and excluded any partners found to be HIV positive at the time of randomisation
- Index subject cohort – used for evaluating correlates of efficacy, drug sharing and transmitted resistance

The primary analysis was stratified by site. The only covariate included in the model was the randomisation group. Analyses of the primary study endpoint were performed to test the rate of HIV-1 acquisition, both combined and separately, between each TDF and FTC/TDF group versus placebo using a Cox regression analysis. The randomisation group was the only predictor used in each analysis. The same reference group (placebo) was used for each study drug group; however, no multiple comparison adjustment was performed.

Individuals who dropped out of the study, were terminated, refused further testing prior to completion of follow-up or died prior to completion of follow-up were non-informatively censored as of their last HIV-1 test. Following death, subjects were assessed as not expected at all follow-up visits. For all other early terminations, subjects were assessed as expected at all follow-up visits, but were not retained. No imputations for missing data were made in the analyses.

The primary endpoint was HIV-1 detection, calculated using the date of first site-detected seroconversion, which was assessed monthly. The event time for HIV infection was the time of the first site-detected positive HIV-1 antibody test. Final determination of seroconversion and whether it

happened after enrolment was based on the Endpoint Committee's assessment. Consistent with an ITT analysis, women who were taken off drug because of pregnancy and breastfeeding, subjects who missed follow-up visits and non-adherent subjects were included in the analysis within their original randomisation group if endpoint information was available within the protocol-specified timeframe of follow-up.

The additional post-study follow-up after the final on-drug visit at 4 and 8 weeks after cessation of study drug was not included in on-study follow-up time so test results from this period were excluded from the primary analysis.

If multiple positive tests were available for an individual, the first positive confirmed test was used as the time of seroconversion, unless the endpoints review committee determined another visit should have been used. Follow-up time for subjects who never seroconverted to HIV-1 was measured from randomisation to last on-study negative HIV-1 test.

Two formal statistical comparisons between each active study drug and the placebo were performed. The first comparison considered the hypothesis of any efficacy (testing the null hypothesis of the hazard ratio [HR] being 1). The second comparison considered the hypothesis of less than 30% efficacy (testing the null hypothesis of the HR being 0.7); this comparison corresponded to the premise for which the study was powered. The significance level for rejection was set at $p = 0.05$ (2-sided). Thus, 1-sided tests with $\alpha = 0.025$ were used for comparison of each active study drug group with the placebo, with no adjustment for multiple comparisons.

The DSMB was established as a group of independent experts who advised the sponsor and the study investigators. The primary responsibility of the DMSB was to periodically review and evaluate the accumulated study data for safety, study conduct and progress and efficacy. The DSMB also made recommendations to the study investigators and the sponsor concerning the continuation, modification or termination of the study. The DSMB considered study-specific data, along with all relevant background knowledge about the disease, study drugs and/or patient population under study. The DSMB maintained the confidentiality of its internal discussions and activities, as well as the contents of all provided reports. Prior to study initiation, the DSMB defined its stopping guidelines, procedures for unblinding, event triggers that would call for an unscheduled review and voting procedures. Guidelines for evaluation of futility were also developed. During the study the DSMB reviewed all reported data at meetings that occurred approximately every 6 months. Prior to study initiation, the schedule of efficacy review was established. It was anticipated that there could be 2-3 interim scheduled efficacy reviews. In developing procedures related to study continuation or discontinuation as part of the DSMB charter, several scenarios were considered, including:

- Decision rules for stopping if both active study drug groups demonstrated efficacy
- Decision rules for stopping the study if both active study drug groups demonstrated substantial AE rates, compared with the placebo group, including rare but significant AEs
- Demonstration of efficacy in 1 of the 2 active study drug groups without (or prior to) demonstration of efficacy in the other active study drug group, including parameters for the level of efficacy to stop follow-up in one group early while continuing follow-up of the remaining group
- Demonstration of efficacy in another ongoing PrEP study
- Differential rates of AEs, including rare but significant AEs, in either or both of the active study drug groups
- Lower than expected HIV-1 incidence rates, lower than expected study drug adherence or higher than expected loss to follow-up in any of the study groups
- Possible futility in one or both of the active study drug groups

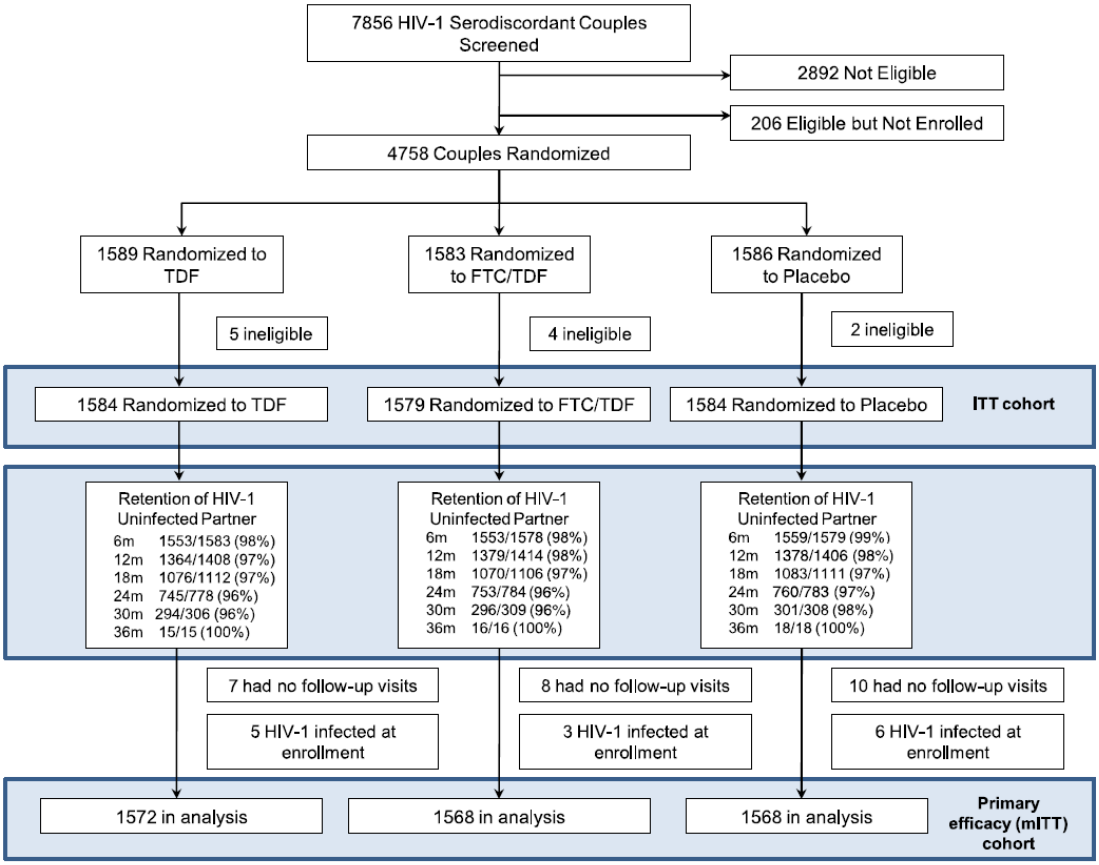
Interim monitoring stopping boundaries for proven efficacy were established based on ruling out efficacy lower than 30%.

Results – Partner's PrEP

Protocol amendment version 3.0 was applied at study initiation. Version 3.0 was amended 7 times between 03 November 2008 and 14 February 2011, mostly for administrative issues. Substantial changes included adding the Jinja site, adding PBMC collection and increasing the study sample size from 3900 to 4700 (see above).

There were 4758 couples that met the selection criteria from which ~1580 ITT subjects were assigned to each treatment group. Retention of the partner subjects in each study drug group was at least 96% over the course of the study. There were 7830 person-years of follow-up for assessment of HIV-1 incidence accrued, with a median 23 months of follow-up (IQR 16–28 months).

Figure 5. CO-US-104-0380: Disposition of Study Subjects



The demographic and baseline characteristics of the enrolled couples were similar across study groups. Partner subjects were predominantly male (61%–64%) with median age of 33 to 34 years. These subjects generally had an income (at least 78%), had a median education of 7 years and >90% had not had sex with an outside partner in the eligibility period. In general the presence of income was lower among the index subjects but was still 67%–68%. Among the index subjects, the median baseline CD4 count ranged from 491 to 499 cells/mm3 and the median plasma HIV-1 RNA level was 3.9 $\log_{10}$ copies/mL.

Couples reported a median of 4 sex acts with 26% to 28% unprotected sex during the month prior to enrolment. Most were married (97%–98%) with a median partnership duration of 7.0 to 7.1 years. HIV-1 sero-discordance had been detected within a median of 0.4–0.5 years prior to study. Similar percentages of partner and index subjects (6%–9%) had a curable STI at enrolment and none was pregnant.

Study medication was dispensed at 96% of all attended visits. The most common reasons for not dispensing study medication at any visit were pregnancy (30%), possible seroconversion (22%) and subject refusal (16%). Renal toxicity accounted for 10% of the reasons for withholding study drug, while other AEs accounted for 11% of the reasons.

Overall, 98% of the dispensed study bottles were returned and 97% of the dispensed study tablets were calculated to have been taken (based on pill counts of returned, unused study drug). At 15% of visits it was reported that at least 1 dose of study drug had been missed during the prior month, but missing 2 or more consecutive doses was reported at only 4% of the visits. Three partner subjects reported that they thought their index partner used their study drug. Overall, 87% of the visits at which adherence was calculated showed study drug coverage of 90% or more.

Eleven partner subjects were ineligible and were therefore excluded from the ITT cohort. As of 10 July 7830 person-years of follow-up time had accumulated in the 4747 eligible HIV-1 partner subjects. During this time, 99 site-reported seroconversion events were recorded. Three of the 99 were determined by the study endpoint committee based on central laboratory confirmatory testing to be false positives. It was later determined that 14 site-reported seroconversion events occurred in partner subjects who were HIV-1 RNA PCR-positive at enrolment, leaving 82 seroconversion events in the mITT cohort and a rate of 1.05 per 100 person-years (95% confidence interval [CI]: 0.83–1.30).

In the mITT cohort, both TDF and FTC/TDF demonstrated significant efficacy compared with placebo while TDF and FTC/TDF were not significantly different from one another.

Table 20. CO-US-104-0380: HIV-1 Seroincidence 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 21. 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

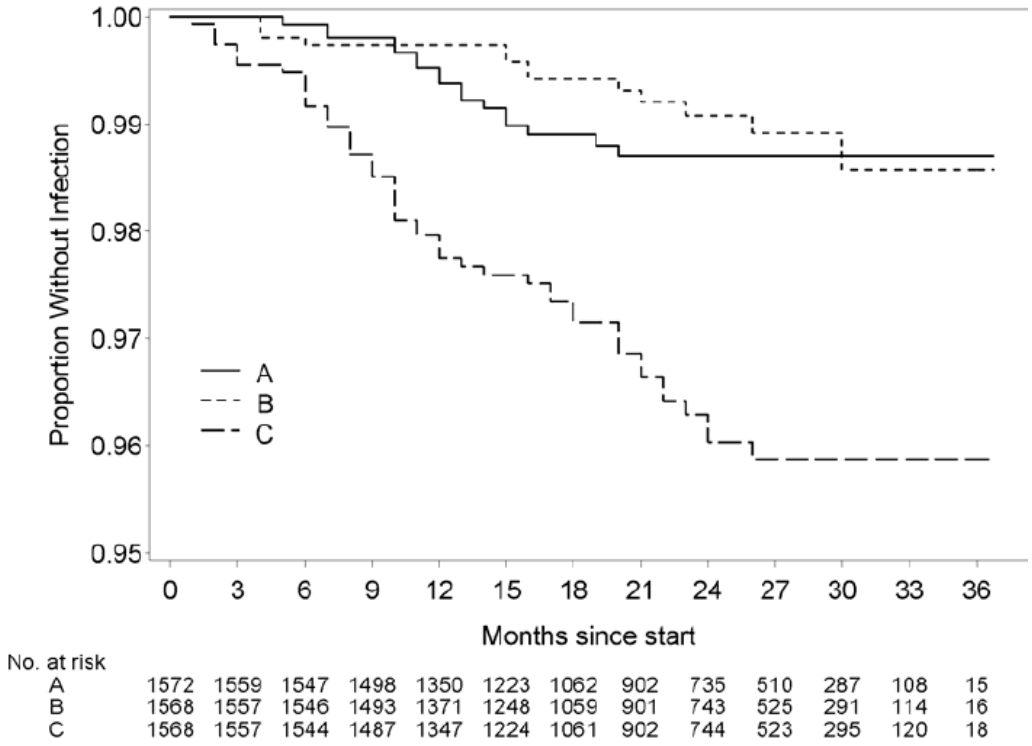
a P-value using Cox's proportional hazards model for the active study drug relative to placebo.

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).

Both TDF and FTC/TDF ruled out efficacy of less than 30% relative to placebo, thereby meeting the predefined primary efficacy endpoint (p = 0.0031 and p = 0.0004, respectively). The HRs for TDF relative to placebo indicated a 67% reduction (95% CI: 44%–81%) in risk of HIV-1 acquisition, and the HRs for FTC/TDF relative to placebo indicated a 75% reduction (95% CI: 55%–87%) in risk of HIV-1 acquisition. In general, results of the efficacy analyses obtained using the ITT cohort were similar to those obtained using the mITT cohort.

The Kaplan-Meier curves for the proportion of partner subjects without infection relative to the months since the start of the study show the proportion remaining without HIV-1 acquisition by study drug group over time. Curves derived from the ITT and mITT cohorts were similar.

Figure 6. CO-US-104-0380: Kaplan-Meier Curves of HIV-1 Survival (mITT)



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

Overall, similar protective trends for TDF and FTC/TDF compared with placebo were observed in each sub-group including gender.

Table 22. 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.

The test for homogeneity of treatment effect was statistically significant for the difference in the effect of TDF versus placebo in the subgroup defined by CD4 level of the index subjects at enrolment (HR = 0.79 for < 350 vs. 0.21 for ≥ 350 cells/mm3; p = 0.03) and in the subgroup defined by the partner's report of unprotected sex at enrolment (HR = 0.13 with unprotected sex vs. 0.47 without; p = 0.05).

Using a case-cohort analysis, detection of tenofovir in plasma samples was compared for partners who received active therapy and did or did not acquire HIV-1. The evaluation included all 17 who had taken TDF and 12/13 who had taken FTC/TDF. The cohort comparison included 100 randomly-selected partner subjects from each of the TDF and FTC/TDF groups (200 subjects in total). Overall, 128 samples were

collected from the case subjects and 902 samples from the controls. Cases were much less likely than controls to have detectable TFV in plasma (actual concentrations were not determined).

Table 23. 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

Percentages of HIV-1 seronegative partners who reported having sex without condoms with their HIV-1 infected partner during the prior month decreased from 27% at baseline to 13% and 9% at 12 and 24 months, respectively. The results were similar across study drug groups. The percentages who reported having sex with an outside partner for any prior month increased from 9% (13% men, 0.4% women) at baseline to 30% (42% men, 9% women) during the study, with similar percentages across study drug groups.

Plasma samples for HIV-1 antiretroviral resistance testing were obtained at the visit at which HIV-1 seroconversion was detected (at which time study medication was withdrawn) and at a second visit within 1 month of seroconversion. An assessment was possible for 92/96 subjects who seroconverted. Two of the 8 in the TDF and FTC/TDF groups found to be infected at randomisation developed resistance to study medications, including one with the K65R mutation and one with the M184V mutation. No subjects who acquired HIV-1 after randomisation either of these mutations but one in the TDF group developed a rare RAM (K65N). Four subjects had virus with mutations K103N or V016A conferring high-level resistance to NNRTIs (2 TDF group, 1 FTC/TDF, 1 placebo).

Approximately 30% of the index subjects reported using ART at some time during study, including short-term use for prevention of mother to child transmission of HIV-1.

Partners PrEP OLE (Baeten et al. Lancet Infectious Diseases 2014)

On July 10 2011 the DSMB recommended that the placebo group should be discontinued because of the demonstration of efficacy reported above. The DSMB recommended that follow-up of subjects assigned to the active PrEP groups be continued in accordance with protocol-defined procedures and that subjects originally assigned to the placebo group should be offered re-randomisation (in a 1:1 ratio) to one of the two treatments in a blinded fashion. At the same time, all study subjects were informed of the interim efficacy results and those assigned to TDF or Truvada were told they were on active treatment but not which one. Thus, all subjects continuing on treatment regardless of the initial randomisation group were kept unaware of the exact treatment they received.

By this means the OLE continued until 30 Dec 2012 and the cumulative data include an additional 3569 p-y of follow-up and 26 additional HIV-1 infections.

Overall, 89% of 1418 placebo subjects consented to re-randomisation to TDF or FTC/TDF. During the entire study there were 64 HIV-1 seroconversion events in individuals assigned to active PrEP (39 TDF and 25 Truvada). Of the 26 (41%; 17 TDF and 9 Truvada) infections that occurred after 10 July 2011 there were 12 subjects (8 TDF; 4 Truvada) for whom the archived plasma showed that they had been infected at the time of initial randomisation (8) or re-randomisation (4). Thus, 52 infections occurred after

randomisation including 31 in the TDF arm (0.71 per 100 p-y) and 21 in the Truvada arm (0.48 per 100 p-y); not significant (HR 0.67, 95% CI 0.39–1.17; p=0.16). HIV-1 incidences in subjects receiving PrEP were similar before and after 10 July 2011. HIV-1 incidence in the placebo group before 10 July 2011 was 2 per 100 p-y. Subgroup analyses also showed no significant differences between active treatments as shown below.

