MEMORANDUM

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TO: FDA Antiviral Products Advisory Committee

FROM: The Review Team for NDA 21-752/S-30

THROUGH: Debra Birnkrant, M.D.
Director, Division of Antiviral Products

DRUG: TRUVADA® (emtricitabine-tenofovir disoproxil fumarate)

SUBJECT: Background Package for NDA 21-752/Supplement 30

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I. Introduction

The Joint United Nations Programme on HIV/AIDS (UNAIDS) estimates that 2.7 million (2.4 million–2.9 million) people were newly infected with human immunodeficiency virus (HIV) in 2010.[1] Globally, the annual number of new HIV infections is declining, although there is significant regional variation. In sub-Saharan Africa, an estimated 1.9 million (1.7 million-2.1 million) people became infected in 2010, accounting for 70% of new HIV infections that year.

The HIV epidemic in the United States, meanwhile, has remained steady with little change in the annual incidence of new infections since 2004. According to the U.S. Centers for Disease Control and Prevention (CDC), between 48,100 and 56,000 people acquire HIV infection in the U.S. annually. About 75% of new U.S. infections occur in men.[2] African-Americans and Hispanics/Latinos are experiencing the heaviest impact of the U.S. epidemic, with rates that are approximately 8 and 3 times the rates in Caucasians, respectively. Each year African-American males have the highest rate of new infections overall, and among women, African-American women experience the highest HIV incidence rates. At the end of 2008, an estimated 1,178,350 persons were living with HIV in the U.S., including 236,400 (20.1%) whose infection was undiagnosed.[3]

Unprotected sex between men who have sex with men (MSM) continues to be the main driver of HIV transmission in the United States. Although MSM represent about 2% of the overall U.S. population aged ≥ 13 years, they account for more than half (56-61%) of new HIV infections annually and represent nearly half of all persons living with HIV in this country.[4,5] Moreover, while the overall HIV incidence in the U.S. has remained relatively stable in recent years, the estimated number of new infections among 13-29 year old MSM has increased significantly (38%) from 2006 to 2009, largely driven by a 48% increase among young African-American MSM (Figure 1).[6]

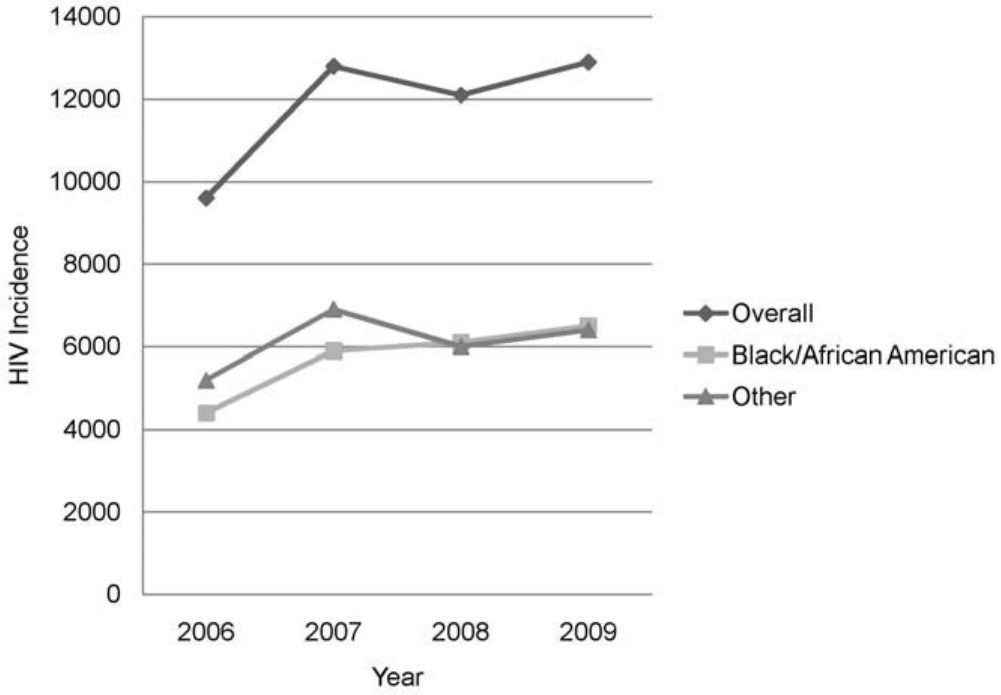

Figure 1: HIV incidence among 13-29 year old men who have sex with men (MSM) overall and by race/ethnicity - United States, 2006-2009. (Prejean 2011)

Despite widespread awareness of the epidemic and causes of HIV infection, MSM in the U.S. continue to engage in sexual and drug-use behaviors that increase the risk of HIV infection. The sexual behavior that carries the highest risk for HIV transmission between MSM is unprotected anal sex.[7] Sexual transmission of HIV has also been associated with drug and alcohol use and nondisclosure of HIV infection.[8]

Risk behavior data collected through 2008 by the CDC's National HIV Behavioral Surveillance (NHBS) system showed that 76% of MSM reported having more than one male sex partner during the past 12 months.[9] Moreover, 54% of MSM reported having unprotected anal intercourse during the past 12 months and 25% reported unprotected anal intercourse with a casual male partner (someone with whom the participant did not feel committed, did not know very well, or had sex with in exchange for something such as money or drugs). Of the MSM whose most recent male partner was a casual partner, 53% did not know the HIV status of their partner. Overall, during their most recent sexual encounter, 12% of MSM engaged in either unprotected insertive or receptive anal sex with an HIV-positive partner or partner of unknown HIV status. In addition, 46% of MSM reported noninjection drug use during the past 12 months and 57% reported binge drinking during the previous 30 days. Approximately half of the men who used alcohol or drugs during their most recent sexual encounter also reported engaging in unprotected anal sex. Finally, while 90% of participants had been tested for HIV during their lifetime, only 62% had been tested during the past 12 months and only 18% had recently participated in a behavioral intervention.

HIV testing data collected as part of the NHBS system indicated an HIV prevalence of 19% among MSM in 2008.[10] Of the HIV-infected MSM, 44% were unaware of their HIV

infection. HIV prevalence and lack of awareness of infection status were highest among young and minority MSM. More than half (55%) of MSM unaware of their infection reported not having an HIV test during the preceding 12 months. Among those who had tested negative during the preceding year, the study found a 6.9% prevalence of new infections.[11]

In comparison, in a CDC-funded study conducted during 2006-2007 in 16 cities within areas with high rates of poverty and HIV morbidity, African-American and Hispanic women aged 18 to 50 years were recruited at venues and by peers for HIV testing. Enrolled women could recruit one or two recent (≤3 months) male sex partners; both partners completed a behavioral interview and were offered optional HIV testing. Analysis was limited to partnerships with HIV test results for both partners. HIV prevalence was reported as 3.3% amongst 933 minority females and their heterosexual partners (1021 partnerships). HIV testing of all individuals confirmed HIV positive status in 21 individuals and identified 41 previously undiagnosed HIV infections. The majority of individuals diagnosed with HIV infection in this study were found to be in serodiscordant relationships.[12]

The principal interventions used to date to prevent HIV transmissions have been voluntary HIV testing, risk reduction counseling, and promotion of condoms. The effectiveness of these interventions, however, has been variable. CDC currently recommends HIV testing at least annually for sexually active MSM to identify HIV infections and prevent ongoing transmission; for MSM with additional risk factors, the recommendation for HIV testing is every 3–6 months.[13] Studies show that persons aware of their HIV infection often take substantial steps to reduce their risk behaviors.[14] The findings from the NHBS, however, suggest that adherence to annual HIV testing for MSM is low and that even among MSM who reported being tested during the past 12 months, a substantial proportion were newly infected. Mathematical modeling done in heterosexual HIV transmission suggests that early infection plays an important part in HIV transmission, accounting for up to 38% of sexual transmissions.[15] Particularly concerning, almost half of the men who tested positive for HIV infection during the NHBS survey were unaware of their infection. Persons who do not know they are infected are estimated to account for more than half of sexually transmitted HIV infections in the U.S.[16] CDC recently broadened its expanded HIV testing initiative to reach more MSM.

Condoms are highly efficacious in preventing sexually transmitted infections[17]; but consistent condom use is infrequent among MSM, thus limiting the effectiveness of condoms in preventing HIV transmission. About half of the men surveyed in the NHBS reported unprotected anal intercourse in the past year, with approximately 12% engaging in unprotected anal sex with a partner of unknown HIV status. Barriers to condom use are varied, but may include personal preference, inability to negotiate condom use with a partner either due to partner pressure or intoxication from alcohol or drug use, or a disconnect between sexual behavior and risk perception. In a recent HIV testing program of MSM at a New England bathhouse, the majority (65%-75%) of men who engaged in

unprotected sex did not believe their risk for HIV infection was high, despite the finding of a high prevalence of sexually transmitted infections.[18]

Behavioral interventions have been shown to reduce risk behavior by 20% to more than 40%.[19,20] Recent participation in behavioral interventions among MSM, however, is reportedly low. In addition, not discussing HIV status and not knowing a partner's HIV status were particularly common findings among the casual partnerships of U.S. MSM surveyed in the NHBS. A high proportion of MSM of all races and ethnicities who engaged in unprotected sex did not discuss their HIV status beforehand.

An alternative approach that has recently demonstrated efficacy in preventing HIV transmission on a population level is the treatment of HIV-infected individuals. The HPTN 052 trial of 3,400 heterosexual couples in Africa found that use of antiretroviral therapy in the HIV-infected partner reduced HIV transmission risk by 92%, in the context of intensive counseling and viral load monitoring.[21] Comparable studies in MSM are lacking. Translating the findings of HPTN 052 into public policy, however, is challenging and requires massive scale-up of antiretroviral therapy for HIV treatment. In addition to identifying persons with undiagnosed HIV infection, high uptake and retention in HIV care by these individuals is necessary for these efforts to result in meaningful reductions in HIV incidence and transmission. In 2006, CDC recommended screening persons aged 13–64 years for HIV infection in health-care settings that have a prevalence of undiagnosed HIV infection of ≥0.1%.[13] As a result of CDC's initiative, 18,432 HIV infections were newly diagnosed between 2007 and 2010.[22] Initiation of HIV care soon after diagnosis is typically recommended, yet a meta-analysis of 28 studies from multiple U.S. regions found that 28% of persons did not enter care within 4 months of HIV diagnosis.[23] In addition, an estimated 41% of HIV-infected persons did not average at least two care visits in a year, as recommended by the U.S. Department of Health and Human Services.[24] Data from CDC suggest that only 51% of diagnosed persons stay in medical care. Consequently, only an estimated 19% to 28% of all HIV-infected persons in the U.S. have a suppressed viral load (Figure 2). [25,26]

Reasons for non-adherence with HIV care and antiretroviral therapy recommendations can vary. In a recent South African cross-sectional study, 20% of newly diagnosed HIV-infected individuals refused therapy; the leading reason for refusal was "feeling healthy" (37%), despite the presence of suppressed CD4+ cell counts and co-morbidities such as active tuberculosis.[27] In another study, about 40% of HIV-infected individuals in serodiscordant couples were not willing to initiate antiretroviral therapy for the purpose of preventing HIV transmission to their partners. These HIV-infected individuals cited concerns about side effects, earlier development of resistance, social stigma, and pill burden as reasons.[28]

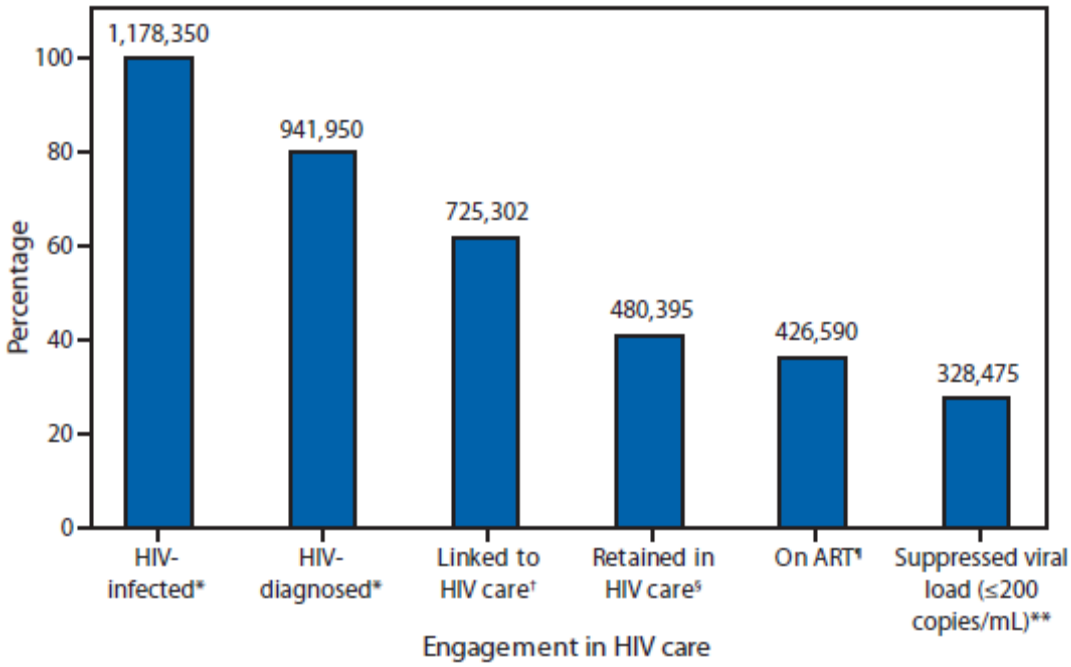

Figure 2: Number and percentage of HIV-infected persons engaged in selected stages of the continuum of HIV care -United States. (CDC MMWR 2011; 60)

In summary, despite the availability of several efficacious prevention modalities, the HIV epidemic in the U.S. continues unabated. The populations most at risk for HIV infection continue to be MSM and minorities. Aside from condoms, which are not being used consistently by the populations at risk, there is no approved product on the market for an HIV prevention indication. Intense efforts to develop a vaccine to prevent against HIV infection have thus far been unsuccessful. Scale-up of universal HIV treatment for infected persons will take significant time and effort, and the success of such a modality as secondary prevention is highly dependent on adherence to care and durable viral suppression.

