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APPLICATION NUMBER:

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MEDICAL REVIEW(S)

CLINICAL REVIEW

Application Type	Supplemental NDA (SE-1)
Application Number(s)	NDA 21-752/S-30
Priority or Standard	Priority
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Division / Office	Division of Antiviral Products / Office of Antimicrobial Products
Reviewer Name(s)	Peter S. Miele, M.D.
Review Completion Date	July 12, 2012
Established Name	emtricitabine/tenofovir disoproxil fumarate
Trade Name	Truvada®
Therapeutic Class	nucleos(t)ide reverse transcriptase inhibitor (NRTI)
Applicant	Gilead Sciences, Inc.
Formulation(s)	200 mg emtricitabine/300 mg tenofovir disoproxil fumarate oral fixed-dose combination tablet
Dosing Regimen	Once daily
Indication(s)	Pre-exposure prophylaxis

Intended Population(s)

(PrEP) to reduce the risk of sexually acquired HIV-1
HIV-1-uninfected adults at high risk of acquiring HIV-1 infection

Template Version: [March 6, 2009](#)

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1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

Approval of this supplemental New Drug Application for TRUVADA® is recommended for the proposed new indication of pre-exposure prophylaxis (PrEP). This recommendation is based on review of the efficacy and safety from two large, prospective, randomized and blinded placebo-controlled Phase 3 clinical trials. The iPrEx trial enrolled 2,499 men who have sex with men (MSM) at high risk for HIV acquisition (with 3,891 person-years of follow-up) and the Partners PrEP trial enrolled 4,747 HIV-uninfected partners in stable serodiscordant relationships (with 7,830 person-years of follow-up). Both trials demonstrated the superiority of once-daily oral TRUVADA over placebo in preventing HIV acquisition through sexual exposure when offered as part of a comprehensive prevention strategy that included monthly HIV testing, risk reduction counseling, provision of condoms, and treatment of any sexually-transmitted infections. In these populations and trial settings, TRUVADA reduced the risk of HIV infection by 42% (95% CI 18-60%, $p=0.001$) relative to placebo in the iPrEx trial in the modified intent-to-treat analysis, and by 75% (95% CI 54-86%) relative to placebo in the Partners PrEP trial. In both trials, efficacy was strongly correlated with drug adherence, as demonstrated by detectable drug levels in post-hoc subgroup analyses of blood samples. Risk reduction was substantially higher (~90%) in subjects with detectable drug concentrations relative to non-adherent subjects with no detectable drug levels. Furthermore, the effectiveness of TRUVADA was demonstrated across multiple subpopulations regardless of gender, race, age, region, or baseline risk characteristics; importantly, statistically significant risk reduction was observed for both males and females in Partners PrEP. Only in MSM who did not report engaging in unprotected receptive anal intercourse (a high risk behavior) was a protective effect of TRUVADA not fully demonstrated, thus highlighting the importance of recommending TRUVADA for PrEP only for adults at high risk of HIV acquisition.

No new safety issues were identified in the course of the review and there were no major issues with the integrity of the submitted data that would preclude this assessment. TRUVADA was generally safe and well-tolerated in an HIV-uninfected population, with a safety profile that was consistent with the current label. The major safety risks associated with TRUVADA (renal, bone, and hepatic flares in the setting of hepatitis B infection) were infrequent in these trials. Moreover, these issues can be monitored and managed in clinical practice. In addition, safety data from other PrEP trials, including submitted data from a Phase 2 trial in 400 U.S. MSM, were consistent with the safety trends noted in the pivotal trials and further support the safety of TRUVADA for a PrEP indication.

The other potential risks specific to a PrEP indication, such as development of drug resistant variants in individuals who seroconvert while taking TRUVADA for PrEP or

behavioral risk compensation, were not observed to any significant degree in the clinical trials. Small numbers of individuals with unrecognized acute or early HIV infection were enrolled in each of trial and among some of these subjects, development of antiviral resistance was observed. As a result, the product label and Risk Evaluation and Mitigation Strategy (REMS) education materials will emphasize the importance of screening potential candidates for PrEP for acute signs and symptoms of HIV infection and for risk behavior in the month preceding evaluation and to use HIV diagnostic methods that are sensitive to detect acute or early infection.

Although the majority of the clinical experience with TRUVADA for a PrEP indication was gathered outside of the United States (U.S. participants only made up 9% of the iPrEx population and none of the Partners PrEP cohort), there is no biological basis to suppose that the efficacy and safety demonstrated in these trials should not apply to a U.S. population. The strength of the protective effect seen across multiple subgroups in these trials, and the lack of any safety differences based on race or region, support this assertion. Moreover, review of the submitted data from the CDC 4323 trial supports the safe use of TRUVADA in a U.S. MSM population, the group most at risk for HIV infection in this country. Additionally, while CDC 4323 enrolled only 400 trial subjects, the adherence observed in this trial indicates that compliance in a U.S. high-risk population may be significantly higher than that observed in the iPrEx trial.

While the two pivotal trials submitted in support of the proposed indication were conducted in populations at very high risk for acquiring HIV, the results convincingly demonstrate the effectiveness of TRUVADA against a variety of HIV sexual exposure routes (rectal sex in iPrEx and penile/vaginal sex in Partners PrEP) that are relevant to all sexually active persons regardless of relationship status. As a result, the PrEP indication for TRUVADA will not be limited to just those populations defined by the pivotal trials, but instead will be extended to all sexually active adults who are considered to be at high risk for infection. High risk for these individuals may be determined by a variety of factors, such as local HIV prevalence rates, involvement in high-risk sexual networks, or other established epidemiological risk factors. The results from the CDC TDF2 trial in Botswana, although not submitted for FDA review, were recently published in a peer-reviewed journal and demonstrate a 62% risk reduction in heterosexual men and women, the vast majority of whom were single. These results provide additional support for a broader indication in all adults at high risk of sexually acquired HIV infection.

It is important to note that another clinical trial of TRUVADA as PrEP, the FEM-PrEP trial, failed to demonstrate a protective effect in high-risk African women and was terminated for futility. Although not reviewed by FDA, analyses presented at a recent scientific meeting by the FEM-PrEP investigators indicate that drug adherence among the trial participants was so poor as to undermine the trial's ability to determine efficacy. This finding provides secondary evidence for the correlation between adherence and efficacy identified in both the iPrEx and Partners PrEP trials and further underscores the

crucial role that adherence plays in the prophylactic efficacy of TRUVADA. Another oral PrEP trial in women, the VOICE trial, terminated the oral tenofovir disoproxil fumarate (TDF) arm as well as the arms evaluating the tenofovir vaginal microbicide gel, but is currently evaluating TRUVADA against placebo. Since the VOICE trial is still ongoing and blinded, little is known about the reasons for the failure of the oral TDF arm, but it is reassuring that TRUVADA is still being studied in that trial, possibly suggesting that some effect is being demonstrated. It should be noted that oral TDF did reduce acquisition of HIV in the Partners PREP trial; however, more remains to be learned about the efficacy of oral TDF alone in preventing sexual acquisition of HIV.

Over the past decade, the incidence of new HIV infections in the United States has shown no signs of abating, despite widespread knowledge of HIV/AIDS and decades of intensive condom promotion. The U.S. Centers for Disease Control (CDC) estimates that approximately 50,000 persons are infected annually with HIV in the United States.¹ Moreover, the HIV epidemic is disproportionately affecting MSM and men and women of color; in some populations, such as young African-American MSM, the rates of new HIV infections have dramatically increased in recent years.

To combat these trends, for the first time in U.S. history, a national strategy has been developed to address the domestic HIV epidemic. The primary objective of the National HIV/AIDS Strategy is to lower the annual number of new infections by 25% in 5 years.² As noted in the strategy, a multipronged approach to HIV prevention is needed, including the combination of condom promotion, risk reduction counseling, treatment of sexually transmitted infections, and increased uptake and retention of HIV-infected individuals in healthcare. However, given the limited effectiveness of current prevention methods and the lack of an available vaccine, there remains an unmet medical need to identify and implement new evidence-based approaches to HIV prevention that can augment existing strategies.

In conclusion, the totality of the data from the various clinical trials of oral PrEP, including the iPrEx and Partners PrEP trials reviewed herein, demonstrate that TRUVADA is an effective and safe intervention for the prevention of HIV if taken as directed and used in combination with a comprehensive risk reduction strategy. Approval of TRUVADA for a PrEP indication would represent the first drug product approved for an HIV prevention indication. Further, the availability of an approved oral PrEP intervention may spur increased HIV testing and diagnosing of HIV infections among individuals who might otherwise remain unaware of their condition. At the end of 2008, CDC estimated that over 1 million persons were living with HIV in the United States, among whom 20% were undiagnosed.³ Studies show that persons aware of

¹ Prejean J et al. Estimated HIV incidence in the United States, 2006–2009. PLoS ONE 6(8): e17502.

² Office of National AIDS Policy. National HIV/AIDS Strategy. Washington, DC: Office of National AIDS Policy; 2010. <http://www.whitehouse.gov/administration/eop/onap/nhas>. Accessed: March 19, 2012.

³ U.S. Centers for Disease Control and Prevention (CDC). HIV surveillance – United States, 1981-2008. MMWR 2011; 60: 689-93.

their HIV infection often take substantial steps to reduce their risk behaviors.⁴ Thus for a number of reasons, approval of TRUVADA for a PrEP indication has the potential to greatly contribute to addressing an unmet medical need and reduce the number of new HIV infections.

1.2 Risk Benefit Assessment

As part of the National HIV Behavioral Surveillance system, the CDC collected HIV testing data in 8,153 U.S. MSM in 2008 and found an HIV prevalence of 19%.⁵ HIV prevalence and lack of awareness of infection status were highest among young and minority MSM. Further, the study found 7% prevalence among MSM who had tested negative during the preceding year. A separate CDC-funded study conducted in 2006-2007 found an HIV prevalence of 3.3% among 933 U.S. minority women and their heterosexual partners (1,021 partnerships).⁶ Given these statistics and the relative risk reduction of 42-75% compared with placebo demonstrated by the two pivotal trials, the benefit of TRUVADA for a PrEP indication is clear for individuals at high risk, provided they adhere to recommended dosing. That said, it is essential that TRUVADA for a PrEP indication be recommended for use only in individuals determined to be at high risk, in order to ensure a favorable risk-benefit assessment.

The major risks associated with use of TRUVADA for a PrEP indication are 1) breakthrough HIV infection, 2) development of drug resistance, and 3) drug toxicity related to kidney, bone, and hepatic flares in persons infected with hepatitis B virus (HBV).

The efficacy of TRUVADA in preventing HIV infection was shown to be strongly correlated to drug adherence, as demonstrated by drug level analyses conducted across multiple trials. Yet despite monthly visits and counseling, overall adherence among MSM in the iPrEx trial and reportedly among heterosexual women in the FEM-PrEP trial appeared to be low. Adherence in the iPrEx trial varied according to age, education, and the reporting of unprotected receptive anal sex. In both pivotal trials, the iPrEx and Partners PrEP trial, age 25 years or older was associated with better adherence. Adherence among U.S. participants in the iPrEx trial appeared to be higher compared with non-U.S. participants, perhaps owing to their older median age. Adherence was also higher among the 400 U.S. MSM studied in the CDC 4323 trial, where again the median age of participants was older than that of the overall iPrEx

⁴ Marks G, Crepaz N, Senterfitt JW, et al. Meta-analysis of high-risk sexual behavior in persons aware and unaware they are infected with HIV in the United States: implications for HIV prevention programs. *J Acquir Immune Defic Syndr* 2005; 39:446–53.

⁵ CDC. Prevalence and awareness of HIV infection among men who have sex with men - 21 cities, United States, 2008. *MMWR* 2010; 59: 1201-7.

⁶ Hageman K, Paz-Bailey G, Ivy W, et al. HIV testing and serostatus knowledge among partnerships at increased risk for HIV infection – heterosexual partner study among black and Hispanic women in 16 cities: US, 2006-2007. 19th Conference on Retroviruses and Opportunistic Infections; 2012 March 5-8; Seattle, WA: Abstract 1049.

cohort. Whether adherence to TRUVADA will be better or worse outside a clinical trial setting is not known at this time and will require further evaluation. Individuals may have any number of reasons for adhering or not adhering to medications. Adherence to an HIV prophylactic intervention may also be influenced by self-perceived risk.

While it is anticipated that most individuals seeking or agreeing to take TRUVADA for a PrEP indication will recognize themselves to be at significant risk for HIV, education about risk behaviors and risk reduction counseling must continue to be major components of any prevention strategy that uses TRUVADA. In addition, regular counseling with respect to drug adherence will be essential for optimal protection. That said, TRUVADA should not be relied upon solely to prevent HIV infection. TRUVADA should only be offered as part of a comprehensive prevention strategy that includes consistent and correct condom use, regular HIV testing, reduction of risk behaviors, and treatment of sexually transmitted infections.

Drug resistance is another risk associated with use of oral PrEP. Analysis of HIV isolates from clinical trial participants who became newly infected while taking PrEP, however, failed to identify any resistance substitutions, likely because of lack of adherence to study drug among these individuals. In the absence of circulating drug concentrations, there is no selective pressure for the emergence of resistance substitutions. Selection of resistance among trial participants may also have been minimized due to monthly monitoring for seroconversion. Where resistance was detected, however, was among the 10 trial participants who were randomized to active drug with undiagnosed early HIV infection. The risk of developing drug resistance in this scenario is serious and can potentially limit treatment options for an infected individual as well as increase the risk of transmission of drug-resistant virus to others. The impact of PrEP on resistance beyond a clinical trial setting is difficult to predict, but resistance is expected to occur among HIV-infected individuals using TRUVADA as PrEP. The frequency of resistance may be minimized by limiting the duration of drug exposure after infection occurs with frequent monitoring for HIV seroconversion, as well as carefully evaluating individuals for early HIV infection prior to initiating PrEP and during its use. Use of an HIV test with a narrow window for detecting acute or early infection, such as an antigen-based test or RNA testing, is recommended where available. In addition, the prescriber should be alert to any signs or symptoms of acute HIV infection. In the iPrEx trial, the majority of the HIV-infected subjects inadvertently enrolled in the trial exhibited symptoms of acute infection that were attributed to respiratory tract infections or other non-HIV causes but the site investigators. Individuals should be screened for signs or symptoms concerning for active, potentially acute infection, and if present, TRUVADA for a PrEP indication should be deferred until absence of HIV infection can be confirmed. Lastly, while the clinical trials conducted monthly HIV testing, such frequency of testing is not practical in a real world setting. Based on interim CDC guidance and the recommendations of the Advisory Committee, HIV monitoring is recommended every 3 months at a minimum, more frequently if the individual's situation warrants it. The adequacy of testing at these recommended

intervals, however, requires evaluation; more than a dozen demonstration projects are currently planned or underway that will assess the impact of less than monthly testing on incidence of seroconversion and development of drug resistance.

With respect to other safety risks, TRUVADA was generally safe and well-tolerated among HIV-uninfected individuals enrolled in the three trials submitted for review. No new safety issues were identified. In general, adverse events were balanced between treatment groups. In iPrEx, unintended weight loss, nausea, and abdominal pain were reported more often in subjects receiving TRUVADA. In Partners PrEP, moderate to severe neutropenia was observed slightly more often in subjects receiving TRUVADA as compared with placebo, but the differences were small (8% versus 6%, respectively). No evidence of hepatic flares was observed among the limited number of subjects with acute or chronic HBV infection enrolled in these trials.

Although a small imbalance was observed in the rates of creatinine elevations between the TRUVADA and placebo groups across multiple trials, renal toxicity was generally uncommon and was mostly mild, rarely serious, and at all times manageable. Discontinuations of medication for any reason were infrequent and generally balanced between groups. In the iPrEx trial, seven subjects discontinued TRUVADA for increased creatinine; however, six of these were able to resume treatment without incident. One subject permanently discontinued TRUVADA because of a Grade 1 creatinine increase and another for Grade 2 hypophosphatemia. In the Partners PrEP trial, six of seven discontinuations were due to renal toxicity, five of which were related to a decline in creatinine clearance <50 mL/min (two TRUVADA, two TDF and one placebo). One of the six subjects in the TDF group was also noted to have hypophosphatemia; however, none had proteinuria or glycosuria. The five cases of decreased creatinine clearance all occurred in women, all of whom had normal values at baseline, although three had low normal creatinine clearances at entry. Renal insufficiency resolved with cessation of the study drug in these five cases, but a Grade 1 creatinine increase in a male subject was still ongoing at exit from the trial.

With respect to bone safety, subjects receiving TRUVADA in the iPrEx trial had small but statistically significant mean decreases in bone mineral density (BMD) compared to baseline and relative to placebo. BMD losses greater than 5% from baseline at the spine were observed in 14% of TRUVADA subjects compared with 6% of placebo subjects. Of note, among subjects with greater than 5% decrease from baseline in BMD at the spine, five (all taking TRUVADA) also had evidence of treatment-emergent graded hypophosphatemia. Similar BMD findings were noted in the CDC 4323 trial; in addition, almost twice as many subjects receiving TDF in the CDC 4323 trial reported new onset back pain compared with subjects receiving placebo. DEXA scans obtained six months after discontinuation of treatment in the iPrEx trial, however, showed that the BMD decreases associated with TRUVADA were reversing towards baseline levels. Importantly, in all clinical trials, bone fractures were balanced between treatment arms and predominantly appeared to be trauma-related.

In conclusion, the decision to prescribe TRUVADA for the prevention of sexual acquisition of HIV infection should carefully weigh the individual's risks for acquiring HIV, their understanding of the importance of adherence to medication, and their potential for development of renal or bone toxicity. Education about use of PrEP and behavioral counseling are essential. Baseline evaluation of individuals should include HIV testing, assessment of renal function, serum phosphorous, and assessment for the presence of risk factors for development of renal or bone toxicities. Consideration should also be given to providing the individual with Vitamin D and calcium supplementation. Periodic evaluation during PrEP administration should include regular HIV testing (at least every 3 months) and monitoring for the development of renal dysfunction. DEXA scans prior to and periodically during treatment may be considered for some individuals.

If healthcare providers prescribe and individuals utilize TRUVADA in the manner recommended for PrEP, in combination with other strategies to prevent HIV infection, the individual at high risk may be spared infection with a serious and life-threatening illness that requires lifelong treatment with a three-drug antiretroviral regimen. That regimen, in line with current treatment guidelines for HIV-infected treatment-naïve patients, will almost certainly contain TRUVADA.

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

A Risk Evaluation and Mitigation Strategy (REMS) is being recommended for the PrEP indication because the risk of developing drug resistance in the setting of ongoing TRUVADA use following HIV infection is considered serious. Development of drug resistant HIV-1 variants may limit treatment options for an individual who has seroconverted while taking TRUVADA for PrEP and may increase the risk of transmitting resistant virus to others. Since the drug product is already approved and widely available for the treatment of HIV infection, a restrictive REMS that links distribution of the drug to documentation of a negative HIV test result is not feasible. These issues were discussed at length at a Center for Drug Evaluation and Research (CDER) Regulatory Briefing (see Section 2.5) and at the Advisory Committee meeting held to discuss this application (see Section 9.3). As such, the goals of the REMS will be to inform and educate prescribers, other healthcare professionals, and uninfected individuals at high risk for acquiring HIV infection about:

- The importance of strict adherence to the recommended dosing regimen
- The importance of regular monitoring of HIV-1 serostatus to avoid continuing to take TRUVADA for a PrEP indication if seroconversion has occurred, in order to reduce the risk of development of resistant HIV-1 variants
- The fact that TRUVADA for a PrEP indication must be considered as only part of a comprehensive prevention strategy to reduce the risk of HIV-1 infection and that other preventive measures should also be used

The elements of the REMS will include:

- A TRUVADA Medication Guide, which will be dispensed with each TRUVADA prescription in accordance with 21 CFR 208.24.
- Elements to Assure Safe Use (ETASU), consisting of:
 - Training and education materials made available to healthcare prescribers who prescribe TRUVADA for a PrEP indication. This will be done via an online website or by print training modules available as hard copy, upon request
 - Targeting training efforts to healthcare prescribers most likely to prescribe PrEP (primary care physicians, internists, family practitioners, infectious diseases specialists, obstetrician-gynecologists, and addiction specialists)
 - Dissemination of a Safety Information Fact Sheet about the potential and known safety risks with TRUVADA for a PrEP indication to select professional organizations
 - Provision of the Safety Information Fact Sheet to MedWatch at the same time it is provided to the select professional organizations
 - Quarterly publication of journal information pieces
 - Distribution of a Dear Healthcare Provider (DHCP) letter
 - Provision of an education slide deck for face-to-face meetings between pharmaceutical representatives and prescribers
 - Provision of a voluntary Healthcare Prescriber-Individual Agreement Form for initiating TRUVADA for PrEP to be signed by both parties and placed in an individual's medical record
 - Although use of this element will not be made mandatory, it may nonetheless serve as a tool for the prescriber and uninfected individual to facilitate discussion and promote understanding about the important safety risks associated with TRUVADA for a PrEP indication.
 - Provision of a voluntary Checklist for Prescribers as a reminder about the management of an individual considering or taking TRUVADA for a PrEP indication, including recommended screening and baseline tests, signs and symptoms of acute HIV infection, vaccination against HBV as needed, and testing for sexually transmitted infections. The Checklist can also be placed in an individual's medical record to indicate that the prescriber has taken the necessary steps to ensure TRUVADA for a PrEP indication will be used appropriately.
- The materials listed in the ETASU will be available through the TRUVADA REMS program website and will remain on the website for a period of 3 years following product approval.

REMS assessments will be required annually from the initial date of the approval of the REMS. Please see the review by the Division of Risk Management for further discussion of the REMS and its assessments.

1.4 Recommendations for Postmarket Requirements and Commitments

Because experience with TRUVADA for a PrEP indication has been mostly limited to the clinical trial setting, postmarketing studies are being required as a condition of approval to collect additional safety data about potential or observed safety issues that either the trials did not fully address or that may have different outcomes once the product is marketed. Multiple demonstration projects, to be conducted both domestically and internationally, are being proposed by various investigators to address some of these issues (see Section 9.4). The Applicant is (b) (4)

To further evaluate the potential for development of viral resistance in individuals who initiate or continue to take Truvada following HIV infection, to provide additional information about the safety of Truvada during pregnancy, and to further evaluate renal and skeletal adverse reactions in this new population, the following postmarketing requirements (PMRs) are being issued:

Postmarketing Requirements

- 1) Collect and analyze data from individuals participating in demonstration projects (trials) who take Truvada for pre-exposure prophylaxis of sexually acquired HIV-1 infection and who seroconvert during follow-up. The following data should be collected and the following analyses conducted on data collected from a minimum of 150 seroconverters over a time period not to exceed 3 years:
 - a. Data regarding the presence or absence of signs and symptoms of acute HIV infection at the study visit or since the last study visit when seroconversion is identified.
 - b. Frequency of screening and screening method(s) used for evaluation of the seroconverter, and in general, at that enrollment site.
 - c. Analyses of baseline samples from early seroconverters to evaluate HIV-1 RNA and the presence or absence of resistance.
 - d. Resistance analyses of viral isolates from seroconverters that include population nucleotide sequence analysis followed by ultrasensitive testing (such as ultra-deep sequencing of proviral DNA or allele-specific PCR) if no resistance is identified by population sequencing.

Timeline: Final protocol submission:	10/12
Interim report submissions:	09/13, 09/14, 09/15

Study completion:	03/16
Final report submission:	09/16

The rationale for specifying 150 seroconverters was based on power calculations so that the lower bound of the 95% confidence interval of the percentage of subjects observed with resistance variants after seroconverting in the demonstration projects is not higher than the upper bound of the 95% confidence interval of the resistance observed in the iPrEx and Partners PrEP trials, which was zero resistance among the emergent seroconversions. If this is observed, then a resistance rate no higher than twice that observed in the registrational trials will be demonstrated.

Additionally, because limited data are available regarding the use of TRUVADA during pregnancy, and it is anticipated that the product will be used by pregnant women for purposes of PrEP, the following PMR is being issued:

- 2) Through collaboration with the Antiretroviral Pregnancy Registry, conduct a prospective observational study in order to collect and analyze data on maternal and fetal outcomes in 200 women who become pregnant while taking TRUVADA for pre-exposure prophylaxis (PrEP) and choose to continue TRUVADA during their pregnancies and in 200 women who become pregnant while taking TRUVADA for PrEP and choose to discontinue it. Collect and analyze data from at least a similarly sized comparator group of pregnant HIV-infected women taking antivirals other than emtricitabine/tenofovir disoproxil fumarate. Data collected on pregnancy outcomes should include but not be limited to: timing of initiation and duration of TRUVADA or other antiretrovirals, HIV seroconversions in mother and infants, spontaneous and elective abortions, spontaneous and scheduled pre-term deliveries, stillbirths, infant weight (normal or low) and infant outcomes, including the presence or absence of congenital malformations.

Timeline: Final protocol submission:	10/12
Interim report submissions:	09/13, 09/14, 09/15, 09/16
Study completion:	09/16
Final report submission:	03/17

The following PMR will provide additional safety data on resistance development in individuals who seroconvert while taking Truvada and on the incidence and severity of renal and skeletal adverse reactions in this population:

- 3) Collect and analyze data from ongoing and planned demonstration projects (trials) including at least 7000 uninfected individuals taking Truvada® for a pre-exposure prophylaxis (PrEP) indication with the objective of examining the association between levels of adherence to the once-daily dosing regimen and risk of seroconversion, resistance development, and renal and skeletal

adverse events. Levels of adherence should measure a gradient of adherence levels rather than the simple dichotomy of 'adherent' versus 'non-adherent' using any available data on drug levels as the measure of adherence. Seroconversion will be assessed every three months, and, upon each seroconversion, resistance testing should be performed. Assessment for renal and skeletal adverse events will be performed every three months, including evaluation of available laboratory data. Analyses will be performed by geographic region, including the United States.

Timeline: Final protocol submission:
Interim report submissions:
Final report submission:



Postmarketing Commitments

To identify an adherence tool that may be more reliable than simple self-reporting and moreover, to identify baseline characteristics that might predict better adherence, the following study is being conducted as a postmarketing commitment (PMC):

- 4) In the context of a U.S. demonstration project (trial) for once-daily Truvada® for a pre-exposure prophylaxis (PrEP) indication, validate an adherence questionnaire using an objective quantitative measure such as drug levels collected over the period of the study. In addition, the trial will utilize subject demographics and responses to a survey on knowledge, attitudes, and behaviors (sexual and non-sexual behaviors related to increased risk of HIV infection) in order to identify baseline characteristics associated with decreasing adherence, as measured objectively by blood drug levels. The trial will enroll a national demographically representative sample that reflects the same target population as described above.

Timeline: Final protocol submission:
Interim report submissions:
Final report Submission:



Lastly, to capture nationally representative drug utilization data, the following PMC was drafted with assistance from the Division of Epidemiology (DEPI):

- 5) Provide comprehensive national drug utilization data to FDA of sufficient detail that use of TRUVADA for a PrEP indication and individuals using Truvada for a PrEP indication can both be characterized. This data should be submitted to FDA every 6 months for three years, for both generic and brand name products containing FTC/TDF, starting at one year following approval of the PrEP indication. The following analyses should be conducted with the data collected:

- a. Total number of prescriptions dispensed across all settings of care
 - i. Total number of prescriptions dispensed, stratified by indication, setting of care, and prescriber specialty
 - ii. Directions for use (*signa*) of prescriptions dispensed
- b. Total number of unique individuals receiving dispensed prescriptions across all settings of care
 - i. Total number of unique patients receiving dispensed prescriptions, stratified by both indication and setting of care
 1. Unique incident users every quarter-year
 2. Unique prevalent users every quarter-year
 - ii. Demographics of users of the product
 - iii. Clinical characteristics of users of the product
- c. Duration of therapy, including definitions of gaps in drug therapy
 - i. Total and stratified by indication
 - ii. Examination of possible ‘intermittent’ use
 - iii. Number of persons switching from PrEP to an HIV treatment regimen
 - iv. Dose adjustments
- d. Comparison of collected drug utilization data to data from demonstration projects performed in the United States in terms of patient demographics, patient clinical characteristics, prescriber specialties, settings of care, and geographic region (when available).

Timeline: Final protocol submission:	01/13
Interim report submissions:	07/13, 01/14, 07/14, 01/15, 07/15, 01/16
Final report submission:	07/16

Certain elements of these PMR/PMC studies and their timelines are currently still being negotiated at the time of this writing.

In addition, the Applicant is also proposing to conduct its own observational study in the form of a registry open to all U.S. prescribers and uninfected individuals (men and women) using TRUVADA for a PrEP indication. The objectives of the Applicant’s study are to characterize the demographics of prescribers and individuals who participate in a comprehensive prevention strategy that includes prescriber self-knowledge of usage recommendations for TRUVADA for a PrEP indication and users’ self-reported adherence to TRUVADA and to a comprehensive prevention strategy, as well as their risk perception and risk behaviors over time.

2 Introduction and Regulatory Background

2.1 Product Information

TRUVADA® is a fixed-dose combination tablet of the nucleoside analogue emtricitabine (FTC) and the acyclic nucleotide analogue tenofovir disoproxil fumarate (TDF). It is indicated for the treatment of human immunodeficiency virus (HIV)-1-infected in adults and pediatric patients 12 years of age and older, in combination with other antiretroviral products. Each tablet contains FTC and TDF at the same dosages recommended for the individual components; i.e., 200 mg of emtricitabine and 245 mg of tenofovir disoproxil (as fumarate, equivalent to 300 mg TDF or 136 mg of tenofovir). The recommended dose of TRUVADA is 1 tablet once daily taken orally.

Efficacy Supplement 30 to New Drug Application (NDA) 21-752 for TRUVADA proposes the following new indication for the TRUVADA tablet: pre-exposure prophylaxis (PrEP) against HIV-1 infection in adults at risk for HIV-1 acquisition. The proposed dosing of TRUVADA for a PrEP indication is the same as the recommended dosing for HIV treatment, namely 1 tablet once daily.

The Applicant makes the following points regarding a PrEP indication for TRUVADA:

- The PrEP indication is based on studies in adults at high risk for sexually acquired HIV-1 infection.
- TRUVADA should only be used as part of a comprehensive prevention strategy because TRUVADA is not always effective in preventing the acquisition of HIV-1.
- All individuals should be counseled to strictly adhere to the TRUVADA dosing schedule because the effectiveness of TRUVADA in reducing the risk of acquiring HIV-1 is strongly correlated with adherence and detectable drug levels.
- Individuals taking TRUVADA for PrEP should have a documented negative HIV test prior to initiating and routinely while taking TRUVADA for PrEP.
 - Individuals who become HIV-infected while taking TRUVADA must take a full antiretroviral regimen, which might include TRUVADA with other agents, to fully suppress virus replication and avoid the development of resistance.
- It is not known whether TRUVADA is safe and effective for pre-exposure prophylaxis of HIV-1 infection acquired through injection drug use.

2.2 Tables of Currently Available Treatments for Proposed Indications

No drug treatment is currently approved for a PrEP indication. Alternatives for HIV prevention include condoms and abstinence.

2.3 Availability of Proposed Active Ingredient in the United States

TRUVADA is currently available and marketed in the United States for the treatment of HIV-1 infection in adults and pediatric patients 12 years of age and older. TRUVADA was first approved on August 2, 2004 in the United States. It was approved in the European Union on February 21, 2005 and is currently approved in 137 countries. Since first approval, cumulative exposure to TRUVADA is estimated to be (b) (4) patient-years of treatment.

The combination of FTC and TDF, as found in TRUVADA, constitutes the nucleos(t)ide backbone component of all preferred combination regimens for treatment-naïve HIV-infected patients as recommended by the U.S. Department of Health and Human Services (DHHS) *Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents*.⁷ As such, FTC and TDF are widely used in the United States as part of most first-line antiretroviral treatment regimens. In addition to being co-formulated in TRUVADA, FTC and TDF are also available as single agents (EMTRIVA® and VIREAD®, respectively) and in fixed-dose combination tablets with third agents efavirenz (ATRIPLA®, approved on July 12, 2006) or rilpivirine (COMPLERA®, approved on August 10, 2011). As of March 31, 2011, the estimated cumulative exposure to TDF as a single-agent is (b) (4) patient-years and to FTC as a single-agent (b) (4) patient-years. Taking into account VIREAD, EMTRIVA, TRUVADA, ATRIPLA, and COMPLERA, the total exposure to TDF or FTC is estimated to be greater than (b) (4) patient-years according to the Applicant.

The most common adverse reactions (incidence greater than or equal to 10%) from registrational clinical trials and postmarketing experience with TRUVADA are diarrhea, nausea, fatigue, headache, dizziness, depression, insomnia, abnormal dreams, and rash, although several of these events, in particular the neuropsychiatric ones, may be related to other co-administered antiretroviral drugs. Renal impairment, including cases of acute renal failure and Fanconi syndrome (renal tubular injury with severe hypophosphatemia), has been reported with use of VIREAD. Therefore, it is recommended that creatinine clearance be calculated in all patients prior to initiating therapy and as clinically appropriate during therapy with TRUVADA. VIREAD has also been associated with decreases in bone mineral density (BMD) at the lumbar spine and hip in treatment-naïve HIV-1-infected adults. Additionally, severe acute exacerbations of hepatitis B virus (HBV) infection have been reported in patients co-infected with HBV and HIV-1 who have discontinued TRUVADA therapy. In some patients, the exacerbations of hepatitis B have been associated with hepatic decompensation and liver failure. VIREAD is currently approved for treatment of HBV infection, but TRUVADA is not. Renal impairment, decreases in BMD, and exacerbations of HBV infection are included in the Warnings and Precautions section of the current TRUVADA

⁷ <http://www.aidsinfo.nih.gov/guidelines/html/1/adult-and-adolescent-treatment-guidelines/0/>. Accessed March 27, 2012.

label. Post-treatment acute exacerbation of HBV infection also appears as a box warning in the TRUVADA label.

A growing body of literature highlights the renal and bone adverse effects associated with tenofovir that are increasingly being recognized in the post-approval period. A recently reported observational study of more than 10,000 HIV-infected patients from the Veterans Health Administration (VA) showed that for each year of tenofovir exposure, the risk of proteinuria rose 34% [95% confidence interval (CI) 25-45%, $p < 0.0001$], risk of rapid decline in kidney function rose 11% (95% CI 3-18%, $p = 0.0033$), and risk of developing chronic kidney disease rose 33% (95% CI 18-51%, $p < 0.0001$).⁸ The risks remained after the researchers controlled for other kidney disease risk factors such as age, race, diabetes, hypertension, smoking and HIV-related factors. Preexisting renal risk factors did not appear to worsen the effects of tenofovir. Other antiretroviral drugs showed weaker or inconsistent associations with kidney disease events. Among those who discontinued tenofovir use, risk of kidney disease events did not appear to decrease during follow-up (although mean follow-up was only 1.2 years after stopping tenofovir). Similarly, another observational VA study of more than 56,600 patients recently reported an increased risk of osteoporotic fractures with cumulative exposure to tenofovir, with a yearly hazard ratio for osteoporotic fracture of 1.16 (95% CI 1.08-1.24, $p < 0.001$) in an univariate model and 1.12 (95% CI 1.03-1.21, $p = 0.011$) in a multivariate model controlling for age, race, diabetes, smoking, body mass index, hepatitis C status and concomitant antiretroviral exposures.⁹ That said, there are limitations to both of these studies. For one, both are observational and retrospective in nature; as such, there may have been incomplete or inadequate control for factors that may have confounded or explained the observed associations. In the VA bone fracture study, osteoporotic fractures were not ascertained and BMD data were not evaluated; thus the fractures cannot be proven to be osteoporotic in nature and the observed associations may not necessarily be causative. In the VA renal study, patients with inadequate data collection were excluded from the study and these patients tended to be on average healthier than the patients included in the study. Also, the association between tenofovir and proteinuria, rapid decline in kidney function, and chronic kidney disease may be overestimated as the association was strongest in the earlier era of the drug's availability on the market compared to later eras and the point estimates for these events are very small.

Clinical trials of TRUVADA in HIV-uninfected individuals are limited, but a small (N=44) community-based observational study of TRUVADA given for non-occupational post-exposure prophylaxis (nPEP) reports that a 4-week course of TRUVADA was generally well-tolerated and associated with high completion rates (72%) compared to historical

⁸ Scherzer R, Estrella M, Li Y, Choi AI, Deeks SG, Grunfeld C, Schlipak MG. Association of tenofovir exposure with kidney disease risk in HIV infection. *AIDS* 2102; 26: 867-75.

⁹ Bedimo R, Maalouf NM, Zhang S, Drechsler H, Tebas P. Osteoporotic fracture risk associated with cumulative exposure to tenofovir and other antiretroviral agents. *AIDS* 2012; 26:825-31.

controls using zidovudine/lamivudine regimens.¹⁰ Abdominal complaints were the most common side effects, with 48% of TRUVADA participants reporting abdominal discomfort, pain, or bloating, compared to 20% of those who used TDF/lamivudine and only 3% of those who used zidovudine/lamivudine ($p < 0.001$). Diarrhea was reported by 38% of those taking TRUVADA and 31% of those taking TDF/lamivudine, compared to only 10% of those who took zidovudine and lamivudine ($p < 0.01$). Abdominal discomfort, however, tended to be mild and resulted in no regimen discontinuations. The only laboratory abnormalities noted among TRUVADA participants were one Grade 1 and one Grade 2 transaminase elevation in two persons.

2.4 Important Safety Issues with Consideration to Related Drugs

Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported with the use of nucleoside analogs, including VIREAD, in combination with other antiretrovirals. A majority of these cases have been in women and obesity and prolonged nucleoside exposure may be risk factors. Particular caution is recommended when administering nucleoside analogs to any patient with known risk factors for liver disease, although cases have also been reported in HIV-1-infected patients with no known risk factors. Lactic acidosis and severe hepatomegaly appear as box warnings in the current TRUVADA label.

2.5 Summary of Presubmission Regulatory Activity Related to Submission

To support the proposed indication, the Applicant, Gilead Sciences, Inc., has submitted human data from clinical trials conducted by other study sponsors, namely DHHS government agencies and academic institutions, which evaluated the use of once-daily TRUVADA as PrEP. The clinical data used in primary support of the proposed new indication are derived from two multinational, Phase 3, randomized, placebo-controlled trials:

1. CO-US-104-0288: The Pre-exposure Prophylaxis Initiative (iPrEx) trial, “A Phase 3, randomized, double-blind, placebo-controlled study of chemoprophylaxis for HIV prevention in initially HIV-1-uninfected men who have sex with men (MSM)”
2. CO-US-104-0380: The Partners PrEP trial, “Parallel comparison of tenofovir and emtricitabine/tenofovir pre-exposure prophylaxis to prevent HIV-1 acquisition within HIV-1 discordant couples”

In addition, safety information from other clinical PrEP trials were submitted as supportive elements, including data from Study CDC 4323, a U.S.-based safety study of

¹⁰ Mayer KH, Mimiaga MJ, Cohen D, Grasso C, Bill R, Van Derwarker R, Fisher A. Tenofovir DF plus lamivudine or emtricitabine for nonoccupational postexposure prophylaxis (NPEP) in a Boston Community Health Center. *J Acquir Immune Defic Syndr* 2008; 47:494-9.

TDF in MSM conducted by the Epidemiology Branch, Division of HIV/AIDS Prevention, Centers for Disease Control and Prevention (CDC) (CO-US-104-0277).

Again, none of these trials was sponsored by the Applicant. Presubmission regulatory activity related to each trial was conducted under the individual Investigational New Drug (IND) for that trial when such an IND was available. For example:

- The iPrEx trial was conducted under an IND held by the Division of AIDS (DAIDS), National Institute of Allergy and Infectious Diseases (NIAID), National Institutes of Health (NIH). Pre-IND consultation was requested on November 28, 2005. Feedback from the Division of Antiviral Products (DAVP) was incorporated into the version of the protocol submitted to the IND on May 11, 2006.
 - A subsequent Phase 2 protocol (HPTN 067, the ADAPT Study), submitted in September 2010 to this IND, is evaluating intermittent dosing of oral PrEP in MSM using open-label FTC/TDF.
- The Partners PrEP trial was conducted under an IND held by principal investigator Connie Celum, MD, MPH, of the International Clinical Research Center (ICRC), University of Washington, Seattle, WA. Pre-IND consultation was requested on May 15, 2007 and the final protocol was submitted with input from the DAVP. The IND opened on August 20, 2007.
- The CDC 4323 trial was not conducted under IND.

The Applicant reports having collaborated with the pivotal trial sponsors to prepare the clinical trial data for regulatory review. Regulatory interactions between the Applicant and the DAVP regarding the use of TDF (with or without FTC) for PrEP are summarized below:

- October 28, 2009, under IND 52,849 (TDF for the treatment of HIV-1 infection):

A Type C meeting was held to discuss the development of a coordinated strategy for the regulatory review of data from the PrEP clinical trials of VIREAD and TRUVADA. At this stage, the two Phase 3 trials under consideration for submission were the iPrEx trial and Study CDC 4370, a clinical trial evaluating the effectiveness of TDF as PrEP in intravenous drug users in Bangkok (see Section 2.6). The DAVP suggested that Study CDC 4323 also be submitted in support of VIREAD for a PrEP indication.
- June 29, 2010: IND 108,930 was opened specifically for TDF, with or without FTC, for a PrEP indication.
- August 11, 2010: Fast Track designation was granted to IND 108,930.
- December 8, 2010, Type B pre-NDA meeting held under IND 108,930:

On November 23, 2010, results from the iPrEx trial were made public and subsequently published.¹¹ A Type B pre-NDA meeting was held on December 8, 2010 to discuss the potential for data from the iPrEx trial to support a supplemental NDA filing and to discuss key aspects related to the content, format, and administrative information necessary to support a regulatory filing for use of TRUVADA as PrEP. The DAVP highlighted the need for a REMS to assure safe product use, including communication and educational plans, and assessments such as comprehension evaluation, as well as the potential need for postmarketing evaluation of product safety, such as monitoring for development of drug resistance among seroconverters.

- March 9, 2011, under IND 108,930:

A Type C meeting was held to further discuss the nature of the anticipated REMS. The key issue raised by the DAVP was the need to include the reduction in the risk of development of resistant HIV-1 variants as a specific goal of the REMS. Further, the DAVP requested that the Applicant consider periodic HIV testing in the proposed REMS as Elements to Assure Safe Use (ETASU). The Applicant expressed concerns about the feasibility of such an ETASU in the context of TRUVADA given that the product is already widely prescribed and available as a treatment for HIV-1 infection.

- June 10, 2011:

A Center for Drug Evaluation and Research (CDER) Regulatory Briefing was held to present the published results of the iPrEx trial and obtain feedback on regulatory means of reducing the risk of developing and spreading resistant HIV variants. The general consensus was that a restrictive REMS with ETASU requiring periodic HIV testing as a condition for dispensing drug would not be feasible as it would adversely impact the availability of the drug for its primary indication (i.e., treatment of HIV-1 infection). Restricted distribution was also not feasible as both drug products found in TRUVADA are approved and available in the United States; moreover, prescribers and individuals considering TRUVADA as PrEP could circumvent a restrictive REMS program to obtain the drug.

- July 10, 2011:

A CDER Director Briefing was held to update center management on developments in the PrEP field since the Regulatory Briefing held in June 2011, and specifically to present the recently reported results from the Partners PrEP

¹¹ Grant RM, Javier R, Lama JR, Anderson PL, McMahan V, Liu AY, Vargas L, et al. Preexposure chemoprophylaxis for HIV prevention in men who have sex with men. *N Engl J Med* 2010; 363:2587-99.

and CDC TDF2 trials in heterosexuals (see Section 2.6). Concurrence was reached on the following:

- Add heterosexual serodiscordant couples and MSM to the proposed PrEP indication for TRUVADA
- Because of the approved indication for treatment of established HIV-1 infection, the REMS for TRUVADA for the proposed PrEP indication should not be linked to the ability to prescribe or dispense drug.
- The proposed REMS for TRUVADA for the PrEP indication would only include a communications-based ETASU, including voluntary prescriber training and education.

The DAVP informed the Applicant of the above points. The Applicant concurred that the planned submission would include data from one of the heterosexual PrEP trials in addition to data from the iPrEx trial to support the proposed PrEP indication.

- August 19, 2011:

An open public meeting was held under the auspices of the non-profit Forum for Collaborative HIV Research (FCHR) regarding PrEP.¹² Invited speakers/panelists included members of the DAVP, industry, community advocates, and PrEP clinical researchers. The following points pertaining to risk mitigation were made:

- Stakeholders overwhelmingly concurred that any restricted drug distribution, mandatory or voluntary registry for prescribers or uninfected individuals taking TRUVADA for the PrEP indication, or documentation of safe use would not be a successful risk mitigation strategy because the two drugs contained in TRUVADA are approved products on the market. As previously noted, prescribers and individuals could circumvent such a risk mitigation program making it ineffective.
- Stakeholders voiced that a proposed TRUVADA PrEP education and outreach program must be part of larger HIV prevention initiatives.
- Stakeholders suggested that postmarketing surveillance carefully monitor to the extent possible the safety of TRUVADA in a non-HIV-1 infected population and for the potential emergence of drug-resistant variants.

2.6 Other Relevant Background Information

In 2010-2011, results from several clinical trials demonstrated that PrEP with antiretroviral agents is a plausible means of reducing the risk of HIV infection. In July 2010, results from the CAPRISA 004 trial were presented at the 18th International AIDS

¹² http://www.hivforum.org/index.php?option=com_content&task=view&id=442&Itemid=79

Conference. This was the first trial to show that an antiretroviral drug could preemptively reduce the risk of HIV acquisition. In CAPRISA 004, 1% tenofovir vaginal gel applied twice a day and peri-coitally reduced HIV acquisition in women by 39% [hazard ratio 0.61; 95% CI 0.40–0.94, $p=0.017$].¹³ In subgroup analyses, efficacy was 54% in women who reported more than 80% adherence to gel use with sex acts in the prior month ($p=0.025$). Tenofovir was detectable in vaginal fluids of 50% of HIV-infected females versus 96% of uninfected females. Exploratory analyses of cervicovaginal tenofovir concentrations indicate that levels greater than 1000 ng/mL may be protective.¹⁴ An incidental finding was a 51% reduction in the incidence of herpes simplex virus (HSV)-2 in the tenofovir gel group, consistent with in-vitro work demonstrating that high mucosal concentrations of tenofovir inhibits HSV-2 replication.¹⁵

This was followed in November 2010 by the release of the iPrEx trial results, in which the daily use of oral FTC/TDF (TRUVADA) reduced HIV acquisition by 44% in MSM. In both trials, there was a strong correlation between reduced HIV acquisition and local exposure to drug in the genital tract (CAPRISA 004) or systemic exposure via plasma (iPrEx). On January 28 2011, based on the results of the iPrEx trial, the CDC issued interim guidance on the use of once-daily TRUVADA as PrEP in MSM.¹⁶ The iPrEx trial will be reviewed in greater detail later in this document.

At the 6th International AIDS Society (IAS) Conference held in July 2011 in Rome, Italy, results from two additional trials, CDC TDF2 and Partners PrEP, reported 62% to 73% protection against HIV acquisition in men and women when daily TDF with or without FTC was used.^{17,18} The Partners PrEP trial in 4,758 HIV-serodiscordant couples from Kenya and Uganda showed no statistical difference in efficacy between TDF and FTC/TDF ($p=0.18$). Both TDF and FTC/TDF significantly reduced HIV risk in both men and women. The Partners PrEP trial is reviewed in greater detail later in this document.

The CDC TDF2 trial in 1,219 HIV-uninfected men and women in Botswana reported 33 new HIV seroconversion events: 9 in the FTC/TDF group and 24 in the placebo group,

¹³ Abdool Karim Q, Abdool Karim SS, Frohlich JA, et al. Effectiveness and safety of tenofovir gel, an antiretroviral microbicide, for the prevention of HIV infection in women. *Science* 2010; 329:1168-74.

¹⁴ Abdool Karim SS, Kashuba A, Werner L, Abdool Karim Q. Drug concentrations after topical and oral antiretroviral pre-exposure prophylaxis: implications for HIV prevention in women. *Lancet* 2011; 378:279-81.

¹⁵ Andrei G, Lisco A, Vanpouille C, et al. Topical tenofovir, a microbicide effective against HIV, inhibits herpes simplex virus-2 replication. *Cell Host Microbe* 2011; 10:379-89.

¹⁶ CDC. Interim Guidance: Preexposure Prophylaxis for the Prevention of HIV Infection in Men Who Have Sex with Men. *MMWR* 2011; 60: 65-8.

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

¹⁸ Baeten J, Celum C. Antiretroviral pre-exposure prophylaxis for HIV-1 prevention among heterosexual African men and women: the partners PrEP study [Oral Presentation]. 6th IAS Conference on HIV Pathogenesis, Treatment and Prevention; 2011 July 17-20; Rome, Italy.

for an overall protective efficacy of 62% (95% CI 22-83%; $p=0.01$). Due to the fewer endpoints, the trial was not powered to demonstrate statistically significant efficacy in each gender, although point estimates suggested a protective effect for both men (80.1%, $p=0.03$) and women (49.4%, $p=0.1$). The trial showed no between-group differences in serious clinical adverse events or laboratory abnormalities. Nausea, vomiting, and dizziness occurred more commonly in the FTC/TDF group and there were minimal but statistically significant declines in BMD T-scores and Z-scores at the forearm, hip and lumbar spine in participants receiving FTC/TDF compared with placebo. Two subjects, one in each treatment group, were found to have drug-resistant HIV-1 strains post-baseline. Retrospective testing revealed that the subject in the FTC/TDF group was enrolled with unrecognized acute wild-type HIV infection. Subsequently, high levels of multiple drug resistance substitutions were detected in this subject's isolates, conferring nucleoside reverse transcriptase inhibitor (NRTI) drug class resistance. The subject in the placebo group, on the other hand, was found to have transient and low levels ($< 1\%$) of the K65R mutation.

In contrast to the previous two trials in heterosexual individuals, a similar trial in African women, FEM-PrEP, evaluating daily oral dosing with FTC/TDF was halted on April 18, 2011 due to futility.¹⁹ The FEM-PrEP trial enrolled 2,120 women considered to be at high-risk for HIV infection in Kenya, Tanzania, and South Africa, of which 2,056 women contributed follow-up data and approximately 80% completed the trial.²⁰ Roughly 60% of the women were younger than 25, about 12% reported having sex for gifts or money with non-primary partners, and only half reported condom use. Women reported an average of 3.7 vaginal sex acts in the 7 days prior to enrollment, consistent with the average of 3.6 acts reported during follow-up.²¹

At the 19th Conference on Retroviruses and Opportunistic Infections (CROI) held in March 2012, the FEM-PrEP investigators presented the final results from the trial. There were a total of 68 HIV seroconversion events: 33 in the FTC/TDF group and 35 in the placebo group, with a 6% relative risk reduction for FTC/TDF (hazard ratio=0.94 [CI 0.59, 1.52]; $p=0.81$); thus, a protective effect of FTC/TDF could not be demonstrated. Despite substantial counseling efforts in the FEM-PrEP trial, inadequate adherence was demonstrated by plasma drug concentrations; detectable drug in blood samples was found in less than half of the infected women or uninfected controls matched to cases by time of infection. Plasma samples from the visit before and from the visit at the time HIV was diagnosed were analyzed. In infected participants, 26% had detectable levels of tenofovir in their blood in the last visit before they tested HIV positive, 21% at the visit

¹⁹ http://www.fhi360.org/en/AboutFHI/Media/Releases/FEM-PrEP_statement041811.htm

²⁰ Van Damme L, Corneli A, Ahmed K, et al. The FEM-PrEP trial of emtricitabine/tenofovir disoproxil fumarate (Truvada) among African women. 19th Conference on Retroviruses and Opportunistic Infections (CROI); 2012 March 5-8; Seattle, WA. [Oral Presentation]

²¹ Family Health International. FEM-PrEP fact sheet. Key findings. <http://www.fhi360.org/NR/rdonlyres/exo44wsp2ibf7d2ssrny7wzxhlb6xbhy6at5rgjwwt37bhy6kjqwqifjmkmtq b7tw5xno4psfseugk/FEMPrEPFactSheetKeyFindings1.pdf>

they tested positive, and 15% at both visits; in non-infected participants whose samples were taken at the same time points, these percentages were 35%, 38%, and 26%, respectively. Drug-resistance data were available for 35 women in the FTC/TDF group and 40 women in the placebo group. Although the K65R mutation was not identified in any participant, four women in the FTC/TDF group and one in the placebo group developed the single M184V FTC resistance substitution. Particularly concerning was the finding that about 70% of the women considered themselves to be at low risk or not at risk for acquiring HIV infection, despite a significant prevalence of sexually transmitted infections at baseline. The study investigators surmised that the trial's ability to assess the efficacy of FTC/TDF as PrEP may have been undermined by poor drug adherence and the low risk perception among participants.