	Tenofovir disoproxil fumarate group			Emtricitabine plus tenofovir disoproxil fumarate group			Hazard ratio for emtricitabine plus tenofovir disoproxil fumarate versus tenofovir disoproxil groups (95% CI)	p value
	Number	Events	Rate*	Number	Events	Rate*		
Overall population								
Modified intention to treat (primary analysis)	2207	31	0·71	2208	21	0·48	0·67 (0·39–1·17)	0·16
Intention to treat	2215	39	0·89	2212	25	0·57	0·64 (0·39–1·06)	0·08
Sex of HIV-1 seronegative partner								0·16
Male	1375	16	0·59	1404	7	0·25	0·42 (0·17–1·03)	
Female	832	15	0·90	804	14	0·88	0·96 (0·46–1·98)	
Age of HIV-1 seronegative partner								0·43
<25 years	233	5	1·07	239	8	1·79	1·71 (0·56–5·26)	
≥25 years	1974	26	0·66	1969	13	0·33	0·49 (0·25–0·96)	
Unprotected sex with study partner in the month before enrolment in the study								0·71
None	1607	20	0·62	1631	14	0·43	0·67 (0·26–1·72)	
Any	600	11	0·95	577	7	0·62	0·68 (0·34–1·34)	
Country								0·15
Kenya	961	10	0·52	967	11	0·57	1·08 (0·46–2·55)	
Uganda	1246	21	0·85	1241	10	0·40	0·47 (0·22–1·01)	
Circumcision status of HIV-1 seronegative men								0·44
Circumcised	753	9	0·61	732	5	0·34	0·56 (0·19–1·67)	
Uncircumcised	620	7	0·56	672	2	0·15	0·27 (0·06–1·29)	
Plasma HIV-1 RNA level of HIV-1 seropositive partner								0·80
<50 000 copies/mL	1798	23	0·64	1794	15	0·42	0·64 (0·34–1·23)	
≥50 000 copies/mL	375	8	1·06	383	6	0·79	0·74 (0·26–2·14)	
CD4 count of HIV-1 seropositive partner								0·09
250–350 cells/μL	425	13	1·53	424	4	0·47	0·31 (0·10–0·96)	
≥350 cells/μL	1782	18	0·51	1784	17	0·48	0·93 (0·48–1·81)	

The p values for the modified intention-to-treat and the intention-to-treat analyses apply to the hypothesis of any evidence of efficacy (ie, testing against a null hypothesis of zero efficacy); p values for the other comparisons correspond to a test for significant interaction in the site-stratified Cox proportional hazards model. Rerandomised participants from the placebo group entered the risk set at the study time corresponding to their assignment to active pre-exposure prophylaxis. *Events per 100 person-years of follow-up.

Table 2: **HIV-1 incidence in the tenofovir disoproxil fumarate and emtricitabine plus tenofovir disoproxil fumarate groups overall and by subgroups**

In a per-protocol sensitivity analysis of the periods when study medication was dispensed, 33 HIV-1 infections occurred (20 TDF; 0.52 per 100 p-y and 13 Truvada; 0.33 per 100 p-y [HR 0.63, 95% CI 0.31–1.27; p=0.20]). Results were similar for the comparison of HIV-1 incidence in the two PrEP groups restricted to periods with a product adherence of at least 80%.

Tenofovir was detected in a plasma sample obtained during the visit at which HIV-1 seroconversion was detected in 14 (27%) of 51 who acquired HIV-1 compared with 1047 (78%) of 1334 samples from subjects who did not acquire HIV-1 (see below). Having detectable plasma TFV was associated with an estimated relative risk reduction for acquiring HIV-1 of 85% for TDF and 93% for Truvada.

In most individuals, PrEP use was consistent during follow-up, with a slight decrease in use over time. Subjects who acquired HIV-1 generally seroconverted during PrEP non-use.

	Tenofovir detected			HIV-1 protection (detection versus no detection of tenofovir)	
	Cases at seroconversion	Cases before seroconversion	Cohort	Hazard ratio (95% CI)	p value
Tenofovir disoproxil fumarate group	11/31 (35%)	102/149 (68%)	545/667 (82%)	0·15 (0·06–0·37)	<0·0001
Emtricitabine plus tenofovir disoproxil fumarate group	3/20 (15%)	42/81 (52%)	502/667 (75%)	0·07 (0·02–0·23)	<0·0001

Data are n/N (%), unless otherwise indicated. Cases were participants who acquired HIV-1 infection after randomisation: 31 in the tenofovir disoproxil fumarate group and 20 in the emtricitabine plus tenofovir disoproxil fumarate group (one individual in this group did not have an available sample and was found to have seroconverted to HIV-1 23 months after randomisation after not having attended other follow-ups). The cohort comparison included individuals from the tenofovir disoproxil fumarate and emtricitabine plus tenofovir disoproxil fumarate groups who were randomly selected from the entire study population. Plasma samples for months 1, 3, 6, 12, 18, 24, 30, and 36 after randomisation or rerandomisation were tested from all cases and cohorts; additionally, for cases, a sample from the visit at which HIV-1 seroconversion was detected was tested.

Table 3: **Detection of tenofovir in plasma and HIV-1 prophylactic effect**

Viral RNA was amplified for assessment of ART resistance from 60/64 (94%) who acquired HIV-1. Two of the 8 subjects retrospectively found to HIV-1 infected at initial randomisation developed HIV-1 with resistance to study medications (one K65R and one M184V mutation). Of the 52 who acquired HIV-1 after randomisation or re-randomisation, 48 had resistance data and mutations K65R, K70E, M184V or M184I were not detected.

The authors concluded that the results did not rule out the potential for a slight difference in HIV-1 protection with TDF vs. Truvada.

Analysis performed across trials (pooled analyses and meta-analysis)

Resistance

Trial	Drug	NRTI Resistance/Infections	
		On Treatment	Baseline
iPrEx	FTC/TDF	0/48	2/2 (**M184V***, M184I)
Partners PrEP	FTC/TDF	0/12	1/3 (**M184V***)
	TDF	0/15	2/5 (**K65R***, D67N+K70R)
TDF2 (CDC)	FTC/TDF	0/9	1/1 (**A62V+K65R+M184V***)

*In pre-treatment sample

iPrEx – Ten subjects had HIV-1 RNA detected in pre-treatment specimens after they were enrolled, of which 3 (2 Truvada) had FTC resistance but none had TFV resistance. No resistance was detected in 48 post-infection samples.

Partner's PrEP – Eight subjects had HIV-1 RNA detected in pre-treatment specimens after they were enrolled of which one in the TDF group had the K65R mutation and one in the Truvada group had the M184V mutation. No resistance was detected in 24 post-infection samples.

CDC TDF2 – one subject had high-levels of K65R, M184V and A62V (conferring cross-NRTI resistance) but this subject had entered the study with unrecognised acute HIV infection. The study team informed the MAH that the subject had received approximately 5 months of blinded Truvada before HIV was confirmed.

- No resistance was observed in **FHI PrEP** for 1 of 2 subjects in the TDF group who seroconverted and for whom a sample was available.
- None of the female subjects who acquired HIV-1 infection developed TFV resistance in **CAPRISA 004**.
- No subject receiving TDF became infected in **CDC 4323**.

Persistence of efficacy

To date, long-term efficacy data on use of Truvada for PrEP do not indicate any loss of effect or detrimental impact on sexual risk factors. The iPrEx OLE study supported efficacy of 84% in subjects who were modestly adherent (2 to 3 doses per week) and 86-100% in subjects with higher adherence (≥ 4 doses per week). Self-reported sexual risk behaviour declined during the study. For example, 34% in the Truvada C/TDF group reported URAI at study start compared with 25% at the end of the OLE.

Supportive studies

Up to the time of the US filing, the main studies in which daily oral Truvada had been evaluated for PrEP were as shown below. The three studies for which CSRs are included in the current application dossier are ringed in orange. The CDC4323 study was primarily designed to assess safety although it also reported on HIV-1 infection rates. Efficacy data from the CDC TDF2 study are described in the summary of efficacy and results are outlined below.

Phase III, IIb				
iPrEx	NIH/DAIDS	Brazil, Ecuador, Peru, South Africa, Thailand, USA	**Adult MSM at high risk**	Daily oral **FTC/TDF**
Partners PrEP	Univ. of Wash	Kenya, Uganda	**Serodiscordant couples**	Daily oral TDF or **FTC/TDF**
CDC TDF2	CDC	Botswana	**Adult heterosexual men and women**	Daily oral **FTC/TDF**
FEM-PrEP	FHI	Kenya, South Africa, Tanzania	**Adult women at high risk**	Daily oral **FTC/TDF**
VOICE	NIH/DAIDS	Uganda, South Africa, Zimbabwe	**Adult women**	Daily oral **FTC/TDF** or TDF or tenofovir vaginal gel
Phase II				
CDC 4323	CDC	USA	**Adult MSM**	Daily oral TDF (Immediate vs. delayed treatment)
FHI PrEP	FHI	Ghana, Cameroon, Nigeria	**Adult women at high risk**	Daily oral TDF

The **FEM-PrEP and VOICE** studies were terminated early. Failure to show efficacy was ascribed to low adherence.

The **FHI PrEP** study evaluated TDF only. It enrolled 936 HIV-negative women at high HIV risk in Ghana, Cameroon and Nigeria who were randomised 1:1 to daily TDF or placebo in a double-blind design. There were two seroconversion events in the TDF arm (0.86 per 100 person-years) and 6 in the placebo arm (2.48 per 100 person-years). This gives a rate ratio 0.35 (95% CI: 0.03 – 1.93). However, the Cameroon

and Nigeria sites closed early due to controversy and logistic issues, respectively, and the trial was not powered to demonstrate efficacy.
Studies that evaluated only topical usages (such as CAPRISA) are not relevant to daily oral administrations and are not described.

Since the US approval of Truvada for PrEP there have been very many additional PrEP trials initiated using a wide range of strategies including further evaluation of oral Truvada. One of these (PROUD) is described briefly based on publications only.

CDC 4323 (CO-US-104-0277)

This was a Phase 2 study in MSM sponsored by CDC. The MAH has not received a clinical study report or final datasets from the CDC 4323 study team but provides a report on the most relevant study information that was shared between CDC and the MAH in 2010 and also publications of the study.

This was a randomised double-blind placebo-controlled trial with four equal groups who received TDF 300 mg orally once daily or matching placebo, either immediately or after a nine-month delay. Subjects were followed for two years. It was determined that overall sample size of 400 would be sufficient to have 72% to 90% chance of observing at least 5 severe AEs in each treatment group, given 3% to 4% baseline risk of severe AE, two-year follow up, and nine-month lead in period for a half of the sample. The delayed arms were designed to help assess potential changes in risk behaviour associated with taking study drug and the results were reported separately.

Participants were recruited in San Francisco, Atlanta and Boston. Subjects were to be healthy biologic males aged 18-60 years who reported any anal sex with another male in the preceding 12 months. They were to be HIV-1 negative by whole blood rapid EIA and HBsAg negative. They were to have calculated $CrCL_{CG}$ ≥70 mL/min with normal haematological, biochemical and urinalysis profiles. Exclusion criteria included active untreated syphilis; uncontrolled hypertension; mutual monogamy for over one year with an HIV-negative partner; history of chronic renal disease; osteoporosis, osteomalacia or osteopenia; bone mineral density (BMD) Z score < -2.5 at the total spine, total hip or femoral neck on screening (DEXA scans done at SFO study site only); current treatment for secondary causes of low bone mineral density.

After randomisation subjects were followed at 1, 3, 6, 9, 12, 15, 18, 21 and 24 months post- enrolment. Delayed arm recipients had an additional visit at ten months (after the first month on study drug). Visits included behavioural assessment via ACASI and risk reduction and adherence counselling. AEs and laboratory abnormalities (except serum creatinine) were graded using the DAIDS toxicity grading tables (January, 2004). Serum creatinine elevations were graded according to the Gilead Sciences Modified NIAID Common Toxicity Grading Scale, with the additional modification that Grade 1 was defined as ≥0.5 mg/dL over baseline. For confirmed Grade 1 or 2 creatinine elevations (2.1-3.0 mg/dL), study drug was withheld and restarted with return of the serum creatinine to within 0.3 mg/dL above baseline. Confirmed recurrence of Grade 1 or 2 elevations led to permanent discontinuation of study product. Confirmed Grade 3 (3.1-6.0 mg/dL) or Grade 4 (>6.0 mg/dL) elevations led to permanent discontinuation. There were 15 pre-defined AESIs.

HIV testing with an FDA-approved rapid test was performed at each visit, followed by an approved confirmatory test for preliminary positives. Participants with positive rapid tests were immediately discontinued from study drug. Confirmed seroconversion led to follow-up every three months for an additional year for safety assessments and referral for appropriate clinical care.

Adherence was assessed by pill counts at each visit, Medication Event Monitoring System (MEMS) caps and self-reporting via ACASI. Pill count or MEMS data were used to estimate exposure to study drug (ESD).
For pill count and MEMS adherence estimates the time covered by directed temporary drug interruptions were excluded from denominators.
All participants were included in baseline analyses. The Treatment Emergent (TE) cohort included all subjects dispensed study drug. Time in the TE cohort began with first dispensing and ended with the first occurrence of completion of follow-up (24 months), 30 days after date of permanent drug interruption or 30 days after last recorded study visit.
Analyses considered each individual AE as an outcome variable regardless of relatedness to study drug and compared treatment groups by time to first reported AE as well as by occurrence of recurrent AEs.
In univariate analyses, simple association of each AE with treatment assignment was studied by modelling time to first reported AE using Cox proportional hazards regression. Furthermore, incidence of recurrent AEs was compared between groups by modelling AE count using generalised estimating equation (GEE) formulation of Poisson regression with total follow-up time used as an offset variable.
In multivariable analysis, in addition to treatment assignment as the main predictor or interest the following covariates were included: study site, immediate or delayed arm assignment, age, race, ethnicity and EST. Multivariable comparison of time to first AE was performed using the extended Cox model which accommodated time-dependent covariate EST.
To avoid underestimating risk, time to first event analysis was performed by selecting the lowest value of ESD between MEMS and pill count estimates calculated for each visit interval. Lowest values were was dichotomised at 80%. The choice of such a threshold was arbitrary given currently evolving knowledge on PrEP effectiveness and absence of established recommendations. For analyses of recurrent events, a summary measure of ESD was obtained by taking the mean value of all available visit-specific estimates for each participant. These were also dichotomised at 80%.
All statistical tests were two-sided and interpreted at alpha=0.05 level of significance. Statistical test results were not adjusted for multiplicity.

Results – CDC 4323

There were 201 randomised to TDF and 199 to placebo of which 331 (83%) completed all study visits. A higher proportion of participants completed all study visits in SFO (180/200; 90%) compared with Atlanta (91/121; 75%) and Boston (60/79; 76%) (p=0.0006). There were 373 (93%) in the TE cohort. All 200 in the immediate arms initiated study drug, compared with 173 (87%) of 200 delayed arm participants (p<0.001) and 325/373 (87%) completed all study visits.
Demographic and selected baseline characteristics were distributed similarly among the four study arms except for higher proportions of African-American race in the placebo arms.

		TDF intermediate (N=101)	Placebo intermediate (N=99)	TDF delayed (N=100)	Placebo delayed (N=100)	p
Age in years, median (range)		38 (20, 60)	39 (18, 60)	39 (18,59)	36 (20, 57)	0.517
Race, n (%)	White	79 (78.2)	65 (65.7)	81 (81.0)	68 (68.0)	0.018
	African American	13 (12.9)	19 (19.2)	10 (10.0)	18 (18.0)	-
	Asian/Pacific Islander	6 (5.9)	3 (3.0)	4 (4.0)	1 (1.0)	-
	Other	3 (3.0)	12 (12.1)	5 (5.0)	13 (13.0)	-
Ethnicity, n (%)	Hispanic	10 (9.9)	10 (10.1)	6 (6.0)	10 (10.0)	0.690
	Non-hispanic	91 (90.1)	89 (89.9)	94 (94.0)	90 (90.0)	-
Education, n (%)	Never graduated from high school	3 (3.0)	2 (2.0)	3 (3.0)	1 (1.0)	0.829
	High school graduate or GED	7 (6.9)	11 (11.1)	7 (7.0)	9 (9.0)	-
	Same college	30 (29.7)	35 (35.4)	38 (38.0)	31 (31.0)	-
	College graduate	61 (60.4)	51 (51.5)	52 (52.0)	59 (59.0)	-
Site, n (%)	Atlanta	31 (30.7)	30 (30.3)	30 (30.0)	30 (30.0)	1.000
	Boston	20 (19.8)				-
	San Francisco	50 (49.5)				-
Male partners last 3 mo, median (IQR)		3 (2,8)	3 (2, 6)	4 (2, 9)	4 (3, 7.5)	0.387
Any unprotected receptive anal sex with male last 3 mo, n (%)		32 (31.7)	35 (35.4)	28 (28.0)	30 (30.0)	0.718

There were 178 temporary drug interruptions among the 373 participants (84 on TDF and 94 on placebo). The median length of temporary drug interruptions for TDF was 37 days (range 2-428 days) vs. 47 days (range 1-533 days; p=0.055) for placebo. There were 66 permanent drug interruptions.

Median exposure to study drug estimated from pill count was 92% (range 79-98 percent). Estimated exposure on drug from MEMS was 77% (range 57-92 percent). When periods of directed drug interruption were removed from this calculation to estimate adherence, results were similar (93% and 79%, respectively).