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.[29] The strategy identifies three critical steps to reduce HIV infections: 1) intensifying HIV prevention efforts in communities where HIV is most heavily concentrated (including MSM, African-Americans, Hispanics/Latinos, and substance users); 2) expanding efforts to prevent HIV infection by using a combination of effective, evidence-based approaches; and 3) educating the general public about the threat of HIV and how to prevent it.

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 novel evidence-based approaches to HIV prevention that can augment the existing strategies. The use of approved antiretroviral drugs in high risk HIV-uninfected

individuals as pre-exposure prophylaxis (PrEP) against HIV infection offers a potential intervention for primary HIV prevention that could potentially contribute to addressing this unmet need. For these reasons, the U.S. Food and Drug Administration (FDA) granted a priority review to the marketing application for TRUVADA® (emtricitabine-tenofovir disoproxil fumarate) for the prevention of sexual acquisition of HIV-1 in adults at risk.

II. Overview of HIV Prevention Trials

In 2010-2011, results from several clinical trials demonstrated proof-of-concept for PrEP as an HIV prevention strategy. Trials evaluating the safety and efficacy of topical 1% tenofovir gel and oral tenofovir disoproxil fumarate (TDF) and emtricitabine-tenofovir disoproxil fumarate (FTC/TDF) have been conducted in African women at risk of heterosexual HIV acquisition (CAPRISA 004, FEM-PrEP, Partners PrEP, CDC TDF2, VOICE), African heterosexual men (Partners PrEP, CDC TDF2), MSM globally (iPrEx), and Thai injection drug users (Bangkok Tenofovir Study). Table 1 summarizes the ongoing and completed human efficacy trials of oral PrEP.

Table 1: 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 futility 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 futility 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

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

CAPRISA 004 was the first trial to show that an antiretroviral drug could reduce the risk of HIV acquisition. In CAPRISA 004, 1% tenofovir vaginal gel applied peri-coitally (before and after sex) reduced HIV acquisition in women by 39% [hazard ratio 0.61; 95% confidence interval (CI) 0.40–0.94, p=0.017].[30] 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.[31] 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.[32]

Subsequently, the iPrEx trial in 2,499 HIV-uninfected MSM reported that daily use of oral FTC/TDF reduced HIV acquisition by 44% [95% CI 15-63].[33] Again efficacy was strongly correlated with adherence; a ~90% risk reduction was estimated among subjects with measurable intracellular drug levels. On January 28, 2011, based on the published results of the iPrEx trial, CDC issued interim guidance on the use of once-daily FTC/TDF as PrEP in MSM.[34] Presently, in the context of the publicized efficacy results of iPrEx,

the uptake, adherence, risk behaviors, and efficacy of FTC/TDF as PrEP are being evaluated in MSM in an open-label extension phase (iPrEx-OLE). The iPrEx trial is discussed in greater detail later in this document.

In July 2011, at the 6th International AIDS Society (IAS) Conference, two additional placebo-controlled trials, CDC TDF2 and Partners PrEP, reported 62% to 73% protection against HIV acquisition in heterosexual men and women when daily oral TDF, with or without FTC, was used.[35,36] 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 for both men and women. The Partners PrEP trial is discussed 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. 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 bone mineral density (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 entered the study with unrecognized acute wild-type HIV infection. Subsequently, high levels of multiple drug resistance mutations 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, a similar trial in African women, FEM-PrEP, evaluating daily oral dosing with FTC/TDF was halted on April 18, 2011 due to futility.[37] The FEM-PrEP trial enrolled 2,120 high-risk women, of which 2,056 contributed follow-up data and approximately 80% completed the trial.[38] The FEM-PrEP trial reported 68 HIV seroconversion events, 33 in the FTC/TDF group and 35 in the placebo; thus, a protective effect of FTC/TDF as PrEP could not be demonstrated. Among pre-specified adverse event categories, only the rates of vomiting and nausea were significantly higher in the FTC/TDF arm. Despite substantial counseling efforts in FEM-PrEP, inadequate adherence was demonstrated by plasma drug concentrations; detectable drug in blood samples was found in less than half of the women evaluated. 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 incidence 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 adherence and the low risk perception among participants.

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 are 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 because protection from HIV infection was not observed.[39] 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 these four oral PrEP trials in women, which used identical antivirals and dosing schedules, are being further investigated at this time; however, as further discussed in this document, adherence to prescribed interventions appears to play a key role.

The completed clinical trials of topical and oral PrEP are graphically depicted in Figure 3 by degree of reported efficacy.[40]

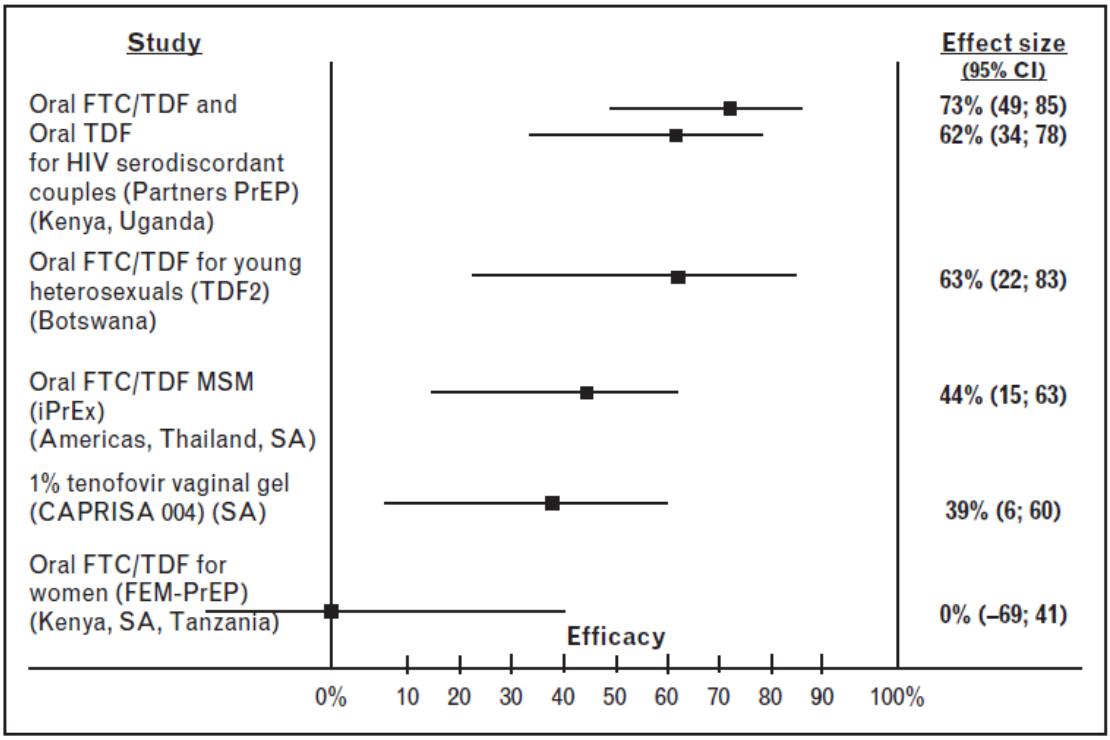

Figure 3: Topical and oral pre-exposure prophylaxis: HIV-prevention efficacy as reported from completed clinical trials. Oral TDF data from VOICE not included as data not yet released. (Karim 2011)

The safety of TDF as PrEP was additionally evaluated in two Phase 2 clinical trials: Study CDC 4323 in U.S. MSM and Study FHI PrEP in African women. In CDC 4323, 400 MSM subjects were randomized to either daily oral TDF or placebo at enrollment or after a 9-month delay.[41] In addition, a BMD substudy was conducted among the 200 subjects enrolled at one site (San Francisco). Results from CDC 4323 showed no notable differences between TDF and placebo in key safety parameters. No significant between-group differences were noted for renal adverse events (i.e., elevations in serum creatinine or reductions in serum phosphorus). New onset back pain was reported by 13% of TDF

versus 6% of placebo subjects. The BMD substudy showed that daily oral TDF resulted in a statistically significant decline in BMD at the total hip and femoral neck compared with placebo, with the largest decline in BMD occurring during the first 12 months of treatment for the TDF immediate-treatment group.[42] In the TDF delayed arm, an initial decrease in BMD was also observed upon initiation of TDF treatment. Of note, the substudy found a higher than expected prevalence of low BMD in these healthy HIV-uninfected men. Low BMD was found in 10% of participants at baseline and was particularly associated with amphetamine and inhalant use. In this trial, 7 HIV seroconversion events reported among 400 MSM participants, but none occurred during treatment with TDF. Furthermore, no evidence of sexual risk compensation was noted among participants during the trial.[43]

Similarly, the FHI PrEP study in 936 HIV-uninfected West African women at high risk for HIV infection did not demonstrate significant differences between TDF and placebo in adverse events or laboratory parameters.[44] No between-treatment differences were observed in renal or hepatic safety (overall or among HBsAg-positive women). Condom use reportedly increased 40% from baseline during the trial and the mean number of reported sexual partners decreased. In this trial, 8 HIV seroconversion events were reported, 2 in the TDF group and 6 in the placebo group, but the trial was not powered to conclusively evaluate the effectiveness of TDF as PrEP.

III. Overview of Tenofovir and Emtricitabine Safety

Emtricitabine (FTC) and tenofovir disoproxil fumarate (TDF) are the two drugs contained in the fixed drug combination of TRUVADA®. TRUVADA was first approved on August 2, 2004 for the treatment of HIV-1 infection in adults over 18 years of age, in combination with other antiretroviral products. FTC and TDF are components of every preferred regimen currently recommended for HIV-1-infected treatment-naïve patients in the Department of Health and Human Services (DHHS) Adult and Adolescent HIV Treatment Guidelines.[45] As such, TRUVADA is one of the most extensively used products for HIV treatment.

Emtricitabine appears to be well tolerated and drug-related adverse events attributed to its use are uncommon. One of the few events considered related to emtricitabine use is discoloration of the palms and soles. Adverse events related to TDF use occur more frequently, although these are generally mild and infrequently result in drug discontinuation. These events will be discussed in the review of clinical trial data.

