CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

Office of Clinical Pharmacology Addendum

Date	July 16, 2012
From	Ruben Ayala, Pharm.D
Subject	Review Addendum
NDA#	021752
Applicant	Gilead, Inc.
Date of Submission	12/15/2011
PDUFA Goal Date	September 16, 2012
Proprietary name / Established (USAN) names	TRUVADA / Tenofovir disoproxil fumarate/emtricitabine
Formulation; Strength	Commercially available Truvada tablet; containing a fixed dose combination of tenofovir disoproxil fumarate 300 mg and emtricitabine 200 mg
Proposed Indication	Prevention of sexually acquired HIV-1 infection in uninfected adults at high risk of acquiring HIV-1 infection.

The purpose of this document is to amend the Office of Clinical Pharmacology review of the sNDA for Truvada for a pre-exposure prophylaxis indication of sexually acquired HIV-1 infection in adults at high risk. This document identifies errors in the original sNDA review and provides corrections. This document also contains the final labeling wording for the Dosage and Administration section as well as an assessment of a bioanalytical report submitted late in the review cycle by the Applicant. The bioanalytical report outlines details of the HPLC-MS/MS method used in assaying the plasma samples collected from subjects who enrolled in the Partners PrEP trial. OCP requested that Gilead submit this bioanalytical report as it was missing from the original sNDA submission.

Briefly, corrections made to the original review do not change the overall recommendation: the application is acceptable from a clinical pharmacology perspective. No technical issues were identified in the bioanalytical report.

List of corrections made to the original review.

The original text in the review is shown in black font, edits are shown with double ~~strikethrough~~, and corrections are shown in blue font and yellow highlight.

Pages 9-10, Section 2.2.4.1:

Was there an exposure-response (i.e., relative risk reduction) relationship for TFV or FTC when used for prevention of HIV-1 infection in MSM in the iPrEx trial?

Original text:

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 trial participants underwent PK sampling at baseline, every 12 weeks (every 24 weeks for PBMC analysis), during the visit when seroconversion was detected, at end of trial visit, and at every follow-up visit. When an HIV-1 infection occurred, PK samples were collected from infected subjects during the clinic visit when the infection was detected. PK samples were also collected from three corresponding control subjects who did become infected during the trial. Two of the control subjects were matched to each HIV-infected subject based on trial site and treatment duration, while the third control subject who reported having URAI in a period that covered the plasma sample date closest to seroconversion for the HIV-1 infected subject.

Revised text:

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 trial participants underwent PK sampling at baseline, every 12 weeks (every 24 weeks for PBMC analysis), during the visit when seroconversion was detected, at end of trial visit, and at every follow-up visit. When an HIV-1 infection occurred, PK samples were collected from infected subjects during the clinic visit when the infection was detected. PK samples were also collected from three corresponding control subjects who did **not** become infected during the trial. Two of the control subjects were matched to each HIV-infected subject based on trial site and treatment duration, while the third control subject who reported having URAI in a period that covered the plasma sample date closest to seroconversion for the HIV-1 infected subject.

Original text:

Non-measurable intracellular concentrations of TFV-DP indicate poor TDF/FTC adherence. In order to assess the impact of medication adherence on efficacy, the distribution of TFV-DP detection status within the 133 HIV-uninfected subjects (i.e., 62% non-measurable vs. 38% measurable) was extrapolated to all HIV-uninfected subjects treated with TDF/FTC in iPrEx (n=1176). Based on the extrapolation, 451 HIV-uninfected subjects treated with TDF/FTC were likely to have measurable TFV-DP concentrations, and 725 were likely to have nonmeasurable concentrations. Next, the event rate of HIV-1 infection for these uninfected subjects was estimated by taking into account the 48 subjects who seroconverted in the TDF/FTC group, who had measurable (n=4) and non-measurable (n=44) concentrations. The event rate in the uninfected group expected to have measurable concentrations was estimated as 4/455 (451 + 4) and the event rate for uninfected subjects with no measurable concentrations was estimated as 44/769 (725 + 44). Figure 3 below displays the conversion rate per patient years. Notably, the seroconversion rate in the TDF/FTC group with non-measurable TFV-DP (3.6%) was not significantly different from the conversion rate in the placebo (4.2%) group. For subjects with measurable intracellular drug concentrations, the HIV seroconversion event rate was 0.5%, which is substantially lower than event rates in the placebo group (4.2%), or in the nonmeasurable drug concentration (3.6%) groups.

Revised text:

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distribution of TFV-DP detection status within the 133 HIV-uninfected subjects (i.e., 62% non-measurable vs. 38% measurable) was extrapolated to all HIV-uninfected subjects treated with TDF/FTC in iPrEx (n=1176). Based on the extrapolation, 451 HIV-uninfected subjects treated with TDF/FTC were likely to have measurable TFV-DP concentrations, and 725 were likely to have nonmeasurable concentrations. Next, the projected event rate of HIV-1 infection for these uninfected subjects was estimated by taking into account the 48 subjects who seroconverted in the TDF/FTC group, and further broken down into those who had measurable (n=4) and non-measurable (n=44) concentrations. Thus, the projected event rate in the uninfected group expected to have measurable concentrations was estimated as 4/455 (451 + 4) and the projected event rate for uninfected subjects ~~with~~ expected to have non-measurable concentrations was estimated as 44/769 (725 + 44). Figure 3 below displays the conversion rate per patient years. Notably, the seroconversion rate in the TDF/FTC group with non-measurable TFV-DP (3.6%) was not significantly different from the conversion rate in the placebo (4.2%) group. For subjects with measurable intracellular drug concentrations, the HIV seroconversion event rate was 0.5%, which is substantially lower than event rates in the placebo group (4.2%), or in the nonmeasurable drug concentration (3.6%) groups.

Page 37, Section 4.1.1:

iPrEx trial

Original text:

In order to assess the impact of TDF/FTC adherence on efficacy, DAVP extrapolated the distribution of non-seroconverters (n=133) with measurable (n=51, 38%) and non-measurable (n=82, 62%) TFV-DP concentrations to all subjects treated with TDF/FTC in iPrEx (n=1176). The analysis estimated that 451 non-seroconverters receiving TDF/FTC were likely to have measurable TFV-DP concentrations, and 725 were likely to have non-measurable TFV-DP concentrations. Next, the Pharmacometrics reviewer estimated the seroconversion rate per patient year for all non-seroconverters in the TDF/FTC group, by adding back in the 48 seroconverter subjects who had measurable (n=4) and non-measurable (n=44) TFV-DP concentrations. Thus, the event rate in the uninfected group that was expected to have measurable concentrations was estimated as 4/(451 + 4) and the event rate for uninfected subjects with no measurable concentrations was estimated as 44/(725 + 44). The analysis revealed that subjects with non-measurable TFV-DP concentrations had a seroconversion rate of 3.6%, which was not significantly different from the seroconversion rate observed in the placebo group (4.2%). In contrast, subjects with measurable TFV-DP concentrations had a seroconversion rate of 0.5%.

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Page 14, Section 2.2.4.3:

What subject characteristics affect the exposure-response relationships (dose-response, concentration-response) for efficacy?

Original text:

Subjects who were 25 years of age or older, had at least a secondary education, and who reported having unprotected receptive anal intercourse (URAI) at screening were more likely to have measurable intracellular tenofovir concentrations relative to their younger, less educated, and non-URAI engaging counterparts within the PK subgroup of non-seroconverter subjects in iPrEX (n=133) (see Figure 8 below). Of note, URAI is a risky sexual behavior believed to be highly correlated with acquisition of HIV-1 infection. The relative risk reduction of acquiring HIV-1 infection was 53% (95% CI: 29-69%) in subjects who reported URAI at screening compared to no URAI reported. A 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 26-69%] compared with 12% in those with less than secondary education). When combining the three subject covariates, the relative risk reduction with TDF/FTC compared with placebo was 85% (95% CI: 58-95%).

Revised Text:

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Page 38, Section 4.1.1:

iPrEx trial

Original Text:

The Applicant reported that pre-exposure prophylaxis with TDF/FTC demonstrated a significant relative risk reduction of 58% (95% CI: 32 to 74%) in acquiring HIV-1 infections among subjects who reported URAI at enrollment. The pharmacometrics reviewer conducted a similar post-hoc exploratory analysis and estimated the relative risk reduction in this subject population to be 53% (95% CI: 29-69%). The post hoc analysis also showed that subjects who were ≥25 years of age and those with secondary education had relative risk reductions of 56% (95% CI: 23-75%) and 52% (95% CI: 26-69%) compared to their counterparts. When combining the three subject covariates, the relative risk reduction with TDF/FTC compared with placebo was 85% (95% CI: 58-95%). However, these post-hoc analyses are exploratory, and no conclusions can be made based on these findings. Trial subjects were not stratified based on these covariates and the iPrEx trial was not large enough to demonstrate efficacy within these subgroups.

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Page 25, Section 3:

Detailed labeling recommendations

Original text:

----------DOSAGE AND ADMINISTRATION----------

- Recommended dose in HIV-1 infected adults and pediatric patients (12 years of age and older and weighing greater than or equal to 35 kg): One tablet (containing 200 mg of emtricitabine and 300 mg of tenofovir disoproxil fumarate) once daily taken orally with or without food. (2.1).

- Dose recommended in HIV-1 infected patients with renal impairment: Creatinine clearance 30-49 mL/min: 1 tablet every 48 hours. (2.2) CrCl below 30 mL/min or hemodialysis: Do not use TRUVADA. (2.2)

- Recommended dose in HIV-1 uninfected adult individuals 18 years of age and older: One tablet (containing 200 mg of emtricitabine and 300 mg of tenofovir disoproxil fumarate) once daily taken orally with or without food. (2.1)

Revised text:

----------DOSAGE AND ADMINISTRATION----------

Treatment of HIV-1 infection (2.1)

- Recommended dose in [redacted] (b) (4) adults and pediatric patients (12 years of age and older and weighing greater than or equal to 35 kg): One tablet [redacted] (b) (4) once daily taken orally with or without food. (2.1).

- [redacted] (b) (4) Recommended dose in [redacted] (b) (4) renally impaired [redacted] (b) (4) HIV-1 infected adult patients: Creatinine clearance 30-49 mL/min: 1 tablet every 48 hours. (2.32) CrCl below 30 mL/min or hemodialysis: Do not use TRUVADA. (2.32)

Pre-exposure Prophylaxis (2.2)

- Recommended dose in HIV-1 uninfected [redacted] (b) (4) individuals 18 years of age and older: One tablet [redacted] (b) (4) once daily taken orally with or without food. (2.21)
- Recommended dose in renally impaired HIV-uninfected individuals: Do not use TRUVADA in HIV-uninfected individuals if CrCl is below 60 mL/min. If a decrease in CrCl is observed in uninfected individuals while using TRUVADA for PrEP, evaluate potential causes and re-assess potential risks and benefits of continued use. (2.3)

Assessment of the bioanalytical report for assaying plasma samples collected in Partners PrEP trial.

The Applicant outsourced the bioanalytical work to the [redacted] (b) (4) received 1210 plasma samples, of which 1100 samples were from subjects who received trial drug and 110 from subjects who received placebo. According to [redacted] (b) (4) all plasma samples were analyzed within the established frozen storage stability of tenofovir, which was at least three years at -70°C. Investigators evaluated tenofovir only in Partners PrEP because tenofovir was the common denominator between Viread and Truvada.

Plasma samples were assayed using a validated HPLC-MS/MS method. There were two calibration ranges for measuring tenofovir in plasma: 5 to 1000 ng/mL and 0.31 to 10 ng/mL. The initial sample runs used a calibration range of 5 to 1000 ng/mL and a sample volume of 50 µL. Any sample in the initial run with tenofovir

concentrations below the limit of quantification (BLOQ) were re-analyzed using a larger sample volume (250 μL) and a calibration range of 0.31 to 10 ng/mL. Hence, the overall calibration range for tenofovir in plasma was 0.31 to 1000 ng/mL.

Validation of the bioanalytical method was adequate based on precision and accuracy results shown in the table below. All calibration standards and quality controls met the pre-set bioanalytical criteria. Investigators defined these criteria as precision (%CV) within ±15%, accuracy (%RE) ≤15%, and coefficient of determination (r^2) ≥0.98.

Table 1 Precision (%CV) and accuracy (% relative error, RE) of calibration standards and QC samples for all analytes evaluated during the trial

	Cal Std			QC	
Analyte	**%CV**	**%RE**	**R^2**	**%CV**	**%RE**
Tenofovir using 5 to 1000 ng/mL calibration range	4.2-9.4	≤2.7	≥0.9942	7.1-9.8	≤3.1
Tenofovir using 0.31 to 10 ng/mL calibration range	1.5-8.7	≤10.4	≥0.9954	4.3-9.8	≤8.0

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/s/

RUBEN C AYALA
07/16/2012

SHIRLEY K SEO
07/16/2012

Office of Clinical Pharmacology Review

sNDA:	021752
Submission date:	12/15/2011
Brand name:	TRUVADA®
Generic name:	Tenofovir disoproxil fumarate/emtricitabine
Clinical pharmacology reviewer:	Ruben Ayala, Pharm.D.
Pharmacometrics reviewer	Jiang Liu, Ph.D.
Acting clinical pharmacology team leader:	Shirley Seo, Ph.D.
Pharmacometrics team leader:	Yaning Wang, Ph.D.
OCP division:	Division of Clinical Pharmacology 4
OND division:	Division of Antiviral Products
Applicant:	Gilead, Inc.
Relevant IND(s):	IND 108930, IND 71859, NDA 21-500, NDA 21-356
Submission type; Code:	Supplement NDA; SDN 30
Formulation; Strength(s):	Commercially available Truvada tablet; containing a fixed dose combination of tenofovir disoproxil fumarate 300 mg and emtricitabine 200 mg
Dosing regimen:	One Truvada tablet by mouth once daily without regard to food
Indication:	Prophylaxis of HIV-1 infection

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Glossary

ADME	Absorption, distribution, metabolism, and excretion
AEs	Adverse events
AIDS	Acquired immune deficiency syndrome
ART	Antiretroviral therapy
AUC	Area under the concentration curve
BA	Bioanalytical
BMD	Bone mineral density
CAVP	Colorado Antiviral Pharmacology Laboratory
CD4 cells	Lymphocyte blood cells often referred to as “white blood cells” or “T-cells” that play an essential role in the immune system.
CL/F	Apparent oral clearance
C_{max}	Maximum concentration
CrCl	Creatinine clearance
CYP	Cytochrome P450 enzymes
CV	Coefficient of variation
DAVP	Division of Antiviral Products
DHHS	Department of Health and Human Services
DSMB	Data safety monitoring board
EDTA	Ethylenediaminetetraacetic acid – an anticoagulant
EIA	Enzyme immunoassays
fmol	Femtomole
FTC	Emtricitabine
FTC-TP	Emtricitabine triphosphate (active component of emtricitabine, refers to intracellular moiety of FTC)
HIV-1	Human immunodeficiency virus type 1
HLA	Human leukocyte antigen
i.e.	That is
IL-2	Interleukin-2
IND	Investigational new drug
Kcal	Kilocalories
LC/MS/MS	Liquid chromatography/mass spectrometry/mass spectrometry
LLOQ	Lower limit of quantification
µg/mL	microgram per milliliter
mg	milligram
mITT	Modified intention-to-treat
mL/min	Milliliters per minute
MRP4	Multidrug resistance protein 4 transporter
MSM	Men who have sex with men
NDA	New Drug Application
ng	nanogram
NRTI	Nucleos(t)ide reverse transcriptase inhibitor
NNRTI	Non-nucleoside reverse transcriptase inhibitor
NSAID	Non-steroidal anti-inflammatory drug
OAT	Organic anion transporter
OCP	Office of Clinical Pharmacology
OND	Office of New Drugs
PBMCs	Peripheral blood mononuclear cells
PCR	Polymerase chain reaction
PDUFA	Prescription drug user fee act
PEP	Post-exposure prophylaxis
PK	Pharmacokinetics
pmol	Picomole
PrEP	Pre-exposure prophylaxis
RNA	Ribonucleic acid

QBR	Question based review
QC	Quality control
QD	Once daily
SD	Standard deviation
SCr	Serum creatinine
sNDA	Supplemental NDA
Seroconversion	The change of a seronegative test from negative to positive, indicating the development of antibodies in response to infection.
Serodiscordant	Term used to describe a couple in which one partner is HIV positive and the other is HIV negative.
SHIV	Simian-human immunodeficiency virus
SIV	Simian immunodeficiency virus
spl	Sample
ss	Steady-state
$t_{1/2}$	Half-life
TDF	Tenofovir disoproxil fumarate
TFV	Tenofovir (refers to plasma concentrations)
TFV-DP	Tenofovir diphosphate (active component of tenofovir, refers to intracellular moiety of TFV)
T_{max}	Time after administration of drug when the maximum plasma concentration is reached.
UGT	UDP-glucuronosyltransferase enzyme
ULOQ	Upper limit of quantification
URAI	Unprotected receptive anal intercourse

1 Executive summary

The HIV-1 epidemic in the United States persists despite preventative measures, such as condoms. Condoms are highly effective in preventing sexually transmitted infections. However, their efficacy is limited because the population at highest risk of HIV-1 infection (men who have sex with men and minorities) use them infrequently. There is currently no approved drug product on the market for an HIV-1 prevention indication.