Figure 7. Correlations between TOD estimates by time in study

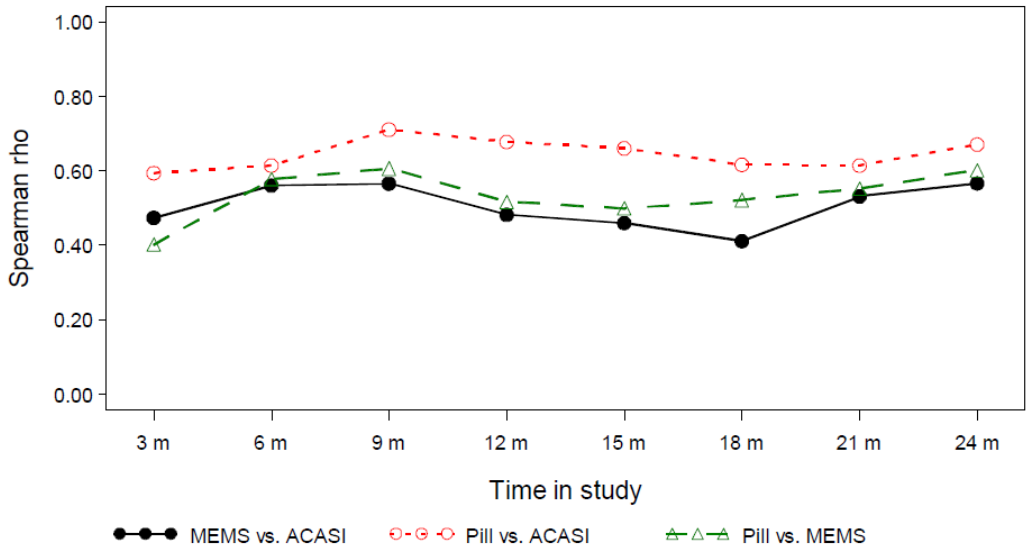
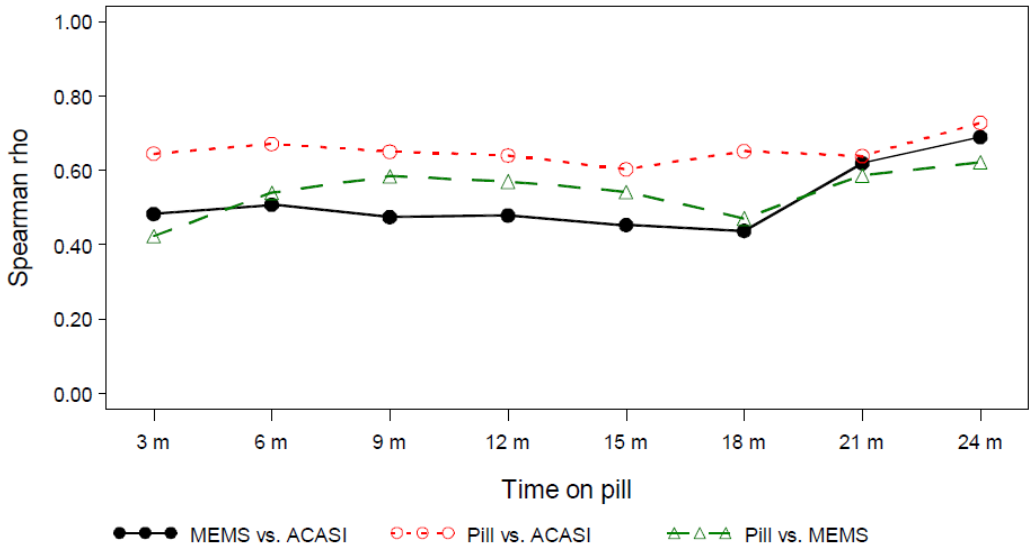


Figure 8. Correlations between TOD estimates by time on pill



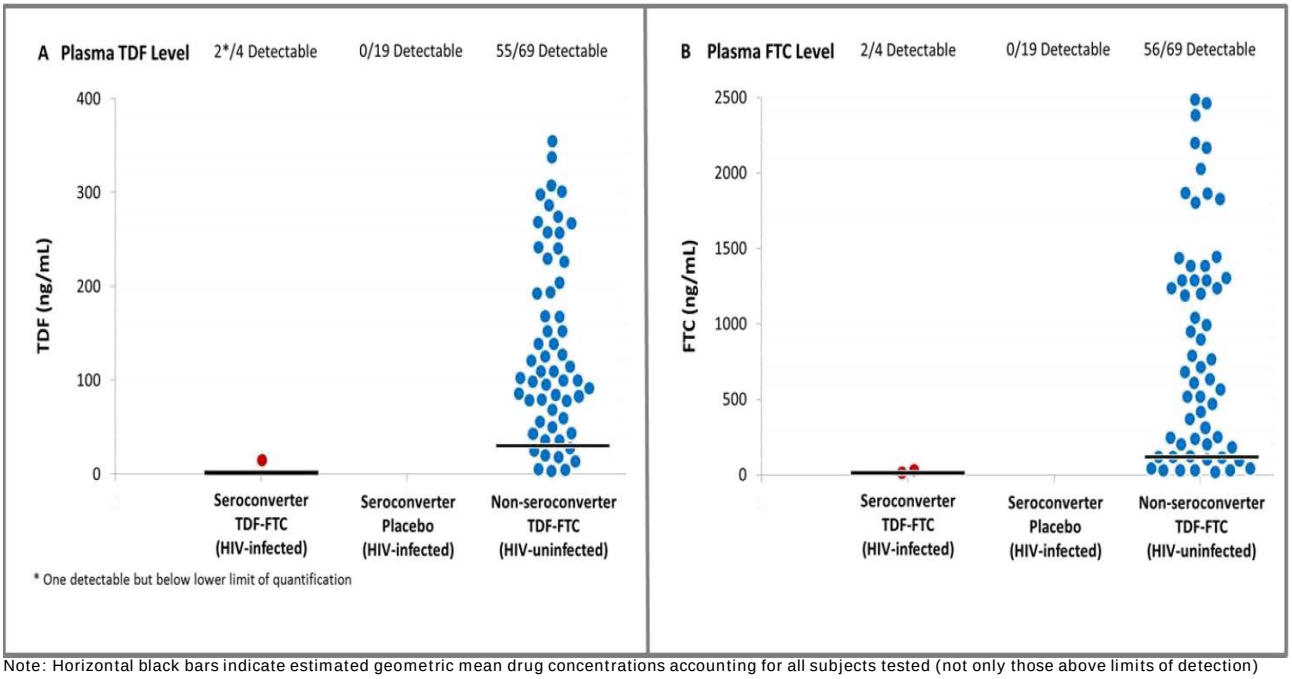
There were 7 seroconversion events, all in subjects randomised to placebo. Three occurred while subjects were taking placebo, three occurred in delayed arm subjects who had not yet started study drug and one was discovered in a screen negative subject found to be seropositive at the one-month visit with a positive confirmatory Western blot. Viral load in a stored specimen from the enrolment visit of this subject was 1,770 copies/mL. No K65R mutations occurred in seroconverting subjects.
When comparing those subjects who began TDF at enrolment with the groups that commenced treatment at 9 months after enrolment, there was no evidence of sexual risk compensation during the study. There were greater decreases in the number of occurrences of unprotected anal sex during the first 9 months in the former group vs. the latter group (p = 0.04). The plasma concentrations of TDF were not available at the time of these analyses and the assessor does not find them reported in the literature.

CDC TDF2

The study was conducted in high-risk heterosexual young men and women. FTC/TDF had an overall protective efficacy of 62.2% (95% CI: 21.5%-83.4%; p = 0.013 vs. placebo [mITT]). In the as-treated population, where follow-up was censored at 30 days after the last reported dose of study drug, FTC/TDF had a protective efficacy of 77.9% (95% CI: 41.2%-93.6%; p < 0.001).
In the overall analysis of the 33 subjects who seroconverted (mITT; 9 Truvada and 24 placebo), the number of men using PrEP who became infected with HIV was significantly smaller in the FTC/TDF group than in the placebo group (p = 0.026); the treatment group difference for women in the overall analysis was not significant (p = 0.107). In the as-treated analysis of the 23 subjects who seroconverted and reported taking study drug within 30 days prior to seroconversion, the number of women using PrEP who became infected with HIV was significantly smaller in the Truvada group than in the placebo group (p = 0.021); the treatment group difference for men in the as-treated analysis was not significant (p = 0.065). While the p-value for men in the as-treated analysis did not reach significance, the study was not powered to draw conclusions based on gender.
Subjects who received Truvada showed correlations between treatment adherence and protection against HIV-1 infection. Among participants randomised to Truvada, TFV was detected in the plasma of 50% of seroconverting subjects at the seroconversion visit and in 79.7% of uninfected controls at similar time

points. Similarly, FTC was detected in 50% and 81.2% of seroconverting subjects and uninfected subjects, respectively.

Figure 9. CDC TDF2: Plasma drug levels (tenofovir and emtricitabine) levels by treatment group seroconversion status



Note: Horizontal black bars indicate estimated geometric mean drug concentrations accounting for all subjects tested (not only those above limits of detection) and according HIV seroconversion status.

Among those with measurable drug levels, the GMCs for plasma TFV were significantly lower in seroconverting subjects vs. uninfected subjects (0.30 ng/mL [95% CI 0.01-8.02 ng/mL] vs. 30.58 ng/mL [95% CI 16.25-57.51 ng/mL]; p = 0.007). The plasma FTC GMC also differed significantly between the two groups (0.54 ng/mL [95% CI 0.01-25.32 ng/mL] vs. 103.3 ng/mL [95% CI 45.44-234.86 ng/mL]; p = 0.009). Neither TDF nor FTC was detected in plasma of the 19 who seroconverted on placebo.

Other studies of Truvada for PrEP

The HIV Prevention Research and Development Database lists numerous completed, ongoing and planned studies involving the use of Truvada for PrEP in various at-risk populations and in one or both genders. Some of these have already reported important results, including the PROUD and IPERGAY studies. IPERGAY concerned “on demand” use of Truvada and not daily prophylaxis and this study has not been included or discussed in this application and as a consequence is not described.

PROUD study in MSM

The MAH did not provide a CSR for this study conducted by the UK MRC and published in 2015. The MAH part funded this study. Since the study evaluated the use of Truvada in MSM a short summary of this study is merited in support of the iPrEx study results. In contrast to iPrEx, PROUD was open-label in a deliberate attempt to assess efficacy in the setting in which PrEP would be introduced into a region/population in which PrEP was not a routine part of risk management in MSM.
This open-label randomised study was conducted at 13 sexual health clinics in England and enrolled HIV-negative MSM who reported anal intercourse without a condom in the previous 90 days. Participants were randomly assigned (1:1) to receive daily Truvada immediately or after a deferral period of 1 year.

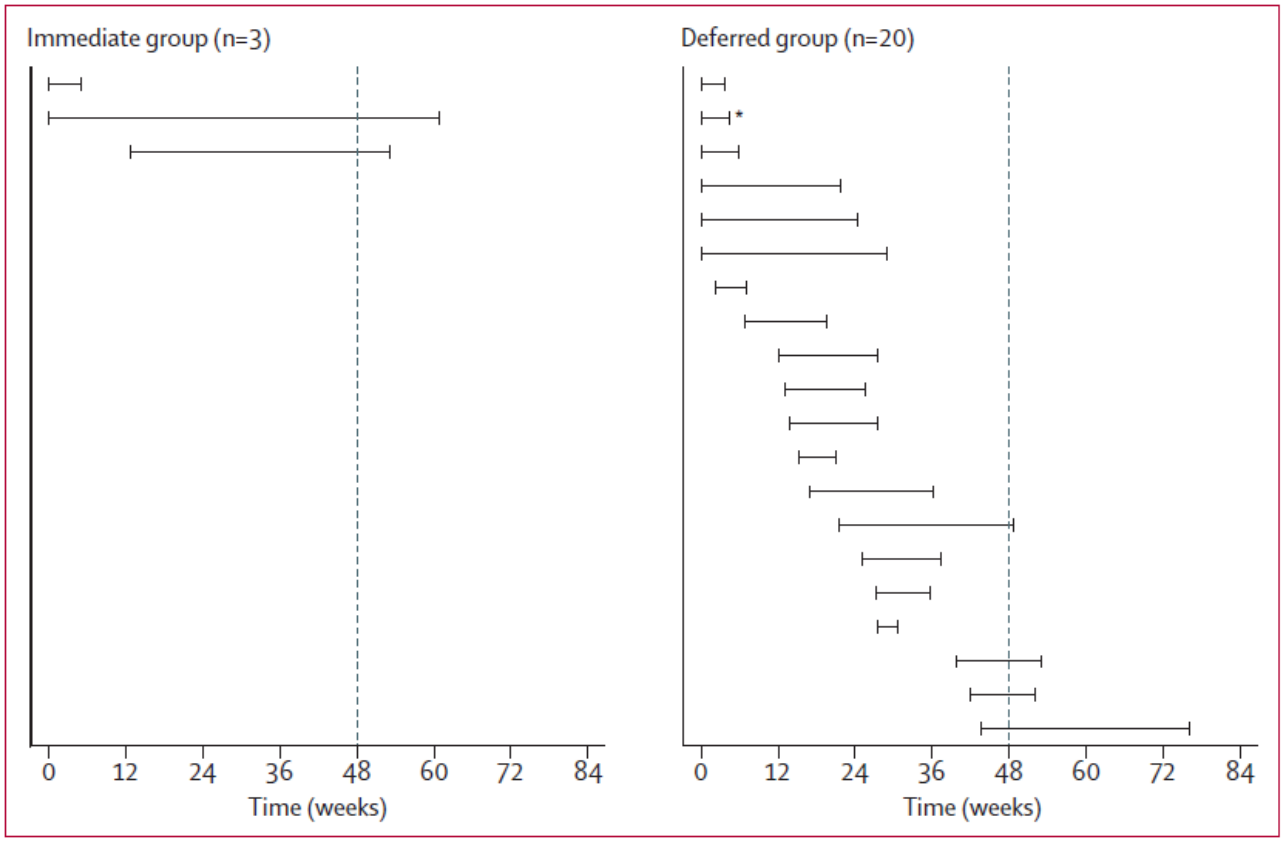
Randomisation was conducted using web-based access to a central computer-generated list with variable block sizes (4, 6 or 8; stratified by clinical site). Follow-up was quarterly.
The study was conducted in a fashion intended to mimic real-life use so that results from local clinical laboratories were used and there was no study screening visit. There was an enrolment visit at which the relevant data were collected and eligibility criteria were checked.
PROUD was initially designed to enrol 5000 participants, which would give adequate power to detect a 50% reduction in HIV incidence from 2.5 to 1.25 infections per 100 person-years. The primary outcomes for the pilot phase were time to accrue 500 participants and retention; secondary outcomes included incident HIV infection during the deferral period, safety, adherence, and risk compensation. For the pilot study there was an arbitrary 10% sample size of 500 and data were initially monitored by a single independent expert not masked to allocation. As it emerged that HIV incidence was much higher than anticipated, an independent DMC was set up in June, 2014. The committee regarded the difference between groups in rate of HIV infection as the important measure for public health policy, and adopted a lower 2.5% confidence limit greater than two infections per 100 person-years as a threshold for notifying the steering committee, although this was not a formal stopping rule.
Analyses included all participants according to their randomised allocation (ITT) and all except individuals with a reactive HIV antigen–antibody result at enrolment (mITT). Incidence rates were compared between the two groups by the rate difference and the rate ratio. Exact 90% CIs were used rather than 95% CIs because the primary interest was in the lower confidence limit. All analyses used data collected up to the date of extraction on June 10, 2015.

Results - PROUD

The pilot phase enrolled 544 subjects from November 2012 to April 30 2014. There were 275 in the immediate group and 269 in the deferred group. Baseline characteristics were well-balanced between the two groups. The median age was 35 years (29–43), 61% were university graduates, 40% were born outside of the UK and 30% were living with a partner. In the previous 12 months, 64% had at least one STI and 36% had received at least one course of PrEP. Also, 44% had used one or more drugs associated with sexual disinhibition in the past 90 days.

On Oct 13 2014 the steering committee recommended that all deferred participants should be offered PrEP. At that time follow-up for HIV incidence was complete for 243 (94%) of 259 patient-years in the immediate group versus 222 (90%) of 245 patient-years in the deferred group. Three HIV infections had occurred in the immediate group (1.2/100 person-years) vs. 20 in the deferred group (9.0/100 person-years) despite 174 non-study prescriptions for PrEP in the deferred group (leaving 167 without prior use of PrEP). These results give a relative reduction of 86% (90% CI 64–96, p=0·0001) and an absolute difference of 7.8/100 person-years (90% CI 4.3–11.3).

Figure 10. Incident HIV infections



Left bound for each HIV case represents last non-reactive HIV test; right bound represents fi rst reactive HIV test. The dotted line represents time when participants in the deferred group became eligible for pre-exposure prophylaxis under the original protocol. *Had a stored enrolment sample that tested positive for HIV RNA but was retained in the analysis.

The three incident infections in the PrEP group concerned one subject with a reactive HIV test at the 4-week visit whose infection is thought to have pre-dated the start of PrEP, one who was HIV reactive at 61 weeks but had not been prescribed study drug since enrolment and one who had a seroconversion illness at 53 weeks but had not been prescribed drug that would have covered use beyond ~week 24.

Questionnaires about sexual behaviour in the previous 90 days were available for 534 at baseline and 406 participants at 1 year. The total number of different anal sex partners showed no significant difference between groups at 1 year (p=0.57) but a larger proportion allocated to PrEP reported URAI (21% *vs* 12%; p=0.03, test for trend).

As shown In Table 24, there was no difference in the occurrence of STIs, including rectal gonorrhoea and chlamydia, between groups, despite a suggestion of risk compensation among some PrEP recipients. The randomised comparison was biased by the greater number of screens for STIs in the PrEP group (mean 4.2 vs 3.6), a consequence of more regular clinic attendance to collect prescriptions.

Table 24. Bacterial sexually transmitted infections

	Immediate	Deferred	Unadjusted odds ratio	Adjusted odds ratio (90% CI)*	p value
Any	152/265 (57%)	124/247 (50%)	1·33	1·07 (0·78–1·46)	0·74
Gonorrhoea†	103/261 (39%)	89/242 (37%)	1·12	0·86 (0·62–1·20)	0·46
Chlamydia†	77/261 (30%)	54/242 (22%)	1·46	1·27 (0·89–1·80)	0·27
Syphilis	30/263 (11%)	22/247 (9%)	1·32	1·29 (0·79–2·10)	0·39
Rectal gonorrhoea or chlamydia	93/258 (36%)	77/238 (32%)	1·18	1·00 (0·72–1·38)	0·99

Infections diagnosed during deferral phase of follow-up. Analysis based on participants with at least one screen.
*Adjusted for the number of screens for specific infection. †Detected in throat, urethra, or rectum.

There were no serious adverse drug reactions. There were 28 AEs (most commonly nausea, headache and arthralgia) that resulted in interruption of PrEP.

2.4.3. Discussion on clinical efficacy

The two main studies were randomised, double-blind and placebo controlled. Testing for new HIV infections was conducted monthly and there was counselling provided on adherence and other preventive measures as well as testing for STIs and assessment of drug concentrations as an indicator of adherence. Safety monitoring included relevant laboratory testing as discussed under *Safety*.

Both studies were powered to show at least 30% efficacy. The results of Partner's PrEP met the pre-defined primary endpoint. The results of iPrEx did not meet the pre-defined primary endpoint but there were clearly fewer HIV-1 infections in the Truvada group and >30% efficacy was shown in secondary analyses in subsets. Both studies showed a strong association between adherence and protection. The CHMP considered information from the primary FDA review to further explore the studies.

Efficacy in iPrEx

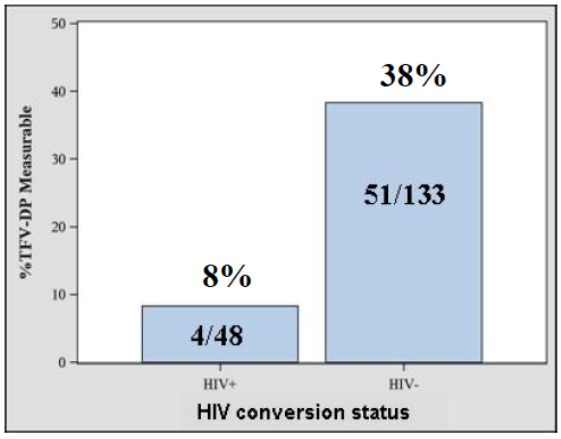
In the mITT population up to the end of the double blind phase, with a median exposure of 77 weeks, subjects had been followed for 4237 person-years. The vast majority was enrolled in Peru.