Among pre-specified adverse event categories in the FEM-PrEP trial, only the rates of vomiting and nausea were significantly higher in the FTC/TDF group. Women in FEM-PrEP were also required to use an effective non-barrier method of contraception. At enrollment, 66% were using injectables and 30% were using oral contraceptives. The overall pregnancy rate was 9%, with the highest pregnancy rates among women using oral contraceptives, suggesting that low adherence to oral medications was not necessarily restricted to the study drugs.

In the Vaginal and Oral Interventions to Control the Epidemic (VOICE) trial, a five-arm trial among 5,028 HIV-uninfected African women in which daily 1% tenofovir gel, daily oral TDF, and daily oral FTC/TDF were being compared to respective gel/oral placebos, the oral TDF and tenofovir vaginal gel arms were stopped in the fall of 2011 by the Data and Safety Monitoring Board (DSMB) because protection from HIV infection was not observed.²² The VOICE trial is presently ongoing comparing oral FTC/TDF to placebo. Of note, no significant safety concerns have been reported in the VOICE trial thus far. The reasons for the vastly different outcomes among the four oral PrEP trials that included women, which used identical antivirals and dosing schedules, are being further investigated at this time; however, as will be further discussed in this review, adherence to prescribed interventions appears to play a key role.

²² <http://www.niaid.nih.gov/news/newsreleases/2011/Pages/VOICEdiscontinued.aspx>

Table 1 provides an overview of the completed and ongoing clinical trials evaluating oral PrEP, both for the prevention of sexually acquired HIV infection as well as prevention of HIV infection acquired through intravenous drug use. The table is based on information made publically available through literature articles, press releases or clinicaltrials.gov.

Table 1: Completed and Ongoing Clinical Trials of Oral PrEP

TRIAL	SPONSOR	LOCATION	POPULATION	INTERVENTION	RESULTS
PHASE III, IIb					
iPrEx	NIH/DAIDS	Brazil, Ecuador, Peru, South Africa, Thailand, USA	Adult MSM at high risk (N=2499)	Daily oral FTC/TDF	Risk reduction 42%
Partners PrEP	University of Washington	Kenya, Uganda	HIV serodiscordant couples (N=4747)	Daily oral TDF or FTC/TDF	Risk reduction TDF 67% FTC/TDF 75%
CDC TDF2	CDC	Botswana	Adult heterosexual men and women 18-39 (N=1219)	Daily oral FTC/TDF	Risk reduction 62%
FEM-PrEP	FHI	Kenya, South Africa, Tanzania	Adult women at high risk 18-35 (N=2120)	Daily oral FTC/TDF	Stopped for fertility April 2011
VOICE (MTN 003)	NIH/DAIDS	Uganda, South Africa, Zimbabwe	Adult women 18-45 (N=5029)	Daily oral FTC/TDF or TDF or tenofovir vaginal gel	Oral TDF and tenofovir gel arms stopped for fertility September 2011 Oral FTC/TDF and oral placebo arms continuing
Bangkok Tenofovir Study (CDC4370)	CDC	Thailand	Adult injection drug users (N=2400)	Daily oral TDF	Ongoing
ANRS IPERGAY	ANRS	Canada, France	Adult MSM (N=300 initial phase; 1900 total)	Intermittent FTC/TDF dosed at time of sexual intercourse	Ongoing
PHASE II					
CDC 4323	CDC	USA	Adult MSM 18-60 (N=373)	Daily oral TDF (immediate vs. delayed treatment)	7 HIV seroconversions, none on treatment.

FHI PrEP	FHI	Ghana, Cameroon, Nigeria	Adult women at high risk 18-35 (N=936)	Daily oral TDF	8 HIV seroconversions (TDF 2, placebo 6)
HPTN 069	NIH/DAIDS	USA	Adult MSM (N=400)	Daily oral MVC or MVC+FTC or MVC+TDF or FTC/TDF	Enrolling
HPTN 067	NIH/DAIDS	South Africa, Thailand	Adult men and women (N=360)	Intermittent dosing of FTC/TDF	Enrolling
PHASE I					
SSAT 040	St. Stephen's AIDS Trust	UK	Adult men and women (N=66)	Single dose intramuscular TMC278LA	Enrolling

Abbreviations: ANRS=French National Agency for Research on AIDS and Viral Hepatitis; CDC=U.S. Centers for Disease Control; DAIDS=Division of AIDS; FHI=Family Health International; MTN=Microbicides Trials Network; MVC=maraviroc; NIH=U.S. National Institutes of Health

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

The submitted datasets consisted of raw data from the individual trial investigators. Although this was anticipated based on pre-NDA communications, the datasets were nonetheless challenging to review. The submitted datasets did not conform to the Clinical Data Interchange Standards (CDISC), traditionally used for regulatory review, as they were originally intended for research purposes. The define files that accompanied the datasets did not always clearly define the variables used, which often required turning to the source clinical report forms (CRF) in order to interpret the data. In addition, the Applicant submitted two versions of the clinical study report (CSR) and datasets for the iPrEx trial, one for the primary analysis and one for the complete trial. Among these were different versions of the datasets, depending on the date of the data lock, with minimal to no explanation of the organization or the data contained within each version. Although the information was complete, working with the datasets was complicated and overly time consuming. Multiple information requests were sent to the Applicant during the review process that included, but were not limited to, efficacy and safety analysis datasets for the pivotal trials, and requests to conduct specific analyses for the supportive safety trial, CDC 4323. The Applicant complied in a timely manner to each request for additional information and none of the subsequently submitted data constituted a major amendment. Nonetheless, the review process was considerably more laborious and time-consuming due to these submission quality issues.

3.2 Compliance with Good Clinical Practices

For both pivotal trials, iPrEx and Partners PrEP, the protocols, protocol amendments, consent forms, study subject information sheets, and any advertisements were submitted by each investigator to a duly constituted Independent Ethics Committee (IEC) or Institutional Review Board (IRB) for review and approval before study initiation. After initial IEC/IRB approval, protocol amendments and all revisions to the consent form or subject information sheet (if applicable) were submitted by the investigator to the IEC/IRB for review and approval before implementation in accordance with regulatory requirements.

Both pivotal trials were conducted under IND and in accordance with recognized international scientific and ethical standards, including but not limited to the International Conference on Harmonization guideline for Good Clinical Practice (ICH GCP) and the original principles embodied in the Declaration of Helsinki. These standards are consistent with the requirements of the U.S. Code of Federal Regulations (CFR) Title 21, Part 312 (21CFR312).

In the iPrEx trial, protocol violations were reviewed by the study sponsor (DAIDS) and protocol chair. Valid protocol violations were limited to 37 subjects (FTC/TDF 16 [1%], placebo 21 [2%]), compromising <2% of the overall study population. 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. No subject violated more than one eligibility criterion. The four events of incorrect study drug dispensation all occurred in the placebo group but did not result in subjects receiving drug from the opposite treatment group.

Table 2: Important Protocol Deviations in the iPrEx Trial (CO-US-104-0288)

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

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

Source: CO-US-104-0288 CSR, page 55.

In the Partners PrEP trial, 53 protocol violations were reported by the investigational sites. These included three protocol violations related to study drug, 21 to eligibility criteria, 13 to expedited adverse events, nine to study procedures, and seven to other reasons, including informed consent, but the submitted CSR neither summarizes nor

tabulates the protocol violations. All subjects who received study drug, however, were evaluated.

The Office of Scientific Investigations (OSI), Division of Good Clinical Practice Compliance, was consulted to conduct audits of representative clinical sites in support of this application. Four foreign clinical sites were selected for inspection, two from each pivotal trial. The inspections revealed no regulatory violations in three of the four sites (Guayaquil, Ecuador in the iPrEx trial and the Tororo, Uganda and Kisumu, Kenya sites in the Partners PrEP trial). A regulatory violation was identified during inspection of one of the iPrEx sites (Lima, Peru) that involved failure to obtain additional informed consent in one subject (Subject 9010691) following confirmation of HIV seroconversion, as per the protocol. This finding does not critically impact the primary efficacy and safety analyses and the effect on overall data integrity is not considered to be significant. Therefore, OSI concluded that the data submitted from these four sites were reliable and acceptable in support of the application.

3.3 Financial Disclosures

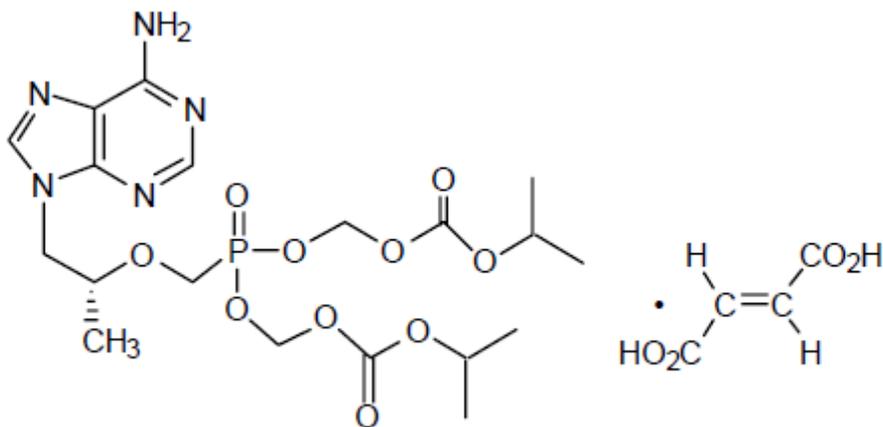
The Applicant has provided documentation certifying that none of the 20 principle investigators in the iPrEx or Partners PrEP trials held any financial interest or arrangements with the sponsor of the respective trials whereby the value of compensation to the investigator for conducting the trial could be affected by the outcome of the trial (as defined in 21 CFR 54.2 (a)); had proprietary interest in the product or significant equity interest in the sponsor of the trial (as defined in 21 CFR 54.2 (bb)); or was the recipient of significant payments of other sorts (as defined in 21 CFR 54.2 (f)). Despite due diligence, the individual trial sponsors were unable to obtain information regarding potential financial interest or agreements in 82/230 (37%) sub-investigators in the iPrEx trial and 3/29 (10%) sub-investigators in the Partners PrEP trial. The use of blinded randomization in these trials, as well as the use of an objective measure for the primary endpoint (i.e., HIV seroconversion), however, reasonably mitigates the potential for bias based on financial interest.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

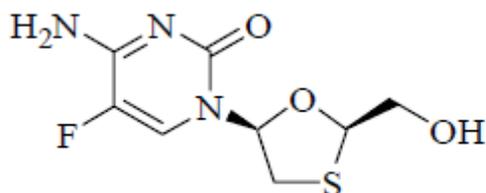
4.1 Chemistry Manufacturing and Controls

The chemistry, manufacturing, and controls for the TRUVADA tablet have not been altered as of a result of the proposed indication. The currently manufactured and approved TRUVADA tablet for the treatment of HIV infection is also proposed for the PrEP indication.

The molecular formula of TDF is $C_{19}H_{30}N_5O_{10}P \cdot C_4H_4O_4$ and it has a molecular weight of 635.52. The structure of TDF is as follows:



Emtricitabine has a molecular formula of $C_8H_{10}FN_3O_3S$ and a molecular weight of 247.24. Emtricitabine has the following structural formula:



There was one potential issue regarding this supplemental application related to potential environmental impact, but with a finding of no significant impact by the Office of Pharmaceutical Science (OPS) Environmental Assessment Staff, this issue has been satisfactorily resolved. Please the CMC review by Dr. Stephen Miller.

4.2 Clinical Microbiology

The use of antiretroviral drugs for HIV prevention was initially demonstrated by a series of controlled studies using macaque models of HIV transmission. These studies showed that treatment with oral or subcutaneous TDF (with or without FTC) either before or shortly after oral, rectal, vaginal, or intravenous inoculation with simian immunodeficiency virus (SIV) or SIV/HIV-1 chimeric virus (SHIV) prevented or delayed the onset of viremia. A key study in rhesus macaques by Garcia-Lerma et al reported that a dosing regimen of daily oral FTC and oral TDF prevented infection via rectal SHIV

exposure in the majority of animals and was associated with delayed infection and lower acute viremia in animals that had breakthrough infections (see Table 3).²³

Table 3: Daily or Intermittent Prophylaxis of Rhesus Macaques

Time of Drug Administration Compared to Inoculation ¹ (group size)	Route/Antiviral/Dose	Number (%) uninfected after 14 challenges	Number (%) infected after 14 challenges	Time to infection: # challenges
Subbarao et al {9496}				
Untreated Controls (4)	NA	0 (0)	4 (100)	1, 1, 2, 11
Daily (4)	PO TDF 22 mg/kg	1 (25)	3 (75)	6, 6, 9
Weekly (4)	PO TDF 22 mg/kg	0 (0)	4 (100)	6, 6, 8, 11
Garcia-Lerma et al {13751}				
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

¹ Inoculations were via the intrarectal route, once weekly for 14 weeks

Abbreviations: TDF = tenofovir disoproxil fumarate; FTC = emtricitabine; TFV = tenofovir; PO = oral; SC = subcutaneous; NA = not applicable

Source: NDA 21-752/S-30 Nonclinical Overview

The collective nonclinical data also showed that a single pre-exposure dose of FTC/TDF was not effective in preventing infection, demonstrating the need for post-exposure dosing, and that the dual agent regimens of FTC and TDF were more efficacious than single agent regimens.²⁴ Additionally, oral FTC/TDF treatment offered complete

²³ Garcia-Lerma JG, Otten RA, Qari SH, Jackson E, Cong ME, Masciotra S, et al. Prevention of rectal SHIV transmission in macaques by daily or intermittent prophylaxis with emtricitabine and tenofovir. *PLoS Med* 2008; 5 (2):e28.

²⁴ Garcia-Lerma G, Cong ME, Zheng Q, Holder A, Martin A, Lin CC, et al. Efficacy of intermittent prophylaxis with tenofovir and emtricitabine against rectal SHIV transmission in macaques and

protection against an FTC-resistant virus containing M184V in macaques.²⁵ For further details on these nonclinical studies, please see the Microbiology review by Dr. Damon Deming.

Resistance issues pertinent to this application are discussed in Section 6.1.5 of this review.

4.3 Preclinical Pharmacology/Toxicology

The toxicological profiles of FTC and TDF are well characterized and adequately addressed in the current Prescribing Information label. The key toxicology findings for FTC/TDF are renal and bone toxicity as discussed in Section 2.3 of this review. Please see the Pharmacology/Toxicology review by Dr. Pritam Verma for further details.

Animal data indicate that neither FTC nor TDF affect male or female fertility or caused reproductive or fetal toxicity. However, tenofovir has been shown to cross the placenta in monkeys and to be excreted in milk. Emtricitabine has also been shown to cross the placenta and the ratio of FTC concentrations in plasma in pregnant mice and rabbits as compared to their fetuses was approximately 0.4. Therefore, caution is appropriate until relevant data are available in pregnant human patients.

Recent clinical data from five HIV-1 infected mothers demonstrate that both tenofovir and emtricitabine are secreted in human breast milk. The proposed label submitted with this application includes this new information in Section 8.3 Nursing Mothers. This information has been approved for the VIREAD label, but not yet for the EMTRIVA label.

4.4 Clinical Pharmacology

4.4.1 Mechanism of Action

Tenofovir disoproxil fumarate is a fumaric acid salt prodrug of tenofovir (TFV), an acyclic nucleoside phosphonate (nucleotide) analog of adenosine 5'-monophosphate. In vivo, the prodrug is cleaved by esterases to form tenofovir. Tenofovir then undergoes intracellular diphosphorylation to form TFV-5'-diphosphate (TFV-DP), which has activity against HIV-1 reverse transcriptase.

Emtricitabine is a synthetic nucleoside analog which also has activity against HIV-1 reverse transcriptase. FTC is phosphorylated by intracellular enzymes to form the active

relationship to systemic and mucosal drug levels [Abstract 83]. 17th Conference on Retroviruses and Opportunistic Infections (CROI); 2010 February 16-19; San Francisco, CA.

²⁵ Cong ME, Youngpairoj AS, Zheng Q, Aung W, Mitchell J, Sweeney E, et al. Protection against rectal transmission of an emtricitabine-resistant simian/human immunodeficiency virus SHIV162p3M184V mutant by intermittent prophylaxis with Truvada. *J Virol* 2011; 85 (15):7933-6.

moiety, FTC-5'-triphosphate (FTC-TP). FTC-TP inhibits the activity of the HIV-1 reverse transcriptase by competing with the natural substrate deoxycytidine 5'-triphosphate.

4.4.2 Pharmacodynamics

In the original marketing application for TDF (NDA 21-356), a formal pharmacokinetic-pharmacodynamic (PK/PD) trial was not conducted to evaluate relationships between dose, concentration, and efficacy. The 300 mg dose of TDF was selected based on safety and efficacy results in HIV-infected subjects in two trials, Studies 901 and 902. In the dose-ranging Study 901, the Applicant tested TDF at 75 mg, 150 mg, 300 mg, and 600 mg once daily given for 15 to 35 days. However, insufficient PK data were available from the 75 mg and 150 mg dose groups to conduct a comprehensive exposure-response analysis. The 300 mg dose produced better antiviral efficacy than 75 and 150 mg, and similar antiviral efficacy compared to 600 mg. Study 902 evaluated the safety and efficacy of tenofovir DF 75 mg, 150 mg, and 300 mg once daily for 48 weeks. This trial did not include a PK evaluation of tenofovir. TDF 300 mg once daily demonstrated better efficacy results than the 75 mg or 150 mg dose groups, with acceptable safety margins. In both TDF trials, decreases in HIV RNA were greater in the 300 mg dose group compared to the 75 mg and 150 mg dose groups. Based on these results, TDF 300 mg once daily progressed to the Phase 3 trials.

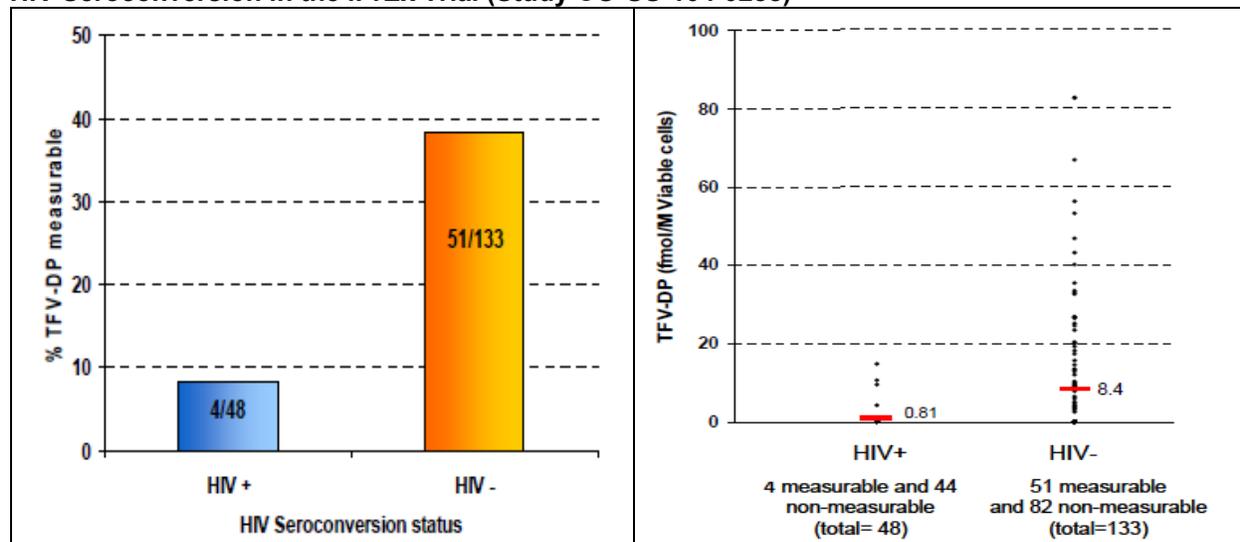
In the original marketing application for emtricitabine (NDA 21-500), Study FTC-101 evaluated the safety, tolerability, PK, and antiviral activity of different dosing regimens of FTC monotherapy in HIV-infected subjects were investigated. The tested doses included FTC 25 mg BID, 100 mg QD, 100 mg BID, and 200 mg QD, and 200 mg BID. All FTC doses produced antiviral activity. However, there was less antiviral activity with doses delivering 50 mg to 100 mg of FTC per day, as compared to ≥ 200 mg of FTC per day. Because no clear increase in antiviral activity was observed after doubling the total daily FTC dose from 200 mg QD to 200 mg BID, the 200 mg QD dosing regimen was selected for further testing in the Phase 3 studies. No additional dose finding trials were conducted during the Phase 2 development for FTC.

With respect to a PrEP indication, the relationship between drug concentration and the protective effect of FTC/TDF against HIV infection has been explored by the iPrEx and Partners PrEP trial investigators. Similar analyses have been conducted or are in progress for other oral PrEP trials, such as the CDC TDF2 and FEM-PrEP trials. The FDA Clinical Pharmacology and Pharmacometrics review teams also performed an independent analysis of the PK data from the iPrEx and Partners PrEP trials to examine the exposure-risk reduction relationship of FTC/TDF; the results are summarized here.

For the iPrEx trial, submitted PK data contained plasma and intracellular concentrations of tenofovir and emtricitabine closest to the date of seroconversion from 48 HIV seroconverters in the FTC/TDF group. The PK data from 144 matched HIV-uninfected controls (11 subjects served as controls twice) were also included. As shown in Figure

1, only 8% of HIV seroconverters had measurable levels of intracellular TFV-DP (above 2.5 fmol/M cells) at the visit closest to the time of seroconversion compared to 38% of the matched HIV- controls (replicated subjects were excluded, $P < 0.0001$). The mean intracellular TFV-DP levels were also higher in the non-seroconverter group compared to the seroconverter group (Figure 1, right),

Figure 1: Summary of Relationship between Measurable Intracellular TFV-DP Concentrations and HIV Seroconversion in the iPrEx Trial (Study CO-US-104-0288)

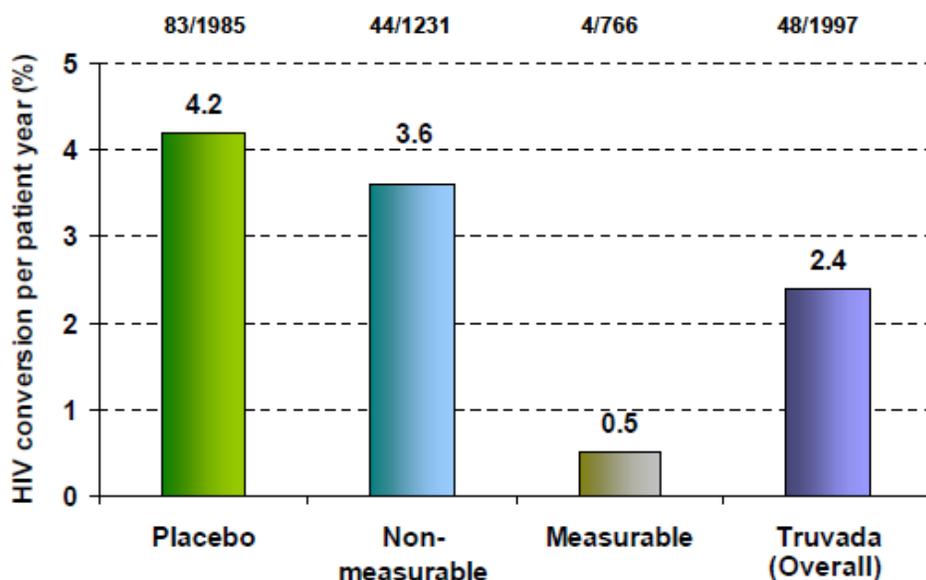


Red line (right figure) depicts mean TFV-DP concentrations in each group.

Source: Clinical Pharmacology Review for NDA 21-752/S-30

Given the long half-life (about 21 days) of intracellular TFV-DP in peripheral blood mononuclear cells (PBMCs), non-measurable intracellular concentrations are indicative of poor drug adherence. In order to assess the impact of drug exposure on efficacy, the distribution of subjects with detectable TFV-DP concentrations among the 133 HIV-uninfected subjects (i.e., 62% non-measurable versus 38% measurable) was extrapolated to all HIV-uninfected subjects within the FTC/TDF group of the iPrEx trial (N=1176). Based on the extrapolation, 451 HIV-uninfected subjects treated with FTC/TDF were likely to have measurable TFV-DP concentrations and 725 subjects were likely to have nonmeasurable concentrations. Next, the event rate of HIV-1 infection for these uninfected subjects was estimated by taking into account the 48 subjects who seroconverted in the FTC/TDF group (four with measurable concentrations and 44 with non-measurable concentrations). The event rate in the uninfected group expected to have measurable concentrations was estimated as 4/455 (451+4) and the event rate for uninfected subjects with no measurable concentrations was estimated as 44/769 (725+44). Figure 2 displays the seroconversion rates per person years.

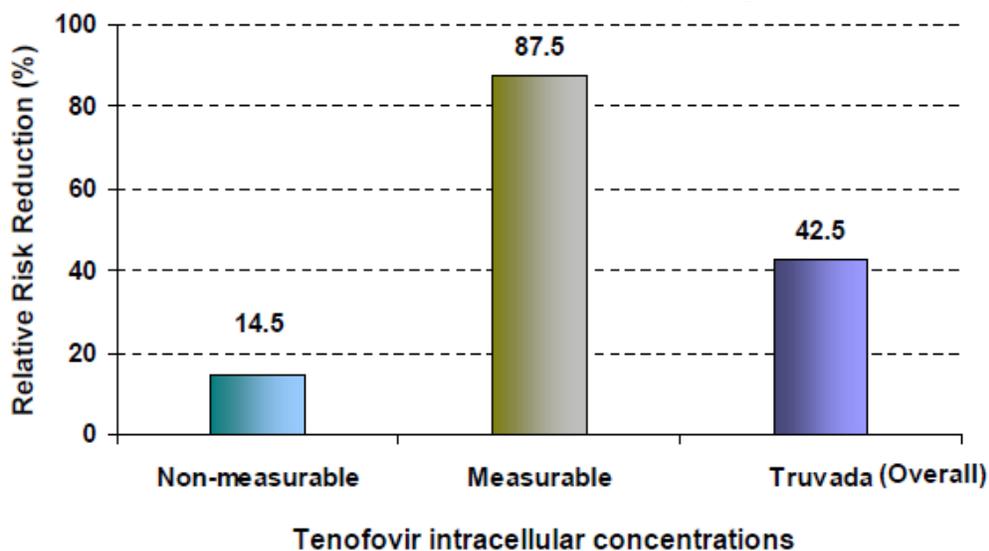
Figure 2: Incidence of HIV Seroconversion by Measurable Intracellular TFV-DP Concentrations in the iPrEx Trial (Study CO-US-104-0288)



Source: Clinical Pharmacology Review for NDA 21-752/S-30

When translating these absolute seroconversion rates to risk reduction for FTC/TDF compared with placebo, the relative risk reduction in subjects with measurable intracellular tenofovir concentrations was 87.5%. In contrast, subjects with non-measurable TFV-DP demonstrated limited additional protection from HIV acquisition (14.5%) compared with placebo (Figure 3).

Figure 3: Risk Reduction in HIV Seroconversion Relative to Placebo based on Measurable Intracellular TFV-DP Concentrations in the iPrEx Trial (Study CO-us-104-0288)

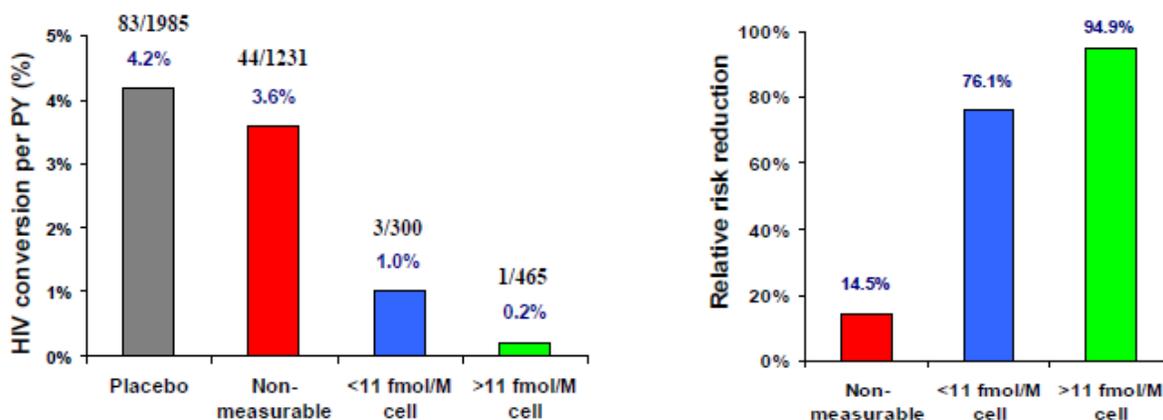


Source: Clinical Pharmacology Review for NDA 21-752/S-30

The exposure-risk reduction relationship in the iPrEx trial was further explored by separating the TFV-DP measurable group into low measurable and high measurable subgroups. Work done by Anderson et al with PK data from the STRAND study, a randomized, crossover PK study of oral TDF in 23 HIV-uninfected subjects assigned to receive either 2, 4, or 7 directly observed doses per week for 6 weeks at each dose, showed that the median steady state intracellular TFV-DP concentrations for TDF taken twice per week, four times per week, and daily were 11, 32 and 42 fmol/M cells, respectively.²⁶

Using the median concentration of 11 fmol/M cell for the twice per week dosing as a cut-off, FDA calculated a seroconversion rate of 1% for iPrEx subjects with low intracellular TFV-DP concentrations (<11 fmol/M cell), while subjects with high measurable concentrations (≥11 fmol/M cell) had a 0.2% seroconversion rate. As a result, the relative risk reduction was estimated as 76.1% for the low measurable group (<11 fmol/M cell) and 94.9% for the high measurable group, suggesting that a dosing frequency greater than twice a week may provide better efficacy than dosing less than twice a week (Figure 4).

Figure 4: Risk Reduction in HIV Seroconversion Relative to Placebo Using a TFV-DP Concentration of 11 fmol/M cells in the iPrEx Trial (Study CO-US-104-0288)



Source: *Pharmacometrics Review for NDA 21-752/S-30*

It is important to note that these estimates are based on exploratory post-hoc analyses of data obtained from small subgroups of trial subjects and not prospective trials, hence the need for ongoing clinical trials evaluating intermittent PrEP to determine other strategies for dosing (e.g. the HPTN 067 trial).

²⁶ Anderson P, Liu A, Buchbinder S, et al. Intracellular tenofovir-DP concentrations associated with PrEP efficacy in MSM from iPrEx. 19th Conference on Retroviruses and Opportunistic Infections (CROI); 2012 March 5-8; Seattle, WA. [Oral Presentation]

Similar exposure-response analyses were conducted by the FDA review team for the Partners PrEP trial; except that the PK analyses were based on serum concentrations since the trial did not collect PBMCs for intracellular measurements. Serum PK samples, however, are not considered to be reliable measures of long-term drug adherence. Nonetheless, as in the iPrEx trial, fewer seroconversions occurred when subjects had consistently measurable tenofovir plasma concentrations. Please see the Clinical Pharmacology and Pharmacometrics reviews by Drs. Ayala and Liu for further exposure-response analyses of FTC/TDF as PrEP.

Lastly, the Applicant has provided the following rationale for proposing FTC/TDF instead of TDF alone as PrEP:

- The combination of FTC plus TDF showed greater efficacy than TDF alone in macaque studies of prevention of transmission of SIV via oral exposure and SHIV via rectal exposure (see Section 4.2).
- Oral FTC plus TDF provided complete protection against an FTC-resistant virus containing the mutation M184V in similar macaque studies. This result suggests that administration of both FTC and TDF may be important in areas of the world where drug-resistant viruses are frequently transmitted (see Section 4.2).
- From a pharmacokinetic perspective, FTC reaches intracellular steady state concentrations faster than tenofovir (~5 days versus 19 days of daily dosing). Emtricitabine also achieves higher concentrations in genital tissues relative to plasma than tenofovir (27-fold greater than plasma vs. 2.5-fold greater with TDF). In contrast, TFV-DP has a longer half-life in the genital tract than FTC-TP (14 versus <2 days). Thus, the combination of FTC plus TDF provides advantages over either product alone (see Section 4.4.3).
- The combination of FTC plus TDF has shown additive to synergistic anti-HIV-1 activity over either agent alone. This observation suggests FTC plus TDF may have an increased chemoprophylactic activity and a higher barrier to resistance than each agent may alone. This hypothesis has been previously confirmed in animal studies.
- In the VOICE clinical trial, the DSMB discontinued both the tenofovir-alone formulations (oral and microbicide gel) for lack of efficacy, while also allowing continuation of dosing for FTC/TDF and its matched placebo (see Section 2.6).

[Medical Officer Comment: The VOICE trial is still ongoing and remains blinded. Therefore, no conclusions about the trial can be made at this time and the trial itself cannot be used to justify use of FTC/TDF over TDF alone for PrEP.]

4.4.3 Pharmacokinetics

Tenofovir and FTC demonstrated linear PK over the dose ranges studied in the original NDA submissions for each. Steady-state plasma concentrations of both drugs were predictable based on single dose PK data. No major metabolites in plasma have been reported for FTC and TFV. The plasma PK of TFV and FTC are similar between HIV-1 infected and uninfected individuals.

A single dose of FTC/TDF delivers intracellular TFV-DP and FTC-TP concentrations that are approximately 15% and 35% of the expected steady-state intracellular concentrations, respectively. Of note, the intracellular half-life of TFV-DP is longer than the plasma half-life of TFV (87-150 hours versus 18.7 hours, respectively). Likewise, the intracellular half-life of FTC-TP is longer than the plasma half-life of FTC (39-50 hours versus 8 hours, respectively).²⁷

The oral bioavailability of tenofovir following administration of a 300 mg dose of TDF is approximately 25% in the fasted state. Maximum tenofovir serum concentrations are achieved in 1.0 ± 0.4 hour. Less than 0.7% of tenofovir binds to human plasma proteins in vitro and binding is independent of concentration over the range of 0.01-25 $\mu\text{g/mL}$. Approximately 70–80% of the intravenous dose of tenofovir is recovered as unchanged drug in the urine. Based on studies using human hepatic microsomes, the inhibitory potential of TDF on drugs metabolized by CYP enzymes is low. Tenofovir is eliminated by a combination of glomerular filtration and active tubular secretion.

The oral bioavailability of FTC is high (93%). Less than 4% of FTC binds to human plasma proteins in vitro and binding is independent of concentration over the range of 0.02 to 200 $\mu\text{g/mL}$. FTC is rapidly absorbed following oral administration of a 200 mg dose, with peak plasma concentrations occurring at 1-2 hours post dose. Approximately 86% of FTC is recovered in the urine and 13% is recovered as metabolites. The FTC metabolites are inactive and include 3'-sulfoxide diastereomers and their glucuronic acid conjugate. Based on in vitro studies, the potential for CYP450 mediated interactions between FTC and other drugs is low. Similar to tenofovir, the primary route of FTC elimination is renal excretion, modulated by glomerular filtration and active renal tubular secretion. Therefore, drugs that are secreted via the same renal tubular transporter could compete with tenofovir or FTC for elimination.

A recent PK study in healthy volunteers given a single oral dose of FTC/TDF measured TFV and FTC concentrations in blood plasma and genital secretions (with an assay lower level of quantification of 0.1 ng/mL); TFV-DP and FTC-TP concentrations were also measured in homogenates prepared from rectal, vaginal, and cervical tissues.²⁸ The study found that exposures to TFV, TFV-DP, FTC, and FTC-TP ranged widely depending on the type of mucosal tissue examined. The area under the concentration-time curve from 24 hours to 14 days ($\text{AUC}_{1-14\text{d}}$) for FTC in genital secretions was 27-fold greater than in plasma, whereas the $\text{AUC}_{1-14\text{d}}$ for TFV was only 2.5-fold greater in genital secretions than in plasma. In rectal tissue, TFV and TFV-DP concentrations were detectable for 14 days and were 100-fold higher than the concentrations in vaginal and cervical tissues. For FTC-TP, concentrations in vaginal and cervical tissue were 10-

²⁷ Anderson PL, Kiser JJ, Gardner EM, Rower JE, Meditz A, Grant RM. Pharmacological considerations for tenofovir and emtricitabine to prevent HIV infection. *J Antimicrob Chemother* 2011; 66 (2): 240-50.

²⁸ Patterson KN, Prince HA, Kraft E, et al. Penetration of tenofovir and emtricitabine in mucosal tissues: implications for prevention of HIV-1 transmission. *Sci Transl Med* 2011; 3 (112):112re4

to 15-fold higher than in rectal tissue; however, FTC-TP concentrations in all tissue types were detected for only two days after the dose.

Please see the Clinical Pharmacology Review by Dr. Ayala for further details regarding FTC and TDF pharmacokinetics.

5 Sources of Clinical Data

5.1 Tables of Studies/Clinical Trials

Trial	Sponsor	Title	Population	Randomized (N)
CO-US-104-0288 iPrEx (IND 71859)	DAIDS, NIAID, NIH	A Phase 3, randomized, double-blind, placebo-controlled study of chemoprophylaxis for HIV prevention in initially HIV-1-uninfected men who have sex with men (MSM)	Adult MSM or transgendered women at high risk for HIV infection	2,499
CO-US-104-0380 Partners PrEP (IND 75365)	University of Washington	Parallel comparison of tenofovir and emtricitabine/tenofovir pre-exposure prophylaxis to prevent HIV-1 acquisition within HIV-1 discordant couples	Serodiscordant adult heterosexual couples	4,758
CO-US-104-0277 CDC 4323	CDC	Phase II Extended Safety Study of Tenofovir Disoproxil Fumarate (TDF) for Prevention of HIV Among HIV-1 Negative Men	Adult MSM	400

5.2 Review Strategy

The Clinical Review for this supplement was conducted by the Medical Officer, Dr. Peter Miele. The review is based primarily on the complete double-blind treatment phases of both the iPrEx and Partners PrEP trials. The Medical Officer was also responsible for the writing of this review. Unless otherwise noted, results reported throughout this review were based on analyses carried out by the Medical Officer or other members of the FDA review team.

Due to the different study populations evaluated in each pivotal trial, safety and efficacy data from these two trials were not pooled and are presented separately by trial. The CDC 4323 trial was not used for the analysis of efficacy, but clinical safety and

behavioral data from the trial were used to support the evaluation of TRUVADA for the proposed PrEP indication. Data from the CDC TDF2, FEM-PrEP, FHI PrEP or VOICE trials were not submitted for review, but high level summaries of these trials were included in the submission and informed the review. In the case of the FEM-PrEP trial, presentations from recent scientific meetings were reviewed by the Medical Officer and are noted in this review. The VOICE trial is still ongoing, thus little information has been made public regarding the discontinuation of the TDF oral and vaginal gel treatment arms.

The Clinical Review is complemented by a Statistical Review of primary and secondary efficacy endpoints by Dr. Thomas Hammerstrom, Mathematical Statistics Reviewer. Review of the HIV resistance data was carried out by Dr. Damon Deming, Microbiology Reviewer, and pharmacokinetic and pharmacometric considerations were reviewed by Dr. Ruben Ayala, Clinical Pharmacology Reviewer, and Dr. Jiang Liu, Pharmacometrics Reviewer. Issues related to the REMS were reviewed by Dr. Carolyn Yancey of the Division of Risk Management. Additionally, consultation regarding labeling of TRUVADA in pregnancy for a PrEP indication was obtained from Dr. Leila Sahin of the Pediatric and Maternal Health Staff.

5.3 Discussion of Individual Studies/Clinical Trials

iPrEx

Study CO-US-104-0288 (iPrEx) was conducted under IND, sponsored by the DAIDS/NIH with protocol oversight chaired between two study centers, the Gladstone Institute of Virology and Immunology at the University of California, San Francisco (UCSF) and the Investigaciones Medicas en Salud in Lima, Peru. Co-funding was provided by The Bill and Melinda Gates Foundation (BMGF). Blinded study drug (FTC/TDF and placebo) was provided by the Applicant. Additionally, the Applicant provided certain analyses (e.g., safety assessments) and served as primary author for the submitted CSR, but did not participate in protocol design, study administration, data accrual, the initial primary data analysis, or the primary publication of the trial results.

The iPrEx trial was designed as a large, randomized, double-blind, placebo-controlled, Phase 3 trial of the safety and efficacy of chemoprophylactic oral FTC/TDF in seronegative MSM at high-risk for acquiring HIV-1 infection. The trial was conducted at 11 study sites in 6 countries: 3 sites in Peru, 1 in Ecuador, 3 in Brazil, 2 in the United States, 1 in Thailand, and 1 in South Africa. Of note, subjects were compensated for participation in the trial.

1. Objectives

The primary objectives 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 seroincidence among HIV-1-uninfected MSM.

The secondary objectives 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 BMD, 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 behavioral correlates of chemoprophylaxis failure or success, including frequency and type of sexual exposure and patterns of adherence. Risk behavior on- and off-study drug was compared. The prevalence of sexually transmitted infections (STIs) was used as one index of sexual risk.

2. Eligibility Criteria

Inclusion:

- Male sex (at birth)
- Provided written informed consent
- Reached the legal age of consent in their region (Protocol Version 3 required subjects be ≥ 18 years of age)
- Not infected with HIV-1
- Evidence of high risk for acquiring HIV-1 infection including any of the following in the 6 months prior to study entry:
 - Did not use a condom during anal intercourse with an HIV-positive male partner or a male partner of unknown HIV-1 status
 - Anal intercourse with > 3 male sex partners (Protocol Version 3 required > 5 male sex partners in the 6 months prior to entry; also certain sites allowed > 5 male sex partners throughout the trial due to the HIV incidence in the local region)
 - Exchanged money, gifts, shelter, or drugs for anal sex with a male partner
 - Had sex with a male partner and was diagnosed with a sexually transmitted infection (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
- 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

- Adequate renal function (creatinine clearance ≥ 60 mL/min estimated by the Cockcroft Creatinine Clearance Formula and serum creatinine level within normal limits) within 28 days of enrollment
 - Protocol Version 3 required serum creatinine level of ≤ 1.2 mg/dL.
 - A general memo retrospectively provided clarification that serum creatinine levels needed *to be less than or equal to the upper limit of normal* to meet eligibility because low serum creatinine levels are not associated with disease; therefore, persons with serum creatinine below the laboratory-defined lower limit of normal were eligible.
- Urine dipstick with a negative or trace result for both glucose and protein within 28 days of enrollment. (This requirement was not present in Protocol Version 3; however, the presence of glycosuria or proteinuria at screening and enrollment was exclusionary in Protocol Version 3 as described below.)
- Adequate hepatic function (per Protocol Version 4, defined as total bilirubin and hepatic transaminases [alanine aminotransferase {ALT} and aspartate aminotransferase {AST}] ≤ 2 x upper limit of normal [ULN] within 28 days of enrollment; Protocol Version 3 required total bilirubin ≤ 1.5 mg/dL and ALT and AST ≤ 2 x ULN.)
- Adequate hematologic function (absolute neutrophil count $\geq 1,500/\text{mm}^3$; platelets within normal limits [platelets $> 150,000/\text{mm}^3$ in Protocol Version 3], and hemoglobin ≥ 10 g/dL within 28 days of enrollment)
- Ability to understand and speak the local language for which an informed consent form was approved by a local IRB.

Exclusion:

- Previously diagnosed active and serious infections, including the following: active tuberculosis infection or osteomyelitis, and all infections requiring parenteral antibiotic therapy
- Active clinically significant medical problems, including cardiac disease (e.g., symptoms of ischemia, congestive heart failure, or arrhythmia), pulmonary disease (steroid-dependent chronic obstructive pulmonary disease), or diabetes requiring hypoglycemic medication
- Previously diagnosed malignancy expected to require further treatment
- Acute hepatitis B infection determined by the following serological results: Hepatitis B core antibody (anti-HBc) positive, hepatitis B surface antibody (anti-HBs) negative, and hepatitis B core antibody IgM (anti-HBc IgM) positive at the screening visit
- Presence of treatment indications for hepatitis B based on local practice standards (added per Protocol Version 4)
- Clinical signs of hepatic cirrhosis (added per Protocol Version 4)
- History of pathological bone fractures not related to trauma
- Receiving ongoing therapy with any of the following: antiretrovirals (including nucleoside analogs, nonnucleoside reverse transcriptase inhibitors, protease

inhibitors or investigational antiretroviral agents), interferon (alpha, beta, or gamma) or interleukin (e.g., IL-2) therapy, aminoglycoside antibiotics, amphotericin B, cidofovir, systemic chemotherapeutic agents, other agents with significant nephrotoxic potential, other agents that may inhibit or compete for elimination via active renal tubular secretion (e.g., probenecid), or other investigational agents (note that Protocol Version 3 also excluded ongoing diuretic therapy)

- Definitely or possibly received antiretroviral drugs or an anti-HIV vaccine while participating in a blinded clinical trial (added per Protocol Version 4)
- Concomitant participation in a clinical trial or cohort study other than substudies of this protocol (added per Protocol Version 4)
- Active alcohol or drug use considered sufficient by the site physician to hinder compliance with any study procedures
- At enrollment, had any other condition that, in the opinion of the investigator, would preclude provision of informed consent, make participation in the study unsafe, complicate interpretation of study outcome data, or otherwise interfere with achieving the trial objectives
- Note that Protocol Version 3 also excluded subjects with glycosuria or proteinuria at both the screening and enrollment visits by urine dipstick tests.

In addition, sites could utilize additional criteria to restrict enrollment to a subset of people who met the protocol-defined enrollment criteria.

3. Trial Design

Enrollment started in 2007 with Version 3 of the protocol, which called for 1,400 persons to be enrolled and followed for 72 weeks. Prior to enrolling the first participant, however, a decision was made to expand the trial to allow observation of at least 85 seroconversion events and thus allow for greater power and generalizability. In November 2009, the DAIDS Data Safety Monitoring Board (DSMB) concluded that fewer than 3000 enrollees and visits through May 1, 2010 should suffice to generate the required number of events. The sample size was chosen to ensure adequate power to rule out efficacy lower than 30% if the true efficacy was at least 60%. Enrollment was closed on December 17, 2009 after 2,499 persons were enrolled. Eligible participants were randomized 1:1 to receive FTC 200 mg/TDF 300 mg (TRUVADA) or placebo and followed every 4 weeks.

An additional amendment (Protocol Version 5) provided for the termination of placebo administration and provision of open-label daily oral FTC/TDF for HIV-1 prevention. The open label extension (OLE) amendment was intended only if FTC/TDF was found to be superior to placebo. Any statistically significant finding of efficacy in the protocol-defined efficacy analyses was considered sufficient to start the extension procedures provided there was also evidence of acceptable safety as judged by the study sponsor. Because the analyses of safety and efficacy from the primary analysis were considered positive, Protocol Version 5 was implemented in

March 2011 (referred to as iPrEx OLE), with variable study site initiation staggering dependent upon site and regulatory timelines.

4. Trial Duration and Procedures

Given the event-driven design, the duration of study drug exposure and on-study follow-up for each subject was not prespecified. Study visits were scheduled every 4 weeks. Each 4-week visit included drug dispensation, pill count, adherence counseling, rapid testing for HIV-1 antibodies, and medical history. Laboratory assessments (serum chemistry and hematology) were performed at Weeks 4, 8, 12, 16, 24, and every 12 weeks thereafter. During the screening period, a computer-assisted structured interview (CASI) collected information on education level, self-identified sex, and alcohol use. The CASI was also used to assess subjects' perceived study-group assignment at Week 12. High-risk behavior was assessed by interview every 12 weeks.

At every scheduled visit, subjects received a comprehensive package of infection prevention services, including HIV-1 testing, risk-reduction counseling (as per national guidelines), condoms, and diagnosis and treatment of symptomatic STIs, including gonorrhea and chlamydia urethritis, syphilis, and HSV-2 as appropriate. In addition, at 24-week intervals, subjects were screened for asymptomatic urethritis, syphilis, antibodies to HSV-2, and genital warts and ulcers; treatment was provided when indicated. Sexual partners were offered treatment of STIs. Subjects were linked to local prevention and treatment services, when required, to receive standard-of-care services. All subjects were instructed to protect themselves from HIV-1 with established methods. Subjects who reported a recent unprotected exposure to an HIV-infected partner were referred for postexposure prophylaxis (PEP) at sites where such therapy was recommended by local guidelines, and the administration of a study drug was temporarily suspended. Vaccination against HBV was offered to all susceptible subjects.

Adherence to treatment 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). Adherence counseling was provided to all subjects to help ensure compliance. Counseling also included reminders to contact study staff with questions about product use, as well as counseling to not share study drugs. For subjects who had problems with compliance, efforts were made to identify strategies to increase their adherence. An interactive, client-centered, motivational interviewing based approach for study pill use was implemented for all subjects starting between November 2009 and February 2010. Called "Next Step" counseling, the approach separated adherence assessment from counseling, 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.

All clinical and laboratory toxicities (apart from creatinine and phosphorus) were managed according to uniform guidelines and graded according to the DAIDS Table for Grading the Severity of Adult and Pediatric AEs (December 2004). Separate guidelines for toxicity related to creatinine and phosphorus were used:

- Participants with confirmed serum creatinine increases >1.5-fold above baseline after repeat testing were to discontinue study drug and have serum creatinine monitored monthly or more frequently at the discretion of the site investigator until serum creatinine decreased to \leq 1.3-fold above baseline at which time study drug could be restarted.
- Participants with confirmed Grade 3 or 4 serum creatinine toxicity or with calculated creatinine clearance <50 mL/min had study medication permanently discontinued and were followed at weekly intervals until the toxicity resolved or stabilized.
- For participants with Grade 2 phosphorus toxicity, phosphorus levels were repeated at the next scheduled visit or within 4 weeks. Study drug was permitted to continue if other signs of renal tubular dysfunction were absent; i.e., no serum bicarbonate (or CO₂) \leq 17 mEq/L, no new glycosuria \geq +1, or no new proteinuria \geq +2.
- For Grade 3 or 4 hypophosphatemia, phosphate was repeated within 1 week. For asymptomatic Grade 3 decreases in phosphorus, subjects could remain on study drug with the following caveats: there should be no other signs of renal tubular acidosis; subjects were treated with oral phosphate supplements; and phosphorus levels would be re-tested weekly until they returned to the normal range, Grade 2 or better. For subjects who interrupted treatment for low phosphorus, study drug could be resumed at the discretion of the site investigator once levels were within the normal range. If Grade 3 or 4 hypophosphatemia recurred after resuming treatment, study drug was discontinued permanently.

Subjects found to have a reactive HIV antibody test were instructed to stop study drug and have blood drawn for confirmation HIV serology, HIV RNA viral load, CD4 T cell counts, and genotypic and phenotypic drug resistance testing as well as additional HBV serology (if clarification of their HBV infection status was needed). Additional plasma was cryopreserved and stored at the visit with the first reactive test. Participants were asked to return in two weeks to receive the results of confirmatory HIV serology.

When a subject tested positive for HIV-1 infection, the final confirmation of HIV-1 seroconversion was based on 1) an algorithm and 2) the assessment of an Endpoints Committee. Based on the algorithm, all reported seroconversion events required:

- an initial positive test on at least one of the two different types of HIV-1 rapid tests, and

- either confirmation by enzyme immunoassays (EIA) or by another test approved by the Medical Director.

The Endpoints Committee reviewed each seroconversion case, and made a recommendation whether a seroconversion was:

- Not confirmed – the subject was not infected
- Confirmed – the subject was infected at enrollment, as detected by HIV polymerase chain reaction (PCR).
- Confirmed – primary efficacy event, or
- Not yet confirmed – further testing needed

If a subject seroconverted within the first three months of trial enrollment, investigators conducted RNA PCR testing using samples collected at enrollment to determine if the HIV infection was present prior to receiving study drug. RNA PCR analysis was also conducted in subjects who missed HIV testing at the 3-month clinic visit and were seropositive at their next visit. For all subjects who seroconverted, investigators attempted to identify the date of seroconversion by sequentially analyzing blood samples collected during previous clinic visits preceding the visit when seroconversion was detected.