An important and potentially serious adverse event associated with TDF is renal toxicity. TDF is structurally similar to two other drugs, adefovir and cidofovir, both believed to cause renal toxicity through mitochondrial injury of proximal renal tubules.[46] In the clinical trials used to support marketing approval of tenofovir disoproxil fumarate, no study subjects discontinued tenofovir due to renal toxicity.[47] Subsequently, post-marketing reports identified cases of acute renal failure, acute tubular necrosis, Fanconi syndrome, proximal renal tubulopathy, interstitial nephritis, hypophosphatemia,

nephrogenic diabetes insipidus, osteomalacia, muscular weakness, and myopathy. An increasing body of evidence, including case reports, case series, and observational studies, support that tenofovir is nephrotoxic due to affects on proximal renal tubules.[48]

Similar to adefovir and cidofovir, tenofovir is excreted through both glomerular filtration and active proximal tubular secretion. Tenofovir is transported into renal proximal tubule cells by anion transporters and secreted into tubules by apical membrane transporters. Either decreased glomerular filtration or drug interactions may lead to intracellular accumulation of tenofovir in renal tubules, and increase the risk for nephrotoxicity.[48] Nephrotoxicity appears to occur primarily through mitochondrial injury. Renal biopsies from a case series of 13 patients with tenofovir nephrotoxicity demonstrated a distinct pattern of proximal tubular injury characterized by severe mitochondrial damage.[49] A case series reviewing the features of renal injury in 22 patients receiving tenofovir also described biopsy findings of acute tubular damage with abnormal mitochondrial morphology.[50]

Tenofovir-associated nephrotoxicity can present as proximal tubular dysfunction with preserved or decreased renal function.[51] Initial clinical signs may include varying degrees of hypophosphatemia, hypouricemia, proteinuria or glycosuria.[52] More severe presentations of proximal tubulopathy include acute tubular injury or Fanconi syndrome, characterized by renal tubular acidosis, normoglycemic glycosuria, aminoaciduria, hypophosphatemia, hypouricemia and tubular proteinuria.[51] Characteristic biopsy findings include proximal tubular injury ranging from mild and localized to severe and diffuse, and varying degrees of tubular atrophy and interstitial fibrosis; moreover, multiple case reports indicate that recovery of renal function is often incomplete following overt tenofovir-associated Fanconi syndrome.[49,53] Phosphate wasting secondary to proximal tubular dysfunction can lead to osteomalacia, bone pain, decreased bone mass, and fractures.[54] Risk factors for development of tenofovir-associated Fanconi syndrome include increased age, low body weight, pre-existing decrease in renal function, and concomitant use of nephrotoxic drugs.[55]

While severe tenofovir-associated renal dysfunction manifesting as Fanconi syndrome or acute tubular injury appears to be rare, subclinical tubular abnormalities can be found in most cohorts of HIV-infected patients, whether taking tenofovir or not. In a cross-sectional study of 99 HIV-infected patients with normal creatinine values, one group found evidence of subclinical proximal tubule injury in 81% of patients on antiretroviral (ARV) drugs, regardless of tenofovir use, and in 53% of treatment-naïve patients.[53] In another cross-sectional study of more than 200 HIV-infected patients with normal creatinine clearance, 22% of patients receiving tenofovir had evidence of abnormal proximal tubule function as compared with 6% on ARV not containing tenofovir and 12% of treatment-naïve patients.[56] Three patients receiving tenofovir in this cohort had evidence of complete Fanconi syndrome. These findings highlight that proximal tubular dysfunction may be observed in the setting of normal glomerular function as measured by creatinine clearance, and may be observed in HIV-infected individuals, regardless of treatment status.

In summary, while serious renal toxicity appears to occur infrequently with tenofovir use, subclinical proximal tubule dysfunction may occur more commonly. However, the incidence of tenofovir-induced tubular dysfunction relative to the incidence observed with other antiretrovirals or with untreated HIV infection, as well as the long-term significance for kidney and bone health, is not yet clear. Prospective monitoring for early identification of renal tubular dysfunction and early intervention to prevent development of the more serious manifestation of Fanconi syndrome and osteomalacia is not standardized at this time. Potential targets for monitoring include serum phosphate, serum creatinine, calculated creatinine clearance, urine protein-creatinine ratio, proteinuria, glycosuria, fractional excretion of phosphate, urine b2-microglobulin, and uricosuria.[57, 58]

The U.S. Product Information label for VIREAD® (tenofovir disoproxil fumarate) currently recommends that creatinine clearance be calculated in all patients prior to initiating therapy and as clinically appropriate during therapy with VIREAD.[47] Routine monitoring of calculated creatinine clearance and serum phosphorus should be performed in patients at risk for renal impairment. In addition, the label recommends considering assessment of bone mineral density (BMD) for adults and pediatric patients who have a history of pathologic bone fracture or other risk factors for osteoporosis or bone loss. It also states that although the effect of supplementation with calcium and vitamin D has not been studied, such supplementation may be beneficial for all patients.

The Infectious Diseases Society of America (IDSA) provides the following guidelines for monitoring renal function in patients receiving TDF: Patients who have an estimated glomerular filtration rate <90 mL/min per 1.73 m^2, patients receiving other medications eliminated via renal secretion, patients with other comorbid diseases (e.g., diabetes or hypertension), or patients receiving ritonavir-boosted protease inhibitor regimens should be monitored at least biannually for measurements of renal function (serum creatinine and calculated creatinine clearance), serum phosphorus, and urine analysis for proteinuria and glycosuria.[59] IDSA rates this recommendation as "B-III" indicating that the evidence to support it is based on opinions of respected authorities, clinical experience, descriptive studies, or reports of expert committees.

IV. FDA Review of iPrEx and Partners PrEP Trials

The Applicant submitted an efficacy supplement to the New Drug Application (NDA) for emtricitabine-tenofovir disoproxil fumarate (TRUVADA®) on December 15, 2011 for a proposed indication of pre-exposure prophylaxis (PrEP) to reduce the risk of sexually acquired HIV-1 in uninfected adults. Clinical trial data to support the proposed indication is derived mainly from the iPrEx and Partners PrEP trials. Key findings from the FDA review of these trials are discussed here.

a. iPrEx

The iPrEx trial was a large, Phase 3, multicenter, international, randomized, double-blind, placebo-controlled trial of once-daily oral administration FTC/TDF (fixed-dosed FTC

200 mg/TDF 300 mg) for HIV prevention in initially HIV-uninfected MSM and transgendered women at high risk for HIV infection. The trial was sponsored by the U.S. National Institutes of Health (NIH), with co-funding provided by the Bill and Melinda Gates Foundation (BMGF). The trial evaluated FTC/TDF as PrEP as compared with placebo, both in combination with provision of condoms and active behavioral intervention. The Applicant's background document provides further details regarding the study design, eligibility criteria, study population demographics and subject disposition.

The FDA review of safety and efficacy in the iPrEx trial is based on data collected through the double-blind period, based on study visits through a November 21, 2010 cut-off date. Study drug dispensation was stopped in all subjects on August 1, 2010, and subjects were asked to return any unused study medication thereafter. Subjects were asked to present to the clinic for 2 more monthly visits to monitor HIV seroconversion. Efficacy based on HIV seroconversion incidence was assessed for the treatment phase (first study drug dispensation date up to the first study visit following July 31, 2010) and for the post-treatment phase (through November 21, 2010). Median duration of exposure to study drug was 77.9 weeks in the FTC/TDF group and 77.1 weeks in the placebo group.

The trial randomized 2,499 subjects to either FTC/TDF or placebo in a 1:1 fashion beginning in July 2007. The intent-to-treat population (ITT) included 2,452 randomized subjects with a post-baseline HIV test (n=1226 in each group). After randomization, 10 subjects were found to have been HIV-infected upon enrollment (FTC/TDF 2, placebo 8). The modified intent-to-treat population (mITT), therefore, included 2,442 subjects (FTC/TDF 1224, placebo 1218).

Efficacy

A total of 147 seroconversion events were reported through November 21, 2010 in the ITT population. Six of these infections occurred during the post-treatment period (after the first post-July 31, 2010 study visit but before November 21, 2010). For the mITT analysis, 131 seroconversion events were reported during the on-treatment period: 48 in the FTC/TDF and 83 in the placebo group. During the on-treatment period, based on 1,998 patient-years in 1224 FTC/TDF subjects and 1,986 patient-years in 1218 placebo subjects, FTC/TDF demonstrated a relative-risk reduction of 42% (95% CI 22-63%) compared with placebo. Through the November 21, 2010 cutoff date, the relative risk reduction in the mITT population was 40% (95% CI 19-60%).

Subgroup efficacy analysis by adherence stratification did not support a correlation between observed risk reduction and self-reported adherence (≥90% adherence). Self-reported adherence was found to be an unreliable measure as it did not correlate with measurable intracellular drug levels in a separate subgroup analysis. However, report of poor adherence was predictive of finding no measurable drug concentrations on blood testing. Risk reduction also did not generally correlate with diagnosis of sexually transmitted infection.

The following are exploratory analyses based on a post-hoc subgroup analysis of FTC and TDF drug concentrations in study subjects receiving FTC/TDF who seroconverted during the trial as compared to matched uninfected controls. Covariates were first identified in study subjects contained within the subgroups that appeared to correlate with greater adherence, as defined by measurable drug concentrations. Outcomes by these covariates were then evaluated within the entire study population. Because these analyses are exploratory, no conclusions can be made based on these findings. Study subjects were not stratified on these covariates and the iPrEx trial was not large enough to convincingly demonstrate efficacy in these subgroups. These are meant to be hypothesis-generating analyses.

Greater risk reduction relative to overall mean risk reduction was observed among participants who reported unprotected receptive anal intercourse (URAI) at baseline (53%; 95% CI 29-69%). Greater relative risk reduction was also observed among participants older than 25 years of age (56% [95% CI 23-75%] compared with 28% in those less than 25 years old) and among participants reporting secondary education or higher (52% [95% CI 28-69%] compared with 12% in those with less than secondary education). Among the cohort of MSM older than 25 years of age, with at least a secondary education or higher, and reported URAI at baseline, the relative risk reduction compared with placebo was 85% (95% CI 68-95%). These subject characteristics also correlated with greater adherence as demonstrated by an analysis of measurable intracellular drug concentrations obtained as part of a post-hoc substudy (Figure 4).

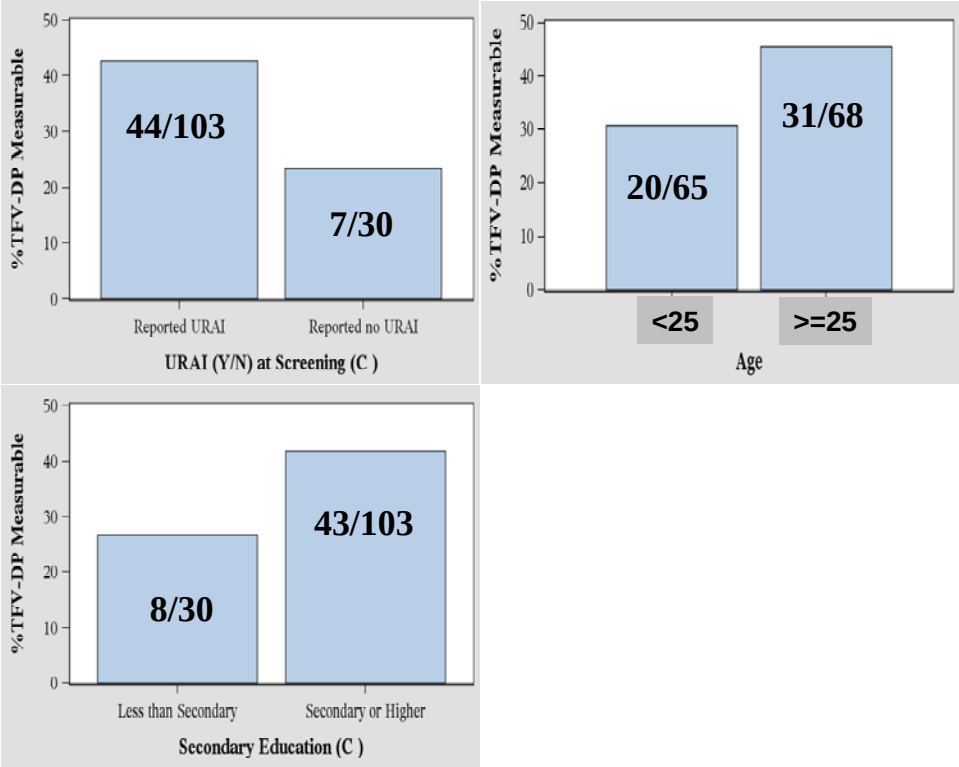

Figure 4: Percentage of subjects in the FTC/TDF group with measurable intracellular drug concentrations by age, URAI, and education level (iPrEx). ***[TFV-DP = tenofovir diphosphate]***

No significant differences in efficacy were observed based on race, ethnicity, or geographic location, although it should be noted that the majority of subjects in the iPrEx trial were Hispanic of mixed race from Latin America. Among U.S. subjects, relative risk reduction was 50%, but this is based on a small number of seroconversion events (n=3).

Use of Post-Exposure Prophylaxis (PEP) during iPrEx

Twenty-five subjects interrupted study drug treatment to initiate post-exposure prophylaxis (PEP), 10 in the FTC/TDF group and 15 in the placebo group; none of these subjects had a seroconversion event during the treatment phase of the trial. One subject in the FTC/TDF group who stopped study medication about a month prior to initiating PEP went on to seroconvert in the post-treatment period, approximately 6 weeks after stopping PEP. Importantly, sensitivity analysis censoring the subjects who interrupted treatment to initiate PEP or analyses treating subjects receiving PEP as infected did not alter the overall efficacy findings.