According to the primary efficacy analysis in the CSR Truvada was associated with a 44% lower incidence of HIV-1 acquisition compared with placebo in the mITT analysis set (95% CI 15% to 63%; p = 0.005) but the analysis did not exclude the null hypothesis of 30% efficacy or less. Results for the ITT analysis set were consistent 47% risk reduction (95% CI: 22% to 64%; p = 0.001). Similar findings applied to analyses based on end of treatment and 8 weeks post-treatment. However, the lower bound of the 95% CI for the relative risk exceeded 30% in those reporting URAI at screening.

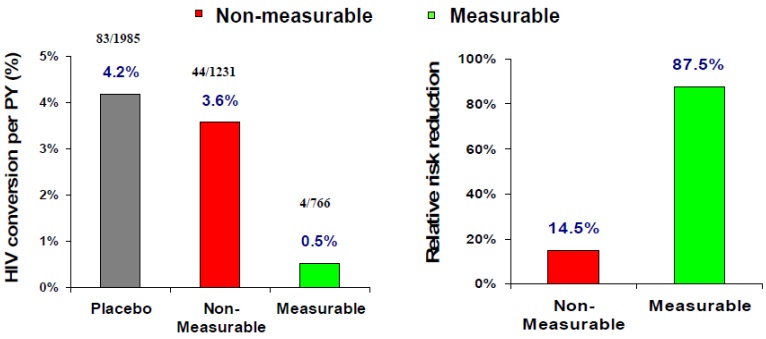
According to the FDA review, at the end of treatment, emergent HIV-1 seroconversion was observed in 131 subjects, 48 in the Truvada group and 83 in the placebo group, indicating a 42% (95% CI: 18% to 60%) reduction in risk. Risk reduction was higher (53%; 95% CI: 34% to 72%) in the 732 Truvada and 753 placebo subjects who reported URAI within the last 12 weeks at screening. Hence, as acknowledged by FDA, their own review gave results very similar to those of the iPrEx team.

Both the FDA and the CSR concluded that the reduction in the rate of HIV-1 acquisition was substantially impacted by study drug adherence. Among subjects for whom ≥ 90% study drug adherence was reported, the relative risk reduction for HIV-1 acquisition was 73% (95% CI: 41% to 88%; p < 0.001).

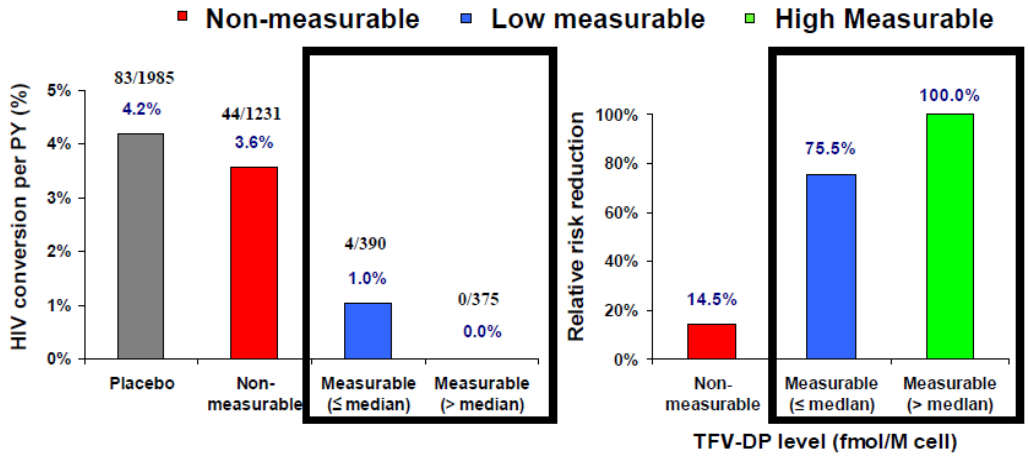
The post hoc case control study of plasma and intracellular drug levels in about 10% of study subjects showed that risk reduction was greatest in subjects with detectable drug in plasma and intracellularly. The FDA figure shows the findings for intracellular TFV-DP as an example.



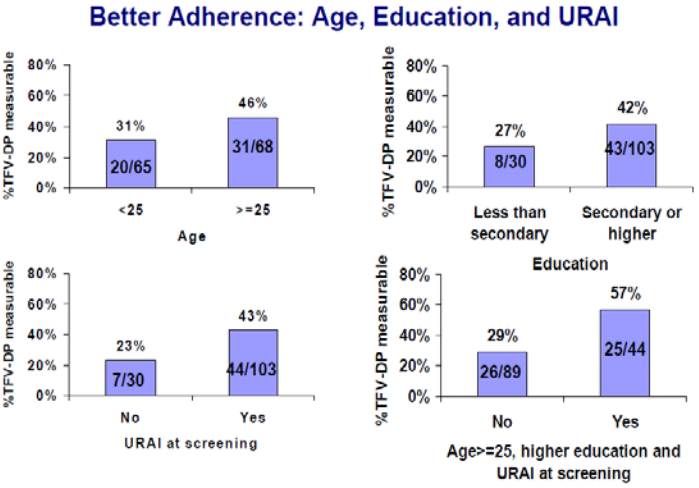
Furthermore, the reduction in risk for HIV-1 infection was 92% (95% CI: 40% to 99%; p < 0.001) among Truvada subjects with quantifiable concentrations vs. those without quantifiable concentrations. The relative risk reduction after adjustment for URAI was 95% (95% CI: 70% to 99%; p < 0.001). The figure below shows efficacy by measurable intracellular TFV-DP.



The FDA also looked at the relationship between plasma TFV and HIV-1 infection according to whether levels were above or below the median of 15.6 pmol/L. Results suggested that those with >median levels had the best protection but even levels that were < median but measurable were associated with better protection than placebo.



Furthermore, better adherence based on intracellular TFV-DP in some subgroups, which was associated with protection.



Subgroup		Event per 100 PY		Relative Risk Reduction
		Placebo	Truvada	
Age	<25	4.5	3.2	28%
	≥ 25	3.8	1.7	56%
Education	Less than Secondary	4.2	3.7	12%
	Secondary or Higher	4.2	2.0	52%
Reported URAI at screening	No	1.5	1.9	-26%
	Yes	5.8	2.7	53%
Age ≥ 25, Secondary/Higher Education and URAI	No	3.9	3.1	23%
	Yes	4.9	0.7	85%

However, the CSR states that there was no significant between-group difference in protection observed on the basis of region (important due to preponderance in Peru), race or ethnicity, male circumcision, level of education, alcohol use or age. Only a report of URAI at screening was associated with significant risk reduction.

Efficacy in Partner's PrEP

As of 10 July 2011, the date at which the DSMB declared that the stopping rules for the study to had been met, 7830 person-years of follow-up time had accumulated in the 4747 eligible HIV-1 partner subjects.

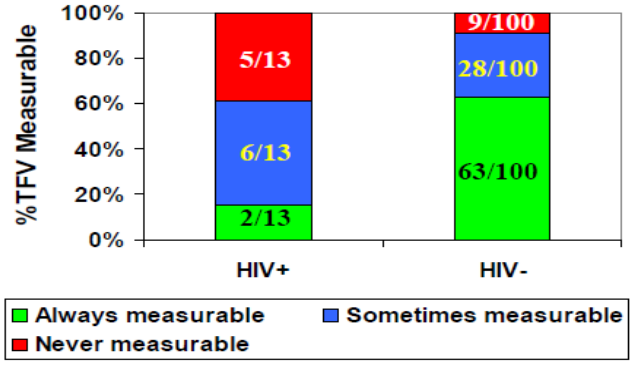
According to the CSR 99 site-reported seroconversion events were recorded during this period. Of these, 3 were false positives and 14 were in partners who were PCR-positive at enrolment. Thus, 82 seroconverting subjects were included in the mITT cohort, giving a sero-incidence rate of 1.05 per 100 person-years (95% CI: 0.83–1.30). These 82 HIV-1 infections comprised 17 TDF, 13 Truvada and 52 placebo patients, with corresponding incidence rates per 100 person-years of 0.65, 0.50 and 1.99. Thus, TDF and Truvada reduced the risk of HIV-1 infection by 67% (95% CI: 44%–81%; p = 0.0031) and 75% (95% CI: 55%–87%; p = 0.0004), respectively. These results met the underlying study premise of > 30% efficacy. The degree of HIV-1 protection was comparable by gender and for most other subgroups.

The test for homogeneity of treatment effects across subgroups achieved statistical significance only for the difference in the effect of TDF vs. placebo by CD4 level of the index subjects at enrolment.

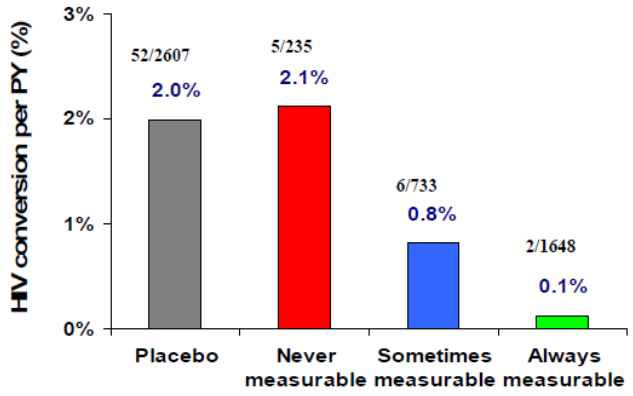
According to the FDA review there were 82 events (same numbers per group as in the CSR) in 7827 person-years of follow up. It is also pointed out 2/13 seroconversion events in the Truvada arm and 3/52 in the placebo arm occurred in women during treatment interruptions for pregnancy. The risk reduction rate agrees with that in the CSR. The FDA conducted additional sensitivity analyses taking into account initiation of ART in the index cases and treatment interruptions due to pregnancy or breastfeeding and found no impact on efficacy. The FDA analysis of efficacy by gender showed the following:

	Men	Women
HIV seroconversion rate (per 100 PY)		
Placebo	1.49	2.81
TDF	0.56	0.81
FTC/TDF	0.24	0.95
Risk Reduction compared with Placebo		
TDF	63% (CI 34-91)	71% (CI 49-94)
FTC/TDF	84% (CI 67-101)	66% (CI 41-92)

The post hoc case control study of plasma drug levels in about 10% of study subjects (13 seroconverting subjects and 100 randomly selected uninfected subjects in the Truvada arm) showed that risk reduction was greatest in subjects with detectable plasma TFV. Efficacy was therefore strongly correlated with adherence.

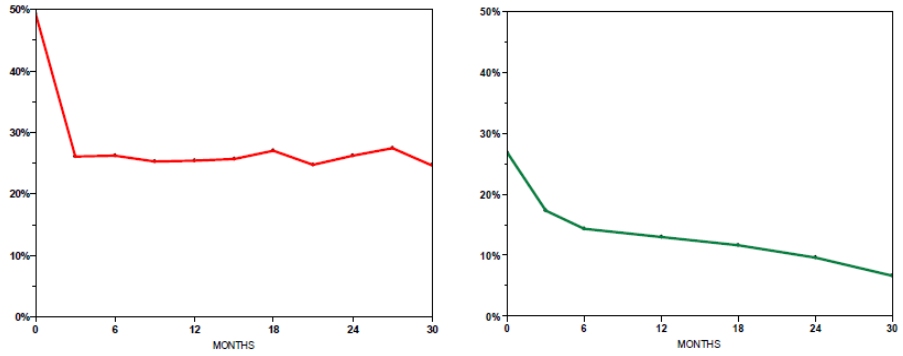


There was no difference in HIV infection rate between placebo subjects and those with no measurable plasma TFV.



Behavioural changes

Rates of unprotected intercourse reported by study subjects appeared to decrease from baseline in both of the main studies over time, as shown in the figure below.



In these two double blind studies there was no appreciable difference in risky behaviours between Truvada and placebo groups as measured by the STI rates.

Any STI*	FTC/TDF	Placebo
Baseline Prevalence	16%	16%
Post-baseline Incidence (rate per 100 PY)	12.6	12.2

* Any STI = syphilis, *Neisseria gonorrhoeae*, *Chlamydia trachomatis*, genital ulcer disease, or herpes simplex virus-2

Any STI*	TDF	FTC/TDF	Placebo
Baseline	10%	11%	12%
1-12 Months	3%	3%	3%
13-24 Months	2%	2%	2%

* Any STI = syphilis, *Neisseria gonorrhoeae*, *Chlamydia trachomatis*, *Trichonomonas vaginalis*, and genital ulcer disease

The published OLE data support the core study report. After re-randomisation of a large proportion of subjects initially assigned to placebo the HIV-1 incidences in subjects receiving PrEP were similar before and after 10 July 2011. Overall, TFV was detected in a plasma sample obtained during the visit at which HIV-1 seroconversion was detected in 14 (27%) of 51 who acquired HIV-1 compared with 1047 (78%) of 1334 samples from subjects who did not acquire HIV-1. Having detectable plasma TFV was associated with an estimated relative risk reduction for acquiring HIV-1 of 85% for TDF and 93% for Truvada. In most individuals, PrEP use was consistent during follow-up, with a slight decrease in use over time. Subjects who acquired HIV-1 generally seroconverted during PrEP non-use.

Overall the core study and OLE showed trends favouring use of Truvada over TDF alone. Since TDF is the main driver of the safety profile of Truvada, there is no strong reason to select TDF alone when it could be associated with lesser protection.

Supportive efficacy data

CDC 4323 was primarily a safety study but it did demonstrate no HIV-1 infections in the Truvada group vs. 7 in the placebo group.

CDC TDF2 provides data on high-risk heterosexuals, in whom Truvada had an overall protective efficacy of 62.2% (95% CI: 21.5%-83.4%; p = 0.013 vs. placebo [mITT]). In the as-treated population, where follow-up was censored at 30 days after the last reported dose of study drug, FTC/TDF had a protective efficacy of 77.9% (95% CI: 41.2%-93.6%; p < 0.001). The rather contrary findings for within-gender efficacy in the mITT and as-treated analyses need to be viewed with caution since the study was not powered to draw conclusions based on gender. This study again showed correlations between treatment adherence and protection against HIV-1 based on plasma TFV and FTC analyses.

The results of **PROUD**, which evaluated daily Truvada, are also relevant to the current application. In contrast to iPrEx, PROUD was open-label in a deliberate attempt to assess efficacy in the setting in which PrEP would be introduced into a region/population in which PrEP was not a routine part of risk management in MSM. Up to the time when the steering committee recommended that all deferred participants should be offered PrEP there had been 3 infections in the immediate group (1.2/100 person-years) vs. 20 in the deferred group (9.0/100 person-years). This difference was detected despite non-study prescriptions for PrEP in the deferred group. The relative risk reduction was 86% (90% CI 64–96, p=0.0001). It was noted in this open-label study that a larger proportion allocated to PrEP reported URAI (21% vs 12%; p=0.03, test for trend) but there was no difference in the occurrence of STIs.

It cannot be dismissed that there have been studies terminated early due to lack of efficacy for TDF or Truvada. In particular, two studies in women (FEM-PrEP and VOICE). It must also be noted that these studies were conducted in African women who may have had relatively low educational levels and that iPrEx showed an association of educational level and age with adherence as measured by drug levels and protection. Overall it seems to be a very consistent finding that if subjects actually take Truvada regularly they can be protected and that the higher the adherence the better the protection.

Finally, this application concerns daily Truvada use. The MAH has reviewed the published results from the Ipergay study but has not been given access to the data for independent evaluation. As a result, the MAH is unable to confirm the findings and an alternative posology cannot be recommended.

2.4.4. Conclusions on the clinical efficacy

The available data from the two main studies support the efficacy of Truvada for HIV-1 PrEP usage. The better the adherence to daily treatment the better is the protection that is afforded. More information on very long-term adherence and behavioural changes are still required. A drug utilisation study is planned in the EU as described in the RMP. Behavioural changes may or may not lead to an increased risk of HIV-1 infection when adherence is high but it will lead to higher rates of other STIs, which is also highly undesirable especially in light of the current problems of resistance of N. gonorrhoeae to first-line and sometimes second line treatments.

2.5. Clinical safety

Introduction

This application dossier rests on data from studies that were not sponsored by the MAH. An integration of safety data across studies has not been provided and it is agreed that this would not be appropriate due to lack of consistency. However, the MAH has re-analysed some of the safety data in accordance with internal standard operating procedures such that the CSRs for the two main studies show tabulations derived from the MAH database. Safety data is described separately for the two main studies and for the CDC 4323 study for which the MAH provided a summary report.

Safety in iPrEx - interim CSR

Safety data presented in the interim CSR include events with onset through 01 May 2011. The focus is on analyses conducted using the MAH's standard analysis methods. Through 01 May 2010, 1540 (62%) of the total subjects had received study drug for at least 1 year (772 [62%] FTC/TDF; 768 [62%] placebo).

Table 25. CO-US-104-0288: Summary of Exposure (Gilead Analysis; Randomized Subjects)

Exposure (Weeks)a	Placebo (N=1248)	FTC/TDF (N=1251)	Total (N=2499)
Mean	67.7	67.1	67.4
Standard Deviation	37.37	38.42	37.89
Minimum	0.1	0.1	0.1
Q1	37.8	36.3	36.9
Median	62.2	62.3	62.3
Q3	100.2	100.3	100.3
Maximum	144.1	145.1	145.1

a Exposure is calculated as the number of weeks from the date of first bottle dispensed to the first occurrence between date of recorded study drug termination or positive HIV-1 test. If neither of these events occurred, the exposure is calculated as the number of weeks from the date of first bottle dispensed to the first occurrence between final study treatment suspension, last bottle dispensing, or study termination.

Table 26. 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.

Adverse events

Using the MAH's windows for AE analyses (TEAEs through 30 days post last dose), TEAEs occurred most commonly in Infections and Infestations (36% per group) and Gastrointestinal Disorders SOCs (13% FTC/TDF, 12% placebo). Three TEAEs were reported for ≥ 5% subjects in either treatment group.