Truvada is a fixed dose combination product that contains emtricitabine (FTC) 200 mg and tenofovir disoproxil fumarate (TDF) 300 mg. FTC is a nucleoside reverse transcriptase inhibitor while TDF is a nucleotide reverse transcriptase inhibitor (both designated as NRTI) and are approved as individual formulations for the treatment of HIV-1 infection in combination with other antiretroviral agents. The combination of FTC and TDF has characteristics that make it a favorable option for preventing HIV-1 infection, including once daily dosing, long-intracellular half-lives of both components, high penetration of FTC and TFV into genital and mucosal tissues, high barrier to resistance, and established tolerability among HIV-1 infected patients.

Gilead submitted an efficacy supplement to the New Drug Application (sNDA) for Truvada for a proposed indication of prevention of sexually acquired HIV-1 infection in uninfected adults at high risk of acquiring HIV-1 infection. In support of this new indication for Truvada, the Applicant submitted the results of two international, placebo-controlled efficacy trials in men who have sex with men (MSM) and in serodiscordant couples. The Applicant has adequately demonstrated the following points in these two trials:

- TDF/FTC achieved greater efficacy in preventing HIV-1 infection compared to placebo in MSM and in serodiscordant couples.
- Medication adherence was highly correlated with prevention of HIV-1 infection.

- Uninfected subjects receiving TDF/FTC had comparable safety and tolerability to uninfected subjects who received placebo.

1.1 Recommendation

The clinical pharmacology information submitted in the application is acceptable. The submission has no major clinical pharmacology issues.

1.2 Phase 4 trial commitments

There are no clinical pharmacology-related Phase 4 trial commitments.

1.3 Summary of clinical pharmacology and biopharmaceutics findings

This sNDA contains results from two pivotal trials evaluating the efficacy of TDF/FTC in preventing the acquisition of HIV-1 infection in MSM (iPrEx trial) and in HIV-1 serodiscordant couples (Partners PrEP trial).

The iPrEx trial was a multicenter, international, randomized, double blind, placebo-controlled trial of once-daily oral administration of TDF/FTC for HIV-1 prevention in MSM at high risk for acquiring HIV-1 infection. A total of 2499 subjects were randomized to receive either TDF/FTC (n=1251) or placebo (n=1248). Along with trial drug, subjects were provided with condoms and active behavioral intervention, or counseling. The trial was event-driven and was set to end when at least 85 seroconversions were observed. The trial was powered to show that TDF/FTC was at least 30% efficacious at preventing HIV-1 infection. This 30% efficacy threshold has been previously used or observed in trials evaluating vaccines for prevention of HIV-1 infection.

Investigators conducted a subgroup analysis to evaluate if tenofovir and emtricitabine plasma and intracellular concentrations (in peripheral blood mononuclear cells [PBMC]) correlated with protection from HIV-1 infection. When a trial participant was deemed an HIV-1 seroconverter, the subject's pharmacokinetic (PK) samples were evaluated for tenofovir and emtricitabine concentrations in plasma and PBMCs. The PK samples collected from three corresponding control non-seroconverters were also evaluated. Two of the control subjects were matched to each HIV-1 seroconverter based on trial site and time on treatment. The seroconverters were also matched to a third control subject who reported having unprotected receptive anal intercourse (URAI) in a period that covered the plasma sample date for the seroconverter. The Applicant used URAI to identify the subpopulation at highest risk for acquiring HIV-1 infection because URAI is a risky sexual behavior believed to be highly associated with acquiring HIV-1 infection.

The modified intent-to-treat population (mITT) included 2442 randomized subjects (TDF/FTC n=1224, placebo n=1218). In this mITT group, 131 seroconversion events were reported during the on-treatment period: 48 in the TDF/FTC group and 83 in the placebo group. The mITT analysis conducted by the Applicant showed that subjects in the TDF/FTC group had a 42% (95% CI: 18-60%) relative risk reduction in acquiring HIV-1 infection compared to

subjects receiving placebo. However, the finding did not exclude the possibility that the true risk reduction with TDF/FTC was 30% or less.

Medication adherence in iPrEx was generally low, as demonstrated by an evaluation of tenofovir plasma and intracellular concentrations. In the PK subgroup analysis, only 38% of non-seroconverter subjects (51/133) had measurable intracellular TFV-DP concentrations, and very few subjects (~9%, 12/133) had intracellular TFV-DP concentrations reflective of once daily TDF/FTC dosing. Based on results from the Strand Study conducted by Peter Anderson *et al*. (2012), healthy subjects receiving once daily TDF/FTC for 6 weeks achieved median intracellular TFV-DP concentrations of ~42 fmol/10^6 viable cells (Interquartile range 31-47). The Strand Study was conducted in healthy subjects who received three different dosing regimens of TDF/FTC, including 2 doses per week, 4 doses per week, or 7 doses per week to evaluate PBMC levels of TFV-DP. In the iPrEx trial, the Applicant reported a relative risk reduction with TDF/FTC of 92% (95% CI: 40-99%) in subjects with measurable intracellular TFV-DP concentrations compared to subjects with non-measurable TFV-DP concentrations. Results suggest that medication adherence, based on having measurable intracellular TFV-DP concentrations, are highly protective from acquiring HIV-1 infection.

The Partners PrEP trial was a multicenter, international, randomized, double-blind, placebo-controlled trial evaluating once-daily oral Viread (TDF 300 mg) or Truvada (TDF/FTC) among uninfected individuals within an HIV-serodiscordant couple, where the HIV-1 infected partner was not eligible for antiretroviral therapy per national guidelines. The trial enrolled 4758 serodiscordant couples. The uninfected partner subjects were randomized in a 1:1:1 ratio to receive TDF (n=1589), TDF/FTC (n=1583), or placebo (n=1586). In addition to drug treatment, subjects received counseling on medication adherence and condom use. Enrolled subjects were followed for a minimum of 24 months up to a maximum of 36 months. The trial is still evaluating TDF/FTC *versus* TDF; the placebo group was discontinued.

Similar to the iPrEx trial, investigators evaluated if tenofovir plasma concentrations correlated with protection from HIV-1 infection in Partners PrEP. The sub-group analysis compared plasma concentrations of TFV collected from seroconverters (cases) *versus* a subset of non-seroconverters (controls) in the TDF and TDF/FTC groups. The PK comparison included 100 randomly selected controls from the TDF/FTC and TDF groups (total 200). A single blood sample for measurement of TFV plasma concentrations was collected every 3 months during the trial. Of note, investigators did not evaluate intracellular concentrations of TFV-DP nor FTC-TP in this trial.

The mITT analysis included 4708 partner subjects; 1572 received TDF, 1568 received TDF/FTC, and 1568 received placebo. In this mITT group, 82 seroconversion events occurred: 13 in the TDF/FTC group, 17 in the TDF group, and 52 in the placebo group. According to the Applicant's mITT analysis, TDF reduced the risk of acquiring HIV-1 infection by 67% (95% CI: 44-81%), while TDF/FTC reduced the risk by 75% (95% CI: 55-87%) relative to placebo. The difference in relative risk reduction between TDF and TDF/FTC was not statistically significant.

In the PK subgroup of the Partners PrEP trial, approximately 62% of subjects receiving TDF/FTC or TDF (140/226) always had measurable plasma TFV concentrations, 27% of subjects (61/226) sometimes had measurable concentrations, while ~11% of subjects (25/226) never had measurable plasma concentrations across all clinic visits. Based on the Applicant's analysis, for partner subjects in the TDF group, having measurable tenofovir concentrations was associated with an 86% reduction in HIV-1 risk (95% CI: 67-95%) compared to having no measurable concentrations. For the partner subjects in the TDF/FTC group, having measurable

tenofovir concentrations was associated with a 90% reduction in HIV-1 risk (95% CI: 56-98%), as compared to having no measurable concentrations at any clinic visit.

In summary, both trials demonstrated that adding TDF/FTC to preventive measures, such as counseling on condom use and reduction of risky sexual behavior, was more effective than placebo, condoms, and counseling alone at preventing HIV-1 infections in HIV-1 uninfected MSM and partners in serodiscordant couples. The relative risk reduction in acquiring HIV-1 infection with TDF/FTC was even greater in subjects with known medication adherence, demonstrated by having measurable intracellular or plasma tenofovir concentrations. Medication adherence in the iPrEx trial was low compared to adherence in Partners PrEP, possibly because subjects in Partners PrEP were in a serodiscordant relationship, and their perceived risk of acquiring HIV-1 infection was higher compared to subjects in iPrEX.

2 Question-Based Review (QBR)

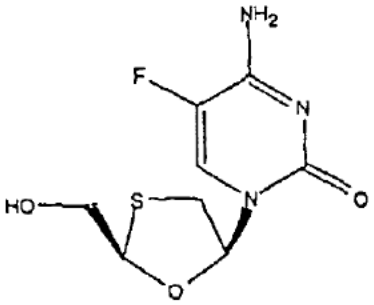
2.1 General attributes of TDF/FTC

TDF/FTC (Truvada) was approved in 2004, while TDF (Viread) was approved in 2001 and FTC (Emtriva) was approved in 2003. As a result, the physical-chemical properties of TDF and FTC are well known. This section summarizes information derived from Truvada's label, Viread's original NDA review (NDA 21-500), and Emtriva's original NDA review (NDA 21-356).

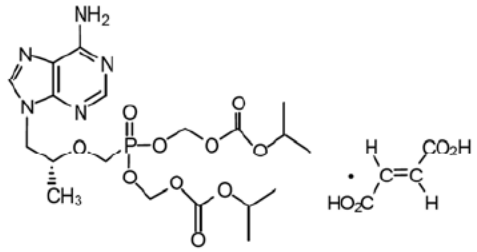
2.1.1 What are the highlights of the chemistry and physical-chemical properties of the drug substances and formulation of the drug product?

Each Truvada tablet contains 200 mg of FTC and 300 mg of TDF. FTC is a synthetic nucleoside analog of cytosine, while TDF is an analog of adenosine 5'-monophosphate. The drugs undergo intracellular phosphorylation to form FTC-5'-triphosphate and TFV-5'-diphosphate, respectively. The phosphorylated drug moieties of FTC and TDF confer antiviral activity. Figure 1 below displays the chemical structures and physical properties of FTC and TDF.

Figure 1 Chemical structures of emtricitabine (left) and tenofovir DF (right).



Emtricitabine
Structural formula: $C_8H_{10}FN_3O_3S$
Molecular weight: 247.24



Tenofovir DF
Structural formula: $C_{23}H_{34}O_{14}N_5P$
Molecular weight: 635.52

2.1.2 What are the proposed mechanism(s) of action and therapeutic indication(s) for TDF/FTC?

FTC is phosphorylated by cellular enzymes (within cells) to form the active moiety, FTC-5'-triphosphate. FTC-5'-triphosphate inhibits the activity of the HIV-1 reverse transcriptase by competing with the natural substrate deoxycytidine 5'-triphosphate. Tenofovir disoproxil fumarate is an oral prodrug of tenofovir. Once absorbed into the systemic circulation, the prodrug is cleaved by esterases to tenofovir. Tenofovir is a nucleotide analog, and it undergoes intracellular di-phosphorylation to inhibit HIV-1 reverse transcriptase.

Truvada is currently approved, in combination with other antiretrovirals, for the treatment of HIV-1 infection in adults and pediatric subjects at least 12 years of age and older.

2.1.3 What are the proposed dosage(s) and route(s) of administration?

The Applicant proposes once daily oral TDF/FTC (300 mg TDF and 200 mg FTC) for prophylaxis of HIV-1 infection using the approved commercial formulation.

2.2 General clinical pharmacology

2.2.1 What are the design features of the clinical pharmacology and clinical trials used to support dosing or claims for TDF/FTC PrEP?

Two pivotal trials provided efficacy and safety information for TDF/FTC for PrEP:

The iPrEx trial (CO-US-104-0288)

This trial was a multicenter, international, randomized, double-blind, placebo-controlled trial of once daily oral administration of TDF/FTC for prevention of HIV-1 infection in uninfected men who have sex with men (MSM) and transgender women at high risk for HIV-1 infection. A total of 2499 subjects were randomized to receive either TDF/FTC (n=1251) or placebo (n=1248). In addition to drug treatment, subjects in both groups received condoms and active behavioral intervention (counseling). The trial duration was event driven: the trial was discontinued when at least 85 seroconversions were detected.

The Partners PrEP trial (CO-US-104-0380)

This trial was a multicenter, international, randomized, double-blind, placebo-controlled trial of PrEP using once-daily oral TDF or TDF/FTC in HIV-uninfected subjects within a serodiscordant couple, where the HIV-infected partner was not eligible for antiretroviral therapy per national guidelines. The trial enrolled 4758 serodiscordant couples. Uninfected partner subjects received TDF (n=1589), TDF/FTC (n=1583), or placebo (n=1586) in a 1:1:1 fashion. Subjects also received condoms and active behavioral intervention as part of their drug treatment. Investigators followed enrolled subjects for a minimum of 24 months up to a maximum of 36 months. The trial is still evaluating TDF vs. TDF/FTC; the placebo group was discontinued after investigators observed evidence of protection from HIV-1 infection in the active drug groups.

2.2.2 What is the basis for selecting the response endpoints or biomarkers and how were they measured in the clinical pharmacology and clinical studies with TDF/FTC for PrEP?

In both clinical trials, the primary efficacy endpoint was the cumulative proportion of subjects who seroconverted while receiving TDF/FTC compared to placebo. This efficacy endpoint is appropriate, as the Applicant is seeking an indication for prevention of HIV-1 infection.

During the trials, subjects underwent monthly HIV-1 testing using a rapid HIV test with a lower limit of detection of HIV-1 RNA ≥ 50 copies/mL. When a subject tested positive for HIV-1 infection, the final confirmation of HIV-1 seroconversion was based on 1) an algorithm and 2) the assessment of an Endpoints Committee. Based on the algorithm, all reported seroconversions required:

- an initial positive test on at least one of the two different types of HIV-1 rapid tests, and
- either confirmation by enzyme immunoassays (EIA) or by another test approved by the Medical Director.

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

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

If a subject seroconverted within the first three months of trial enrollment, investigators conducted RNA PCR testing using samples collected at enrollment to determine if the HIV-1 infection was present prior to receiving trial treatment. RNA PCR analysis was also conducted in subjects who missed HIV-1 testing at the 3-month clinic visit and were seropositive at their next visit. For all subjects who seroconverted, investigators attempted to identify the date of seroconversion by sequentially analyzing blood samples collected during previous clinic visits preceding the visit when seroconversion was detected.

2.2.3 Are the active moieties in the plasma and PBMCs appropriately identified and measured to assess PK parameters and exposure response relationships with TFV and FTC?

Yes, a validated LC/MS/MS method was used for identification and quantification of the active moieties of tenofovir and emtricitabine. In the iPrEx trial, plasma and PBMC samples were analyzed for quantification of TFV and FTC, and TFV-DP and FTC-TP, respectively. In the Partners PrEP trial, plasma samples were analyzed for quantification of TFV and FTC. For more details on the bioanalytical methods, refer to section 2.6 below.

2.2.4 Exposure-response

2.2.4.1 Was there an exposure-response (i.e., relative risk reduction) relationship for TFV or FTC when used for prevention of HIV-1 infection in MSM in the iPrEx trial?

Medication adherence with TDF/FTC was paramount in preventing the acquisition of HIV-1 infection in both the iPrEx and Partners PrEP trials. Investigators in the iPrEx trial implemented several tools for monitoring medication adherence, including monthly counseling, pill counts, and collection of plasma and PBMC samples. Self-reported medication adherence was high (≥90%) in iPrEx, but this observation did not correlate with measurable drug concentrations in the PK subgroup analysis. PK sampling in the iPrEX trial was sparse, with PBMC samples collected in 24-week intervals throughout the trial. Despite the sparse PK data available, both the Applicant and the pharmacometrics reviewer demonstrated that subjects with measurable intracellular TFV-DP concentrations had a greater relative risk reduction in acquiring HIV-1 infection compared to subjects with non-measurable drug concentrations and those receiving placebo.

In the PK subgroup analysis, tenofovir was selected as the marker for medication adherence rather than emtricitabine, because tenofovir intracellular concentrations are generally measurable for a longer period of time relative to emtricitabine. The intracellular half-life of TFV-DP is longer than the plasma half-life of TFV (87-150 hours vs. 39-50 hours, respectively). Subjects with poor TDF/FTC adherence may demonstrate one or more of the following patterns in tenofovir plasma and intracellular concentrations:

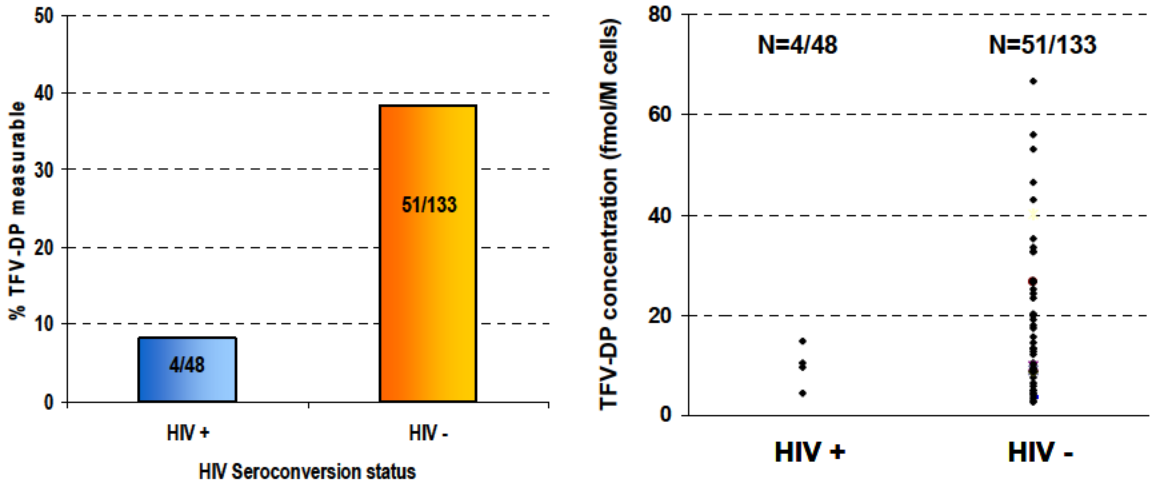
- Undetectable plasma and undetectable intracellular concentrations, possibly reflecting no TDF/FTC intake for more than 20 days before clinic visit.
- Undetectable plasma and low measurable intracellular concentrations, possibly reflecting recent TDF/FTC intake within 20 days before clinic visit.
- High measurable plasma and low measurable or undetectable intracellular concentrations, possibly reflecting TDF/FTC intake just before clinic 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 trial participants underwent PK sampling at baseline, every 12 weeks (every 24 weeks for PBMC analysis), during the visit when seroconversion was detected, at end of trial visit, and at every follow-up visit. When an HIV-1 infection occurred, PK samples were collected from infected subjects during the clinic visit when the infection was detected. PK samples were also collected from three corresponding control subjects who did become infected during the trial. Two of the control subjects were matched to each HIV-infected subject based on trial site and treatment duration, while the third control subject who reported having URAI in a period that covered the plasma sample date closest to seroconversion for the HIV-1 infected subject.