If the subject was determined to be HIV negative, they would return to their original study visit schedule. If they were determined to be HIV positive, they received counseling and were referred to study sites and clinics where free or low-cost HIV treatment programs were available. At study visits 4, 8, and 12 weeks after the first reactive HIV test, and every 12 weeks thereafter until the end of their study participation, participants were asked to provide 53 mL of blood for plasma viral RNA testing, CD4 T cell counts and specimen storage.

5. Prespecified Subgroup PK Analysis

A prespecified subgroup analysis was performed to investigate whether drug concentrations correlated with protective effect. All trial participants underwent PK sampling at baseline, every 12 weeks (every 24 weeks for peripheral-blood mononuclear cells [PBMC]), at end of trial visit, and at every follow-up visit. When an HIV-1 infection occurred, PK samples were collected from infected subjects during the clinic visit when the seroconversion was detected. Subjects who seroconverted during treatment were matched with two seronegative case-control subjects, one from each study group, who were matched for study site and time on treatment. Seroconverters were also matched to a third control subject who reported unprotected receptive anal intercourse (URAI) in the period that covered the plasma sample date for the seroconverter. Plasma was tested for FTC and tenofovir (TFV) concentrations, and PBMCs were tested for FTC triphosphate (FTC-TP) and TFV diphosphate (TFV-DP), the active intracellular metabolites of FTC and TFV, respectively. Because of the intracellular PK properties of TFV-DP, PBMC drug

concentrations are considered better long term measures of drug adherence (see the Clinical Pharmacology review by Dr. Ayala).

6. DEXA Substudy

All participants who enrolled at a study site with DEXA capacity were invited to participate in a substudy involving DEXA scanning at baseline, all 24 week visits, the visit when study drug is stopped (unless a participant had a DEXA scan during the previous 8 weeks) and 24 weeks after stopping study drug until the predetermined substudy sample size (N=500) was reached. Measurements of BMD at the lumbar spine and proximal femur (femoral neck, trochanter, and total hip) were obtained, as well as assessments of fat distribution. Any participant in the substudy who seroconverted during the trial had a DEXA scan as soon as possible after the positive HIV confirmatory test and then every 24 weeks until the end of trial. For the analyses of BMD, all scans up to and including February 28, 2011 were included; scans performed on or after the date of HIV infection were excluded.

The following table shows the schedule of events in the iPrEx trial:

Table 4: Study Flow Chart (CO-US-104-0288)

Study Visit Week	Screening	0 ¹	4	8	12	16	20	24	28	32	36	40	44	48 ²	4 week visits after week 48	12 week visits after week 48	24 week visits after week 48	Stop ³	Stop+4 (first follow-up visit)	Stop+8 (second follow-up visit)	Stop+12 16 and 20 for HBsAg+ subjects	Stop +24 for HBsAg+ subjects	SC1 Serocon -version reactive rapid test	SC2 Serocon -version Western Blot results ⁴	4 and 8 week SP visits	12 week SP visits	24 week SP visits	Stop+24 DEXA exam 6 months Post-Exit			
Target Day ⁵	-1 to -28	0	28	56	84	112	140	168	196	224	252	280	308	336	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a		
Test/Procedure																															
CLINICAL ASSESSMENT																															
Screen/enroll informed consent	X	X																													
Inclusion/exclusion criteria	X																														
Pre and post-test counseling	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X							
Structured behavioral interview	X				X			X			X			X		X	X	X		X		X				X	X	X			
Medical history	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
Physical exam ⁶	X							X						X		X	X	X		X		X				X	X	X			
Risk reduction and condoms	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Adherence check			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X		X									
Pill count			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X		X									
Drug dispensing		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X					X								
LABORATORY ASSESSMENT																															
Chemistries	X	X ⁷	X	X	X	X		X			X			X		X	X	X	X	X	X ⁸	X ⁸	X		X ⁸	X ⁸	X ⁸				
CBCs	X	X	X	X	X	X		X			X			X		X	X	X		X		X			X ⁸	X ⁸	X ⁸			X	
Urine dipstick test	X							X						X		X	X														
Serum HBV testing ⁹	X																	X ⁹				X ⁹									
Serum hepatitis C (HCV) testing		X																													
STI evaluation	X							X						X		X	X										X				
HIV antibody rapid test	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X ⁴						X	
Confirmatory HIV antibody testing	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X ⁴							X	
HIV-1 plasma RNA																							X		X	X					
Drug resistance testing																						X ¹⁰									
CD4 T cell counts																						X			X	X	X				
DEXA scan ¹¹		X ¹¹						X ¹¹						X ¹¹		X ¹¹	X ¹¹					X		X ¹¹			X ¹¹	X ¹¹			
Serum storage	X	X	X	X	X	X		X			X			X		X	X	X	X	X	X	X	X ⁴	X	X	X	X	X	X ¹¹		
Plasma storage		X			X			X			X			X		X	X	X	X	X	X	X	X ⁴	X	X	X	X	X			
PBMC storage ¹²		X						X						X		X	X				X	X	X	X	X	X	X	X			
Blood volumes (ml) ¹²	13	53	13	13	23	13		53						53		23	53	53	23	53	20	53	53	20 ⁶	53	53	53	53			

1. The enrollment visit is considered to be at 0 weeks.
 2. The duration of participants on study drug follow-up is variable. The procedure shown for the first 48 weeks of on study drug follow-up will be repeated until the participant stops taking the study drug.
 3. Procedures listed at the stop visit will be done at the visit when the study participant stops taking study medication instead of the procedures at their regularly scheduled visit. For those participants in the DEXA and metabolic substudy, the DEXA scan will not be done if a DEXA scan was done in the previous eight weeks.
 4. The procedures for the SC2 visit will be repeated for participants receiving their Western Blot confirmatory analysis until they are determined to be HIV negative or HIV positive according to Appendix 3. If the Western Blot result is positive no blood will be drawn at this visit. If the Western Blot result is negative or indeterminate 20 ml of blood will be drawn for additional testing according to Appendix 3.
 5. For all follow-up visits, a window period ± 5 days of the target day is considered valid.
 6. Participants will also have a physical exam at a visit where one is not scheduled if a medical history prompts one.
 7. Only creatinine levels will be assessed at the enrollment visit.
 8. Only ALT and AST will be done at the 4, 8, 12, and 24 week seropositive visits and the 12, 16, 20, and 24 week post-stop visits of HBsAg+ participants.
 9. HBV serology panels will be repeated at study exit or when stopping study drug and SC1 on those susceptible to HBV or with ambiguous HBV infection status. HBV serologies may be repeated 12 weeks after participants receive the complete HBV vaccination series.
 10. Drug resistance testing (genotypic and phenotypic) will be done at the SC1 visit. Genotyping will be performed also at the last seropositive visit and at interim timepoints as needed to determine the timing of viral genetic shifts.
 11. Bone mineral density, fat distribution, and fasting lipids will be assessed by DEXA in an optional substudy (see section 9.10).
 12. If the study sites do not have capacity for viable cell cryopreservation, a smaller volume of blood will be drawn at visits when cell storage was scheduled.

Source: iPrEx Study Protocol Version 4.0

7. Endpoints

The primary efficacy endpoint of the blinded treatment phase was the incidence of documented HIV-1 seroconversion defined by the predefined follow-up HIV-1 testing algorithm.

The primary safety endpoints of the blinded treatment phase of this study were the incidences of AEs, specifically defined as the following:

- Grade 1 or higher creatinine toxicity confirmed by repeat testing.
- Grade 3 or higher phosphorus toxicity confirmed by repeat testing.
- Grade 2, 3, or 4 laboratory abnormalities other than creatinine or phosphorus.
- Grade 2, 3, or 4 AEs.

Other endpoints included hepatic transaminase elevations among subjects with detectable HBsAg; changes in BMD, fat distribution, and fasting lipids from baseline among subjects enrolled in the DEXA substudy; HIV-1 drug resistance, plasma HIV-1 RNA level, and CD4 T-cell counts among HIV seroconverters; reported risk behavior; STI prevalence; pill counts and reported adherence. Antiviral immune responses and concentrations of FTC and TFV and their active intracellular metabolites were measured in subjects with seroconversion plus two matched uninfected case controls.

Partners PrEP

Study CO-US-104-0380 (Partners PrEP) was conducted under IND, sponsored by the University of Washington. As with the iPrEx trial, funding for the trial was obtained from the BMGF and pharmaceutical support from the Applicant. The Applicant also served as primary author for the CSR, but did not participate in protocol design, study administration, data accrual, the initial primary data analysis, or any publication related to the trial.

The Partners PrEP trial was a large, Phase 3, multicenter, randomized, double-blind, placebo-controlled, 3 group trial designed to evaluate the safety and efficacy of PrEP with either TDF or FTC/TDF administered orally once daily for the prevention of HIV-1 acquisition among HIV-1 uninfected individuals within a stable, HIV-1 serodiscordant partnership. The trial was conducted in 4 sites in Kenya and 5 sites in Uganda. The protocol provided for participants to be compensated for their time and effort in the trial, and/or be reimbursed for costs associated with travel to study visits, time away from work, and childcare. Throughout the study protocol and this review, HIV-1 uninfected members of the couple are referred to as “partner subjects” and HIV-1 infected members of the couple are referred to as “index subjects.”

1. Objectives

The primary objectives were:

- To determine if once-daily, oral PrEP with TDF or FTC/TDF provides additional protective benefit in preventing HIV-1 acquisition among HIV-1 uninfected persons within heterosexual HIV-1 discordant couples who are also receiving standard prevention interventions.
- To assess the safety of daily PrEP by comparing AEs rates among HIV-1 uninfected individuals randomized to TDF or FTC/TDF PrEP to those randomized to placebo.

The secondary objectives were:

- To evaluate the efficacy of PrEP by level of HIV-1 exposure, defined by the frequency of sexual activity and viral load in the HIV-1 infected partner
- To assess efficacy of PrEP by gender of the HIV-1 uninfected partner
- To measure the effect on efficacy of other factors, including CD4 count of the HIV-1 infected partner and, for both partners, HSV-2 serostatus, STIs, and male circumcision
- To assess adherence to once daily TDF and FTC/TDF PrEP among HIV-1 uninfected persons within HIV-1 discordant couples, and the effect of adherence on efficacy of PrEP to prevent HIV-1 acquisition
- To evaluate the frequency of PrEP drug sharing between uninfected and infected partners within HIV-1 discordant couples, as measured by drug assays in both partners
- To compare risk behaviors among HIV-1 discordant couples previously enrolled in the Partners in Prevention trial (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 behaviors when the HIV-1 infected versus HIV-1 uninfected partner is receiving study drug
- To assess the effect of TDF and FTC/TDF chemoprophylaxis on the rate of congenital abnormalities and growth among infants born to HIV-1 uninfected female subjects who became pregnant during the trial (and in whom study drug is stopped at the time pregnancy is detected, using monthly pregnancy testing)
- Among HIV-1 seroconverters, to assess the effect of PrEP on: plasma HIV-1 viral load and CD4 cell counts during the first 12 months after HIV-1 seroconversion; frequency of genotypic and phenotypic antiretroviral drug resistance; other clinical, immunologic, and virologic parameters of HIV-1 disease

Tertiary objectives included:

- To utilize stored samples for evaluation of immunogenetic and virologic determinants of HIV-1 transmission between transmitting and nontransmitting HIV-1 discordant couples, including viral phenotype and genotype, HIV-1 co-receptor usage, innate immune function polymorphisms, human leukocyte antigen (HLA) match and other host genetic factors

2. Eligibility Criteria

	HIV-1 seronegative partners	HIV-1 seropositive partners
Inclusion Criteria	<ul style="list-style-type: none"> • HIV-1 uninfected based on parallel negative HIV-1 rapid tests, at study screening and enrollment visits • Age ≥18 and ≤65 years • Sexually active <ul style="list-style-type: none"> - defined as six or more episodes of vaginal intercourse with the HIV-1 seropositive study partner in the 3 previous months - plan to remain in the relationship for the study period • Adequate renal function <ul style="list-style-type: none"> - creatinine clearance ≥60 ml/min, and - serum creatinine ≤1.3 mg/dL (men) or serum creatinine ≤1.1 mg/dL (women) • Adequate hepatic function <ul style="list-style-type: none"> - total bilirubin ≤1.5x upper limit of normal, and - hepatic transaminases (ALT and AST) <2x upper limit of normal • Adequate hematologic function <ul style="list-style-type: none"> - absolute neutrophil count >1,300/mm³ - platelets >125,000/mm³ - hemoglobin >11 g/dL • No evidence of chronic active hepatitis B infection <ul style="list-style-type: none"> - negative hepatitis B surface antigen test • Able and willing to provide adequate locator information for study retention purposes • Able and willing to provide written informed consent 	<ul style="list-style-type: none"> • HIV-1 infected based on positive EIA • Age ≥18 years • Sexually active <ul style="list-style-type: none"> - defined as six or more episodes of vaginal intercourse with the HIV-1 seronegative study partner in the 3 previous months - plan to remain in the relationship for the study period • CD4 cell count ≥250 cells/mm³ • No history of any clinical AIDS-defining diagnoses and not otherwise meeting national guidelines for initiation of antiretroviral therapy. <i>Note: In July 2010, Kenya guidelines increased CD4 eligibility for initiation of antiretroviral therapy from <200 to <350 cells/μL and thereafter study eligibility was determined based on those updated guidelines.</i> • Able and willing to provide adequate locator information for study retention purposes • Able and willing to provide written informed consent
Exclusion Criteria	<ul style="list-style-type: none"> • Current pregnancy or planning to become pregnant • Current breastfeeding • Repeated positive (≥1+) urine dipstick tests for glycosuria or proteinuria • Active and serious infections • Ongoing therapy with: antiretroviral therapy; metformin; aminoglycoside antibiotics; amphotericin B; cidofovir; systemic chemotherapeutic agents; other agents with significant nephrotoxic potential • History of pathological bone fractures not related to trauma • Enrolled in another HIV-1 vaccine or prevention trial • Known plans to re-locate or travel away from the study site for more than two consecutive months during study period 	<ul style="list-style-type: none"> • Enrolled in an HIV-1 treatment trial • Current use of antiretroviral therapy

Source: NDA 21-75/S-30 Efficacy Amendment (March 22, 2012)

3. Trial Design

Eligible HIV-uninfected partner subjects were randomized in a 1:1:1 ratio to receive either TDF 300 mg, FTC 200 mg/TDF 300 mg, or placebo. Because TDF and FTC/TDF tablets are dissimilar in appearance, all partner subjects took two tablets daily. As in the iPrEx trial, subjects were followed monthly for HIV testing, adherence monitoring, risk reduction counseling, and treatment of any STIs. In addition, female participants were tested monthly for pregnancy. Referral for male circumcision, PEP according to national policies, and HBV vaccination were also offered.

The trial was designed with an event-driven duration, with the sample size of 4700 (1566 per treatment group) HIV-1 serodiscordant couples defined to achieve the target number of study endpoints, with 24 to 36 months of follow-up per participant, and an anticipated HIV-1 incidence of 2.75 per 100 person-years (PY) in the placebo group. The trial was overseen by an independent DSMB that reviewed all reported safety and efficacy data at meetings that occurred approximately every 6 months. Interim monitoring stopping boundaries for proven efficacy were pre-established based on ruling out efficacy lower than 30%.

4. Trial Duration and Procedures

Enrollment began in June 2008. Study visits were scheduled every 4 weeks for partner subjects. Each 4-week visit included study drug dispensation, pill count, adherence counseling, HIV-1 rapid testing, and risk-reduction counseling in addition to laboratory testing and medical evaluations. Diagnosis and treatment of symptomatic STIs was done as clinically indicated, with specific STI symptomatology collected quarterly. Subjects were linked to local prevention and treatment services, when required, to receive standard-of-care services. All subjects were instructed to protect themselves from HIV-1 with established methods. Vaccination against HBV was offered to all susceptible subjects. Women were tested for pregnancy monthly. Women who became pregnant stopped using study drug during pregnancy and while breastfeeding.

HIV-1 infected index partners were followed quarterly for issues relevant to the secondary and tertiary study endpoints, such as HIV-1 risk assessments and counseling, medical history, HIV-1 staging, use of ART and prophylactic treatments for opportunistic infection, and STI evaluations. Blood collection and CD4 cell counts were performed on the HIV-1 infected partner every 6 months. In addition, for couples where the uninfected partner subject seroconverted, drug levels were measured in the HIV-1 infected partners at the visit closest to the seroconversion event to determine whether evidence of drug sharing was associated with early viral resistance in the seroconverting partner subject.

Adherence in partner subjects was measured throughout by survey and pill count. Adherence counseling was provided to all subjects at each visit. Specifically, counseling included reminders to contact study staff with questions about product use, as well as counseling to not share the study agent (including with the index partner). For subjects who had adherence problems, efforts were made to identify strategies to increase their rates of product use during the trial.

All clinical and laboratory toxicities (apart from creatinine and phosphorus) were managed according to uniform guidelines and graded according to the DAIDS AE Grading Table (December 2004). The only exceptions were that Grade 1 creatinine toxicity was defined as being at least 1.5 times the subject's baseline serum creatinine level, even if serum creatinine was in the normal or Grade 0 range, and Grade 2 creatinine toxicity was defined as a creatinine clearance less than 50 mL/min, even if the creatinine value was in the normal or Grade 1 range. Guidelines for toxicity related to renal dysfunction (including creatinine and phosphorus) were similar to those used in the iPrEx trial detailed above. Safety monitoring also focused on infants born to HIV-1 uninfected female participants. The following AEs in the partner subjects were protocol-defined as Expedited AEs (EAEs) and had additional reporting requirements: death, all Grade 3-4 events, SAES, fetal loss, congenital abnormalities/birth defects, Grade 2 creatinine elevations, and bone fractures.

Partner subjects who seroconverted during the trial were instructed to stop the study drug. HIV-1 seroconversions were confirmed by centralized laboratory testing and evaluation by a study endpoints committee that was blinded to the study randomizations. Seroconverters had clinical laboratory specimens collected for serum chemistries and complete blood counts (obtained at the seroconversion visit), as well as blood and genital samples for assessment of HIV-1 viral levels and CD4 counts. The samples were archived for drug resistance testing (including potentially genotypic and phenotypic) at the central laboratory. Resistance testing using samples from the first two post-seroconversion visits was conducted in a batched fashion, using genotypic testing. HIV-1 seroconverters were provided with or referred for HIV-1 clinical care in accordance with national guidelines.

As noted previously, all subjects were planned to be followed for a minimum of 24 months up to a maximum of 36 months. The follow-up schedule was designed to yield a sufficient accumulation of person-years to accrue a prespecified number of HIV-1 seroconversion endpoints to adequately evaluate the primary study outcome. Importantly, follow-up of up to 36 months for some study subjects was planned to provide long-term adherence and safety data. On 10 July 2011, following the third planned interim review of the data and with 99 site-reported seroconversions evaluated, the DSMB declared that the stopping rule for the study had been met and recommended that the results be publically reported and that placebo dosing be discontinued due to demonstration of PrEP efficacy for HIV-1 prevention. After July 10, 2011, all subjects in the placebo group were informed of their randomization and placebo medication was discontinued. Subjects in the active study drug groups were informed that they were receiving PrEP, but were not informed as to which active study drug they were receiving. This application therefore includes updated data collected through the July 10, 2011 cut-off date.

5. Endpoints

The primary efficacy endpoint was the incidence of confirmed HIV-1 seroconversion among partner subjects.

A secondary analysis was conducted to evaluate adherence to study drug, although no formal PK endpoints were evaluated. Within the active study drug groups, a comparison was conducted of tenofovir plasma levels for partner subjects who acquired HIV-1 during the trial relative to a cohort of 100 randomly selected partner subjects who did not acquire HIV-1. Blood samples for evaluation of tenofovir plasma concentrations were obtained from both cases and cohorts at months 1, 3, 6, 12, 18, 24, 30, and 36. Additionally, plasma samples were collected from seroconverters during the visit at which HIV-1 seroconversion was detected.

Safety was evaluated by a review of serious adverse events (SAEs), protocol-defined EAEs, including all Grade 3 and 4 events, and all other Grade 1+ laboratory and Grade 2+ clinical AEs occurring in the partner subjects.

CDC 4323

The CDC 4323 trial entitled, “Phase II Extended Safety Study of Tenofovir Disoproxil Fumarate (TDF) among HIV-1 Negative Men” was sponsored by the Epidemiology Branch, Division of HIV Prevention, National Center for HIV, TB, and STD Prevention, Centers for Disease Control and Prevention (CDC). The Applicant provided study drug products. The trial was complete in July 2009. As part of this marketing application, the Applicant has provided raw datasets, a draft manuscript from the CDC, and a protocol for the trial (Version 1.6 dated February 16, 2007). In addition, a publication regarding the DEXA substudy of CDC 4323 is referenced.²⁹

1. Objective

The objective of the trial was to evaluate the clinical safety of daily TDF as PrEP among HIV-negative MSM.

2. Trial Design

The trial was randomized, double-blind, placebo controlled in design. Participants were randomized 1:1:1:1 to TDF or placebo, either immediately or after a 9-month delay, and were followed for two years. The delayed arms were designed to help assess potential changes in risk behavior associated with taking study drug. It was determined that overall sample size of 400 would be sufficient to have 72% to 90% chance of observing at least five 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 half of the sample. Participants were recruited from three U.S. cities: San Francisco, Atlanta, and Boston.

3. Eligibility

Eligible participants were healthy biologic males, 18-60 years of age, who reported any anal sex with another male in the preceding 12 months, were HIV-1 negative by whole blood rapid enzyme immunoassay (EIA), had a calculated Cockcroft-Gault creatinine clearance ≥ 70 mL/min, were hepatitis B surface antigen negative, and had normal hematologic, biochemistry, 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 Z score < -2.5 at the total spine, total hip or femoral neck on screening (DEXA scans done at San Francisco site only); current treatment for secondary causes of low bone mineral density; participation in other longitudinal HIV studies; current antiretroviral use; current or planned therapy with nephrotoxic agents, probenecid, metformin, or experimental or

²⁹ Liu A, Vittinghoff E, Sellmeyer DR, et al. Bone mineral density in HIV-negative men participating in a tenofovir pre-exposure prophylaxis randomized clinical trial in San Francisco. PLoS One 2011; 6 (8): e23688.

investigational agents; previous or expected requirements for the administration of immunosuppressive/immunomodulatory therapy; gastrointestinal malabsorption syndrome or chronic nausea/vomiting; or medical or social conditions that would interfere with or contraindicate study participation.

4. Trial Duration and Procedures

Enrollment began in 2005. Study visits occurred at 1, 3, 6, 9, 12, 15, 18, 21, and 24 months post enrollment. Delayed arm recipients had an additional visit at ten months (after the first month on study drug). Visits included HIV rapid testing, AE assessment, symptom-directed physical examination, blood and urine collection for laboratory testing, STI testing, behavioral assessment via audio computer assisted self interview (ACASI), and risk reduction and adherence counseling. Participants were followed for 24 months, even if study drug was discontinued.

Clinical 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. All graded elevations were repeated for confirmation. 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. For confirmed Grade 3 (3.1-6.0 mg/dL) or Grade 4 (>6.0 mg/dL) elevations, study drug was permanently discontinued.

Adherence to study drug was measured by three methods: pill counts conducted at each visit, Medication Event Monitoring System (MEMS) caps, and self-report via ACASI (in which participants were asked to estimate the percentage of days they took study drug over the preceding month on a visual analog scale).

Participants with positive rapid tests were immediately discontinued from study drug; those with positive confirmatory tests remained off drug. Viral load, CD4 count, and HIV-1 genotype studies were obtained. Seroconverting participants were referred for appropriate clinical care and were followed every three months for an additional year for safety assessments.

5. DEXA Substudy

At the San Francisco site, 200 MSM enrolled. DEXA was performed at enrollment, 12 months, and 24 months in the immediate arm to evaluate BMD changes over time. After detection of a number of individuals with low BMD at baseline, a protocol amendment was approved within 9 months of study initiation to conduct baseline DEXA measurements in all eligible individuals during screening, and to exclude individuals with a Z score < -2.5 at the lumbar spine (L2-L4), total hip, or femoral neck and individuals currently receiving treatment for secondary causes of low BMD.

DEXA evaluation was not performed in participants found to be ineligible prior to DEXA procedures during the screening process. DEXA scanning was also added for delayed arm participants at 9 and 24 months of follow-up. Study drug was discontinued in participants with a >5% drop in BMD from baseline. For the longitudinal analysis of TDF effect on BMD, 184 MSM were included who completed a baseline and at least one DEXA scan during study follow-up.

6. Endpoints

Primary outcomes were clinical safety, assessed by incidence of AEs and laboratory abnormalities, and behavioral changes among participants dispensed drug. Secondary outcomes included adherence and description of number and resistance characteristics of incident HIV-1 infections.

6 Review of Efficacy

Efficacy Summary

In this supplemental NDA, clinical data from two large, randomized, double-blinded, placebo-controlled trials in diverse populations provide strong evidence of the efficacy of FTC/TDF in reducing the risk of HIV infection in high-risk uninfected individuals. In many ways, the trial designs for the iPrEx and Partners PrEP trials were similar, except that the iPrEx trial evaluated oral FTC/TDF as PrEP in high-risk MSM and the Partners PrEP trial evaluated oral FTC/TDF, as well as oral TDF, as PrEP in heterosexual men and women in stable HIV serodiscordant relationships. Both trials used the standard dosing regimen for FTC/TDF; i.e., one fixed-dose combination tablet of FTC 200 mg/TDF 300 mg taken orally once daily. Both trials included monthly HIV testing, risk reduction counseling, provision of condoms, and testing for any symptomatic STIs as part of their treatment procedures, and both trials used the cumulative incidence of documented HIV seroconversion as the primary efficacy endpoint, which is appropriate for the indication under consideration. In both trials, the endpoint was confirmed by a testing algorithm and endpoints committee.

In the iPrEx trial, 2,499 high-risk MSM were randomized to FTC/TDF or placebo. Ten subjects were found to have been HIV-infected at enrollment through retrospective RNA testing of baseline blood samples (FTC/TDF 2, placebo 8). Of note, most of these ten subjects had signs and symptoms of acute HIV infection at the time of enrollment that the investigators attributed to upper respiratory tract infections or other non-HIV causes. As of the November 21, 2010 data cut-off date, 75% of subjects had completed the trial and 25% had terminated early. Early terminations were mostly due to lost to follow-up, relocation, or subject refusal to continue; a small group of subjects (N=7) also reported AEs in association with their early withdrawal from the trial. Given the event-driven

nature of the trial, follow-up was variable, but the median duration of exposure was 77 weeks with no differences between groups. Subject demographics and baseline risk characteristics were also comparable between the two treatment groups. In general, this was a young cohort with a mean age of 27 years, and roughly half of the participants were under 25 years of age. The majority was from Latin America (Peru or Ecuador) and most subjects had completed a secondary education. Participants from the United States made up only 9% of the population and tended to be older (mean age: 38 years old). Consistent with the inclusion criteria, the MSM followed in this trial were at high risk for HIV acquisition, with 59% reporting URAI in the three months pre-enrollment and 80% reporting URAI with a partner of HIV positive or unknown status in the six months pre-enrollment. The mean number of sex partners in the three months pre-enrollment was 18. A substantial proportion also reported transactional sex (41%). Baseline prevalence for any STI (including syphilis, gonorrhea, chlamydia, genital ulcer disease, or HSV-2) was 16%.

In the modified intent-to-treat analysis for the total double-blind treatment phase, with a data cut-off of November 21, 2010, 48 confirmed HIV seroconversion events were observed in the FTC/TDF group post-baseline compared with 83 in the placebo group. The risk reduction for FTC/TDF relative to placebo was 42% (95% CI 18-60%, $p=0.001$). The superiority of FTC/TDF over placebo persisted during the 8 weeks following discontinuation of study drug, with a relative risk reduction of 40% (95% CI 19-60%); however, as with the primary analysis, the null hypothesis of efficacy 30% or less could not be rejected. The efficacy of FTC/TDF was consistent across subgroups with no significant differences. Subjects who reported URAI at baseline demonstrated a 53% risk reduction, whereas a protective effect could not be demonstrated in subjects who did not report URAI given the low HIV incidence in this subgroup. Greater numerical risk reduction was also observed among subjects 25 years and older and among those who had higher education (completed secondary education or beyond). These subgroups were also among those most likely to be adherent to drug dosing as demonstrated by measurable intracellular drug concentrations in a PK subgroup analysis. Indeed, overall efficacy in the iPrEx trial was strongly correlated with drug adherence as demonstrated in the PK substudy; however, drug adherence in the trial was generally poor, with less than 10% of subjects having PK values consistent with daily drug dosing. In the PK substudy, measurable intracellular TFV-DP concentrations were observed in only 8% of the HIV seroconverters compared with 38% of the HIV-uninfected matched controls. The risk reduction among subjects with measurable drug concentrations was 90% (95% CI 71-98%) relative to subjects with undetectable drug concentrations. Relative to placebo, the absolute risk reduction for subjects having measurable drug concentrations was estimated at 87.5% (95% CI 66-95%). Post-exposure prophylaxis (PEP) was utilized by only 1% of subjects and use of PEP did not change the overall efficacy results when sensitivity analyses were performed.

Pharmacokinetic data from the iPrEx trial strongly suggested that HIV seroconversion occurred during periods of low drug exposure, and by extension, periods of low drug

adherence. Consistent with this observation, and the fact that resistance substitutions are generally not observed in the absence of selective drug pressure, no substitutions associated with NRTI drug resistance were identified among subjects randomized to FTC/TDF who seroconverted during follow-up. In contrast, drug resistance was observed in 2/2 FTC/TDF subjects who were enrolled in the trial with undiagnosed early HIV infection. In at least one of these cases, the resistance appeared to emerge during treatment. Potentially because of poor adherence and low or no drug exposure, the use of oral FTC/TDF as PrEP did not affect HIV viral load or CD4 counts in seroconverters, a secondary endpoint, when compared with placebo.

In the Partners PrEP trial, 4,747 partner subjects were randomized to TDF, FTC/TDF or placebo. Fourteen partner subjects were later found to have been HIV-infected at enrollment (TDF 5, FTC/TDF 3, placebo 6). As of July 10, 2011, when the placebo group was terminated, 98% of participants were still in follow-up; less than 1% terminated early and most of those were due to death or subject refusal. Median duration of follow-up was 23 months, with no notable difference between groups. The study population in this trial was predominately male (62%) with a mean age of 34 years; 56% of the population was from Uganda. Nearly all couples were married and had been in their relationship for a mean of 9 years. The couples were aware of their HIV serodiscordance for a mean of 1.2 years. Mean viral load in index subjects was 3.9 log₁₀ copies/mL. At baseline, couples reported a mean of 6 sex acts in the preceding month with their primary partner, with 26-28% reporting unprotected sex during the same time period. Sex outside the partnership was infrequent overall, but was reported by 13% of male partner subjects. Nearly half of the male partner subjects were circumcised. Hormonal contraception use was reported by 47% of female partner subjects. STIs were diagnosed in 5-11% of subjects at baseline, with a slight predominance among women, likely owing to the frequency of *Trichomonas vaginalis* diagnoses.

In the primary mITT analysis of Partners PrEP, confirmed HIV seroconversion events were reported in 82 subjects post-baseline: TDF 17, FTC/TDF 13, placebo 52. The risk reduction relative to placebo was 67% (95% CI 44-81%) for TDF and 75% (95% CI 54-86%) for FTC/TDF, both with a P value <0.0001. There was no statistically significant difference in risk reduction between TDF and FTC/TDF. The protective effect of TDF or FTC/TDF was seen across multiple subgroups without significant difference within subgroups. Both TDF and FTC/TDF significantly reduced the risk of HIV infection in both men and women as compared with placebo and there was no significant difference between the two drugs. The relative risk reduction for TDF was 63% in men and 71% in women; for FTC/TDF, it was 84% in men and 66% in women. Of the 45 women who seroconverted, five did so during treatment interruption for pregnancy or breastfeeding (TDF 2, placebo 3). In the placebo group, the incidence of seroconversion was 2.4% per person-years among women who did not use hormonal contraception versus 3.2% among women who did; however, any conclusions regarding this finding are limited by the relatively small number of seroconversions when female subgroups are reviewed.

Initiation of ART in the index partner, which occurred in 28% of index subjects during the trial evenly distributed across treatment groups, did not change the overall efficacy results when sensitivity analyses were performed.

As in the iPrEx trial, adherence to drug dosing was strongly correlated with efficacy in the Partners PrEP trial. Unlike in the iPrEx trial, where PBMCs were collected for intracellular drug measurements, the Partners PrEP trial only collected plasma samples for drug measurements, which are not as reliable as intracellular drug concentrations for determining long-term drug adherence. Nonetheless, the Partners PrEP trial collected plasma samples at regular time intervals and the consistency of measurable plasma drug concentrations across multiple timepoints was used for the subgroup analysis of adherence and efficacy. In the Partners PrEP trial, the proportion of partner subjects in the FTC/TDF group who always had measurable plasma tenofovir concentrations across multiple timepoints was higher among the subjects who remained uninfected (63%) compared with those who seroconverted (15%). For partner subjects in the FTC/TDF group, having a detectable level of tenofovir in plasma at the seroconversion visit window was associated with a 90% (95% CI 56–98%) reduction in risk of HIV infection as compared with having undetectable levels. For partner subjects who always had detectable plasma concentrations across multiple timepoints, the risk reduction relative to placebo was estimated at 94% (95% CI 75-99%). Age 25 years or older was associated with better FTC/TDF adherence, but overall drug adherence was high in this trial. The differences in drug adherence between the Partners PrEP and iPrEx trials may be related to the differences in perceived risk between the two populations studied: one with a known risk for HIV acquisition (Partners PrEP) and the other with possibly poor risk perception (iPrEx). Other social factors may have also influenced adherence.

Disinhibition or risk compensation was not observed in either of these trials. In both trials, subjects reported a decrease in unprotected sex acts compared to baseline. Also, the incidence of STIs decreased compared to baseline prevalence rates in both trials.

6.1 Indication

The proposed indication for this application is pre-exposure prophylaxis to reduce the risk of sexually acquired HIV-1 in adults at high risk. The proposed indication is supported by the primary efficacy results from the iPrEx and Partners PrEP trials, analyses of which are presented in Section 6.1.4.

6.1.1 Methods

Due to the different subject populations and trial designs in the iPrEx and Partners PrEP trials, efficacy data from these two trials were not pooled, but are instead presented separately. Both trials, however, used the same primary efficacy endpoint: the incidence of documented HIV-1 seroconversion among participants. The endpoint was confirmed

by a testing algorithm and endpoints committee in each trial and is appropriate to the indication being sought.

For the iPrEx trial, a modified-intent-to-treat (mITT) analysis was used for the primary efficacy endpoint. The mITT analysis excluded subjects who were retrospectively found to have been HIV-infected upon enrollment as well as those who never had an HIV test post-baseline. In contrast to the trial sponsors who used a May 1, 2010 cut-off date for the primary analysis, the FDA review of efficacy used the complete double-blind treatment phase, which for each subject was defined as the date of study drug initiation until the first study visit after July 31, 2010, when all study drug dispensation was stopped in the trial. Additional efficacy data through 8 weeks after the last dose of blinded study drug were also analyzed. The data cut-off date for the efficacy analyses is November 21, 2010.

For the Partners PrEP trial, a similar mITT analysis was used for the primary endpoint through a July 10, 2011 cut-off date, when the DSMB recommended discontinuation of the placebo group. The mITT analysis for the Partners PrEP trial, in addition to excluding subjects who were HIV-infected upon enrollment or who never had a post-baseline follow-up test, also excluded 11 subjects who were found to be ineligible for the trial after randomization (see Section 6.1.3, Table 8).

6.1.2 Demographics

iPrEx

The demographics and baseline characteristics for subjects who received at least one dose of study drug in the iPrEx trial (N=2,499) are presented in Table 5. The two treatment groups were balanced in terms of age, race, education, region and baseline risk behaviors. Overall, this was a young cohort of MSM with a mean age of 27 years (range: 18-67 years); roughly half were less than 25 years of age. Since the trial initiated at the Peruvian and Ecuadorian sites, the majority (68%) of randomized participants were from these two countries and consequently identified as mixed race and of Hispanic/Latino ethnicity. Caucasian subjects made up 17% of the population, while Black or African/American subjects made up 9% and Asian subjects 5%. Participants from the United States only constituted 9% of the total randomized population and tended to be older than non-U.S. subjects (mean age 38 years). The majority (78%) of participants reported having completed secondary education or having some post-secondary education. Only 29 randomized subjects (1%) identified as women (FTC/TDF 15, placebo 14).

Overall, the MSM randomized in the iPrEx trial were at high risk for HIV infection. The mean number of sex partners reported in the 3 months preceding enrollment was 18, with more than half (56%) reporting 10 or more partners (FTC/TDF 57%, placebo 55%). Nearly 60% of the randomized MSM reported URAI within the past three months, while

41% reported transactional sex within the past six months. The majority (80%) reported URAI with a partner of HIV positive or unknown status within the past 6 months. The prevalence of syphilis and HSV-2 was 13% and 36%, respectively, with comparable rates between the two treatment groups. Among the 45 (2%) subjects with evidence of urethritis, roughly one third tested positive for gonorrhea or chlamydia by PCR. The majority of participants (86%) were uncircumcised.

Approximately two-thirds of randomized subjects were susceptible to HBV infection and of these, 94% accepted vaccination. Twelve subjects (1%) with chronic HBV infection detected at screening were enrolled and four additional acute HBV infections were detected as AEs after enrollment when elevated liver transaminases were observed (FTC/TDF 2, placebo 2).

Table 5: Subject Demographics and Baseline Characteristics - Randomized Population (CO-US-104-0288)

	Number of Subjects (%)		
	FTC/TDF (N=1251)	Placebo (N=1248)	Total (N=2499)
AGE			
mean, years	27	27	27
AGE GROUP			
18-24	597 (48)	665 (53)	1262 (51)
25-29	269 (22)	238 (19)	507 (20)
30-39	248 (20)	224 (18)	472 (19)
≥ 40	137 (11)	121 (10)	258 (10)
RACE			
White	223 (18)	208 (17)	431 (17)
Black/African American	117 (9)	97 (8)	214 (9)
Asian	62 (5)	65 (5)	127 (5)
Indigenous/Native American	9 (1)	15 (1)	24 (1)
Mixed/Other	840 (67)	863 (69)	1703 (68)
ETHNICITY			
Hispanic/Latino	900 (72)	905 (73)	1805 (72)
non-Hispanic/Latino	351 (28)	343 (27)	694 (28)
EDUCATION			
No schooling	3 (<1)	3 (<1)	6 (<1)
Some primary school, but not completed	45 (4)	37 (3)	82 (3)
Completed primary school	36 (3)	32 (3)	68 (3)
Some secondary school, but not completed	195 (16)	172 (14)	367 (15)
Completed secondary school	430 (34)	453 (36)	883 (35)
Vocational/trade school	245 (20)	250 (20)	495 (20)
Attended college or university	201 (16)	213 (17)	414 (17)
Graduate/professional school	79 (6)	76 (6)	155 (6)

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Decline to state	2 (<1)	3 (<1)	5 (<1)
Missing	15 (1)	9 (1)	24 (1)
COUNTRY			
City (Site)			
PERU	700 (56)	700 (56)	1400 (56)
Lima (INMENSA)	250 (20)	250 (20)	500 (20)
Lima (Impacta)	220 (18)	220 (18)	440 (18)
Iquitos (ACSA)	230 (18)	230 (18)	460 (18)
BRAZIL	186 (15)	184 (15)	370 (15)
Rio de Janeiro (FIOCRUZ)	100 (8)	100 (8)	200 (8)
Rio de Janeiro (Praça Onze)	47 (4)	47 (4)	94 (4)
Sao Paulo (USP)	39 (3)	37 (3)	76 (3)
ECUADOR	150 (12)	150 (12)	300 (12)
Guayaquil (Equidad)	150 (12)	150 (12)	300 (12)
USA	113 (9)	114 (9)	227 (9)
San Francisco (SFDPH)	70 (6)	70 (6)	140 (6)
Boston (Fenway)	43 (3)	44 (4)	87 (4)
THAILAND	57 (5)	57 (5)	114 (5)
Chiang Mai (RIHES)	57 (5)	57 (5)	114 (5)
SOUTH AFRICA	45 (4)	43 (3)	88 (4)
Cape Town (DTHF)	45 (4)	43 (3)	88 (4)
CIRCUMSIZED			
Yes	162 (13)	171 (14)	333 (13)
No	1085 (87)	1073 (86)	2158 (86)
Missing	4 (<1)	4 (<1)	8 (<1)
RISK BEHAVIORS			
Number of Male Partners Last 12 Weeks, mean	18	18	18
URAI Last 12 Weeks	732 (59)	753 (60)	1485 (59)
No URAI Last 12 Weeks	172 (14)	167 (13)	339 (14)
Missing URAI Status	347 (28)	328 (26)	675 (27)
URAI with HIV+/Unknown Status Partner Last 6 Months	992 (79)	1009 (81)	2001 (80)
Known HIV+ Partner Last 6 Months	22 (2)	32 (3)	54 (2)
Transactional Sex Last 6 Months	517 (41)	510 (41)	1027 (41)
STI at SCREENING			
Syphilis Diagnosed	164/1240 (13)	162/1239 (13)	326/2479 (13)
Herpes Simplex Virus Type 2	458/1241 (37)	430/1243 (35)	888/2484 (36)
Urine Leukocyte Esterase Positive	23 (2)	22 (2)	45 (2)
Gonorrhea PCR Positive	7/20 (35)	5/22 (23)	12/42 (29)
Chlamydia PCR Positive	8/20 (40)	8/22 (36)	16/42 (38)

HEPATITIS B STATUS			
Susceptible to HBV infection	827 (66)	803 (64)	1630 (64)
Immune due to natural infection	247 (20)	222 (18)	469 (19)
Immune due to prior vaccination	149 (12)	190 (15)	339 (14)
Chronic HBV infection	6 (1)	6 (1)	12 (1)
Indeterminate ^a	21 (2)	27 (2)	48 (2)

Abbreviations: HBV = Hepatitis B virus; PCR = polymerase chain reaction; STI = sexually transmitted infection; URAI = unprotected receptive anal intercourse

a) Indeterminate Hepatitis B Status = anti-Hepatitis B surface antibody negative, anti-Hepatitis B core antigen positive, Hepatitis B surface antigen negative

Source: Study CO-US-104-0288 ELIG, BASICS, DEMO datasets

Partners PrEP

The demographics and baseline characteristics for the intent-to-treat (ITT) population in the Partners PrEP trial (N=4,747) are presented in Table 6. The three treatment groups were balanced in terms of age, gender, circumcision status, education, country/region, and baseline risk behaviors. Partner subjects were predominantly male (62% overall) and their mean age was 34 years (range: 18-64 years). Subjects tended to have an income (78%) and a mean education of 7 years. Nearly all couples were married (98%) and the mean duration of the partnerships was 9 years. Couples were aware of their HIV serodiscordance for a mean of 1.2 years. Mean viral load among the HIV-infected index subjects was 3.9 log₁₀ copies/mL and less than one-fifth of index partners had a viral load ≥50,000 copies/mL. Mean CD4 T-cell count was greater than 550 cells/mm³. A majority (78%) of couples had children, with a mean of 2 children per couple; 22% of couples had no children. Contraception use was reported by 44-48% of female partner subjects.

Overall, couples reported a mean of 6 sex acts with their primary partner in the month prior to enrollment, with 26-28% reporting unprotected sex. Sex outside the partnership was infrequent overall, but was reported more frequently among male partner subjects (13%) than female partner subjects (<1%). Half of the male partner subjects were fully circumcised.

STI data were available in 98% of the partner subjects. STIs were diagnosed in 5-11% of subjects at baseline, with a slight predominance among women. This may have been in part due to *Trichomonas vaginalis* being the most common STI diagnosed, accounting for 75% of the total infections. In addition, the proportion of subjects with HSV-2 was higher among women than men (75% versus 44%, respectively). In general, STI prevalence rates were comparable across the three treatment groups, although the proportion of women with STIs such as gonorrhea, chlamydia, and trichomonas was a bit higher in the placebo group than the active groups (11% versus 7%, respectively).

Table 6: Subject Demographics and Baseline Characteristics – Intent-to-Treat Population (CO-US-104-0380)

	Number of Subjects (%)			
	TDF (N=1584)	FTC/TDF (N=1579)	Placebo (N=1584)	Total (N=4747)
AGE				
mean, years	34	35	35	34
AGE GROUP				
18-24	184 (12)	177 (11)	172 (11)	533 (11)
25-34	721 (46)	690 (44)	688 (43)	2099 (44)
35-44	480 (30)	498 (32)	513 (32)	1491 (31)
≥ 45	199 (13)	214 (14)	211 (13)	624 (13)
GENDER				
MALE	986 (62)	1013 (64)	963 (61)	2962 (62)
Full circumcision ^a	533 (54)	540 (53)	509 (53)	1582 (53)
Not circumcised ^a	451 (46)	473 (47)	454 (47)	1378 (47)
Sex with non-study partner past month ^a	146 (15)	134 (13)	118 (12)	398 (13)
HSV-2 seropositive	415/947 (44)	428/976 (44)	423/927 (46)	1266/2850 (44)
Syphilis	30/974 (3)	34/1010 (3)	34/952 (4)	98/2936 (3)
Other STI ^b	44/982 (5)	57/1010 (6)	60/957 (6)	161/2649 (6)
FEMALE	598 (38)	566 (36)	621 (39)	1785 (38)
Contraception used ^a	263 (44)	275 (49)	299 (48)	837 (47)
Sex with non-study partner past month ^a	4 (<1)	0	4 (<1)	8 (<1)
HSV-2 seropositive	420/559 (75)	386/531 (73)	452/585 (77)	1258/1675 (75)
Syphilis	29/595 (5)	26/562 (5)	28/617 (5)	83/1774 (5)
Other STI ^b	42/569 (7)	36/547 (7)	66/593 (11)	144/1709 (8)
EDUCATION				
mean, years	7	7	7	7
INCOME				
Any income	1275 (81)	1236 (78)	1259 (80)	3770 (79)
COUNTRY (site)				
UGANDA	884 (56)	881 (56)	887 (56)	2652 (56)
Tororo	213 (13)	212 (13)	213 (13)	638 (13)
Mbale	199 (13)	200 (13)	201 (13)	600 (13)
Kampala	191 (12)	194 (12)	194 (12)	579 (12)
Kabwohe	176 (11)	173 (11)	178 (11)	527 (11)
Jinja	105 (7)	102 (7)	101 (6)	308 (7)
KENYA	700 (44)	698 (44)	697 (44)	2095 (44)
Kisumu	209 (13)	210 (13)	210 (13)	629 (13)
Thika	166 (11)	166 (11)	163 (10)	495 (10)

Eldoret	162 (10)	162 (10)	162 (10)	486 (10)
Nairobi	163 (10)	160 (10)	162 (10)	485 (10)
COUPLE CHARACTERISTICS				
Married	1543 (97)	1540 (98)	1552 (98)	4635 (98)
Years living together (mean)	9	9	9	9
Years aware of discordant HIV status (mean)	1.2	1.2	1.2	1.2
Number of sex acts with partner past month (mean)	6	6	6	6
Any unprotected sex with partner in past month	442 (28)	416 (26)	409 (26)	1267 (27)
Index partner HIV-1 plasma RNA (mean, log ₁₀ copies/mL)	3.9	3.9	3.9	3.9
Index partner HIV-1 viral load ≥ 50,000 copies/mL	270 (17)	272 (17)	292 (18)	834 (18)
Index partner CD4 count (mean, cells/mm ³)	551	561	550	554
Couples with children	1241 (78)	1211 (77)	1242 (78)	3694 (78)
Number of children (mean)	2	2	2	2
Couples without children	343 (22)	368 (23)	342 (22)	1053 (22)

Abbreviations: STI = sexually transmitted infection; RNA = ribonucleic acid

a) Denominator for percentages is number of male or female subjects in treatment group.

b) Other STI: *Neisseria gonorrhoeae*, *Chlamydia trachomatis*, or *Trichomonas vaginalis*

Source: Study CO-US-104-0380 KEYVARS dataset

6.1.3 Subject Disposition

iPrEx

In iPrEx, a total of 4,906 subjects were screened between July 10, 2007 and December 17, 2009. Of these, 841 subjects were eligible but did not enroll and 1566 (32%) were considered screen failures. Reasons for ineligibility included: HIV-positive status in 410 subjects, laboratory criteria in 405, low HIV risk in 247, and other reasons in 504. The remaining 2,499 subjects were eligible for participation and were randomized to receive a bottle of blinded study drug (FTC/TDF 1251 [50%], placebo 1248 [50%]).

Of the 2,499 randomized subjects, 2,452 (FTC/TDF 1,226 [98%], placebo 1,226 [98%]) had at least one on-study follow-up HIV test through November 21, 2010 and made up the ITT population. The remaining 47 subjects (FTC/TDF 25 [2%], placebo 22 [2%]) did not have an on-study follow-up HIV test and were thus excluded from ITT population. Ten additional randomized subjects (FTC/TDF 2 [$<1\%$], placebo 8 [1%]) were retrospectively found to have been HIV-1 infected upon enrollment (via HIV-1 RNA testing on enrollment samples) and had study drug discontinued at the next follow-up visit, generally within 2 months of enrollment. Exclusion of these 10 subjects constituted the mITT population (N=2,442).

Among the 10 subjects found to have HIV infection at enrollment, five had symptoms of an acute viral syndrome at enrollment, two had symptoms 1 week later (prompting an interim study visit), one had an anal sore, and one had leucopenia at enrollment. In these subjects, the clinicians did not suspect acute HIV-1 infection, because the symptoms were attributed to an upper respiratory tract infection, sinusitis, or other non-HIV cause.

[Medical Officer Comment: Given the lower number of subjects found to have HIV at enrollment in the FTC/TDF group compared with the placebo group (2 versus 8, respectively), it is possible that FTC/TDF may have acted as post-exposure prophylaxis (PEP) for some participants randomized to that treatment group, but this supposition remains speculative given the small number of subjects and absence of baseline RNA analysis in all randomized subjects.]

As of the November 21, 2010 data cut-off date, 75% of subjects had completed the trial, with comparable rates between the two treatment groups. Subjects had variable duration of follow-up, ranging from 1 day to 160 weeks. A total of 1,882 (75%) subjects had received study drug for at least 1 year (FTC/TDF 950 [76%], placebo 932 [75%]) and 804 (32%) subjects had received study drug for 2 years (FTC/TDF 392 [31%], placebo 412 [33%]). The median duration of exposure was 77.3 weeks (interquartile range [IQR] 52–119 weeks), with no notable difference between the two groups.

A total of 613 subjects (FTC/TDF 311 [25%], placebo 302 [24%]) discontinued the trial early. The most common reasons reported for exiting the trial early were lost to follow-up (207 subjects: FTC/TDF 115 [9%], placebo 92 [7%]); subject relocation (158 subjects: FTC/TDF 77 [6%], placebo 81 [6%]); and subject refusal (147 subjects: FTC/TDF 67 [5%], placebo 80 [6%]). There were 9 deaths (FTC/TDF 2 [$<1\%$], placebo 7 [1%]): 8 subjects died before the November 21, 2010 data cut-off date and 1 subject in the placebo group died on January 2, 2011 from a thermal burn sustained in a fire (See Section 7.3.1). Table 7 lists the disposition of subjects through the November 21, 2010 data cut-off date.