Table 27. CO-US-104-0288: Treatment-Emergent Clinical Adverse Events Reported for at Least 5% of Subjects in Either Treatment Group (Gilead Analysis; Randomized Subjects)

AEs by System Organ Class and Preferred Term, n (%)[a]	Placebo (N=1248)	FTC/TDF (N=1251)
Any AE	705 (56%)	683 (55%)
Infections and Infestations	446 (36%)	445 (36%)
Pharyngitis	79 (6%)	70 (6%)
Urethritis	59 (5%)	47 (4%)
Psychiatric Disorders	114 (9%)	94 (8%)
Depression	58 (5%)	39 (3%)

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.

Depression was the only MedDRA preferred terms with an absolute difference in incidence of ≥ 2% between treatment groups.

TEAEs that occurred at an incidence of ≥ 2% and with higher incidence in the FTC/TDF vs. placebo group were headache and syphilis (each 4% FTC/TDF, 3% placebo), abdominal pain and weight decreased (each 2% FTC/TDF, 1% placebo) and nausea (2% FTC/TDF, < 1% placebo). No differences in the overall safety profile of FTC/TDF vs. placebo were apparent by age, race or region. In both treatment groups the incidence of clinical AEs was higher among subjects aged ≥ 40 years (n = 258; 66% FTC/TDF and 78% placebo) vs. younger subjects (n = 2241; 53% FTC/TDF and 54% placebo).

Using the DAIDs grading, most clinical AEs were mild (Grade 1) or moderate (Grade 2) in severity. Grade 3 or 4 TEAEs occurred in 9% (111 FTC/TDF, 112) but no PT exceeded 1% per group.

The most common treatment-related AEs by PT were headache (14 FTC/TDF, 6 placebo), upper abdominal pain (9 vs. 8) and diarrhoea (10 vs. 4). Grade 3 or 4 TEAEs considered by the investigator to be related to study drug were reported for 3 FTC/TDF (attempted suicide, headache and tooth fracture) and 4 placebo (major depression, suicidal ideation, peripheral sensory neuropathy, arthralgia, and pain in extremity) subjects.

No AEs of interest were predefined but rates of the commonest events in the SmPC are shown in Table 28.

Table 28. CO-US-104-0288: Incidence of Treatment-Emergent Clinical AEs for Key Events Identified in the FTC/TDF Reference Safety Information (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.

Serious adverse event / deaths / other significant events

Nausea was more commonly reported on the monthly medical history questionnaires during the first 4 weeks of study drug use in the FTC/TDF group (9% vs. 5% for placebo) and then decreased to comparable levels at subsequent visits.

TEAEs in the Renal and Urinary Disorders MedDRA SOC were balanced between treatment groups (42 [3%] vs. 50 [4%]) with no Grade 3 or 4 AEs in the FTC/TDF group and no treatment-emergent SAEs.

Bone fractures occurred in 13 [1%] FTC/TDF and 9 [< 1%] placebo subjects. Bone fractures were generally reported to be traumatic and did not appear to be pathologic. A review of BMD results (hip and spine; see below for subset findings) showed no apparent correlation between BMD and the fracture events.

Deaths

Five subjects had fatal AEs (1 FTC/TDF and 4 placebo) but none was considered by the investigator to be related to study drug. The subject in the FTC/TDF group had a motor vehicle accident.

SAEs

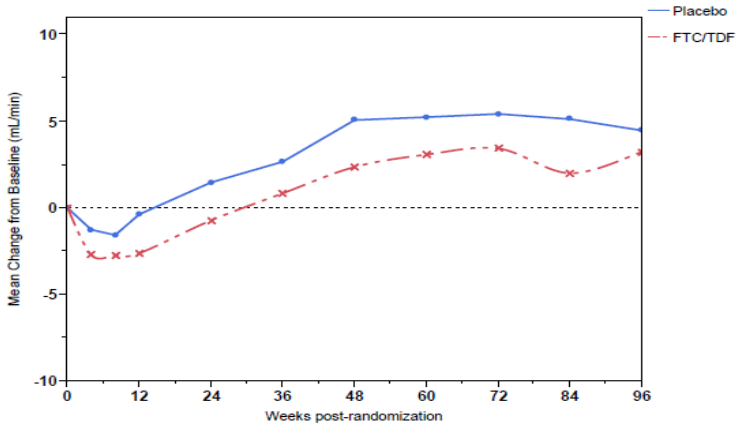
By MedDRA PT the most common SAEs were suicide attempt (10 FTC/TDF, 9 placebo), depression (2 vs. 7) and suicidal ideation (2 vs. 5). SAEs considered by the investigator to be related to study drug were reported for 3 vs. 2 subjects. Serious laboratory toxicities were reported for 11 (< 1%) vs. 12 (< 1%). The rate of SAEs was higher in both treatment groups among subjects aged ≥ 40 years (11% vs. 5%) compared to those < 40 years (3% vs. 4%).

Discontinuations due to AEs

Laboratory toxicities leading to study drug discontinuation were reported for 3 FTC/TDF and 5 placebo subjects with no notable pattern for types of events or associated MedDRA SOCs.

Laboratory findings

No statistically significant differences were observed in the incidence of abnormalities of key laboratory assessments of any toxicity grade. A higher incidence of mild-to-moderate elevations in serum creatinine was observed in the FTC/TDF group (25 [2%] vs. 14 [1%]) but no Grade 3 or 4 serum creatinine results were observed in the FTC/TDF group. Seven FTC/TDF and 3 placebo patients had a treatment interruption due to serum creatinine but 6/7 resumed FTC/TDF without further problems.



Changes in CrCl over time by treatment arm

The MAH's severity grading scale for serum creatinine showed no Grade 3 or 4 abnormalities. No events of Fanconi syndrome were reported and no subjects had renal TEAEs leading to discontinuation.

Other observations

No patterns in vital sign changes or physical findings suggestive of a treatment-related effect were apparent with the exception of assessments of weight. The average weight increased at Week 12 in the placebo group, but not the FTC/TDF group (0.9% vs. 0%, p = 0.002), and then increased about 1.5% per year in both groups. Weight loss > 5%, intentional or unintentional, was recorded for 15% in each group.

DEXA analyses of BMD

There were 503 participants (247 FTC/TDF) in the optional BMD sub-study. Approximately half (48%) were between 18 and 24 years of age and thus considered likely to still be accruing bone mass. At baseline, 38% had low BMD (T-score < -1) in the spine and 16% had low BMD at the hip with no differences between groups. Mean BMD tended to increase in the placebo group and decrease in the

FTC/TDF group, resulting in statistically significant differences (-0.4 to -1.0% across total hip, spine, femoral neck and trochanter) between the groups by Week 24.

There was no difference between groups at any time point evaluated in the incidence of low BMD using World Health Organization (WHO) or International Society for Clinical Densitometry criteria. The subject incidence of total hip BMD T-score definitive of osteoporosis (< -2.5) at any time point was 0/202 vs. 1/202 and the rate for osteopenia (1.0 to -2.5) was 39 (19%) vs. 34 (17%).

Table 29. CO-US-104-0288: Mean (Standard Error) Percentage Change in BMD (data from the iPrEx Study Team) (iPrEx Analysis; Subjects Who Participated in the DEXA Substudy)

	Placebo	FTC/TDF	Difference (95% CI)	P-value
Total hip				
Wk 24	(n = 199) +0.35 (0.13)	(n = 197) -0.33 (0.13)	-0.68 (-1.05 to -0.31)	<0.001
Wk 48	(n = 122) +0.91 (0.22)	(n = 122) -0.06 (0.21)	-0.96 (-1.56 to -0.36)	0.002
Wk 72	(n = 60) +0.51 (0.28)	(n = 55) +0.24 (0.28)	-0.26 (-1.03 to 0.51)	0.50
Spine				
Wk 24	(n = 200) +0.29 (0.20)	(n = 198) -0.66 (0.20)	-0.95 (-1.50 to -0.40)	0.001
Wk 48	(n = 122) +0.13 (0.24)	(n = 121) -0.40 (0.24)	-0.54 (-1.22 to 0.14)	0.121
Wk 72	(n = 60) -0.10 (0.31)	(n = 55) -0.96 (0.31)	-0.87 (-1.71 to -0.02)	0.045

At least a 7% decrease from baseline in total hip BMD was observed in 6 subjects [3%] in each treatment group. Results were generally consistent for categorical analyses of the spinal BMD although numbers with a ≥ 5% decrease from baseline were higher (22/202 [11%] vs. 12/203 [6%]). Numbers with a "marked change" were 3/202 vs. 2/203.

DEXA analyses of body fat

In the 503 sub-study subjects the mean limb fat at baseline was comparable between treatment groups. Modest gains were observed in both treatment groups at 24-week assessments, with smaller gains in the FTC/TDF group through Week 48. These results were consistent with the assessments of trunk fat and total body fat.

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The updated exposure data are shown in Table 30.

Table 30. CO-US-104-0288: Summary of Exposure (Gilead Analysis; Randomized Subjects)

Exposure (Weeks)a	Placebo (N=1248)	FTC/TDF (N=1251)	Total (N=2499)
Mean	81.9	81.8	81.8
Standard Deviation	40.88	41.65	41.26
Minimum	0.1	0.1	0.1
Q1	52.0	52.3	52.1
Median	77.1	77.9	77.3
Q3	118.1	119.7	118.9
Maximum	163.0	161.1	163.0

Through the 21 November 2010 data cut-off, 950 (76%) FTC/TDF subjects had been exposed for at least 1 year and 392 (31%) for at least 2 years.

Using the MAH's standard approach (window definitions) there were no major differences between treatment groups although the reporting rates did increase, including a 16% increase over the number of subjects reporting at least 1 clinical AE. Similar findings applied when using the iPrEx team approach.

Table 31. CO-US-104-0288: Overall Summary of Treatment-emergent Adverse Events (Gilead Analysis; Randomized Subjects)

	Primary Analysis (01 May 2010 Data Cutoff)		Complete Double-blind Analysis (21 November 2010 Data Cutoff)	
Adverse Event Category, n (%)[a]	Placebo (N=1248)	FTC/TDF (N=1251)	Placebo (N=1248)	FTC/TDF (N=1251)
Any clinical AE	705 (56%)	683 (55%)	904 (72%)	884 (71%)
Any laboratory AE	411 (33%)	422 (34%)	464 (37%)	469 (37%)
Study drug-related AE[b]	59 (5%)	77 (6%)	65 (5%)	87 (7%)
Grade 3 or 4 clinical AE	112 (9%)	111 (9%)	143 (11%)	148 (12%)
Grade 3 or 4 study drug-related clinical AE	4 (< 1%)	3 (< 1%)	4 (< 1%)	3 (< 1%)
Clinical AE that caused permanent discontinuation of study drug	20 (2%)	22 (2%)	42 (3%)	41 (3%)
Laboratory AE that caused permanent discontinuation of study drug	5 (< 1%)	3 (< 1%)	7 (< 1%)	7 (< 1%)
Any clinical SAE	51 (4%)	48 (4%)	68 (5%)	70 (6%)
Any laboratory SAE	12 (< 1%)	11 (< 1%)	18 (1%)	19 (2%)
Study drug-related clinical SAE	2 (< 1%)	1 (< 1%)	1 (< 1%)	1 (< 1%)
Death[a]	4 (< 1%)	1 (< 1%)	6 (< 1%)[c]	2 (< 1%)[c]

Using the MAH's evaluation windows for AE analyses TEAEs occurred most commonly in SOCs of infections and infestations (55% FTC/TDF, 56% placebo), gastrointestinal disorders (20% vs. 19%) and psychiatric disorders (12% vs. 13%). By PT, 10 TEAEs were reported in ≥ 5% of subjects in either group.

Table 32. CO-US-104-0288: Treatment-Emergent Clinical Adverse Events Reported for at Least 5% of Subjects in Either Treatment Group at the Time of the Primary Analysis or Complete Double-blind Analysis (Gilead Analysis; Randomized Subjects)

AEs by System Organ Class and Preferred Term, n (%)[a]	Primary Analysis (01 May 2010 Data Cutoff)		Complete Double-blind Analysis (21 November 2010 Data Cutoff)	
	Placebo (N=1248)	FTC/TDF (N=1251)	Placebo (N=1248)	FTC/TDF (N=1251)
Any AE	705 (56)	683 (55)	904 (72)	883 (71)
Infections and Infestations	446 (36)	445 (36)	698 (56)	685 (55)
Pharyngitis	79 (6)	70 (6)	183 (15)	154 (12)
Parasitic infection intestinal	13 (1)	6 (< 1)	149 (12)	126 (10)
Nasopharyngitis	25 (2)	30 (2)	69 (6)	77 (6)
Urethritis	59 (5)	47 (4)	82 (7)	61 (5)
Syphilis	37 (3)	45 (4)	53 (4)	63 (5)
Secondary syphilis	21 (2)	27 (2)	49 (4)	65 (5)
Gastrointestinal Disorders	146 (12)	157 (13)	232 (19)	248 (20)
Diarrhoea	47 (4)	43 (3)	90 (7)	81 (6)
Psychiatric Disorders	114 (9)	94 (8)	156 (13)	151 (12)
Depression	58 (5)	39 (3)	79 (6)	71 (6)
Musculoskeletal and Connective Tissue Disorders	70 (6)	71 (6)	129 (10)	122 (10)
Back pain	30 (2)	24 (2)	61 (5)	58 (5)
Nervous System Disorders	62 (5)	76 (6)	104 (8)	104 (8)
Headache	41 (3)	56 (4)	74 (6)	79 (6)

TEAEs that occurred at a frequency ≥ 2% and with a higher frequency in the FTC/TDF group were syphilis and secondary syphilis (each 5% FTC/TDF vs. 4% placebo), abdominal pain (4% vs. 2%), tinea cruris and gastroenteritis (3% vs. 2%), weight decreased (3% vs. 1%) and fungal skin infection, cellulitis, gastrointestinal infection, tinea pedis, nausea, dyspepsia and insomnia (each 2% vs. 1%). By MedDRA PT all Grade 3 or 4 TEAEs occurred in < 1% in both treatment groups. No differences in the overall safety profile of FTC/TDF compared with placebo were apparent when TEAEs were evaluated by age, race or region. As before, the frequency of clinical AEs was higher among older subjects in both treatment groups.

Headache (14 [1%] FTC/TDF, 10 [< 1%] placebo) was the only treatment-related AE reported in 1% of the FTC/TDF group. Grade 3 or 4 TEAEs considered by the investigator to be related to study drug were reported for 3 in the FTC/TDF group and 4 in the placebo group. For the AEs that predominate in the Truvada SmPC, the frequency was low with small differences in the rates reported for nausea and weight decreased.

Table 33. CO-US-104-0288: Frequency of Treatment-Emergent Clinical AEs for Key Events Identified in the FTC/TDF Reference Safety Information (Gilead Analysis; Randomized Subjects)

AEs by Preferred Term, n (%)[a]	Primary Analysis (01 May 2010 Data Cutoff)		Complete Double-blind Analysis (21 November 2010 Data Cutoff)	
	Placebo (N=1248)	FTC/TDF (N=1251)	Placebo (N=1248)	FTC/TDF (N=1251)
Diarrhea	47 (4%)	43 (3%)	90 (7%)	81 (6%)
Vomiting	2 (< 1%)	3 (< 1%)	3 (< 1%)	6 (< 1%)
Nausea	7 (< 1%)	19 (2%)	14 (1%)	21 (2%)
Flatulence	10 (< 1%)	14 (1%)	13 (1%)	13 (1%)
Weight decreased	14 (1%)	27 (2%)	18 (1%)	32 (3%)
Dizziness	2 (< 1%)	4 (< 1%)	4 (< 1%)	5 (< 1%)

TEAEs in the Renal and Urinary Disorders MedDRA SOC were balanced between treatment groups (71 [6%] FTC/TDF vs. 64 [5%] placebo) and none was Grade 3 or 4 in the FTC/TDF group.

Up to 01 May 2010 there had been 5 deaths (one FTC/TDF). However, as noted in the interim CSR, another two deaths (one FTC/TDF) occurred shortly after the cut-off date and were mentioned in the prior report. The additional FTC/TDF patient had experienced acute hepatic failure and died on 05 August 2010 (Study Day 603) but study drug levels were <LLQ a year before the onset of acute hepatic failure. The cause of death was reported as upper digestive haemorrhage, associated with liver failure and angiocentric T cell lymphoma. The following liver function parameters increased ~2 to 8 fold from 29 April 2010 (Study Day 504) to 22 July 2010 (Study Day 589; the last recorded values): alkaline phosphatase (107 to 188 IU/L), ALT (22 to 178 IU/L) and AST (29 to 167 IU/L). Death was considered unrelated to study drug by the investigator and probably not related to study drug by the DAIDS medical officer. The additional placebo patient had pulmonary TB.

In the final report a further 2 deaths are reported, both in the placebo group, taking the total to 2 FTC/TDF and 7 placebo subjects. None was considered drug-related.

Clinical SAEs were reported for 70 (6%) in the FTC/TDF group and 68 (5%) in the placebo group. Laboratory SAEs were reported for 19 (2%) and 18 (1%), respectively. By MedDRA PT SAEs were reported for ≤ 1% per treatment group. The most common were suicide attempt (14 [1%] FTC/TDF, 12 [< 1%] placebo, depression (6 vs. 11) and suicidal ideation (4 vs. 6). Clinical SAEs considered by the investigator to be related to study drug occurred in one subject per group Suicide attempt in FTC/TDF subject). The rates of SAEs in those aged ≥ 40 years were 11% FTC/TDF vs. 6% placebo but the rates for those < 40 years were 5% in both groups. No pattern in the types of events among the older subjects was apparent.

Nearly twice as many subjects had permanently discontinued study drug due to a clinical AE or laboratory AE at the time of the final CSR compared to the interim CSR data cut-off dates but rates remained similar between the treatment groups (3% due to clinical AEs and <1% due to laboratory AEs. By MedDRA PT all TEAEs leading to study drug discontinuation were reported for < 1% per treatment group. Approximately half of the subjects (44/83) who discontinued study drug due to a clinical AE did so due to a psychiatric disorder, as required by the protocol (any suicidal ideation is regarded as Grade 4 according to the DAIDS grading table, and study drug had to be discontinued for Grade 4 AEs).

Laboratory AEs are shown in Table 34. No statistically significant differences were observed in the frequency of abnormalities of laboratory assessments. A greater number of subjects in the FTC/TDF

treatment group had Grade 1 or Grade 2 elevations in serum creatinine but there were no higher Grade abnormalities.