Figure 2, left plot, below shows that a lower proportion of HIV-1 seroconverters had measurable levels of intracellular TFV-DP at the time of seroconversion compared with matched HIV-1 uninfected controls (8% [4/48] vs. 38% [51/133], respectively). Within the subjects with measurable concentrations, the median TFV-DP concentration was higher in non-seroconverters (15.6 fmol/10^6 viable cells [range: 2.49 to 82.4]) than in seroconverters (10.2 fmol/10^6 viable cells [range: 4.19 to 14.7]). These results suggest that having measurable TFV-

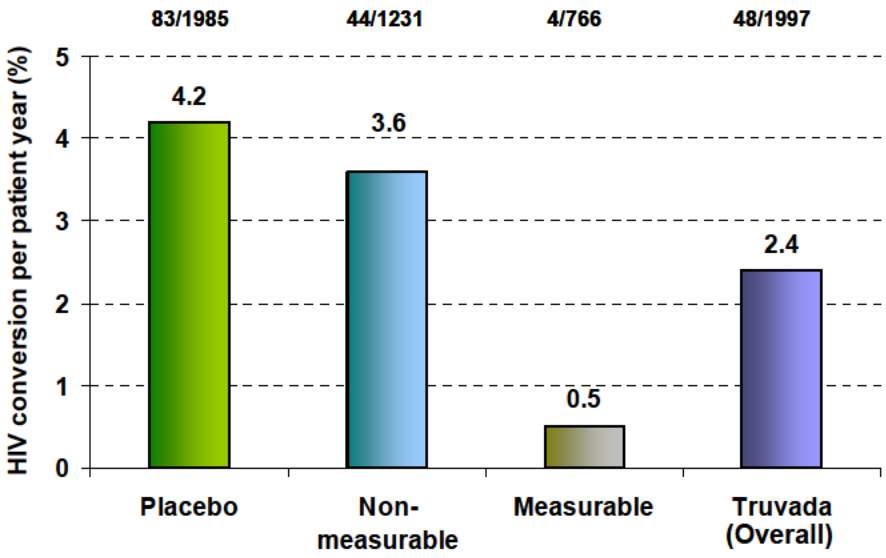
DP concentrations provides greater protection from acquiring HIV-1 infection than not having measurable TFV-DP concentrations. However, having measurable TFV-DP concentrations may not completely protect from HIV-1 infection, as illustrated by four subjects who seroconverted despite having measurable concentrations at the clinic visit when seroconversion was detected. Conversely, a subject with non-measurable TFV-DP concentrations may not necessarily acquire HIV-1 infection, as illustrated by 82 subjects in the uninfected group. Of note, drug concentrations obtained in subjects at the clinic visit when seroconversion is detected may not reflect concentrations around the time of exposure to HIV-1.

Figure 2 A greater proportion of non-seroconverters had measurable intracellular TFV-DP concentrations relative to seroconverters based on a PK sample collected during the date closest to the clinic visit when HIV-1 infection was detected (iPrEx trial).



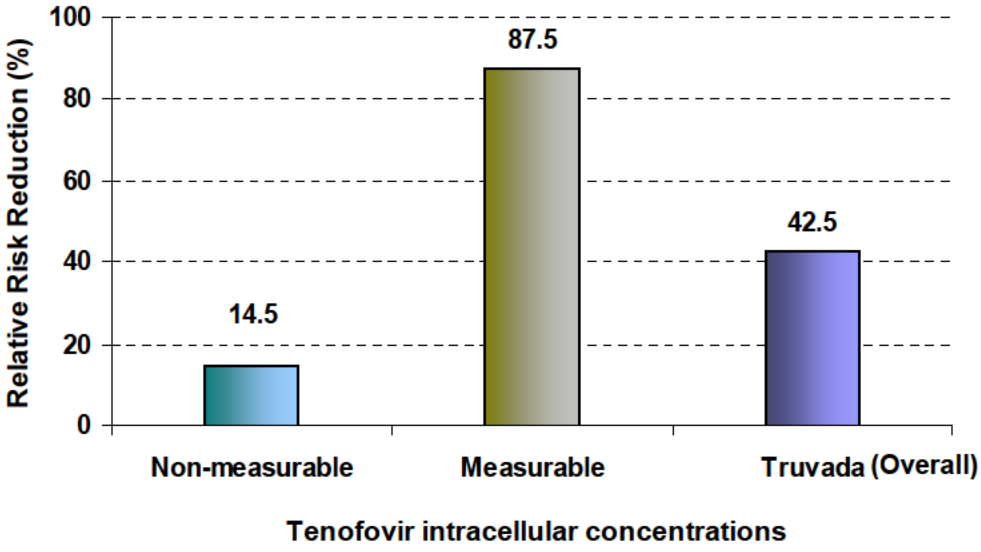
Non-measurable intracellular concentrations of TFV-DP indicate poor TDF/FTC adherence. In order to assess the impact of medication adherence on efficacy, the distribution of TFV-DP detection status within the 133 HIV-uninfected subjects (i.e., 62% non-measurable vs. 38% measurable) was extrapolated to all HIV-uninfected subjects treated with TDF/FTC in iPrEx (n=1176). Based on the extrapolation, 451 HIV-uninfected subjects treated with TDF/FTC were likely to have measurable TFV-DP concentrations, and 725 were likely to have non-measurable concentrations. Next, the event rate of HIV-1 infection for these uninfected subjects was estimated by taking into account the 48 subjects who seroconverted in the TDF/FTC group, who had measurable (n=4) and non-measurable (n=44) concentrations. The event rate in the uninfected group expected to have measurable concentrations was estimated as 4/455 (451 + 4) and the event rate for uninfected subjects with no measurable concentrations was estimated as 44/769 (725 + 44). Figure 3 below displays the conversion rate per patient years. Notably, the seroconversion rate in the TDF/FTC group with non-measurable TFV-DP (3.6%) was not significantly different from the conversion rate in the placebo (4.2%) group. For subjects with measurable intracellular drug concentrations, the HIV seroconversion event rate was 0.5%, which is substantially lower than event rates in the placebo group (4.2%), or in the non-measurable drug concentration (3.6%) groups.

Figure 3 Event rates in all subjects – placebo and TDF/FTC groups (iPrEX).



When translating these absolute conversion rates to relative risk reduction of TDF/FTC versus the placebo group, the risk reduction in subjects in the TDF/FTC group with measurable intracellular tenofovir concentrations was considerably higher (87.5%). In contrast, the TDF/FTC group with non-measurable TFV-DP demonstrated limited additional protection from acquiring HIV-1 infection (14.5%) compared to the placebo group (See Figure 4 below).

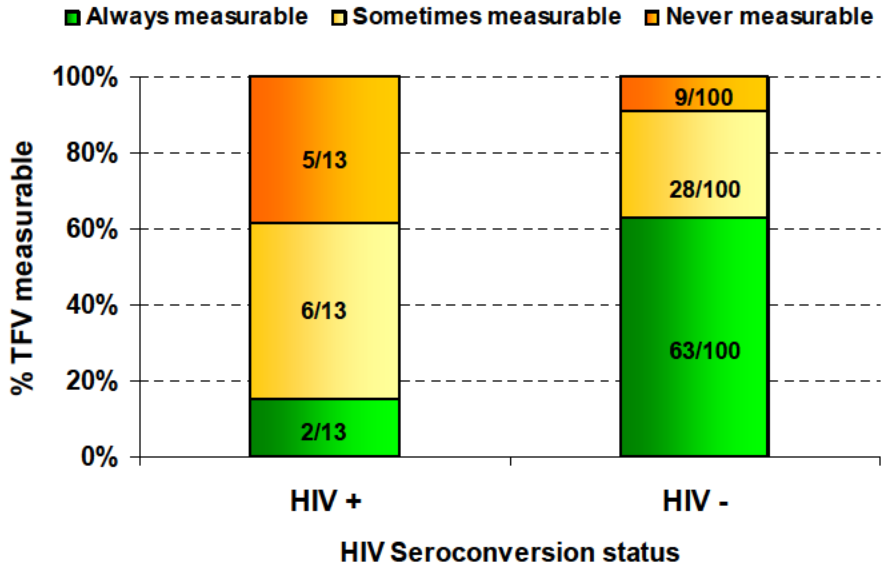
Figure 4 Relative risk reduction in acquiring HIV infection (compared with placebo) based on intracellular TFV-DP concentration status (iPrEx).



2.2.4.2 Was there an exposure-response (i.e., relative risk reduction) relationship for TFV when used for prevention of HIV-1 infection in uninfected partners, who were in a serodiscordant couple, in the Partners PrEP trial?

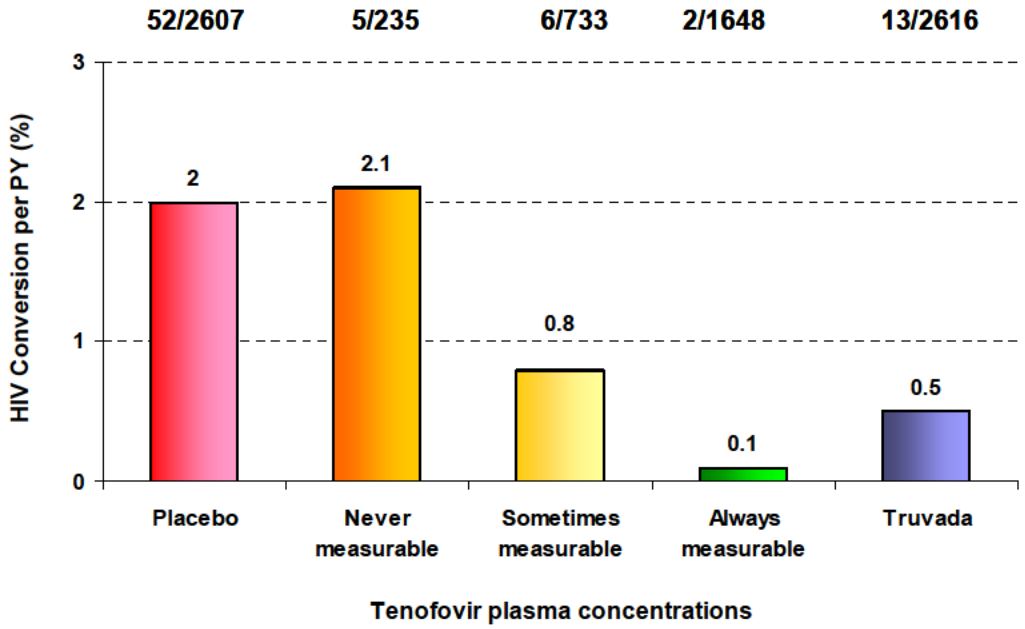
The case-cohort sub-study within the Partners PrEP trial was designed to evaluate if TDF/FTC exposures correlated with protection from HIV-1 infection. In this trial, only plasma TFV concentrations were measured from the blood samples collected at multiple visits (PK visits at Month 1, 3, 6, 12, 18, 24, 30, and 36). The case-cohort subgroup was classified into three categories: subjects who always had measurable TFV concentrations, subjects who sometimes had measurable concentrations and subjects who never had measurable concentrations across all clinic visits during the trial. As shown in Figure 5 below, the non-seroconverter group had a much higher percentage (63%) of subjects with always measurable concentrations compared to the seroconverter group (15%), indicating better medication adherence in the HIV-1 negative subjects.

Figure 5 Percentage of subjects with plasma tenofovir concentrations that were always measurable, sometimes measurable, or never measurable by seroconversion status (Partners PrEP, TDF/FTC group only).



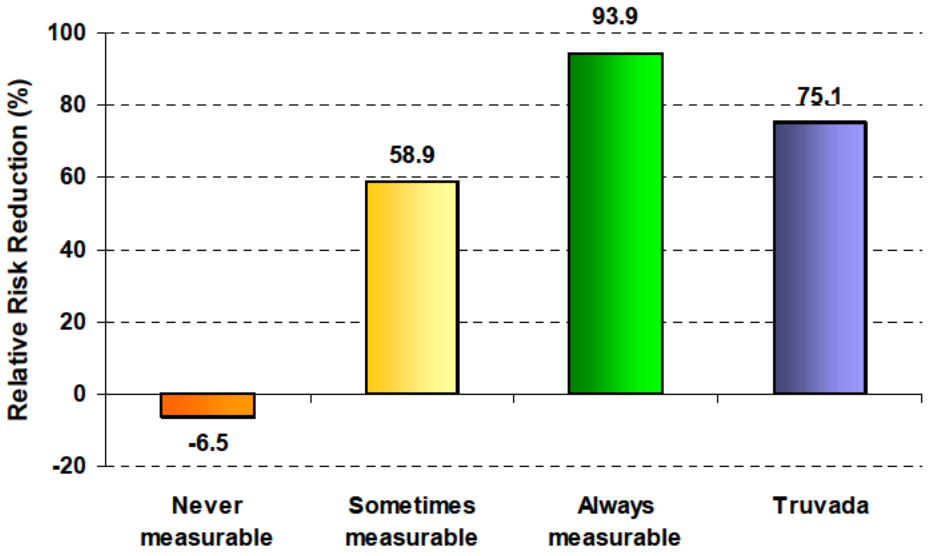
In order to assess the impact of drug adherence on efficacy in Partners PrEP, the distribution of TFV measurable status within the 100 HIV-uninfected subjects, which was, 63% always measurable, 28% sometimes measurable, and 9% never measurable was extrapolated to the entire 1566 HIV-uninfected subjects treated with TDF/FTC in Partners PrEP. As demonstrated in Figure 6 below, subjects in the never measurable category had a seroconversion rate (2.1%) which was not significantly different from subjects in the placebo group (2%). In contrast, subjects with always measurable TFV concentrations had an event rate of 0.1%.

Figure 6 Seroconversion event rates in placebo and TDF/FTC subgroups (Partners PrEP).



When translating these absolute conversion rates to relative risk reduction with TDF/FTC versus placebo, the TDF/FTC group with always measurable TFV concentrations had a relative risk reduction of 93.9% compared to placebo. Conversely, subjects in the TDF/FTC group with never measurable concentrations had a relative risk reduction of acquiring HIV-1 infection that was not significantly different from that of placebo (see Figure 7 below). This finding is consistent with what was shown for the iPrEx trial.

Figure 7 Relative risk reduction in acquiring HIV-1 infection (compared with placebo) based on plasma tenofovir concentrations in Partners PrEP.