General Safety

The safety analysis conducted by the FDA analyzed data from 2,499 randomized subjects from study visits through November 21, 2010. Any evaluation or interpretation of safety data from iPrEx must take into account that adherence in the trial was found to be low. A post-trial case control study of plasma and intracellular emtricitabine and tenofovir concentrations revealed that less than half of the subjects tested in the FTC/TDF group

had measurable drug levels. FDA review of intracellular TFV-DP concentrations from a cohort of HIV seroconverters and matched uninfected controls estimated that about 10% of study participants had intracellular drug concentrations consistent with daily dosing. Another one-third of study subjects also appeared to be taking drug, but not as consistently.

In general, no significant between-group differences were noted in important safety parameters: deaths, serious adverse events, adverse events leading to drug discontinuation, or adverse events of moderate to severe toxicity (i.e., DAIDS toxicity grading scale Grade ≥2). Adverse events judged by the investigators to be study drug-related that were reported marginally more frequently in the FTC/TDF than in the placebo group included hypophosphatemia, headaches, dizziness, diarrhea, nausea, and gastroenteritis. The following events were reported more commonly in the FTC/TDF group regardless of causality: unintended weight loss, flatulence, vomiting, and abdominal pain. The majority of these events were mild or moderate in severity and, with the exception of headache and gastrointestinal disorders, generally did not lead to study drug discontinuation.

Study drug, both FTC/TDF and placebo, were most commonly stopped or interrupted for psychiatric disorders, the vast majority of which were not considered related to treatment. No significant differences or trends in clinical laboratory parameters were noted between the two treatment groups, with the exception of a greater median decrease from baseline in total leukocyte count in the FTC/TDF as compared with the placebo group. Subjects older than 40 years of age in both treatment groups had a higher frequency of clinical adverse events relative to younger subjects, but the small sample size in the over 40 years of age cohort (n = 258 subjects, 10% of the overall total) precludes significant conclusions. Lastly, among the 16 subjects enrolled with chronic or acute hepatitis B virus infection, no evidence of hepatic flare during treatment or after discontinuation of study drug was observed.

Renal Safety

Treatment-emergent adverse events of increased creatinine were reported for 2% of subjects in both groups (FTC/TDF 29, placebo 21). Most of these events (90%) were mild and less than half were considered drug-related. Recurrent events of increased creatinine were reported for only two subjects, one in each treatment group. Elevated serum creatinine led to temporary study drug interruption in six subjects in the FTC/TDF group (versus three subjects in the placebo group) and permanent discontinuation in one subject in the FTC/TDF group (versus none in placebo). Most of these cases were considered drug-related, but were mild and resolved with removal of the study drug; however, one of these subjects also had evidence of hypophosphatemia and acidosis at other time points. Study drug was resumed without recurrence of elevated creatinine in the six FTC/TDF subjects. The one FTC/TDF subject who discontinued due to renal toxicity initially had study drug held for a serum creatinine value approximately 20% above baseline. Creatinine values continued to increase off treatment, however, and study drug was never resumed; serum creatinine values returned to baseline levels 12 weeks

later. This subject also had intermittent trace proteinuria during follow-up, but no evidence of hypophosphatemia or low serum bicarbonate.

Throughout the treatment period, mean serum creatinine and creatinine clearance values (estimated by the Cockcroft-Gault equation) remained close to baseline for both treatment groups (Figure 5). Serum creatinine elevations were observed uncommonly and were generally mild (Grade 1), regardless of toxicity grading scale used. The percentages of subjects with graded creatinine elevations were comparable between the two treatment groups. Only two subjects had a serum creatinine value greater than 2.0 mg/dL at any time point during follow-up, one in each treatment group. In both cases, serum creatinine was within normal limits on repeat testing.

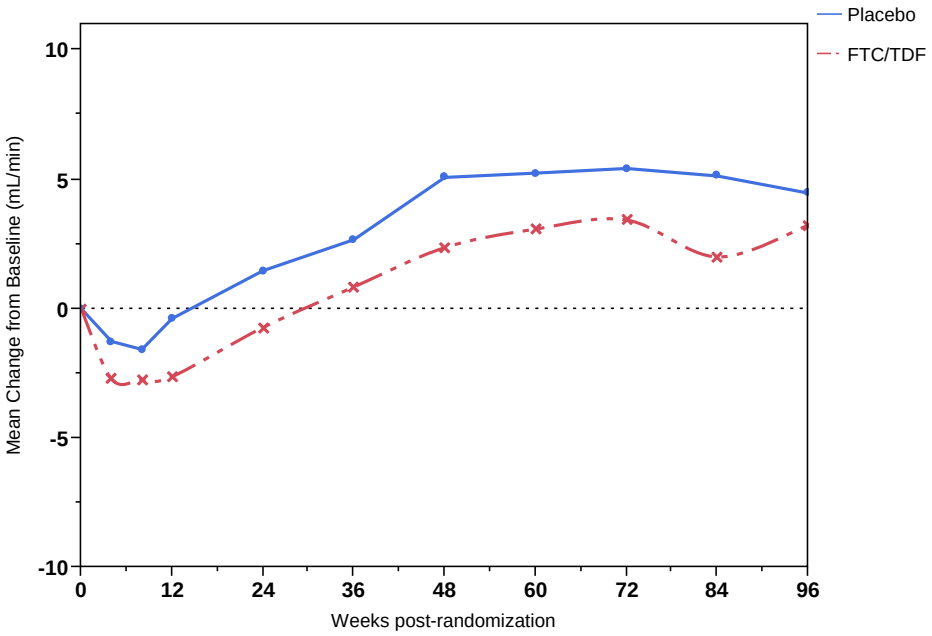

Figure 5: Mean change from baseline in creatine clearance (mL/min) using Cockcroft-Gault equation, by week (iPrEx).

Hypophosphatemia was reported in 6% of subjects in both treatment groups. Most cases were mild to moderate in severity. Drug-related hypophosphatemia of moderate to severe severity was seen more frequently in the FTC/TDF group compared with the placebo group (4% versus 3%), including four cases of severe (Grade 3) hypophosphatemia in the FTC/TDF group compared with one case in the placebo group. Hypophosphatemia as a cause for study drug discontinuation or interruption was also observed more frequently in the FTC/TDF group than in the placebo group, but the overall numbers were small (5 vs. 2). These cases tended to be severe (Grade 3) and were considered drug-related more often than not. Adverse events of hypophosphatemia appeared to resolve with interruption of study drug and four of the five FTC/TDF subjects were able to resume treatment. However, intermittent recurrent low serum phosphorus values were noted in

all four subjects after resumption of FTC/TDF (although two had low values at baseline) and increased serum creatinine was reported for one of these subjects at end of treatment. In addition, three of these FTC/TDF subjects developed transient low serum bicarbonate during treatment and one reported a bone fracture (foot). None of the five FTC/TDF subjects reported new onset back pain or bone pain and only one was enrolled in the BMD substudy and evidenced no significant change from baseline in BMD during treatment. For the total study population, though, mean phosphorus values remained consistent with baseline values throughout the trial in both treatment groups.

Review of the submitted urinalysis data revealed that proteinuria and glucosuria were detected at comparable rates between the groups. Most urinalysis abnormalities were mild and isolated findings. There were, however, seven subjects with concurrent, albeit mild, proteinuria and normoglycemic glycosuria (FTC/TDF 5, placebo 2), two of whom also had hypophosphatemia reported during the same visit (FTC/TDF 1, placebo 1). None of these subjects developed creatinine abnormalities; however, four of the FTC/TDF subjects were found to have treatment-emergent graded hypophosphatemia during follow-up (compared with one subject in the placebo group). For three of these four FTC/TDF subjects, the urinary abnormalities preceded the hypophosphatemia. None of these FTC/TDF subjects reported back pain, bone pain or bone fracture, although one subject with concurrent proteinuria and normoglycemic glycosuria and treatment-emergent graded hypophosphatemia that was detected 3 months after the urinary abnormalities was also found to have decreased BMD >5% from baseline at the spine at Weeks 24 and 72. Urinary phosphorus and urinary uric acid were not evaluated as part of this trial.

In conclusion, while renal failure or Fanconi syndrome was not reported in this trial, these cases of concurrent proteinuria, glycosuria and hypophosphatemia, observed predominately in the FTC/TDF treatment group, may be potentially concerning for subclinical proximal renal tubulopathy, although the limited numbers and poor adherence observed in this trial, as assessed by drug level monitoring, preclude reliable interpretation.

Bone Safety

In the iPrEx trial, treatment-emergent bone fractures were uncommon (2% in the FTC/TDF group and 1% in the placebo group) and none were considered pathological or drug-related. New onset back pain was reported at equal rates (5%) among subjects in both treatment groups. Among the 503 subjects enrolled in the bone mineral density (BMD) substudy, approximately half were between the ages of 18 and 24 years old and thus considered likely to still be accruing bone mass. Excluding dual-energy X-ray absorptiometry (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 from baseline in BMD 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 was observed in 14% of subjects in

the FTC/TDF group compared with 6% in the placebo group. 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.

Among the 353 subjects who had DEXA scans obtained 6 months after discontinuation of study medication, results showed that the BMD decreases observed in the FTC/TDF group during treatment were 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. Vitamin D and parathyroid hormone levels were not evaluated as part of this trial.

Drug Resistance

Ten subjects were enrolled in the iPrEx trial during acute HIV infection; their infection was not detected until after randomization when their HIV rapid testing became positive. Among these 10 subjects, 8 were in the placebo group and 2 were in the FTC/TDF. Several of these 10 subjects reportedly had signs and symptoms suggestive of acute HIV infection (e.g., fever, fatigue, pharyngitis, and lymphadenopathy) that were attributed to possible upper respiratory tract infection.

Resistance was detected after 4 weeks of FTC/TDF prophylaxis in 2/2 subjects who were unknowingly 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, indicating that resistance emerged during treatment. 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 due to insufficient viral RNA in the sample; therefore, it is unclear if the M184I substitution was selected during the trial or if it was borne by the transmitted virus.

Among the 48 subjects enrolled in the FTC/TDF group who became HIV-infected during the treatment phase of the trial, no evidence of genotypic 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 polymerase chain reaction assay that is sensitive to the presence of low levels of variants (0.5% of the viral quasi-species) expressing specific resistance-associated substitutions (i.e., K65R, K70E, M184V, and M184I) was conducted. None of the assayed variants were detected among subjects in the FTC/TDF group who became infected during the trial. The results of the genotypic analyses are consistent with the pharmacokinetic finding of no measurable drug concentrations among most subjects who failed chemoprophylaxis.

Drug Concentration and Medication Adherence

Assessment of adherence by pill count or adherence questionnaire suggested a high level of adherence in the iPrEx trial. However, a post-hoc assessment of the correlation between subject-reported adherence and objective measures based on peripheral blood mononuclear cell (PBMC) drug concentrations demonstrated that high self-reported adherence was poorly predictive of measurable intracellular concentrations of the active forms of each drug, tenofovir-diphosphate (TFV-DP) and emtricitabine-triphosphate (FTC-TP). Low or missing self-reported adherence, on the other hand, was predictive of non-measurable drug concentrations.

Plasma concentrations of both tenofovir and emtricitabine, as well as intracellular concentrations of TFV-DP and FTC-TP, were objective measures of medication adherence obtained in subjects receiving FTC/TDF. A subject with full medication adherence should have measurable plasma and intracellular concentrations of drug at each pharmacokinetic (PK) sampling study visit. Analysis of efficacy and adherence using tenofovir concentration as a marker for exposure to FTC/TDF is presented in this section.

The intracellular half-life of TFV-DP is longer than the plasma half-life of tenofovir (87-150 hours vs. 17 hours, respectively), so intracellular TFV-DP levels can remain measurable for a longer period of time than plasma concentrations of tenofovir. Thus, intracellular TFV-DP levels provide direct evidence of drug exposure over a longer duration of time. In contrast, tenofovir concentrations are usually measurable in systemic circulation within 30 minutes of drug administration. Tenofovir plasma concentrations, therefore, may be observed in a subject who self-administered FTC/TDF immediately prior to a study visit but who may not have been consistently adherent to medication dosing otherwise. Subjects with poor medication adherence may demonstrate one or more of the following patterns in tenofovir plasma and intracellular concentrations:

- Undetectable plasma and undetectable intracellular concentrations, possibly reflecting no FTC/TDF intake for more than 20 days prior to study visit.

- Undetectable plasma and low measurable intracellular concentrations, possibly reflecting recent FTC/TDF intake within 20 days before study visit.

- High plasma and undetectable or low measurable intracellular concentrations, possibly reflecting FTC/TDF intake just before study visit.

Investigators in the iPrEx trial conducted a pre-specified subgroup analysis to evaluate if tenofovir and emtricitabine plasma and intracellular concentrations correlated with protection from HIV-1 infection. All study participants underwent PK sampling at baseline, every 12 weeks, at the seroconversion visit, end of study visit, and every post-study drug follow-up visit. When a study participant was deemed a seroconverter, the PK samples closest to the date of seroconversion were evaluated for tenofovir and emtricitabine concentrations in plasma and PBMCs. The PK samples collected from three

corresponding control subjects who did not seroconvert during the trial were also evaluated. Two of the control subjects were matched to each HIV-infected subject based on study site and treatment duration, while the third control subject was matched based on reported unprotected receptive anal intercourse (URAI).