Table 34. CO-US-104-0288: Number of Subjects With Graded Laboratory Abnormalities (Data Through 21 November 2010; iPrEx Analysis; Randomized Subjects)

Laboratory Adverse Event	Treatment	Maximum Toxicity Grade				Number of Participants	Number of Events	P-value
		1	2	3	4			
Alk. Phosphatase	Placebo	53	3	1	0	57	73	0.87
	FTC/TDF	55	3	1	0	59	87	
ALT	Placebo	194	61	17	5	277	438	0.49
	FTC/TDF	178	63	17	4	262	405	
AST	Placebo	175	40	16	5	236	328	0.81
	FTC/TDF	175	36	16	5	232	314	
Total Bilirubin	Placebo	115	59	9	0	183	291	0.41
	FTC/TDF	122	41	4	1	168	280	
Amylase	Placebo	87	17	8	1	113	156	0.93
	FTC/TDF	85	21	6	2	114	171	
Creatinine[a]	Placebo	21	2	1	0	24	25	0.28
	FTC/TDF	27	5	0	0	32	37	
Glucosuria (High)	Placebo	297	54	4	0	355	518	0.19
	FTC/TDF	280	40	1	1	322	443	
HypoPhosphotimia	Placebo	110	91	10	0	211	292	0.78
	FTC/TDF	81	110	13	0	204	300	
CO2/Bicarbonate (Low)	Placebo	135	1	0	0	136	185	0.53
	FTC/TDF	143	2	0	0	145	221	
Total Leukocyte (Low)	Placebo	5	1	0	0	6	7	0.76
	FTC/TDF	4	1	0	0	5	5	
Absolute Neutrophiles (Low)	Placebo	25	5	1	1	32	47	0.79
	FTC/TDF	23	6	1	0	30	40	
Total Hemoglobin	Placebo	62	15	4	0	81	117	0.09
	FTC/TDF	49	9	4	0	62	99	
Platelet (Low)	Placebo	8	3	0	0	11	12	0.69
	FTC/TDF	7	3	2	1	13	15	
Sodium (Low)	Placebo	114	3	1	2	120	132	0.30
	FTC/TDF	132	2	1	1	136	160	
Sodium (High)	Placebo	234	8	1	0	243	329	0.77
	FTC/TDF	232	5	1	1	239	322	
Potassium (Low)	Placebo	35	0	0	0	35	37	0.49
	FTC/TDF	41	0	0	0	41	48	
Potassium (High)	Placebo	25	2	0	1	28	30	0.21
	FTC/TDF	35	3	0	0	38	45	

No events of Fanconi syndrome were reported and no subjects had SAEs associated with renal toxicity. One subject in the FTC/TDF group withdrew due to dysuria.

FTC and TDF decrease HBV viral load. Subjects with total bilirubin, ALT or AST >2xULN or with clinical signs of cirrhosis were excluded from the study. The occurrence of hepatic flares (increase in AST or ALT to >5×ULN at any visit or an increase to >2.5×ULN for 3 months, within 24 weeks of permanently stopping study drug) in HBsAg+ subjects who discontinued study drug was assessed by post-treatment laboratory evaluations. The CSR reports these data up until September 2011. There were only 16 HBsAg+ subjects, of which 12 had chronic infection (6 in each group) and 4 had acute infection (2 in each group). None was infected with HCV. None of these subjects experienced a hepatic flare after stopping study drug.

Assessment of BMD via DEXA showed that a total hip BMD T-score definitive of osteoporosis at any post-baseline on-study drug time point occurred in 0/211 FTC/TDF and 2/214 placebo subjects while osteopenia was described for 41/211 (19%) and 38/214 (18%), respectively. One FTC/TDF subject had at least a 7% decrease from baseline in total hip BMD. Results were generally consistent for categorical analyses of the spinal BMD although the numbers with a ≥ 5% decrease from baseline at any post-baseline on-study drug time point were higher (30/214 [14%]) for the FTC/TDF vs. placebo group (14/216 [6%]). Despite this, marked changes occurred in 7/214 subjects [3%] vs. 4/216 subjects [2%].

Statistically significant mean (SE) percent decreases from baseline in total hip BMD were noted in the FTC/TDF group compared with the placebo group at last post-stop scan and at all post-stop scans. No other statistically significant mean (SE) percent changes from baseline or stop-study drug scans to post-stop scans in BMD were noted during the study. In the interval between the last on-study-drug BMD evaluation and the last post-stop BMD evaluation the mean BMD for total hip and spine increased in the FTC/TDF group but remained stable in the placebo group.

Table 35. CO-US-104-0288: Mean (Standard Error) Percentage Changes From Baseline Scan and Stop-study Drug Scan to the Last Post-stop Scan in BMD (T-test Results, Data From the iPrEx Study Team) (iPrEx Analysis; Subjects Who Participated in the DEXA Substudy)

	Mean (SE) % Change[a]			p-value
	Placebo	FTC/TDF	Difference[b]	
% Change from baseline[c]				
Total hip	0.47 (0.21)	–0.25 (0.23)	–0.72 (0.31)	0.021
Spine	–0.09 (0.28)	–0.47 (0.31)	–0.39 (0.41)	0.352
Trochanter	0.12 (0.28)	–0.55 (0.33)	–0.67 (0.43)	0.120
Femoral neck	0.93 (0.33)	0.29 (0.43)	–0.64 (0.54)	0.236
% Change from stop-study drug scan[a]				
Total hip	0.15 (0.15)	0.29 (0.17)	0.14 (0.23)	0.548
Spine	0.01 (0.22)	0.56 (0.26)	0.56 (0.34)	0.105
Trochanter	0.15 (0.22)	0.56 (0.27)	0.42 (0.35)	0.238
Femoral neck	0.75 (0.27)	0.70 (0.26)	–0.05 (0.38)	0.900

Table 36. CO-US-104-0288: Least Square Mean (Standard Error) Percentage Changes From Baseline Scan and Stop-study Drug Scan to All Post-stop Scans in BMD (Mixed Model Results, Data From the iPrEx Study Team) (iPrEx Analysis; Subjects Who Participated in the DEXA Substudy)

	LS Mean (SE) % Change[a]			p-value
	Placebo	FTC/TDF	Difference[b]	
% Change from baseline[c]				
Total hip	0.40 (0.19)	–0.25 (0.18)	–0.65 (0.26)	0.014
Spine	–0.07 (0.26)	–0.42 (0.24)	–0.35 (0.35)	0.331
Trochanter	0.04 (0.27)	–0.66 (0.26)	–0.70 (0.37)	0.060
Femoral neck	0.74 (0.31)	0.08 (0.30)	–0.66 (0.43)	0.129
% Change from stop-study drug scan[a]				
Total hip	0.04 (0.19)	0.22 (0.18)	0.18 (0.26)	0.497
Spine	–0.07 (0.26)	0.46 (0.24)	0.53 (0.35)	0.128
Trochanter	–0.03 (0.27)	0.37 (0.26)	0.40 (0.37)	0.277
Femoral neck	0.61 (0.31)	0.51 (0.30)	–0.10 (0.43)	0.808

Modest gains in limb fat were observed in both treatment groups through the study, at each of the 24-week on-drug assessments, with smaller gains observed in the FTC/TDF group compared with placebo through Week 72. Although the number of subjects with assessments was smaller at the Week 96 visit, the mean increases in limb fat were similar between both treatment groups at that time point. Likewise, mean increases in limb fat were similar between both treatment groups when measured from the last dose of study drug to the Week 24 Post-Stop Drug assessment.

Safety in Partner's PrEP

Table 37. 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

The only individual events reported by ≥10% in the TDF group were neutrophil count decreased (38%), blood phosphorous decreased (28%), malaria (19%), haemoglobin decreased (16%) and platelet count decreased (12%). These same events were reported by generally similar percentages in the FTC/TDF and placebo groups but a slightly greater percentage in the FTC/TDF group had decreases in neutrophil count (44% vs. 37%–38%). URTI was reported in 10% in the FTC/TDF group and 8% to 9% in the other study drug groups. Non-serious AEs were not assessed for severity.

Table 38. 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)

For the AESIs, 269 subjects (5-7% per group) had AEs associated with increases in blood creatinine levels of which none was serious but in 1% per group these were EAEs. Of all reported increases in blood creatinine only 19, 20 and 13 per group were confirmed on repeat testing, none was Grade 4 and nearly all were Grade 1 (50% increase over baseline but WNL). Decreases in blood phosphorous levels were experienced in 28-30% per group and 6-7% had EAEs. One in the FTC/TDF group was serious but it resolved and did not result in a change in study drug administration. None of the confirmed events were Grade 4, and most were Grade 2.

Of the 34 (0.7%) bone fractures (all EAEs; 12, 9 and 13 per group) 10 were serious but were considered not related to study drug and were due to trauma. Diarrhoea was reported infrequently in 2%–3% per group. A decrease in weight was reported as an AE for 9, 4 and 6 per group with EAEs in 6 TDF subjects and in 1 in each of the other groups. The most common EAEs are shown below.

Table 39. CO-US-104-0380: Expedited Adverse Events Reported for at Least 1% 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)
Blood phosphorus decreased	108 (7)	104 (7)	99 (6)	311 (7)
Neutrophil count decreased	66 (4)	103 (7)	69 (4)	238 (5)
Haemoglobin decreased	39 (2)	32 (2)	38 (2)	109 (2)
Malaria	28 (2)	31 (2)	39 (2)	98 (2)
Abortion spontaneous	19 (1)	26 (2)	22 (1)	67 (1)
Diarrhoea haemorrhagic	17 (1)	17 (1)	15 (1)	49 (1)
Blood creatinine increased	10 (1)	17 (1)	10 (1)	37 (1)
Platelet count decreased	12 (1)	11 (1)	11 (1)	34 (1)
Aspartate aminotransferase increased	9 (1)	9 (1)	5 (0)	23 (0)
Dysentery	11 (1)	9 (1)	2 (0)	22 (0)

In the TDF, FTC/TDF, and placebo groups, 8, 8, and 9 partner subjects, respectively, died during the study. There were no clear trends of concern.

Most SAEs were associated with abnormal clinical laboratory findings, especially decreased neutrophils or Hb and increased transaminases. There was no clear trend by treatment group.

Discontinuations due to AEs occurred in only 6 subjects and all were due to increases in blood creatinine that were confirmed on repeat testing. All except one Grade 1 increase were of Grade 2 and none was considered related to the study drug by the safety monitor. These Grade 2 increases were associated with estimated CrCL drops to <50 mL/min, in most cases from a baseline of just greater than 50 mL/min.

Abnormal laboratory results were repeated on a different sample for confirmation. In the vast majority of cases, confirmatory testing was of lower grade or normal. The following is based on any rather than confirmed abnormalities.

Using the MAH's definitions, nearly all abnormal creatinine or phosphorous results were Grade 1.

Table 40. 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)

Other clinical laboratory toxicities concerned abnormal ANC count (15.3%), Hb (5.6%), platelet count (3.6%), AST (2.0%) and ALT (1.4%). Toxicities associated with neutrophils were seen more commonly in the FTC/TDF group (17.8% and 3.9% Grade 3 or 4) than in the TDF group (15.0%; 2.6% Grade 3 or 4) or placebo group (13.2%; 1.8% Grade 3 or 4). No other noteworthy differences were observed between study groups.

Pregnancy occurred in 18%, 13% and 14% in the TDF, FTC/TDF and placebo groups, respectively. Of these 288 pregnancies, 178 have completed with 90 live births. The pregnancy loss rate across all completed pregnancies was lower in TDF group (40% vs. 57% FTC/TDF and 54% placebo). Spontaneous abortions occurred almost entirely at < 20 weeks. Five of the 90 live births died within 1 to 3 months of birth. Medical abortion is not legal in either Kenya or Uganda and women terminating unwanted pregnancies may instead report spontaneous abortion/miscarriage.

Safety in CDC 4323 (CO-US-104-0277)

A total of 2,428 TEAEs were reported by 334 (90%) participants of which 76% were Grade 1/mild and 21% were Grade 2/moderate. There were 62 Grade 3 or 4 AEs in 37 subjects. The pre-defined AESIs are shown in Table 41.

Table 41. Adverse events of interest: frequencies and rates per 100 person-years

	Recurrent Events				First Reported Events			
	TDF	Placebo	Rate Ratio	p[6]	TDF	Placebo	Hazard Ratio	p[7]
Grade 3 or 4 AE	36 (13.19)	26 (9.93)	1.13 (0.61, 2.11)	0.703	20 (7.87)	17 (6.79)	1.16 (0.61, 2.21)	0.654
Diarrhoea	42 (15.39)	57 (21.77)	0.7 (0.47, 1.05)	0.086	33 (14.31)	45 (21.33)	0.68 (0.43, 1.06)	0.089
Back pain	31 (11.36)	14 (5.35)	1.84 (0.94, 3.59)	0.074	23 (9.14)	12 (4.75)	1.89 (0.94, 3.81)	0.073
Headache	27 (9.89)	33 (12.6)	0.82 (0.5, 1.36)	0.447	24 (9.9)	28 (12.31)	0.83 (0.48, 1.44)	0.508
Nausea	27 (9.89)	13 (4.96)	1.6 (0.8, 3.19)	0.183	20 (8)	12 (4.82)	1.7 (0.83, 3.48)	0.146
Depression	25 (9.16)	32 (12.22)	0.72 (0.4, 1.28)	0.264	18 (6.97)	24 (10.02)	0.7 (0.38, 1.29)	0.248
Fatigue	24 (8.79)	17 (6.49)	1.09 (0.56, 2.1)	0.803	17 (6.89)	15 (6.19)	1.11 (0.55, 2.22)	0.777
Flatulence	21 (7.7)	22 (8.4)	0.96 (0.52, 1.78)	0.896	18 (7.33)	18 (7.7)	0.95 (0.5, 1.84)	0.889
Dizziness	17 (6.23)	9 (3.44)	1.92 (0.8, 4.63)	0.147	14 (5.45)	7 (2.76)	2.02 (0.82, 5.01)	0.128
Fracture (any site)	15 (5.5)	5 (1.91)	1.92 (0.49, 7.5)	0.349	6 (2.25)	3 (1.16)	1.92 (0.48, 7.69)	0.355
Bone density decreased[8]	9 (6.29)	5 (3.65)	1.72 (0.6, 4.98)	0.315	9 (6.32)	5 (3.66)	1.67 (0.56, 5)	0.357
Abdominal pain upper	6 (2.2)	2 (0.76)	5.76 (0.7, 47.35)	0.103	6 (2.28)	1 (0.38)	6.08 (0.73, 50.46)	0.095
Hypophosphataemia	3 (1.1)	7 (2.67)	0.72 (0.16, 3.18)	0.664	3 (1.11)	4 (1.55)	0.74 (0.17, 3.3)	0.691
Proteinuria	1 (0.37)	1 (0.38)	0.96 (0.06, 15.21)	0.977	1 (0.37)	1 (0.38)	0.94 (0.06, 15)	0.963
Blood creatinine increased	0 (0)	2 (0.76)	N/A	N/A	0 (0)	2 (0.77)	N/A	N/A

In multivariate analyses, back pain was noted to be significantly associated with receipt of TDF. Review of study records of participants reporting back pain revealed no recorded fractures. Those with back pain did not show an association with markers as shown below (but BMD was only assessed in a subset; see below).

Changes from Baseline at End of Treatment	TDF (n=201)	Placebo (n=199)
New Onset Back Pain, n (%)	18 (9)	10 (5)
Mean age	38	43
Mean % Δ Creatinine	-3%	0.2%
Mean % Δ Phosphorus	2%	5%
Mean % Δ Alkaline Phosphatase	4%	6%
>3% ↓ in BMD at Total Hip or L1-L4 Spine, n (%)	5 (28)	4 (40)
>5% ↓ in BMD at Total Hip or L1-L4 Spine, n (%)	4 (22)	3 (30)

There were 9 TDF and 5 placebo subjects with fractures, of which 4 and 2 involved the foot. The others were at scattered sites.

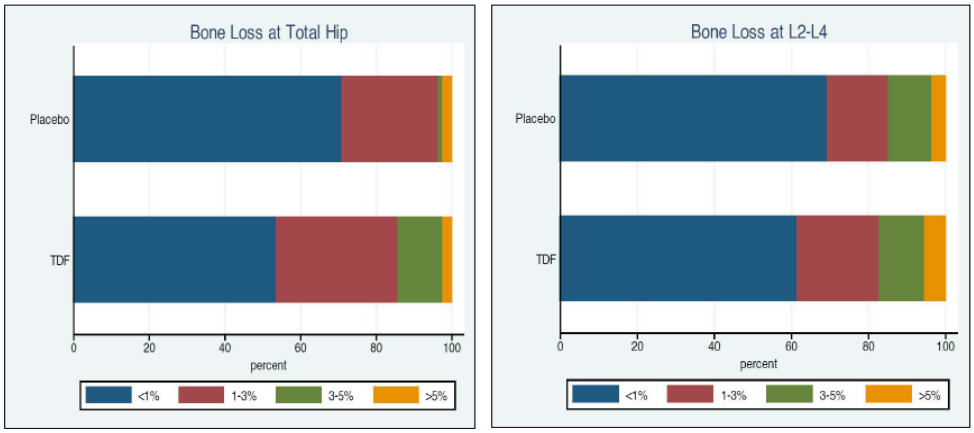
No grade 3 or 4 creatinine elevations were recorded while grade 1 and 2 elevations were uncommon, and occurred with similar frequency in the TDF and placebo groups (Grade 1 - 1 TDF vs. 4 placebo; Grade 2 – 1 vs. 2. Confirmed elevated creatinine values ≥0.5 mg/dL over baseline occurred in two placebo subjects. Mild to moderate hypophosphatemia was relatively common and occurred with similar rates in TDF vs. placebo arms. Grade 3 hypophosphatemia occurred in 4 TDF vs. 1 placebo subject and grade 4 was reported in one placebo subject.

There were 29 SAEs reported by 10 TDF and 8 placebo subjects, of which the most common was depression (4 vs. 2). One TDF subject had pulmonary oedema, appendicitis, prostate cancer, coronary artery disease, hypercholesterolaemia, mania, poisoning, seroma and spinal fracture. One SAE resulted in death in a TDF subject secondary to combined opiate and alcohol intoxication.

In the SFO subset, low BMD (Z score ≤-2.0) was observed more frequently than expected in this MSM population with median age 41 years. Significant baseline correlates were amphetamine use (OR 5.9), inhalants (OR 4.6) and MVI/calcium/Vitamin D use (OR -0.26). Two with low baseline BMD had vitamin D

deficiency and one had hypogonadism. TDF was associated with small but statistically significant decreases in BMD at the femoral neck (1.1% decrease) and total hip (0.8% decrease).