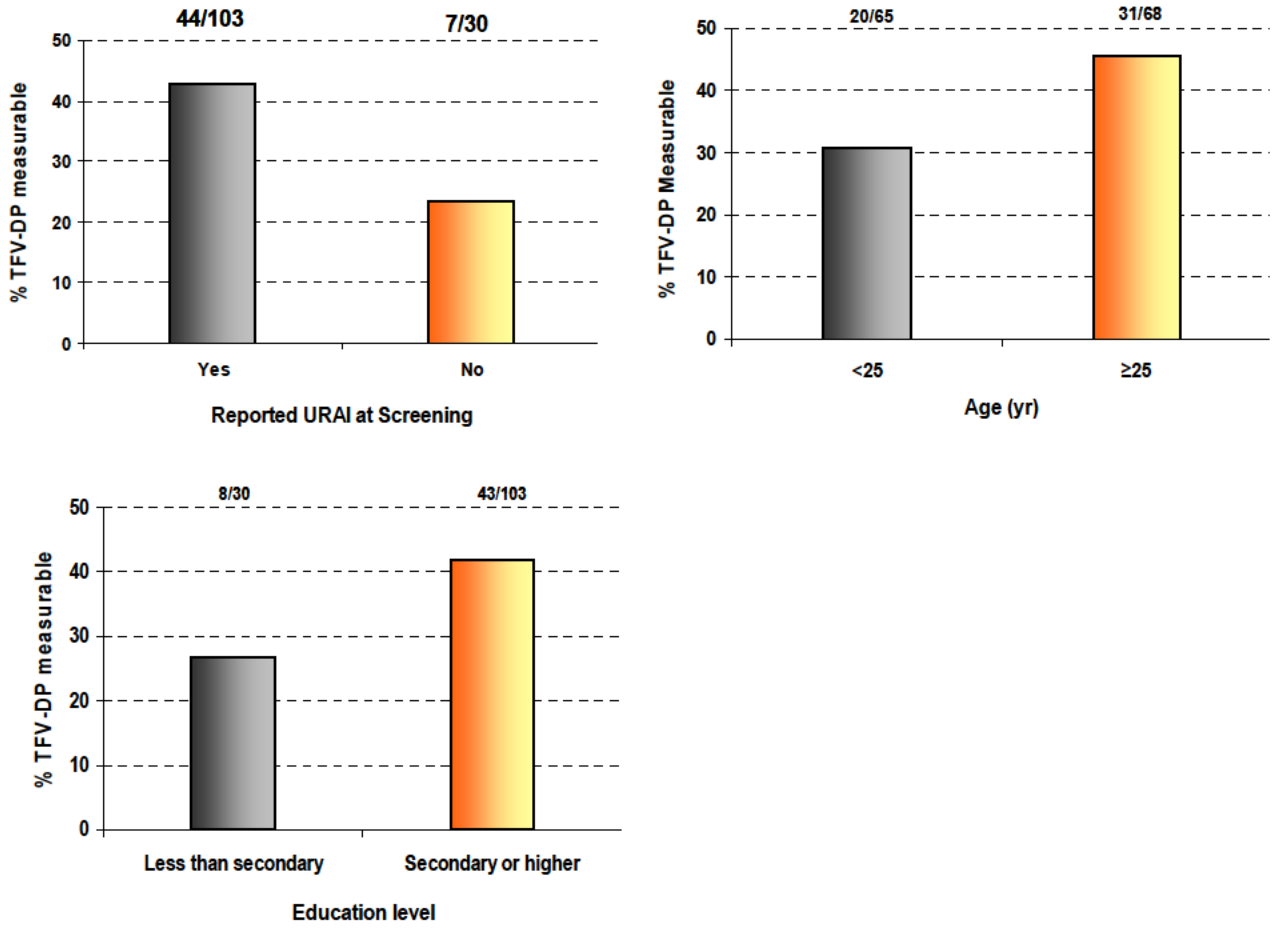
Overall, high medication adherence, demonstrated by having consistently measurable plasma tenofovir concentrations or having measurable intracellular concentrations, was associated with reduced risk of acquiring HIV-1 infection. Fewer seroconversions occurred when subjects had either consistently measurable tenofovir plasma concentrations (in Partners PreP) or measurable intracellular concentrations (in iPrEX).

2.2.4.3 What subject characteristics affect the exposure-response relationships (dose-response, concentration-response) for efficacy?

The analyses presented in section 2.2.4.1 and 2.2.4.2 above suggest that subjects who adhered to TDF/FTC (based on measurable drug concentrations) in both pivotal trials had higher protection from HIV-1 infection relative to subjects with poor adherence. The next step was to identify a population of subjects who are more likely to adhere to TDF/FTC treatment for PrEP, and thus derive the most benefit from treatment. The pharmacometrics reviewer conducted a post-hoc, exploratory analysis based on measurable TFV concentrations in subjects who did not seroconvert while receiving TDF/FTC during the iPrEx trial. Covariates (age, sexual behavior, education level, etc) were first identified in trial 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 trial population. Because these analyses are exploratory, no conclusions can be made based on these findings.

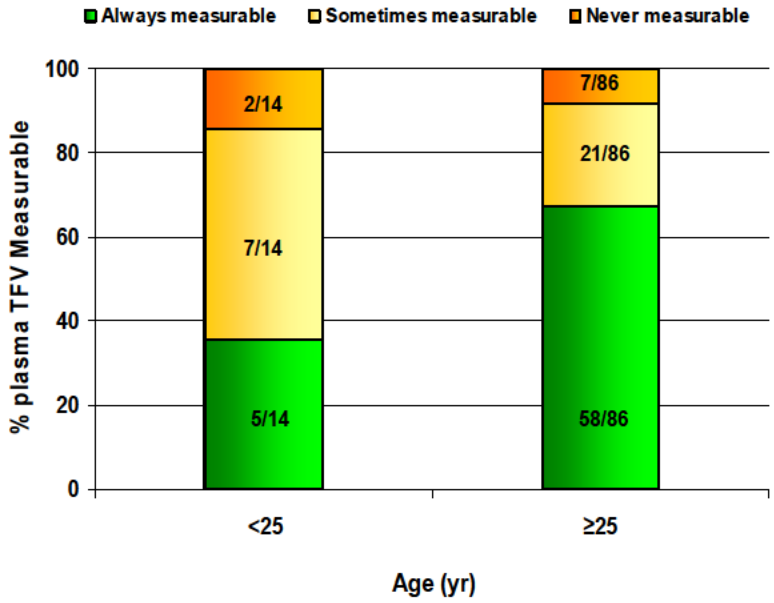
Subjects who were 25 years of age or older, had at least a secondary education, and who reported having unprotected receptive anal intercourse (URAI) at screening were more likely to have measurable intracellular tenofovir concentrations relative to their younger, less educated, and non-URAI engaging counterparts within the PK subgroup of non-seroconverter subjects in iPrEx (n=133) (see Figure 8 below). Of note, URAI is a risky sexual behavior believed to be highly correlated with acquisition of HIV-1 infection. The relative risk reduction of acquiring HIV-1 infection was 53% (95% CI: 29-69%) in subjects who reported URAI at screening compared to no URAI reported. A 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 26-69%] compared with 12% in those with less than secondary education). When combining the three subject covariates, the relative risk reduction with TDF/FTC compared with placebo was 85% (95% CI: 58-95%).

Figure 8 Percentage of subjects in the TDF/FTC group with measurable intracellular drug concentrations by URAI, age, and education level (iPrEx).



The pharmacometrics reviewer conducted a similar exploratory analysis using data from the Partners PrEP trial. Based on plasma tenofovir concentrations, age greater than or equal to 25 years of age correlate with better TDF/FTC adherence, although sample sizes were small in the comparative cohort (see Figure 9 below).

Figure 9 Percentage of subjects with measurable plasma tenofovir concentrations by age in Partners PrEP trial.



2.2.4.4 What is the justification for administering TDF/FTC, instead of TDF for pre-exposure prophylaxis of HIV-1 infection?

The Applicant provided the following important considerations for using TDF/FTC *versus* TDF for pre-exposure prophylaxis of acquiring HIV-1 infection.

- The combination of FTC plus TDF showed greater efficacy than TDF alone in macaque studies of prevention of transmission of simian immunodeficiency virus (SIV) via oral exposure and simian-human immunodeficiency virus (SHIV) via rectal exposure.

- Oral FTC plus TDF provided complete protection against an FTC-resistant virus containing the mutation M184V in similar macaque studies. This result suggests that administration of both FTC and TDF may be important in areas of the world where drug-resistant viruses are frequently transmitted.

- From a pharmacokinetic perspective, FTC reaches intracellular steady state concentrations faster than tenofovir (~5 days versus 19 days of daily dosing). FTC also achieves higher concentrations in genital tissues relative to plasma than tenofovir (27-fold greater than plasma vs. 2.5-fold greater with TDF). In contrast, TFV-DP has a longer half-life in the genital tract than FTC-TP (14 versus <2 days). Thus, the combination of FTC plus TDF provides advantages over either product alone.

- The combination of FTC plus TDF has shown additive to synergistic anti-HIV-1 activity over either agent alone. This observation suggests FTC plus TDF may have an increased chemoprophylactic activity and a higher barrier to resistance than each agent may alone. This hypothesis has been previously confirmed in animal studies.

- In the VOICE clinical trial, the data safety monitoring board (DSMB) discontinued both the tenofovir-alone formulations (oral and microbicide gel) for lack of efficacy, while also allowing continuation of dosing for TDF/FTC and its matched placebo. The VOICE trial (or MTN-003) enrolled up to 5000 HIV-1 uninfected women in Africa to test the safety and effectiveness of an investigational microbicide gel containing TDF versus oral TDF and oral TDF/FTC.

2.2.4.5 Is the dose and dosing regimen selected by the Applicant consistent with the known relationship between dose-concentration-response, and is there any unresolved dosing or administration issue with TDF/FTC for PrEP?

Subjects who received TDF/FTC in the iPrEx and Partners PrEP trials received commercially available Truvada tablets on a once daily regimen. FDA previously approved this regimen for treatment of HIV-1 infection. The dose-concentration-response relationship for HIV-1 prophylaxis has not been elucidated.

Tenofovir DF 300 mg

In the original NDA submission for Viread (NDA 21-356), the applicant did not conduct a formal PK/PD trial to evaluate relationships between dose, concentration, and efficacy. The 300 mg dose of tenofovir disoproxil fumarate was selected based on safety and efficacy results in HIV-infected subjects in 2 trials, 901 and 902. In dose-ranging trial 901, the Applicant tested tenofovir DF at 75 mg, 150 mg, 300 mg, and 600 mg once daily given for 15 to 35 days. However, insufficient PK data were available from the 75 mg and 150 mg dose groups to conduct a comprehensive exposure-response analysis. The 300 mg dose produced better antiviral efficacy than 75 and 150 mg, and similar antiviral efficacy compared to 600 mg.

Trial 902 evaluated the safety and efficacy of tenofovir DF 75 mg, 150 mg, and 300 mg once daily for 48 weeks. This trial did not include a pharmacokinetic evaluation of tenofovir. Once daily tenofovir DF 300 mg demonstrated better efficacy than 75 mg or 150 mg dose groups, with acceptable safety margins. In both trials with tenofovir DF, decreases in HIV RNA were greater in the 300 mg dose group compared to the 75 mg and 150 mg dose groups. Based on these results, tenofovir DF 300 mg once daily progressed to the Phase 3 trials.

Emtricitabine 200 mg

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

2.2.5 What are the PK characteristics of TFV and FTC and its major metabolite(s)?

TFV and FTC demonstrate linear PK over the dose ranges studied in support of the original NDA submissions. Steady-state plasma concentrations of both drugs were predictable based on single dose PK data. No major metabolites in plasma have been reported for FTC and TFV. A single dose of TDF/FTC delivers intracellular TFV-DP and FTC-TP concentrations that are approximately 15% and 35% of the expected steady-state intracellular concentrations, respectively. Table 1 below summarizes the single-dose PK characteristics of TFV and FTC in adults. PK data on intracellular concentrations of TFV-DP and FTC-TP were obtained from the literature. Notably, the plasma and intracellular half-lives of tenofovir are longer than the respective half-lives of emtricitabine.

Table 1 Single dose mean pharmacokinetic parameters for emtricitabine and tenofovir in adults

	Plasma (Mean)*				PBMCs (Median)**	
Drug	AUC_{0-tau} (ng*hr/mL) (SD)	C_{max} (ng/mL) (SD)	C_{min} (ng/mL) (SD)	$T_{1/2}$ (h) (SD)	TFV-DP and FTC-TP, respectively (fmol/10^6 cells) (range)	$T_{1/2}$ (h)
Tenofovir 300 mg QD	2968 (1156)	349 (121)	66.5 (37.6)	18.7 (13.5)	65.8 (44.5 – 100)	87 – 150
Emtricitabine 200 mg QD	8000 (1200)	1720 (910)	47 (24)	8.2 (2.6)	4700 (3400 – 6200)	39 – 50

*Source: currently approved Truvada label.
**Source: reviewed in Anderson, PL et al, *J Antimicrob Chemother,* 2011.

2.2.5.1 *What are the single dose and multiple dose PK parameters of TFV and FTC*?

The pharmacokinetic characteristics of TFV are similar following single and multiple oral daily doses of Viread 300 mg in HIV-1 infected subjects.

Table 2 below compares the pharmacokinetics of tenofovir in plasma following the first dose and again following 12 and 24 weeks of once daily dosing. Tenofovir C_{max} and AUC_{ss} values on Week 24 were lower than those observed in Week 12; however, these PK differences were not statistically significant.

Table 2 Mean pharmacokinetic parameters (±SD) for tenofovir in serum following administration of tenofovir DF 300 mg once daily at Day 1, Week 12, and 24 weeks.

	C_{max} (ng/mL)	AUC* (ng*h/mL)	C_{min} (ng/mL)	T_{max} (h)	$T_{1/2}$ (h)	CLcr (mL/hr/kg)	CL/F (mL/hr/kg)
Day 1 N=9	282 (139.2)	2929 (750)	46.2 (21.5)	2.4 (0.8)	12.1 (2.6)	97 (19)	660 (242)
Week 12 N=7	348.6 (121)	2968 (1156)	66.5 (37.6)	2.1 (0.8)	18.7 (13.5)	93 (19)	680 (322)
Week 24 N=7	256 (77)	2341 (491)	36.9 (16.8)	2.6 (1.0)	14.4 (4.6)	91 (21)	773 (270)

* For Day 1, AUC=$AUC_{0-\infty}$
For Weeks 12 and 24, AUC=AUC_{0-T}

Source: Original NDA review for Viread

Likewise, the plasma pharmacokinetic characteristics of emtricitabine are similar following single and multiple oral doses of Emtriva 200 mg QD. Although it appears that the $t_{1/2}$ is ~3 hours following a single dose while it is 9-10 hours following multiple dosing (10 days of once daily dosing) (see Table 3 below), the reviewer for the original Emtriva NDA concluded

that the $t_{1/2}$ difference was explained by the difference in collecting samples 12 hours vs. 24 hours post-dose administration. The reviewer concluded that the 9-10 hour $t_{1/2}$ is a more accurate estimate of half-life for FTC, based on when steady state is reached.

Table 3 FTC PK parameter estimates (Arithmetic mean, %CV) after a single dose (Day 1) and at steady state (Day 10) following a dose regimen of FTC 200 mg QD.

Treatment	Day	C_{max} (µg/mL)	T_{max} (h)	C_{min} (µg/mL)	AUC_{tau} (µg *h/mL)	$t_{1/2}$ (h)	CL/F (mL/min)
200 mg QD (n=8)	1	1.54 (38)	2.25 (46)	-	7.1* (19)	2.98 (14)	489 (22)
200 mg QD (n=8)	10	1.72 (53)	2.0 (48)	0.047 (24)	8.0 (15)	8.24 (31)	425 (15)

*AUC0-∞. Source: Original NDA review for Emtriva.

2.2.5.2 How does the PK of TFV and FTC and its major active metabolites in healthy subjects compare to that in HIV-1 infected patients?

The plasma pharmacokinetics of tenofovir and emtricitabine are similar between HIV-1 infected and uninfected subjects.

2.2.5.3 What are the ADME properties of TFV and FTC?

Tenofovir DF

The oral bioavailability of tenofovir following administration of a 300 mg dose of tenofovir DF is approximately 25% in the fasted state. Maximum tenofovir serum concentrations are achieved in 1.0 ± 0.4 hour. Less than 0.7% of tenofovir binds to human plasma proteins *in vitro* and the binding is independent of concentration over the range of 0.01-25 µg/mL. Approximately 70 – 80% of the intravenous dose of tenofovir is recovered as unchanged drug in the urine. Tenofovir is eliminated by a combination of glomerular filtration and active tubular secretion.

Tenofovir DF undergoes rapid enzymatic hydrolysis yielding tenofovir in plasma. *In vitro*, tenofovir DF was rapidly hydrolyzed ($t_{1/2}$ < 5 minutes) in human plasma, intestinal homogenate, and liver homogenate. In these *in vitro* assessments, no metabolites of tenofovir were detected with or without the addition of cofactors required for metabolism. In studies using human hepatic microsomes, TDF or TFV did not inhibit CYP enzymes CYP3A4, CYP2D6, CYP2C9, CYP2E1, and CYP1A. These results indicate that the inhibitory potential of tenofovir DF on drugs metabolized by CYP enzymes is low.

Emtricitabine

Following oral administration with Emtriva 200 mg, FTC is rapidly absorbed with peak plasma concentrations occurring at 1-2 hours post dose. The oral bioavailability of FTC is high (93%). Less than 4% of emtricitabine binds to human plasma proteins *in vitro* and the binding is independent of concentration over the range of 0.02 to 200 µg/mL. Approximately 86% of FTC was recovered in the urine and 13% was recovered as metabolites. The metabolites of

emtricitabine are inactive and include 3'-sulfoxide diastereomers and their glucuronic acid conjugate.

An *in vitro* study was conducted to evaluate the potential for FTC to inhibit human cytochrome P450 (CYP) 1A2, 2A6, 2B6, 2C9, 2C19, 2D6, 2E1, and 3A4/5 activities and UGT as determined with probe substrates. At concentrations up to 14-fold higher than those observed *in vivo*, FTC did not inhibit any of the CYP enzymes listed above. Based on these results the potential for CYP450 mediated interactions involving FTC with the other drug products is low.

Similar to tenofovir, the primary route of FTC elimination is by renal excretion, modulated by glomerular filtration and active renal tubular secretion. Therefore, drugs that are secreted via the same renal tubular transporter could compete with FTC for elimination.

2.2.5.4 What is the inter- and intra-subject variability of PK parameters in healthy subjects and patients, and what are the major causes of variability?

Tenofovir DF

PK variability of tenofovir in plasma was similar between healthy subjects and HIV-infected patients (%CV ~25-40). This PK variability may be due to cleaving of the prodrug and absorption of tenofovir.

Emtricitabine

The PK variability of FTC in plasma was similar in healthy subjects and HIV-1 infected patients (%CV ~15-53). The source of this variability is unknown.