Table 7: Subject Disposition through November 21, 2010 Data Cut-off Date (CO-US-104-0288)

	FTC/TDF	Placebo	Total
Randomized	1251 (100)	1248 (100)	2499 (100)
No HIV testing in follow-up	25 (2)	22 (2)	47 (2)
Followed on study (ITT)	1226 (98)	1226 (98)	2452 (98)
HIV infected at baseline	2 (<1)	8 (1)	10 (<1)
mITT population	1224 (98)	1218 (98)	2442 (98)
Completed Trial	940 (75)	946 (76)	1886 (75)
Early Termination	311 (25)	302 (24)	613 (25)
Reason for Termination			
Death	2 (<1)	7 (1)	9 (<1)
Subject refused	67 (5)	80 (6)	147 (6)
Relocated	77 (6)	81 (6)	158 (6)
Investigator decision	31 (2)	22 (2)	53 (2)
Lost to follow-up	115 (9)	92 (7)	207 (8)
Other	19 (2)	20 (2)	39 (2)

Abbreviations: ITT = intent-to-treat; mITT = modified intent-to-treat

Source: Study CO-US-104-0288 BASICS dataset

For the 53 subjects who terminated the trial early due to an investigator's decision, the majority were terminated due to poor adherence. In one subject (Subject 9116754), the termination was associated with an AE of multiple trauma injuries and the investigator decided to remove the subject from the trial as the subject had neurological sequelae as a result of his injuries.

For the 147 subjects who terminated the trial early due subject refusal, the majority discontinued the trial due to time constraints. Five of these subjects reported AEs in conjunction with their decision to stop the trial (FTC/TDF 3, placebo 2). The AEs for the 3 FTC/TDF subjects (Subjects 8831459, 9313084, 9313410) included dysuria, diarrhea, and gastritis.

For the 39 subjects who terminated the trial early due to other reasons, the majority were either lost to follow-up, chose to terminate due to time constraints, were incarcerated, or had relocated. In one subject (Subject 9117836), the termination was associated a psychiatric disorder (psychosis) that was preceded by the AEs of depression and anxiety at two previous study visits.

A total of 99 subjects (FTC/TDF 48 [4%], placebo 51 [4%]) permanently discontinued study drug due to an AE (see Section 7.3.3). Of these, 73 subjects (FTC/TDF 38 [3%], placebo 35 [3%]) remained in the trial through completion. The remaining 26 subjects (FTC/TDF 10 [<1%], placebo 16 [1%]) did not complete the trial and are included among the 613 subjects in Table 7 who terminated the trial prematurely. Of the 26 subjects who discontinued study drug due to an AE and did not complete the trial, six died (FTC/TDF 2, placebo 4) and are included among the total of nine deaths observed in the trial,

seven refused further participation (FTC/TDF 4, placebo 3), one relocated (FTC/TDF 1, placebo 0), seven were terminated due to investigator decision (FTC/TDF 3, placebo 4), four were lost to follow-up (FTC/TDF 0, placebo 4), and one was terminated for other reasons (FTC/TDF 0, placebo 1).

Partners PrEP

A total of 7,856 HIV-serodiscordant couples were screened, of which 4,758 couples were randomized. Of the couples screened but not randomized, 206 were eligible but did not enroll and 2,892 were found to be ineligible. The most common reasons for ineligibility were HIV-infected index subjects meeting national criteria for ART initiation or already taking ART (59%), and pregnancy (2%), breastfeeding (0.4%), or chronic active HBV infection (10%) among HIV-uninfected partner subjects. Less than 3% of couples failed screening due to creatinine elevation, glycosuria or proteinuria in the partner subject.

Within the 4,758 randomized couples, uninfected partner subjects were randomized into one of the following three treatment groups: 1,589 to TDF, 1,583 to FTC/TDF, and 1,586 to placebo. All but 11 of these subjects were included in the ITT cohort; the 11 excluded subjects were determined after randomization to have not met the eligibility criteria for the trial and were withdrawn from follow-up. The eligibility violations that led to study termination in these 11 subjects are summarized below:

- Three partner subjects (Subjects 5400210, 5518111 and 5518314) were found after randomization to have been hepatitis B surface antigen (HBsAg) positive at the screening visit; one was detected within one month of randomization, one within five months and one within 12 months. In one case (Subject 5400210), there had been an error in the reporting of the HBsAg result from the laboratory; for the other two, a transcription and interpretation error occurred for the result received. Study drug was immediately and permanently discontinued, the couples were followed for study-defined post-study drug stop visits (monthly for two months) to monitor safety after withdrawal of study drug and then the couples were terminated from the trial. There was no evidence of hepatitis flare among these participants after cessation of study drug, based on monitoring of liver function tests. The reporting procedures for laboratory results were subsequently reviewed and revised.
- One partner subject (Subject 5400912) was determined within one month after randomization to have had an absolute neutrophil count at the screening visit that did not meet the minimum level required for study eligibility (i.e., >1300 cells/mm³). A repeat neutrophil count remained below the eligibility cut-off. Study drug was stopped, the couple was followed for study-defined post-study drug stop visits (monthly for two months) to monitor safety after withdrawal of study drug and then the couple was terminated from the trial.

- Three partner subjects (Subjects 5206718, 5419919 and 5717514) were determined within one month after randomization to have had a hemoglobin result at the screening visit that did not meet the minimum level required for study eligibility (i.e., >11 g/dL). After the error was detected, the participants were retested but continued to fail to meet the hemoglobin eligibility criterion. Study drug was stopped, the couples were followed for study-defined post-study drug stop visits (monthly for two months) to monitor safety after withdrawal of study drug and then the couples were terminated from the study.
- Two partner subjects (Subjects 5509716 and 5716913) were determined within one and three months, respectively, after randomization to have had a creatinine clearance at the screening visit that did not meet the minimum level required for study eligibility (i.e., ≥ 60 mL/min). After the error was detected, the participants were re-tested but continued to fail to meet the creatinine clearance eligibility criterion. Study drug was stopped, the couples were followed for study-defined post-study drug stop visits (monthly for two months) to monitor safety after withdrawal of study drug and the couples were terminated from the trial. Neither participant experienced a decline in creatinine clearance during treatment with study product.
- One partner subject (Subject 5527717) was determined within four months after randomization to have enrolled in the trial with a person who was not her stable sexual partner. The participant missed six visits following enrollment due to being incarcerated. The participant then attended the 7-month visit and one study defined post-study visit.
- One partner subject (Subject 5345919) was determined immediately following randomization to have had a positive pregnancy test at the enrollment visit. Although randomization procedures were conducted, the participant was not actually dispensed study drug. The couple was terminated from the study on the same day.

Of the remaining 4,747 partner subjects, 25 had no follow-up testing and 14 were found to have been HIV-1 infected at enrollment. The number of occult HIV infections was again greatest in the placebo group. These 39 subjects (25 +14) were excluded from the mITT cohort. The mITT cohort represents 99% of all randomized partner subjects and was used for the primary analysis of efficacy. Table 8 shows subject disposition through the July 10, 2011 data cut-off date.

As of the data cut-off date, only 1% of partner subjects had completed the trial (i.e., the 36 months of follow-up). Nearly all (98%) of participants were still in follow-up. A total of 7,830 person-years of follow-up for assessment of HIV-1 incidence were accrued, with a median 23 months of follow-up (IQR 16-28 months), with no notable difference between treatment groups in median duration of exposure. Only 1% of partner subjects had terminated the trial early. The reasons for premature termination included death (N=27), subject refusal (N=15), and investigator decision (N=5), each compromising $\leq 1\%$ of the

randomized population. No subject terminated the trial for reasons associated with adverse event.

Table 8: Subject Disposition through July 10, 2011 Data Cut-off Date (CO-US-104-0380)

	TDF	FTC/TDF	Placebo	Total
Randomized	1589 (100)	1583 (100)	1586 (100)	4758 (100)
Ineligible (withdrawn from follow-up)	5 (<1)	4 (<1)	2 (<1)	11 (<1)
Followed on study (ITT)	1584 (>99)	1579 (>99)	1584 (>99)	4747 (>99)
No HIV testing in follow-up	7 (<1)	8 (1)	10 (1)	25 (1)
HIV infected at baseline	5 (<1)	3 (<1)	6 (<1)	14 (<1)
mITT population	1572 (99)	1568 (99)	1568 (99)	4708 (99)
Completed Trial ^a	15 (1)	16 (1)	18 (1)	49 (1)
Still in Follow-up	1555 (98)	1546 (98)	1552 (98)	4653 (98)
Early Termination	16 (1)	17 (1)	14 (1)	47 (1)
Reasons for Termination				
Death	10 (1)	8 (1)	9 (1)	27 (1)
Subject refused	4 (<1)	7 (<1)	4 (<1)	15 (<1)
Investigator decision	2 (<1)	2 (<1)	1 (<1)	5 (<1)
Adverse event ^b	0	0	0	0

Abbreviations: ITT = intent-to-treat; mITT = modified intent-to-treat

a) Includes subjects who completed protocol-defined 36 months of follow-up.

b) Seven subjects permanently discontinued study drug due to an adverse event, but none exited the trial early.

Source: Study CO-US-104-030 KEYVARS dataset

6.1.4 Analysis of Primary Endpoint(s)

iPrEx

In the iPrEx trial, a total of 147 HIV seroconversion events were identified in the ITT population through the November 21, 2010 data cut-off date. Six of these infections occurred during the 8 week period post-treatment (i.e., after the first post-July 31, 2010 study visit but before November 21, 2010). Four additional HIV seroconversion events were reported after the cut-off date.

For the mITT analysis, 137 HIV seroconversion events were reported through the November 21, 2010 cut-off date. Of these, 131 were reported during the on-treatment period and were used for the primary endpoint analysis: 48 in the FTC/TDF and 83 in the placebo group (Table 9). Based on 1,998 person-years in 1,224 FTC/TDF subjects and 1,986 person-years in 1,218 placebo subjects, the HIV seroconversion event rate per 100 PY was 2.4 for the FTC/TDF group and 4.2 for the placebo group during the treatment period, for a hazard ratio of 0.574 (95% CI 40-82%, p=0.001) by Cox regression for FTC/TDF compared with placebo and a corresponding relative-risk

reduction of 42% (95% CI 18-60%, p=0.001). The risk reduction with FTC/TDF was statistically significant; however, it did not exclude the null hypothesis of 30% or lower relative risk reduction. Through the November 21, 2010 cutoff date, the relative risk reduction in the mITT population was 40% (95% CI 19-60%). Results for the ITT analyses were consistent with the mITT analyses. Please see the statistical review by Dr. Hammerstrom for further discussion of the primary endpoint analysis.

Table 9: HIV Seroconversions through November 21, 2010 Data Cut-off Date (CO-US-104-0288)

	Number of Subjects with HIV Seroconversion Events (%)		
	FTC/TDF	Placebo	Total
mITT population	N=1224	N=1218	N=2442
Through End of Treatment (July 31, 2010)	48 (4)	83 (7)	131 (5)
Through End of Treatment + 8 weeks	52 (4)	85 (7)	137 (6)
ITT population	N=1226	N=1226	N=2452
Through End of Treatment (July 31, 2010)	50 (4)	91 (7)	141 (6)
Through End of Treatment + 8 weeks	54 (4)	93 (8)	147 (6)

Abbreviations: mITT = modified intent-to-treat; ITT = intent-to-treat

Source: Study CO-US-104-0288 UPDATE dataset

Partners PrEP

In the Partners PrEP trial, there were a total of 96 HIV seroconversion events in the ITT cohort and 82 events in the mITT cohort through July 10, 2011. Evaluation of the primary endpoint was based on the mITT analysis, for which there were 17 events in the TDF group, 13 in the FTC/TDF group, and 52 in the placebo group (Table 10). The corresponding HIV incidence rates per 100 PY were 0.65, 0.50, and 1.99, respectively. Relative to placebo, TDF reduced the risk of acquiring HIV infection by 67% (95% CI 44-81%), while FTC/TDF reduced the risk by 75% (95% CI 54-86%), both with P values <0.0001 by Cox regression. The difference in treatment effect between TDF and FTC/TDF was not significant. Please see the statistical review by Dr. Hammerstrom for further discussion of the primary endpoint analysis.

Table 10: HIV Seroconversions through July 10, 2011 Data Cut-off Date (CO-US-104-0380)

	Number of Subjects with HIV Seroconversion Events (%)			
	TDF	FTC/TDF	Placebo	Total
mITT population	N=1572	N=1568	N=1568	N=4708
	17 (1)	13 (1)	52 (3)	82 (2)
ITT population	N=1584	N=1579	N=1584	N=4747
	22 (1)	16 (1)	58 (4)	96 (2)

Abbreviations: mITT = modified intent-to-treat; ITT = intent-to-treat

Source: Study CO-US-104-0380 KEYVARS dataset

6.1.5 Analysis of Secondary Endpoints(s)

Medication Adherence

A key objective of both the iPrEx and Partners PrEP trials was to assess adherence to an oral PrEP intervention among uninfected participants. Both trials measured adherence to study drug through multiple measures, including self-reporting (through interviews and pill counts) and pill dispensation records. In addition, the iPrEx trial included a pre-specified PK subgroup analysis to investigate whether intracellular PBMC drug concentration, an objective measure of drug adherence, correlated with efficacy.

In the iPrEx trial, self-reported drug adherence was comparable between the two treatment groups. Mean self-reported adherence was 88% over the course of the trial, with over 60% of subjects reporting $\geq 90\%$ adherence with prescribed drug dosing. Less than 5% of participants reported $< 50\%$ adherence. According to pill dispensations and quantities, overall pill use decreased from 99% to 91% over the first year, a trend that contradicted adherence by pill counts and self-reports. Given the overall high degree of self-reported adherence, no significant differences in drug adherence were noted by age, region, country, or other baseline factors. In a post hoc assessment conducted by the investigators of the correlation between subject-reported adherence and objective exposure based on detectable drug concentrations, high self-reported drug adherence was poorly predictive of measurable intracellular drug concentrations.³⁰ Low or missing self-reported adherence, on the other hand, was predictive of non-measurable drug concentrations. In this analysis, adherence from the entire study cohort (N=approximately 2,045) was correlated with objective exposure based on drug concentrations testing of PBMC from a representative subgroup (N=179 samples, all obtained at Week 24 from the FTC/TDF group). The detection rate for TFV-DP or FTC-TP was 73% among subjects ≥ 25 years of age compared with 44% in younger subjects

³⁰ Amico K, Liu A, McMahan V, Anderson PL, Lama JR, Guanira J. Adherence indicators and pre-exposure prophylaxis (PrEP) drug levels in the iPrEx study [Poster]. Paper presented at: 18th Conference on Retroviruses and Opportunistic Infections (CROI); February 27 - March 2, 2011; Boston, MA.

($p < 0.001$).³¹ In addition, the detection rate for intracellular drug levels was 97% among subjects from U.S. sites compared with 50% among non-U.S. subjects ($p < 0.0001$); however, the number of U.S. subjects included in the analysis was presumably small. *[Medical Officer Comment: In the PK dataset submitted to FDA, the number of U.S. subjects with PBMC data was only four. Of these, three had measurable intracellular drug levels.]*

Since intracellular TFV-DP concentrations can remain measurable for a longer period of time (21 days) than plasma tenofovir concentrations, intracellular TFV-DP levels can provide direct evidence of drug exposure over time and thus serve as more reliable measures of drug adherence. In the iPrEx PK substudy, intracellular TFV-DP concentrations were detected in only 4/48 (8%) HIV seroconverters in the FTC/TDF group compared with 51/133 (38%) HIV-uninfected matched controls from the same treatment group. Given the estimated duration of detectable TFV-DP in PBMCs with the assay methods used, subjects with no measurable intracellular drug concentrations were presumed to have missed more than a week of sequential drug dosing. Further, full adherence with daily drug dosing appeared to occur in less than 10% of subjects (N=12/181). Among subjects with measurable intracellular drug concentrations, the median TFV-DP concentration was higher among uninfected subjects (15.6 fmol/10⁶ viable cells [range: 2.49 to 82.4]) compared with seroconverters (10.2 fmol/10⁶ viable cells [range: 4.19 to 14.7]). In a comparison of subjects with and without measurable intracellular drug concentrations, the presence of measurable drug concentrations reduced the risk of HIV acquisition by 90% (95% CI 71-98%; $p < 0.001$). After adjusting for potential confounders (i.e., URAI at screening, URAI at the time of specimen draw, total number of sex partners at screening, age, secondary education and body mass index), the relative risk reduction was 87% (95% CI 59-97%; $p < 0.001$).

[Medical Officer Comment: Subject 9212637 had detectable drug levels at the seroconversion visit; however, he also had plasma drawn on the date he was RNA positive but antibody negative and no drug was detected on that date. If Subject 9212637 is counted as not having a measurable drug concentration, then the risk reduction for having measurable drug concentrations is 94% (or 92% after adjustment for potential confounders)].

Having measurable TFV-DP concentrations, however, may not completely protect from HIV-1 infection, as illustrated by the four subjects who seroconverted despite having quantifiable concentrations at the visit when seroconversion was detected; although, as the case of Subject 9212637 illustrates, how accurately these drug concentrations reflect the intracellular concentrations around the time of HIV exposure is unclear. Further, although HIV seroconversions were not observed among subjects with

³¹ Anderson PL, Lama JR, Buchbinder S, et al. Interpreting detection rates of intracellular emtricitabine-triphosphate (FTC-TP) and tenofovir-diphosphate (TFV-DP) in the iPrEx Trial [Oral Presentation]. Paper presented at: 18th Conference on Retroviruses and Opportunistic Infections (CROI); February 27 - March 2, 2011; Boston, MA.

intracellular TFV-DP concentrations above 15.6 fmol/M viable cells, a minimal intracellular drug concentration necessary for efficacy could not be established as part of this review because of the multiple limitations of this data.

In order to further assess the impact of drug adherence on efficacy, FDA reviewers extrapolated the findings from the PK subgroup analysis to the entire FTC/TDF-treated cohort to derive absolute event rates for subjects assumed to have measurable intracellular drug concentrations. With that, FDA estimated an absolute risk reduction of 87.5% (95% CI 66-95%) relative to placebo in subjects assumed to have measurable drug levels. In contrast, the estimated relative risk reduction in subjects assumed not to have measurable drug concentrations was only 14.5% (95% CI -22 - 40%). Please see Section 4.4.2 and the Clinical Pharmacology review by Drs. Ayala and Liu for the methodology used in these exploratory analyses.

In the Partners PrEP trial, measurements of adherence were based on monthly pill counts of returned study tablets. Overall, drug adherence in this trial was high: 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). Only three partner subjects ever reported that they thought their index partner used their study drug. A secondary analysis was conducted to evaluate drug adherence using tenofovir plasma concentrations taken across multiple time points. Plasma tenofovir concentrations in partner subjects who seroconverted within each active treatment group were compared to a cohort of randomly selected partner subjects who did not seroconvert.

Overall, the efficacy trends observed in the Partners PrEP trial corroborate the findings from the iPrEx trial and reaffirm that the principle that greater drug adherence correlated with protection from HIV infection. Within the FTC/TDF treatment group of Partners PrEP, the proportion of partner subjects with always measurable plasma tenofovir concentrations at all visits (plasma drug levels available for a mean of six study visits) was significantly higher among HIV-uninfected subjects (63%) than among seroconverters (15%). In the case-cohort subgroup analysis, 91/100 (91%) HIV-uninfected cohorts in the FTC/TDF group had measurable plasma tenofovir concentrations at some point during the trial compared with 8/13 (62%) of seroconversion cases in the same treatment group, keeping in mind that plasma tenofovir concentrations are a less reliable measure of drug adherence than intracellular drug levels. For example, a subject could take FTC/TDF several hours prior to the study visit and have drug levels consistent with adherence, even though they may not otherwise be taking study drug. For partner subjects in the FTC/TDF group, having a detectable level of tenofovir, as compared with having an undetectable level, was associated with a 90% (95% CI 56–98%; $p=0.002$) reduction in HIV risk. As in the iPrEx trial, age 25 years or older was associated with better FTC/TDF adherence, although sample sizes were small in the comparative cohort. FDA estimated an absolute risk reduction of 94% (95% CI 75-99%) relative to placebo for the FTC/TDF-treated subjects

who were assumed to always have measurable tenofovir plasma concentrations. Please see Section 4.4.2 and the Clinical Pharmacology review for further details of these exploratory exposure-response analyses.

In the Partners PrEP trial, an ancillary project was implemented in 2009 at three Ugandan sites with additional objective adherence measures: MEMS caps and monthly then quarterly unannounced home visits and pill counts. Subjects with unannounced pill count adherence <80% received counseling intervention. A total of 1,147 partner subjects enrolled. Median adherence by unannounced pill count was 99% and by MEMS 92%. A total of 14 HIV seroconversions were identified within this subgroup: 14 among subjects randomized to placebo (333 person-years) and 0 among subjects randomized to active treatment (616 person-years). The results showed that high PrEP adherence in the setting of active monitoring and counseling support was associated with a high degree of protection from HIV-1 transmission. Moreover, real-time adherence monitoring could identify individuals for targeted adherence support in order to maximize PrEP effectiveness.

The reasons for differing drug adherence among the various clinical trials of oral PrEP, or the reasons for greater drug adherence in the Partners PrEP trial compared with the iPrEx trial or other trials of high-risk individuals, such as the FEM-PrEP trial, are not entirely clear. However, qualitative data based on in-depth interviews with a subgroup of Partners PrEP couples suggest that HIV serodiscordance itself can destabilize a relationship and, in that context, PrEP may be viewed by participants as a means of preserving the relationship while safeguarding individual health.³² Thus, a desire to maintain a stable relationship may provide added incentive to adherence. Where discord in the relationship persists, adherence suffers. Another potential explanation is that the risk to an uninfected partner in a known serodiscordant relationship is clear and readily identifiable, and this knowledge may strongly influence adherence. Among MSM and other high-risk individuals not in a known serodiscordant union, multiple studies have shown that risk perception is often at odds with engagement in high risk behavior. This disconnect might also affect drug adherence, as was postulated for the FEM-PrEP trial.

Drug Resistance

The emergence of drug resistant HIV variants in association with oral PrEP is both an individual and public health concern. Drug resistance, however, was infrequently observed in the two pivotal trials, as well as in most clinical trials of oral PrEP to date. In all PrEP trials, substitutions conferring NRTI drug resistance have only been identified

³² Ware NC, Wyatt MA, Haberer JE, et al. What's love got to do with it? Explaining adherence to oral antiretroviral pre-exposure prophylaxis for HIV-serodiscordant couples. *J Acquir Immune Defic Syndr* 2012; 59 (5):463-8.

among subjects who were enrolled into the trials with undiagnosed acute HIV infection at baseline (i.e., negative rapid HIV antibody test at enrollment).

In the iPrEx trial, drug resistance was detected after 4 weeks of FTC/TDF prophylaxis in 2/2 subjects who were unknowingly HIV-infected at the time of enrollment. An FTC-associated amino acid substitution in HIV-1 reverse transcriptase, M184V, was detected in the Week 4 isolate of one subject, but was absent in the baseline isolate, suggesting that resistance in this subject emerged during treatment with FTC/TDF. Another FTC-associated substitution, M184I, was detected in the Week 4 isolate of the second subject; however, the baseline sample did not yield genotypic data because of insufficient viral RNA in the sample, and therefore it remains unclear if the M184I substitution was selected during the therapy or was borne by the transmitted virus.

In the Partner's PrEP trial, 14 subjects (TDF 5, FTC/TDF 3, placebo 6) were enrolled with undiagnosed early HIV infection. Two of the five subjects in the TDF group had detectable variants expressing drug resistance at the time of antibody seroconversion, one with a K65R-expressing variant at Week 16 and the other with a variant bearing the combination of D67N and K70R at Week 60. One of the three subjects in the FTC/TDF group had an M184V-expressing variant detected at Week 12. Genotypic analyses of the baseline isolates for the subjects with the M184V and K65R-expressing viruses indicated that resistance emerged during treatment by Weeks 12 and 16, respectively. Genotypic analysis of the baseline isolate (or of an isolate from the HIV-infected index partner) was not conducted in the subject with the D67N plus K70R-expressing virus, thus it is unclear if the resistance was transmitted or emergent in this case. No resistance was detected among the five remaining subjects in the TDF and FTC/TDF groups who were HIV-infected at baseline; however, PK data with which to assess adherence in these subjects was lacking.

In both pivotal trials, among the 75 subjects randomized to active treatment who seroconverted post-enrollment and for whom evaluable RNA data are available (48 in the FTC/TDF group of iPrEx and 15 and 12 in the TDF and FTC/TDF groups of Partners PrEP, respectively), no evidence of substitutions conferring NRTI resistance was detected by population nucleotide sequence analysis, which has a limit of sensitivity for minority species comprising approximately 25% or more of the viral quasi-species. A second genotypic analysis using an allele-specific reverse-transcriptase PCR assay sensitive to the presence of low level variants (0.5% of the viral quasi-species) expressing specific resistance-associated substitutions (i.e., K65R, K70E, M184V, and M184I) also failed to detect any variants among the 48 FTC/TDF subjects in the iPrEx trial.

Four individuals in the Partners PrEP trial who were infected post-enrollment (TDF 2, FTC/TDF 1, placebo 1) were found to have K103N or V106A mutations conferring high-level resistance to non-nucleoside reverse transcriptase inhibitors (NNRTI). This NNRTI

resistance is unlikely to have been selected by the study medications and most likely reflects transmitted resistance.

To summarize, no substitutions associated NRTI drug resistance were identified among subjects who became HIV-infected during the treatment phase of either pivotal trial, which is consistent with the poor adherence observed among those who failed oral PrEP. In contrast, five cases of NRTI resistance were found among ten subjects who were enrolled into the trials with unrecognized HIV infection and who subsequently received either TDF or FTC/TDF. These occurrences of emergent drug resistance with oral PrEP highlight the need to carefully screen individuals and to rule out acute or early HIV-1 infection prior to initiating oral PrEP.

Table 11 summarizes the genotypic resistance data from the iPrEx and Partners PrEP trials. Resistance data from the CDC TDF2 trial in Botswana that used oral FTC/TDF as PrEP is also included. Please see the Microbiology Review by Dr. Deming for further discussion of drug resistance issues as they relate to this application.

Table 11: Summary of Genotypic Resistance Data in Clinical Trials of Oral PrEP

Trial	Drug	NRTI Resistance/Number of Infections	
		Seroconverters on Treatment	HIV-1 Infected at 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)
CDC TDF 2	FTC/TDF	0/9	1/1 (A62V+K65R+M184V*)

* Confirmed wild-type virus in pre-treatment sample
Source: Microbiology Review for NDA 21-752/S-30

Effect of PrEP on Incident HIV-1 Infections

The effect of oral PrEP on incident HIV infection was evaluated in both pivotal trials. Among seroconverters in each trial, no significant differences in CD4 T-cell counts were noted between the active and placebo groups over time. No significant differences in plasma HIV-1 RNA levels were noted between the FTC/TDF and placebo groups in the iPrEx trial through Week 60. In the Partners PrEP trial, however, median viral load was significantly lower at the time of seroconversion in the active groups compared with the placebo group. The difference between the TDF and placebo groups was -0.7 log₁₀ copies/mL, and between the FTC/TDF and placebo groups it was -0.3 log₁₀ copies/mL. These findings suggest that some antiviral activity may have been occurring at the time

of seroconversion, although the sample sizes are small and drug exposures at the time of exposures are unknown. Please see the Microbiology Review by Dr. Deming for further details.

6.1.6 Other Endpoints

Behavioral Changes

This section will focus on the risk behavior trends observed during treatment with oral PrEP. A potential concern surrounding the implementation of an oral PrEP intervention is the possibility that it may lead to risk compensation and increased disinhibition. However, there was no evidence of post-baseline disinhibition among participants in either pivotal trial submitted in support of this application, or in other clinical trials of oral PrEP where such information has been reported (e.g., the CDC 4323, CDC TDF2, and FHI PrEP trials).^{33,34,35} In these trials, information on risk behavior changes has been mostly self-reported collected through interviews, but objective measures such as STI rates over time have also been analyzed.

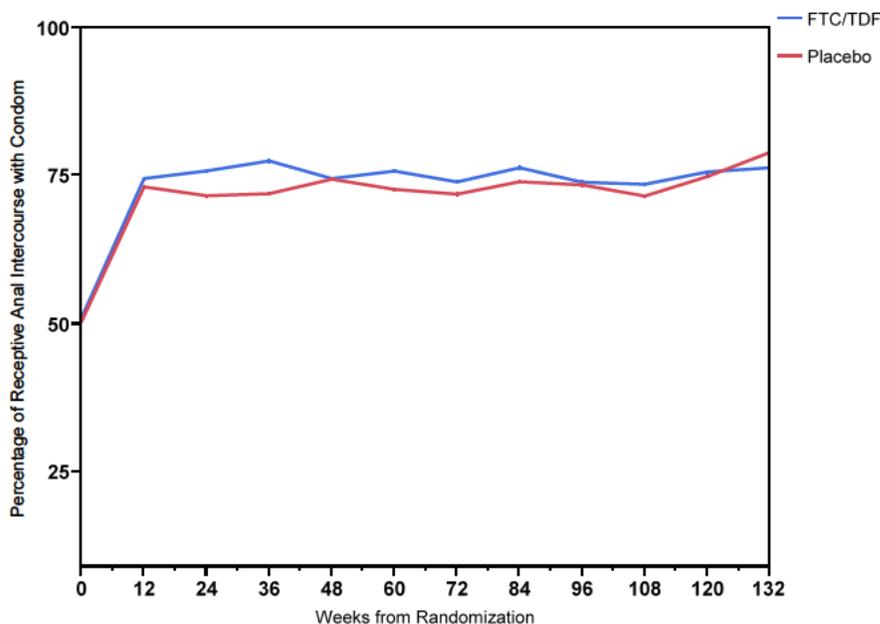
In the iPrEx trial, subjects received a comprehensive package of HIV prevention services, including HIV-1 testing, risk-reduction counseling, condoms, and diagnosis and treatment of any symptomatic STIs at every monthly visit. During the course of the trial, the reported number of receptive anal sex partners decreased from a baseline mean of 12 partners in previous 3 months to less than half of that during follow-up. The number of URAI partners also decreased as did the percentage of anal sex partners who used a condom (from approximately 50% at baseline to 75% during follow-up). These behavioral trends were comparable between treatment groups (Figure 5).

³³ Liu A, Vittinghoff E, Chillag K, et al. No evidence of sexual risk compensation among HIV-uninfected men who have sex with men (MSM) participating in a tenofovir pre-exposure prophylaxis (PrEP) trial. 6th IAS Conference on HIV Treatment and Prevention; 2011 July 17-20; Rome, Italy: Abstract MOPE381.

³⁴ Thigpen MC, Kebaabetswe PM, Smith DK, et al. Daily oral antiretroviral use for the prevention of HIV infection in heterosexually active young adults in Botswana: results from the TDF2 study. 6th IAS Conference on HIV Pathogenesis, Treatment and Prevention; 2011 July 17-20; Rome, Italy: Abstract WELBC01.

³⁵ Peterson L, Taylor D, Roddy R, et al. Tenofovir disoproxil fumarate for prevention of HIV infection in women: a phase 2, double-blind, randomized, placebo-controlled trial. PLoS Clin Trials 2007; 2:e27.

Figure 5: Mean Percentage of Subjects Reporting Receptive Anal Intercourse with Condoms by Study Week (CO-US-104-0288)



Source: Study CO-US-104-0288 DERBRA dataset

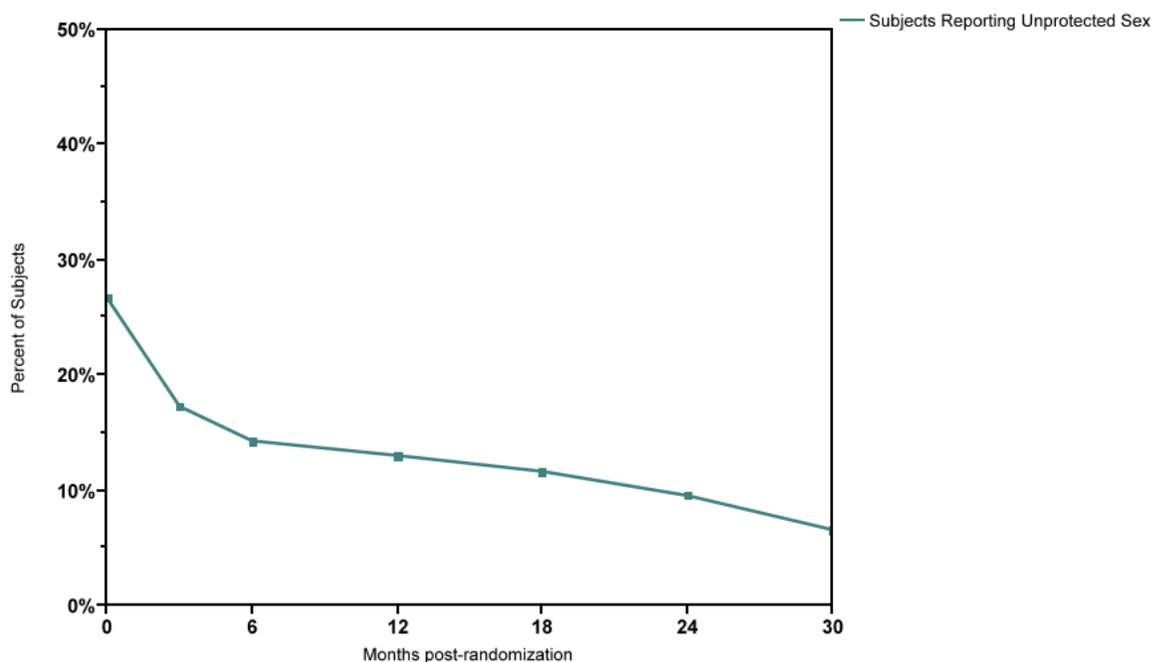
In the Partners PrEP trial, subjects also received a monthly comprehensive package of HIV prevention services. As in the iPrEx trial, the proportion of subjects reporting unprotected sex decreased post-enrollment. At baseline, 27% of subjects overall reported any unprotected sex in the past month; by Month 6 this percentage had decreased by approximately half (Table 12, Figure 6).

Table 12: Proportion of Subjects Reporting Any Unprotected Sex in Past Month by Study Month (CO-US-104-0380)

Study Month	Number of Subjects	Number (%) of Subjects Reporting Any Unprotected Sex in Past Month
0	4758	1271 (27%)
3	4564	789 (17%)
6	4480	640 (14%)
12	3925	511 (13%)
18	3058	356 (12%)
24	2139	204 (10%)
30	852	56 (7%)
35	118	11 (9%)

Source: Study CO-US-104-0380 ADCONDOM dataset

Figure 6: Mean Percentage of Subjects Reporting Any Unprotected Sex in Past Month by Study Month (CO-US-104-0380)



Source: Study CO-US-104-0380 ADCONDOM dataset

In the Partners PrEP trial, however, the proportion of partner subjects reporting sex outside their primary relationship appeared to increase during follow-up. This was noticed in both male and female participants, but the increase was exponentially greater among female participants (Table 13). If real, the significance of these findings is not clear.

Table 13: Proportion of Partner Subjects Reporting Outside Sex Partners by Study Month (CO-US-104-0380)

Study Month	Overall		Women		Men	
	Total	Number (%) with Outside Partners	Total	Number (%) with Outside Partners	Total	Number (%) with Outside Partners
0	4758	407 (9)	1792	8 (0.5)	2966	399 (14)
3	4565	414 (9)	1733	16 (0.9)	2832	398 (14)
6	4492	444 (10)	1710	20 (1.2)	2782	424 (15)
12	3950	485 (12)	1507	25 (1.7)	2443	460 (19)
18	3090	379 (12)	1141	20 (1.8)	1949	359 (18)
24	2168	292 (13)	798	21 (2.6)	1370	271 (20)
30	867	111 (13)	336	6 (1.8)	531	105 (20)

Source: Study CO-US-104-0380 ADCONDOM dataset

While the above measures are self-reported and subject to bias, STI rates also decreased during the course of each trial and appear to corroborate the self-reported behavioral trends. In the iPrEx trial, the baseline prevalence for any STI (including syphilis, gonorrhea, chlamydia, genital ulcer disease, or HSV-2) was 16%. Post-baseline, the incidence of any STI was 12.6 per 100 PY in the FTC/TDF group and 12.2 in the placebo group. In the Partners PrEP trial, the baseline prevalence of any STI (which includes the above listed STIs plus trichomonas, but not HSV-2) was 10-12%. Post-baseline, the proportion of partner subjects with any STI diagnosis decreased to 3% in the first year and 2% in the second year, across all treatment groups.

In summary, in a setting of routine and intensive risk reduction counseling and condom promotion, no evidence of behavioral disinhibition was observed among oral PrEP participants in these pivotal trials. Whether similar behavioral findings can be inferred for a non-clinical trial setting is unknown.

6.1.7 Subpopulations

iPrEx

In the iPrEx trial, no significant differences in efficacy were observed among subpopulations based on race, ethnicity, region, baseline STI status, circumcision, alcohol intake, or the reporting of transactional sex. Greater risk reduction relative to the overall mean risk reduction was observed among participants who reported URAI at baseline (53%). Greater numerical risk reduction was also observed among participants who were 25 years of age or older (56% compared with 28% in those less than 25 years old) and among participants who reported secondary education or higher (52% compared with 12% in those with less than secondary education). As demonstrated in Table 14, among the cohort of MSM older than 25 years of age, with at least a secondary education or higher, and reported URAI at baseline (N=287), the relative risk reduction compared with placebo was 85%. Of note, based on the available PK data from the case-control substudy, these same covariates also correlated with greater drug adherence as determined by the relative proportion of subjects with measurable intracellular TFV-DP concentrations.

Table 14: Relative Risk Reduction in Subgroups with Greater Drug Adherence (CO-US-104-0288)

Subgroup		Placebo		FTC/TDF		Relative Risk Reduction % (95%CI)
		N	Event per 100 PY	N	Event per 100 PY	
Age	<25	665	4.5	597	3.2	28 (-15, 54)
	≥25	583	3.8	654	1.7	56 (23, 75)
Education	Less than Secondary	244	4.2	279	3.7	12 (-74, 55)
	Secondary or Higher	992	4.2	955	2.0	52 (26, 69)
High Risk Sex (i.e., Reported URAI at screening)	No	495	1.5	519	1.9	-25 (-175, 44)
	Yes	753	5.8	732	2.7	53 (29,69)
Age≥25, Secondary/Higher education and URAI	No	961	3.9	934	3.1	23 (-14, 47)
	Yes	287	4.9	317	0.7	85 (58, 95)

Source: Pharmacometric Review for NDA 21-752/S-30

Based on the differences observed in relative risk reduction within each of these subgroups, it appears that the overall risk reduction seen in the iPrEx trial with FTC/TDF relative to placebo was most likely due to better drug adherence and not some other factor, such as differential condom usage or other behaviors to decrease risk. Please see the Pharmacometrics review by Dr. Liu for further discussion of the PK subgroup analyses and the adherence effect.

Whereas the relative risk reduction for MSM who reported URAI at baseline was 53%, no protective benefit was observed among MSM who did not report URAI. In this subgroup, the seroconversion rate per 100 person years was 1.9 for the FTC/TDF group and 1.5 in the placebo group.

The interactions between drug adherence, risk behavior, and efficacy were also further explored. Unprotected sex inflated risk in both treatment groups. There was, however, no particular evidence that adherence improved with riskier behavior or that even if such occurred, that it had any effect on the overall efficacy. Please see the Statistical Review by Dr. Hammerstrom for further details.

Partners PrEP

A significant protective effect of TDF or FTC/TDF compared with placebo was observed in the Partners PrEP trial regardless of gender, age, education, country, male circumcision, reporting of unprotected sex, use of hormonal contraception in women, or

baseline HIV characteristics of the index subject. Although overall seroconversion rates were higher for partner subjects when the index subject viral load was $\geq 50,000$, no differences in treatment effect were observed for TDF and FTC/TDF based on index partner viral load.

In the mITT cohort, 45 HIV seroconversion events were observed among women: 8 in the TDF group; 9 the FTC/TDF group and 28 in the placebo group. Among men, 37 seroconversion events were observed: 9 in the TDF group, 4 in the FTC/TDF group, and 24 in the placebo group. Within the placebo group, the HIV incidence rate per 100 PY was 1.49 for men and 2.81 for women. This disparity in seroconversion rates is consistent with other observational data that indicate that women are at greater risk of acquiring HIV than men in this population. Nonetheless, both TDF and FTC/TDF reduced the risk of HIV acquisition in both men and women. Compared with placebo, TDF reduced risk of HIV infection by 63% (95% CI 34-91%) for men and 71% (95% CI 49-94%) for women. The relative risk reduction for FTC/TDF compared with placebo was 84% (95% CI 67-101%) for men and 66% (95% CI 41-92%) for women. There was no statistical difference between the two treatment groups in terms of efficacy by gender. Table 15 lists the HIV incidence rate and relative risk reduction for TDF and FTC/TDF by gender in the Partners PrEP trial.

Table 15: HIV Incidence and Relative Risk Reduction by Gender (CO-US-104-0380)

	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)

Abbreviations: CI = 95% confidence interval; PY = person-years

Notably, of the 45 women with post-enrollment seroconversion events, five became HIV-infected during treatment interruptions of more than 3 months due to pregnancy or breastfeeding (TDF 2, FTC/TDF 0, placebo 3). Exclusion of these five women from the efficacy analyses, however, did not significantly alter the overall findings.

6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

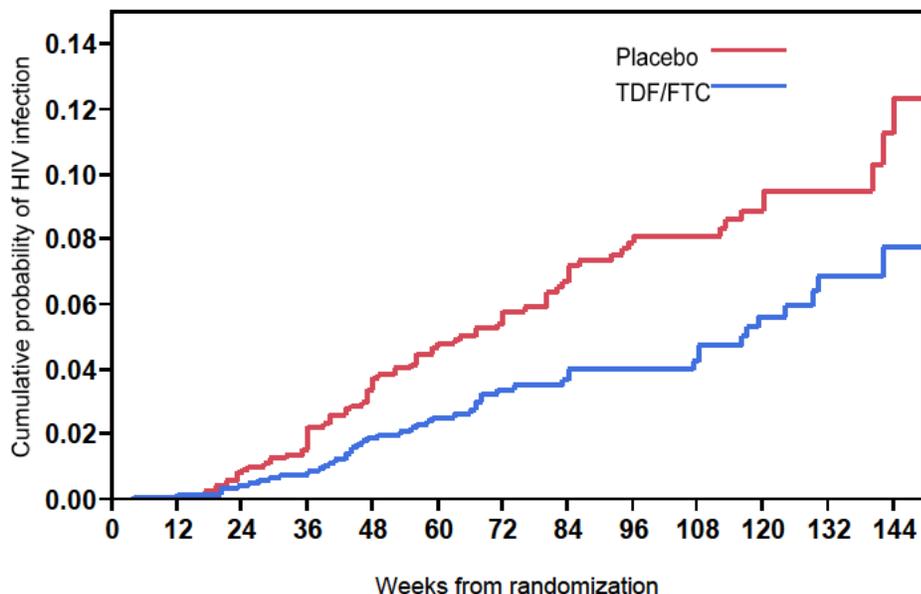
In both the iPrEx and Partner's PrEP trials, study drug administration was conducted in accordance with the current prescribing information for TRUVADA (fixed-dose combination tablet of FTC 200 mg/TDF 300 mg, administered orally once daily). As

discussed in Section 6.1.5 of this review, exposure-response analyses conducted for each trial have provided strong evidence of the drug's effectiveness and have shown that efficacy is strongly correlated with greater drug adherence, as demonstrated by measurable drug concentrations. While it is probable that most participants in these trials were not fully adherent with the prescribed dosing recommendation, a more specific dose-concentration response relationship for HIV-1 prophylaxis has not been elucidated. Therefore, the recommended dosing for TRUVADA for a PrEP indication remains one tablet once daily.

6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

Long-term efficacy data of FTC/TDF as PrEP are not available. However, there is no scientific reason to suspect that the efficacy of a prophylactic measure should vary over time if taken consistently. In the iPrEx trial, although the duration of study drug exposure and follow-up were variable given the event-driven design of the trial, the superiority of FTC/TDF over placebo in reducing the risk of HIV seroconversion was observed throughout the double-blinded treatment phase (Figure 7). In the analysis that included all HIV seroconversion events through 8 weeks after the last dose of study drug, the FTC/TDF group continued to demonstrate superiority, with a relative risk reduction of 40% (95% CI 19-60%) compared with placebo in the mITT analysis.

Figure 7: Cumulative HIV Incidence by Treatment Time (CO-US-104-0288)

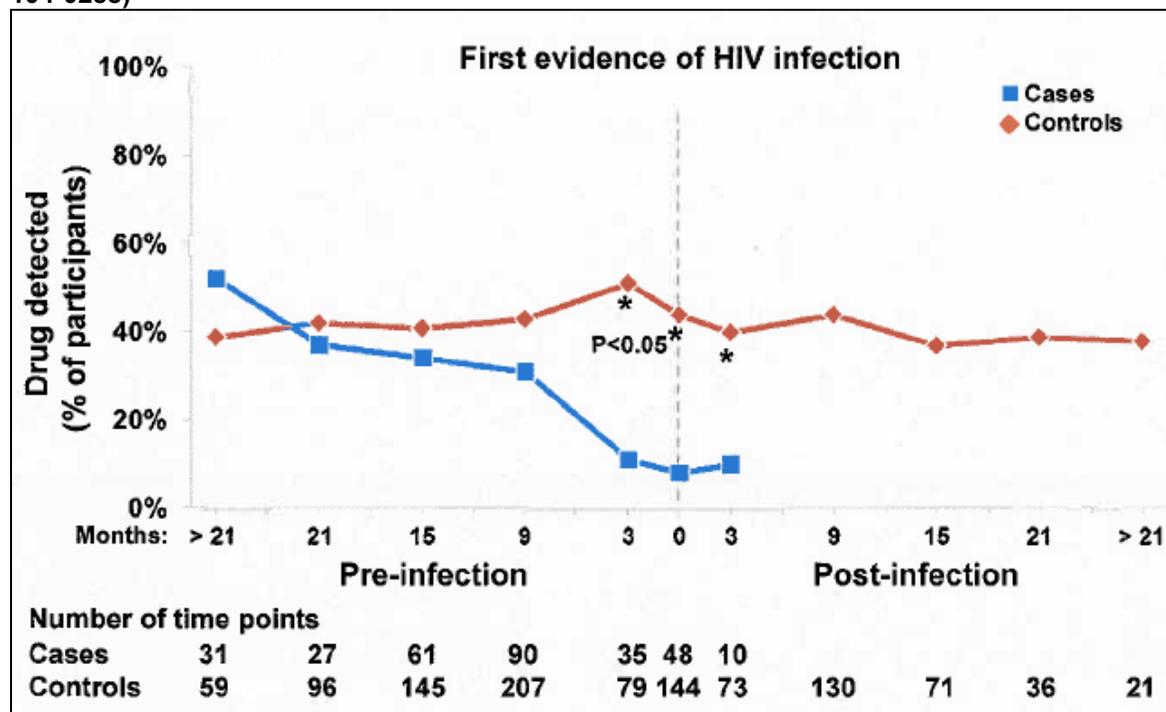


Source: Study CO-US-104-0288 UPDATE dataset

On the other hand, adherence to a daily oral prophylactic measure may vary over time and thus impact the treatment effect over time. Unpublished PK data from the case-control substudy in the iPrEx trial suggest that HIV seroconversions occurred during

periods of low drug exposure, which in turn reflected periods of low drug adherence. Since the proportion of subjects with measurable drug concentration was comparable between cases and controls early in treatment, these findings suggest that adherence to drug dosing waned over time among participants who eventually became HIV-infected (Figure 8).

Figure 8: Case-Control Substudy: Study Drug Detection by Time Relative to HIV Infection (CO-US-104-0288)



Source: NDA 21-752/S-30 Advisory Committee meeting presentation

6.1.10 Additional Efficacy Issues/Analyses

Use of Post-Exposure Prophylaxis in iPrEx

In the iPrEx trial, 33 (1%) subjects (FTC/TDF 13 [1%], placebo 20 [2%]) received PEP following a recent exposure to a known HIV-infected partner. Four subjects (FTC/TDF 1, placebo 3) received PEP on more than one occasion (Subjects 8730115, 9433416, 9534377, and 9534482), with one subject in the placebo group receiving PEP on four separate occasions (Subject 9433416).

Seven subjects (FTC/TDF 3, placebo 4) received PEP after all study drug dispensation had ceased in the trial (i.e., after July 31, 2010). These seven subjects initiated PEP between August 14, 2010 and December 6, 2010. Three (3) of these subjects appeared to have initiated PEP within a month after stopping study drug. Two subjects, one in

each group (Subjects 8730115 and 9534377), received PEP before and after July 31, 2010 end of treatment time point.

Twenty-eight subjects received PEP only before end of treatment (FTC/TDF 12, placebo 16). Of these, 25 (1%) subjects had study medication interrupted in order to initiate PEP (FTC/TDF 10 [1%], placebo 15 [1%]). In the remaining three cases, the subject had stopped taking study drug more than a month before initiating PEP.

Within the double-blinded treatment phase of the trial, which provided the time frame for the primary efficacy analyses, no HIV seroconversion event was reported among any subject who initiated PEP. One subject treated with PEP in the FTC/TDF group had a seroconversion event in the post-treatment period. Subject 965309 stopped study medication on May 5, 2010 because of suicide attempts. He did not restart study medication thereafter. He began PEP with lamivudine/zidovudine on June 19, 2010. This regimen was switched to lopinavir/ritonavir plus stavudine and lamivudine on June 21, 2010, which he took through July 20, 2010. He had a negative HIV rapid test on August 19, 2010, but tested positive on September 3, 2010, which was confirmed by Western Blot on October 1, 2010.

FDA conducted sensitivity analyses of the iPrEx data that assumed 1) that all 12 FTC/TDF subjects who received PEP and did not seroconvert would have become HIV-infected on the day PEP began if PEP had not been given and 2) that there would have been no change in the number and timing of the HIV infections in the placebo group. An alternative analysis discarded those 12 FTC/TDF subjects who received PEP and did not seroconvert while retaining all 20 placebo subjects who received PEP during any time period and the one FTC/TDF subject who became infected some time after PEP ended. The results of these analyses indicated that the use of PEP in the iPrEx trial did not significantly affect the overall efficacy results. Please see the Statistical Review by Dr. Hammerstrom for further details on these sensitivity analyses.

Use of Antiretroviral Therapy in Index Subjects in Partners PrEP

In the Partners PrEP trial, FDA identified 1,472 (31%) index subjects who initiated ART post-randomization; of these, 1,314 (28%) started ART during the trial (as treatment for HIV infection or as prevention of mother-to-child HIV transmission). The proportion of index subjects who initiated ART during the trial was evenly divided among the three treatment groups.

Since the risk of HIV transmission to the partner subject would be reduced if ART therapy significantly lowered the index subject's viral load, FDA conducted sensitivity analyses to evaluate the effect of initiation of ART in the index subject on PrEP efficacy. Of note, five partner subjects (TDF 3, FTC/TDF 0, placebo 2) acquired HIV infection after their index partner had started ART, so treatment as prevention was not absolute

in its protection. All of these seroconversion events occurred within three months of ART initiation, so full viral suppression in the index subject would not necessarily have been expected.

The FDA sensitivity analysis censored any partner subject whose index partner initiated ART at the start of the ART regimen. An alternative analysis excluded all partner subjects whose index partners initiated ART, unless the partner subject became HIV infected. The results of these sensitivity analyses showed that initiation of ART in the index subjects did not significantly affect the original efficacy conclusions, since the use of ART impacted all treatment groups equally, as would be expected from a successfully blinded randomized trial. Please see the Statistical Review by Dr. Hammerstrom for further details.

7 Review of Safety

Safety Summary

The safety of FTC/TDF for a PrEP indication is supported by two, large, randomized, double-blinded, placebo-controlled trials in diverse populations: the iPrEx trial in MSM from six countries globally and the Partners PrEP trial in heterosexual men and women in serodiscordant relationships in Kenya and Uganda. In addition, supportive safety data are provided by the CDC 4323 trial in 400 U.S. MSM. The safety assessments employed in these trials and study populations selected for evaluation are considered appropriate for the proposed indication. Drug exposures were generally adequate for the Partners PrEP and CDC 4323 trials, but were possibly suboptimal for a safety assessment in the iPrEx trial due to overall poor adherence.

In these trials, FTC/TDF was generally well tolerated amongst HIV-uninfected individuals and no new safety issues were identified. Major safety results (i.e., deaths, serious adverse events, adverse events leading to drug discontinuation, or adverse events of moderate to severe toxicity) were balanced between the active and placebo groups in each trial. In the iPrEx trial, unintended weight loss, nausea, and abdominal pain were reported more often in subjects receiving FTC/TDF. In the Partners PrEP trial, moderate to severe neutropenia was observed slightly more frequently in subjects receiving FTC/TDF compared with placebo, although the differences were small (8% versus 6%, respectively)..