BMD Loss at Month 24 Compared to Baseline



Overall bone fractures at any site were not significantly associated with receipt of TDF but the power to detect differences in fracture rates is limited by the sample size.

2.5.1. Discussion on clinical safety

The safety profile of Truvada when used for PrEP was entirely as expected based on the wealth of experience with this combination within complete ART regimens. The CHMP considered information from the FDA safety review.

With regard to the known renal effects of TFV it should be noted that the study populations generally anticipated to use PrEP are likely to have low rates of factors that have been associated with renal abnormalities during TDF treatment (including higher age, lower CrCL, underlying diabetes and concomitant nephrotoxic agents). The FDA's table summarises the effects on creatinine and phosphorus.

	CDC 4323 [a]		iPrEx [b]		Partners [b]		
	TDF (N=184)	Placebo (N=186)	TDF/FTC (N=1225)	Placebo (N=1226)	TDF (N=1575)	FTC/TDF (N=1570)	Placebo (N=1573)
Elevated Serum Creatinine – n (%)							
Grade 1	5 (3)	9 (5)	10 (1)	7 (1)	3 (<1)	6 (<1)	4 (<1)
Grade 2	1 (1)	1 (1)	1 (<1)	1 (<1)	1 (<1)	0	0
Grade 3	0	1 (1)	0	0	0	0	0
Grade 4	0	0	0	0	0	0	0
Low Serum Phosphorus – n (%)							
Grade 1	14 (8)	14 (8)	135 (11)	120 (10)	321 (20)	337 (21)	351 (22)
Grade 2	37 (20)	29 (16)	13 (1)	10 (1)	89 (6)	83 (5)	81 (5)
Grade 3	2 (1)	3 (2)	0	0	11 (1)	12 (1)	10 (1)
Grade 4	0	0	0	0	0	1 (<1)	0

a) DAIDS AE Grading Table 2004 b) Applicant Grading Scheme

The data are shown below for categorical changes in serum creatinine. Essentially there were no major differences between active and placebo groups.

Serum Creatinine	CDC 4323		iPrEx		Partners PrEP	
	TDF (N=184)	Placebo (N=181)	FTC/TDF (N=1225)	Placebo (N=1226)	TDF arms (N=3145)	Placebo (N=1573)
Creatinine ≥ 20% from baseline,* n (%)	18 (10)	13 (7)	136 (11)	114 (9)	420 (13)	138 (9)
Baseline Mean Creatinine (mg/dL)	0.91	0.95	0.78	0.76	0.67	0.67
At 12 Months Mean creatinine (mg/dL)	1.03 (+22%)	1.13 (+20%)	0.86 (+11%)	0.83 (+9%)	0.82 (+21%)	0.80 (+19%)

*≥ 20% increase on more than two visits or on any two consecutive visits

- When available, no correlation with proteinuria or glycosuria
- Corresponding mean serum phosphorus unchanged compared to baseline

This finding also applied to urinalysis findings (FDA summary table).

Urinalysis Abnormalities	iPrEx		Partners PrEP		
	FTC/TDF (N=1171)	Placebo (N=1190)	TDF (N=1577)	FTC/TDF (N=1571)	Placebo (N=1574)
Recurrent proteinuria, n (%)	92 (8)	69 (6)	15 (1)	16 (1)	20 (1)
- and graded creatinine increase	5 *	4	0	0	0
Proteinuria with glycosuria, n (%)	6 (<1)	4 (<1)	2 (<1)	2 (<1)	3 (<1)
- and graded hypophosphatemia	5/6	2/4	2/2	1/2	2/3
- and BMD loss >5%	2/5	0	N/A	N/A	N/A

* Includes subject who permanently discontinued FTC/TDF due to increased creatinine

As described above for CDC 4323, there was a trend to greater decreases in BMD in subjects who received TDF in this study. When data were examined for those with ≥ or < 20% increases in serum creatinine from baseline, associations were apparent with effects on BMD and ALP.

	TDF (N=184)	Placebo (N=181)
Creatinine ≥ 20% ↑ from Baseline, in DEXA substudy	n/N=13/18	n/N=8/13
• and ≥ 3% ↓ in BMD from Baseline in Total Hip OR Lumbar Spine, n (%)	10/13 (77)	3/8 (37)
– with any ≥ 20% ↑ Alkaline phosphatase, n (%)	9/10 (90)	2/3 (67)
Creatinine < 20% ↑ from Baseline, in DEXA substudy	n/N=81/166	n/N=84/161
• and ≥ 3% ↓ in BMD from Baseline in Total Hip OR Lumbar Spine, n (%)	46/81 (57)	38/84 (45)
– with any ≥ 20% alkaline phosphatase, n (%)	40/46 (87)	13/38 (34)

2.5.2. Conclusions on clinical safety

The safety profile of Truvada for PrEP can be expected to be similar to that already very well recognised when it is used for treatment of HIV-1. The difference is therefore not in the safety profile per se when Truvada is used for treatment vs. prophylaxis but in the benefit-risk relationship when Truvada is given to subjects who are not yet infected and in whom HIV-1 infection could be wholly prevented if appropriate non-pharmacological measures were to be adequately and consistently employed.

The main point is that PrEP is used entirely because human behaviour is fallible. Ultimately, since it has been concluded that Truvada works if it is taken, it is for subjects and their physicians to discuss to what extent it is acknowledged that adequate preventive measures will not always be applied and to weigh up the benefit of the additional protection that may be afforded by daily oral prophylaxis against the risks of renal and bone effects as well as the lesser and more minor side effects that can occur.

2.5.3. PSUR cycle

The PSUR cycle remains unchanged.

The annex II related to the PSUR, refers to the EURD list which remains unchanged.

2.6. Risk management plan

The CHMP received the following PRAC Advice on the submitted Risk Management Plan:

The PRAC considered that the risk management plan version 12 is acceptable.

The MAH is reminded that, within 30 calendar days of the receipt of the Opinion, an updated version of Annex I of the RMP template, reflecting the final RMP agreed at the time of the Opinion should be submitted to h-eurmp-evinterface@emea.europa.eu.

The CHMP endorsed the Risk Management Plan version 12 with the following content:

Safety concerns

Table 42. Summary Table of Safety Concerns

Important Identified Risks	FTC, TDF	Post-treatment hepatic flares in HBV infected patients
	TVD	HIV-1 acquisition, including infection resulting from non-adherence (PrEP indication)
	TVD	Development of resistance in patients with unrecognized or acute HIV-1 infection (PrEP indication)
	TDF	Renal toxicity
	TDF	Bone events due to proximal renal tubulopathy/loss of BMD
	TDF	Interaction with didanosine
	TDF	Pancreatitis
Missing Information	TDF	Safety in children (including long-term safety)
	FTC, TDF	Safety in elderly patients
	FTC, TDF	Safety in pregnancy
	FTC, TDF	Safety in lactation
	TDF	Safety in patients with renal impairment

Pharmacovigilance plan

Table 43. Ongoing and Planned Studies/Activities in the Post Authorization Pharmacovigilance Development Plan (Categories 1 3)

Study / Title	Objectives	Safety Concerns Addressed	Status (Planned, Started)	Date for Submission of Interim or Final Reports (Planned or Actual)
Non-interventional studies (Category 3)				
Antiretroviral Pregnancy Registry	To collect information on the risk of birth defects in patients exposed to FTC or TDF during pregnancy	*Missing information*: Safety in pregnancy (FTC, TDF)	Started	In the Truvada PSUR (DLP and periodicity as described in the List of EU reference dates and frequency of submission of PSURs)
Mitochondrial Collaborative Committee (MITOC) Mitochondrial toxicity in children with in utero exposure to nucleoside reverse transcriptase inhibitor (NRTIs)	To investigate the association of NRTI exposure during pregnancy with mitochondrial dysfunction	*Missing information*: Safety in pregnancy (FTC, TDF)	Started	31 May 2015 (Submitted)
GS-US-276-0101 A Prospective, Observational Study of Pregnancy Outcomes among Women exposed to Truvada for PrEP indication nested in the Antiretroviral Pregnancy Registry	Observational study collecting data on pregnancy outcome of women who become pregnant while taking Truvada for pre-exposure prophylaxis,	*Missing information*: Safety in pregnancy (FTC, TDF)	Ongoing	Final report planned Q1 2017
GS-US-276-0103 A Prospective, Observational Study of Individuals Who Seroconvert While Taking Truvada for Pre-Exposure Prophylaxis (PrEP)	Collect and analyze data from individuals who take Truvada for pre-exposure prophylaxis of sexually acquired HIV-1 infections and who seroconvert during follow-up	*Important identified risks:* HIV-1 acquisition, including infection resulting from non-adherence (TVD PrEP indication) Development of resistance in patients with unrecognized or acute infection (TVD PrEP indication)	Ongoing	Final report planned Q3 2018
GS-US-276-0104 Seroconversions, Resistance, Adverse Events and Drug Adherence among Subjects taking Truvada for PrEP: A Nested Case Control study	Collect and analyze data examining the association between levels of adherence to the once-daily dosing regimen and risk of seroconversion, resistance development, and renal and skeletal adverse events.	*Important identified risks:* HIV-1 acquisition, including infection resulting from non-adherence (TVD PrEP indication) Development of resistance in patients with unrecognized or acute infection	Ongoing	Final report planned Q2 2019

Study / Title	Objectives	Safety Concerns Addressed	Status (Planned, Started)	Date for Submission of Interim or Final Reports (Planned or Actual)
		(TVD PrEP indication) Renal toxicity (TDF) Bone events due to proximal renal tubulopathy/loss of BMD (TDF)		
GS-US-276-0105 A Prospective, Observational, Drug Utilization Study of Subjects Taking Truvada for Pre-exposure Prophylaxis in the USA	Provide nationally representative drug utilization data for use of Truvada for a pre-exposure prophylaxis indication including both TVD and for the single-ingredient products containing emtricitabine or tenofovir disoproxil fumarate.	*Important identified risks:* HIV-1 acquisition, including infection resulting from non-adherence (TVD PrEP indication) Development of resistance in patients with unrecognized or acute infection (TVD PrEP indication)	Ongoing	Final report planned Q1 2017
GS-EU-276-4027 A Drug Utilization Study of Truvada for Pre-Exposure Prophylaxis in the European Union	To provide information on the effectiveness of the additional risk minimization measures and to describe the usage patterns and reported adherence to the use of Truvada for PrEP	*Important identified risks:* HIV-1 acquisition, including infection resulting from non-adherence (TVD PrEP indication) Development of resistance in patients with unrecognized or acute infection (TVD PrEP indication)	Planned	Protocol planned September 2016
Other data (Category 3)				
Monitoring of reversibility of renal tubulopathy in clinical trials	To collect information on the reversibility of renal tubulopathy following the discontinuation of tenofovir DF in adult and pediatric patients	*Important identified risk*: Renal toxicity (TDF)	Ongoing activity	Ongoing activity

Risk minimisation measures

Safety Concern	Routine Risk Minimization Measures	Additional Risk Minimization Measures

Safety Concern	Routine Risk Minimization Measures	Additional Risk Minimization Measures
Important Identified Risks		
Post-treatment hepatic flares in HBV infected patients (FTC, TDF)	Section 4.4 of the Truvada SmPC warns about the risk of exacerbation of hepatitis in HBV infected patients following discontinuation of Truvada.	None
HIV-1 Acquisition, including infection resulting from non-adherence (TVD – PrEP)	Section 4.4 of the Truvada SmPC and the Truvada Package Leaflet warn that Truvada should only be taken as part of a comprehensive prevention strategy and that the individual should be counselled to strictly adhere to the recommended Truvada dosing schedule.	Distribution of risk minimization material directed to the prescriber and the individual at risk, to healthcare providers who are likely to prescribe Truvada for PrEP.
Development of resistance in patients with unrecognized or acute HIV-1 infection (TVD – PrEP)	Sections 4.3 and 4.4 of the Truvada SmPC and the Truvada Package Leaflet warn that Truvada should only be used in individuals confirmed to be HIV-negative prior to initiating and routinely while taking Truvada for PrEP.	Distribution of risk minimization material directed to the prescriber and the individual at risk, to healthcare providers who are likely to prescribe Truvada for PrEP.
Renal toxicity (TDF)	Section 4.2 of the Truvada SmPC states that Truvada should only be used in individuals with creatinine clearance below 80 mL/min if the potential benefits of treatment are considered to outweigh the potential risks. Section 4.4 of the Truvada SmPC provides guidance on calculating creatinine clearance at baseline and the regular monitoring of renal function during Truvada use. In individuals at risk for renal impairment, more frequent monitoring of renal function is required. Section 4.4 of the Truvada SmPC states that use of Truvada should be avoided with concurrent or recent use of nephrotoxic medicinal products and that if concomitant use of Truvada and nephrotoxic agents is unavoidable, renal function should be monitored weekly. Section 4.4 of the Truvada SmPC states that cases of acute renal failure after initiation of high dose or multiple NSAIDs have been reported in HIV-1 infected patients treated with TDF and with risk factors for renal dysfunction. If Truvada is coadministered with an NSAID, renal function should be monitored adequately. Section 4.4 of the Truvada SmPC states that the potential risks and benefits associated with coadministration of LDV/SOF with tenofovir disoproxil fumarate given in conjunction with a boosted HIV protease inhibitor (e.g. atazanavir or darunavir) should be considered, particularly in patients at increased risk of renal dysfunction, and that patients receiving LDV/SOF concomitantly with tenofovir disoproxil fumarate and a boosted HIV protease inhibitor should be monitored for adverse reactions related to tenofovir disoproxil fumarate. Section 4.5 of the Truvada SmPC provides guidance that coadministration of tenofovir disoproxil fumarate with LDV/SOF and atazanavir/ritonavir or darunavir/ritonavir should be used with caution with frequent renal monitoring if other alternatives are not available, and that when LDV/SOF is coadministered with tenofovir disoproxil fumarate and efavirenz or rilpivirine no dose adjustment is recommended but renal function should be closely monitored. Section 4.5 of the Truvada SmPC provides information on interactions due to elimination of FTC and TDF by the kidneys and provides recommendations against the use of Truvada with nephrotoxic medications. Section 4.8 of the Truvada SmPC recommends that renal function should be monitored in any individual receiving Truvada as Truvada may cause renal damage.	*Educational initiatives* 'HIV and the Kidney' educational program HIV renal educational brochure (including creatinine clearance slide ruler)

Safety Concern	Routine Risk Minimization Measures	Additional Risk Minimization Measures
	Renal ADRs associated with the TDF component of Truvada are provided in Section 4.8 of the Truvada SmPC. Section 4.8 of the Truvada SmPC states that proximal renal tubulopathy generally resolved or improved after tenofovir disoproxil fumarate discontinuation. Individuals at risk of renal impairment (such as individuals with baseline renal risk factors, advanced HIV disease, or individuals receiving concomitant nephrotoxic medications) are at increased risk of experiencing incomplete recovery of renal function despite tenofovir disoproxil fumarate discontinuation. *For treatment of HIV-1 infection:* Section 4.2 of the Truvada SmPC also contains recommendations on dosing in mild renal impairment (Cl_{cr} 50-80 mL/min) and moderate renal impairment (Cl_{cr} 30-49 mL/min) and states that Truvada is not recommended for patients with severe renal impairment (creatinine clearance <30 mL/min) and patients who require hemodialysis. Section 4.4 of the Truvada SmPC states that a higher risk of renal impairment has been reported in patients receiving tenofovir disoproxil fumarate in combination with a ritonavir or cobicistat boosted protease inhibitor. A close monitoring of renal function is required in these patients. In patients with renal risk factors, the coadministration of tenofovir disoproxil fumarate with a boosted protease inhibitor should be carefully evaluated. Section 4.4 of the Truvada SmPC contains a warning statement that renal function should be re-evaluated within a week should serum phosphate decrease < 1.5 mg/dL, or creatinine clearance decrease to < 50 mL/min in any patient receiving Truvada. Consideration should be given to interrupting treatment with Truvada in patients with creatinine clearance < 50mL/min or decreases in serum phosphate to <1.0mg/dL (0.32mmol/L). Interrupting treatment with Truvada should also be considered in case of progressive decline of renal function when no other cause has been identified. Section 4.4 of the Truvada SmPC contains a recommendation that dose interval adjustments for HIV-1 patients with creatinine clearance 30-49 mL/min should be made. Section 4.4 of the Truvada SmPC contains a warning that a careful benefit-risk assessment is needed when Truvada is used in patients with creatinine clearance < 60 mL/min and that renal function should be closely monitored. Section 4.4 of the Truvada SmPC contains a warning that the clinical response to treatment should be closely monitored in patients receiving Truvada at a prolonged dosing interval. Section 4.4 of the Truvada SmPC states that Truvada is not recommended for patients with severe renal impairment (creatinine clearance < 30 mL/min) or on dialysis as the appropriate dose dose adjustments cannot be achieved with the combination tablet. Section 4.4 of the Truvada SmPC states that Truvada is not recommended for patients with severe renal impairment (creatinine clearance < 30 mL/min) or on dialysis as the appropriate dose adjustments cannot be achieved with the combination tablet. *For PrEP:* Section 4.2 and 4.4 of the Truvada SmPC states that Truvada has not been studied in HIV-1 uninfected individuals with creatinine clearance < 60 mL/min and is therefore not recommended for use in this population. Section 4.4 of the Truvada SmPC also contains a warning statement that renal function should be re-evaluated within a week should serum phosphate decrease < 1.5 mg/dL, or creatinine clearance decrease to < 60 mL/min in any individual receiving Truvada. Consideration should be given to interrupting use of Truvada in individuals with creatinine clearance < 60mL/min or decreases in	

Safety Concern	Routine Risk Minimization Measures	Additional Risk Minimization Measures
	serum phposphate to <1.0mg/dL (0.32 mmol/L). Interrupting treatment with Truvada should also be considered in case of progressive decline of renal function when no other cause has been identified.	
Bone events due to proximal renal tubulopathy/loss of BMD (TDF)	Section 4.4 of the Truvada SmPC warns about loss of BMD associated with TDF and that more pronounced decreases in BMD were seen in patients treated with tenofovir disoproxil fumarate as part of a regimen containing a boosted protease inhibitor and provides guidance that alternative treatment regimens should be considered for patients with osteoporosis that are at a high risk for fractures. Sections 4.4 and 4.8 of the Truvada SmPC provide a description of bone events associated with TDF-associated proximal renal tubulopathy.	None
Interaction with didanosine (TDF)	Sections 4.4 and 4.5 of the Truvada SmPC warn that coadministration of tenofovir DF and didanosine is not recommended and there is a statement in Section 4.8 of the Truvada SmPC regarding the risk of lactic acidosis and pancreatitis associated with the interaction between TDF and didanosine.	None
Pancreatitis (TDF)	Sections 4.4 and 4.5 of the Truvada SmPC warn about the risk of pancreatitis associated with the interaction between TDF and didanosine and state that co-administration is not recommended. Pancreatitis is included as an ADR to TDF in Section 4.8 of the Truvada SmPC.	None
Missing Information		
Safety in children (including long-term safety (TDF)	Sections 4.2 and 4.8 of the Truvada SmPC note that the safety and efficacy of Truvada has not yet been studied in children < 18 years old and therefore Truvada is not recommended in this population.	None
Safety in elderly patients (FTC, TDF)	Sections 4.2 and 4.4 of the Truvada SmPC note that Truvada has not been studied in individuals over the age of 65 years, and should be administered with caution in this patient population.	None
Safety in pregnancy (FTC, TDF)	Section 4.6 of the Truvada SmPC provides information on pregnancy in humans for the FTC and TDF components and in animals for all components of Truvada and notes that Truvada may be considered during pregnancy, if necessary.	None
Safety in lactation (FTC, TDF)	Section 4.6 of the Truvada SmPC provides information on secretion of FTC and TDF in human milk and notes that Truvada should not be used during breastfeeding.	None
Safety in patients with renal impairment (TDF)	Section 4.2 of the Truvada SmPC states that Truvada should only be used in individuals with creatinine clearance below 80 mL/min if the potential benefits are considered to outweigh the potential risks. *For treatment of HIV-1 infection* Section 4.2 of the Truvada SmPC also contains recommendations on dosing in mild renal impairment (Cl_{cr} 50-80 mL/min) and moderate renal impairment (Cl_{cr} 30-49 mL/min) and states that Truvada is not recommended for patients with severe renal impairment (creatinine clearance <30 mL/min) and patients who require hemodialysis. *For PrEP* Sections 4.2 and 4.4 of the Truvada SmPC states that Truvada has not been studied in HIV-1 uninfected individuals with creatinine clearance < 60 mL/min and is therefore not recommended for use in this population.	None

2.7. Update of the Product information

As a consequence of the new indication, sections 4.1, 4.2, 4.3, 4.4, 4.5, 4.7, 4.8, 4.9, 5.1, 5.2 and 5.3 of the SmPC are updated. The annex II is updated to include additional risk minimisation measures.