2.3 Intrinsic factors

2.3.1 What intrinsic factors influence exposure and/or response, and what is the impact of any differences in exposure on efficacy or safety responses?

Limited PK data were collected in the iPrEX and Partners PrEP trials to assess the effect of intrinsic factors on TDF/FTC's efficacy and safety when given for PrEP. Based on Truvada's label, renal impairment is the only intrinsic factor that influences the exposure of tenofovir and emtricitabine. Decreased renal function decreases the clearance of both drugs. The dosing recommendations in subjects with moderate and severe renal impairment are listed in section 2.3.2.1 below. The effects of race, gender, age, and hepatic impairment on the PK of TDF/FTC are as follows.

Race

No pharmacokinetic differences due to race have been identified following the administration of Emtriva. The pivotal trials with Viread had insufficient numbers from racial and ethnic groups other than Caucasian to determine the potential pharmacokinetic differences among these populations following the administration of Viread.

Gender

Emtricitabine and tenofovir pharmacokinetics are similar in male and female subjects.

Pediatric subjects

The safety and efficacy of Truvada for prophylaxis of HIV-1 infection has not been established in pediatric subjects <18 years of age. However, Truvada is currently approved for treatment of HIV-1 in pediatric patients ≥12 years of age weighing ≥35 kg. Emtricitabine and tenofovir exposures in this pediatric population were similar to those achieved in adults receiving once daily Emtriva 200 mg and once daily Viread 300 mg.

Geriatric subjects

The pharmacokinetics of emtricitabine and tenofovir have not been fully evaluated in the elderly population (65 years of age and older). Because decreased renal function is correlated with older age, it is likely that the PK of both TFV and FTC may be altered in the geriatric population.

Hepatic Impairment

The PK characteristics of tenofovir following a 300 mg dose of Viread have been studied in non-HIV infected subjects with moderate to severe hepatic impairment. There were no substantial alterations in tenofovir pharmacokinetics in subjects with moderate or severe hepatic impairment compared to subjects with normal hepatic function. In contrast, the PK of emtricitabine has not been studied in subjects with hepatic impairment. Of note, emtricitabine is metabolized to a minor extent (~13%) by hepatic enzymes. The impact of hepatic impairment on emtricitabine exposures is unknown.

Renal Impairment

The PK of emtricitabine and tenofovir are altered in subjects with renal impairment. Refer to section 2.3.2.1 below.

2.3.2 Based upon known exposure-response relationships and their variability in the groups studied, what TDF/FTC dosage regimen adjustments, if any, are recommended for each of these groups?

Based on the current label for Truvada for HIV-1 treatment, no dose adjustments are recommended based on age, gender, race, and hepatic impairment status, except for renal impairment (see section 2.3.2.1 below).

2.3.2.1 Renal impairment

Emtricitabine and tenofovir are primarily eliminated by the kidney; thus, the drugs' PK properties are altered in subjects with renal impairment. Renal impairment, including cases of acute renal failure and Fanconi syndrome (renal tubular injury with severe hypophosphatemia) has been reported with the use of Viread. Thus, modification of the dosing interval for TDF/FTC in subjects with creatinine clearance between 30-49 mL/min is recommended in the Truvada

label. Subjects with creatinine clearance below 30 mL/min, and those subjects with end-stage renal disease should not receive TDF/FTC. No dosage adjustment is necessary for patients with mild renal impairment (CrCl: 50-80 mL/min), but these subjects should undergo routine laboratory monitoring of creatinine clearance and serum phosphorus. Table 4 displays the current dosing recommendations of TDF/FTC for HIV-1 infected patients with renal impairment.

Table 4 Dosage adjustment for HIV-1 infected patients with altered creatinine clearance.

	Creatinine Clearance (mL/min)[a]		
	≥50	30–49	<30 (Including Patients Requiring Hemodialysis)
Recommended Dosing Interval	Every 24 hours	Every 48 hours	TRUVADA should not be administered.

a. Calculated using ideal (lean) body weight

Neither the iPrEx nor the Partners PrEP trial evaluated the efficacy of TDF/FTC for a prophylaxis indication in subjects with CrCl <60 mL/min. Furthermore, the benefit-risk ratio is not the same for HIV-1 infected an uninfected subjects receiving TDF/FTC for treatment or prevention, respectively. Thus, uninfected subjects with CrCl <60 mL/min should not receive TDF/FTC for HIV-1 prophylaxis. Of note, discussions between the review team and the Applicant are currently ongoing to determine whether TDF/FTC for HIV-1 prevention should be recommended for subjects with CrCl <60 mL/min.

2.3.2.2 What pregnancy and lactation use information is there in the application?

According to the current Truvada label, TDF/FTC is Pregnancy Category B. Animal reproduction studies failed to demonstrate a risk to the fetus and there are no adequate and well-controlled studies in pregnant women OR animal studies have shown an adverse effect, but adequate and well-controlled studies in pregnant women have failed to demonstrate a risk to the fetus in any pregnancy trimester. Thus, TDF/FTC should be used during pregnancy only if clearly needed for treatment of HIV-1 infection. Because the HIV-1 virus is secreted in human milk, HIV-1 infected mothers should not breast-feed their infants. Tenofovir was secreted in animal milk, but it is unknown whether tenofovir is secreted in human milk. Thus, mothers should be instructed not to breastfeed if they are receiving TDF/FTC.

The current supplemental application contains limited information regarding the use of TDF/FTC for PrEP during pregnancy and lactation. In the Partners PrEP trial, pregnancies were reported in 16% of all female partner subjects (n=288/1785): TDF 18% (n=112/598), TDF/FTC 13% (n=80/566), and placebo 15% (n=96/621). However, all women who became pregnant during the trial discontinued trial medication for the duration of the pregnancy and during breastfeeding. Investigators followed these pregnant women until they gave birth to evaluate potential congenital abnormalities after having taken TDF or TDF/FTC. The percentage of live births was greatest in the TDF group (71%) compared with the TDF/FTC 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 TDF/FTC group. 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 was considered related to trial drug.

2.4 Extrinsic factors

2.4.1 What extrinsic factors influence dose-exposure and/or –response and what is the impact of any differences in exposure on response?

Herbal products (unless they affect renal function or inhibit renal transporters), diet, smoking, and alcohol are unlikely to influence the dose-exposure, and/or response of TDF/FTC for PrEP based on the known metabolic and excretion routes of tenofovir and emtricitabine.

2.4.2 Drug-drug interactions and their influence on exposure/response.

Drug-drug interactions are more likely to exacerbate adverse events associated with TDF/FTC than to affect its efficacy in HIV-1 treatment, and possibly in HIV-1 prophylaxis. Tenofovir is not subject to hepatic metabolism. Thus, drugs that induce or inhibit hepatic enzymes are unlikely to alter the PK of tenofovir.

The Truvada label lists results from clinical trials evaluating the drug-drug interaction potential between tenofovir and entecavir, methadone, oral contraceptives, ribavirin, and tacrolimus. Results from these trials were negative, except for entecavir. Tenofovir increased the AUC of entecavir by 13% during co-administration relative to entecavir alone. Generally, this information supports the observation that tenofovir is unlikely to affect the PK of drugs that undergo hepatic metabolism (and *vice versa*).

Similarly, drugs that induce or inhibit hepatic enzymes may not affect the PK of emtricitabine during co-administration because emtricitabine is primarily excreted in urine. However, emtricitabine is slightly (13%) metabolized by hepatic enzymes. The effect of drugs that induce hepatic enzymes on the PK of emtricitabine has not been evaluated.

The kidneys excrete emtricitabine and tenofovir by a combination of glomerular filtration and active tubular secretion. Based on Truvada's label, no drug-drug interactions due to competition for renal excretion have been observed; however, co-administration of TDF/FTC with drugs that are eliminated by active tubular secretion may increase concentrations of emtricitabine, tenofovir, and/or the co-administered drug. An increase in tenofovir concentrations may lead to renal and bone toxicity previously reported with Viread use. Examples of drugs that may alter the PK of tenofovir during co-administration include (val) acyclovir, cidofovir, (val) ganciclovir, NSAIDs, ritonavir, and probenecid – Note; this list is not exhaustive and not exclusive to HIV-uninfected subjects.

2.5 General biopharmaceutics

2.5.1 What is the effect of food on the bioavailability (BA) of TFV and FTC? What dosing recommendation should be made, if any, regarding administration of the product in relation to meals or meal types?

Based on its current label, TDF/FTC may be administered with or without food. Administration of TDF/FTC following a high fat meal (734 kcal; 49 grams of fat) or a light meal (373 kcal; 8 grams of fat) delayed the time of tenofovir C_{max} by approximately 0.75 hour. The mean increases in tenofovir AUC and C_{max} were approximately 35% and 15%, respectively, when administered with a high fat or light meal, compared to administration in the fasted state. Food did not affect the PK of FTC. The slight increase in tenofovir is clinically insignificant. Thus, TDF/FTC can be taken without regard to food.

2.6 Analytical section

2.6.1 How are the active moieties measured (free, bound, or total) in the clinical pharmacology and biopharmaceutic trials?

Total tenofovir and emtricitabine concentrations were measured in plasma (TFV, FTC) and in PBMCs (TFV-DP, FTC-TP). In plasma, FTC and TFV are the main moieties after administration of TDF/FTC. Less than 4% of FTC is bound to plasma proteins; thus, measuring free FTC versus total FTC is similar. TFV has even less plasma protein binding (0.7%) than FTC. TFV and FTC were measured using validated high-pressure liquid chromatography with MS/MS detection (LC/MS/MS).

In PBMCs, the total concentrations of TFV-DP and FTC-TP were measured indirectly based on FTC and TFV concentrations using a validated LC/MS/MS method. The bioanalytical steps for measuring TFV-DP and FTC-TP included three stages: a de-phosphorylation stage, a de-saltation stage, and a concentrating stage. Human PBMCs were harvested from whole blood, lysed, and suspended. TFV-DP and FTC-TP were isolated from the suspension and underwent de-phosphorylation with acid phosphatase to form TFV and FTC. TFV and FTC were de-salted and concentrated, making it possible for detection using an LC/MS/MS method. The LC/MS/MS method was validated for relating the concentrations of FTC and TFV to their corresponding intracellular FTC-TP and TFV-DP concentrations.

2.6.2 Which metabolites have been selected for analysis and why?

No metabolites were measured in the PK samples collected during the pivotal trials. Tenofovir and emtricitabine do not have major plasma metabolites.

2.6.3 What bioanalytical methods were used to assess drug concentrations?

iPrEx Trial – PBMC samples

The University of Colorado Denver, Antiviral Pharmacology Laboratory (CAVP) received a total of 1129 PBMC samples collected from subjects in the iPrEx trial. All trial samples were stored frozen at approximately -70°C. The long-term storage stability under frozen conditions was at least 18 months. According to CAVP, PBMC samples were analyzed within the stability period. Approximately 59% of samples (663/1129) collected from the iPrEx trial were extracted, analyzed, and reported. The samples were processed for TFV-DP and FTC-TP using two validated LC/MS/MS methods. Method 'TFV-DP Only' was used to analyze two sample runs, and 'IC_NA' was used to analyze 22 runs. CAVP does not specify why it used two methods for

sample analysis. After reviewing the bioanalytical report, it became apparent that method 'IC_NA' had a lower limit of quantification than method 'TFV-DP Only' (2.5 vs. 50 fmol/spl) (see table below). In order to derive the concentrations of TFV-DP in units of fmol/10^6 cells, the results that were obtained using LC/MS/MS analysis were divided by the number of PBMCs assayed.

iPrEx Trial – Plasma samples

CAVP received 1466 plasma samples in EDTA anticoagulant collected from subjects in the iPrEx trial. All plasma samples were stored at -70°C prior to analysis. The long-term storage stability under frozen conditions was at least 3 years. According to CAVP, plasma samples were analyzed within the storage stability period. Approximately 26% of all plasma samples (378/1466) were extracted, analyzed, and reported. Plasma samples were analyzed for tenofovir and emtricitabine using one validated LC/MS/MS method.

Partners PrEP trial – Plasma samples only

The (b) (4) analyzed plasma samples collected from the Partners PrEP trial. The Applicant submitted a standard operating procedure for sample bioanalysis and a validated report summarizing top line results of the bioanalytical method used for analyzing plasma samples collected from Partners PrEP. In a recent communication with the Applicant, the OCP reviewer requested the bioanalytical report for the Partners PrEP trial. The report will be submitted at a later point in time. The following table summarizes the *in vitro* analytical methods used for the determination of plasma and PBMC concentrations of tenofovir and emtricitabine.

Table 5 Summary of bioanalytical parameters derived from the LC/MS/MS methods used for analysis of PBMC and plasma samples collected during the iPrEx and Partners PrEP trials.

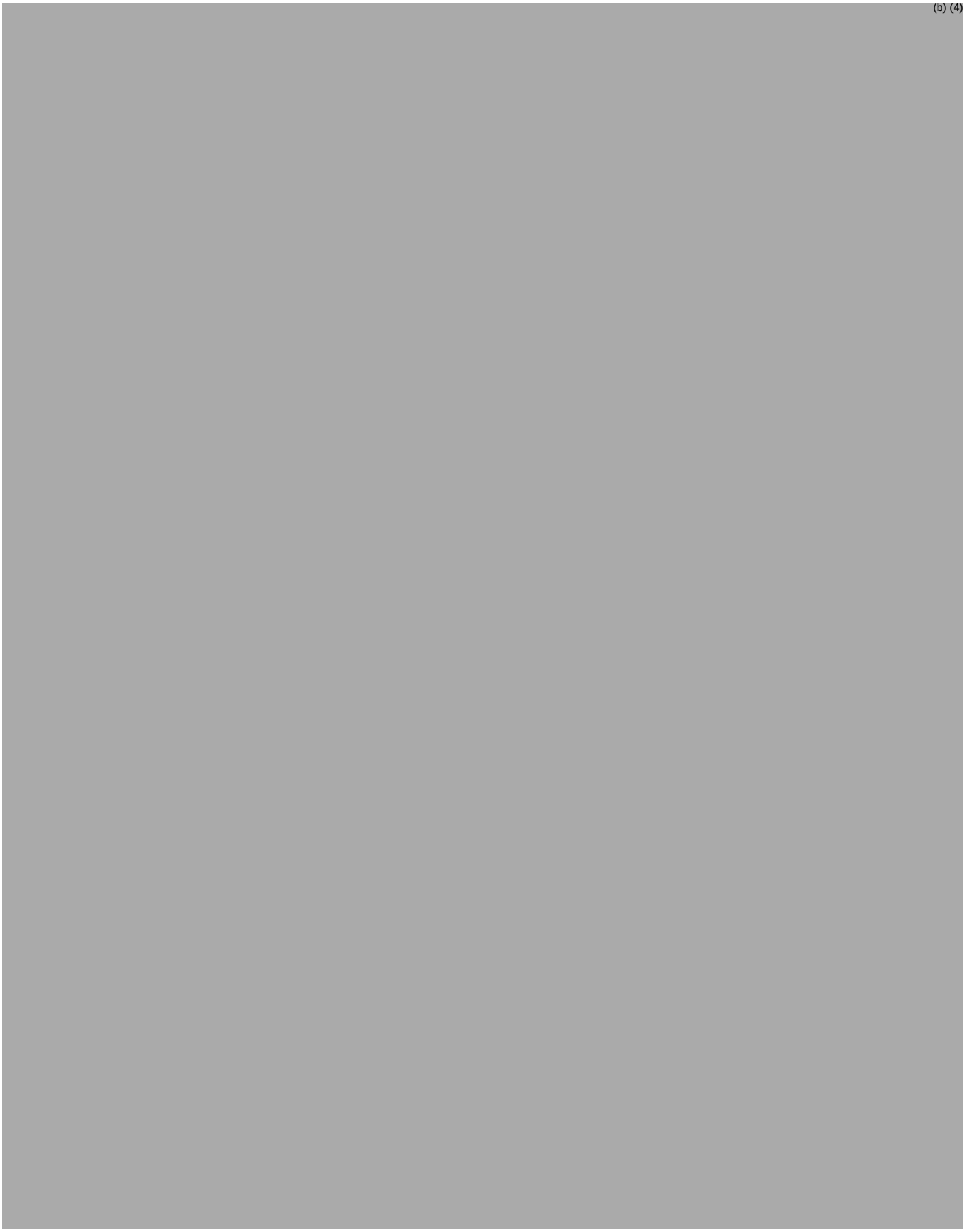
Analyte	Method	Trial	LLOQ	ULOQ	Linear range	Between run precision (%CV)	Between run bias (% deviation)	QC samples
TFV-DP	TFV-DP only	iPrEx	50 fmol/spl	10000 fmol/spl	50 - 10000 fmol/spl	1.3 – 10.2	≤ 1.8	150, 750, 7500 fmol/spl
TFV-DP	IC_NA	iPrEx	2.5 fmol/spl	2000 fmol/spl	2.5 – 2000 fmol/spl	9.0 – 13.1	≤ -5.5	15, 150, 1500 fmol/spl
FTC-TP	IC_NA	iPrEx	0.1 pmol/spl	200 pmol/spl	0.1 – 200 pmol/spl	3.5 – 5.1	≤ -7.5	1.5, 15, 150 pmol/spl
TFV	ID 10445	iPrEx	10 ng/mL	1500 ng/mL	10 – 1500 ng/mL	3.3 – 5.9	≤ 7.1	30, 300, 1200 ng/mL
FTC	ID 10445	iPrEx	10 ng/mL	1500 ng/mL	10 – 1500 ng/mL	4.2 – 6.6	≤ 10.4	30, 300, 1200 ng/mL
TFV	No ID provided	Partners	*0.3 ng/mL	1000 ng/mL	0.3 – 1000 ng/mL	5.1 – 15.1	≤ 11	15, 200, 850 ng/mL
FTC	No ID provided	Partners	*0.3 ng/mL	1000 ng/mL	0.3 – 1000 ng/mL	5.1 – 15.1	≤ 11	15, 200, 850 ng/mL