Submitted data contained plasma and intracellular concentrations of tenofovir and emtricitabine collected from 181 subjects receiving FTC/TDF (seroconverters [n=48] and their respective controls after removing data from 11 subjects who served as controls twice [n=133]). Figure 6 displays the proportion of subjects within the seroconverter and non-seroconverter groups with measurable intracellular concentrations of TFV-DP. These data represent the PK sample collected closest to the study visit when seroconversion was detected. The results show that a lower proportion of HIV seroconverters had measurable levels of intracellular TFV-DP at the time of seroconversion compared with matched HIV-uninfected controls (8% vs. 38%, respectively).

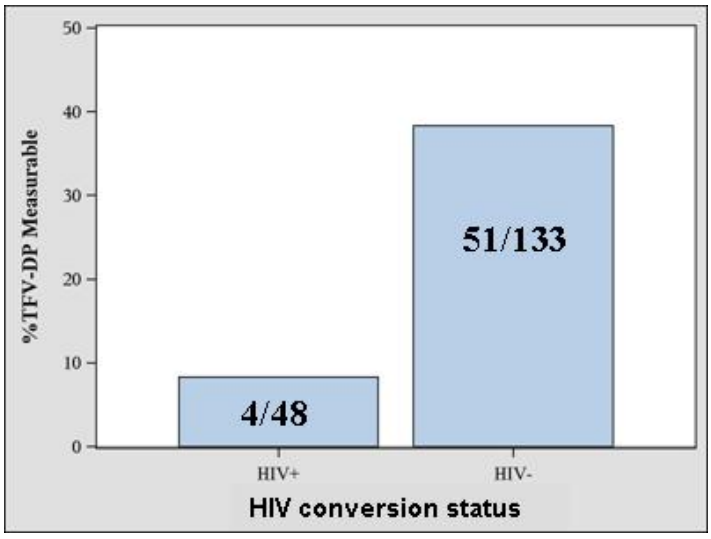

Figure 6: Proportion of subjects in the seroconverter (HIV+) and non-seroconverter (HIV-) groups who had measurable intracellular TFV-DP levels (iPrEx).

Non-measurable intracellular concentrations indicate poor medication adherence. In order to assess the impact of medication adherence on efficacy, the proportion of subjects with measurable intracellular TFV-DP within the 133 HIV-uninfected subjects was assumed to represent the overall proportion of patients with measurable intracellular TFV-DP among all HIV-uninfected subjects (n=1203). As shown in Figure 7, the seroconversion rate observed in the placebo group (4.2%) was not significantly different from the event rate in the treatment group if intracellular concentrations were not measurable (3.6%). For subjects with measurable intracellular drug concentrations, the HIV seroconversion event rate was substantially lower than event rates in the overall population, the placebo group, or the non-measurable drug concentration group (0.5% versus 2.4%, 4.2%, and 3.6%, respectively). These results suggest that increased medication adherence (based on detectable intracellular TFV-DP concentrations) reduced the risk of acquiring HIV infection in the iPrEx trial (Figure 8).

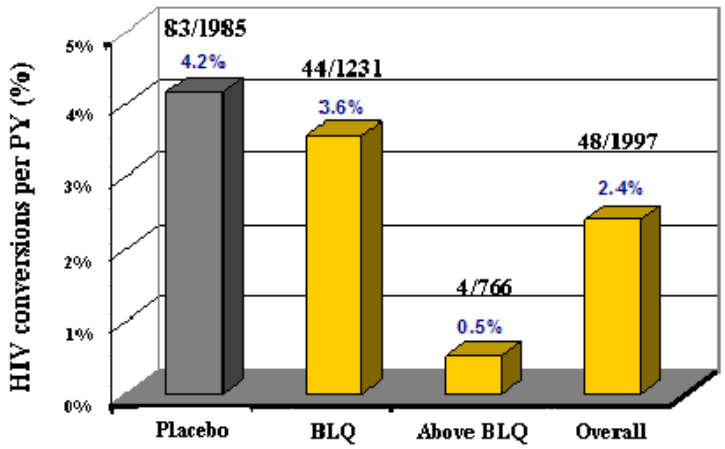

Figure 7: Event rates in all subjects - placebo and FTC/TDF groups (iPrEx). ***[BLQ = below level of quantification]***

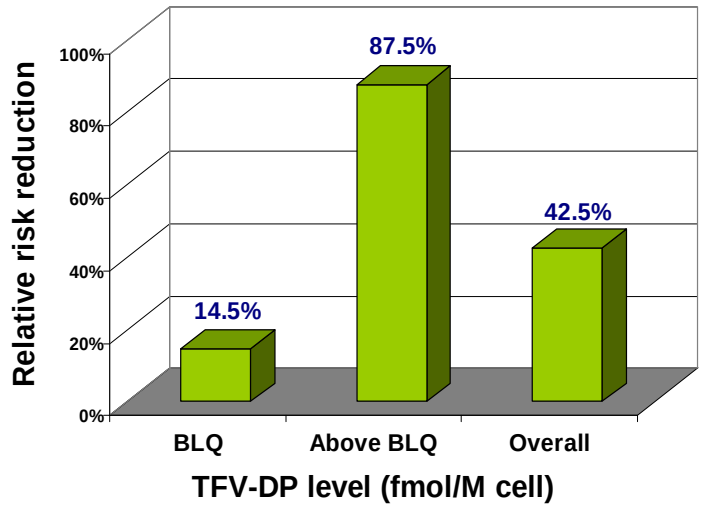

Figure 8: Relative risk reduction in acquiring HIV infection (compared with placebo) based on intracellular TFV-DP concentrations (iPrEx). ***[BLQ=below level of quantification]***

Behavioral Changes

Attitudinal and behavioral changes were also assessed as part of the iPrEx trial. There was no clear evidence of post-baseline sexual disinhibition or risk compensation observed among subjects during follow-up. In both treatment groups, the reported numbers of receptive anal intercourse sexual partners decreased from baseline, while the percentage of those partners who used condoms increased. The incidence of sexually transmitted infections did not differ significantly from baseline.

b. Partners PrEP

The Partners PrEP trial was a large Phase 3, multicenter, international, randomized, double-blind, placebo-controlled trial of PrEP with once-daily oral TDF (300 mg) or FTC/TDF (fixed-dose FTC 200 mg/TDF 300 mg) among HIV-uninfected individuals within an HIV-serodiscordant partnership, where the HIV-infected partner was not eligible for antiretroviral therapy per national guidelines. The trial was sponsored by the University of Washington with funding from the BMGF. The trial enrolled 4,758 serodiscordant couples in Uganda and Kenya beginning in June 2008. The HIV-uninfected partners were randomized in a 1:1:1 ratio to receive TDF, FTC/TDF, or placebo. Eleven of these partner subjects were determined after randomization to have not met the eligibility criteria for the trial and were withdrawn from the trial. Thus, the ITT cohort is 4,747 partner subjects. Additionally, 14 partner subjects were retrospectively found to be HIV-infected at randomization and 25 additional partner subjects had no follow-up visits. The mITT cohort, therefore, is comprised of 4,708 partner subjects. The Applicant's background document contains further details regarding the study design, eligibility criteria, subject demographics and subject disposition in Partners PrEP.

The Partners PrEP trial had an independent Data Safety Monitoring Board (DSMB) review all reported data approximately every 6 months. Interim monitoring stopping boundaries for proven efficacy were pre-established based on ruling out efficacy lower than 30%, a threshold for significance discussed in previous scientific meetings of HIV prevention. On July 10, 2011, following one of the planned interim reviews of the data, the DSMB recommended that the results be publically reported and placebo dosing discontinued due to demonstration of PrEP efficacy. 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. The trial is currently ongoing comparing TDF to FTC/TDF in a blinded manner. The FDA review of safety and efficacy in the Partners PrEP trial, therefore, is based on the double-blind data collected through the July 10, 2011 cut-off date.

Efficacy

In Partners PrEP, 82 post-randomization HIV infections were identified in the mITT cohort: TDF 17, FTC/TDF 13, and placebo 52. The corresponding incidence rates per 100 person-years were 0.65%, 0.50%, and 1.99%, respectively, based on 2,605 patient-years in 1,579 TDF subjects, 2,618 patient-years in 1,576 FTC/TDF subjects, and 2,608 patient-years in 1,578 placebo subjects. Compared with placebo, TDF reduced the risk of acquiring HIV infection by 67% (95% CI 49-85%), while FTC/TDF reduced the risk by 75% (95% CI 60-90%); the difference in treatment effect between TDF and FTC/TDF was not significant.

Efficacy of TDF and FTC/TDF could not be correlated with self-reported adherence because the majority of participants reported very high levels of adherence. However, in an adherence and counseling substudy that enrolled 1,147 uninfected partners (data not reviewed by the FDA), overall efficacy of PrEP was found to be 100% (95% CI 87-

100%, p<.001).[60] By plasma drug concentration analysis, age greater than 25 years old or having an HIV-infected partner with viral <50,000 copies/mm^3 appeared to correlate with better adherence, although sample sizes were small in the comparative cohorts (Figure 9).

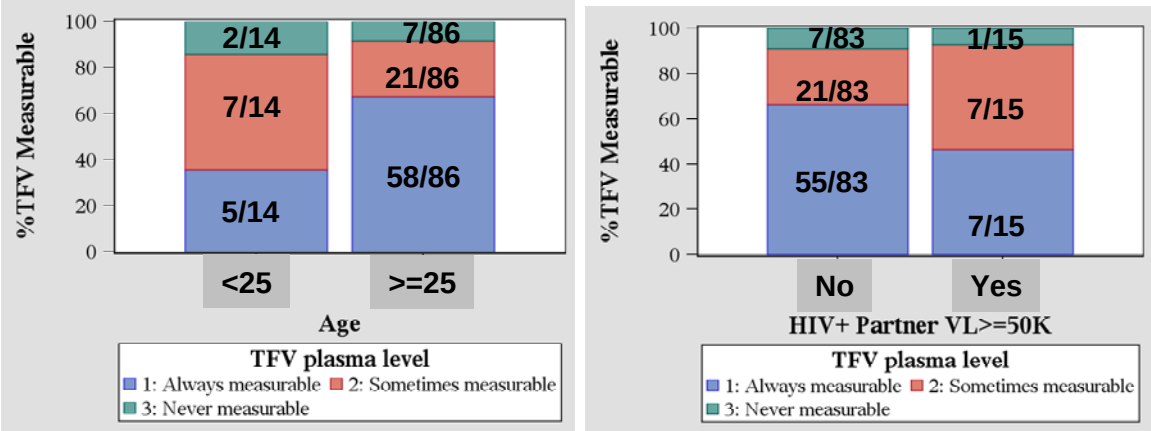

Figure 9: Percentage of subjects with measurable plasma tenofovir concentrations, by age and index partner viral load (Partners PrEP).

Overall seroconversion rates were 2.52% for women (45/1785) and 1.25% for men (37/2962); however, there were no significant differences in the protective effect of TDF and FTC/TDF based on gender. The non-significant differences in risk reduction observed between males and females may be related to treatment interruptions in women due to pregnancy and breastfeeding. Relative risk reduction compared with placebo was 63% (95% CI 34-91%) for men and 71% (95% CI 49-94%) for women receiving TDF, and 84% (95% CI 67-101%) for men and 66% (95% CI 41-92%) for women receiving FTC/TDF. Additionally, a positive and consistent protective effect for TDF and FTC/TDF was generally seen within each subgroup analyzed (age, education, male circumcision, use of hormonal contraception in women, or baseline HIV characteristics of the index partner, etc). Although seroconversion rates were higher for partner subjects when the index partner viral load was ≥50,000, no differences in treatment effect for TDF and FTC/TDF based on index partner viral load were observed.

Use of Antiretrovirals in HIV-infected Index Partners

In the Partners PrEP trial, FDA identified 1,314 index partners, divided evenly across the three treatment arms, who initiated antiretroviral (ARV) therapy during follow-up. If ARV therapy suppressed the index partner's viral load to undetectable levels, then the risk of HIV transmission would be reduced (as demonstrated by the results of the HPTN 052 trial). FDA conducted a sensitivity analysis to evaluate the impact of ARV in the index partner on the efficacy of PrEP. The analysis censored uninfected subjects whose partners started ARV therapy at the time of ARV initiation, unless the subject became HIV infected at some point thereafter. The results of the analysis demonstrated a relative risk reduction of 67% (95% CI 49-85) for TDF and 75% (95% CI 60-90%) for FTC/TDF compared with placebo, findings consistent with the primary analysis results. Thus, the overall efficacy results for the Partners PrEP trial were not significantly affected by the use of ARV in the HIV-infected index partners.