Permanent drug discontinuations due to adverse events were infrequent in the pivotal trials (4% in iPrEx and <1% in Partners PrEP) and were generally balanced between treatment groups. In both arms of the iPrEx trial, study drug was most commonly stopped or interrupted for psychiatric disorders, the vast majority of which were not considered to be treatment-related. Seven subjects in the iPrEx trial interrupted FTC/TDF for increased serum creatinine; however, six resumed treatment without

notable incident. One subject permanently discontinued FTC/TDF for a Grade 1 creatinine elevation that later resolved off treatment. Another subject permanently discontinued FTC/TDF for Grade 2 hypophosphatemia in association with persistent glycosuria that was considered to be possibly related to study drug.

In the Partners PrEP trial, there were a total of seven permanent drug discontinuations, six of which were due to renal toxicity (FTC/TDF 2, TDF 3, placebo 1). In five of these cases, the renal toxicity in question was a decline in creatinine clearance <50 mL/min (TDF 2, FTC/TDF 2, placebo 1). All five discontinuations due to low creatinine clearance occurred in women, all of whom had normal creatinine clearance upon enrollment, although three had low normal values at entry. One of the six subjects with renal toxicity (in the TDF group) was also noted to have hypophosphatemia, but none had evidence of proteinuria or glycosuria during follow-up. Renal insufficiency resolved with cessation of the study drug in the five female cases, while the one case of Grade 1 creatinine increase in a male subject was still ongoing at exit from the trial. Treatment interruptions due to increased creatinine tended to occur more frequently than discontinuations (47 subjects [1%] versus 6 subjects [<1%], respectively). Treatment interruptions due to hypophosphatemia or low serum bicarbonate, however, were uncommon (<1%).

No significant differences or trends in clinical laboratory parameters were noted among the treatment groups in both pivotal trials, with the exception of a greater median decrease from baseline in total leukocyte count in the FTC/TDF group of the iPrEx trial and a greater proportion of subjects in the FTC/TDF group of the Partners PrEP trial with decrease neutrophil counts, both as compared with placebo. Among subjects randomized to FTC/TDF in both trials, hypophosphatemia was the most common \geq Grade 2 treatment-related adverse event (causality as determined by the site investigators), reported in 4% of subjects in the iPrEx trial and 14% of subjects in the Partners PrEP trial (compared with 3% and 13% in the placebo groups, respectively).

With further respect to renal safety, treatment-emergent creatinine elevations were reported in 2% of subjects per treatment group in the iPrEx trial and in 7% of FTC/TDF subjects in the Partners PrEP trial (compared with 5% in the placebo group). Increased creatinine as a serious adverse event was infrequent, reported in only 1% of all subjects in the iPrEx trial, with comparable rates between groups; all serious cases in the FTC/TDF group (N=8) were Grade 1. No serious events related to renal function were reported in the Partners PrEP trial. For subjects randomized to FTC/TDF, median time to onset of creatinine events was 24 weeks in the iPrEx trial (compared with 37 weeks in the placebo group) and 48 weeks in the Partners PrEP trial (compared with 43 weeks in the placebo group). There were no differences in either trial between the active and placebo groups in the median duration of creatinine elevation. For both trials, the rates of graded serum creatinine or serum phosphorus laboratory abnormalities were comparable among the treatment groups, as were the rates of proteinuria and glycosuria on urine dipstick. Mean changes from baseline in serum creatinine,

creatinine clearance, or serum phosphorus were small or negligible at all time points for all treatment groups in both trials.

No events of Fanconi syndrome were reported in either trial. There were, however, a small number of cases that were possibly suggestive of proximal renal tubulopathy, as determined by the presence of concurrent proteinuria, glycosuria, and hypophosphatemia. In the iPrEx trial, there were seven such cases (FTC/TDF 5, placebo 2) and in the Partners PrEP trial there were five cases (TDF 2, FTC/TDF 1, placebo 2). None of these twelve cases was associated with back pain, bone pain, or bone fractures, as might be seen with osteomalacia, although two of these subjects in the iPrEx trial had evidence of bone mineral density loss on post-baseline DEXA scans. The small number of these cases, however, precludes any reliable conclusions.

Review of the CDC 4323 trial data revealed similar safety trends to those reported above. A categorical analysis of subjects with recurrent $\geq 20\%$ increase in serum creatinine from baseline across the three trials (iPrEx, Partners PrEP, CDC 4323) revealed a small but consistent imbalance between the active and placebo treatment groups for each trial, with greater proportions seen in the TDF-based treatment groups. The percent differences were greatest in the CDC 4323 and Partners PrEP trials, perhaps owing to better drug adherence in these trials. These differences, however, were not associated with a difference in the incidence of proteinuria or glycosuria or with mean changes in serum phosphorus over time. In the CDC 4323 trial, the difference between the TDF and placebo groups in the proportion of subjects with $\geq 3\%$ BMD loss from baseline was greater among subjects with recurrent $\geq 20\%$ serum creatinine increases than among subjects without creatinine increase, although the clinical relevance of this finding is not clear.

With respect to bone safety, in both the iPrEx and CDC 4323 trials, small but significant decreases in BMD compared to baseline were noted in the TDF-based groups relative to placebo. Of note, similar findings have been reported for the CDC TDF2 trial in heterosexual men and women treated with FTC/TDF. Among the 45 subjects in the iPrEx trial with $\geq 5\%$ BMD decrease from baseline at the spine, five (all in the FTC/TDF group) also had evidence of treatment-emergent graded hypophosphatemia. DEXA scans obtained six months after discontinuation of treatment in the iPrEx trial, however, suggested that the BMD decreases observed with FTC/TDF use were reversing towards baseline levels. Importantly, no differences in fracture rates were observed between treatment groups across multiple trials. The vast majority of fractures reported in the three submitted trials were trauma-related, with wide variation in time to onset.

No evidence of hepatic flares was noted among the 19 study subjects with chronic or acute hepatitis B infection followed in the two pivotal trials. Likewise no significant between-group trends were noted in pregnancy outcomes among the 267 women in the Partners PrEP trial who became pregnant during treatment, although the relative pregnancy rate was lowest and the spontaneous abortion rate highest in the FTC/TDF

group, keeping in mind that women were tested for pregnancy on a monthly basis and the significance of these pregnancy losses, the majority of which were early, is not clear. Also, no analyses were conducted with respect to age, concomitant medication use or other factors that may help to explain the potential differences. All women who became pregnant were instructed to stop study drug as soon as they had a positive pregnancy test.

Lastly, no significant difference was noted in the incidence of treatment-emergent adverse events by gender. Adverse event rates were slightly higher for subjects older than 40 years of age across both pivotal trials compared with subjects younger than 40 years, but the rates groups within each age group were comparable between the active and placebo groups.

7.1 Methods

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

The review of safety in support of the proposed indication is based on clinical trial data from the iPrEx and Partners PrEP trials, with additional supportive safety from the CDC 4323 trial in a population of 400 U.S. MSM. Specifically, the renal and bone laboratory data from CDC 4323 were utilized for this review. Please see Section 5.1 for a tabular listing of these trials.

7.1.2 Categorization of Adverse Events

In both pivotal trials, AEs were coded using the Medical Dictionary for Regulatory Activities (MedDRA), Version 10.0. MedDRA Preferred Terms (PT) that essentially described the same or similar events were pooled when deemed appropriate for the purposes of this safety review, particularly for renal and bone events potentially related to tenofovir toxicity and for events leading to study drug discontinuation. For example, the terms “Blood phosphorus decreased” and “Hypophosphatemia” were often pooled in analyses of low serum phosphorus.

All AEs were graded using the DAIDS AE Grading Table, except that in the iPrEx trial, Grade 1 creatinine toxicity was defined as ≥ 1.5 x the participant’s baseline serum creatinine (baseline serum creatinine was defined as the average of the serum creatinine measurements taken at screening and at enrollment) OR estimated creatinine clearance of < 50 ml/min, even if serum creatinine was in the normal or Grade 0 range. In the Partners PrEP trial, Grade 1 creatinine toxicity was defined as being at least 1.5 times the subject’s baseline serum creatinine level, even if serum creatinine was in the normal or Grade 0 range; Grade 2 creatine toxicity was defined as a creatinine clearance less than 50 mL/min, even if the creatinine value was in the normal or Grade 1 range.

Treatment-emergent AEs were defined as events that occurred after study drug dispense date, while on study drug treatment, and for 30 days post the treatment stop date. AEs that were present on the study drug dispense date were excluded from the safety analyses. All deaths captured in the database are reported regardless of when they occurred in relation to the last dose of study drug. Treatment-related AEs were defined as those events reported by the site investigator as definitely, probably, or possibly related to study drug.

The Applicant provided descriptive summaries generated for all treatment-emergent AEs, laboratory test results, and changes from baseline by visit. Creatinine clearance was calculated using the Cockcroft-Gault equation. Baseline was considered the last assessment prior to initiation of study drug for all laboratory tests except creatinine, creatinine clearance, and eGFR for which baseline was considered as the average of the last 2 assessments prior to the initiation of study drug. All laboratory tests were graded using the DAIDS grading schedule. Additionally, serum creatinine and phosphorus were graded and summarized using the Applicant's internal grading schedule to accommodate cross-trial comparisons. DEXA data from the iPrEx trial were derived from the database available in September 2011, and included visits through February 28, 2011.

7.1.3 Pooling of Data across Studies/Clinical Trials to Estimate and Compare Incidence

In general, pooling of data across trials was not performed for this review because of the different subject populations, methodologies, and drug interventions (FTC/TDF and/or TDF) used in each clinical trial. In addition, the quality of the submitted datasets was such that pooling of data would have been logistically complicated. Wherever possible, however, incidences of key primary safety issues were compared among trials.

7.2 Adequacy of Safety Assessments

7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

iPrEx

The iPrEx trial randomized 1,251 MSM to FTC/TDF treatment. Subject demographics of the randomized subjects were representative of a young high-risk MSM population (see Table 5). Older MSM (≥ 40 years old) made up only 10% of the population. Additional safety data in this age group would be useful to have since the risk-benefit assessment with regards to renal and bone healthy may differ for an older HIV-uninfected male population. Data from the CDC 4323 trial, which enrolled U.S. MSM exclusively and had an older mean age of participants and a greater degree of drug adherence as per

MEMS than iPrEx, provided some insight into this issue. In addition, the population of the iPrEx trial was predominately Hispanic/Latino of mixed race. However, the extensive post-approval experience of TRUVADA does not indicate a differential safety risk based on race or ethnicity; therefore, data from the iPrEx trial are applicable to the intended population in that regard. Lastly, although the median duration of exposure to FTC/TDF was reported as 77.9 weeks through the November 21, 2010 cut-off date, with a median (Q1, Q3) compliance of 94.4% (82.4%, 99.3%) by self-reported pill counts, drug adherence by self-reported measures was found to be grossly unreliable in this trial when compared to blood drug levels (see Section 6.1.5). Therefore, the actual extent of study drug exposure in this trial is not certain, but is presumably less than would be estimated based on self-reported adherence. The poor adherence to study medication should be taken under consideration when interpreting the overall safety findings of the iPrEx trial.

Partners PrEP

The Partners PrEP trial randomized 1,579 heterosexual adults to FTC/TDF and 1,584 to TDF alone. Median duration of follow-up was 23 months (Q1, Q3: 16 to 28). Study drug was dispensed at 96% of all attended study visits, and 97% of all dispensed tablets were estimated to have been taken, based on pill counts of returned, unused study drug. The total exposure for the safety follow-up period, therefore, was 2,638 person-years for FTC/TDF and 2,631 person-years for TDF. Subject demographics were representative of HIV-serodiscordant couples, an intended population for the indication. Mean age of participants was 34, which is applicable to heterosexual men and women of child-bearing potential who may be at risk for HIV infection. Although a differential safety risk profile based on gender has not been reported for FTC or TDF, the Partners PrEP trial did enroll an adequate number of women (FTC/TDF 566, TDF 598), so that the data from this trial may be considered applicable to sexually active women of childbearing age. The number of men randomized to active treatment (TDF 986, FTC/TDF 1013) is also significant since PrEP trials in heterosexual men are limited. Results from the CDC TDF2 trial have not been peer reviewed or published yet; moreover, the number of heterosexual men randomized to FTC/TDF in that trial was approximately 320. Of note, the subject population in the Partners PrEP trial was exclusively African; however, as previously described, no differences in safety based on race or ethnicity have been identified for FTC or TDF, so that the data from this trial may be considered applicable to other races/ethnicities. Moreover, results from the Partners PrEP trial might be relevant to a U.S. African-American population, although differences such as diet, body mass index, and co-morbid conditions between the two populations should be taken into account. Lastly, given the high adherence and longer duration of exposure, data from the Partners PrEP trial may provide a better estimate of the true safety of FTC/TDF in an uninfected population than the iPrEx trial.

Table 16 summarizes the drug exposure reported for both trials.

Table 16: Summary of Drug Exposures (Studies CO-US-104-0288 and -0380)

Treatment Groups	iPrEx		Partners PrEP	
	N	Median Exposure, weeks (Q1, Q3)	N	Median Exposure, weeks (Q1, Q3)
FTC/TDF	1251	78 (52,120)	1579	95 (67,116)
TDF			1584	95 (67,115)
Placebo	1248	78 (52,118)	1584	95 (68,115)

Source: Study CO-US-104-0288 BASICS dataset and Study CO-US-104-0380 KEYVARS dataset

7.2.2 Explorations for Dose Response

No formal explorations of an exposure-safety response have been completed for a PrEP indication to date. As noted in Section 6.1.8, both pivotal trials evaluated the currently recommended dosing regimen for TRUVADA (fixed-dose combination tablet of FTC 200 mg/TDF 300 mg, administered orally once daily). Other clinical trials of oral PrEP have likewise thus far evaluated daily dosing with TRUVADA or TDF 300 mg only. As noted in Section 4.4.2, the dosages of TDF 300 mg and FTC 200 mg once daily were originally selected for treatment of HIV-1 infection based on their antiviral activity. Also, as noted in Section 4.4.2, pharmacometrics modeling indicates that efficacy is highly correlated with adherence; however, the safety and efficacy of any oral dosing regimen other than the recommended daily dosing for TRUVADA have not been established for a prophylactic indication. As noted in Section 2.5, the ADAPT trial (HPTN 067) under an IND held by DAIDS/NIH, is currently evaluating intermittent dosing of oral FTC/TDF as PrEP in an MSM population.

7.2.3 Special Animal and/or In Vitro Testing

No special animal or in vitro safety testing was performed or required.

7.2.4 Routine Clinical Testing

The routine clinical testing performed during the two pivotal Phase 3 clinical trials and the supportive Phase 2 safety trial (CDC 4323) are considered appropriate for the study population under evaluation (healthy adults) and the proposed indication (PrEP).

7.2.5 Metabolic, Clearance, and Interaction Workup

The metabolism, clearance, and drug-drug interactions of FTC and TDF are well described in the current labeling for TRUVADA.

7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

No new adverse events were reported in the course of these clinical trials that would warrant evaluation for potential adverse events for similar drugs in the NRTI drug class.

7.3 Major Safety Results

7.3.1 Deaths

iPrEx

A total of nine (<1%) deaths were reported in the iPrEx trial (FTC/TDF 2 [<1%], placebo 7 [1%]): eight subjects died before the November 21, 2010 data cutoff and one subject in the placebo group died on [REDACTED] (b) (6) from a thermal burn sustained in a fire. None of the nine deaths was considered to be related to study drug by the investigators. The causes of death for the two subjects in the FTC/TDF group (Subjects 9123922 and 9736428) were acute hepatic failure and road traffic accident, respectively. The death of Subject 9123922 is discussed here.

Subject 9123922 was a 38-year-old male who enrolled in iPrEx on December 11, 2008. He was diagnosed with acute lymphoproliferative angiocentric T-cell lymphoma on June 5, 2010 (Study Day 542). Concurrently, liver function parameters were noted to have increased approximately 2- to 8-fold from April 29, 2010 (Study Day 504) to July 22, 2010 (Study Day 589), i.e., the last recorded serum chemistry laboratory values for this subject: alkaline phosphatase increased from 107 to 188 IU/L, alanine aminotransferase (ALT) from 22 to 178 IU/L, and aspartate aminotransferase (AST) from 29 to 167 IU/L. Study drug was discontinued on July 23, 2010 (Study Day 590). On [REDACTED] (b) (6) (Study Day [REDACTED] (b) (6)), the subject experienced acute hepatic failure and died. The cause of death was reported as upper digestive hemorrhage, associated with liver failure and angiocentric T-cell lymphoma. The investigator considered the event to be unrelated to study drug. Per the Applicant, study drug levels for Subject 9123922 were reportedly below the level of quantification a year prior (August 20, 2009) to the onset of the acute hepatic failure (UCSF data on file).

The causes of death for the seven subjects in the placebo group (Subjects 8932184, 9015185, 9015887, 9116378, 9117067, 9635795, and 9116736) were, respectively: head trauma, pulmonary tuberculosis, traffic accident as pedestrian, knife injury, gun shot wound, thermal burn, and death due to unknown cause after reportedly undergoing

a plastic surgery procedure outside the country of enrollment (the death occurred approximately 4.5 months after last dose of study drug). Table 17 lists the all the deaths reported in this trial up to a cut-off date of September 11, 2011.

Table 17: Deaths Listing (CO-US-104-0288) Cut-off Date: 09-11-2011

Treatment	Subject	Age	Site	Cause of Death	Study Day
TDF/FTC	9123922	38	Lima	Acute liver failure/acute lymphoma	(b) (6)
	9736428	18	Chiang Mai	Road traffic accident	
Placebo	8932184	23	Rio de Janeiro	Head trauma	
	9015185	24	Lima	Pulmonary tuberculosis	
	9015887	23	Lima	Road traffic accident	
	9116378	32	Lima	Abdominal knife wound	
	9116736	28	Lima	Unknown	
	9117067	19	Lima	Gun shot wound	
	9635795	18	Cape Town	Fire/thermal burn	

Source: Study CO-US-104-0288 BASICS, TERM, DERA datasets and case report forms

Partners PrEP

A total of 27 (1%) deaths were reported among the partner subjects in the Partners PrEP trial as of the July 10, 2011 data cut-off date (TDF 10 [1%], FTC/TDF 8 [1%], and placebo 9 [1%]). Two of the deaths in the FTC/TDF group, one resulting from pulmonary embolism and the other resulting from an influenza-like illness, were considered by the investigators to be possibly related to the study drug; the coordinating center's safety monitor, however, assessed both events as probably not related to the study drug. Both the investigators and the safety monitor assessed all other reported deaths as either probably not related or not related to the relevant study drug. Table 18 lists all deaths reported in this trial through the cut-off date of July 10, 2011.

Table 18: Deaths Listing (CO-US-104-0380) Cut-off Date: 07-10-2011

Treatment	Subject	Age	Gender	Site	Cause of Death	Study Day
TDF	5026414	57	Male	Tororo	Acute abdomen	(b) (6)
	5104718	29	Male	Nairobi	Alcohol poisoning	
	5137810	32	Male	Nairobi	Road traffic accident	
	5221015	46	Male	Mbale	Cerebrovascular accident	
	5426914	46	Male	Kampala	Lung abscess	
	5542314	44	Male	Kabwohe	Esophageal cancer	
	5702014	38	Male	Eldoret	Gastroenteritis shigella	
	5712611	30	Male	Eldoret	Alcohol poisoning	
	5712915	24	Male	Eldoret	Fall	

						(b) (6)
	5818116	24	Male	Jinja	Road traffic accident	
FTC/TDF	5019215	59	Male	Tororo	Influenza like illness	
	5043111	36	Female	Tororo	Pulmonary embolism	
	5118715	62	Male	Nairobi	Pulmonary tuberculosis	
	5304312	43	Male	Thika	Road traffic accident	
	5505111	31	Female	Kabwohe	Road traffic accident	
	5522417	24	Female	Kabwohe	Gastroenteritis	
	5627517	46	Male	Kisumu	Poisoning	
	5703511	47	Male	Eldoret	Gun shot wound	
Placebo	5035610	47	Male	Tororo	Diabetic complications	
	5106610	23	Male	Nairobi	Electrocution	
	5113918	45	Male	Nairobi	Hematemesis	
	5135714	40	Male	Nairobi	Febrile infection	
	5227713	38	Male	Mbale	Hypotension	
	5408819	33	Female	Kampala	Road traffic accident	
	5516116	33	Male	Kabwohe	Suicide	
	5542419	55	Male	Kabwohe	Road traffic accident	
	5628319	36	Male	Kisumu	Road traffic accident	

Source: Study CO-US-104-0380 KEYVARS dataset and case report forms

7.3.2 Nonfatal Serious Adverse Events

iPrEx

In iPrEx, 165 subjects reported 211 treatment-emergent serious adverse events (SAE) through the November 21, 2010 cut-off date. The frequency of SAEs was similar between the two treatment groups (FTC/TDF 83 [7%], placebo 82 [7%]). Most of the SAEs were reported within the following MedDRA System Organ Class (SOC) categories: Psychiatric Disorders; Investigations; Injury, Poisoning, and Procedural Complications; Infections and Infestations; and Gastrointestinal Disorders. By MedDRA PT, all treatment-emergent SAEs occurred at a rate $\leq 1\%$. The more common SAEs were related to suicide (attempt or ideation), depression, or laboratory toxicities (blood creatinine increase). No notable differences were observed between the two treatment groups in terms of frequency or pattern of treatment-emergent clinical or laboratory SAEs. Table 19 summarizes treatment-emergent SAEs, by MedDRA SOC and PT, which were reported in more than 1 subject in either treatment group.

Table 19: Treatment-Emergent Serious Adverse Events (Any Causality) Reported in More Than One Subject in Any Treatment Group (CO-US-104-0288)

System Organ Class	Preferred Term	Number of Subjects (%)		
		FTC/TDF (N=1251)	Placebo (N=1248)	Total (N=2499)
Any SAE		83 (7)	82 (7)	165 (7)
Psychiatric Disorders		28 (2)	29 (2)	57 (2)

	Suicide attempt	14 (1)	12 (1)	26 (1)
	Depression	6 (<1)	11 (1)	17 (1)
	Suicidal ideation	4 (<1)	6 (<1)	9 (<1)
	Depression suicidal	1 (<1)	4 (<1)	5 (<1)
	Major depression	4 (<1)	0	4 (<1)
	Depressed mood	0	2 (<1)	2 (<1)
Investigations		18 (1)	17 (1)	35 (1)
	Blood creatinine increased	8 (1)	7 (1)	15 (1)
	AST increased	4 (<1)	2 (<1)	6 (<1)
	Lipase increased	2 (<1)	2 (<1)	4 (<1)
	ALT increased	1 (<1)	2 (<1)	3 (<1)
	Blood sodium decreased	1 (<1)	2 (<1)	3 (<1)
	Blood amylase increased	2 (<1)	0	2 (<1)
Injury, Poisoning and Procedural Complications		15 (1)	17 (1)	32 (1)
	Contusion	2 (<1)	2 (<1)	4 (<1)
	Foot fracture	1 (<1)	2 (<1)	3 (<1)
	Traumatic brain injury	1 (<1)	2 (<1)	3 (<1)
	Gun shot wound	0	2 (<1)	2 (<1)
	Limb crushing injury	0	2 (<1)	2 (<1)
Infections and Infestations		12 (1)	10 (1)	22 (1)
	Appendicitis	3 (<1)	2 (<1)	5 (<1)
	Pneumonia	3 (<1)	1 (<1)	4 (<1)
	Cellulitis	1 (<1)	2 (<1)	3 (<1)
	Pulmonary tuberculosis	1 (<1)	2 (<1)	3 (<1)
Gastrointestinal Disorders		5 (<1)	3 (<1)	8 (<1)
	Inguinal hernia	2 (<1)	1 (<1)	3 (<1)
Social Circumstances		2 (<1)	4 (<1)	6 (<1)
	Victim of crime	0	2 (<1)	2 (<1)

Abbreviations: ALT = alanine aminotransferase; AST = aspartate aminotransferase

Source: Study CO-US-104-0288 DERAЕ dataset

A total of 170 clinical (non-laboratory) SAEs were reported among 138 subjects (FTC/TDF 70 [6%], placebo 68 [5%]). Of these, 149 (88%) were DAIDS Grade 3 or 4 in severity and were reported in 123 subjects, with a higher proportion of Grade 3 SAEs in the FTC/TDF group:

- Grade 3 clinical SAEs (N=59): FTC/TDF 32 (54%), placebo 27 (46%)
- Grade 4 clinical SAEs (N=64): FTC/TDF 31 (48%), placebo 33 (52%)

Grade 4 clinical SAEs were predominately psychiatric disorders, while Grade 3 events were associated with infections, injuries, or psychiatric disorders. There were no clinical SAEs related to renal function. Nine (<1%) subjects reported SAEs related to bone fractures (FTC/TDF 5, placebo 4), but none of these was considered related to study drug.

Clinical SAEs considered by the investigator to be related to study drug (i.e., definitely, probably, possibly related) were reported in only two subjects total (one in each group). These SAEs included a suicide attempt (Grade 4) on Study Day 329 in one FTC/TDF subject (Subject 9635309) considered possibly related and Grade 3 peripheral sensory neuropathy that began on Study Day 19 in one placebo-treated subject (Subject 8944918), considered probably related. Both events resolved without sequelae, although study drug was permanently discontinued for the SAE of attempted suicide, as any suicidal ideation or attempt was regarded as Grade 4 according to the DAIDS toxicity grading table and the protocol called for discontinuation of study drug for all Grade 4 events.

A total of 41 laboratory SAEs were reported among 37 subjects (FTC/TDF 19 [2%], placebo 18 [1%]). About half of these events were DAIDS Grade 4 in severity, while 4% and 7% were Grades 3 and 2, respectively. Of the Grade 4 laboratory SAEs, one-fourth were related to increased transaminases; the rest were due to increased lipase or amylase or decreased sodium, glucose, or white blood cells (WBC). None of the Grade 4 laboratory events related to renal function. There were only two Grade 3 laboratory SAEs: one case of increased AST in an FTC/TDF subject and one case of decreased serum phosphorus in a placebo subject. Overall, the event rates for laboratory SAEs by type were similar between the two treatment groups and no between-group patterns were noted.

Increased creatinine as an SAE was reported in 15 (1%) subjects (FTC/TDF 8 [1%], placebo 7 [1%]). All 8 SAEs of increased creatinine in the FTC/TDF group were DAIDS Grade 1. Increased creatinine as an SAE of greater than DAIDS Grade 1 was reported in two subjects in the placebo group (both Grade 2). Hypophosphatemia as an SAE was reported in only two subjects (Grades 2 and 3), both in the placebo group.

Laboratory SAEs considered by the investigator to be related to study drug were reported for nine subjects total (FTC/TDF 4 [<1%], placebo 5 [<1%]). Among the four FTC/TDF subjects, three had Grade 1 serum creatinine increases and one had Grade 3 elevated AST. In all four cases in the FTC/TDF group, the laboratory SAE was considered "possibly related" to study drug. None of the four cases, however, required permanent study drug discontinuation; study drug was temporally interrupted for two of the SAEs of increased creatinine and for the one SAE of elevated AST. In all four cases, the laboratory SAEs resolved.

Partners PrEP

In the Partners PrEP trial, 381 treatment-emergent SAEs were reported in 315 (7%) partner subjects. The frequency of treatment-emergent SAEs was consistent across the three treatment groups (7% in each group). Most SAEs were reported within the following MedDRA SOCs: Infections and Infestations; Investigations; Injury, Poisoning, and Procedural Complications; Gastrointestinal Disorders; and Pregnancy, Puerperium and Perinatal Conditions. By MedDRA PT, no SAE was reported in >1% of partner subjects, except for malaria which occurred in 2% of subjects in each treatment group. Overall, no between-group trends in SAEs were observed given the comparable frequencies, severity grades, and types of AEs reported within each group. Table 20 summarizes treatment-emergent SAEs, by MedDRA SOC and PT, reported in more than one subject in any treatment group.

Table 20: Treatment-Emergent Serious Adverse Events (Any Causality) Reported in More Than One Subject in Any Treatment Group (CO-US-104-0380)

System Organ Class	Preferred Term	Number of Subjects (%)			
		TDF (N=1584)	FTC/TDF (N=1579)	Placebo (N=1584)	Total (N=4747)
Any SAE		104 (7)	107 (7)	104 (7)	315 (7)
Infections and Infestations		46 (3)	34 (2)	42 (3)	122 (3)
	Malaria	27 (2)	25 (2)	34 (2)	86 (2)
	Febrile infection	1 (<1)	2 (<1)	1 (<1)	4 (<1)
	Typhoid fever	1 (<1)	2 (<1)	1 (<1)	4 (<1)
	Gastroenteritis	2 (<1)	0	1 (<1)	3 (<1)
	Pelvic inflammatory disease	3 (<1)	0	0	3 (<1)
	Pneumonia	0	1 (<1)	2 (<1)	3 (<1)
	Appendicitis	2 (<1)	0	0	2 (<1)
	Dysentery	2 (<1)	0	0	2 (<1)
Investigations		19 (1)	31 (2)	18 (1)	68 (1)
	Neutrophil count decreased	13 (1)	17 (1)	9 (1)	39 (1)
	Platelet count decreased	1 (<1)	5 (<1)	4 (<1)	10 (<1)
	AST increased	4 (<1)	2 (<1)	2 (<1)	8 (<1)
	Hemoglobin decreased	1 (<1)	5 (<1)	2 (<1)	8 (<1)
	ALT increased	3 (<1)	2 (<1)	2 (<1)	7 (<1)
Injury, Poisoning and Procedural Complications		8 (1)	17 (1)	18 (1)	43 (1)

	Road traffic accident	0	5 (<1)	5 (<1)	10 (<1)
	Soft tissue injury	2 (<1)	2 (<1)	3 (<1)	7 (<1)
	Head injury	0	3 (<1)	3 (<1)	6 (<1)
	Alcohol poisoning	2 (<1)	0	0	2 (<1)
	Lower limb fracture	0	0	2 (<1)	2 (<1)
Pregnancy, Puerperium and Perinatal Conditions ^{a, b}		14 (2)	12 (2)	10 (2)	36 (2)
	Abortion spontaneous	7 (1)	8 (1)	6 (1)	21 (1)
	Normal delivery	5 (1)	2 (<1)	2 (<1)	9 (1)
Gastrointestinal Disorders		12 (1)	11 (1)	10 (1)	33 (1)
	Peptic ulcer	4 (<1)	1 (<1)	2 (<1)	7 (<1)
	Inguinal hernia	1 (<1)	3 (<1)	3 (<1)	7 (<1)
	Abdominal pain	1 (<1)	2 (<1)	2 (<1)	5 (<1)
	Gastritis	3 (<1)	0	0	3 (<1)
Nervous System Disorders		4 (<1)	1 (<1)	4 (<1)	9 (<1)
	Loss of consciousness	2 (<1)	0	0	2 (<1)
General Disorders and Administration Site Conditions		1 (<1)	2 (<1)	0	3 (<1)
	Influenza like illness	0	2 (<1)	0	2 (<1)

Abbreviations: ALT = alanine aminotransferase; AST = aspartate aminotransferase

a) All serious adverse events in the Pregnancy, Puerperium and Perinatal Conditions SOC are counted regardless of temporal relationship with study drug

b) Denominator for percentages is number of women enrolled in the respective treatment group

Source: Study CO-US-104-0380 ADAE dataset

A total of 300 treatment-emergent clinical (non-laboratory) SAEs were reported among 252 partner subjects (TDF 85 [5%], FTC/TDF 78 [5%], placebo 89 [6%]), with SAEs in the Infections and Infestations SOC being the most frequently reported. In contrast to the iPrEx trial, psychiatric SAEs were infrequently reported (8 subjects total), including one event each of depression and major depression in the FTC/TDF group, three events of attempted suicide (one in each treatment group), and one completed suicide in the placebo group.

Approximately 53% of the treatment-emergent clinical SAEs were DAIDS Grade 3 in severity, while 23% were Grade 2 and 16% were Grade 4. There was a similar

distribution of clinical SAEs by severity across the three treatment groups, with slightly less Grade 3 SAEs in the FTC/TDF group and slightly more Grade 4 SAEs in the placebo group. The leading Grade 4 clinical SAE was spontaneous abortion, while the leading Grade 3 event was malaria; for each of these AE preferred terms, the event was reported in comparable percentages within each treatment group. None of the reported treatment-emergent clinical SAEs were related to renal function. On the other hand, there were nine bone fracture SAEs reported among seven partner subjects (TDF 2, FTC/TDF 2, placebo 3). None of the clinical SAEs, including the bone fractures, was considered related to study drug by the coordinating center's safety monitor.

A total of 21 (1%) women reported spontaneous abortions as SAEs in this trial, with comparable frequencies across the treatment groups based on the number of women enrolled. SAEs in the Pregnancy, Puerperium and Perinatal Conditions MedDRA SOC were reported regardless of temporal relationship to study drug. Given the 288 pregnancies reported during the blinded treatment period (TDF 112, FTC/TDF 80, placebo 96), the rates of spontaneous abortion reported as SAEs by number of pregnancies were 6%, 10%, and 6% for the three treatment groups, respectively, and 7% for the trial overall. Background miscarriage rates for Kenya and Uganda are unreliable given the illegal status of induced abortion in those countries, but studies indicate that the overall rate of spontaneous abortion in recognized pregnancies is 10-20%.³⁶ It is worth noting that the Partners PrEP protocol mandated monthly pregnancy testing in all female partner subjects and that most of the spontaneous abortions where the age at gestation was known occurred early in the pregnancy (less than 20 weeks). Thus, it is reasonable to assume that many of the pregnancy losses reported in the trial were "chemical pregnancies" that would in other settings probably go undetected and be lost without notice (see Section 7.6.2). Analyses of these events by age, concomitant medication use, or other factors were not carried out, but the numerical difference between the groups is small and may represent reporting differences or random variation.

Nine normal deliveries were also reported as SAEs, but all occurred beyond 30 days after study drug discontinuation and thus are not considered treatment-emergent by this reviewer. Congenital ankyglossia was reported among two infants born to female partner subjects previously treated with TDF; otherwise no congenital disorders were reported in more than one infant born to a partner subject in any given treatment group.

A total of 81 treatment-emergent laboratory SAEs were reported among 67 partner subjects, predominantly in the FTC/TDF group (TDF 19 [1%], FTC/TDF 31 [2%], placebo 17 [1%]). All laboratory SAEs were DAIDS Grade 4. The most common laboratory SAE was decreased neutrophil count occurring in 1% of total subjects, with a small numerical predominance in the two active groups compared with the placebo

³⁶ Regan L, Rai R. Epidemiology and the medical causes of miscarriage. *Baillieres Best Pract Clin Obstet Gynaecol* 2000; 14 (5):839.

group (see Table 20 for a tabulation of the leading laboratory SAEs). Two laboratory SAEs were considered by both the investigators and the coordinating center's safety monitor to be possibly related to study drug. These included a Grade 4 increase in ALT and a Grade 4 increase in AST, both occurring in the same partner subject (Subject 5523314); this subject was in the placebo group. Given that overall similar events were reported at similar rates in the active and placebo treatment groups, no safety trends for laboratory SAEs were observed in this trial.

7.3.3 Dropouts and/or Discontinuations

iPrEx

In the iPrEx trial, 99 subjects permanently discontinued study treatment due treatment-emergent AEs, regardless of causality (FTC/TDF 48 [4%], placebo 51 [4%]). Eighty-three subjects (3%) discontinued due to clinical AEs and 16 (1%) due to laboratory AEs. In more than half of the subjects who discontinued study drug due to a clinical AE (44/83), the AE in question was a psychiatric disorder. The more common AEs leading to study drug discontinuation were depression (including suicidal ideation or attempt), pulmonary tuberculosis, ALT and AST increases, and gastrointestinal disorders (e.g. diarrhea, gastritis). Laboratory AEs were mostly reported under the Investigations MedDRA SOC, but some were also reported under other SOCs such as Metabolism and Nutrition Disorders. By MedDRA PT, no AE was reported in $\geq 1\%$ of subjects. Overall, the AE frequencies were comparable between the treatment groups and no patterns regarding specific types of AEs or SOCs were noted between the two treatment groups. Median time (Q1, Q3) to onset of AEs leading to study drug discontinuation was 50 weeks (24, 79). Table 21 lists the AEs leading to permanent discontinuation of study drug that were reported in more than 1 subject in either treatment group.

Table 21: Treatment-Emergent Adverse Events (Any Causality) Leading to Permanent Study Drug Discontinuation Reported in More Than One Subject in Any Treatment Group (CO-US-104-0288)

System Organ Class	Preferred Term	Number of Subjects (%)		
		FTC/TDF (N=1251)	Placebo (N=1248)	Total (N=2499)
Any AE		48 (4)	51 (4)	99 (4)
Psychiatric Disorders		22 (2)	22 (2)	44 (2)
	Depression	6 (<1)	9 (1)	15 (1)
	Major depression	4 (<1)	4 (<1)	8 (<1)
	Suicide attempt	4 (<1)	2 (<1)	6 (<1)
	Depression suicidal	3 (<1)	2 (<1)	5 (<1)
	Suicidal ideation	0	4 (<1)	4 (<1)
Investigations		6 (<1)	6 (<1)	12 (<1)
	ALT increased	4 (<1)	2 (<1)	6 (<1)
	AST increased	4 (<1)	2 (<1)	6 (<1)

Infections and Infestations		1 (<1)	8 (1)	9 (<1)
	Pulmonary tuberculosis	1 (<1)	6 (<1)	7 (<1)
Gastrointestinal Disorders		6 (<1)	2 (<1)	8 (<1)
	Diarrhea	3 (<1)	0	3 (<1)
	Gastritis	2 (<1)	0	2 (<1)
Metabolism and Nutrition Disorders		1 (<1)	4 (<1)	5 (<1)
	Hyperglycemia	0	2 (<1)	2 (<1)
Nervous System Disorders		4 (<1)	1 (<1)	5 (<1)
	Headache	2 (<1)	0	2 (<1)

Abbreviations: ALT = alanine aminotransferase; AST = aspartate aminotransferase

Source: Study CO-US-104-0288 DRAE dataset

Adverse events leading to permanent drug discontinuation under the Renal and Urinary Disorders SOC were reported in only three subjects (FTC/TDF 1 [$<1\%$], placebo 2 [$<1\%$]). These renal AEs included one event each of hematuria and proteinuria in the placebo group and one event of Grade 2 dysuria in a subject in the FTC/TDF group considered possibly related to study drug (Subject 8831459). In addition, two subjects in the FTC/TDF group permanently discontinued study drug because of renal-associated laboratory AEs: one subject with Grade 1 creatinine increase considered to be probably not related to study drug (Subject 8831412 – see Table 22) and one subject with Grade 2 hypophosphatemia considered to be possibly related to study drug (Subject 9433750 – see Table 23).

Treatment-emergent, treatment-related AEs (defined by the investigator as possibly, probably, or definitely related to study drug) that led to permanent study drug discontinuation were reported in 23 subjects, with the majority occurring in the FTC/TDF group (FTC/TDF 17 [1%], placebo 6 [$<1\%$]). The most common of these AEs (reported in more than two subjects total) were: ALT increase (FTC/TDF 2, placebo 1), diarrhea (FTC/TDF 2, placebo 0), headache (FTC/TDF 2, placebo 0), AST increase (FTC/TDF 1, placebo 1), and major depression (FTC/TDF 0, placebo 2). Among the 17 FTC/TDF subjects who discontinued study drug due to a treatment-related AE, the median time to AE onset was 33 ± 5 weeks from start of treatment and the median duration of AE was 37 ± 11 days. All FTC/TDF-related AEs resolved with discontinuation of the drug, except for one subject with Grade 2 depression and one subject with abnormal behavior, both of which were still ongoing at the end of participation in the trial.

Treatment-emergent AEs leading to temporary study drug interruptions were reported for 196 subjects (FTC/TDF 104 [8%], placebo 92 [7%]). As with events leading to permanent drug discontinuation, AEs leading to temporary drug interruption were mainly reported under the MedDRA SOCs of Psychiatric Disorders; Investigations; Infections and Infestations; Gastrointestinal Disorders; Nervous System Disorders; and Metabolism and Nutrition Disorders. By MedDRA PT, none of the AEs leading to temporary study drug interruption were reported in $\geq 1\%$ of subjects. As a group, AEs

related to depression and suicidal ideation/attempt were the most common AEs leading to temporary study drug interruption. The overall rates of psychiatric disorders as a cause for treatment interruption were similar between the two treatment groups (FTC/TDF 33 [3%], placebo 34 [3%]), but numerically twice as many subjects reported the MedDRA PT of “depression” in the placebo group as in the FTC/TDF group (FTC/TDF 7 [1%], placebo 14 [1%]). Median time (Q1, Q3) to onset for these psychiatric disorders was 62 weeks (39, 94), with the vast majority of these events (90%) considered probably not related or not related by the investigators. Of note, the overall rates of moderate to severe depression observed in the iPrEx trial (6%) were consistent with those reported in the registrational trials of FTC/TDF for the treatment indication (7%); moreover, the rates of depression and all psychiatric disorders were comparable between the active and placebo arms in the iPrEx trial.³⁷

Serum creatinine increases leading to temporary study drug interruption were reported in ten subjects (FTC/TDF 7 [1%], placebo 3 [$<1\%$]). In nine of these, study drug was eventually restarted; one FTC/TDF subject (Subject 8831412) had study drug permanently discontinued. Among the seven FTC/TDF subjects, two of the events were considered serious and five were considered related to the study drug. Mean age for the FTC/TDF subjects was 34 years and median time to onset of the creatinine increase was 83 days (11 weeks) from start of treatment. Median time to resolution was 3 weeks (IQR 4-29 weeks). Among the FTC/TDF subjects, the AEs of creatinine increase resolved with removal of study drug and no recurrences were reported in the six subjects who resumed FTC/TDF. One subject (Subject 8831616) also had evidence of hypophosphatemia and low serum bicarbonate at various time points. Table 22 summarizes the seven cases of study drug interruption due to the AE of serum creatinine increase in the FTC/TDF treatment group.

Table 22: Subject Listing of Treatment-Emergent Blood Creatinine Increases Leading to Temporary Study Drug Interruption in the FTC/TDF Treatment Group (CO-US-104-0288)

Subject	Age	Severity Grade	SAE	Onset Week	Duration (weeks)	Discontinued Study Drug?	AE Status
8831412	29	1	No	32	3	Yes	Resolved
8831616	47	1	No	4	5	No	Resolved
8932382	48	1	Yes	8	4	No	Resolved
8932399	25	1	Yes	12	3	No	Resolved
9321920	25	1	No	4	20	No	Resolved
9433960	33	1	No	29	1	No	Resolved
9635386	33	2	No	12	2	No	Resolved

Source: StudyCO-US-104-0288 DERA E dataset

³⁷ See Truvada labeling, Adverse Reactions from Clinical Trials Experience, Section 6.1, at http://www.accessdata.fda.gov/drugsatfda_docs/label/2011/021752s027lbl.pdf

The case of the subject who permanently discontinued FTC/TDF due to a creatinine increase (Subject 8831412) is summarized here:

- This was a 29-year-old man who started study medication on 07/14/09. Baseline serum creatinine was 1.18 mg/dL. A Grade 1 creatinine elevation was reported on 2/25/10 (Week 32). Serum creatinine at that time was 1.36 mg/dL. The event was not serious and was considered probably not related to study medication. Study drug was temporarily held on 3/05/2010; however, the serum creatinine continued to increase over next two weeks (serum creatinine 1.45 mg/dL on 3/04/10 and 1.66 mg/dL on 03/18/10). Study drug was never resumed. Serum creatinine values decreased with study drug discontinuation; serum creatinine was 1.2 mg/dL by Week 44. No graded hypophosphatemia was reported in this subject. Trace proteinuria was detected on two visits (including one of the visits post-study drug discontinuation when increased creatinine was still evident).

An additional 10 subjects interrupted study drug due to hypophosphatemia (FTC/TDF 5, placebo 2) or proteinuria (FTC/TDF 0, placebo 3). None of these events were SAEs. For the five FTC/TDF subjects who interrupted study drug due to hypophosphatemia, mean age was 33, median time to onset was 36 weeks (IQR 8-57), and median duration of AE was 24 days (IQR 12-50). In four of the five cases, the AE was considered possibly or probably related to study drug; in the other case, the event was considered unrelated (Subject 9117503). Four of the five events were Grade 3 and the other was Grade 2. All events resolved with cessation of study drug and, in four of the five cases, study drug was resumed. Recurrent intermittent hypophosphatemia, however, was noted in all four cases but did not lead to further study drug interruption. Of note, two of the five cases had low serum phosphorus values at baseline. One subject (Subject 9433750) permanently discontinued FTC/TDF due to hypophosphatemia reported on Study Day 401; this subject had had a prior AE of hypophosphatemia on Study Day 264 for which the study drug was not held and which had normalized on repeat testing. This subject was also noted to have persistent glycosuria at the time of study drug discontinuation. Table 23 summarizes the five cases of hypophosphatemia that led to treatment interruption in the FTC/TDF treatment group.

Table 23: Subject Listing of Treatment-Emergent Hypophosphatemia Leading to Temporary Study Drug Interruption in the FTC/TDF Treatment Group (CO-US-104-0288)

Subject	Age	Severity Grade	Onset Week	Duration (weeks)	Discontinued Study Drug?	AE Status	Recurred
8730001	23	3	8	3	No	Resolved	Yes
9117503	31	3	1	2	No	Resolved	Yes
9433478	32	3	36	6	No	Resolved	Yes
9433750	31	2	57	8	Yes	Resolved	No
9534034	49	3	59	1	No	Resolved	Yes

Source: StudyCO-US-104-0288 DERAIE dataset

Partners PrEP

In Partners PrEP, treatment-emergent AEs leading to permanent study drug discontinuation were infrequent, occurring in seven (<1%) partner subjects overall. In six of these cases, the AE that led to study drug discontinuation was the MedDRA PT 'blood creatinine increased', which was confirmed on repeat testing (Table 24). Median time to onset for the six cases of creatinine AE was 42 weeks (IQR 4-78 weeks). None of the six events was considered related to study drug by the site investigators. With the exception of one 34-year-old male partner subject in the TDF group (Subject 5400817), who had a Grade 1 increase in serum creatinine (2-fold increase from baseline), all of the events were Grade 2. Of note, the five Grade 2 increases were events in which creatinine clearance declined to less than 50 mL/min, in most cases from a baseline of just greater than 50 mL/min, but were otherwise not associated with Grade 2 serum creatinine abnormalities by the DAIDS toxicity table. The study protocol defined that any decrease of creatinine clearance to less than 50 mL/min was a Grade 2 event, even if the creatinine value itself was within normal limits or was Grade 1.

All five cases of decreased creatinine clearance occurred in women. Mean age of the five women was 42 years. Median duration of low creatinine clearance in these women was 29 days (IQR 11-73). One subject (Subject 5022810) with decreased creatinine clearance also had concurrent hypophosphatemia, but none of the women had abnormalities on urinalysis. Creatinine clearance improved to baseline levels in all five women with cessation of study drug (Figure 9).

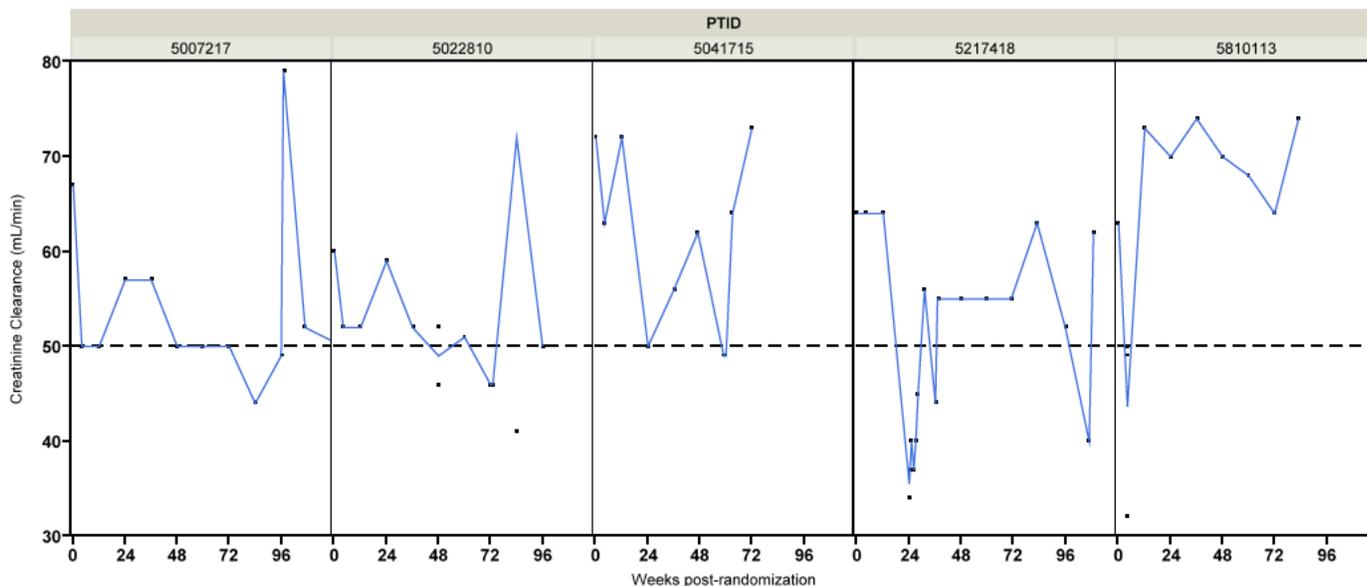
In the male subject with the Grade 1 creatinine increase (Subject 5400817), serum creatinine was still elevated at trial exit. Table 24 summarizes the six cases of drug discontinuation due to treatment-emergent creatinine toxicity.

Table 24: Subject Listing of Treatment-Emergent Blood Creatinine Increases or Creatinine Clearance Decreases Leading to Permanent Study Drug Discontinuation (US-CO-104-0380)

Treatment Group	Subject	Gender	Age	Severity Grade	SAE	Onset Week	Duration (weeks)	AE Status
TDF	5022810	Female	30	2	No	72	2	Resolved
	5217418	Female	50	2	No	24	7	Resolved
	5400817	Male	34	1	No	3	31	Ongoing
FTC/TDF	5007217	Female	55	2	No	84	13	Resolved
	5041715	Female	38	2	No	59	4	Resolved
Placebo	5810113	Female	40	2	No	4	1	Resolved

Source: Study CO-US-104-0380 ADAE dataset

Figure 9: Creatinine Clearance Changes over Time in Five Female Partner Subjects Who Permanently Discontinued Study Drug due to Decreased Creatinine Clearance (CO-US-104-0380)



An additional 59-year-old male partner subject in the placebo group (Subject 5520516) permanently discontinued study drug on Study Day 758 due to esophageal carcinoma that was considered unrelated to study drug.

In contrast to the above, 239 treatment-emergent AEs led to temporary study drug interruptions in 186 partner subjects (TDF 63 [4%], FTC/TDF 64 [4%], placebo 59 [4%]). The majority of these AEs mapped to the Investigations SOC, with increased blood creatinine being the primary AE by MedDRA PT. Approximately 43% of these events were SAEs and most (75%) were \geq DAIDS Grade 2. A little over a third of the AEs were considered study drug related by the site investigators, but only two were considered drug related by the safety monitor: one event each of increased AST and increased ALT occurring in the same subject (Subject 5523314) in the placebo group (see Section 7.3.2). No AE by MedDRA PT was reported in $>1\%$ of subjects in any treatment group. Overall, there were no notable between-group trends by severity or type regarding AEs that led to treatment interruption. Table 25 summarizes the treatment-emergent AEs that led to temporary study drug interruption in more than 1 partner subject in any treatment group.