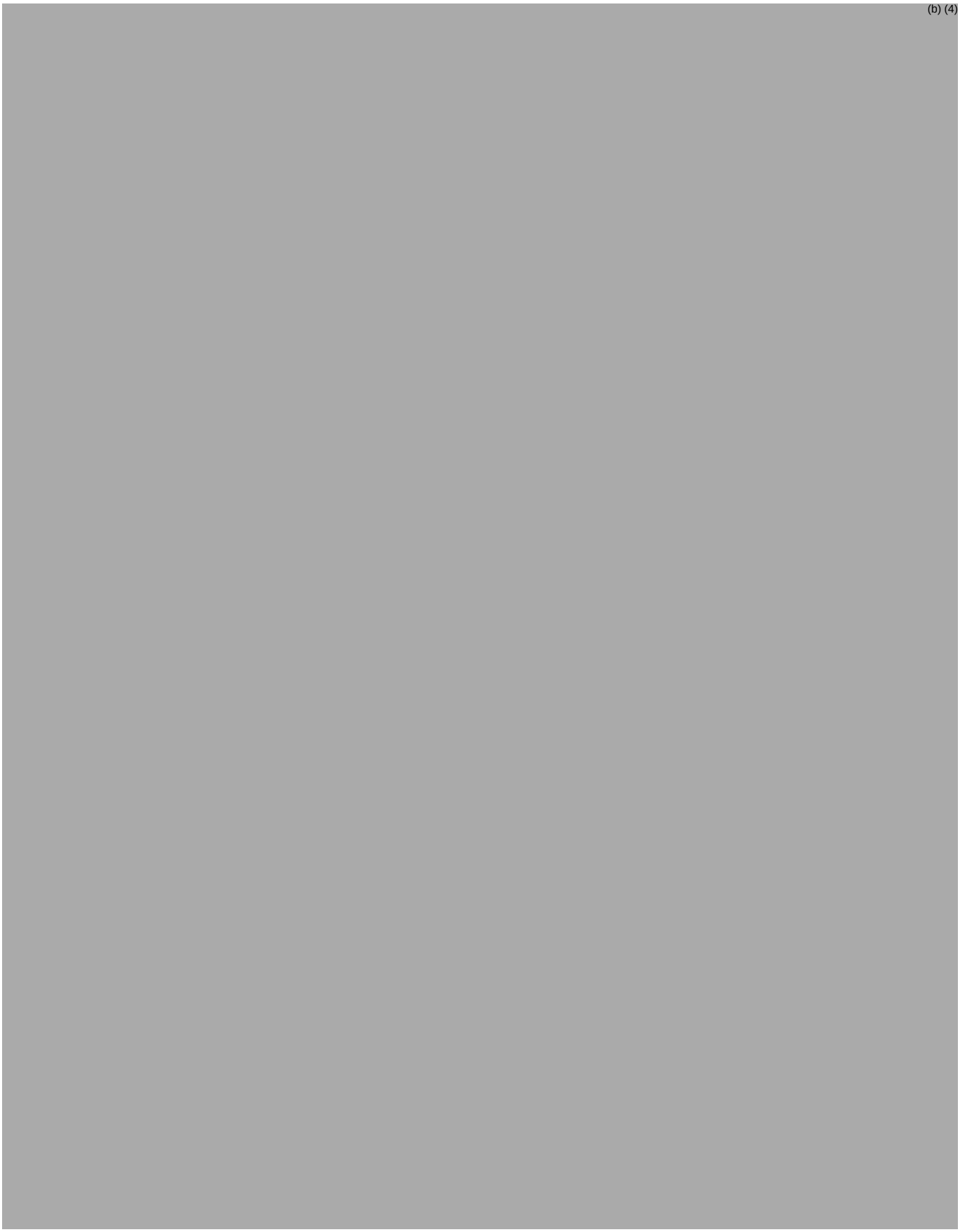
*The documents submitted by the Applicant state that the LLOQ for measuring TFV and FTC in plasma was 5 ng/mL. However, in a recent communication with the Applicant, the LLOQ was specified to be 0.3 ng/mL instead of 5 ng/mL.

3 Detailed labeling recommendations

The Clinical Pharmacology reviewer recommends the following labeling changes shown in blue and edits in track changes. The following section shows only clinical pharmacology-related edits in the proposed label for Truvada. The clinical pharmacology recommended labeling changes reflect the current thinking of the review team at the time of finalizing this review. Final labeling language may be modified pending discussions between the Division of Antiviral Products and the Applicant.

Proposed Language from Applicant	OCP proposed changes
(b) (4)	


(b) (4)


(b) (4)

4 Appendices

4.1 Clinical pharmacology and biopharmaceutics individual study review

4.1.1 iPrEx trial

Study CO-US-104-0288 (iPrEx study): Chemoprophylaxis for HIV prevention in men

Trial period

The trial initiated in July 10, 2007. The first cutoff date for evaluation of safety and efficacy data occurred on May 01, 2010. The second cutoff date occurred on November 21, 2010.

Trial sites

The trial was conducted in eleven sites across six countries: Brazil (3), Ecuador (1), Peru (3), South Africa (1), Thailand (1), and the United States (2).

Trial objectives

The primary objectives of this trial were to determine if:

- Oral daily TDF/FTC reduced HIV-1 seroincidence among HIV-1 uninfected MSM.
- Oral daily TDF/FTC was associated with comparable rates of adverse events compared with placebo in HIV-1 uninfected MSM.

The secondary objectives were to determine if:

- Hepatic viral flares occurred in subjects who are hepatitis B surface antigen positive (HBsAg+) during and after TDF/FTC chemoprophylaxis.
- Significant changes in bone mineral density, body fat distribution, or fasting lipids occurred during and after TDF/FTC chemoprophylaxis.
- Prior exposure to TDF/FTC chemoprophylaxis affected the course of HIV-infection, as predicted by plasma RNA level, CD4 counts, drug resistance assays, and other clinical, virological, or immunological parameters.
- Failure or success of chemoprophylaxis correlated with risky behaviors, including frequency and type of sexual exposure, patterns of medication adherence, and prevalence of sexually transmitted infections (STIs).

Trial population

The trial randomized 2499 non-HIV infected MSM subjects at high risk of becoming infected with HIV-1 (criteria described in the Key Inclusion Criteria section) to receive either TDF/FTC or placebo in a 1:1 manner (1251 in TDF/FTC arm, 1248 in placebo arm).

Trial design

This was a multicenter, international, randomized, double blind, placebo-controlled trial of once daily oral TDF/FTC for prevention of HIV-1 infection in MSM and transgender women at high risk for acquiring HIV infection. The trial duration was event-driven, and continued until at least 85 seroconversions were observed. The trial was powered to show that TDF/FTC was at least 30% efficacious in preventing HIV-1 infection. Previous trials evaluating vaccines for HIV-1 PrEP used the efficacy cutoff of 30%.

All subjects were instructed to attend monthly clinic visits. On these visits, subjects underwent rapid testing for HIV-1 infection. Rapid tests for HIV-1 are qualitative immunoassays that detect antibodies to HIV-1. For most people, HIV-1 antibodies reach detectable levels two to six weeks after infection. In other people, it may take several months for the antibody response to reach detectable levels. Thus, a negative rapid test may not exclude HIV-1 infection. Rapid tests are prone to give false positive results, and any positive HIV-1 result should be confirmed by an enzyme immunoassay.

Also on a monthly basis, subjects received a comprehensive package emphasizing risk-reduction of HIV infection, condom use, and diagnosis and treatment of STIs. High-risk behavior was recorded by interview every 12 weeks. Education level, self-identified sex, and alcohol use was recorded at screening. Medication adherence was monitored by interview (self-reported), counting empty pill bottles, by pill counts, and through routine PK assessments using both plasma and intracellular matrices to measure drug levels.

In a pre-specified subgroup analysis, the Applicant evaluated if tenofovir and emtricitabine plasma and intracellular concentrations correlated with protection from HIV-1 infection. All trial participants underwent blood sampling at baseline, every 12 weeks (24 weeks for PBMC analysis), during the visit when seroconversion was detected, at the end-of-trial visit, and at every follow-up visit. When a subject seroconverted, the subject's 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 non-seroconverters were also evaluated. Two of the control subjects were matched to each HIV-1 infected subject based on trial site and treatment duration. The third control subject was selected based on having reported unprotected receptive anal intercourse (URAI) in a period that covered the specimen date (closest to time of seroconversion) for the HIV-1 infected subject.

Key inclusion criteria

- Male sex at birth
- ≥18 years of age
- No HIV-1 infection
- Engaged in high risk behavior defined as:

- Did not use a condom during anal intercourse with an HIV+ male partner or a male partner of unknown HIV-1 status in the previous 6 months.
- Engaged in anal intercourse with >5 male partners in the 6 months prior to trial entry (Initially >3 partners, but the protocol was amended to include >5 partners based on HIV-1 incidence in the local region).
- Exchanged money, gifts, shelter, or drugs for anal sex with a male partner in the previous 6 months.
- Had sex with a male partner and was diagnosed with a sexually transmitted infection (STI) in the previous 6 months or at screening.
- Had sex with an HIV-1 infected male partner with whom condoms were not used consistently in the previous 6 months.

- Demonstrated adequate renal function within 28 days of enrollment (CrCl ≥60 mL/min estimated using Cockcroft-Gault formula and SCr within normal limits).

Key exclusion criteria

- Infections requiring parenteral antibiotics, active tuberculosis infection, or osteomyelitis.
- Acute hepatitis B infection.
- Hepatic cirrhosis.
- History of pathological bone fractures not related to trauma.
- Concomitant medications (see list below).
- Active alcohol or drug use that may hinder compliance with trial procedures.

Rationale for dose selection

The dose, dosing interval, and route of administration of TDF/FTC were selected based on currently approved recommendations for treatment of HIV-1 infection.

Trial treatment and administration

Subjects were randomized in a 1:1 ratio to receive either TDF/FTC or matched placebo tablets. Subjects were also instructed to take their assigned tablets orally, once daily, without regard to food. Drug dosing initiated within 24 hours of enrollment.

Concomitant medications

The list of prohibited medications included nucleoside analogs, non-nucleoside reverse transcriptase inhibitors, protease inhibitors, investigational antivirals, interferon (α, β, γ), interleukin (e.g., IL-2), aminoglycoside antibiotics, amphotericin B, cidofovir, systemic chemotherapeutic agents, drugs with significant nephrotoxic potential, drugs that may inhibit or compete for elimination via active renal tubular secretion (e.g., probenecid), and/or other investigational agents.

Trial results

Subject characteristics and demographics

The baseline subject characteristics in the TDF/FTC and placebo groups were similar. All subjects were born male, although 29 (1.2%) of these subjects identified themselves as female. Subjects ranged from 18 to 67 years of age. In the TDF/FTC group, subjects had a mean age of ~9 months older than the placebo group (27.5 yrs TDF/FTC, 28.6 yrs placebo). Subjects were predominantly identified as mixed race/other (68% TDF/FTC, 70% placebo), white (18% TDF/FTC, 17% placebo), or black/African American (9% TDF/FTC, 8% placebo). No other notable differences in demographics and baseline characteristics were observed between both treatment groups. Most trial subjects originated from South America. Three Peruvian sites had the highest proportion of subject enrollment (~56%, n=1400 subjects). In contrast, the two sites in the United States enrolled a combined 9% of subjects in iPrEx.

Treatment duration

The median (Q1, Q3) duration of drug exposure was 77.3 (52.1, 118.9) weeks, with no notable difference between the TDF/FTC (77.9 weeks) and placebo (77.1 weeks) groups. Duration of drug exposure varied from 1 day and 4 weeks to 160 weeks across subjects. A total of 1882 (75%) subjects received drug for at least 1 year (950 TDF/FTC, 932 placebo) and 804 (32%) subjects overall received study drug for 2 years (392 TDF/FTC, 412 placebo).

Primary efficacy

The results presented in the primary efficacy and subgroup efficacy sections reflect the Applicant's analyses. For a detailed review of the pharmacometrics reviewer's analyses, see Appendix 3 (Section 4.2).

The mITT analysis included all subjects who were randomized in iPrEx, received at least one bottle of study medication, and had at least one post baseline HIV-1 seroconversion test. The mITT analysis population included 2442 subjects (TDF/FTC 1224, placebo 1218).

For the Applicant's mITT analysis, 131 seroconversion events were reported during the on-treatment period: 48 in the TDF/FTC group and 83 in the placebo group. TDF/FTC demonstrated a relative risk reduction of 42% (95% CI: 18% to 60%) in preventing HIV-1 infections relative to placebo. The relative risk reduction was 92% (95% CI: 40 to 99%) among subjects in the TDF/FTC group for whom intracellular drug concentrations were quantifiable. After adjustment for reported URAI, the relative risk reduction with TDF/FTC was 95% (95% CI: 70 to 99%). Figure 10 below displays the relation between measurable concentrations of TDF/FTC drug components and HIV-1 seroconversions.

Figure 10 Applicant's summary of the relation between measurable levels of TDF/FTC drug components and HIV-1 seroconversions (iPrEx ITT analysis).

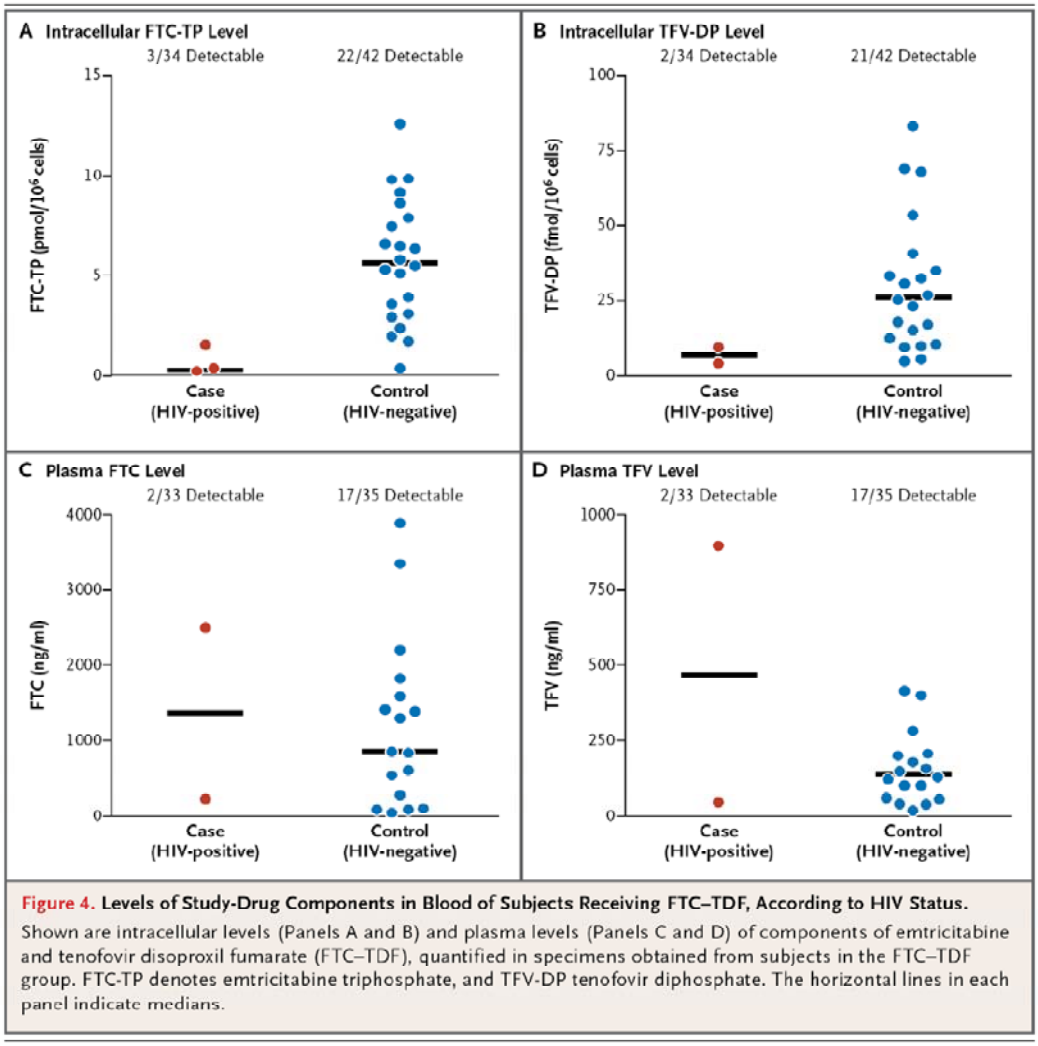
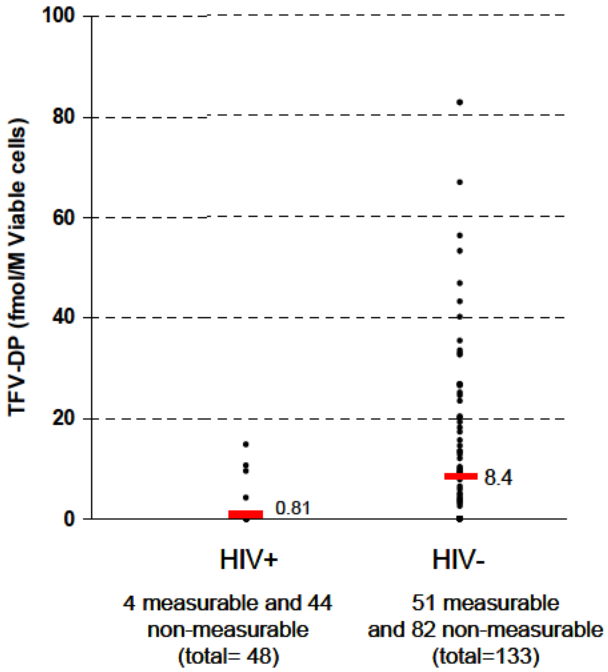


Figure 4. **Levels of Study-Drug Components in Blood of Subjects Receiving FTC–TDF, According to HIV Status.**
Shown are intracellular levels (Panels A and B) and plasma levels (Panels C and D) of components of emtricitabine and tenofovir disoproxil fumarate (FTC–TDF), quantified in specimens obtained from subjects in the FTC–TDF group. FTC-TP denotes emtricitabine triphosphate, and TFV-DP tenofovir diphosphate. The horizontal lines in each panel indicate medians.