Furthermore, the MAH performed minor linguistic amendments. The Package Leaflet is updated in accordance. In addition, the MAH took the opportunity of this variation to perform minor linguistic amendments in the translations of the product information for Truvada.

2.7.1. User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the MAH show that the package leaflet meets the criteria for readability as set out in the Guideline on the readability of the label and package leaflet of medicinal products for human use.

3. Benefit-Risk Balance

Benefits

Beneficial effects

The current application to add an indication for use of daily Truvada for HIV pre-exposure prophylaxis (PrEP) is principally based on CO-US-104-0288 (iPrEx), which was conducted in MSM. This was an event-driven study such that by the cut-off date for the primary analysis 1540/2499 (62%) of subjects had been on study for ≥ 1 year.

The study reported relative effectiveness of 44% (mITT) and 47% (ITT) in the primary analysis. The lower bounds of the 95% CI were above zero but below the pre-defined cut-off of 30%. Results for EOT and 8 weeks post-EOT gave very similar results to those for the primary analysis. However, in mITT subjects reporting ≥90% pill adherence the relative efficacy was 73% (41%, 88%) and for those with quantifiable plasma or intracellular drug levels the relative efficacy was 92% (40%, 99%), even in those reporting URAI. Thus, as in previous studies, efficacy of oral Truvada depended on adherence. Adherence and efficacy were related to age, level of education and reporting URAI at screening.

The number of sexual partners with whom respondents had receptive anal intercourse decreased after study enrolment, and the percentage of those partners who used a condom increased with similar results in each treatment group at each time point. No significant between-group differences were found in the incidence of syphilis (p = 0.49), gonorrhoea (p = 0.74), chlamydia (p = 0.43), genital warts (p = 0.53) or genital ulcers (p = 0.62) during follow-up.

A second study (CO-US-104-0380; Partner's PrEP) provides efficacy data in HIV-1 discordant couples. At the time the study was conducted and at the locations involved the index cases were not to be considered in need of HIV treatment. In reality, most if not all of them would now be given ART if resident in the EU. With 4758 couples involved, there were 7830 person-years and median 23 months of follow-up for assessment of HIV-1 incidence.

In the mITT population the HRs for TDF relative to placebo indicated a 67% reduction (95% CI: 44%–81%) in risk of HIV-1 acquisition while the HRs for FTC/TDF relative to placebo indicated a 75% reduction (95% CI: 55%–87%) in risk of HIV-1 acquisition. Overall, similar protective trends for TDF and FTC/TDF compared with placebo were observed in each sub-group including gender. Using a case-cohort analysis, detection of tenofovir in plasma samples was compared for partners who received active therapy and did or did not acquire HIV-1. Cases were much less likely than controls to have detectable TFV in plasma (actual concentrations were not determined).

Percentages of HIV-1 seronegative partners who reported having sex without condoms with their HIV-1 infected partner during the prior month decreased from 27% at baseline to 13% and 9% at 12 and 24

months, respectively. In contrast, the percentages who reported having sex with an outside partner for any prior month increased from 9% at baseline to 30% during the study.

Both these studies had extensions, which have been reported in the literature. Participants in iPrEx were offered open label Truvada. The HIV incidence on PrEP was 53% (95% CI 26 to 70) lower than in the placebo group of the randomised phase (3.93 infections per 100 p-y) and 51% (95% CI 23 to 69) lower than during the gap between the randomised phase and the OLE (3.81 infections per 100 p-y). HIV incidence was strongly inversely related to detection of TFV-DP in dried blood spots.

Participants in Partner's PrEP who had been assigned to placebo were offered re-randomisation (in a 1:1 ratio) to TDF or Truvada in a blinded fashion. All subjects continuing on treatment regardless of the initial randomisation group were kept unaware of the exact treatment they received until 30 Dec 2012. The cumulative data include an additional 3569 p-y of follow-up and 26 additional HIV-1 infections. Of the additional 26 (17 TDF and 9 Truvada) infections 12 (8 TDF; 4 Truvada) had been infected at the time of initial randomisation (8) or re-randomisation (4). Thus, 52 infections occurred after randomisation in subjects on active treatment, including 31 in the TDF arm (0.71 per 100 p-y) and 21 in the Truvada arm (0.48 per 100 p-y); not significant (HR 0.67, 95% CI 0.39–1.17; p=0.16). Having detectable plasma TFV was associated with an estimated relative risk reduction for acquiring HIV-1 of 85% for TDF and 93% for Truvada. HIV-1 incidences in subjects receiving PrEP were similar before and after the DSMB intervened to stop the placebo group, in which HIV-1 incidence was 2 per 100 p-y.

Other supportive data come from CDC TDF2 in heterosexual men and women and CDC 4323 in MSM only. CDC TDF2 compared Truvada with placebo and reported HIV seroconversion in 9 Truvada and 24 placebo group subjects. These numbers gave an overall protective efficacy of 62.2% (95% CI: 21.5%-83.4%; p = 0.013 [mITT]). In the as-treated population FTC/TDF had a protective efficacy of 77.9% (95% CI: 41.2%-93.6%; p < 0.001). Among participants randomised to Truvada, TFV was detected in the plasma of 50% of seroconverting subjects at the seroconversion visit and in 79.7% of uninfected controls at similar time points. Similarly, FTC was detected in 50% and 81.2% of seroconverting subjects and uninfected subjects, respectively. CDC 4323 was not powered for efficacy but it demonstrated no HIV-1 infections in the daily TDF group vs. 6 infections in subjects randomised to the placebo group.

More recently, data were reported from the pilot phase of PROUD in MSM. At the time when the steering committee recommended that all deferred participants should be offered PrEP follow-up for HIV incidence was complete for 243 (94%) of 259 patient-years in the immediate daily Truvada group versus 222 (90%) of 245 patient-years in the deferred group. Three HIV infections had occurred in the immediate group (1.2/100 person-years) vs. 20 in the deferred group (9.0/100 person-years) despite 174 non-study prescriptions for PrEP in the deferred group (leaving 167 without prior use of PrEP). These results give a relative reduction of 86% (90% CI 64–96, p=0·0001) and an absolute difference of 7.8/100 person-years (90% CI 4.3–11.3). In this open-label study the total number of different anal sex partners showed no significant difference between groups at 1 year (p=0.57) but a larger proportion allocated to PrEP reported URAI (21% *vs* 12%; p=0.03, test for trend). There was no difference in the occurrence of STIs, including rectal gonorrhoea and chlamydia, between groups.

Uncertainty in the knowledge about the beneficial effects

There are two issues that are expected to impact on the benefit of once daily Truvada in routine use over longer periods than have been studied within formal clinical trial settings.

The first is the potential for dwindling adherence to daily dosing, which has already been shown very clearly to impact on efficacy. The second is that taking an oral PrEP will prompt at least some individuals to engage in more risky behaviours, which could result in a higher rate of seroconversion despite PrEP compared to the trial settings, especially if also accompanied by dwindling adherence. In iPrEx and

Partner's PrEP the assessment of behavioural change suggested that being on a study without knowledge of treatment assignment actually reduced risky behaviours to some extent from screening visit reports.

The most relevant investigation of these risks within a clinical trial setting was in the open label PROUD study. However, in this study that was specifically intended to mimic routine use, a proportion of subjects in the delayed group acquired access to PrEP anyway. Therefore it is difficult to interpret the overall findings but, despite some access to PrEP in the delayed group, a larger proportion allocated to PrEP reported URAI (21% *vs* 12%; p=0.03, test for trend). On the other hand, several studies found that those engaging in URAI were more likely to be adherent and derived high levels of protection despite this behaviour.

Risks

Unfavourable effects

The safety profile of Truvada is very well known. When used for PrEP in HIV-1 uninfected subjects the safety profile was entirely as expected based on the wealth of experience with this combination within complete ART regimens.

With regard to the known renal effects of TFV it should be noted that the study populations generally anticipated to use PrEP are likely to have low rates of factors that have been associated with renal abnormalities during TDF treatment (including higher age, lower CrCL, underlying diabetes and concomitant nephrotoxic agents). This may explain why there were not major differences in renal markers between active and placebo groups in the two main PrEP studies reported in this application. There was a consistent trend to greater decreases in BMD vs. placebo in subjects who received TDF or Truvada for PrEP. These observations are described in the SmPC and adequately reflected in the RMP. There is no reason to think that subjects taking TDF as part of PrEP are at any different risk to those taking it for treatment.

Another important risk not directly related to safety is that subjects could acquire HIV-1 despite PrEP and continue to expose the virus to Truvada until such time as the infection is discovered and a full ART regimen is commenced as necessary. This raises the risk of development of clinically important resistance. Thus far it appears that the risk is likely low but it is adequately addressed in the SmPC and PL so that subjects prescribed PrEP are tested for HIV-1 acquisition at frequent intervals. There is an additional risk that this could occur in persons who have an acute HIV-1 infection when initially prescribed PrEP with negative laboratory tests. Thus the SmPC includes a warning against starting PrEP if there is any clinical suspicion of acute infection at the time.

Uncertainty in the knowledge about the unfavourable effects

With long term PrEP use the safety profile can be expected to resemble that already documented for use of Truvada within treatment regimens. The risk of selecting for resistance as described above cannot be predicted at this time.

Effects Table

Effect	Short Description	Truvada	Placebo	Uncertainties / Strength of evidence
Protection in MSM	**iPrEx** DB, PC, RCT To assess HIV infection rates	mITT 36/1224 Relative effectiveness 44% (95% CI 15%, 63%); p=0.005	mITT 64/1217	Supported by similar results at EOT and 8 weeks post-EOT. Lower 95% CI above zero but below 30%

Effect	Short Description	Truvada	Placebo	Uncertainties / Strength of evidence
		8/1224 in those with ≥90% reported pill adherence Relative effectiveness 73% (95% CI 41%, 83%); p=<0.001	30/1217 in those with ≥90% reported pill adherence	Supported by relative effectiveness 92% (95% CI 40%, 99%); p =<0.001) in subjects with quantifiable levels
Protection in partners of HIV+ persons	**Partner's PrEP** DB, PC, RCT To assess HIV infection rates	Truvada 13/1576 (75% reduction; 55, 87%) TDF 17/1579 (67% reduction; 44, 81%)	52/1578	In the mITT population TDF and FTC/TDF each demonstrated significant efficacy compared with placebo while TDF and FTC/TDF were not significantly different from one another. ITT results similar.
Decrease in BMD	Known risk with TDF	**iPrEx** BMD decreased	**iPrEx** BMD increased	Significant differences (-0.4 to -1.0% across total hip, spine, femoral neck and trochanter) between the groups by Week 24.
Proximal renal tubulopathy and Fanconi's syndrome	Known risk with TDF	No cases so far in PrEP use	No cases	Risk can be expected especially with prolonged use; patients most at risk of renal effects may not be common users of PrEP

Benefit-Risk Balance

Importance of favourable and unfavourable effects

Truvada has been shown to provide some degree of protection against HIV-1 infection in persons who put themselves at risk. The degree of protection has been repeatedly shown to be related to the level of adherence, supported by finding drug in plasma and/or intracellularly, although the minimum concentrations that are needed to provide protection have not been identified. Thus, if taken regularly, Truvada can be regarded as having benefit in persons unwilling or unable to take adequate behavioural steps to prevent infection.

The safety profile of Truvada for PrEP can be expected to be similar to that already very well recognised when it is used for treatment of HIV-1.

The difference in the benefit risk relationship when Truvada is used for treatment vs. prophylaxis is therefore not in the safety profile *per se* but in the benefit that may be expected when Truvada is given to subjects who are not yet infected and in whom HIV-1 infection could be wholly prevented if appropriate non-pharmacological measures were to be adequately and consistently employed.

Benefit-risk balance

Ultimately, since it has been concluded that Truvada works if it is taken, it is for subjects and their physicians to discuss to what extent it is acknowledged that adequate preventive measures will not always be applied and to weigh up the benefit of the additional protection that may be afforded by daily oral prophylaxis against the risks of renal and bone effects as well as the lesser and more minor side effects that can occur.

Discussion on the Benefit-Risk Balance

The benefit-risk balance is favourable provided that PrEP use is considered by experienced physicians to be appropriate for individual patients and provided that monitoring of the individual for HIV-1 infection and ADRs of TDF is adequate.

4. Recommendations

Outcome

Based on the review of the submitted data, the CHMP considers the following variation acceptable and therefore recommends the variation to the terms of the Marketing Authorisation, concerning the following change:

Variation accepted		**Type**	**Annexes affected**
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I, II and IIIB

Extension of the indication to add Pre-exposure prophylaxis (PrEP) in combination with safer sex practices to reduce the risk of sexually acquired HIV-1 in adults at high risk. As a consequence, sections 4.1, 4.2, 4.3, 4.4, 4.5, 4.7, 4.8, 4.9, 5.1, 5.2 and 5.3 of the SmPC are updated. The annex II is updated to include additional risk minimisation measures. Furthermore, the MAH performed minor linguistic amendments. The Package Leaflet is updated in accordance. In addition, the MAH took the opportunity of this variation to perform minor linguistic amendments in the translations of the product information for Truvada.

The variation leads to amendments to the Summary of Product Characteristics and Package Leaflet and to the Risk Management Plan (RMP).

Conditions and requirements of the marketing authorisation

- **Periodic Safety Update Reports**

The marketing authorisation holder shall submit periodic safety update reports for this product in accordance with the requirements set out in the list of Union reference dates (EURD list)) provided for under Article 107c(7) of Directive 2001/83/EC and published on the European medicines web-portal.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

- **Risk management plan (RMP)**

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

When the submission of a PSUR and the update of a RMP coincide, they should be submitted at the same time.

In addition, an updated RMP should be submitted:

At the request of the European Medicines Agency;

Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

- **Additional risk minimisation measures**

The Marketing Authorisation Holder (MAH) shall ensure that all physicians who are expected to prescribe/use Truvada in adult patients are provided with a physician educational pack containing the Summary of Product Characteristics and an appropriate educational brochure, as detailed below:

- HIV renal educational brochure
- PrEP educational brochure for prescribers entitled 'Important Safety Information for Prescribers About Truvada for a Pre-exposure Prophylaxis (PrEP) Indication'
- PrEP Checklist for prescribers
- PrEP educational brochure for the individual at risk entitled 'Important Information About Truvada to Reduce the Risk of getting Human Immunodeficiency Virus (HIV) Infection'
- PrEP reminder card

HIV renal educational brochure:

The HIV renal educational brochure should contain the following key messages:

- That there is an increased risk of renal disease in HIV infected patients associated with tenofovir disoproxil fumarate-containing products such as Truvada

- That Truvada should only be used for PrEP in patients with impaired renal function (CrCl< 80 mL/min) if the potential benefits are considered to outweigh the potential risks and is not recommended for use in HIV-1 uninfected individuals with CrCl < 60mL/min

- That use of Truvada should be avoided with concomitant or recent use of nephrotoxic medicinal products. If Truvada is used with nephrotoxic medicinal products, renal function should be closely monitored according to the recommended schedule

- That patients should have their baseline renal function assessed prior to initiating Truvada therapy

- The importance of regular monitoring of renal function during Truvada therapy

- Recommended schedule for monitoring renal function considering the presence or absence of additional risk factors for renal impairment

- Instructions on the use of the creatinine clearance slide ruler

PrEP educational brochure for prescribers:

- Reminder of the key safety information regarding the use of Truvada for PrEP

- Reminder of factors to help identify individuals at high risk of acquiring HIV-1

- Reminder on the risk of development of HIV-1 drug resistance in undiagnosed HIV-1–Infected individuals

- Provides safety information on adherence, HIV testing, renal, bone and HBV status.

PrEP Checklist for prescribers:

- Reminders for evaluations/ counselling at the initial visit and follow-up.

PrEP educational brochure for the individual at risk (to be provided by healthcare provider [HCP]):

- Reminders on what the patient should know before and while taking Truvada to reduce the risk of getting HIV infection

- Reminder on the importance of strict adherence to the recommended dosing regimen

- Provides information on how to take Truvada

- Provides information on the possible side effects

- Provides information on how to store Truvada.

PrEP reminder card for individuals at risk (to be provided by HCP):

- Reminders to adhere to the dosing schedule

- Reminder to attend scheduled clinic visits