Table 25: Treatment-Emergent Adverse Events (Any Causality) Leading to Temporary Study Drug Interruption Reported in More Than One Subject in Any Treatment Group (CO-US-104-0380)

System Organ Class	Preferred Term	Number of Subjects (%)			
		TDF (N=1584)	FTC/TDF (N=1579)	Placebo (N=1584)	Total (N=4747)
Any AE		63 (4)	64 (4)	59 (4)	186 (4)
Investigations		44 (3)	52 (3)	38 (2)	134 (3)

	Blood creatinine increase	16 (1)	17 (1)	14 (1)	47 (1)
	Neutrophil count decreased	11 (1)	16 (1)	8 (1)	35 (1)
	Blood phosphorus decreased	3 (<1)	4 (<1)	5 (<1)	12 (<1)
	Platelet count decreased	1 (<1)	5 (<1)	4 (<1)	10 (<1)
	AST increased	4 (<1)	2 (<1)	2 (<1)	8 (<1)
	ALT increased	3 (<1)	2 (<1)	2 (<1)	7 (<1)
	Hemoglobin decreased	1 (<1)	4 (<1)	2 (<1)	7 (<1)
	Blood bicarbonate decreased	4 (<1)	0	0	4 (<1)
Infections and Infestations		14 (1)	7 (<1)	8 (1)	29 (1)
	Malaria	4 (<1)	1 (<1)	3 (<1)	8 (<1)
	Pelvic inflammatory disease	4 (<1)	0	0	4 (<1)
Renal and Urinary Disorders		3 (<1)	6 (<1)	9 (1)	18 (<1)
	Proteinuria	2 (<1)	4 (<1)	4 (<1)	10 (<1)
	Glycosuria	1 (<1)	1 (<1)	5 (<1)	7 (<1)
Gastrointestinal Disorders		2 (<1)	5 (<1)	5 (<1)	12 (<1)
	Abdominal pain	1 (<1)	2 (<1)	0	3 (<1)
	Abdominal pain lower	0	0	2 (<1)	2 (<1)
	Vomiting	0	2 (<1)	0	2 (<1)

Abbreviations: ALT = alanine aminotransferase; AST = aspartate aminotransferase

Source: Study CO-US-104-0380 ADAE dataset

Looking specifically at laboratory events, since these were the leading causes of temporary treatment interruption, 162 laboratory AEs led to study drug interruption in 120 partner subjects, with a slight numerical predominance in the FTC/TDF group (TDF 37 [2%], FTC/TDF 48 [3%], placebo 35 [2%]). The majority of these AEs were under the Investigations SOC, but a couple (i.e., proteinuria and glycosuria) were in the Renal and Urinary Disorders SOC. Half of the laboratory AEs leading to treatment interruption were regarded as drug-related by the site investigators and for nearly half of the subjects who interrupted study drug due to a laboratory AE, the laboratory event in question was DAIDS Grade 4, with a greater proportion of Grade 4 events again reported in the FTC/TDF group. All Grade 4 laboratory events were hematological or hepatic in nature and the vast majority resolved with treatment interruption and did not

recur when treatment was resumed. In six partner subjects, Grade 4 laboratory AEs consisting of decreased neutrophils (FTC/TDF 2), decreased platelets (FTC/TDF 1, placebo 1), and decreased hemoglobin (FTC/TDF 1, placebo 1) were still ongoing at exit from the trial, but none of these was considered study drug related by the safety monitor.

7.3.4 Significant Adverse Events

iPrEx

In iPrEx, treatment-emergent, treatment-related AEs (defined by the investigator as possibly, probably, or definitely related to study drug) were reported in 332 subjects, with a slight predominance in the FTC/TDF group (FTC/TDF 188 [15%], placebo 144 [12%]). The vast majority (83%) of these treatment-related AEs were DAIDS Grade 2, while Grade 1 events made up 9%, Grade 3 events 7%, and Grade 4 events 1%. The more common treatment-related \geq Grade 2 AEs were reported under the MedDRA SOCs of Investigations (FTC/TDF 70 [6%], placebo 81 [7%]), Gastrointestinal Disorders (FTC/TDF 48 [4%], placebo 40 [3%]), Nervous System Disorders (FTC/TDF 26 [2%], placebo 16 [1%]), Metabolism and Nutrition Disorders (FTC/TDF 27 [2%], placebo 14 [1%]), and Psychiatric Disorders (FTC/TDF 10 [1%], placebo 17 [1%]).

Treatment-related clinical AEs were reported in 152 subjects (FTC/TDF 87 [7%], placebo 65 [5%]). All treatment-related clinical AEs were at least DAIDS Grade 2 in severity, with only seven (<1%) subjects total experiencing Grade 3 or 4 treatment-related clinical AEs (FTC/TDF 3, placebo 4).

Treatment-related laboratory AEs were reported in 206 subjects (FTC/TDF 111 [9%], placebo 95 [8%]). Most treatment-related laboratory AEs were Grade 2, with 28 subjects experiencing Grade 3 or 4 treatment-related laboratory events (Grade 3: FTC/TDF 14 [1%], placebo 11 [1%]; Grade 4: TDF/FTC 0, placebo 3 [<1%]).

The most common treatment-related AE \geq DAIDS Grade 2 by MedDRA PT was hypophosphatemia, with equal proportions in the two treatment groups (FTC/TDF 27 [2%], placebo 29 [2%]). However, when this PT was pooled with the second most common treatment-related \geq Grade 2 AE, “blood phosphorus decreased”, low serum phosphorus as a treatment-related AE was reported slightly more frequently in the FTC/TDF group (FTC/TDF 53 [4%], placebo 42 [3%]). Ninety percent of these low serum phosphorus events were Grade 2, while the remaining 10% were Grade 3. Other treatment-related AEs that occurred more frequently in the FTC/TDF group compared with the placebo group were headache and migraine and several gastrointestinal disorders (e.g. diarrhea, nausea, gastroenteritis). The MedDRA PTs of “blood creatinine increased” and “bone density decreased” were reported in two subjects each in the FTC/TDF group compared to one subject each in the placebo group. On the other hand, “proteinuria” was reported in four subjects in the placebo group compared with two

subjects in the FTC/TDF group. For each of these treatment-related AEs of interest, the absolute numbers were too small to make reliable comparisons. In general, the event rates for \geq Grade 2 treatment-related AEs were comparable between the two treatment groups. Table 26 lists the treatment-related \geq DAIDS Grade 2 AEs by MedDRA PT occurring in more than 1 subject per treatment group.

Table 26: Treatment-Emergent Treatment-Related Adverse Events \geq DAIDS Grade 2 Reported in More Than One Subject in Either Treatment Group (CO-US-104-0288)

Preferred Term	Number of Subjects (%)		
	FTC/TDF (N=1251)	Placebo (N=1248)	Total (N=2499)
Any Grade 2-4 AE	188 (15)	144 (12)	332 (13)
Blood phosphorus decreased	27 (2)	29 (2)	56 (2)
Hypophosphatemia	26 (2)	13 (1)	39 (2)
Headache	14 (1)	10 (1)	24 (1)
Blood bilirubin increased	9 (1)	14 (1)	23 (1)
Abdominal pain upper	12 (1)	10 (1)	22 (1)
ALT increased	10 (1)	10 (1)	20 (1)
AST increased	8 (1)	11 (1)	19 (1)
Diarrhea	10 (1)	4 (<1)	14 (1)
Nausea	8 (1)	4 (<1)	12 (1)
Flatulence	5 (<1)	6 (1)	11 (<1)
Gastritis	5 (<1)	6 (1)	11 (<1)
Blood glucose increased	3 (<1)	8 (1)	11 (<1)
Depression	4 (<1)	4 (<1)	8 (<1)
Blood amylase increased	3 (<1)	4 (<1)	7 (<1)
Dyspepsia	3 (<1)	4 (<1)	7 (<1)
Proteinuria	2 (<1)	4 (<1)	6 (<1)
Dizziness	4 (<1)	0	4 (<1)
Migraine	3 (<1)	1 (<1)	4 (<1)
Blood glucose decreased	2 (<1)	2 (<1)	4 (<1)
Insomnia	2 (<1)	2 (<1)	4 (<1)
Neutropenia	1 (<1)	3 (<1)	4 (<1)
Abdominal pain	0	4 (<1)	4 (<1)
Anxiety	0	4 (<1)	4 (<1)
Gastroenteritis	3 (<1)	0	3 (<1)
Blood creatinine increased	2 (<1)	1 (<1)	3 (<1)
Bone density decreased	2 (<1)	1 (<1)	3 (<1)
Fatigue	2 (<1)	1 (<1)	3 (<1)
Myalgia	2 (<1)	1 (<1)	3 (<1)
Arthralgia	1 (<1)	2 (<1)	3 (<1)
Major depression	0	3 (<1)	3 (<1)
Back pain	2 (<1)	0	2 (<1)

Hypersensitivity	2 (<1)	0	2 (<1)
Hypersomnia	2 (<1)	0	2 (<1)
Rash maculopapular	2 (<1)	0	2 (<1)
Urticaria	2 (<1)	0	2 (<1)

Abbreviations: ALT = alanine aminotransferase; AST = aspartate aminotransferase

Source: StudyCO-US-104-0288 DERAЕ dataset

Treatment-related DAIDS Grade 3 or 4 AEs were reported in 34 (1%) subjects with an even distribution between the two treatment groups. Seven of these subjects had treatment-related clinical AEs (FTC/TDF 3, placebo 4), while 28 had treatment-related laboratory AEs (14 in each treatment group). Grade 3 AEs were reported in a slightly higher proportion of subjects in the FTC/TDF group compared with the placebo group, but the difference was small (FTC/TDF 16 [1%], placebo 13 [1%]). These Grade 3 AEs tended to be laboratory toxicities. Grade 4 AEs were reported in five subjects in the placebo group (two subjects with ALT increase, two subjects with major depression, and one subject with neutropenia) compared to one subject in the FTC/TDF group (suicide attempt in Subject 9635309). Overall, given the small numbers of individual events, there was no apparent trend between the two treatment groups with respect to the nature or frequency of severe or life-threatening treatment-related AEs. Table 27 lists the DAIDS Grade 3 and 4 treatment-related AEs that were reported in more than 1 subject in either treatment group.

Table 27: Treatment-Emergent Treatment-Related Adverse Events ≥ DAIDS Grade 3 in More Than One Subject in Either Treatment Group (CO-US-104-0288)

DAIDS Grade	Preferred Term	Number of Subjects (%)		
		FTC/TDF (N=1251)	Placebo (N=1248)	Total (N=2499)
Any Grade 3 or 4 AE		17 (1)	17 (1)	34 (1)
Grade 3	Any Grade 3 AE	16 (1)	13 (1)	29 (1)
	AST increased	3 (<1)	5 (<1)	8 (<1)
	ALT increased	3 (<1)	3 (<1)	6 (<1)
	Blood phosphorus decreased	3 (<1)	3 (<1)	6 (<1)
	Hypophosphatemia	4 (<1)	1 (<1)	5 (<1)
Grade 4	Any Grade 4 AE	1 (<1)	5 (<1)	6 (<1)
	ALT increased	0	2 (<1)	2 (<1)
	Major depression	0	2 (<1)	2 (<1)
	Neutropenia	0	1 (<1)	1 (<1)
	Suicide attempt	1 (<1)	0	1 (<1)

Abbreviations: ALT = alanine aminotransferase; AST = aspartate aminotransferase

Source: StudyCO-US-104-0288 DERAЕ dataset

Partners PrEP

A total of 3,820 treatment-emergent, treatment-related AEs (defined by the investigator as possibly, probably, or definitely related to study drug) were reported in 1,068 partner subjects with similar percentages across treatment groups (TDF 532 [34%], FTC/TDF 566 [36%], placebo 510 [32%]). Half of these treatment-related AEs were DAIDS Grade 1 and the vast majority (98%) consisted of laboratory toxicities, with comparable distribution among the three treatment groups. Thirty-eight (38) partner subjects had 49 treatment-related AEs that were considered serious (TDF 8 [1%], FTC/TDF 16 [1%], placebo 14 [1%]). Again, most SAEs were laboratory toxicities. All SAEs, however, were also assessed for causality by the safety monitor and of the 49 SAEs considered to be treatment-related by the site investigators, only two were considered possibly related by the safety monitor: one event each of Grade 4 increased AST and Grade 4 increased ALT in one placebo subject (Subject 5523314).

Of the AEs considered treatment-related by the site investigators, DAIDS Grade 2-4 AEs were reported in 1,037 (22%) partner subjects, with a slightly higher proportion in the FTC/TDF group (TDF 320 [20%], FTC/TDF 379 [24%], placebo 338 [21%]). Three-fourths of the ≥ Grade 2 events were Grade 2. Of the remaining Grade 3-4 treatment-related AEs, there was again a small difference between the FTC/TDF group and the other two groups (TDF 104 [7%], FTC/TDF 122 [8%], placebo 107 [7%]).

As with iPrEx, all treatment-related clinical AEs were at least DAIDS Grade 2, with only six partner subjects total reporting a Grade 3-4 treatment-related clinical event (all in the placebo group). Treatment-related ≥ Grade 2 AEs that were reported in more than 1 subject in any treatment group tended to be laboratory AEs. By MedDRA PT, there were no significant differences among the treatment groups with respect to the types of treatment-related ≥ DAIDS Grade 2 events reported. As in iPrEx, the most commonly reported ≥ Grade 2 treatment-related AE by MedDRA PT was hypophosphatemia, with similar percentages reported among the three treatment groups. Table 28 summarizes the ≥ DAIDS Grade 2 treatment-emergent, treatment-related AEs (as defined by the site investigators) that were reported in more than 1 subject in any treatment group.

Table 28: Treatment-Emergent Treatment-Related (as Defined by Site Investigators) Adverse Events ≥ DAIDS Grade 2 in More Than One Subject in Any Treatment Group (CO-US-104-0380)

Preferred Term	Number of Subjects (%)			
	TDF (N=1584)	FTC/TDF (N=1579)	Placebo (N=1584)	Total (N=4747)
Any Grade 2-4 AE	320 (20)	379 (24)	338 (21)	1037 (22)
Blood phosphorus decreased	179 (11)	218 (14)	202 (13)	599 (13)
Neutrophil count decreased	93 (6)	124 (8)	98 (6)	315 (7)
Platelet count decreased	33 (2)	34 (2)	31 (2)	98 (2)
Hemoglobin decreased	30 (2)	33 (2)	30 (2)	93 (2)
Blood bicarbonate decreased	20 (1)	17 (1)	15 (1)	52 (1)

AST increased	13 (1)	13 (1)	15 (1)	41 (1)
ALT increased	9 (1)	6 (<1)	8 (1)	23 (1)
Proteinuria	6 (<1)	10 (1)	7 (<1)	23 (1)
Blood bilirubin increased	4 (<1)	4 (<1)	4 (<1)	12 (<1)
White blood cell count decreased	2 (<1)	3 (<1)	4 (<1)	9 (<1)
Diarrhea	3 (<1)	3 (<1)	2 (<1)	8 (<1)
Blood creatinine increased	3 (<1)	0	5 (<1)	8 (<1)
Gastroenteritis	2 (<1)	2 (<1)	0	4 (<1)
Abdominal pain	0	2 (<1)	1 (<1)	3 (<1)
Abdominal pain upper	2 (<1)	0	1 (<1)	3 (<1)
Asthenia	2 (<1)	1 (<1)	0	3 (<1)
Respiratory tract infection	2 (<1)	1 (<1)	0	3 (<1)
Glycosuria	1 (<1)	0	2 (<1)	3 (<1)
Hypertension	0	0	3 (<1)	3 (<1)
Fatigue	2 (<1)	0	0	2 (<1)
Malaria	0	0	2 (<1)	2 (<1)

Abbreviations: ALT = alanine aminotransferase; AST = aspartate aminotransferase

Source: Study CO-US-104-0380 ADAE dataset

When the analysis of common treatment-related AEs was limited to DAIDS Grade 3-4 events, the results were similar to those found in Table 28, with the same types of AEs in the same descending order of frequency but with lower rates. The main difference was that all DAIDS Grade 3-4 AEs in more than 1 subject in any treatment group were in the Investigations SOC (i.e., laboratory toxicities).

7.3.5 Submission Specific Primary Safety Concerns

This section summarizes adverse events of interest related to the use of FTC/TDF, with specific reference to bone and renal safety and hepatic flares in subjects with HBV infection.

Renal

No events of Fanconi syndrome were reported in either the iPrEx or Partners PrEP trials. There were, however, a small number of cases that were possibly suggestive of proximal renal tubulopathy, as determined by the presence of concurrent proteinuria, glycosuria, and hypophosphatemia. In the iPrEx trial, there were seven such cases (FTC/TDF 5, placebo 2) and in the Partners PrEP trial there were five cases (TDF 2, FTC/TDF 1, placebo 2). The small number of cases, however, precludes definitive conclusions. See Section 7.4.2 for further discussion of these cases.

In the iPrEx trial, the rates of treatment-emergent AEs of the Renal and Urinary Disorders SOC were equal between treatment groups (FTC/TDF 73 [6%], placebo 73 [6%]). None of these AEs was serious and all were Grade 1 or 2, except for four AEs in

the placebo group that were Grade 3 (two AEs of renal colic in one subject, one AE of hematuria, and one AE of ureteral calculus). There were 55 AEs of increased serum creatinine, of any grade and causality, reported in 50 subjects (FTC/TDF 29 [2%], placebo 21[2%]). Median age for these subjects was 29 years (IQR 23-38 years) and median time to onset was 25 weeks (IQR 12-68 weeks). Roughly a quarter of these events were serious, with equal distribution between the groups, but 90% were Grade 1. Treatment-emergent Grade 2 increased creatinine was only reported in five subjects (FTC/TDF 3, placebo 2). As noted in Section 7.3.3, increased creatinine led to permanent study drug discontinuation in only one subject (Subject 8831412 in the FTC/TDF group).

In the Partners PrEP trial, treatment-emergent AEs of the Renal and Urinary Disorders SOC were equal among treatment groups (TDF 61 [4%], FTC/TDF 60 [4%], placebo 68 [4%]). None of these AEs was serious and all were Grade 1 or 2, except for three AEs that were Grade 3: glycosuria in one placebo subject, urinary retention in one FTC/TDF subject, and proteinuria in one TDF subject, none of which was considered treatment-related. Treatment-emergent AEs associated with increased serum creatinine levels, of any grade or causality, were reported in 251 partner subjects, with similar rates across treatment groups: TDF 73 (5%), FTC/TDF 100 (6%), and placebo 78 (5%). None of the creatinine increases was serious and most were not confirmed upon repeat testing. Confirmed increases were reported for 51 (1%) subjects: TDF 19, FTC/TDF 20, and placebo 12. None of the confirmed events was ≥ DAIDS Grade 2 and most (89%) were Grade 1. Median (Q1, Q3) time to onset was 25 weeks (9, 81). Of note, the study protocol defined any increase in creatinine of more than 50% over baseline, even when within normal limits, as at least a Grade 1 AE. Thus, a number of the Grade 1 creatinine increase events were 50% increases over baseline, but were still within normal limits. As noted in Section 7.3.3, five female partner subjects discontinued study drug for decreased creatinine clearance <50 mL/min and one male subject discontinued for a Grade 1 serum creatinine increase AE.

In Table 29, laboratory abnormalities for increased serum creatinine and decreased serum phosphorus are displayed for the two pivotal trials, as well as for Study CDC 4323. Because the individual trials used different toxicity grading schemes, cross-trial comparisons are not always obvious, but the trends show no significant differences between the active and placebo groups throughout.

Table 29: Graded Serum Creatinine and Serum Phosphorus Laboratory Abnormalities across Clinical Trials (Studies CO-US-104-0288, -0380, -0277)

Toxicity Grade	Number of Subjects (%)						
	CDC 4323 ^a		iPrEx ^b		Partners PrEP ^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							
Grade 1	4 (2)	6 (3)	10 (1)	7 (1)	3 (<1)	6 (<1)	4 (<1)

Grade 2	1 (1)	2 (1)	1 (<1)	1 (<1)	1 (<1)	0	0
Grade 3	0	0	0	0	0	0	0
Grade 4	0	0	0	0	0	0	0
Low serum phosphorus							
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) Toxicity grading for serum creatinine in CDC 4323 used Gilead Sciences, Inc grading scheme (see below), with addition that any value ≥ 0.5 over baseline was Grade 1. For serum phosphorus, toxicity grading used DAIDS AE Grading Table 2004
- b) Gilead Sciences, Inc. (GSI) serum creatinine grading scheme: Grade 0 ≤ 1.5 mg/dL, Grade 1 = 1.5 mg/dL to 2 mg/dL, Grade 2 = 2 mg/dL to 3 mg/dL, Grade 3 = 3 mg/dL to 6 mg/dL, and Grade 4 ≥ 6 mg/dL. GSI phosphorus grading scheme: Grade 1 = lower limit of normal range (LLN) to 2.0 mg/dL, Grade 2 = 2.0 mg/dL to 1.5 mg/dL, Grade 3 = 1.5 mg/dL to 1.0 mg/dL, and Grade 4 ≤ 1.0 mg/dL

Source: Study CO-US-104-0288 DERLAB dataset, Study CO-US-104-0380 ADSAFETY dataset, Study CO-US-104-0277 ACRCCL dataset

Comparison of urinalysis data from the iPrEx and Partners PrEP trials did not reveal any significant differences between the active and placebo groups in terms of recurrent proteinuria, or proteinuria associated with glycosuria or increased creatinine (Table 30). Review of the urinalysis data from the CDC 4323 trial revealed similar trends. Most findings of proteinuria or glycosuria were isolated and were trace or 1+ on dipstick. In the iPrEx trial, the one subject who permanently discontinued FTC/TDF due to a Grade 1 increase in serum creatinine also had evidence of trace proteinuria on more than one occasion. The proteinuria was still evident in conjunction with increased creatinine post-discontinuation of FTC/TDF (see Section 7.3.3). Also in the iPrEx trial, five of the six subjects in the FTC/TDF group with concurrent proteinuria and glycosuria also had evidence of graded hypophosphatemia during follow-up. In these cases, the urine abnormalities were either trace or 1+ and typically preceded or were reported in conjunction with the onset of graded hypophosphatemia. Further, two of these five subjects also had evidence of BMD loss $>5\%$ from baseline on DEXA scans obtained either on treatment or post-treatment. The urinalysis data is discussed further in Section 7.4.2.

Table 30: Comparison of Urinalysis Abnormalities between Pivotal Trials (Studies CO-US-104-0288 and -0380)

Urinalysis Abnormalities	Number of Subjects (%)				
	iPrEx		Partners PrEP		
	FTC/TDF (N=1171)	Placebo (N=1190)	TDF (N=1577)	FTC/TDF (N=1571)	Placebo (N=1574)
Recurrent proteinuria	92 (8)	69 (6)	15 (1)	16 (1)	20 (1)
➤ and graded creatinine increase	5 *	4	0	0	0
Proteinuria with glycosuria	6 (<1)	4 (<1)	2 (<1)	2 (<1)	3 (<1)

➤ and graded low PO4	5/6	2/4	2/2	1/2	2/3
➤ and BMD loss >5%	2/5	0	N/A	N/A	N/A

Abbreviations: BMD = bone mineral density; PO4 = serum phosphorus

* Includes Subject 8831412 who permanently discontinued FTC/TDF due to increased serum creatinine

Source: Study CO-US-104-0288 DERLAB, DERBONE, and UA datasets and Study CO-US-104-0380 ADSAFETY and RENTOX datasets

Because clinicians will often report small increases in serum creatinine with TDF use that do not meet criteria for a graded elevation in a clinical trial, and that often do not appear to resolve, FDA further conducted a categorical analysis of elevated serum creatinine across the clinical trials for which laboratory data were available: iPrEx, Partners PrEP and CDC 4323. For the Partners PrEP trial, the TDF-containing groups were pooled. Also included in the analysis was the iPrEx cohort predicted to be highly adherent based on PK subgroup analysis, namely subjects who were 25 years of age or older, with secondary education or higher, and who reported URAI at baseline. A 20% increase in serum creatinine from baseline over multiple visits (more than two visits or any two consecutive visits not including unscheduled confirmatory visits) was chosen as the cut-off for the categorical analysis. Correlations between increased serum creatinine and other markers of renal tubulopathy and bone demineralization were then assessed.

As shown in Table 31, a small but consistent imbalance was observed across the three trials between the TDF-containing groups and placebo groups in the proportions of subjects with increased serum creatinine. The differences were greatest in the CDC 4323 and Partners PrEP trials. Within each trial, there was no significant difference in mean age between the treatment and placebo groups for subjects with increased creatinine. Mean increases in serum creatinine of $\geq 20\%$ from baseline were also observed at one year in both the CDC 4323 and Partners PrEP trials, but not in the iPrEx trial. The lower mean change from baseline in the iPrEx trial (9-11%) may reflect the poorer adherence in that trial, even among those subjects predicted to be more compliant with dosing, where mean change from baseline at one year was 6-14%. Where urinalysis data were available, there did not appear to be a correlation between increased serum creatinine and the incidence of proteinuria or glycosuria. Mean serum phosphorus values also did not change significantly from baseline within this cohort. Furthermore, increase creatinine did not seem to correlate with increased levels of alkaline phosphatase, nor were there significant differences between the active and placebo arms with respect to alkaline phosphatase increases regardless of creatinine elevation. Note that these are exploratory analyses and the sample sizes may be too small to detect differences.

Table 31: Categorical Analysis of Serum Creatinine Increase ≥ 20% from Baseline and Associated Laboratory Findings across Clinical Trials (Studies CO-US-104-0288, -0380, -0277)

	Number of Subjects [%N] (%n)							
	CDC 4323		iPrEx		iPrEx "high adherent" ^a		Partners PrEP	
	TDF (N=184)	Placebo (N=186)	FTC/TDF (N=1225)	Placebo (N=1226)	FTC/TDF (N=317)	Placebo (N=287)	TDF groups (N=3145)	Placebo (N=1573)
Creatinine ≥ 20% increase from baseline ^b	n=18 [10]	n=13 [7]	n=136 [11]	n=114 [9]	n=30 [9]	n=21 [7]	n=420 [13]	n=138 [9]
Mean Age (years) ^c	40	39	27	27	32	35	38	36
➤ and any graded low PO4	5 (27) [3]	5 (38) [3]	24 (18) [2]	16 (14) [1]	5 (17) [2]	3 (14) [1]	108 (25) [3]	40 (29) [3]
➤ and any graded low CO2	1 (6) [1]	3 (23) [2]	20 (15) [2]	12 (11) [1]	5 (17) [2]	5 (24) [2]	2 (<1) [<1]	0
➤ and any proteinuria ≥ 1+	1 (6) [2]	2 (15) [1]	19 (9) [2]	15 (13) [1]	5 (17) [2]	2 (10) [1]	12 (3) [<1]	4 (3) [<1]
➤ and any glycosuria ≥ 1+	2 (11) [1]	0	3 (2) [<1]	3 (3) [<1]	0	0	3(<1) [<1]	0
➤ and any ≥ 20% increase in alkaline phosphatase	11 (61) [6]	7 (54) [4]	6 (4) [1]	4 (4) [<1]	4 (13) [1]	1 (5) [<1]	N/A	N/A

Abbreviations: CO2 = serum bicarbonate; PO4 = serum phosphorus; N/A = not available

a) The iPrEx high adherent cohort is defined by presence of URAI at baseline, age 25 years or older, and secondary education or higher

b) Creatinine ≥ 20% increase from baseline on more than two visits or on any two consecutive visits excluding unscheduled confirmatory visits.

c) In Study CDC 4323, overall mean age for the TDF and placebo groups was 39 and 37 years old, respectively.

Bone

In the iPrEx trial, a total of 38 subjects reported bone fractures (FTC/TDF 21 [2%], placebo 17 [1%]). The bone fractures were generally reported to be traumatic in nature (e.g., motor vehicle accident, injuries from physical activities) and did not appear to be pathologic. Fractures typically occurred in the extremities and were consistent with traumatic injury. No evidence of impaired or delayed fracture healing was apparent when post-fracture follow-up information was available. Among subjects with bone fractures, only two had toxicity-emergent, confirmed graded hypophosphatemia by either the DAIDS or GSI toxicity schemes (FTC/TDF 1, placebo 1); the subject in the FTC/TDF group (Subject 9534020) with hypophosphatemia had traumatic wrist and radial fractures. Back pain was reported by 5% of subjects in this trial, with equal distribution between the two groups. Back pain did not appear to correlate with graded hypophosphatemia. Bone pain was only reported by one subject (in the placebo group).

In the Partners PrEP trial, 32 subjects had 35 bone fractures (TDF 10, FTC/TDF 9, placebo 13); none were considered drug related or pathological and 34/35 of the fractures were trauma-related (a left tibia fibula fracture in a placebo subject is missing additional information). There were 11 fractures of upper extremities, including 1 wrist fracture (Colles' fracture) in a FTC/TDF subject, but all were trauma-related. None of these 32 subjects had any graded serum chemistry abnormalities reported. Back pain was uncommon in this trial, reported by only 14 subjects (<1%), and bone pain was limited to one subject in the FTC/TDF group (Grade 2). Neither back nor bone pain appeared to correlate with serum chemistry abnormalities.

In the CDC 4323 trial, 14 subjects reported bone fractures (TDF 9, placebo 5). None of the bone fractures was considered drug-related. One subject in the immediate TDF group (Subject S197) had multiple vertebral fractures reported after a paragliding accident. Two additional subjects in the same group also reported wrist fractures. Bone pain as an AE was not reported in this trial.

In CDC 4323 trial, back pain was more likely among TDF recipients (TDF 27 [13%], placebo 14 [7%]). Nine subjects with back pain also had hypophosphatemia (TDF 8, placebo 1). The hypophosphatemia in these cases was \geq DAIDS Grade 2, although only one subject (in the TDF group) had Grade 3 low serum phosphorus. New onset back pain was reported by 18 (9%) subjects in the TDF group compared with 10 (5%) subjects in the placebo group. None of the cases of new onset back pain was associated with vertebral fractures. Back pain and bone fracture (hand fracture) together were only reported in one subject (Subject 198). FDA review of the cases of new onset back pain showed no differences in terms of mean change in serum creatinine, serum phosphorus, alkaline phosphatase, or BMD from baseline between the treatment groups (Table 32). FDA also looked at adverse events in the Musculoskeletal and Connective Tissue SOC and did not find an imbalance between the TDF and placebo groups.

Table 32: Treatment-Emergent New Onset Back Pain (CO-US-104-0277)

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 % change in serum creatinine	-3%	0.2%
Mean % change in serum phosphorus	2%	5%
Mean % change in 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)

Abbreviations: BMD = bone mineral density

Source: Study CO-US-104-0277 AE dataset

BMD data were available from the iPrEx and CDC 4323 trials in MSM. In the iPrEx trial, 503 subjects were enrolled in the DEXA substudy, of which approximately half were between the ages of 18 and 24 years old and thus considered likely to still be accruing bone mass. Excluding DEXA scans obtained after seroconversion, mean BMD tended to increase in the placebo group and decrease in the FTC/TDF group during treatment. Small (> -1.2%), but statistically significant, greater mean percentage decreases in BMD from baseline were noted in the FTC/TDF group compared with the placebo group for total hip at Weeks 24 and 48 ($p < 0.001$) and for spine at Weeks 24 and 72 ($p < 0.05$). Decreases >5% from baseline in BMD of the spine were observed in 13% of subjects in the FTC/TDF group compared with 6% in the placebo group (Table 33). Among all subjects with >5% decrease from baseline in BMD at the spine, five subjects (all in the FTC/TDF group) also had evidence of treatment-emergent graded hypophosphatemia. Moreover, three subjects (again, all in the FTC/TDF group) had >5% decrease in BMD at both spine and total hip during treatment.

Table 33: Categorical Analysis of Treatment-Emergent Bone Mineral Density Loss Compared to Baseline (Any Post-baseline Scan on Treatment) – DEXA Substudy (CO-US-104-0288)

Bone Mineral Density Changes	Number of Subjects (%)		
	FTC/TDF (N=247)	Placebo (N=256)	Total (N=503)
Age (mean)	30	29	29
SPINE			
> 5% decrease from baseline	31 (13)	14 (6)	45 (9)
• Hypophosphatemia AE	5 (2) ^a	0	5 (1)
• Graded low serum phosphorus	5 (2) ^a	1 (<1)	6 (1)
• Low back pain	2 (1) ^b	0	
> 5% decrease from baseline and T-score < -2	9 (4)	6 (2)	15 (3)
> 5% decrease from baseline and Z-score < -2	8 (3)	4 (2)	12 (2)
Marked change in BMD ^d	7 (3)	4 (2)	11 (2)
Low back pain	1 (<1)	0	1 (<1)

TOTAL HIP			
> 7% decrease from baseline	1 (<1) ^c	0	1 (<1)
> 5% decrease from baseline and T-score < -2	0	1 (<1)	1 (<1)
> 5% decrease from baseline and Z-score < -2	0	1 (<1)	1 (<1)
Marked change in BMD ^d	0	0	0
SPINE and TOTAL HIP			
> 5% decrease from baseline	3 (1) ^e	0	3 (1)

Abbreviations: BMD = bone mineral density

a) Five FTC/TDF subjects with hypophosphatemia: 9433008, 9437050, 9635161, 9635246, 9736022

b) Two FTC/TDF subjects with low back pain: 9123077, 9150618

c) Subject 9022583

d) Marked change defined as >5% BMD loss on consecutive scans

e) Three FTC/TDF subjects with >5% BMD loss at spine and total hip: 9123840, 9150856, 9736520

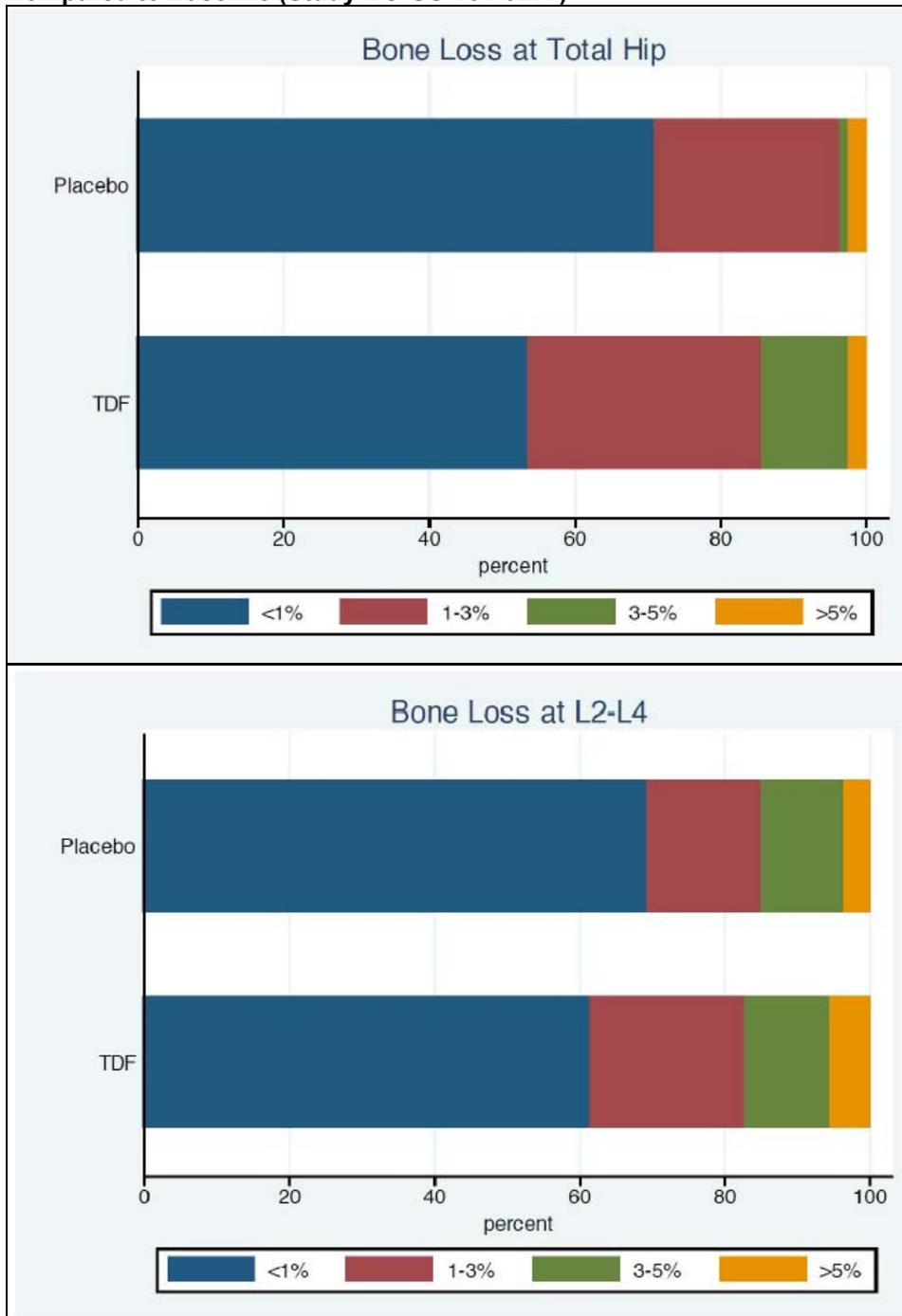
Source: Study CO-US-104-0288 DERBONE dataset

Among the 353 subjects in the iPrEx substudy who had DEXA scans obtained 6 months after study drug discontinuation, the BMD decreases observed during treatment in the FTC/TDF group appeared to be reversing towards baseline levels. In general, no notable trends were observed between BMD changes and reports of new onset back pain, bone fractures, or laboratory findings of renal dysfunction. Levels of Vitamin D or parathyroid hormone were not evaluated as part of this trial.

BMD data from the CDC 4323 trial, which overall reported higher drug exposures based on MEMS data, corroborated the BMD loss observed with FTC/TDF in the iPrEx trial. Of note, in the CDC 4323 DEXA substudy, low baseline BMD (Z score ≤ -2.0) was observed more frequently than expected among the enrolled MSM subjects (N=184).³⁸ Baseline demographic factors that correlated with low BMD at baseline included use of amphetamines or inhalants. An inverse correlation was found with intake of Vitamin D or multivitamins. Nonetheless, at the end of treatment (Month 24), a greater proportion of subjects in the TDF group had $\geq 3\%$ BMD loss compared to baseline at both the total hip and lumbar spine than did subjects in the placebo group. At Month 24, 14% of TDF subjects enrolled in the DEXA substudy had $\geq 3\%$ BMD loss at the total hip compared with 3% in the placebo group; 17% had $\geq 3\%$ BMD loss at L2-L4 spine compared with 15% in the placebo group. If a cut-off $\geq 1\%$ BMD loss is used instead, the differences between the TDF and placebo group are greater (Figure 10).

³⁸ Liu AY, Vittinghoff E, Sellmeyer DE, et al. Bone mineral density in HIV-negative men participating in a tenofovir pre-exposure prophylaxis randomized clinical study in San Francisco. PLoS One 2011; 6(8):e23688.

Figure 10: Categorical Analysis of Bone Mineral Density Loss at End of Treatment (24 Months) Compared to Baseline (Study CO-US-104-0277)



Source: NDA 21-752/S-30 Integrated Summary of Safety

BMD data from the CDC TDF2 study in heterosexual adult men and women in Botswana confirm the bone safety trends noted in the iPrEx and CDC 4323 trials.³⁹ Among 221 participants enrolled into the bone densitometry sub-study, there were minimal but statistically significant declines in BMD T scores and Z scores at the forearm, hip, and lumbar spine in participants receiving TDF-FTC compared with placebo (P=0.004 for forearm and P<0.001 for hip and lumbar spine). Five participants in the TDF-FTC group and four in the placebo group experienced a bone fracture during study participation (P=0.69).

When the results of the FDA categorical analysis of elevated serum creatinine are applied to the DEXA findings of CDC 4323, it appears that about half of subjects in the CDC 4323 trial with creatinine increases also had elevations in alkaline phosphatase (Table 31). This finding was not observed in the iPrEx trial, and may have been related to the younger mean age of iPrEx participants or other factors. Similar elevations in alkaline phosphatase, however, were also observed among subjects without increased creatinine.

Nonetheless, among subjects with increased creatinine, there was a two-fold difference between the TDF and placebo groups in the percentage of subjects with ≥3% BMD loss at either the hip or lumbar spine (Table 34). This was in contrast to subjects without creatinine increases, where the percentages were 57% vs. 45% for TDF and placebo, respectively. For all subjects with BMD loss, with or without increased creatinine, elevations in alkaline phosphate were seen more frequently with TDF than placebo. No difference was observed between the treatment groups in use of concomitant medications, such as non-steroidal anti-inflammatory agents or acyclovir.

³⁹ Thigpen MC, Kebaabetswe PM, Paxton LA, et al. Antiretroviral preexposure prophylaxis for heterosexual HIV transmission in Botswana. *N Engl J Med* 2012. DOI:10.1056/NEJMoa1110711

Table 34: Categorical Analysis of Serum Creatinine Elevation and Bone Mineral Density Loss at End of Treatment Compared to Baseline (Study CO-US-104-0277)

Subjects with Post-baseline Creatinine Measurements	TDF (N=184)	Placebo (N=186)
Creatinine \geq 20% \uparrow from Baseline (N), in DEXA substudy (n)	n/N=13/18	n/N=8/13
➤ And \geq 3% BMD loss from baseline in Total Hip or Lumbar Spine	10/13 (77%)	3/8 (37%)
○ With any \geq 20% \uparrow alkaline phosphatase	9/10 (90%)	2/3 (67%)
Creatinine $<$ 20% \uparrow from Baseline (N), in DEXA substudy (n)	n/N=81/166	n/N=84/173
➤ And \geq 3% BMD loss from baseline in Total Hip or Lumbar Spine	46/81 (57%)	38/84 (45%)
○ With any \geq 20% \uparrow alkaline phosphatase	40/46 (87%)	13/38 (34%)

It is important to remember that these findings are based on an exploratory analysis with a very small number of subjects; therefore, the strength of any association or clinical relevance is not certain.

Hepatitis B Virus Infection

A secondary objective of the iPrEx trial was to determine if hepatic viral flares occurred in subjects who were hepatitis B surface antigen positive (HBsAg+) during and after FTC/TDF chemoprophylaxis. A hepatic flare was defined as an increase in AST or ALT to $>5 \times$ ULN at any visit, or an increase to $>2.5 \times$ ULN for 3 months, within 24 weeks of permanently stopping study drug. Subjects who were HBsAg+ were tested for elevated transaminases if they had signs or symptoms of hepatitis during the trial. HBsAg+ subjects who discontinued study drug were asked to return for a medical history and liver function tests at 4, 8, 12, 16, 20, and 24 weeks after study drug was stopped. Liver function data for HBsAg+ subjects were collected through September 2011.

In the iPrEx trial, there were only 16 HBsAg+ subjects: 12 had chronic infection (six in each group) and four had acute infection (two in each group). After stopping study drug, 11 subjects with chronic infection had liver function tests performed at one or more post-discontinuation visits (from 1 to 7 visits). Liver function testing remained within normal limits at all post-discontinuation visits for ten subjects, with no evidence of hepatic flares. In one subject (Subject 9219978), Grade 1 liver function test elevations were seen at the post-discontinuation Week 12 visit, with AST of 61 U/L (ULN = 41 U/L) and ALT of 90 U/L (ULN = 38 U/L), and at the post-discontinuation Week 20 visit, with AST of 37 U/L and ALT of 60 U/L. This subject had off-protocol testing done at post-discontinuation Week 24 with AST of 41 U/L and ALT of 52 U/L. These elevations did

not meet protocol criteria for hepatic flares. Post-discontinuation testing was not available in one subject who had moved away (Subject 9117332). All subjects with chronic hepatitis B infection tested negative for hepatitis C antibodies.

Among the four subjects in the iPrEx trial diagnosed with acute hepatitis B infection, two had evidence of acute HBV infection at enrollment. Three resolved to immunity. The fourth subject (Subject 9015834) was non-compliant with study visits and missed visits between Weeks 4 and 68. He was noted to be HBsAg+, anti-HBc+, and anti-HBc IgM+ at Week 68, with normal liver function tests; this subject had no further follow-up due to the subject's time constraints.

Among the three HBsAg+ partner subjects inadvertently randomized to study drug in the Partners PrEP trial (see Section 6.1.3), there was no evidence of hepatic flares after removal of study drug, based on monthly monitoring of liver function tests for two months after cessation of study drug.

In sum, no evidence of hepatic flares was observed among the 19 study subjects with chronic or acute HBV infection followed in the two pivotal trials.

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

iPrEx

In the iPrEx trial, 80% of randomized subjects reported a treatment-emergent AE during follow-up. Clinical AEs were reported in 72% of subjects and laboratory AEs were reported in 37%. Table 35 provides a high-level overview of the AEs reported in this trial by treatment group and for the trial as a whole. As shown in the table, AE rates were comparable between the two groups for most major categories.

Table 35: Overall Summary of Treatment-Emergent Adverse Events (CO-US-104-0288)

Adverse Events	Number of Subjects (%)		
	FTC/TDF (N=1251)	Placebo (N=1248)	Total (N=2499)
Any AE	987 (80)	1016 (81)	2003 (80)
Any clinical AE	884 (71)	904 (72)	1788 (72)
Treatment-related clinical AEs	87 (7)	65 (5)	152 (6)
Treatment-related clinical AEs Grade 3,4	3 (<1)	4 (<1)	7 (<1)
Treatment-related clinical AEs that led to permanent discontinuation of study drug	41 (3)	42 (3)	83 (3)
Any laboratory AE	469 (37)	464 (37)	933 (37)

Treatment-related laboratory AEs	111 (9)	95 (8)	206 (8)
Treatment-related laboratory AEs Grade 3,4	14 (1)	14 (1)	28 (1)
Laboratory AEs that led to permanent discontinuation of study drug	7 (1)	7 (1)	14 (1)
Treatment-related laboratory AEs that led to permanent discontinuation of study drug	3 (<1)	3 (<1)	6 (<1)
Any SAE	83 (7)	82 (7)	165 (7)
Any clinical SAE	70 (6)	68 (5)	138 (6)
Treatment-related clinical SAEs	1 (<1)	1 (<1)	2 (<1)
Any laboratory SAE	19 (2)	18 (1)	37 (1)
Treatment-related laboratory SAEs	4 (<1)	5 (<1)	9 (<1)
Deaths	2 (<1)	7 (1)	9 (<1)

Abbreviations: AE = adverse event; SAE = serious adverse event
Source: Study CO-US-104-0288 DERAE dataset

The most commonly reported AEs in the iPrEx trial were under the following SOCs: Infections and Infestations, Investigations, Gastrointestinal Disorders, Psychiatric Disorders, and Injury, Poisoning and Procedural Complications. The rates of commonly reported AEs were generally comparable between the FTC/TDF and placebo groups.

Treatment-emergent clinical AEs that occurred at a frequency $\geq 2\%$ and that had a higher rate of reporting in the FTC/TDF group than in the placebo group were syphilis and secondary syphilis (each FTC/TDF 5%, placebo 4%); abdominal pain (FTC/TDF 4%, placebo 2%); tinea cruris and gastroenteritis (FTC/TDF 3%, placebo 2%); weight decreased (FTC/TDF 3%, placebo 1%); and fungal skin infection, cellulitis, gastrointestinal infection, tinea pedis, nausea, dyspepsia, and insomnia (each FTC/TDF 2%, placebo 1%). Using the iPrEx team-defined evaluation windows (i.e., all treatment-emergent events through the November 21, 2010 cut-off date, regardless of whether study drug had been discontinued for > 30 days), the following AEs were noted to occur at a statically significant higher frequency within the FTC/TDF group compared with the placebo group: abdominal pain (47 subjects FTC/TDF, 25 subjects placebo; $p=0.01$) and weight decreased (34 subjects FTC/TDF, 19 subjects placebo; $p=0.04$). Table 36 tabulates the most common clinical AEs by MedDRA SOC and PT occurring in $\geq 5\%$ of subjects in either treatment group, using the Applicant's definition of treatment-emergent (i.e., AEs occurring during treatment or within 30 days of stopping study drug).

Table 36: Treatment-Emergent Adverse Events (Any Causality, Any Severity) in ≥ 5% of Subjects per Treatment Group (CO-US-104-0288)

System Organ Class	Preferred Term	Number of Subjects (%)		
		FTC/TDF (N=1251)	Placebo (N=1248)	Total (N=2499)
Any Adverse Event		987 (80)	1016 (81)	2003 (80)
Infections and Infestations		685 (55)	698 (56)	1383 (55)
	Pharyngitis	154 (12)	183 (15)	337 (14)
	Parasitic infection intestinal	126 (10)	149 (12)	275 (11)
	Nasopharyngitis	77 (6)	69 (6)	146 (6)
	Urethritis	61 (5)	82 (7)	143 (6)
	Syphilis	63 (5)	53 (4)	116 (5)
	Secondary syphilis	65 (5)	49 (4)	114 (5)
Investigations		448 (36)	439 (35)	887 (36)
	ALT Increased	98 (8)	110 (9)	208 (8)
	Blood glucose increased	94 (8)	94 (8)	188 (8)
	Blood bilirubin increased	80 (6)	98 (8)	178 (7)
	Blood phosphorus decreased	85 (7)	69 (6)	154 (6)
	AST increased	60 (5)	73 (6)	133 (5)
Gastrointestinal Disorders		248 (20)	232 (19)	480 (19)
	Diarrhea	81 (7)	90 (7)	171 (7)
Psychiatric Disorders		151 (12)	156 (13)	307 (12)
	Depression	71 (6)	79 (6)	150 (6)
Nervous System Disorders		104 (8)	104 (8)	208 (8)
	Headache	79 (6)	74 (6)	153 (6)
Musculoskeletal and Connective Tissue Disorder		122 (10)	129 (10)	251 (10)
	Back pain	58 (5)	61 (5)	119 (5)

Abbreviations: ALT = alanine aminotransferase; AST = aspartate aminotransferase

Source: Study CO-US-104-0288 DERAЕ dataset

Based on the registrational trials and postmarketing experience with FTC/TDF, AEs commonly associated with FTC/TDF include diarrhea, vomiting, nausea, flatulence, and dizziness. In the iPrEx trial, the frequency of these AEs was low in both groups, with a small but appreciable difference noted only for nausea (FTC/TDF 21 [2%], placebo 14 [1%]) and abdominal pain (FTC/TDF 45 [4%], placebo 25 [2%]). Perhaps consistent with these differences, weight decrease was also observed more frequently in the FTC/TDF group (FTC/TDF 33 [3%], placebo 18 [1%]).

According to the iPrEx investigators, skin darkening, an adverse reaction associated with FTC and described in the EMTRIVA label, was reported on monthly medical histories less frequently in the FTC/TDF group than in the placebo group (8 versus 19 subjects, respectively, p=0.03). In the submitted AE dataset, there were only two instances of AEs with preferred term “skin hyperpigmentation”, both in subjects in the FTC/TDF group (Subjects 8932098 and 9635314). If the search was broadened to include the non-specific term “dermatitis”, the number of subjects was equal between the two groups (8 subjects each). It is possible that some of these reports of skin darkening were not recorded as AEs but noted in the CRFs anyway.

Treatment-emergent laboratory AEs were reported for 469 subjects (37%) in the FTC/TDF group and 464 subjects (37%) in the placebo group. The most common laboratory AEs (occurring in ≥5% of subjects within a treatment group) are listed in Table 36, under the Investigations SOC. All remaining laboratory AEs occurred in <5% of subjects within each treatment group.

Partners PrEP

In the Partners PrEP trial, treatment-emergent AEs were reported in 84% of partner subjects, with comparable proportions among the treatment groups. Approximately half of randomized subjects had clinical AEs, while 71% had laboratory AEs. The proportion of subjects with laboratory-related AEs was slightly greater in the FTC/TDF group (74%) compared with the other two groups (70% each for TDF and placebo). Table 37 provides a high-level overview of AEs reported in this trial.