Reviewer's comment: Of note, the Applicant included PK data from 76 subjects in the figure shown above, presumably available up to the first data cutoff date of May 01, 2010. The full dataset contains PK results from 181 subjects: 48 seroconverters and 133 non-seroconverters, as shown below.

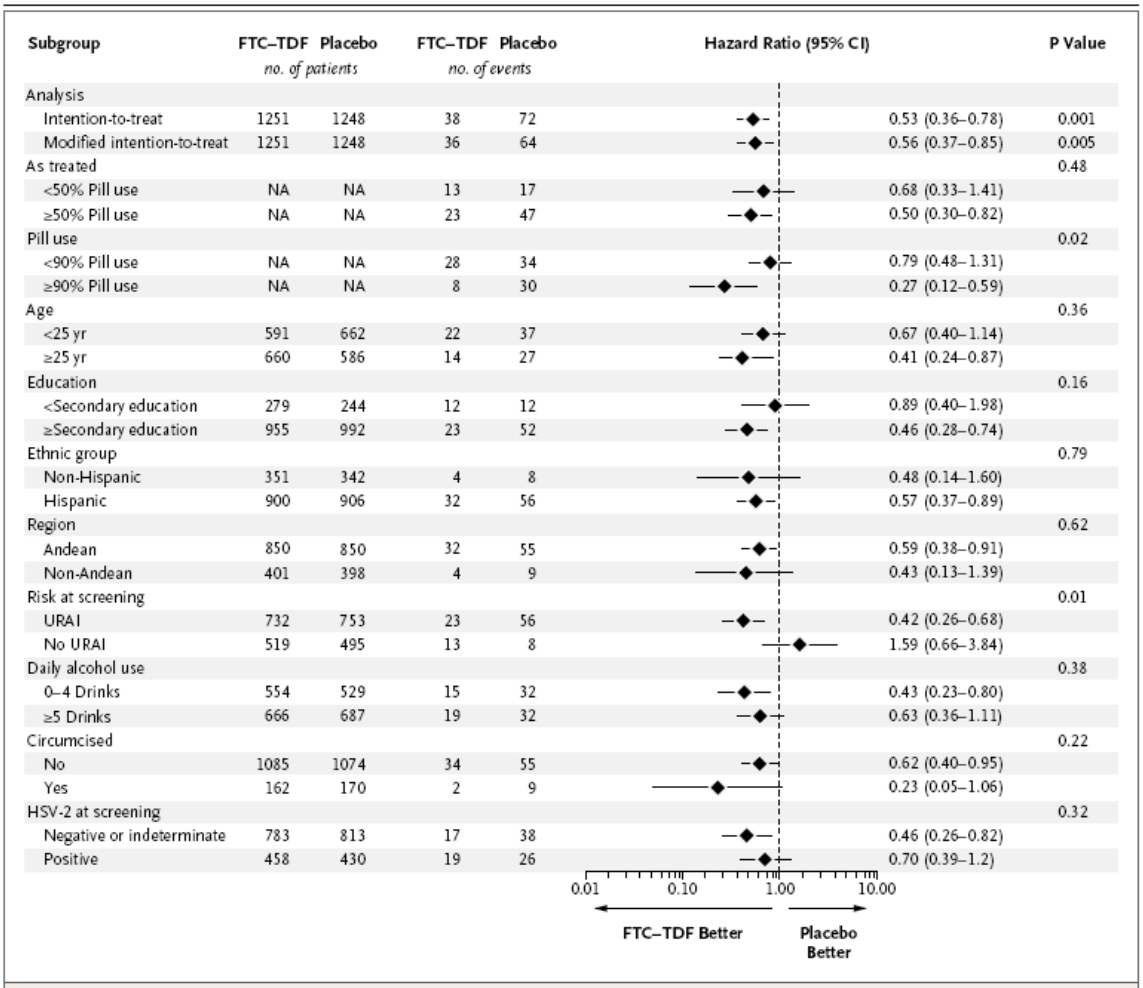
Figure 11 Summary of the relation between measurable levels of TFV-DP and HIV-1 seroconversions (iPrEx mITT population [n=181]). The red line depicts mean TFV-DP concentrations in each group.



Subgroup efficacy

In the TDF/FTC group, subjects who reported URAI at baseline had a relative risk reduction of 58% (95% CI: 32 to 74%) in acquiring HIV-1 infections, compared to subjects reporting no URAI. Conversely, the relative risk reduction was not significant among subjects who did not engage in URAI. Moreover, a trend of greater relative risk reduction in HIV-1 acquisition with TDF/FTC was observed in subjects who were ≥25 years of age, had ≥secondary education, used ≤4 alcoholic drinks per day, and were HSV-2 negative at screening. However, these findings were not statistically significant, and should be interpreted with caution due to small subject numbers and the exploratory nature of this subgroup analysis (see Figure 12 below).

Figure 12 Hazard ratio comparisons of HIV-1 infection risk within pre-defined subgroups (mITT analysis).



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

Figure 3. HIV Incidence among Subjects Receiving FTC–TDF, According to Subgroup.

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

Safety results

Generally, safety findings for TDF/FTC were comparable to those observed with of placebo. During the double-blind treatment period, 2027 (81%) subjects reported at least one adverse event (998 [80%] TDF/FTC, 1029 [81%] placebo). Clinical AEs that occurred at an incidence of ≥ 2% were:

- Diarrhea (6% TDF/FTC, 7% placebo)
- Pharyngitis (12% TDF/FTC, 15% placebo)
- Intestinal parasitic infection (10% TDF/FTC, 15% placebo)

- Urethritis (5% TDF/FTC, 7% placebo)
- Nasopharyngitis (6% both groups)
- Depression (6% both groups)
- Headache (6% both groups)
- Back pain (5% both groups)
- Weight decreased (3% TDF/FTC, 1% placebo)
- Nausea (2% TDF/FTC, 1% placebo)

A modest decrease in least square mean BMD by week 24 were observed in the TDF/FTC group (-0.28% to -0.92%) compared to the placebo group. The number of subjects who experienced a ≥5% decrease in spinal BMD from baseline at any post baseline time point was higher in the TDF/FTC group (30/214 subjects [14%]) compared to placebo group (14/216 [6%]). BMD decreases were reversing toward baseline upon discontinuation of TDF/FTC.

Mild to moderate elevations in serum creatinine were observed with higher incidence in the TDF/FTC treatment group compared with the placebo group (2% TDF/FTC, 1% placebo). One incidence of grade 3 serum creatinine was observed in the placebo group, and none in the TDF/FTC group.

Reviewer's comment: Based on plasma and intracellular assessments of tenofovir and emtricitabine concentrations, adherence to the once daily regimen was low in iPrEx (~7% of subjects in PK subgroup, n=12/181). Thus, the adverse events reported in this trial reflect safety data from subjects who were generally non-adherent to a daily regimen of TDF/FTC. The pharmacometrics reviewer's analysis showed an 87.5% relative risk reduction for the TDF/FTC group as compared with placebo. The results were consistent with the Applicant's analysis.

Bioanalysis of PK samples

PBMC samples

The University of Colorado Denver, Antiviral Pharmacology Laboratory (CAVP) received a total of 1129 PBMC samples collected from subjects in the iPrEx trial. All trial samples were stored frozen at approximately -70°C. The long-term storage stability under frozen conditions was 18 months. According to CAVP, PBMC samples were analyzed within the stability period. Approximately 59% of samples (663/1129) collected from the iPrEx trial were extracted, analyzed, and reported. The samples were processed for TFV-DP and FTC-TP concentrations using two validated LC/MS/MS methods (see Table 6 below).

Plasma samples

CAVP received 1466 plasma samples in EDTA anticoagulant collected from subjects in the iPrEx trial. All plasma samples were stored at -70°C prior to analysis. The long-term storage stability under frozen conditions was 3 years. According to CAVP, plasma samples were analyzed within the storage stability period. Approximately 26% of all plasma samples (378/1466) were extracted, analyzed, and reported. Plasma samples were analyzed for tenofovir and emtricitabine concentrations using one validated LC/MS/MS method.

Table 6 Summary of bioanalytical parameters derived from the LC/MS/MS methods used for analysis of PBMC and plasma samples collected during the iPrEX trial.

Analyte	Method	Trial	LLOQ	ULOQ	Linear range	Between run precision (%CV)	Between run bias (% deviation)	QC samples
TFV-DP	TFV-DP only	iPrEx	50 fmol/spl	10000 fmol/spl	50 - 10000 fmol/spl	1.3 – 10.2	≤ 1.8	150, 750, 7500 fmol/spl
TFV-DP	IC_NA	iPrEx	2.5 fmol/spl	2000 fmol/spl	2.5 – 2000 fmol/spl	9.0 – 13.1	≤ -5.5	15, 150, 1500 fmol/spl
FTC-TP	IC_NA	iPrEx	0.1 pmol/spl	200 pmol/spl	0.1 – 200 pmol/spl	3.5 – 5.1	≤ -7.5	1.5, 15, 150 pmol/spl
TFV	ID10445	iPrEx	10 ng/mL	1500 ng/mL	10 – 1500 ng/mL	3.3 – 5.9	≤ 7.1	30, 300, 1200 ng/mL
FTC	ID10445	iPrEx	10 ng/mL	1500 ng/mL	10 – 1500 ng/mL	4.2 – 6.6	≤ 10.4	30, 300, 1200 ng/mL

Discussion

The iPrEx trial provides evidence of the efficacy of TDF/FTC in preventing HIV-1 infection in MSM at high risk for acquiring HIV-1 infection. Once daily TDF/FTC was associated with a relative risk reduction of 42% (95% CI: 18%-60%) in acquiring HIV infections relative to placebo. The primary efficacy outcome exceeded the prevention target of relative risk reduction of 30%; although the lower bound of the 95% CI did not exclude 30%.

Assessment of adherence by pill count or adherence questionnaire suggested a high level of TDF/FTC adherence (≥90%) in the iPrEx trial. However, high self-reported adherence was poorly predictive of measurable intracellular concentrations of TFV-DP. In fact, only 30% of all subjects (55/181) in the PK subgroup had any measurable intracellular TFV-DP concentrations. When comparing TFV-DP concentrations based on seroconversion status, 8% of seroconverters (4/48) and 38% of non-seroconverters (51/133) had measurable TFV-DP concentrations. Moreover, the median TFV-DP concentrations in seroconverters was lower (10.2 fmol/M viable cells) than in non-seroconverters (15.6 fmol/M viable cells). This finding suggested that the higher the medication adherence (based on TFV-DP concentrations) the greater protection against acquiring HIV-1 infection.

In order to assess the impact of TDF/FTC adherence on efficacy, DAVP extrapolated the distribution of non-seroconverters (n=133) with measurable (n=51, 38%) and non-measurable (n=82, 62%) TFV-DP concentrations to all subjects treated with TDF/FTC in iPrEx (n=1176). The analysis estimated that 451 non-seroconverters receiving TDF/FTC were likely to have measurable TFV-DP concentrations, and 725 were likely to have non-measurable TFV-DP concentrations. Next, the Pharmacometrics reviewer estimated the seroconversion rate per patient year for all non-seroconverters in the TDF/FTC group, by adding back in the 48 seroconverter subjects who had measurable (n=4) and non-measurable (n=44) TFV-DP concentrations. Thus, the event rate in the uninfected group that was expected to have measurable concentrations was estimated as 4/(451 + 4) and the event rate for uninfected subjects with no measurable concentrations was estimated as 44/(725 + 44). The analysis revealed that subjects with non-measurable TFV-DP concentrations had a seroconversion rate of 3.6%, which was not significantly different from the seroconversion rate observed in the

placebo group (4.2%). In contrast, subjects with measurable TFV-DP concentrations had a seroconversion rate of 0.5%.

When translating the absolute HIV-1 seroconversion rates to relative risk reduction of HIV-1 infection, subjects with measurable TFV-DP concentrations had a relative risk reduction of 87.5% compared to subjects receiving placebo. Conversely, subjects with non-measurable TFV-DP concentration had a relative risk reduction of 14.5% compared to placebo. In a similar analysis, the Applicant concluded that subjects with known medication adherence, based on measurable TFV-DP concentrations, had a relative risk reduction of 92% (95% CI: 40-99%). Of note, the Applicant's analysis compared the relative risk reduction estimated from subjects with measurable TFV-DP concentrations *versus* subjects with non-measurable TFV-DP concentrations in the TDF/FTC group. The pharmacometrics reviewer estimated the relative risk reduction for subjects with measurable and non-measurable TFV-DP concentrations compared to placebo. Overall, both the pharmacometrics reviewer and the Applicant demonstrated that increased medication adherence based on measurable intracellular TFV-DP concentrations, reduced the risk of acquiring HIV-1 infection while poor adherence was not significantly different from placebo.

The Applicant reported that pre-exposure prophylaxis with TDF/FTC demonstrated a significant relative risk reduction of 58% (95% CI: 32 to 74%) in acquiring HIV-1 infections among subjects who reported URAI at enrollment. The pharmacometrics reviewer conducted a similar post-hoc exploratory analysis and estimated the relative risk reduction in this subject population to be 53% (95% CI: 29-69%). The post hoc analysis also showed that subjects who were ≥25 years of age and those with ≥secondary education had relative risk reductions of 56% (95% CI: 23-75%) and 52% (95% CI: 26-69%) compared to their counterparts. When combining the three subject covariates, the relative risk reduction with TDF/FTC compared with placebo was 85% (95% CI: 58-95%). However, these post-hoc analyses are exploratory, and no conclusions can be made based on these findings. Trial subjects were not stratified based on these covariates and the iPrEx trial was not large enough to demonstrate efficacy within these subgroups.

Conclusions

TDF/FTC demonstrated a 42% relative risk reduction in acquiring HIV-1 infection compared to placebo. Fewer seroconversions occurred when subjects had consistently measurable intracellular TFV-DP concentrations. A relative risk reduction of 87.5% was estimated for subjects with measurable TFV-DP concentrations relative to placebo. Conversely, the estimated relative risk reduction in subjects with non-measurable TFV-DP concentration was slightly higher (14.5%), but not significantly better than placebo. Overall, high medication adherence, demonstrated by having consistently measurable intracellular tenofovir concentrations, was associated with a greater reduced risk of acquiring HIV-1 infection. Medication adherence contributed greatly to the outcome of this trial.

4.1.2 Partners PrEP Trial

Trial CO-US-104-0380: Parallel comparison of tenofovir and emtricitabine/tenofovir pre-exposure prophylaxis to prevent HIV-1 acquisition within HIV-1 discordant couples.

Trial period

The trial began in June 19, 2008 (first subject screen) and the data cutoff occurred on July 10, 2011. This report includes data collected through July 10, 2011. The Data Safety Monitoring Board (DSMB), during an interim analysis, discovered that the active groups (TDF and TDF/FTC) demonstrated efficacy at preventing HIV-1 acquisition, as compared with placebo. Therefore, the placebo group was discontinued. Currently, the TDF and TDF/FTC groups are still ongoing and blinded.

Trial sites

The trial was conducted in nine sites across two countries: four sites in Kenya (Eldoret, Kisumu, Nairobi, and Thika) and five sites in Uganda (Jinja, Kabwohe, Kampala, Mbale, and Tororo).

Trial objectives

The primary objectives of this trial were to:

- Determine if once daily Viread (TDF) or Truvada (TDF/FTC) prevent HIV-1 acquisition among HIV-1 uninfected partner subject within heterosexual serodiscordant couples, who are also receiving standard prevention interventions.
- Assess the safety of daily TDF or TDF/FTC by comparing rates of adverse events (AEs) *versus* placebo.

The secondary objectives were to:

Factors influencing efficacy

- Evaluate the efficacy of PrEP by monitoring the level of HIV-1 exposure for uninfected partners within HIV-1 serodiscordant couples, defined by the frequency of sexual activity and the HIV-1 viral load in the HIV-1 infected partner.
- Assess the efficacy of PrEP by gender of the uninfected partner.
- Measure the effect of other factors on efficacy, including CD4 counts (HIV-1 infected subject only) and for both partners: herpes simplex virus type 2 (HSV-2) serostatus, sexually transmitted infections (STIs), and male circumcision.