General Safety

The same definition for adverse events used for the iPrEx analysis was used for the review of safety in the Partners PrEP trial. The FDA review of safety was based on data from 4,747 partner subjects in the ITT cohort with study visits through July 10, 2011. Adherence in Partners PrEP was reportedly high by multiple measures, including measurement of plasma tenofovir levels, such that safety results from this trial may be interpreted with a greater degree of confidence.

Overall, there were no significant differences between treatment groups with respect to deaths, serious adverse events, adverse events leading to study drug interruption, or adverse events of moderate to severe toxicity (i.e., DAIDS toxicity grading scale, Grade ≥2). Adverse events of moderate to severe intensity judged by the site investigators to be drug-related were reported in 22% of subjects overall (TDF 20%, FTC/TDF 24%, and placebo 21%). The vast majority of these events were related to laboratory abnormalities. Drug-related clinical events were reported in 1% of subjects and all were of at least moderate severity; severe clinical events were only reported in 6 subjects (all in the placebo group). The leading moderate to severe adverse event assessed as related to study drug was hypophosphatemia, reported in 11% of subjects in the TDF group, 14% in the FTC/TDF group, and 13% in the placebo group; however, only 6% of subjects in each treatment arm had serum phosphorus values <2.0 mg/dL at any given time point during follow-up. Moderate to severe neutropenia was also observed more frequently in the FTC/TDF group compared with the other groups; by laboratory testing, neutropenia of any grade was reported in 18% of subjects in the FTC/TDF group compared with 15% in the TDF group and 13% in the placebo group. Otherwise, the rates for Grade ≥2 drug-related events were similar across treatment groups.

Adverse events that led to permanent study drug discontinuation were reported in only seven subjects overall, but six of these were associated with Grade 2 renal toxicity. In these cases, the renal toxicity specifically related to a decline in creatinine clearance < 50 mL/min (TDF 3, FTC/TDF 2, and placebo 1); only the subject in the placebo group had an increased creatinine value. One of these subjects (in the TDF group) was also noted to have hypophosphatemia; however, none were found to have proteinuria or glycosuria. Five of these six cases were reported in women, including four in the active treatment groups. Estimated creatinine clearance was within normal limits in all five women at the time of enrollment, although three had estimated creatinine clearance between 60 and 65 mL/min at baseline. The renal insufficiency resolved with cessation of the study drug in the five cases reported in women; the one case in a male subject in the TDF group was still ongoing at exit from the trial.

Study drug was temporarily interrupted for increased serum creatinine in 1% of subjects and for hypophosphatemia in 0.25%, with comparable percentages in each treatment group. Overall, laboratory abnormalities were the leading cause of treatment interruption in this trial, reported in 3% of total subjects, with similar rates across the groups. In addition to creatinine increases and hypophosphatemia, other laboratory findings that led

to treatment interruption included neutropenia, thrombocytopenia, low hemoglobin, low serum bicarbonate, increases in hepatic transaminases, and presence of proteinuria or glycosuria. For each of these findings, however, the rates were <1% within each group. In most cases the abnormalities resolved with treatment interruption and did not recur when treatment was resumed.

Renal Safety

Treatment-emergent increased creatinine was reported in 5% of subjects in the TDF group, 7% in the FTC/TDF group, and 5% in the placebo group. Drug-related creatinine toxicity, however, was only reported in eight (0.2%) subjects overall, three in the TDF group and five in the placebo group, all of which were moderate events. None of the increased creatinine events was serious and most were not confirmed upon repeat testing. Confirmed blood creatinine increases were reported in 1% of subjects overall, with similar frequencies across treatment groups, and were mostly mild (Grade 1). Of note, the study protocol defined any increase in creatinine of more than 50% over baseline as at least a Grade 1 adverse event, even when the creatinine value was within normal limits. Thus, a number of the Grade 1 serum creatinine increase events represented 50% increases over baseline, but the creatinine values themselves were within normal limits.

Using the Applicant's laboratory toxicity grading scale, 14 subjects (TDF 4, FTC/TDF 6, placebo 4) were identified with graded serum creatine abnormalities; 13 of which had Grade 1 creatinine values (1.5 to 2.0 mg/dL). One subject (in the TDF group) achieved a Grade 2 creatinine value (2.0 to 3.0 mg/dL). Likewise, graded laboratory abnormalities in serum phosphorus were identified in 28% of subjects overall; three-fourths had Grade 1 values. Serum phosphorus values of Grade ≥2 were identified in 6% of subjects overall, with comparable frequencies among the groups.

Abnormalities on urine dipstick were also generally consistent among the treatment groups, with 4% of subjects in the active groups having at least one incidence of proteinuria compared with 3% in the placebo group. Over 50% of the proteinuria findings in any group were isolated events and most were trace or 1+ on urine dipstick. Glycosuria, in contrast, was rare and reported in less than 1% of subjects overall, with no discernable differences among the treatment groups. Five subjects in this trial (TDF 2, FTC/TDF 1, placebo 2) had concurrent findings of ≥1+ proteinuria and glycosuria in the setting of hypophosphatemia. Serum glucose was not reported in this trial, thus the incidence of normoglycemic glycosuria could not be determined. None of these five subjects had evidence of serum creatinine abnormalities, but one subject in the FTC/TDF group had an estimated creatinine clearance of 69 mL/min (baseline 76 mL/min). Moreover, none of these subjects reported bone pain, bone fractures, or back pain.

In general, mean changes from baseline in serum creatinine, creatinine clearance (by the Cockcroft-Gault equation), and serum phosphorus values were negligible at all time points for all three treatment groups. Figure 10 shows the mean change from baseline in creatinine clearance for the three groups through Week 96; beyond Week 96, the number

of participants with evaluable laboratory results rapidly diminished, making between-group comparisons less informative.

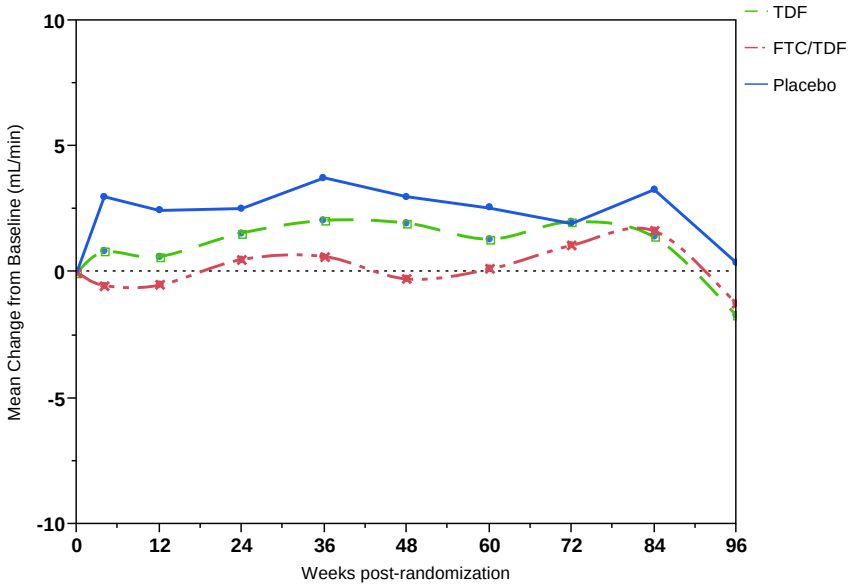

Figure 10: Mean change from baseline in creatinine clearance (mL/min) using Cockcroft-Gault equation, by week (Partners PrEP).

Bone Safety

In the Partners PrEP trial, 35 bone fractures were reported in 32 subjects for an overall rate 0.7%, with similar frequencies across treatment groups. None of the fractures were considered drug-related or pathological and nearly all were related to trauma. None of the 32 subjects with bone fractures had evidence of either graded serum chemistry abnormalities or abnormalities on urinalysis. Only one subject (a 37-year-old woman in the FTC/TDF group) complained of Grade 2 bone pain/tenderness about 8 months into treatment, but this subject too had no evidence of laboratory abnormalities.

New onset back pain, not associated with trauma, was reported in 14 subjects overall (TDF 7, FTC/TDF 3, placebo 4). Among these, three subjects (one in each group) had laboratory evidence of graded hypophosphatemia; none had detected abnormalities on urinalysis. DEXA testing was not conducted as part of this trial.

Drug Resistance

In the Partner's PrEP trial, 14 subjects (TDF 5, FTC/TDF 3, placebo 6) were enrolled with undiagnosed HIV infection (HIV-1 antibody test negative at the time of enrollment). Two of the five subjects in the TDF group had detectable variants expressing resistance at the time of 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 of the subjects with the M184V and K65R-expressing viruses indicated that resistance emerged 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. There were no pharmacokinetic data with which to assess adherence for the five remaining subjects in the TDF and FTC/TDF groups who were infected at baseline and who had no resistance detected at the time of seroconversion.

Genotypic resistance was not detected by population nucleotide sequence analysis of viruses isolated from the 17 subjects in the TDF cohort or the 13 subjects in the FTC/TDF cohort who became HIV-infected during treatment.

Drug Concentration and Medication Adherence

As previously noted, adherence in the Partners PrEP trial was reportedly high (97%) by pill count. The trial sponsor conducted an analysis comparing plasma concentrations of tenofovir collected from all subjects within the active treatment groups who seroconverted during the trial (cases) versus concentrations of a subset of subjects who did not seroconvert (controls). The PK comparisons included 100 randomly selected controls from the FTC/TDF and TDF arms (total 200). All cases and controls underwent PK sampling during study months 1, 3, 6, 18, 24, 30, and 36. Additionally, plasma samples were tested from case subjects during the visit at which HIV-1 seroconversion was detected. The current database includes tenofovir concentrations collected from 228 subjects; 115 in the TDF group and 113 in the FTC/TDF group. Tenofovir plasma concentrations are available from the 17 case subjects who seroconverted while receiving TDF and from the 13 subjects who received FTC/TDF.

Investigators only measured tenofovir plasma concentration and did not evaluate intracellular concentrations of TFV-DP in this trial. Figure 11 displays the percentage of subjects who had plasma drug concentrations (taken across all available PK sampling timepoints) that were always measurable, sometimes measurable, or never measurable, stratified by seroconversion status.

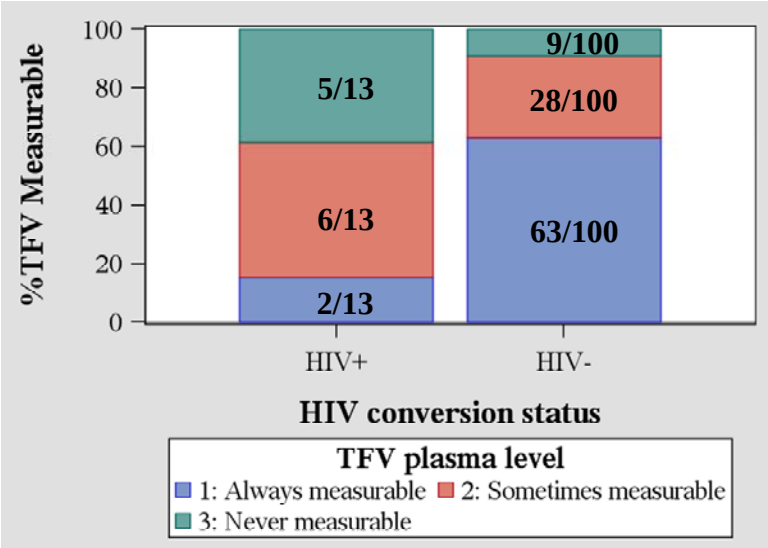

Figure 11: Percentage of subjects with plasma tenofovir concentrations that were always measurable, sometimes measurable, or never measurable, by seroconversion status (Partners PrEP).

The proportion of subjects with always measurable plasma tenofovir concentration at all visits was significantly higher among the HIV-uninfected subjects (63%) than among the HIV-infected subjects (15%). Similar to the analysis conducted for iPrEx, the relative proportions of subjects within the three categories of measurable plasma concentrations observed among the 100 control subjects were assumed to represent the overall proportions of subjects among all HIV-uninfected subjects (n=1576). As demonstrated in Figure 12, the HIV seroconversion rate in the treatment group if plasma concentrations were never measurable (2.1%) was not significantly different from the event rate observed in the placebo group (2%). The seroconversion event rate for subjects with always measurable plasma concentrations was substantially lower than the event rates in the overall population or the placebo group (0.1% vs. 0.5% and 2.0%, respectively). These results suggest that increased medication adherence (based on consistently measurable plasma TFV concentrations) reduced the risk of acquiring HIV infection in the Partners PrEP trial (Figure 13).