Table 37: Overall Summary of Treatment-Emergent Adverse Events (CO-US-104-0380)

Adverse Events	Number of Subjects (%)			
	TDF (N=1584)	FTC/TDF (N=1579)	Placebo (N=1584)	Total (N=4747)
Any AE	1311 (83)	1341 (85)	1321 (83)	3973 (84)
Any clinical AE	817 (52)	802 (51)	866 (55)	2485 (52)
Treatment-related clinical AEs ^a	17 (1)	22 (1)	21 (1)	60 (1)
Treatment-related clinical AEs Grade 3,4	0	1 (<1)	6 (<1)	7 (<1)
Treatment-related clinical AEs that led to permanent discontinuation of study drug	0	0	0	0
Any laboratory AE	1101 (70)	1163 (74)	1106 (70)	3370 (71)
Treatment-related laboratory AEs ^a	524 (33)	553 (35)	500 (32)	1577 (33)
Treatment-related laboratory AEs Grade 3,4	99 (6)	118 (8)	96 (6)	313 (7)
Laboratory AEs that led to permanent discontinuation of study drug	3 (<1)	2 (<1)	1 (<1)	6 (<1)

Treatment-related laboratory AEs that led to permanent discontinuation of study drug	0	0	0	0
Any SAE	104 (7)	107 (7)	104 (7)	315 (7)
Any clinical SAE	85 (5)	78 (5)	89 (6)	252 (5)
Treatment-related clinical SAEs				
as defined by site investigator	0	3 (<1)	4 (<1)	7 (<1)
as defined by safety monitor	0	0	0	0
Any laboratory SAE	19 (1)	31 (2)	17 (1)	67 (1)
Treatment-related laboratory SAEs				
as defined by site investigator	8 (1)	13 (1)	11 (1)	32 (1)
as defined by safety monitor	0	0	1 (<1)	1 (<1)
Deaths	10 (1)	8 (1)	9 (1)	27 (1)

a) Treatment-related as defined by the site investigators

Abbreviations: AE = adverse event; SAE = serious adverse event

Source: Study CO-US-104-0380 ADAE dataset

The most commonly reported AEs in the Partners PrEP trial were in the Investigations or Infections and Infestations SOCs. In contrast to the iPrEx trial, treatment-emergent diarrhea was only reported in approximately 2.5% of total subjects, with similar percentages among the three treatment groups. Nausea was only reported in one subject (FTC/TDF) and weight loss was reported in 18 (<1%) subjects total (TDF 9, FTC/TDF 3, placebo 6). The only treatment-emergent AE reported with ≥2% higher frequency in the TDF or FTC/TDF treatment group compared with the placebo group was decreased neutrophil count (TDF 38 %, FTC/TDF 44%, placebo 36%). For all other treatment-emergent AEs, the frequency rates among treatment groups were comparable. Table 38 summarizes the common treatment-emergent AEs reported in ≥5% of subjects in any treatment group.

Table 38: Treatment-Emergent Adverse Events (Any Causality, Any Severity) in ≥ 5% of Subjects per Treatment Group (CO-US-104-0380)

System Organ Class	Preferred Term	Number of Subjects (%)			
		TDF (N=1584)	FTC/TDF (N=1579)	Placebo (N=1584)	Total (N=4747)
Any Adverse Event		1315 (83)	1343 (87)	1321 (83)	3979 (84)
Investigations		1096 (69)	1160 (75)	1099 (69)	3355 (71)
	Neutrophil count decreased	595 (38)	687 (44)	572 (36)	1854 (39)
	Blood phosphorus decreased	436 (28)	459 (29)	465 (29)	1360 (29)
	Hemoglobin decreased	224 (14)	214 (14)	207 (13)	645 (14)
	Platelet count	181 (11)	187 (12)	169 (11)	537 (11)

	decreased				
	Blood bicarbonate decreased	110 (7)	112 (7)	125 (8)	347 (7)
	AST increased	93 (6)	104 (7)	96 (6)	293 (6)
	Blood creatinine increased	75 (5)	107 (7)	83 (5)	265 (6)
	ALT increased	90 (6)	87 (6)	73 (5)	250 (5)
Infections and Infestations		652 (41)	634 (40)	688 (43)	1974 (42)
	Malaria	291 (18)	273 (17)	293 (18)	857 (18)
	Upper respiratory tract infection	119 (8)	151 (10)	133 (8)	403 (9)
	Respiratory tract infection	100 (6)	85 (5)	112 (7)	297 (6)
	Urinary tract infection	102 (6)	83 (5)	98 (6)	283 (6)

Abbreviations: ALT = alanine aminotransferase; AST = aspartate aminotransferase

Source: Study CO-US-104-0380 ADAE dataset

7.4.2 Laboratory Findings

iPrEx

Laboratory safety assessments were performed at each study visit. Standard laboratory assessments included serum chemistry, hematology, and urine dipstick evaluations. A total of 2451 subjects had at least 1 post-baseline laboratory value (FTC/TDF 1225, placebo 1226).

No significant differences or trends in clinical laboratory parameters were noted between the two treatment groups, except for greater median decrease from baseline in total leukocyte count in the FTC/TDF group compared with the placebo group at most time points. Mean serum creatinine values remained close to baseline throughout the trial in both treatment groups, as did mean creatinine clearance. There were no notable trends within or between treatment groups for these renal laboratory parameters.

By DAIDS toxicity grade, there were no statistically significant differences between the two treatment groups in the frequency of emergent laboratory abnormalities of any severity grade (emergent laboratory abnormalities defined as values that represent a >1 increase in toxicity grade from baseline value). Using the protocol-specified toxicity grading scheme for creatinine elevations, a greater number of subjects in the FTC/TDF treatment group had Grade 1 or Grade 2 elevations in serum creatinine compared with the placebo group (FTC/TDF 32 [3%], placebo 23 [2%]). No Grade 3 or 4 creatinine abnormalities were observed in the FTC/TDF group, whereas one subject in the placebo group had a Grade 3 creatinine laboratory abnormality. The frequencies of

graded emergent phosphorus abnormalities (using the DAIDS toxicity grading scale) were overall similar between the two groups, with a slightly higher rate of Grade 2-3 toxicities in the FTC/TDF group compared with the placebo group (FTC/TDF 123 [10%], placebo 101 [8%]). Low platelet counts \geq Grade 2 also occurred in twice as many subjects in the FTC/TDF group as in the placebo group, but the absolute numbers were very small (FTC/TDF 6 versus placebo 3). Of note, while serum samples were collected to assess lipid profiles in participants of the DEXA substudy, these data have not been analyzed and were not submitted for review.

Table 39 lists the proportion of subjects in each treatment group with emergent laboratory abnormalities, by maximum toxicity grade (DAIDS or otherwise specified); this analysis counts all post-baseline laboratory results, including those reported beyond 30 days after study drug discontinuation.

Table 39: Emergent Laboratory Abnormalities by Maximum DAIDS Toxicity Grade (CO-US-104-0288)

Laboratory Test	Maximum DAIDS Toxicity Grade	Number of Subjects (%)		
		TDF/FTC (N=1225)	Placebo (N=1226)	Total (N=2451)
ALT (IU/L)	1	178 (15)	194 (16)	372 (15)
	2	63 (5)	61 (5)	124 (5)
	3	17 (1)	17 (1)	34 (1)
	4	4 (<1)	5 (<1)	9 (<1)
AST (IU/L)	1	175 (14)	175 (14)	350 (14)
	2	36 (3)	40 (3)	76 (3)
	3	16 (1)	16 (1)	32 (1)
	4	5 (<1)	5 (<1)	10 (<1)
Total Bilirubin (mg/dL)	1	122 (10)	115 (9)	237 (10)
	2	41 (3)	59 (5)	100 (4)
	3	4 (<1)	9 (1)	13 (1)
	4	1 (<1)	0	1 (<1)
Alkaline Phosphatase (IU/L)	1	55 (5)	53 (4)	108 (4)
	2	3 (<1)	3 (<1)	6 (<1)
	3	1 (<1)	1 (<1)	2 (<1)
	4	0	0	0
Creatinine (mg/dL) ^a	1	27 (2)	21 (2)	48 (2)
	2	5 (<1)	2 (<1)	7 (<1)
	3	0	1 (<1)	1 (<1)
	4	0	0	0

Phosphorus (mg/dL)	1	81 (7)	110 (9)	191 (8)
	2	110 (9)	91 (7)	201 (8)
	3	13 (1)	10 (1)	23 (1)
	4	0	0	0
Bicarbonate (mEq/L)	1	143 (12)	135 (11)	278 (11)
	2	2 (<1)	1 (<1)	3 (<1)
	3	0	0	0
	4	0	0	0
Total Leukocyte Count (cells/mm ³)	1	4 (<1)	5 (<1)	9 (<1)
	2	1 (<1)	1 (<1)	2 (<1)
	3	0	0	0
	4	0	0	0
Absolute Neutrophil Count (/mm ³)	1	23 (2)	25 (2)	48 (2)
	2	6 (1)	5 (<1)	11 (1)
	3	1 (<1)	1 (<1)	2 (<1)
	4	0	1 (<1)	1 (<1)
Total Hemoglobin (g/dL)	1	49 (4)	62 (5)	111 (5)
	2	9 (1)	15 (1)	24 (1)
	3	4 (<1)	4 (<1)	8 (<1)
	4	0	0	0
Platelets (/mm ³)	1	7 (1)	8 (1)	15 (1)
	2	3 (<1)	3 (<1)	6 (<1)
	3	2 (<1)	0	2 (<1)
	4	1 (<1)	0	1 (<1)

Abbreviations: ALT = alanine aminotransferase; AST = aspartate aminotransferase

a) Grade 1 creatinine toxicity was defined in the protocol according to the following: as the higher grade based on the Division of AIDS (DAIDS) AE Grading Table (i.e. $\geq 1.1 \times$ upper limit of normal [ULN]); or Grade 1 as defined by creatinine $> 1.5 \times$ the subject's baseline serum creatinine (baseline serum creatinine defined as the average of the serum creatinine measurements taken at screening and at enrollment; in Protocol Version 3, baseline was defined as Baseline only); or estimated creatinine clearance of < 50 mL/min.

Source: Study CO-US-104-0288 DAIDSGRD dataset

Using its own internal severity grading scale for creatinine and phosphorus laboratory results, and analyzing all post-baseline values regardless of temporal association to study drug discontinuation, the Applicant calculated the rates for emergent creatinine and phosphorus laboratory toxicities (emergent laboratory abnormalities defined as values that increased at least one toxicity grade from baseline at any time point post-

baseline). As shown in Table 40, by this analysis, about 1% of subjects reported any graded serum creatinine toxicity in either treatment group. A slightly higher proportion of subjects in the FTC/TDF group reported graded toxicities in serum phosphorus compared with the placebo group (FTC/TDF 148 [12%], placebo 130 [11%]), but most of these cases were mild (Grade 1); Grade 2 phosphorus toxicities were reported in only 1% of subjects in either treatment group. No Grade 3 or 4 abnormalities were observed in either treatment group by this grading scheme.

Table 40: Emergent Creatinine and Phosphorus Laboratory Abnormalities by Maximum Toxicity Grade – Applicant’s Toxicity Grading Scheme (CO-US-104-0288)

Laboratory Test	Maximum Toxicity Grade ^a	Number of Subjects (%)		
		FTC/TDF N=1225	Placebo N=1226	Total N=2451
Creatinine (mg/dL)	1	10 (1)	7 (1)	17 (1)
	2	1 (<1)	1 (<1)	2 (<1)
	3	0	0	0
	4	0	0	0
Phosphorus (mg/dL)	1	135 (11)	120 (10)	255 (10)
	2	13 (1)	10 (1)	23 (1)
	3	0	0	0
	4	0	0	0

a) Gilead Sciences, Inc. (GSI) serum creatinine grading scheme: Grade 0 ≤ 1.5 mg/dL, Grade 1 = 1.5 mg/dL to 2 mg/dL, Grade 2 = 2 mg/dL to 3 mg/dL, Grade 3 = 3 mg/dL to 6 mg/dL, and Grade 4 ≥ 6 mg/dL. GSI phosphorus grading scheme: Grade 1 = lower limit of normal range (LLN) to 2.0 mg/dL, Grade 2 = 2.0 mg/dL to 1.5 mg/dL, Grade 3 = 1.5 mg/dL to 1.0 mg/dL, and Grade 4 ≤ 1.0 mg/dL

Source: Study CO-US-104-0288 DERLAB dataset

Creatinine levels did not change significantly from baseline during the course of the trial in either treatment group. Mean changes from baseline creatinine were fairly comparable between the groups at most time points (Table 41). Minor elevations in serum creatinine values appeared to occur during the first six months of treatment and after Week 96; however, after Week 96 the number of subjects decreased rapidly so that the results cannot be interpreted with any confidence (Figure 11).

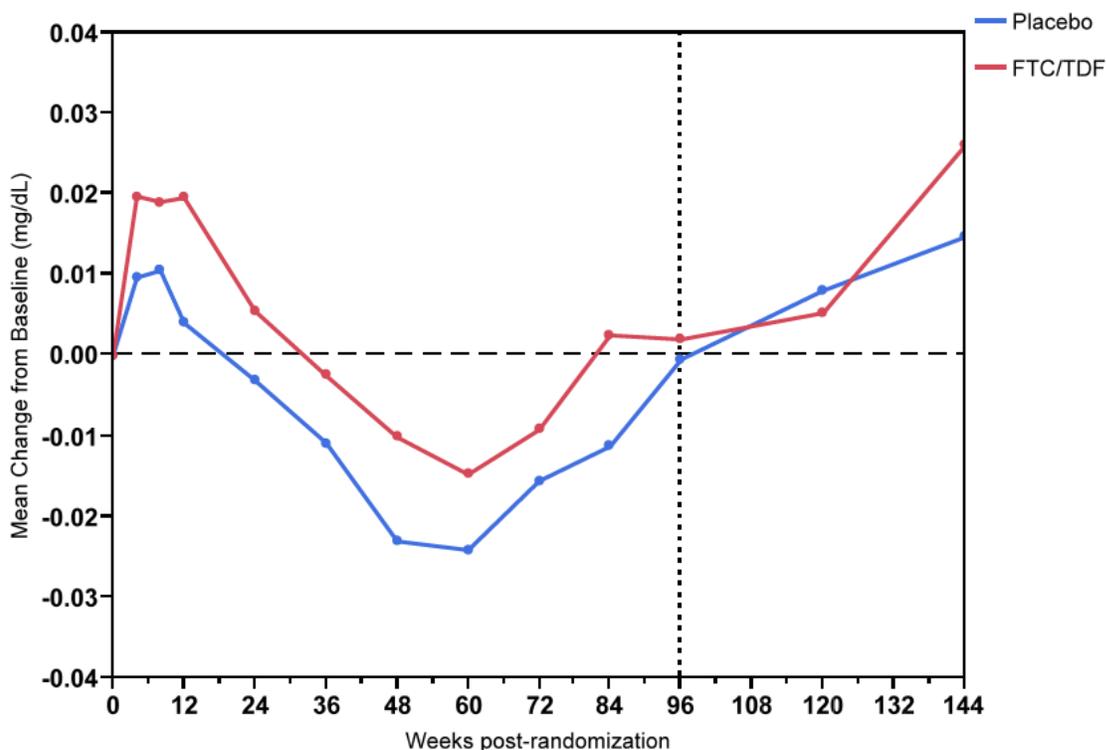
Table 41: Serum Creatinine (mg/dL) Mean Change from Baseline by Study Week (CO-US-104-0288)

Study Week	Number of Subjects	Mean Change from Baseline (mg/dL)	
		FTC/TDF	Placebo
Week 4	2262	0.01	0.02
Week 8	2247	0.01	0.02
Week 12	2172	0.00	0.02
Week 24	1977	-0.00	0.01
Week 36	1901	-0.01	-0.00
Week 48	1761	-0.02	-0.01
Week 60	1595	-0.02	-0.01

Week 72	1357	-0.02	-0.01
Week 84	1077	-0.01	0.00
Week 96	853	-0.00	0.00
Week 120	585	0.01	0.01
Week 144	211	0.01	0.03
Week 164	9	0.05	0.03

Source: Study CO-US-104-0288 DERLAB dataset

Figure 11: Serum Creatinine (mg/dL) Mean Change from Baseline by Study Week (CO-US-104-0228)



A similar trend is noted when calculated creatinine clearance is evaluated over time. Mild decreases in creatinine clearance tended to occur during the first six months of treatment (Table 42). Although probably not clinically significant, slightly greater mean decreases in creatinine clearance were noted in the FTC/TDF group compared with the placebo group during these early months. Again, after Week 96 the sample size diminished rapidly so that the results should be interpreted with caution.

Table 42: Calculated Creatinine Clearance (mL/min) Mean Change from Baseline by Study Week^a (CO-US-104-0288)

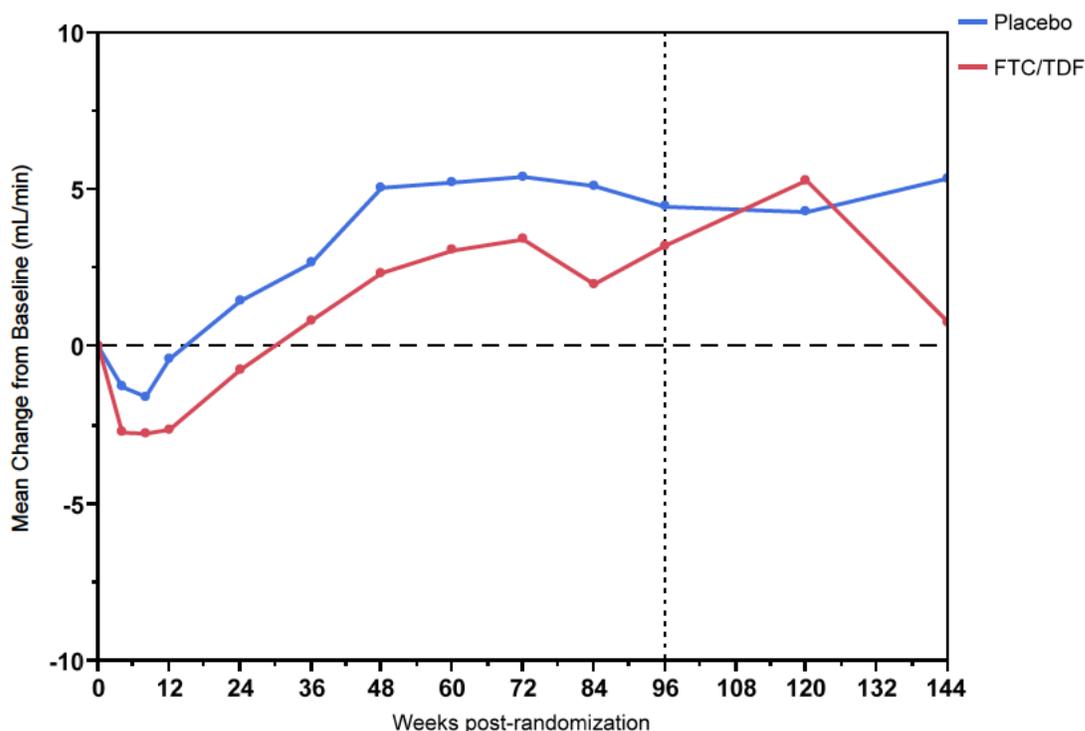
Study Week	Number of Subjects	Mean Change from Baseline (mL/min)	
		FTC/TDF	Placebo
Week 72	1357	-0.02	-0.01
Week 84	1077	-0.01	0.00
Week 96	853	-0.00	0.00
Week 120	585	0.01	0.01
Week 144	211	0.01	0.03
Week 164	9	0.05	0.03

Week 4	2262	-2.72	-1.27
Week 8	2247	-2.75	-1.58
Week 12	2172	-2.63	-0.38
Week 24	1977	-0.73	1.47
Week 36	1901	0.84	2.67
Week 48	1761	2.36	5.07
Week 60	1595	3.08	5.24
Week 72	1357	3.43	5.43
Week 84	1077	2.00	5.13
Week 96	853	3.23	4.47
Week 120	585	5.31	4.30
Week 144	211	0.80	5.37
Week 164	9	1.40	-10.76

a) Calculated Creatinine Clearance using the Cockcroft-Gault equation

Source: Study CO-US-104-0288 DERLAB dataset

Figure 12: Calculated Creatine Clearance (mL/min) Mean Change from Baseline by Study Week (CO-US-104-0228)



Mean serum phosphorus levels, on the other hand, remained fairly consistent with baseline values throughout in both treatment groups (Table 43). No clear pattern was noted for serum phosphorus decreases with respect to time on treatment (Figure 13). As noted previously, most reported serum phosphorus abnormalities were mild in

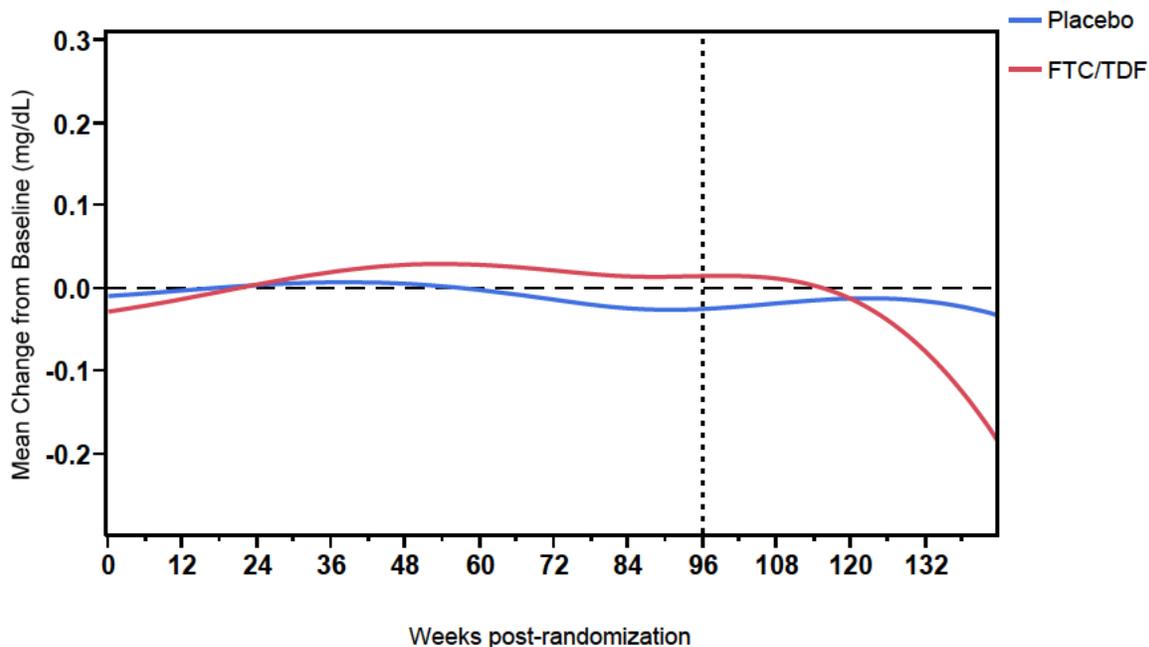
severity. Again, after Week 96 the sample size diminished rapidly so that results should be interpreted with caution.

Table 43: Serum Phosphorus (mg/dL) Mean Change from Baseline by Study Week (CO-US-102-0288)

Study Week	Number of Subjects	Mean Change from Baseline (mg/dL)	
		FTC/TDF	Placebo
Week 4	2256	-0.05	-0.01
Week 8	2253	-0.03	-0.02
Week 12	2167	-0.01	0.01
Week 24	1969	0.01	0.01
Week 48	1755	0.05	0.01
Week 60	1580	0.03	0.00
Week 72	1346	0.04	0.01
Week 84	1064	-0.06	-0.07
Week 96	837	0.01	-0.04
Week 120	566	0.02	0.00
Week 144	205	-0.09	0.00
Week 164	9	-0.55	-0.12

Source: Study CO-US-104-0288 DERLAB dataset

Figure 13: Serum Phosphorus (mg/dL) Mean Change from Baseline by Study Week (CO-US-104-0288)



Urinalysis (UA) testing by dipstick was obtained at screening in all 2,499 randomized subjects. Any UA with $\geq 1+$ proteinuria or glycosuria on screening was re-tested to ensure subject eligibility for the trial. Post-baseline urine testing was reported in 2,361 subjects (FTC/TDF 1,171, placebo 1,190). For the analysis of UA results, each post-baseline UA result with proteinuria or glycosuria \geq trace was counted separately for each subject. All subjects with at least one event of \geq trace findings were then tabulated by treatment group. As can be seen in Table 44, there were no significant differences between the two groups in the rates of proteinuria or glycosuria of any degree.

Table 44: Urinalysis Abnormalities Post-baseline (CO-US-104-0288)

Urine Dipstick Result		Number of Subjects (%)		
		FTC/TDF (N=1171)	Placebo (N=1190)	Total (N=2361)
Urine Protein	Any	171 (15)	169 (14)	340 (14)
	Trace	129 (11)	109 (9)	238 (10)
	1+	80 (7)	85 (7)	165 (7)
	2+	11 (1)	15 (1)	26 (1)
	3+	2 (<1)	2 (<1)	4 (<1)
	4+	0	1 (<1)	1 (<1)
Urine Glucose	Any	20 (2)	26 (2)	46 (2)
	Trace	5 (<1)	8 (1)	13 (1)
	1+	17 (2)	11 (1)	28 (1)
	2+	2 (<1)	5 (<1)	7 (<1)
	3+	1 (<1)	3 (<1)	4 (<1)
	4+	0	1 (<1)	1 (<1)

Source: Study CO-US-104-0288 UA dataset

In the iPrEx trial, 340 subjects (FTC/TDF 171 [16%], placebo 169 [14%]) had evidence of proteinuria on at least one occasion during a follow-up visit. Most findings of proteinuria were either trace or 1+ on urine dipstick. Proteinuria $\geq 1+$ was reported in 89 (8%) and 92 (8%) of FTC/TDF and placebo subjects, respectively. Among the subjects with proteinuria, 92/171 (54%) in the FTC/TDF group and 69/169 (41%) in the placebo group had proteinuria detected on more than one occasion.

Nine subjects (FTC/TDF 5, placebo 4) were identified with proteinuria in conjunction with toxicity-emergent creatinine increases, most of which were Grade 1 by the GSI toxicity scheme. Acidosis was not apparent during the study visits when these renal abnormalities were identified, although low bicarbonate was detected at other visits in three subjects (FTC/TDF 2, placebo 1). One of these nine subjects (Subject 8831412) permanently discontinued FTC/TDF due to creatinine elevation, but there were no laboratory reports consistent with low bicarbonate in this subject at any time point.

In contrast, glycosuria of any degree was infrequent, reported in only 46 subjects (FTC/TDF 20 [2%], placebo 26 [2%]) at any visit. Most events of glycosuria were trace or 1+ on urine dipstick and the majority were isolated findings. One subject in the FTC/TDF group (Subject 9433750), however, interrupted study drug for persistent glycosuria in association with hypophosphatemia.

Twelve subjects, six in each group, had evidence of both glycosuria and proteinuria identified at some point during the trial, although not necessarily at the same visit; none of these had creatinine elevations. Ten of these subjects (FTC/TDF 6, placebo 4), however, did have both glycosuria and proteinuria identified at the same study visit, among which seven subjects (FTC/TDF 5, placebo 2) eventually developed toxicity-graded hypophosphatemia. In five of these subjects (all in the FTC/TDF group), the UA abnormalities preceded or were reported in conjunction with the onset of hypophosphatemia. Most of the UA abnormalities were either trace or 1+ on urine dipstick. Only three (FTC/TDF 1, placebo 2) with concurrent proteinuria and glycosuria had $\geq 1+$ protein and $\geq 1+$ glucose, but all three were also hyperglycemic at the time. Even so, the one subject in the FTC/TDF group (Subject 9534566) also had Grade 1 hypophosphatemia at the time of the UA abnormalities.

Of the five subjects with concurrent glycosuria, proteinuria, and hypophosphatemia, none had reports of back pain, bone pain, or bone fractures, as might be seen with osteomalacia, although one subject in the FTC/TDF group (Subject 9433008) was found to have $>5\%$ BMD loss compared to baseline at the spine at Weeks 24 and 72 during treatment. This subject's UA and serum phosphorus abnormalities were not detected until Week 60. An additional subject with proteinuria, glycosuria and hypophosphatemia in the FTC/TDF group (Subject 9433240) was found to have a $>5\%$ decrease in BMD at the spine on post-treatment scan, a year after discontinuing study drug.

In summary, although no cases of clinical renal failure or Fanconi syndrome were reported in the iPrEx trial, five subjects in the FTC/TDF group were identified with concurrent glycosuria, proteinuria, and hypophosphatemia compared with two subjects in the placebo group. Among the five FTC/TDF subjects, two also had evidence of BMD decreases from baseline at the spine, although the timing between the renal and bone findings does correlate strongly. Nonetheless, these cases are potentially concerning for the presence of subclinical proximal renal tubulopathy. The limited number of cases, however, precludes any reliable conclusions; any suggestion regarding the possibility of mild or partial proximal renal tubulopathy occurring in this trial remains speculative at this point.

Partners PrEP

A total of 4,718 partner subjects had at least one post-baseline laboratory value (TDF 1,575, FTC/TDF 1,570, and placebo 1,573). Using the Applicant's grading scheme, 1309 partner subjects had graded creatinine or phosphorus toxicities; the numbers and percentages were similar for any toxicity grade across the treatment groups. The vast majority of laboratory abnormalities were Grade 1. With respect to creatinine toxicity, only one partner subject (in the TDF group) had an emergent Grade 2 laboratory result. No partner subject in any treatment group reported a Grade 3 or 4 creatinine toxicity.

Emergent Grade 1 low serum phosphorus was observed in 21% of partner subjects, while Grade 2 values were seen in 5%; approximately 1% of participants had > Grade 2 phosphorus toxicities. Again, the percentages for each toxicity grade were similar across the treatment groups. Partner subjects with emergent creatinine or phosphorus laboratory abnormalities are tabulated in Table 45 using the Applicant's toxicity grading scheme.

Table 45: Emergent Creatinine and Phosphorus Laboratory Abnormalities by Maximum Toxicity Grade – Applicant's Toxicity Grading Scheme (CO-US-104-0380)

Laboratory Test	Maximum Toxicity Grade ^a	Number of Subjects (%)			
		TDF (N=1575)	FTC/TDF (N=1570)	Placebo (N=1573)	Total (N=4718)
Creatinine (mg/dL)	1	3 (<1)	6 (<1)	4 (<1)	13 (<1)
	2	1 (<1)	0	0	1 (<1)
	3	0	0	0	0
	4	0	0	0	0
Phosphorus (mg/dL)	1	321 (20)	337 (22)	351 (22)	1009 (21)
	2	89 (6)	83 (5)	81 (5)	253 (5)
	3	11 (1)	12 (1)	10 (1)	33 (1)
	4	0	1 (<1)	0	1 (<1)

a) Gilead Sciences, Inc. (GSI) serum creatinine grading scheme: Grade 0 ≤ 1.5 mg/dL, Grade 1 = 1.5 mg/dL to 2 mg/dL, Grade 2 = 2 mg/dL to 3 mg/dL, Grade 3 = 3 mg/dL to 6 mg/dL, and Grade 4 ≥ 6 mg/dL. GSI phosphorus grading scheme: Grade 1 = lower limit of normal range (LLN) to 2.0 mg/dL, Grade 2 = 2.0 mg/dL to 1.5 mg/dL, Grade 3 = 1.5 mg/dL to 1.0 mg/dL, and Grade 4 ≤ 1.0 mg/dL

Source: CO-US-104-0380 ADSAFETY database

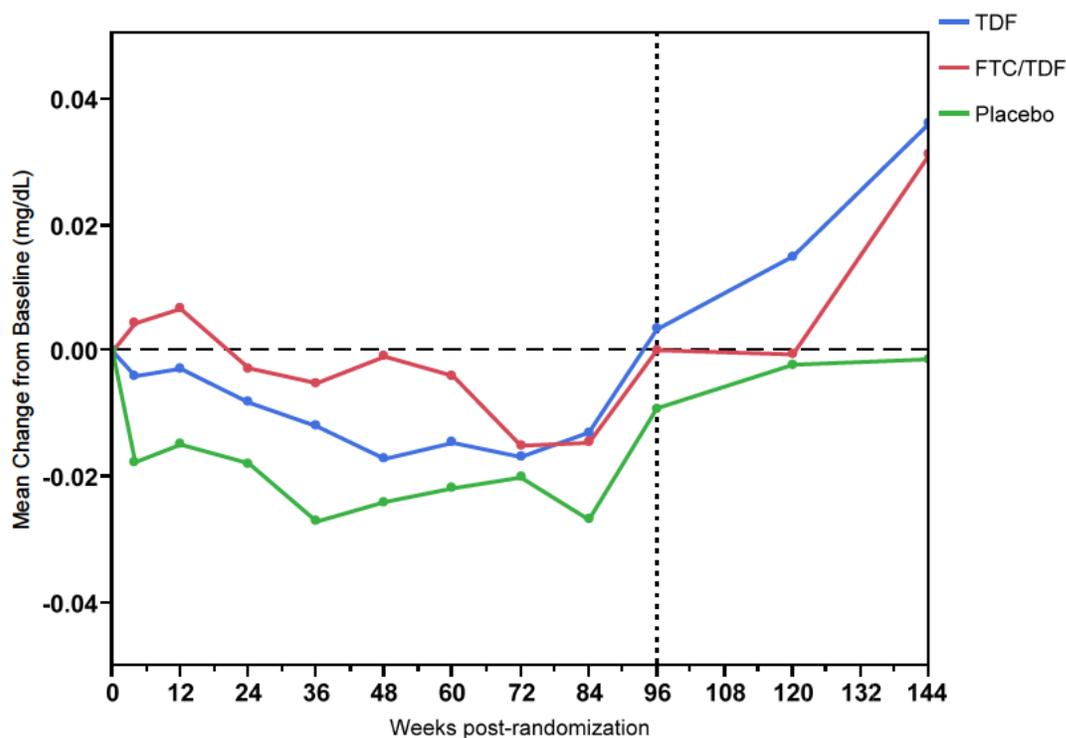
Mean changes from baseline serum creatinine were negligible in all treatment groups at each timepoint through the second year of treatment; beyond Week 96; however, the sample size rapidly diminished thus precluding reliable interpretation (Table 46 and Figure 14). Individual subject changes in creatinine clearance from baseline were also generally small and similar across treatment groups at most time points throughout the trial.

Table 46: Serum Creatinine (mg/dL) Mean Change from Baseline by Study Week (CO-US-104-0380)

Study Week	Number of subjects	Mean Change from Baseline (mg/dL)		
		TDF	FTC/TDF	Placebo
Week 4	4592	0.00	0.00	-0.02
Week 12	4484	0.00	0.01	-0.01
Week 24	4393	-0.01	0.00	-0.02
Week 36	4189	-0.01	-0.01	-0.03
Week 48	3858	-0.02	0.00	-0.02
Week 60	3488	-0.01	0.00	-0.02
Week 72	2996	-0.02	-0.02	-0.02
Week 84	2532	-0.01	-0.01	-0.03
Week 96	2105	0.00	0.00	-0.01
Week 120	843	0.02	0.00	0.00
Week 144	48	0.04	0.03	0.00

Source: Study CO-US-104-0380 ADSAFETY dataset

Figure 14: Serum Creatinine (mg/dL) Mean Change from Baseline by Study Week (CO-US-104-0380)



Similarly, mean changes from baseline in creatinine clearance values were small and generally similar across treatment groups at most time points; changes in the placebo

group tended to be greater, though (Table 47). Beyond Week 96, the sample sizes rapidly diminished and do not permit reliable comparisons (Figure 15).

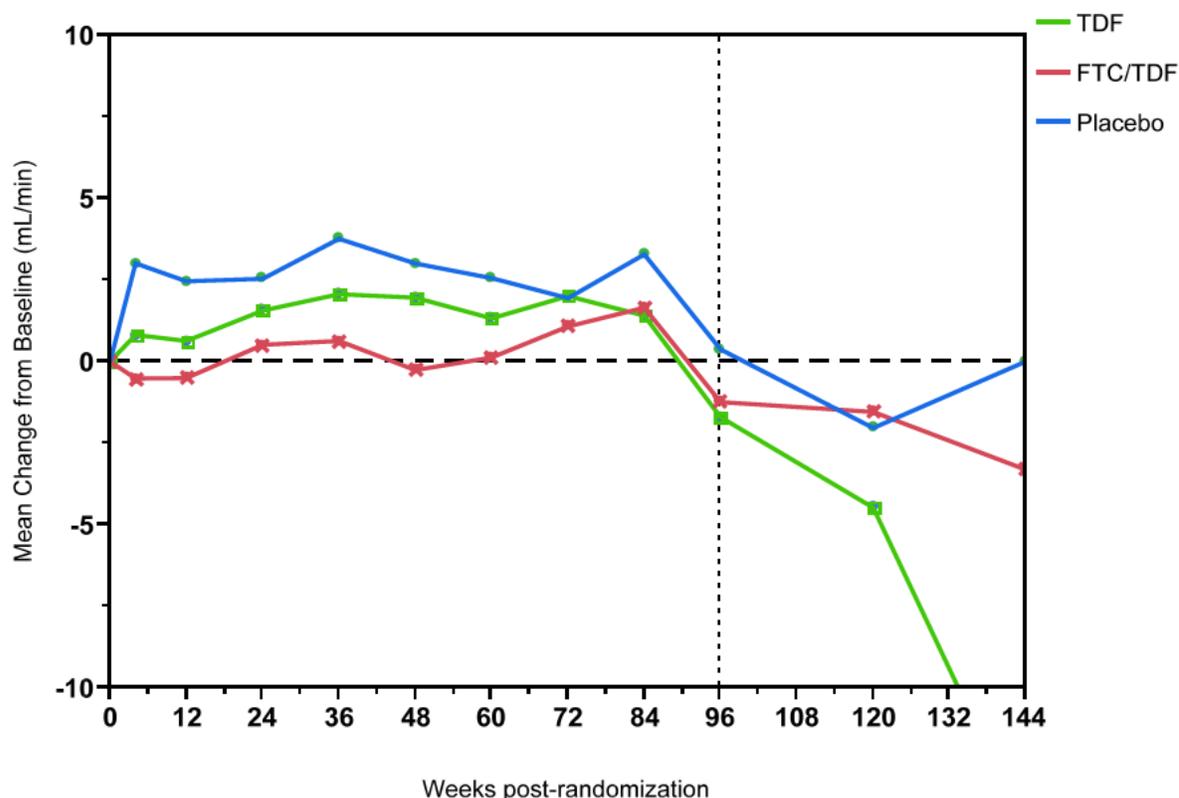
Table 47: Creatinine Clearance (mL/min) Mean Change from Baseline by Study Week^a (CO-US-104-0380)

Study Week	Number of subjects	Mean Change from Baseline (mL/min)		
		TDF	FTC/TDF	Placebo
Week 4	4592	0.81	-0.52	3.01
Week 12	4484	0.63	-0.51	2.46
Week 24	4393	1.56	0.51	2.53
Week 36	4189	2.06	0.63	3.76
Week 48	3858	1.96	-0.26	3.01
Week 60	3488	1.32	0.12	2.56
Week 72	2996	2.01	1.07	1.94
Week 84	2532	1.41	1.65	3.28
Week 96	2105	-1.71	-1.24	0.37
Week 120	843	-4.48	-1.54	-2.04
Week 144	48	-14.38	-3.31	0.00

a) Calculated Creatinine Clearance using the Cockcroft-Gault equation

Source: Study CO-US-104-0380 ADSAFETY dataset

Figure 15: Creatinine Clearance (mL/min) Mean Change from Baseline by Study Week CO-US-104-0380)



Mean changes from baseline in serum phosphorus were negligible across treatment groups at all time points during the first two years of treatment (Table 48). The largest decrease in mean serum phosphorus levels tended to occur early, within the first month of treatment, in all three groups; changes from baseline thereafter appeared to remain constant at least through the second year of treatment (Figure 16). Beyond Week 96, the sample size rapidly diminished for reliable comparisons to be made.

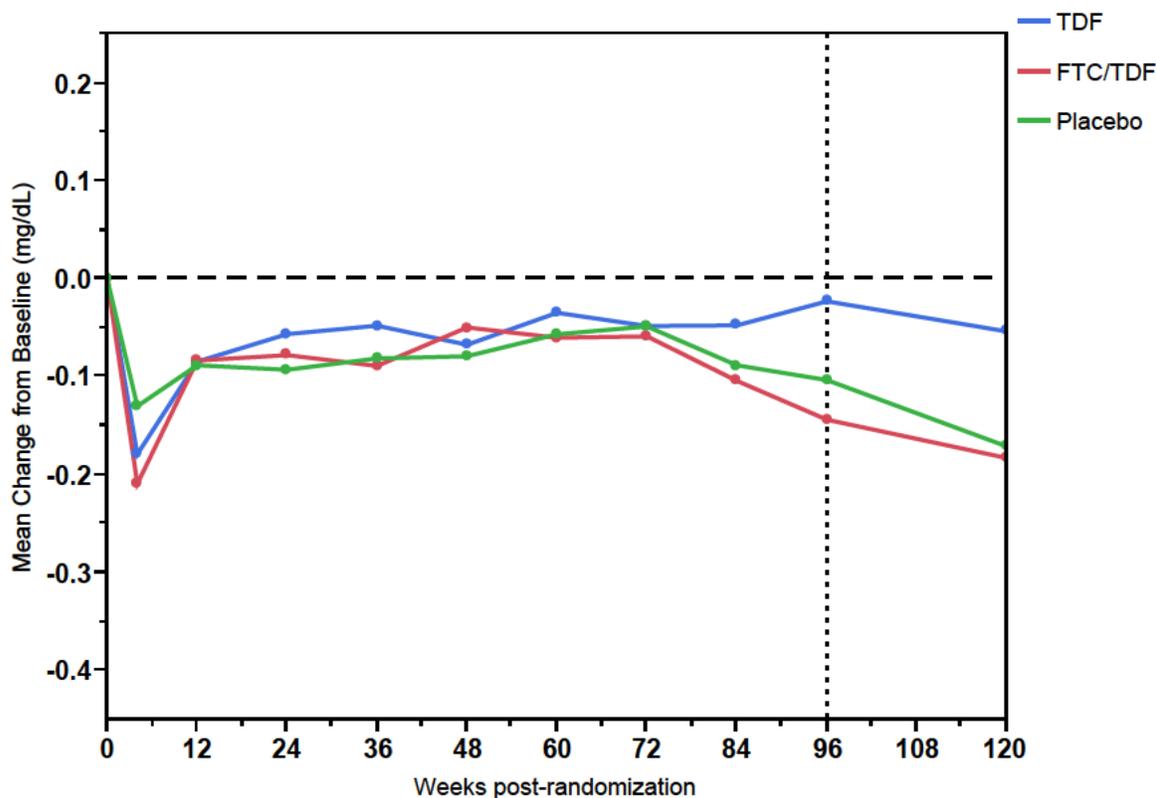
Table 48: Serum Phosphorus (mg/dL) Mean Change from Baseline by Study Week (CO-US-104-0380)

Study Week	Number of Subjects	Mean Change from Baseline (mg/dL)		
		TDF	FTC/TDF	Placebo
Week 4	4921	-0.18	-0.21	-0.13
Week 12	4729	-0.08	-0.08	-0.09
Week 24	4601	-0.06	-0.08	-0.09
Week 36	4414	-0.05	-0.09	-0.08
Week 48	4045	-0.07	-0.05	-0.08
Week 60	3648	-0.03	-0.06	-0.06
Week 72	3133	-0.05	-0.06	-0.05

Week 84	2674	-0.05	-0.10	-0.09
Week 96	2192	-0.02	-0.14	-0.10
Week 120	879	-0.05	-0.18	-0.17
Week 144	51	-0.21	0.02	-0.42

Source: Study CO-US-104-0380 ADSAFETY dataset

Figure 16: Serum Phosphorus (mg/dL) Mean Change from Baseline by Study Week (CO-US-104-0380)



Other laboratory data submitted from the Partners PrEP trial included AST, ALT, total bilirubin, bicarbonate, total white blood cell count, absolute neutrophil count, hemoglobin and platelet count values. These evaluations were collected at each study visit. The DAIDS toxicity grading scheme was used to grade all laboratory abnormalities reported on treatment. Graded laboratory toxicities were further reviewed by the UW-ICRC team and classified as confirmed, not confirmed, or not yet confirmed. As in the iPrEx trial, data regarding cholesterol and lipid laboratory testing was not submitted for review; further, it does not seem that such data were collected per the Partners PrEP protocol.

Table 49 lists the proportion of subjects in each treatment group with confirmed laboratory toxicities, using the highest toxicity grade achieved post-baseline, regardless

of baseline toxicity grade. [Medical Officer Comment: Toxicity grades for baseline laboratory values were not included in the submitted analysis dataset.]

Table 49: Emergent Laboratory Abnormalities by Maximum DAIDS Toxicity Grade (CO-US-104-0380)

Laboratory Test	Maximum DAIDS Toxicity Grade ^a	Number of Subjects (%)			
		TDF (N=1575)	FTC/TDF (N=1570)	Placebo (N=1573)	Total (N=4718)
ALT (IU/L)	1	11 (1)	17 (1)	11 (1)	39 (1)
	2	7 (<1)	5 (<1)	5 (<1)	17 (<1)
	3	2 (<1)	1 (<1)	1 (<1)	4 (<1)
	4	3 (<1)	2 (<1)	2 (<1)	7 (<1)
AST (IU/L)	1	17 (1)	13 (1)	17 (1)	47 (1)
	2	9 (1)	11 (1)	8 (1)	28 (1)
	3	5 (<1)	5 (<1)	2 (<1)	12 (<1)
	4	4 (<1)	1 (<1)	2 (<1)	7 (<1)
Total Bilirubin (mg/dL)	1	11 (1)	9 (1)	14 (1)	34 (1)
	2	4 (<1)	3 (<1)	5 (<1)	12 (<1)
	3	0	0	0	0
	4	0	1 (<1)	0	1 (<1)
Bicarbonate (mmol/L)	1	3 (<1)	1 (<1)	2 (<1)	6 (<1)
	2	4 (<1)	2 (<1)	4 (<1)	10 (<1)
	3	0	0	0	0
	4	0	0	0	0
Total Leukocyte Count (10 ³ /μL)	1	6 (<1)	9 (1)	10 (1)	25 (1)
	2	0	1 (<1)	1 (<1)	2 (<1)
	3	0	0	0	0
	4	0	0	0	0
Absolute Neutrophil Count (10 ³ /μL)	1	114 (7)	119 (8)	105 (7)	338 (7)
	2	82 (5)	101 (6)	75 (5)	258 (6)
	3	37 (2)	52 (3)	28 (2)	117 (3)
	4	5 (<1)	9 (1)	1 (<1)	15 (<1)
Total Hemoglobin (g/dL)	1	46 (3)	43 (3)	27 (2)	116 (3)
	2	34 (2)	22 (2)	32 (2)	88 (2)
	3	24 (2)	15 (1)	18 (1)	57 (1)
	4	0	4 (<1)	1 (<1)	5 (<1)

Platelets (10 ³ /μL)	1	31 (2)	23 (2)	27 (2)	81 (1)
	2	22 (1)	23 (2)	26 (2)	71 (2)
	3	8 (1)	2 (<1)	2 (<1)	12 (<1)
	4	1 (<1)	3 (<1)	4 (<1)	8 (<1)

Abbreviations: ALT = alanine aminotransferase; AST = aspartate aminotransferase
Source: CO-US-104-0380 ADLAB dataset

Overall, the most common graded laboratory toxicities were those associated with decreased absolute neutrophil counts (15%), decreased total hemoglobin (6%), decreased platelet counts (4%), increased AST (2%) and increase ALT (1%). All other graded laboratory abnormalities were reported by ≤1% of subjects per treatment group. Most of the events were ≤ DAIDS Grade 2 in severity. Grade 3-4 laboratory abnormalities were reported in ≤4% of partner subjects per treatment group, with decreased absolute neutrophil count being the most common ≥ Grade 3 toxicity event. By laboratory test and toxicity grade, the proportions of subjects with abnormalities were generally comparable across treatment groups. The proportion of subjects with graded low absolute neutrophil, however, was greatest in the FTC/TDF group (18%) compared with the TDF group (15%) or placebo group (13%). DAIDS Grade 3-4 low neutrophil counts were also most frequent in the FTC/TDF group: FTC/TDF 61 (4%) versus TDF 42 (3%) and placebo 29 (2%).

Urinalysis results were obtained in 4,722 partner subjects during follow-up: TDF 1,577, FTC/TDF 1,571, and placebo 1,574. For the analysis of UA results, all post-baseline results ≥ trace protein or glucose were counted as separate events; subjects with either of these findings at any time point were then tabulated by treatment group (Table 50).

Table 50: Urinalysis Post-baseline Abnormalities (GS-US-104-0380)

Urine Dipstick Result		Number of Subjects (%)			
		TDF (N=1577)	FTC/TDF (N=1571)	Placebo (N=1574)	Total (N=4722)
Protein	Any	61 (4)	62 (4)	51 (3)	174 (4)
	Trace	26 (2)	32 (2)	19 (1)	77 (2)
	1+	33 (2)	30 (2)	29 (2)	92 (2)
	2+	9 (1)	7 (1)	5 (<1)	21 (<1)
	3+	2 (<1)	3 (<1)	4 (<1)	9 (<1)
	4+	0	0	1 (<1)	1 (<1)
Glucose	Any	8 (1)	6 (<1)	11 (1)	25 (1)
	Trace	2 (<1)	0	1 (<1)	3 (<1)
	1+	3 (<1)	3 (<1)	7 (<1)	13 (<1)
	2+	2 (<1)	3 (<1)	1 (<1)	6 (<1)
	3+	0	0	2 (<1)	2 (<1)
	4+	1 (<1)	0	1 (<1)	2 (<1)

Source: Study CO-US-104-0380 RENTOX dataset

As can be seen in Table 50, rates of UA abnormalities were generally consistent across treatment groups. Over 50% of the proteinuria events in any group were isolated findings and most were trace or 1+. Proteinuria $\geq 1+$ on urine dipstick was observed in 3% of partner subjects in any treatment group. Glycosuria, in contrast, was uncommon and reported in less than 1% of subjects overall, with no discernable differences between groups.

Thirteen subjects had findings of proteinuria or glycosuria at any visit during follow-up (TDF 5, FTC/TDF 3, placebo 5), among which seven subjects had both proteinuria and glycosuria at the same study visit (TDF 2, FTC/TDF 2, placebo 3). Six of these seven subjects were male and median age was 35 years old (range 28 to 61 years). Five of these seven subjects had concurrent $\geq 1+$ proteinuria and $\geq 1+$ glycosuria and toxicity-emergent hypophosphatemia (TDF2, FTC/TDF 1, placebo 2). Serum glucose levels were not included in the submitted datasets for this trial; therefore, the glycemic state of these subjects at the time of the UA findings could not be determined. None of the seven subjects had increased serum creatinine levels, although one subject in the FTC/TDF group (Subject 5531519) had a reported estimated creatinine clearance of 69 mL/min at the time of the UA abnormalities (baseline creatinine clearance 76 mL/min). None of the subjects had reports of bone pain, back pain or bone fractures.

The small number of subjects with concurrent $\geq 1+$ proteinuria and glycosuria and hypophosphatemia and the comparable rates among the treatment groups make interpretation of these findings difficult and preclude any reliable conclusions regarding possible evidence of proximal renal tubulopathy in this trial.

7.4.3 Vital Signs

As noted in Section 7.4.1, the incidence of weight loss in the iPrEx trial was higher in the FTC/TDF group than in the placebo group (3% versus 1%, respectively). In contrast, no significant differences in weight changes were noted among the treatment groups in the Partners PrEP trial. Otherwise, no patterns in vital sign changes or physical findings suggestive of a treatment-related effect were apparent in the pivotal trials.

7.4.4 Electrocardiograms (ECGs)

No routine ECG monitoring was performed during the pivotal or supportive trials.

7.4.5 Special Safety Studies/Clinical Trials

Safety data from the CDC 4323 trial in U.S. MSM were reviewed in support of this application. Key renal and bone findings from CDC 4323 were incorporated into Section 7.3.5 where relevant.