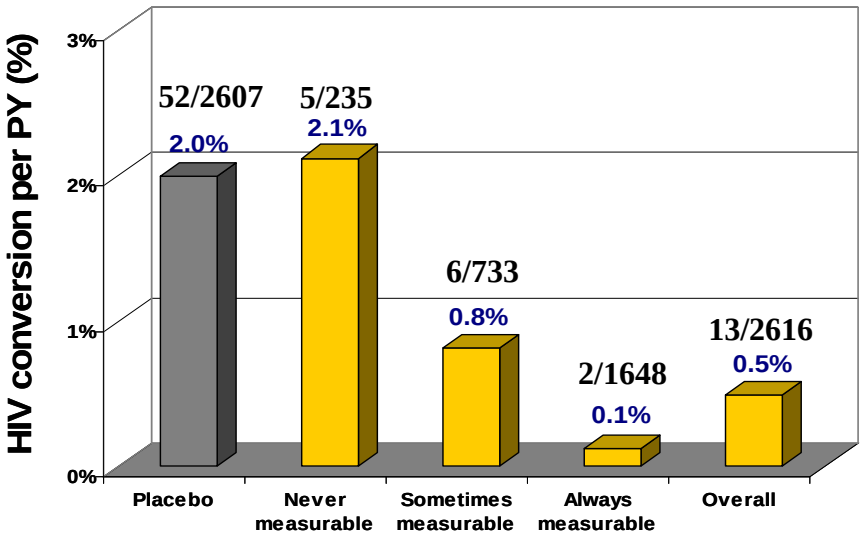

Figure 12: Seroconversion event rates in all subjects -placebo and active groups (Partners PrEP).

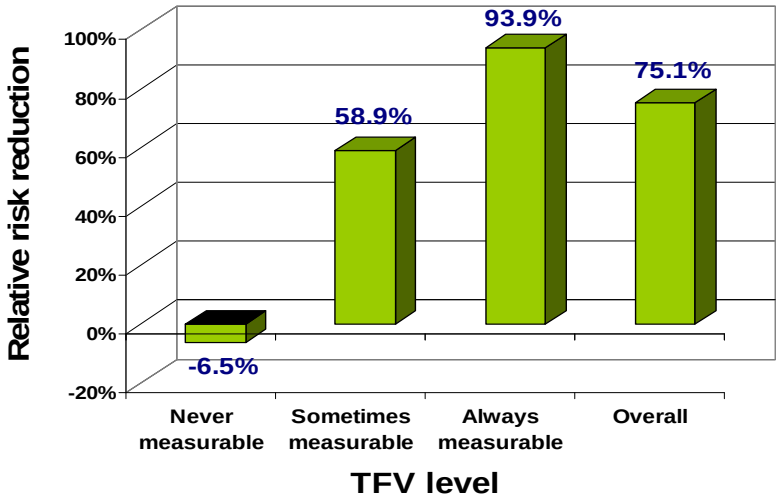

Figure 13: Relative risk reduction in acquiring HIV infection (compared with placebo) based on plasma drug concentrations (Partners PrEP).

Behavioral Changes

Significant risk compensation was not observed in this trial. Over the course of follow-up, the percentage of subjects reporting any unprotected sex in the previous month decreased from a baseline value of 27% to approximately 10% at 24 months, with similar trends across the three groups. The absence of risk compensation is further corroborated by rates of sexually transmitted infections that remained constant over time.

The percentage of partner subjects reporting sex with persons outside their partnership appeared to increase over the duration of the trial, from 9% at baseline to 13% at 24 months. The increase was evident in both men and women: 0.5% at baseline to 2.6% at

24 months in women and 14% at baseline to 20% at 24 months in men. The significance of these findings is not clear.

Pregnancies

Pregnancies were reported in 15% of female partner subjects: TDF 18%, FTC/TDF 13%, and placebo 14%. All women who became pregnant during the trial interrupted study medication for the duration of the pregnancy and breastfeeding. Of the 45 female subjects who had HIV seroconversion events during the trial, five (TDF 2, FTC/TDF 0, placebo 3) became infected while being off study medication for >3 months due to pregnancy or breastfeeding. Exclusion of these five women from the efficacy analyses did significantly alter the overall findings.

Of the 288 pregnancies identified in the trial, 264 had completed as of a March 16, 2012 safety update. Of the completed pregnancies, 167 (63%) resulted in live births and 97 (37%) in pregnancy loss (TDF 30, FTC/TDF 35, placebo 32). The percentage of live births was greatest in the TDF group (71%) compared with the FTC/TDF group (54%) or placebo (63%). Spontaneous abortion was the main reason for pregnancy loss, accounting for approximately 80% of the losses, with a higher percentage in the FTC/TDF arm. Congenital ankyloglossia was reported in two infants born to mothers in the TDF treatment group, but overall no between-group trends in congenital abnormalities were noted among newborns. None of the observed congenital abnormalities were considered related to study drug.

V. Review of Safety Data from Other Clinical Trials and Post-Marketing Reports

Overt renal toxicity was not noted in registrational trials of tenofovir disoproxil fumarate. During one to two years of on-treatment follow-up, the most common adverse reactions (incidence greater than or equal to 10%, Grades 2–4) identified from any of the three large controlled clinical trials in treatment-naïve HIV-infected subjects included rash, diarrhea, headache, pain, depression, asthenia, and nausea. Similarly, in the clinical trials conducted in subjects with chronic hepatitis B infection and compensated liver disease, less than 1% of subjects treated with TDF experienced a confirmed increase in serum creatinine of 0.5 mg/dL from baseline. Of note, back pain was reported in more than 5% of subjects treated with TDF.

A number of studies have attempted to assess the risk of renal disease associated with exposure to TDF. In a recent metanalysis that surveyed eight studies totaling 7,496 participants, the risk difference for acute renal injury (variably defined in each study) for tenofovir compared with non-tenofovir control was estimated to be 0.7% (95% CI 0.2-1.2%).[61] No significant risk differences were found for chronic kidney failure (0.2%; 95% CI -1.5 to 0.2%) or end-stage kidney failure requiring long-term dialysis (0.2%; 95% CI -0.3 to 0.7%).

A separate study involving a 4-year follow-up of 10,343 tenofovir-treated patients (3700 person-years) in an expanded access program (EAP) disclosed a serious renal adverse event in 0.5%, the serious adverse event of *renal failure* in 0.3%, and a serious event in the category of *Fanconi/ renal tubular disorder/ hypophosphatemia/ glycosuria* in <0.1%.[62] This analysis, however, had several limitations. First, it was limited by the relatively brief duration of treatment in the EAP, which was a mean of 13 weeks in the U.S., 24 weeks in the European Union/Australia and 29 weeks in Canada. Second, adverse event reporting was considered voluntary in some of the countries. Third, only serious adverse events were assessed, not renal events leading to drug discontinuation or non-serious renal adverse events. Any of these factors may have led to an underestimation of the true incidence of renal events of interest. In the same article, the authors assessed the TDF post-marketing safety database (which included 455,392 person-years of TDF exposure) for serious adverse drug reactions (SADR). They found a reporting rate of 43.3/100,000 person years for any renal SADR, 24.2/100,000 person years for *renal failure* and a rate of 22.4/100,000 person years for a SADR in the category of *Fanconi/ renal tubular disorder/ hypophosphatemia/ glycosuria*. Again, review of postmarketing data is limited by the voluntary nature of adverse drug reaction reporting.

Multivariate analysis of postmarketing clinical data have shown that advanced age, low body weight, higher serum creatinine levels before starting TDF treatment, comorbidities (diabetes, hypertension, HCV coinfection), concomitant nephrotoxic medications, advanced HIV infection (low CD4 counts, AIDS), and, in some studies, male sex were risk factors for tenofovir-induced reduction in glomerular filtration rate (GFR). The odds of developing significant renal function reduction were 3.7 times higher for patients receiving TDF plus ritonavir-boosted protease inhibitor regimes than for those receiving TDF plus non-nucleoside reverse transcriptase inhibitor-based therapy, even adjusting for HIV viral load.[51]

A review of the Adverse Events Reporting System (AERS) conducted by the FDA Division of Pharmacovigilance for TDF for the hepatitis B virus indication through February 16, 2012, yielded 23 reports of renal failure 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 re-challenge. Overall, there were four reports of Fanconi syndrome, but all were confounded by co-morbid conditions or concurrent illness. One case of acute renal failure was also identified in a healthy individual taking FTC/TDF for post-exposure prophylaxis (PEP). Nine additional cases were reported under preferred terms *osteoporosis*, *osteopenia*, and *osteomalacia* in hepatitis B 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 were either confounded by co-morbid conditions or lacked sufficient information needed to make a determination of causality.

VI. Risk Benefit Assessment

The efficacy of FTC/TDF in the prevention of sexual acquisition of HIV-1 infection in uninfected individuals at risk was supported by the two large clinical trials submitted for review. In both trials, PrEP was utilized as an adjunctive intervention to behavioral counseling and provision of condoms at each study visit.

In iPrEx, a trial evaluating efficacy of PrEP in MSM, a 42% (CI 22-63%) risk reduction was observed with FTC/TDF, a statistically significant finding, but one that did not exclude the possibility that the true risk reduction was 30% or less (a threshold previously discussed at scientific meetings). Adherence in this trial, however, appeared to be low overall, as demonstrated by a post-hoc evaluation of tenofovir plasma and intracellular concentrations.

In Partners PrEP, a trial evaluating efficacy of PrEP in heterosexual serodiscordant couples, the predefined threshold for clinically meaningful risk reduction was also 30%. In fact, a 75% risk reduction (CI 60-90%) was observed in study subjects receiving FTC/TDF and a 67% risk reduction (CI 49-85%) was observed in study subjects receiving TDF alone, each in comparison to placebo. Findings were consistent when analyzed by gender: a 66% (CI 41-92%) risk reduction was observed in women receiving FTC/TDF and a 71% risk reduction (CI 49-94%) in women receiving TDF, each in comparison to placebo. For men, the risk reductions were comparable: 63% (CI 34-91%) with TDF and 84% (CI 67-101%) with FTC/TDF. Based on these observations, one can refute with high confidence the possibility that the true risk reduction of either drug is less than 30%.

Other PrEP studies conducted to date, described in this document but not submitted with the application, have had mixed findings. Central to putting these disparate results into context have been the numerous drug level analyses conducted by the investigators of these trials. In a post-hoc analysis of plasma tenofovir levels in Partners PrEP, 40% of individuals who seroconverted were found to have measurable plasma tenofovir, as compared with 80% of matched uninfected controls. Estimated risk reduction was 94% compared with placebo for subjects who had measurable plasma tenofovir concentrations at every visit where data was collected. In iPrEx, 8% of seroconverters had measurable intracellular tenofovir concentrations (intracellular levels being a more reliable method for evaluating consistent adherence), as compared to 38% of matched uninfected controls. In iPrEx, estimated risk reduction was 88% for subjects with any measurable intracellular tenofovir level; this finding is notable in the context that exploratory analyses indicate that full adherence with study medication occurred in only 10% of study subjects.

Similar drug level analyses in other trials support that efficacy of PrEP is clearly correlated with adherence and that the failure of the FEM-PrEP trial to show efficacy of FTC/TDF for prevention of HIV infection in women at risk could likely be attributed to poor drug adherence. Importantly, 70% of women enrolled in FEM-PrEP reported that

they did not perceive themselves to be at risk for acquisition of HIV, and this disconnect between behavior and perceived risk may have influenced adherence. Another possible reason for poor adherence may have been that study subjects did not believe they would derive benefit from taking study medication, since there was the possibility that they were receiving placebo. Regardless, drug level analysis revealed that adherence was so low as to preclude the trial's ability to assess the efficacy of FTC/TDF as PrEP.[38]

In sum, individuals may have any number of reasons or influences that increase or decrease adherence to medications. Some believe that PrEP clinical trials represent ideal circumstances that cannot be replicated in a real world setting. At this time, however, it is not known if adherence to PrEP will be better or worse outside the clinical trial setting.

Analysis of HIV isolates from individuals who became infected while taking PrEP have failed to identify resistance mutations that developed following seroconversion, consistent with the finding that study subjects who seroconverted were generally not adherent to medication. Selection of resistance among trial participants may have been minimized due to monthly monitoring for seroconversion. The impact of PrEP on resistance beyond a clinical trial setting is difficult to predict, but resistance is expected among infected individuals using PrEP. The frequency of resistance might be minimized by limiting the duration of drug exposure after infection occurs with frequent monitoring for HIV seroconversion.

In terms of safety, FTC/TDF appeared to be well tolerated overall amongst HIV-uninfected individuals in these clinical trials. No new safety issues were identified. In general, adverse events appeared to be balanced between active and control arms. In iPrEx, unintended weight loss, nausea, vomiting, flatulence, and abdominal pain were reported more often in subjects receiving FTC/TDF. In Partners PrEP, moderate to severe neutropenia was observed more frequently in subjects receiving FTC/TDF or tenofovir as compared with placebo.

Discontinuations were infrequent and generally balanced between groups. In iPrEx, seven subjects discontinued FTC/TDF for increased creatinine; however, six resumed treatment without notable incident. One subject permanently discontinued. In Partners PrEP, six of seven discontinuations were due to a decline in creatinine clearance < 50 mL/min (two FTC/TDF, three 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. Five of these six cases were reported in women; all six had normal creatinine clearance at enrollment, but three were observed to have low normal creatinine clearance at baseline. Renal insufficiency resolved with cessation of the study drug in five cases and one was still ongoing at exit from the trial.

In the iPrEx trial, in a population of MSM with lower baseline BMD scores as compared with the overall population, subjects receiving FTC/TDF had small but statistically significant mean decreases in BMD relative to placebo throughout the trial. Decreases greater than 5% from baseline in BMD of the spine were observed in 14% of subjects in the FTC/TDF group compared with 6% in the placebo group. Of note, amongst subjects

with greater than 5% decrease from baseline in BMD at the spine, five (all in the FTC/TDF group) also had evidence of treatment-emergent graded hypophosphatemia. Similar BMD findings were noted in CDC 4323, the TDF safety trial in U.S. MSM; in addition, almost twice as many subjects receiving TDF in the CDC trial reported new onset back pain compared with subjects receiving placebo. DEXA scans obtained six months after discontinuation of treatment in the iPrEx trial showed that the BMD decreases noted with FTC/TDF treatment were reversing towards baseline levels. Importantly, in both iPrEx and Partners PrEP, bone fractures were trauma-related and balanced between treatment arms.

The decision to prescribe FTC/TDF for the prevention of sexual acquisition of HIV infection should carefully weigh the individual risks for acquiring HIV, their understanding of the importance of adherence to medication, and their potential for development of renal toxicity. Education about PrEP and behavioral counseling are critically important. 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 of the individual during PrEP administration should include regular HIV testing and monitoring for the development of renal dysfunction. DEXA scans prior to and periodically during treatment may be considered for some individuals.

If physicians prescribe and individuals utilize FTC/TDF in the manner described for PrEP, in combination with other strategies to prevent HIV infection, the individual at 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 FTC/TDF.

VII. Risk Evaluation and Mitigation Strategy

A discussion of the proposed Risk Evaluation and Mitigation Strategy (REMS) for TRUVADA® for a PrEP indication is included as an appendix to this document.

VIII. Preliminary Topics for Advisory Committee 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?

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APPENDIX

Risk Evaluation and Mitigation Strategy (REMS)

The Food Drug Administration Amendments Act (FDAAA) of 2007 authorizes FDA to require pharmaceutical sponsors to develop and comply with a Risk Evaluation and Mitigation Strategy (REMS) for a drug if FDA determines that a REMS is necessary to ensure that the benefits of the drug outweigh the risks. A REMS is a required risk management plan that uses risk minimization strategies beyond the professional labeling. The elements of a REMS can include: a Medication Guide or patient package insert (PPI), a communication plan to healthcare providers, elements to assure safe use, and an implementation system. FDAAA also requires that all approved REMS for New Drug Applications (NDA) and Biologics License Applications (BLA) products have a timetable for submission of assessments of the REMS. These assessments are prepared by the Applicant and reviewed by FDA.

A Medication Guide provides FDA approved patient-focused labeling, and can be required as part of the approved labeling if FDA determines one or more of the following apply:

- Patient labeling could help prevent serious adverse events.
- The product has serious risks that could affect a patient's decision to use or continue to use the drug.
- Patient adherence to directions is crucial to product effectiveness.

A communication plan consists of FDA approved materials used to aid a sponsor's implementation of the REMS or inform healthcare providers about serious risk(s) of an approved product. This can include, for example, "Dear Healthcare Professional" letters, collaboration with professional societies, and education pieces (letters, drug fact sheets, etc) to inform prescribers of the risks and the safe use practices for the drug.

Elements to assure safe use (ETASU) can include one or more of the following requirements:

- Healthcare providers who prescribe the drug have particular training or experience or special certifications
- Pharmacies, practitioners, or healthcare settings that dispense the drug are specially certified
- The drug may be dispensed only in certain healthcare settings
- The drug may be dispensed to patients with evidence of safe-use conditions
- Each patient must be subject to monitoring
- Patients must be enrolled in a registry

Because ETASU can impose significant burdens on the healthcare system and reduce patient access to treatment, ETASU are required only if FDA determines that the product could be approved only if, or would be withdrawn unless, ETASU are required to

mitigate a specific serious risk listed in the labeling. Accordingly, the statute [FDCA 505-1(f)(2)] specifies that ETASU:

- Must be commensurate with specific serious risk(s) listed in the labeling.
- Cannot be unduly burdensome on patient access to the drug.
- To minimize the burden on the healthcare delivery system, must, to the extent practicable, conform with REMS elements for other drugs with similar serious risks and be designed for compatibility with established distribution, procurement, and dispensing systems for drugs.

History of Truvada for a PrEP indication and Risk Management

FDA approved TRUVADA® [emtricitabine (200 mg) and tenofovir disoproxil fumarate (300 mg)] tablets for use in combination with other antiretroviral agents (such as non-nucleoside reverse transcriptase inhibitors or protease inhibitors) for the treatment of established HIV-1 infection in adults on August 2, 2004, and in pediatric patients 12 years of age and older on July 8, 2011. Currently, there are no required REMS for any FDA-approved antiretroviral product.

The risk of developing drug resistant HIV-1 variants may occur in persons who continue to take TRUVADA for a pre-exposure prophylaxis (PrEP) indication following HIV seroconversion. Because of this risk, FDA required the applicant submit a proposed REMS for TRUVADA for a PrEP indication.

Proposed REMS for Truvada for a PrEP indication

The proposed REMS for TRUVADA for a PrEP indication includes the following elements: a Medication Guide, prescriber training and education not linked to product distribution as an ETASU, and a Timetable for Submission of Assessments of the REMS. Education of prescribers and uninfected individuals considering or taking TRUVADA for a PrEP indication is the key focus of this proposed REMS program.

The proposed REMS includes the following goals and elements:

I. Goals

The goals of the REMS for TRUVADA for a PrEP indication are:

To inform and educate prescribers, other healthcare professionals, and individuals at high risk for acquiring HIV-1 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 if seroconversion has occurred, to reduce the risk of development of drug-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.

II. REMS Elements

A. Medication Guide

A Medication Guide for uninfected individuals is to support education of uninfected individuals taking TRUVADA for a PrEP indication about the serious risk of acquiring HIV-1 infection and the subsequent development of drug-resistant variants if TRUVADA use is continued following seroconversion.

B. Element to Assure Safe Use

Prescriber training and education (under an ETASU) that is not linked to drug access. Training and education will target the following likely prescribers for TRUVADA for a PrEP indication:

- Primary care prescribers including internal medicine, family practice, and general medicine physicians
- Infectious disease specialists
- Emergency medicine physicians
- Obstetrician-gynecologists
- Addiction specialists

The proposed *TRUVADA for a PrEP Indication Healthcare Professional Education Program* includes training and education materials directed to prescribers and materials for prescribers to educate uninfected individuals considering or taking TRUVADA for a PrEP indication. The Education Program will consist of the following materials to support the training and educational process:

- Full Prescribing Information
- Medication Guide
- Training Guide for Healthcare Providers includes the importance of screening for sexually transmitted infections (STIs), the need for a negative HIV-1 test result before starting TRUVADA for a PrEP indication in an uninfected individual, the importance of the individual's strict adherence to the recommended daily dosage, and safer sex practices.
- Prescriber Safety Brochure: Important Safety Information about TRUVADA for a PrEP Indication includes key serious risk information about TRUVADA, the importance of comprehensive management with regular monitoring of HIV-1 serostatus to avoid taking TRUVADA for a PrEP indication if HIV-1 seroconversion occurred, and the importance of an uninfected individual's adherence to the recommended dosage regimen.

- Individual Safety Brochure: Important Safety Information about TRUVADA for a PrEP indication includes the key serious risk information about TRUVADA for a PrEP indication, what screening tests are recommended before starting TRUVADA for a PrEP indication, the importance of regular testing for HIV-1 serostatus while taking TRUVADA for a PrEP indication, and key information to tell their healthcare provider.
- TRUVADA for a PrEP Indication Wallet Card (for an uninfected individual taking TRUVADA for a PrEP indication) includes brief information about a negative HIV-1 test result right before starting and while taking TRUVADA for a PrEP indication, the recommended daily dosage regimen and the importance of taking TRUVADA for a PrEP indication as part of a comprehensive prevention plan.

In order to facilitate prescriber training and education, the applicant will disseminate information about the potential and known ongoing safety risks associated with use of TRUVADA for a PrEP indication to select professional organizations for outreach to healthcare prescribers likely to prescribe TRUVADA for a PrEP indication.

C. Timetable for Submission of Assessment

The applicant must submit REMS assessments to FDA at 6 months, 18 months, 3 years and 7 years from the approval date of the REMS. The 6-month assessment must report the number and types, by specialty, of prescribers who have completed the training and education for TRUVADA for a PrEP indication as well as drug-use data for TRUVADA for a PrEP indication.

REMS Assessment Plan

The REMS assessment plan will provide the following information that will be used to assess whether the REMS is meeting its intended goals.

1. Estimates of the number of TRUVADA prescriptions for a PrEP indication.
2. Number of prescribers who have undergone training.
3. A Knowledge, Attitude and Behavior (KAB) Survey for prescribers who prescribed TRUVADA for a PrEP indication targeting prescriber's KAB about the key risk messages for HIV-1 testing, compliance with the comprehensive program, and risk behavior to assess the effectiveness of the REMS outreach and education.
4. A survey of individuals' understanding of the risks associated with TRUVADA for a PrEP indication based on prescriber counseling and understanding of the Medication Guide.
5. With respect to the REMS goals, an assessment of the extent to which the elements are meeting the goals or whether the goals and/or elements should be modified.

Discussion

FDA believes that in order to approve TRUVADA for a PrEP indication, a REMS is required that includes a comprehensive ongoing training and education program for prescribers and individuals considering use of TRUVADA for a PrEP indication, a program that emphasizes the importance of regular monitoring for HIV-1 serostatus and behavior education to reinforce the importance of safer sex practices. FDA, however, does not believe that access to TRUVADA (for a PrEP indication) should be restricted to only trained prescribers or to uninfected individuals with documentation of safe use conditions (a negative HIV-1 test). Therefore, the REMS should not include a registry of uninfected individuals taking TRUVADA for a PrEP indication, required monitoring of HIV-1 serostatus, or restriction of access to TRUVADA based on documentation of safe use (e.g., negative HIV-1 test result). The public health benefit of TRUVADA for a PrEP indication can only be achieved with access to TRUVADA and strict adherence with the recommended dosage regimen. These are the two key factors to achieve efficacy for TRUVADA for a PrEP indication. FDA believes that the educational efforts in the proposed REMS are sufficient to support the recommended REMS program.

There are a number of challenges in assessing whether or not the REMS is effective. It will be challenging to capture and report prescriber and individual usage data for TRUVADA for a PrEP indication. There is no specific International Statistical Classification of Disease and Related Health Problems (ICD-9) Code to identify an uninfected individual taking TRUVADA for a PrEP indication. As stated above**,** TRUVADA was approved for use in combination with at least one other antiretroviral medication for treatment of established HIV-1 infection, so use of TRUVADA when prescribed without other concomitant antiretroviral drugs may give some indication of the extent of TRUVADA use for a PrEP indication.

For the same reasons, it will be challenging to measure the proportion of prescribers of TRUVADA for a PrEP indication who have undergone the REMS training and education. It may not be likely that prescribers of TRUVADA for established HIV infection will also be prescribing TRUVADA for PrEP without other concomitant antiretroviral therapy; however, this information is unknown.

Finally, it will be difficult to determine whether the REMS has had an impact in reducing the risk of development of resistant HIV-1 variants because the proposed REMS does not include documentation of safe use with required monitoring of a negative HIV-1 test result. The proposed REMS does not include a registry of uninfected individuals prescribed TRUVADA for a PrEP indication or documentation of safe use, such as a negative HIV-1 test result. The Applicant proposes to capture uninfected individuals and drug-usage data through a pharmacy vendor analysis of a subset of persons taking TRUVADA without concomitant antiretroviral products as the likely users of TRUVADA for a PrEP indication. The proposed data capture, however, will not capture when and if an individual acquired HIV-1 infection while taking TRUVADA for a PrEP indication, or if this acquisition of HIV-1 infection is directly linked to the development of resistant HIV-1 variants.