In the CDC 4323 trial, 373 (93%) participants were randomized and dispensed study drug at least once. This was an older cohort of MSM compared with the overall iPrEx population, with a mean age of 37 years. Overall, 331 participants (83%) completed all study visits. Median drug exposure as determined by pill count was 92% (range 79-98%); by MEMS, it was lower at 77% (range 57-92%). Of the 373 subjects who received study drug, 91% reported AEs; most of which (96%) were mild or moderate in severity. A total of 102 \geq Grade 3 AEs occurred among 64 participants, with comparable rates between the groups; only about a third of these AEs were considered drug-related. Frequencies of commonly reported AEs did not differ significantly between the TDF and placebo groups. As noted in Section 7.3.5, back pain was reported more frequently in the TDF group. Nausea also occurred mildly more frequently in the TDF group compared with the placebo group (13% versus 8%, respectively). With respect to renal safety, no \geq Grade 3 creatinine elevations were noted in the trial per the GSI grading scheme. Grade 1 and 2 elevations were uncommon, and occurred with similar frequency in the TDF and placebo groups: ten Grade 1 creatinine elevations (TDF 4 [2%], placebo 6 [3%]) and two Grade 2 elevations (TDF 1 [1%], placebo 2 [1%]) (see Table 29). Confirmed elevated creatinine values of \geq 0.5 mg/dL over baseline occurred in two participants; both were in the placebo group and both were discontinued from study drug per the protocol. Mild to moderate hypophosphatemia was relatively common among study participants, and occurred with similar rates between the two groups (see Table 29). As noted in Section 7.3.5, a greater proportion of subjects in the TDF group than in the placebo group had \geq 3% BMD decreases at the total hip and spine at the end of treatment compared to baseline. TDF was associated with small but statistically significant BMD loss compared to baseline at the femoral neck (-1.1%) and total hip (-0.8%). Fractures were uncommon and predominately trauma-related (TDF 9, placebo 5).

7.4.6 Immunogenicity

The immunogenicity potential of FTC/TDF was not explored in these trials.

7.5 Other Safety Explorations

7.5.1 Dose Dependency for Adverse Events

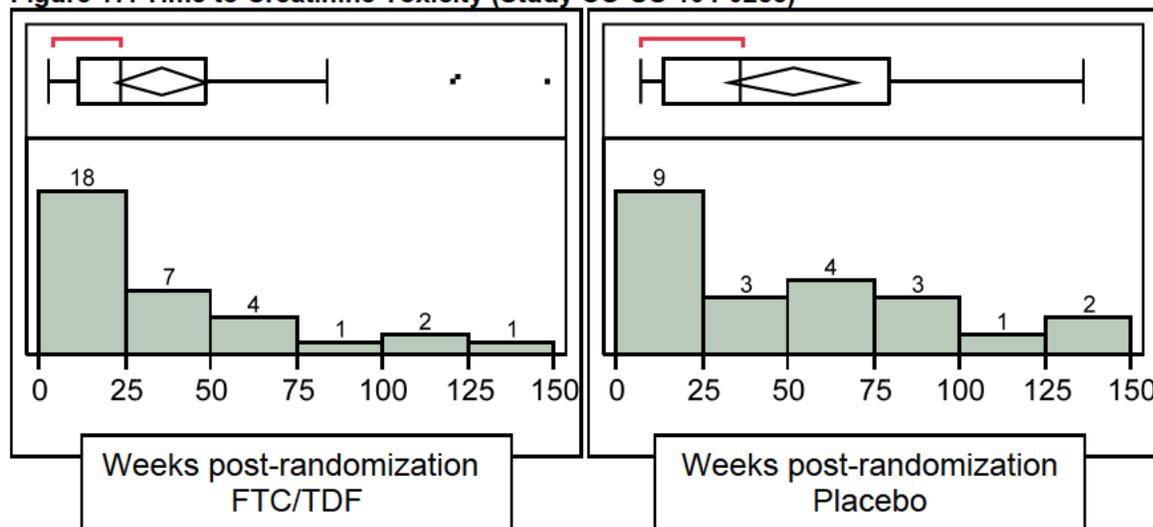
Only one dosing regimen of FTC/TDF was evaluated in the pivotal trials; therefore, analysis of dose dependency for AEs was not applicable. Among subjects with available PK data, no correlation was observed between detectable blood concentrations and incidence of key adverse events; however, the number of these subjects was limited.

7.5.2 Time Dependency for Adverse Events

The more significant AEs associated with FTC/TDF are renal and bone toxicity. In the iPrEx trial, median time to creatinine toxicity was 25 weeks (IQR 12-68 weeks). Median

time to onset of creatinine elevation was less in the FTC/TDF group (24 weeks) compared with the placebo group (37 weeks) (see Figure 17). Mean duration of creatinine elevation was equal between both groups (22 days).

Figure 17: Time to Creatinine Toxicity (Study CO-US-104-0288)



In the Partners PrEP trial, median time to creatinine adverse events was 48 weeks (IQR 16-73 weeks) for the trial overall as well as for the individual TDF and FTC/TDF groups; median time to events for the placebo group was less at 43 weeks. Duration times for the AEs were comparable between the groups (median 5 days overall).

In both the iPrEx and CDC 4323 trials, BMD decreases compared to baseline were more apparent during the first year of active treatment and then appeared to plateau. As noted in Section 7.3.5, in the iPrEx trial, a return to baseline BMD values was noted in the FTC/TDF group within 6 months of stopping study drug.

Since nearly all bone fractures reported in these clinical trials appeared to be trauma-related, there was wide variation with respect to timing. Analysis of a time dependency for bone fractures, therefore, would be unreliable. That said, no difference in the time to bone fracture events was noted between the active and placebo arms for each trial.

Based on monthly medical history questionnaires, the iPrEx investigators reported that the incidence of nausea was highest during the first 4 weeks of the trial, with 9% of subjects in the FTC/TDF group reporting nausea compared with 5% in the placebo group. The incidence of nausea diminished over time thereafter. After 96 weeks of treatment, <2% of subjects in both groups reported nausea. Note that these percentages are at odds with what was reported in the AE datasets, where only 1.4% of subjects overall reported an AE with preferred term “nausea” (FTC/TDF 21 [1.7%], placebo 14 [1.1%]). Even if other preferred terms in the Gastrointestinal Disorders SOC,

such as “gastritis”, “dyspepsia”, or “vomiting”, are included in the analysis of nausea, the rates for the entire follow-up are still only 4% and 2% for the FTC/TDF and placebo groups, respectively. As with the reports of skin darkening, it appears that the monthly questionnaires captured more information than what is reflected by the AE reports. Nausea in the Partners PrEP trial, on the other hand, was not a significant finding and was reported as an AE in only one subject (in the FTC/TDF group).

In the iPrEx trial, both treatment groups experienced a mean increase in body weight of between 3% and 4% by the end of 96 weeks. DEXA assessments of limb fat, trunk fat, and total body fat for subjects who participated in the substudy (N=503) were generally consistent with the on-study assessments of body weight. A slower increase in body weight was observed among subjects on FTC/TDF compared with subjects on placebo through the first 12 weeks; thereafter, observed body weight was balanced between the treatment groups during follow-up.

7.5.3 Drug-Demographic Interactions

In subgroup analyses by race and region, there were some differences in AE incidence by race and region in the iPrEx trial, but given the general balance between the treatment groups there were no notable differences that appeared to be attributable to study drug. For instance, treatment-emergent clinical SAEs were more common in subjects in North America (11% in both treatment groups) compared with other regions (range 2-7%). The results, however, were balanced between the FTC/TDF and placebo groups. By race, no notable differences were observed between treatment groups or across racial groups in the incidence of SAEs. The study population of the Partners PrEP trial, on the other hand, was racially homogenous and from the same region of eastern Africa (Kenya and Uganda) and, therefore, does not lend itself to subgroup analyses by race or region.

In subgroup analyses by gender in the Partners PrEP trial, the incidence for most treatment-emergent AEs was balanced between men and women and between treatment groups by gender (Table 51). For SAEs, there was a slightly greater incidence among female subjects in the FTC/TDF group (10%) than among male subjects in the FTC/TDF groups of either the Partners PrEP or iPrEx trial (range 6-7%), but the percentage was comparable to the placebo group (8%). This difference in SAE rates may be in part due to the number of women with AEs in the Pregnancy, Puerperium, and Perinatal Conditions SOC (N=83; TDF 28, FTC/TDF 30, placebo 25), among which 21 women had spontaneous abortions reported as SAEs (TDF 7, FTC/TDF 8, placebo 6) (see Section 7.3.2). There were also differences by gender in the incidence of clinical AEs and AEs related to creatinine toxicity, but the rates between the active and placebo treatment groups were balanced within each gender. Also, the reported incidence of AEs related to creatinine elevation was higher than the rates of confirmed creatinine increases. For confirmed creatinine increases, the rates were comparable between the treatment groups and by gender. Nonetheless, of the seven subjects who permanently

discontinued study drug due to an adverse event in the Partners PrEP trial, four were women in the TDF-based groups who discontinued due to creatinine clearance below 50 mL/min.

Table 51: Treatment-emergent Adverse Events by Gender (Study CO-US-104-0380 and -0288)

Adverse Event	Number of Subjects (%)					
	Men in iPrEx		Partners PrEP			
	FTC/TDF (N=1251)	Placebo (N=1248)	Men		Women	
FTC/TDF (N=1013)			Placebo (N=963)	FTC/TDF (N=566)	Placebo (N=621)	
Any AE	987 (80)	1016 (81)	857 (85)	809 (84)	484 (86)	512 (83)
Any SAE	83 (7)	82 (7)	56 (6)	68 (7)	59 (10)	50 (8)
Grade 3-4 AEs	196 (16)	191 (15)	199 (20)	188 (20)	131 (23)	108 (17)
Clinical AEs	884 (71)	904 (72)	461 (46)	493 (51)	341 (60)	373 (60)
Laboratory AEs	469 (37)	464 (37)	758 (75)	698 (73)	405 (72)	408 (67)
AEs leading to drug discontinuation	48 (4)	49 (4)	0	1 (<1)	4 (1)	1 (<1)
AEs related to creatinine toxicity ^a	29 (2)	21 (2)	48 (5)	32 (3)	52 (9)	46 (7)
AEs related to bone fractures	19 (2)	15 (1)	6 (0.6)	9 (1)	3 (0.5)	3 (0.5)

Abbreviations: AE= adverse event; SAE = serious adverse event

a) AEs related to creatinine toxicity are not limited to confirmed creatinine elevations for the Partners PrEP trial

Multivariate analysis of postmarketing clinical data has identified older age as a risk factor, among others, for tenofovir-induced renal dysfunction.⁴⁰ Glomerular filtration is recognized to independently decrease with age. Given the limited proportion of subjects older than 40 years of age studied in the iPrEx trial (10%), the FTC/TDF and placebo groups from both pivotal trials were pooled for the subgroup analysis by age (Table 52). A cut-off age of 40 years was chosen because the physiological differences between subjects <40 and ≥40 years of age were considered to be more significant than among subjects within the 18-40 year old range. The results of the pooled analysis demonstrated a difference in the overall incidence of AEs between subjects older and younger than 40 years (87% versus 81%, respectively). The difference was more pronounced for laboratory AEs than clinical AEs, although the difference was appreciable for both. A similar trend was also noted for Grade 3-4 AEs and AEs related to renal and bone toxicity. That said, there were no notable differences between the

⁴⁰ Fernandez-Fernandez B, Montoya-Ferrer A, Sanz AB, et al. Tenofovir nephrotoxicity: 2011 update. AIDS Res Treat 2011; doi:10.1155/2011/354908.

active and placebo groups within the older age subgroup, and no apparent pattern in the types of AEs that occurred among older subjects.

Table 52: Treatment-Emergent Adverse Events by Age, Pooled Analysis (Studies CO-US-104-0288 and -0380)

Adverse Event	Number of Subjects (%)			
	<40 years of age		≥40 years of age	
	FTC/TDF (N=2263)	Placebo (N=2304)	FTC/TDF (N=567)	Placebo (N=528)
Any AE	1832 (81)	1877 (81)	496 (87)	460 (87)
SAEs	147 (7)	163 (7)	51 (9)	38 (7)
Grade 3-4 AEs	413 (18)	379 (16)	113 (20)	108 (20)
Clinical AEs	1328 (57)	1432 (62)	358 (63)	338 (64)
Laboratory AEs	1251 (55)	1209 (52)	381 (67)	361 (68)
AEs leading to drug discontinuation	42 (2)	43 (2)	8 (1)	8 (2)
AEs related to creatinine toxicity ^a	93 (4)	68 (3)	36 (6)	31 (6)
AEs related to bone fractures	21 (1)	19 (1)	13 (2)	15 (3)

Abbreviations: AE= adverse event; SAE = serious adverse event

a) AEs related to creatinine toxicity are not limited to confirmed creatinine elevations for the Partners PrEP trial

7.5.4 Drug-Disease Interactions

Since subjects randomized to these clinical trials were considered to be healthy, an evaluation of a drug-disease interaction is not applicable.

7.5.5 Drug-Drug Interactions

No new or updated information regarding drug-drug interactions with FTC/TDF from that previously submitted to NDA 21-752 for TRUVADA tablets was submitted with this supplement.

7.6 Additional Safety Evaluations

7.6.1 Human Carcinogenicity

The human carcinogenicity potential of FTC/TDF is considered to be low. In previous nonclinical studies, TDF did not show any carcinogenic potential in a long-term oral study in rats. A long-term oral carcinogenicity study in mice showed a low incidence of duodenal tumors, considered likely related to high local concentrations in the gastrointestinal tract at the high dose of 600 mg/kg/day. The mechanism of tumor formation in mice and potential relevance for humans is uncertain. TDF was mutagenic in the in vitro mouse lymphoma assay and negative in an in vitro bacterial mutagenicity test (Ames test). In an in vivo mouse micronucleus assay, TDF was negative at doses

up to 2000 mg/kg when administered to male mice. Long-term carcinogenicity studies of FTC in rats and mice did not show any carcinogenicity potential. Emtricitabine was not mutagenic or clastogenic in conventional genotoxicity assays.

Given the relatively short duration of follow-up in these pivotal trials, evaluation of human carcinogenicity was not an objective. In the iPrEx trial, there were only two reports of malignancy, both involving lymphoma and both occurring in the FTC/TDF group: one case of non-Hodgkin's lymphoma in a 21-year-old subject reported on Study Day 910 and one case of angiocentric lymphoma in a 38-year-old subject reported on Study Day 542. Neither case was considered to be related to study drug. In the Partners PrEP trial, three cases of malignancy were reported during follow-up, all in the placebo group: one case of cervical cancer in a 40-year-old woman, one case of Kaposi's sarcoma in 53-year-old man, and one case of esophageal carcinoma in a 59-year-old man.

7.6.2 Human Reproduction and Pregnancy Data

TRUVADA is classified as a Pregnancy Category B agent. No evidence has been identified to date for an increased risk for teratogenic effects or adverse pregnancy outcomes associated with the use of FTC or TDF, alone or in combination; however, no adequate and well-controlled trials have been conducted in pregnant women.

Limited human reproduction and pregnancy data were available from the Partners PrEP trial. Evaluation of the effect of FTC/TDF or TDF on pregnancy was not an objective of this trial. All female partner subjects who became pregnant during treatment were instructed to immediately interrupt study drug for the duration of the pregnancy and while breastfeeding. Therefore, the duration of drug exposure during pregnancy was limited.

As of the July 10, 2011 data cut-off date, 288 pregnancies were reported in 267 women (TDF 112 [18%], FTC/TDF 74 [13%], placebo 88 [14%]). The incidence of pregnancy (per 100 female partner subject-years) was lowest in the FTC/TDF group (8.8) compared with the other two groups (TDF 11.9, placebo 10).

In the 120-day safety update submitted to this supplement on March 16, 2012 (data cut-off January 31, 2012), updated pregnancy data were provided for the 288 pregnancies. A total of 262 (91%) pregnancies had completed as of the update; 64% resulted in live births and 36% resulted in pregnancy loss. Spontaneous abortion, where the age at gestation was known, tended to occur less than 20 weeks into the pregnancy. It should be noted that it is not always possible to clearly distinguish between induced abortion and spontaneous abortion or miscarriage in this setting, specifically since medical abortion is not legal in either Kenya or Uganda. In addition, because the protocol mandated monthly pregnancy testing, many of the pregnancies reported in the trial were very early pregnancies ("chemical pregnancies") that would in other settings probably

go undetected and be lost without notice. Moreover, the rates of pregnancy loss observed in this trial are consistent with studies that report an overall miscarriage rate of 31% for pregnancies in general, including clinically recognized spontaneous abortions.⁴¹ Analyses of pregnancy outcomes by maternal age, concomitant medication use, or other factors were not conducted, but the numerical difference between the treatment groups is small and may represent reporting differences or random variation.

Table 53: Summary of Pregnancies in Partner Subjects - Outcomes as of January 31, 2012 (Study CO-US-104-0380)

	Number of Female Partner Subjects (%)			
	TDF (N=598)	FTC/TDF (N=566)	Placebo (N=621)	Total (N=1785)
Pregnancy reported	105 (18)	74 (13)	88 (14)	267 (15)
Number of pregnancies, n	112	80	96	288
Number of pregnancies completed, n	103	74	85	262
Live births, n (%) ^a	73 (71)	40 (54)	54 (63)	167 (64)
Pregnancy loss, n (%) ^a	30 (29)	34 (46)	31 (37)	95 (36)
Spontaneous abortion	23	31	23	77
Induced abortion	7	3	8	18

a) Percentage based on number of pregnancies completed

Source: Study CO-US-104-0380 ADPREG dataset

As noted in Section 6.1.7, five (2%) of the 267 women who interrupted study drug for pregnancy seroconverted during the time they were off treatment. The risk of HIV infection during pregnancy and the use of FTC/TDF for its prevention are discussed in Section 9.2 as part of the labeling considerations for this indication.

Among the live births, five infants died within 1 to 3 months of birth (TDF 1, FTC/TDF 2, placebo 2). Causes of death are listed in (Table 54). Congenital abnormalities were reported in 13 infants (TDF 5, FTC/TDF 4, placebo 4). The only congenital abnormalities reported in more than one infant were ankyloglossia congenital (TDF 2, FTC/TDF 1) and umbilical hernia (FTC/TDF 1, placebo 3). Other abnormalities noted among infants born to mothers in the FTC/TDF group were syndactyly and ventricular septal defect (one infant each). In the TDF group, hypospadias and polydactyly (one infant each) were also noted. None of the congenital abnormalities were considered to be related to study drug.

⁴¹ Wilcox AJ, Weinberg CR, O'Connor JF et al. Incidence of early loss of pregnancy. N Engl J Med 1988; 319 (4):189.

Table 54: Adverse Events in Newborns of Partner Subjects (Study CO-US-104-0380)

Study Drug	Partner Subject Number	Visit	Preferred Term	Status	Date of Death
TDF	5016917	3 Month	Diarrhoea	Death	(b) (6)
FTC/TDF	5526011	1 Month	Bronchopneumonia	Death	
FTC/TDF	5417319	1 Month	Sepsis	Death	
Placebo	5435018	1 Month	Sepsis neonatal	Death	
Placebo	5121013	3 Month	Malaria	Death	

Source: Clinical Study Report for Study CO-US-104-0380, page 98.

A postmarketing requirement to evaluate TRUVADA in pregnant women will be issued as a condition of approval for this supplement (see Section 1.4).

7.6.3 Pediatrics and Assessment of Effects on Growth

Both pivotal trials in this supplement enrolled adults 18 years and older. The effect of FTC/TDF on growth was not evaluated in these trials.

The Applicant submitted a pediatric plan as part of this supplement. A waiver was requested for children <16 years of age for the following reasons:

- (a) Necessary studies are impossible or highly impracticable (Federal Food, Drug and Cosmetic Act (FDCA), as amended by PREA, Section 505B(a)(4)(B)(i)).
- (c) The product fails to represent a meaningful therapeutic benefit over existing therapies for pediatric patients and is unlikely to be used in a substantial number of all pediatric age groups or the pediatric age group(s) for which a waiver is being requested (FDCA, as amended by PREA, Section 505B(a)(4)(B)(iii)).

A partial waiver was requested for adolescent females 16 to <18 years of age based on the low incidence of HIV in this population and the low feasibility of enrolling adolescent girls that identify with higher-risk behavior.

A deferral of pediatric studies was requested for adolescent males 16 to <18 years of age. Based on the estimated incidence, prevalence rate, and route of transmission in MSM, the group of adolescent MSM 16-18 years of age was considered most appropriate for pediatric studies of oral PrEP. The proposed pediatric plan is based on three trials to be conducted in the United States by the Adolescents Trial Network (ATN) and sponsored by the National Institute of Child Health and Human Development (NICHD), summarize in Table 55. Pre-IND consultation was obtained by NICHD in January 2012.

Table 55: Summary of Proposed Pediatric Trials of TRUVADA for PrEP in U.S. Adolescent Males

Trial	Title	Age Groups
ATN 110	Project PrEPare Phase II - An Open label Demonstration Project of Pre-Exposure Prophylaxis Use among Young Men who Have Sex with men (MSM) in the United States	Ages 18-22 (N=200)
ATN 113	Project PrEPare Phase II - An Open label Demonstration Project of Pre-Exposure Prophylaxis Use among 16 & 17 year old MSM in the United States	Ages 16-17 (N=100)
ATN 117 - substudy of ATN 110 & 113	Renal, endocrine, and bone changes in response to treatment with co-formulated tenofovir-emtricitabine for pre-and-post-exposure HIV prophylaxis (PrEP) in HIV uninfected young men who have sex with men	Ages 16-22 (N=100) - <i>at least</i> 50% <18 <i>years of age</i>

The Pediatric Review Committee (PeRC) reviewed this application on April 18, 2012 and concurred with the full waiver in pediatric subjects 0-16 years because the trials would be impossible or highly impractical. It was noted that according to 21 CFR 201.57(f)(9)(i), the pediatric age group is defined as "birth to 16 years"; therefore, trials conducted in adolescents ≥16 years are not required under the Pediatric Research Equity Act (PREA).

The Applicant has communicated its commitment to [REDACTED] (b) (4)

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

No new or updated information regarding overdose, drug abuse potential, withdrawal or rebound from that previously submitted to NDA 21-752 for TRUVADA is presented in this supplement.

7.7 Additional Submissions / Safety Issues

Information from the 120-day safety update has been incorporated into the main body of this review where appropriate. In general, there were no new safety concerns associated with FTC/TDF as used for PrEP. Specifically, additional data from the iPrEx trial regarding newly reported bone fractures and changes to data associated with previously reported bone fractures, and from the Partners PrEP trial regarding newly reported pregnancy outcomes (Section 7.6.2) were consistent with the safety reporting contained in the original submission. The update also included new drug level testing data reported in the FEM-PrEP trial, which was incorporated into Section 2.6 and which is consistent with previously reported analyses that demonstrate a strong correlation between drug adherence and treatment effect. No further relevant data from other clinical trials of PrEP, beyond that already been included in this review, has been made publically available.

8 Postmarket Experience

There are no postmarketing data pertaining to the use of TRUVADA or TDF as PrEP.

As part of this review, the DAVP requested the Division of Pharmacovigilance (DPV) to conduct data mining of the postmarketing Adverse Event Reporting System (AERS) database for TDF and the hepatitis B indication. This was done to inform the risk/benefit assessment for a PrEP indication as HBV patients were considered to be more representative of healthy individuals than HIV-1 infected patients. The data mining included AE cases through February 16, 2012. Twenty-three reports of renal failure were identified using the preferred terms of “renal failure”, “blood creatinine increased”, “acute renal failure”, “Fanconi syndrome”, and “Fanconi syndrome acquired”. Fifteen of the 23 cases reported pre-existing renal impairment, diabetes mellitus, prior renal toxicity with adefovir, or renal events in conjunction with deteriorating liver function. Thirteen of the 23 cases had a positive dechallenge with TDF and one had a positive rechallenge. Overall, there were four reports of Fanconi syndrome, but all four were confounded by co-morbid conditions or concurrent illness. In addition, one case of acute renal failure was also identified in a healthy individual taking FTC/TDF for post-exposure prophylaxis.

Nine additional cases were reported under preferred terms “osteoporosis”, “osteopenia”, and “osteomalacia” in HBV patients, two of which had fractures. One of these cases involving multiple atraumatic fractures in a patient with previous history of vertebral fractures on adefovir therapy had a diagnosis of secondary osteomalacia and was included among the four cases of Fanconi syndrome. Most cases of bone-related adverse events, however, were either confounded by co-morbid conditions or lacked sufficient information to make a determination of causality.

In addition to the above postmarketing information, the three-year safety data from the original registrational trials of TDF for HBV (Studies 102 and 103), which were open-label after Week 48, were consistent with the known safety profile of the drug.⁴² In this cohort of 527 subjects, creatinine and creatinine clearance remained stable over 3 years, with a mean change in creatinine of -0.02 mg/dL at Week 144. One subject had a serious AE related to increased creatinine (in the setting of chronic hypertension), which resolved after dose reduction to every other day, and one subject discontinued TDF due increased creatinine (unconfirmed 0.5 mg/dL increase). An additional two subjects experienced a ≥ 0.5 mg/dL increase in serum creatinine, but both remained on study through Week 144, after dose reduction. Decrease in serum phosphorus < 2 mg/dL was experienced by four subjects ($< 1\%$), which resolved on continued TDF therapy without

⁴² Heathcote EJ, Marcellin P, Buti M, et al. Three-year efficacy and safety of tenofovir disoproxil fumarate treatment for chronic hepatitis B. *Gastroenterology* 2011;140:132–143.

intervention. Lastly, fractures occurred infrequently and none were considered related to study drug (0.8% in the first year, 1.7% in the second year, and 1% in the third year).

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9 Appendices

9.1 Literature Review/References

A literature review of the epidemiology of HIV in the United States was conducted to evaluate the unmet need the proposed indication seeks to meet. Additionally, literature regarding the nephrotoxicity associated with tenofovir use was reviewed to inform the review of safety for this application and to provide background for the Advisory Committee. Other literature references are footnoted as they occur in the body of this review.

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Clinical Review

Peter S. Miele, M.D.

NDA 21-752/S-30

TRUVADA® (emtricitabine/tenofovir disoproxil fumarate)

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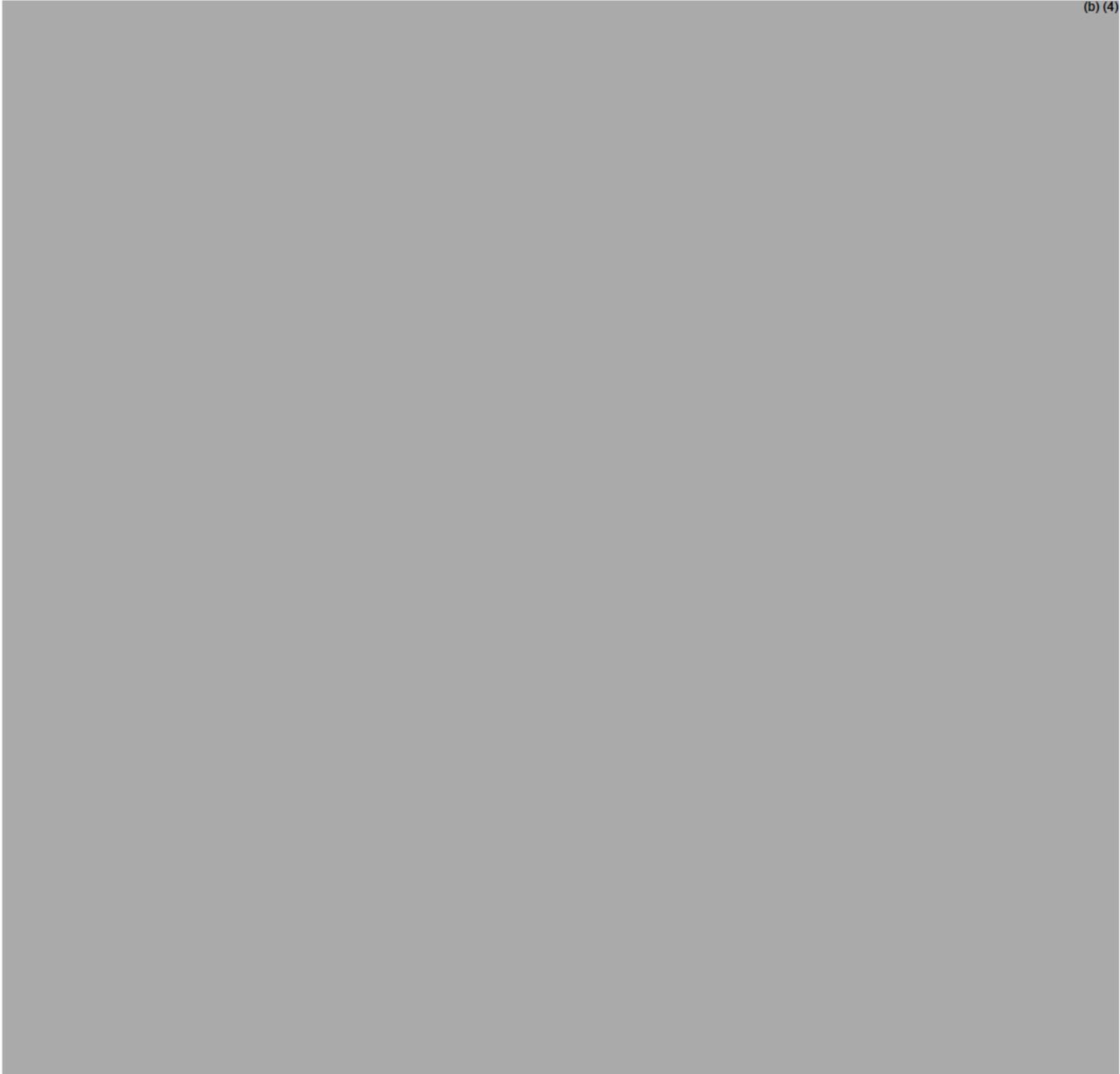
9.2 Labeling Recommendations

At the time of this writing, labeling negotiations are still in progress and final labeling has not been established. This section provides a summary of the FDA recommended major changes to the Applicant’s proposed labeling with justification for each. The recommended changes are in **blue** and edits to the Applicants language are in **track changes**.

Proposed Language from Applicant	FDA Proposed Changes
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(b) (4)

16 pages of draft labeling have been withheld immediately following this page as b4 (CCI/TS)



In addition to the above listed label recommendations, revisions to the Highlights of Prescribing Information, Section 17 Patient Counseling Information, and the Medication Guide were revised in accordance with the main body of the label. Again, final labeling is subject to change pending ongoing negotiations with the Applicant.

9.3 Advisory Committee Meeting

An Antivirals Drugs Advisory Committee (AVDAC) meeting was convened on May 10, 2012. Prior to the meeting, the members and temporary voting members were provided the background materials from the FDA and the Applicant. The following topics were proposed by FDA for discussion:

1. Does the current application support a favorable risk-benefit assessment adequate to approve TRUVADA® for a PrEP indication in:
 - a. HIV-uninfected men who have sex with men (MSM)?
 - b. HIV-uninfected partners in serodiscordant couples?
 - c. Other individuals at risk for acquiring HIV through sexual activity?

If no, what additional data are needed to support a favorable risk-benefit assessment adequate to approve TRUVADA for this indication?

If yes, please address the following topics:

2. Discuss laboratory testing during administration of TRUVADA for a PrEP indication.
 - a. How frequently should HIV testing be recommended?
 - b. Which safety assessments and how frequently should safety monitoring be recommended?
3. Please comment on the following aspects of the Applicant's proposed Risk Evaluation and Mitigation Strategy (REMS).
 - a. Prescriber education program including appropriate target prescribers.
 - b. What metrics could be considered in the REMS assessment?
 - c. What additional strategies could be used to improve the REMS?
4. Should any postmarketing studies be conducted (e.g. emergence of drug resistance, behavioral changes, patterns of use)?
5. Does the currently available evidence on the efficacy of TRUVADA for a PrEP indication make the conduct of placebo-controlled trials of primary HIV prevention unethical?

The AVDAC meeting ran for over 12 hours, in large part due to the number of presentations from the FDA and the Applicant, the number of Open Public Hearing speakers (a total of 37), and the length of the ensuing discussion. Below is a summary of the meeting and key points discussed by members of the committee.

- The majority of the committee agreed that the current application supports a favorable risk-benefit assessment adequate to approve TRUVADA for a PrEP

indication in HIV-uninfected MSM (question #1a) and in HIV-uninfected partners in serodiscordant couples (question #1b). Those who voted “Yes” stated that there was positive efficacy data demonstrated in both populations. Those who voted “No” noted concerns about placing individuals at undue risk and also expressed that there was not sufficient efficacy data because there was a limited number of African-American MSM subjects and lack of African-American female representation in the trials. For question #1c, more than half of the committee members agreed that the current application supports a favorable risk-benefit assessment adequate to approve TRUVADA for a PrEP indication in other individuals at risk for acquiring HIV through sexual activity. Those who voted “Yes” agreed that the benefit was greater than the risk. Those who voted “No” or abstained stated that there was inadequate data for this indication.

- There was a general consensus that further efficacy and safety data are needed through postmarketing observational studies to address long-term use of TRUVADA in terms of kidney toxicity and development of drug resistance.
- There was a general consensus that baseline HIV testing is crucial. Repeat testing was recommended at a frequency of every two to four months.
- Committee members recommended the following safety assessments:
 - Hepatitis B virus testing at baseline. This would be an opportunity to vaccinate susceptible patients.
 - Baseline renal function test and frequent monitoring of renal function, including monitoring for evidence of proximal tubulopathy. It was recommended that testing be performed more often in patients with risk factors for kidney disease such as diabetes, hypertension, hepatitis C, and injection drug use.
 - Testing for STIs.
 - Baseline bone mineral density test and routine monitoring.
 - Monitoring for drug resistance.
- Several committee members stated that a negative HIV test should be a requirement in the REMS. FDA noted that such a requirement would essentially result in restricted distribution, negatively impacting the availability of the TRUVADA for both treatment and prevention. FDA provided reasons for why restricted distribution would not be feasible or appropriate for this indication given the current availability of the drug for treatment. The committee thus recommended that the Applicant take a more active approach to educating prescribers and consumers. Recommendations included:
 - Creating a checklist and/or contract between provider and consumer detailing the expectations of each
 - Involving the community in creating materials for patients and physicians.

- Utilizing interpersonal communication by having community advocacy groups, organizations, and professional societies serve as mentors and role models.
 - Incorporating testimonials in education programs and marketing tools.
 - Educating non-HIV health care providers on how to recognize the symptoms of acute HIV seroconversion.
 - Continuing education (CE) programs to attract health care providers who need CE credits to retain their professional license.
 - Creating effective social marketing campaigns to educate patients.
- The committee recommended that the REMS assessment be proactive and forceful. The following metrics in the REMS assessment were recommended:
 - Create a method to capture data on how many prescriptions are written for TRUVADA for the PrEP indication.
 - Obtain data on the appropriateness in which a physician prescribes TRUVADA for the PrEP indication. Physician registries were recommended to capture this data.
 - Create a tool to capture noncompliance, including reasons for noncompliance and/or discontinuation of drug.
 - Assess each point in the CDC interim guidance for use of PrEP in MSM
 - Due to time limitations, topics 4 and 5 were not addressed at length.

Internal FDA discussions were held following the AVDAC, including a Center Director Debriefing, to discuss the AVDAC recommendations for the REMS. There was general agreement that the prescriber training and educational materials should be strengthened to more actively educate prescribers and individuals about the known and potentially serious risks associated with use of TRUVADA for a PrEP indication. However, the DRISK, DAVP, senior OSE, and CDER leadership concurred that restrictions on access to TRUVADA for a PrEP indication were not feasible based on the current availability of the product and the individual moieties in the United States.

9.4 Proposed Demonstration Projects

Because the effectiveness of any biomedical intervention is dependent on its uptake and adherence by the target populations, the use of TRUVADA for a PrEP indication is in some ways also a behavioral intervention. Clinical trials, however, may not entirely predict usage and compliance with a bio-behavioral intervention in a real-world setting. For this reason, several translational studies have been proposed to characterize the implementation of oral PrEP and evaluate the acceptability, use, and adherence to prevention strategies that include TRUVADA for a PrEP indication. The following table lists the demonstration projects being proposed at the time the application was submitted. A variety of different investigators will be sponsoring these projects. It is estimated that up to 30,000 individuals will be participating in these demonstration

projects; the Applicant will be seeking access to the data from these projects. Some of these projects will provide information related to seroconversion, including presence or absence of symptoms of acute retroviral syndrome, screening methods, and resistance analyses in seroconverters. Others will provide information related to adherence via surveys and attitudes towards PrEP. The Applicant, for example, is proposing its own demonstration project to capture the demographics and knowledge, attitude, and behaviors of prescribers and individuals using TRUVADA for a PrEP indication.

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TRUVADA® (emtricitabine/tenofovir disoproxil fumarate)

Table 56: Proposed PrEP Demonstration Projects

Study Identifier(s)	Study Sponsor	Study Title	Intervention/Duration of Drug Treatment	Number of Subjects	Population/Entry Criteria	Geographic Location
Active-Enrolling/Ongoing						
CO-US-164-0404 iPrEx OLE (IND 71, 859)	DAIDS, NIAID	Open Label Extension of Active Daily Oral FTC/TDF for HIV-1 Prevention Among Participants in the Trial "Chemoprophylaxis for HIV Prevention in Men"	<ul style="list-style-type: none"> Daily oral Truvada Treatment: 72 weeks Anticipated LPLV: June 2012 	Planned: 1,500 Enrolled: 326 Completed: 0	<ul style="list-style-type: none"> Former iPrEx study participants Former ATN 082 study participants Former CDC MSM Safety study participants (Boston and SF sites only) Adult MSM High risk for HIV infection HIV-1 seronegative 	<ul style="list-style-type: none"> USA Peru Ecuador Brazil Thailand South Africa
Planned						
CO-US-164-0432 SF & Miami PrEP Demo	DAIDS, NIAID	Implementation of HIV Pre-exposure Prophylaxis (PrEP): A Demonstration Project	<ul style="list-style-type: none"> Daily oral Truvada Treatment: 12 months Anticipated Start: March 2012 	500 (total) 100 (treatment)	<ul style="list-style-type: none"> Adult MSM and transgender females at high risk for HIV infection ≥ 18 years of age HIV-1 seronegative 	US
CO-US-164-0441 CDC PrEP MSM Demo	CDC	PrEP MSM Demonstration Project	<ul style="list-style-type: none"> Daily oral Truvada Treatment: 12 months Anticipated Start: February 2012 	1,200	<ul style="list-style-type: none"> Adult MSM ≥ 18 years of age HIV-1 seronegative 	US
CO-US-164-0451 TDF2 OLE	CDC	Open Label Extension (OLE) of Active Daily Oral TDF/FTC for HIV-1 Prevention Among Former Participants in the trial "Study of the Safety and Efficacy of Daily Oral Antiretroviral Use for the Prevention of HIV Infection in Heterosexually Active Young Adults in Botswana" (TDF-2 Trial)	<ul style="list-style-type: none"> Daily oral Truvada Treatment: 12 months Anticipated Start: February 2012 	900	<ul style="list-style-type: none"> Former TDF2 study participants Young adult males and females Ages 18-39 years Heterosexual HIV-1 seronegative 	Botswana
CO-US-164-0452 PCS 110	ATN, NICHD	Project PrEPare – An Open Label Demonstration Project of Pre-Exposure Prophylaxis Use among YMSM in the United States	<ul style="list-style-type: none"> Daily oral Truvada Treatment: 48 weeks Anticipated Start: March 2012 	200	<ul style="list-style-type: none"> Young adult MSM Ages 18-22 years High risk for HIV infection HIV-1 seronegative 	US

(b) (4)

CO-US-164-0454 PROUD	MRC	Pre-exposure Option for Preventing HIV in the UK: an Open-label Randomisation to an Immediate or Deferred Offer	<ul style="list-style-type: none"> Daily or peri-coital oral Truvada 12 months on treatment, 12 months follow-up Anticipated Start: March 2012 	500 (pilot phase) 5,000 (trial)	<ul style="list-style-type: none"> Adult MSM who have URAI ≥ 18 years of age HIV-1 seronegative 	UK
CO-US-164-0455 PCS 113	ATN, NICHD	Project PrEPare – An Open Label Demonstration Project of Pre-Exposure Prophylaxis Use among 16 & 17 Year Old MSM in the United States	<ul style="list-style-type: none"> Daily oral Truvada Treatment: 48 weeks Anticipated Start: March 2012 	100	<ul style="list-style-type: none"> Adolescent MSM Ages 16-17 years High risk for HIV infection HIV-1 seronegative 	US

(b) (4)

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TRUVADA® (emtricitabine/tenofovir disoproxil fumarate)

Study Identifier(s)	Study Sponsor	Study Title	Intervention/Duration of Drug Treatment	Number of Subjects	Population/Entry Criteria	Geographic Location
CO-US-164-0463 MTN 018/ CHOICE (IND 55,690)	DAIDS, NIAID	Committed to Having Options for Interventions to Control the Epidemic: A Follow-up Study to MTN-003	<ul style="list-style-type: none"> Any study product found to be safe and effective in VOICE study Treatment: 12 months Anticipated Start: June 2012 	4,300	<ul style="list-style-type: none"> Former VOICE study participants and some Non-VOICE participants Adult females Ages 18-50 years Heterosexual intercourse in prior 3 months HIV-1 seronegative 	Sub-Saharan Africa
(b) (4)						
CO-US-164-D201	University of Washington	An Open-label, Pilot Demonstration and Evaluation Project of Antiretroviral-Based HIV-1 Prevention Among High-Risk HIV-1 Serodiscordant African Couples	<ul style="list-style-type: none"> Daily oral Truvada Treatment: 24 months Anticipated Start: TBD 	TBD	<ul style="list-style-type: none"> Adult heterosexual HIV-1 serodiscordant couples Subjects who did not participate in the Partners PrEP Study Sexually active ≥ 18 years of age 	<ul style="list-style-type: none"> Kenya Uganda
GX-US-164-0465 Gilead PrEP Demonstration Project	Gilead	The Gilead PrEP Demonstration Project, a phase IV Observational Study of Subjects Taking Truvada as Part of a Comprehensive HIV Prevention Strategy	<ul style="list-style-type: none"> Daily oral Truvada Duration: 36 months (recruitment open ~2.5 years) Anticipated Start: June 2012 	Up to 1,000	<ul style="list-style-type: none"> Adult males and females ≥ 18 years of age High risk sexual behavior HIV-1 seronegative 	US

ATN = Adolescent Trials Network, CDC = Centers for Disease Control and Prevention, CHRP = California HIV/AIDS Research Program, DAIDS = Division of AIDS, FHI = Family Health International, FTC = emtricitabine, HIV = human immunodeficiency virus, iPrEx = Pre-exposure initiative, LPLV = last patient last visit, MDPH = Miami Department of Public Health, MRC = Medical Research Council, MSM = men who have sex with men, NIAID = National Institute of Allergy and Infectious Diseases, NICHD = National Institute of Child Health and Human Development, OLE = open-label extension, PCS = protocol concept sheet, PrEP = pre-exposure prophylaxis, SFDPH = San Francisco Department of Public Health, TBD = to be determined, TDF = tenofovir DF, TDF/FTC = tenofovir DF/emtricitabine, UCSF = University California San Francisco, URAI = unprotected receptive anal intercourse, VOICE = vaginal and oral interventions to control the epidemic, YMSM = young men who have sex with men

Source: NDA 21-752/S-30

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/s/

PETER S MIELE
07/12/2012

KENDALL A MARCUS
07/13/2012

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
	<p>Pivotal Study #2: 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)</p> <p style="text-align: center;">Indication: PrEP in HIV-1 serodiscordant couples</p>				
15.	Do all pivotal efficacy studies appear to be adequate and well-controlled within current divisional policies (or to the extent agreed to previously with the applicant by the Division) for approvability of this product based on proposed draft labeling?	<input checked="" type="checkbox"/>			Draft labeling states, "TRUVADA is indicated for pre-exposure prophylaxis (PrEP) to reduce the risk of acquiring HIV-1". The pivotal studies, however, only evaluated efficacy of PrEP in the context of sexual exposures.
16.	Do the endpoints in the pivotal studies conform to previous Agency commitments/agreements? Indicate if there were not previous Agency agreements regarding primary/secondary endpoints.	<input checked="" type="checkbox"/>			
17.	Has the application submitted a rationale for assuming the applicability of foreign data to U.S. population/practice of medicine in the submission?		<input checked="" type="checkbox"/>		
SAFETY					
18.	Has the applicant presented the safety data in a manner consistent with Center guidelines and/or in a manner previously requested by the Division?	<input checked="" type="checkbox"/>			
19.	Has the applicant submitted adequate information to assess the arrhythmogenic potential of the product (e.g., QT interval studies, if needed)?			<input checked="" type="checkbox"/>	Truvada is already approved and no arrhythmogenic issues have been identified since approval.
20.	Has the applicant presented a safety assessment based on all current worldwide knowledge regarding this product?	<input checked="" type="checkbox"/>			
21.	For chronically administered drugs, have an adequate number of patients (based on ICH guidelines for exposure ¹) been exposed at the dose (or dose range) believed to be efficacious?	<input checked="" type="checkbox"/>			Duration of Truvada therapy for PrEP is not defined and will likely be case-dependent. Between the two pivotal trials, 2830 subjects were exposed to once daily Truvada for PrEP. Median duration of exposure was 62.3 weeks for CO-US-146-0288 (iPrEx) and 23 months

¹ For chronically administered drugs, the ICH guidelines recommend 1500 patients overall, 300-600 patients for six months, and 100 patients for one year. These exposures MUST occur at the dose or dose range believed to be efficacious.

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
					for CO-US-104-0380 (Partners PrEP).
22.	For drugs not chronically administered (intermittent or short course), have the requisite number of patients been exposed as requested by the Division?	<input checked="" type="checkbox"/>			See above.
23.	Has the applicant submitted the coding dictionary ² used for mapping investigator verbatim terms to preferred terms?		<input checked="" type="checkbox"/>		For CO-US-146-0288 (iPrEx), all AEs were coded using MedDRA Version 10; for CO-US-104-0380 (Partners PrEP), it is not clear which version of MedDRA was used. A coding dictionary was not found.
24.	Has the applicant adequately evaluated the safety issues that are known to occur with the drugs in the class to which the new drug belongs?	<input checked="" type="checkbox"/>			
25.	Have narrative summaries been submitted for all deaths and adverse dropouts (and serious adverse events if requested by the Division)?	<input checked="" type="checkbox"/>			
OTHER STUDIES					
26.	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?	<input checked="" type="checkbox"/>			Nonclinical overview includes animal studies of PrEP. A study summary (including draft manuscript), CRFs, and datasets for Study CDC 4323 are included in Module 5.
27.	For Rx-to-OTC switch and direct-to-OTC applications, are the necessary consumer behavioral studies included (e.g., label comprehension, self selection and/or actual use)?			<input checked="" type="checkbox"/>	
PEDIATRIC USE					
28.	Has the applicant submitted the pediatric assessment, or provided documentation for a waiver and/or deferral?	<input checked="" type="checkbox"/>			
ABUSE LIABILITY					
29.	If relevant, has the applicant submitted information to assess the abuse liability of the product?			<input checked="" type="checkbox"/>	No new or updated information regarding overdose or drug abuse is presented within this sNDA
FOREIGN STUDIES					
30.	Has the applicant submitted a rationale for assuming the applicability of foreign data in the submission to the U.S.		<input checked="" type="checkbox"/>		

² The “coding dictionary” consists of a list of all investigator verbatim terms and the preferred terms to which they were mapped. It is most helpful if this comes in as a SAS transport file so that it can be sorted as needed; however, if it is submitted as a PDF document, it should be submitted in both directions (verbatim -> preferred and preferred -> verbatim).

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
	population?				
DATASETS					
31.	Has the applicant submitted datasets in a format to allow reasonable review of the patient data?		<input checked="" type="checkbox"/>		Raw datasets in SAS transport format were submitted. The submitted datasets are in a non-standardized format (i.e., not CDISC SDTM). Data elements are not clearly defined; the define pdf file is inadequate to easily identify the data elements. There is no clear explanation in the define file of data origins, other than annotated CRF.
32.	Has the applicant submitted datasets in the format agreed to previously by the Division?	<input checked="" type="checkbox"/>			
33.	Are all datasets for pivotal efficacy studies available and complete for all indications requested?	<input checked="" type="checkbox"/>			
34.	Are all datasets to support the critical safety analyses available and complete?	<input checked="" type="checkbox"/>			
35.	For the major derived or composite endpoints, are all of the raw data needed to derive these endpoints included?	<input checked="" type="checkbox"/>			
CASE REPORT FORMS					
36.	Has the applicant submitted all required Case Report Forms in a legible format (deaths, serious adverse events, and adverse dropouts)?	<input checked="" type="checkbox"/>			
37.	Has the applicant submitted all additional Case Report Forms (beyond deaths, serious adverse events, and adverse drop-outs) as previously requested by the Division?			<input checked="" type="checkbox"/>	
FINANCIAL DISCLOSURE					
38.	Has the applicant submitted the required Financial Disclosure information?	<input checked="" type="checkbox"/>			
GOOD CLINICAL PRACTICE					
39.	Is there a statement of Good Clinical Practice; that all clinical studies were conducted under the supervision of an IRB and with adequate informed consent procedures?	<input checked="" type="checkbox"/>			

IS THE CLINICAL SECTION OF THE APPLICATION FILEABLE? Yes

The following requests were sent to the Applicant on January 20, 2012; the applicant confirmed that requested items would be provided during the review cycle:

1. Please provide a dataset for each study, CO-US-104-0288 and CO-US-104-0380, which lists by clinical site and treatment arm: the number of participants screened, enrolled, and discontinued; site specific efficacy effect size and variance; and the number of AEs, SAEs, deaths, and protocol violations. In addition, include the full contact information for each investigator/clinical site.

File name: 5_Clinical Filing Checklist for NDA_BLA or Supplement 010908

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

2. Please provide an analysis dataset for each study, CO-US-104-0288 and CO-US-104-0380, consisting of subject ID, subject's demographics and baseline characteristics, clinical site, assigned and actual treatment arm, special study features such as index participant or partner, flags for analysis populations (intention-to-treat [ITT], modified ITT [mITT], per protocol [PP], and safety population [SP]), date of screening, date of randomization, first date of study medication, first date of HIV-1 seroconversion, HIV-1 RNA at seroconversion, date of discontinuation, reason for discontinuation, last visit date, and other important covariates such as adherence to study drug as well as other antiviral drugs.

All input datasets used for the generation of analysis datasets should be submitted to the CDER EDR. SAS programs for the generation of the two analysis datasets should also be provided. Additionally, SAS programs for the primary efficacy and safety endpoints should be provided.

3. In addition to the above, all datasets should include a column identifying the actual treatment arm for each subject.
4. The MEDRAPT columns in the CO-US-104-0288 AE datasets and the MEDTERM 1 column in the CO-US-104-0380 AE dataset appear to include PT, SOC and LLT terms all within the same entry field. To facilitate review of the safety endpoints, different MedDRA codes should be separated into individual columns for each reported AE, one entry per column, with appropriate column headers.
5. Please indicate which version of MedDRA was used for coding in CO-US-104-0380.
6. Please confirm that the datasets included in the CO-US-104-0288 addendum contain cumulative data from enrollment through the November 1, 2010 cut-off and thus encompass all of the data presented in the primary analysis datasets. In addition, please clarify the distinction between datasets with a July 29, 2011 cut-off and those with a September 09, 2011 cut-off included in the addendum.
7. Please indicate which dataset(s) were used to generate Table 1.1.1.1 in the CO-US-104-0288 CSR. Similarly, indicate which dataset(s) were used to generate Figures 8-1 and 8-2 in the CO-US-104-0380 CSR, since the report indicates that pre-existing tables from were used the DSMB report.
8. Please provide analysis datasets for laboratory testing for each study, CO-US-104-0288 and CO-US-104-0380, that includes:
 - Subject ID
 - Treatment assignment
 - Date of lab test
 - Study Day
 - Lab test code
 - Lab category (hematology, chemistry, coagulation, viral load, lipids, etc.)
 - Baseline lab value
 - Date of baseline lab value
 - Lab test result in standard units
 - Unit of measurement
 - Reference range lower limit

File name: 5_Clinical Filing Checklist for NDA_BLA or Supplement 010908

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

- Reference range upper limit
- Reference range indicator for lab test result: normal, high, low
- Change from baseline value
- Toxicity Grade (DAIDS)
- Visit Number or Study Week
- Visit name: Screening, Baseline, Treatment, Follow-up, etc.
- Flag indicating whether subject was taking study drug at time of lab test
- Drug start date
- Drug stop date

The following additional comment will be sent in the 60-Day Filing Letter:

9. Please submit a rationale for assuming the applicability of foreign data in the submission to the U.S. population.

Peter S. Miele, M.D.	February 8, 2012
_____ Reviewing Medical Officer	_____ Date
Kendall A. Marcus, M.D.	February 8, 2012
_____ Clinical Team Leader	_____ Date

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

PETER S MIELE
02/13/2012

KENDALL A MARCUS
02/13/2012