Adherence

- Assess the adherence to once daily TDF and TDF/FTC PrEP among uninfected partners within HIV-1 serodiscordant couples, and the effect of adherence on efficacy of PrEP.
- Evaluate the frequency of PrEP drug sharing between the uninfected and HIV-1 infected partners within the serodiscordant couple, as measured by drug assays.

Risk compensation

- Characterize the association of once daily TDF or TDF/FTC with change in sexual behavior of uninfected partners within HIV-1 serodiscordant couples.

- Compare the risk behaviors among HIV-1 serodiscordant couples previously enrolled in the Partners in Prevention trial (which evaluated the efficacy of HSV-2 suppressive therapy when given to HIV-1 infected partner for preventing HIV-1 transmission), by examining changes in sexual behaviors when the HIV-1 infected *versus* uninfected partner was receiving a trial drug.

Safety

- Assess the effect of TDF and TDF/FTC on the rate of congenital abnormalities and growth among infants born to HIV-1 uninfected female subjects who became pregnant during the trial (and in whom trial drug was stopped at the time of pregnancy detection, using monthly pregnancy tests).

Effect of PrEP on early HIV-1 disease

- To assess the effect of PrEP on plasma HIV-1 viral load and CD4 cell counts during the first 12 months after HIV-1 seroconversion; frequency of genotypic and phenotypic antiretroviral drug resistance, and other clinical, immunologic, and virologic parameters of HIV-1 disease in uninfected partners who seroconverted during the trial.

The tertiary objective was to:

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

Trial population

The trial randomized 4758 partner subjects in a 1:1:1 ratio to receive either TDF (n=1589), TDF/FTC (n=1583), or placebo (n=1586). Eligible subjects were part of a heterosexual couple in which one subject was HIV-1 infected and the other partner was uninfected.

Trial design

This was a multicenter, international, randomized, double blind, placebo-controlled, three-group trial powered to show that TDF/FTC was at least 30% efficacious in preventing HIV-1 infection. Previous trials evaluating vaccines for HIV-1 PrEP used the minimum efficacy cutoff of 30%.

The trial enrolled both index (HIV+) and partner subjects (HIV-) within a serodiscordant couple. However, only the partner subjects were randomized to receive trial drugs, monitored for adverse events, and followed for HIV-1 seroconversion. Partner subjects were followed for a minimum of 24 months and up to a maximum of 36 months. Partner subjects underwent monthly rapid HIV-1 testing at the clinic. As previously mentioned, rapid tests for HIV-1 are qualitative immunoassays that detect antibodies to HIV-1. A positive rapid test for HIV-1 should be confirmed by an enzyme immunoassay. Subjects who seroconverted were asked to stop intake of trial drug. A blood sample was drawn for a confirmatory HIV-1 serology (EIA) test. Index subjects (already HIV+) were monitored for HIV-1 disease progression at quarterly visits,

and were referred for antiretroviral therapy (ART) if they met the national criteria due to CD4 decline or clinical symptoms. The index subject corresponding to a newly seroconverted partner subject was asked to provide blood during a clinic visit as close as possible to the date when the partner subject's specimens were collected at the time of seroconversion.

Additional monthly assessments included structured interviews to assess medication adherence, pill counts, collection of behavioral information, HIV-1 infection risk reduction and condom promotion, contraception counseling and provision/referral, and collection of medical history. In the event of a pregnancy, partner women were instructed to stop taking trial drug during pregnancy and breastfeeding. These women continued with follow-up visits, including monthly HIV-1 testing.

Investigators also conducted a sub-group analysis comparing plasma concentrations of tenofovir collected from seroconverter subjects (cases) within the TDF and TDF/FTC groups, and from 100 randomly selected non-seroconverters (controls) in the same active groups. Blood samples for evaluation of tenofovir plasma concentrations were obtained from both cases and controls at months 1, 3, 6, 12, 18, 24, 30, and 36. Additionally, plasma samples were collected from seroconverters during the visit at which HIV-1 seroconversion was detected.

Reviewer's comment: Investigators did not analyze peripheral blood mononuclear cell (PBMCs) drug concentrations.

Key inclusion criteria

Partner subjects (HIV-1 uninfected)

- ≥18 years of age and not more than 65 years
- Part of a heterosexual couple, and have met the following criteria:
  - Sexually active (defined as having had vaginal intercourse with the partner subject at least 6 times in the last 3 months).
  - Planned to remain in the relationship for the duration of the trial period; each trial site developed appropriate criteria for determining if a couple was likely to remain in the relationship (i.e., married, duration of partnership, cohabitation, children in the home).
- HIV-uninfected based on parallel negative HIV-1 rapid test at screening and enrollment.
- Adequate renal function, defined as CrCl ≥60 mL/min estimated using the Cockcroft-Gault creatinine formula and a SCr level ≤1.3 mg/dL for men and ≤1.1 mg/dL for women, as measured within 56 days of enrollment. The trial drugs were discontinued if estimated CrCl was confirmed on repeat testing as <50 mL/min at any time during the trial.
- Adequate hepatic function defined by total bilirubin of not more than 1.5 times the upper limit of normal and hepatic transaminases less than 2 times the upper limit of normal, as measured within 56 days of enrollment.

Index subjects (HIV-1 infected)

- Part of a heterosexual couple, and have met the following criteria:
  - Sexually active (defined as having had vaginal intercourse with the partner subject at least 6 times in the last 3 months).

- Planned to remain in the relationship for the duration of the trial period.
- HIV-1 infected based on positive enzyme immunoassay
- CD4 cell count of at least 250 cells/mm^3 and did not otherwise meet national guidelines for initiation of ART.
- No history of clinical AIDS-defining diagnoses

Key exclusion criteria

Partner subjects

- Pregnancy and breastfeeding.
- Active and serious infections requiring parenteral antibiotics, active tuberculosis infection, or osteomyelitis.
- Receiving any of the prohibited medications listed in the concomitant section (see below).
- Hepatic impairment

Index subjects (HIV-1 infected)

- Current use of antiretroviral therapy (ART)
- Current enrollment in another HIV-1 treatment trial.

Rationale for dose selection

The dose, schedule, and route of administration of TDF and TDF/FTC were selected based on currently approved dosing and administration recommendations for HIV-1 treatment for each respective drug product.

Trial treatment and administration

Partner subjects were instructed to ingest trial drugs once daily without regard to food. Because TDF and TDF/FTC tablets look different, partner subjects in the active drug groups ingested two tablets daily: one active drug and one placebo tablet. For example, subjects in the TDF group received an active TDF tablet and one TDF/FTC placebo tablet, while subjects in the TDF/FTC group received one active TDF/FTC tablet and one placebo TDF tablet. Subjects randomized to placebo received one placebo TDF/FTC tablet and one placebo TDF tablet once daily.

Concomitant medications

Partner subjects were not allowed to receive an ongoing therapy with any of these drugs at enrollment and during the trial: ART, including nucleoside analogs, NNRTIs, protease inhibitors or investigational antiretroviral agents, interferon (alpha, beta, gamma) or interleukin (e.g., IL-2), metformin, aminoglycoside antibiotics, amphotericin B, cidofovir, systemic chemotherapeutic agents, or other agents with significant nephrotoxic potential (e.g., probenecid), and/or investigational agents. If the partner subject required post-exposure

prophylaxis (PEP) for a reported HIV-1 exposure at any time during the trial, the trial drug was discontinued during the PEP period.

Trial results

Subject characteristics and demographics

The demographic and baseline characteristics of the enrolled couples were similar across trial groups. Most partner subjects (HIV-) were predominantly males (61 to 64%) and had a mean age of approximately 33 years of age. Most partner subjects had a median education level of 7 years, and reported not having sex with an outside partner (>90%). The index subjects (HIV+) across all trial groups had similar demographic and baseline characteristics within the categories of age, years of education, and sex with an outside partner. The median baseline CD4 cell count ranged from 491 to 499 cells/mm^3. The median plasma HIV-1 RNA level in the index partner was 3.9 log_{10} copies/mL.

Overall, couples across all groups reported a median of four sex acts, and 26 to 28% reported having unprotected sex during the month prior to enrollment. Most of the couples were married (97 to 98%) with a median partnership duration of 7.0 to 7.1 years. Across groups, similar percentages of partner and index subjects (6 to 9%) had a curable STI at enrollment. No female partner was pregnant at trial enrollment; however, 16% of female partners (n=288/1785) or index subjects became pregnant during the trial.

Medication adherence

Medication adherence in the Partners PrEP trial was high. Overall, 98% of the dispensed trial bottles were returned, and the investigators estimated that 97% of the dispensed drug tablets were taken (based on pill counts of returned, unused trial drug).

Primary efficacy

The trial randomized 4758 partner subjects in the TDF (n=1589), TDF/FTC (n=1583), and placebo (n=1586) groups. Fifty of these partner subjects did not meet trial criteria for the mITT analysis (no follow-up visit, or HIV-1 infection at enrollment, etc). Thus, the mITT analysis, included 4708 partner subjects; 1572 in TDF, 1568 in TDF/FTC, and 1568 in placebo.

Ninety-nine (99) site-reported seroconversions were recorded as of July 10, 2011, the date when the trial stopping rules were met. Of these seroconversions, 3 were false positives, and 14 occurred in partner subjects who were HIV-1 RNA PCR positive at enrollment. Hence, the mITT cohort included 82 seroconverters. Of the 82 seroconverters, 17, 13, and 52 occurred in partner subjects randomized to TDF, TDF/FTC, and placebo groups, respectively.

In the mITT cohort, both TDF and TDF/FTC demonstrated significant efficacy compared to placebo. The relative risk reduction of acquiring HIV-1 infection in subjects receiving TDF was 67% (95% CI: 44-81%) relative to placebo. The relative risk reduction of TDF/FTC was 75% (95% CI: 55-87%) compared to placebo. Although numerically different, the relative risk reduction ratios for TDF and TDF/FTC were not statistically significantly different from one another. Both TDF and TDF/FTC ruled out efficacy of less than 30% relative to placebo; thereby, meeting the pre-specified primary efficacy endpoint (p=0.0031 and p=0.0004, respectively).

The pharmacometrics reviewer conducted an analysis to evaluate if measurable plasma TFV concentrations correlated with protective effect from acquiring HIV-1 infection relative to placebo. Both seroconverters and their respective controls in the TDF/FTC group (n=113) were separated into three categories based on plasma TFV concentration and seroconversion status. The categories included 1) subjects who always had measurable concentrations across all clinic visits, 2) subjects who sometimes had measurable concentrations, and 3) subjects who never had measurable concentrations at any study visits during the trial. As shown in Table 7 below, a higher proportion of subjects in the non-seroconversion group (63%) were always measurable compared to subjects (15%) in the seroconverter group. These results suggest better medication adherence decreases the risk of acquiring HIV-1 infection.

Table 7 Percentage of subjects with plasma TFV concentrations that were always measurable, sometimes measurable, or never measurable by seroconversion status in the Truvada group only.

TFV plasma concentrations	HIV-1 Positive	HIV-1 negative
Always measurable	15.4% (n=2/13)	63% (n=63/100)
Sometimes measurable	46.1% (n=6/13)	28% (n=28/100)
Never measurable	38.5% (n=5/13)	9% (n=9/100)

In order to assess the impact of drug adherence on efficacy in Partners PrEP, the distribution of TFV measurable status within the 100 HIV-uninfected subjects: 63% always measurable, 28% sometimes measurable, and 9% never measurable was extrapolated to the entire 1566 HIV-uninfected subjects treated with TDF/FTC. As shown in Table 8 below, subjects in the never measurable category had a seroconversion rate (2.1%) which was not significantly different from subjects in the placebo group (2%). In contrast, subjects with always measurable TFV concentrations had an event rate of 0.1%. When translating these absolute conversion rates to relative risk reduction with TDF/FTC versus placebo, the TDF/FTC group with always measurable TFV concentrations had a relative risk reduction of 93.9% compared to placebo. Conversely, subjects in the TDF/FTC group with never measurable concentrations had a relative risk reduction of acquiring HIV-1 infection (-6.5%) that was not significantly different from that of placebo. Overall, these findings suggest that high medication adherence, based on always having measurable TFV plasma concentrations during all clinic visits, greatly reduces the relative risk of acquiring HIV-1 infection compared to placebo.

Table 8 Seroconversion event rates and the respective relative risk reduction in subjects with never measurable, sometimes measurable, and always measurable concentrations in the TDF/FTC group relative to placebo.

Group	N	Event rate per patient-years (%)	Relative risk reduction relative to placebo (%)
Placebo	52/2607	2.0	-
Never measurable	5/235	2.1	-6.5
Sometimes measurable	6/733	0.8	58.9
Always measurable	2/1648	0.1	93.9
Truvada	13/2616	0.5	75.1

Secondary efficacy endpoints

The secondary analysis included evaluations (hazard ratios) of the incidence of HIV-1 infection within specific subgroups including gender, age, male circumcision status, country, any unprotected sex reported within the month prior to trial enrollment. For the index subject, the subgroup analysis included HIV-1 plasma viral load and CD4 count at enrollment. Overall, TDF and TDF/FTC demonstrated similar, but greater protective effects compared to placebo in all subgroups (see Table 9 below). However, statistical significance ($p<0.05$) was only achieved for the difference in the effect of TDF *versus* placebo by CD4 cell level of the index subjects at enrollment.

Table 9 Hazard ratio comparisons of HIV-1 infection risk by subgroup (mITT analysis)

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

Abbreviation: CI = 95% confidence interval

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

Subgroup PK analysis

In total, the PK database contains PK data collected from 226 subjects: 113 in the TDF/FTC group and 113 in the TDF group. In the TDF/FTC group, plasma tenofovir concentrations are available from 13 seroconverters and 100 non-seroconverters. In the TDF group, plasma tenofovir concentrations are available from 17 seroconverters (after removing 2 subjects who were HIV+ at enrollment), and 96 non-seroconverters.

Based on the Applicant's analysis, for partner subjects in the TDF group, having a measurable tenofovir concentration was associated with an 86% risk reduction in acquiring HIV-1 (95% CI: 67 to 95%; p<0.001). For the partner subjects in the TDF/FTC group, having measurable tenofovir concentrations, as compared to non-measurable concentrations, was associated with a 90% reduction in HIV-1 risk (95% CI: 56 to 98%; p=0.002) (see Table 10 below).

Table 10 Risk estimate for HIV-1 protection based on having measurable and non-measurable tenofovir plasma concentrations.

	Number/ Total Samples (%) with Tenofovir measured		Risk Estimate for HIV-1 Protection: measured versus non-measurable Tenofovir	
	Case	**Cohort**	**Hazard Ratio (95% CI)**	**p-value**
TDF group	6/17 (35.3)	363/437 (83.1)	0.14 (0.05, 0.33)	<0.001
TDF/FTC group	3/12 (25.0)	375/465 (80.6)	0.10 (0.02, 0.44)	0.002

Reviewer's comment: For the subgroup PK analysis, the Applicant excluded one seroconverter case (subject 5017613) from the TDF/FTC group because the subject did not have a PK sample at enrollment, but was later found to have seroconverted during the month 23 visit. The subject missed all previous clinic visits except for the month 23 visit. Thus, the Applicant's calculation of relative risk reductions in the TDF/FTC group included only 12 of the 13 seroconverters. When conducting a similar PK analysis, the pharmacometrics reviewer included the missing subject (total=13). The subject had a non-measurable tenofovir plasma concentration during the month 23 visit, and was assumed non-adherent to trial drug.

Bioanalysis of plasma samples

The (b) (4) analyzed plasma samples collected from the Partners PrEP trial. The Applicant submitted two documents: a standard operating procedure for sample bioanalysis and a validated report summarizing top line results of the LC/MS/MS method used for plasma sample analysis. Submission of the complete bioanalytical report has been requested but still pending. Table 11 below summarizes the *in vitro* analytical methods used for the determination of plasma concentrations of tenofovir and emtricitabine.

Table 11 Summary of bioanalytical parameters derived from the LC/MS/MS method used for analysis of plasma samples collected during the Partners PrEP trial (based on supportive documents, and not the actual BA report).

Analyte	Method	LLOQ	ULOQ	Linear range	Between run precision (%CV)	Between run bias (% deviation)	QC samples
TFV and FTC	No ID provided	*0.3 ng/mL	1000 ng/mL	0.3 – 1000 ng/mL	5.1 – 15.1	≤ 11	15, 200, 850 ng/mL

*The documents submitted by the Applicant state that the LLOQ for measuring TFV and FTC in plasma was 5 ng/mL. However, in a recent email communication with the Applicant, the LLOQ was specified to be 0.3 ng/mL instead of 5 ng/mL.

Discussion

The Partners PrEP trial provides evidence of the efficacy of TDF/FTC and TDF in preventing HIV-1 infection in subjects who are in a heterosexual serodiscordant couple. In the Applicant's mITT analysis, the relative risk reduction of acquiring HIV-1 infection in subjects receiving TDF was 67% (95% CI: 44-81%) relative to placebo. In contrast, the relative risk reduction of TDF was 75% (95% CI: 55-87%) compared to placebo. Both TDF and TDF/FTC ruled out efficacy of less than 30% relative to placebo. Although numerically different, the relative risk reduction associated with TDF and TDF/FTC were not statistically significantly different from one another.

According to the Applicant, the relative risk reduction for partner subjects in the TDF group who had measurable TFV plasma concentration was 86% (95% CI: 67-95%) compared to subjects with non-measurable concentrations. Similarly, the relative risk reduction for subjects with measurable TFV plasma concentrations in the TDF/FTC group was 90% (95% CI: 56-98%) compared to subjects with non-measurable concentrations. Of note, the Applicant's analysis estimates the relative risk reduction of HIV-1 infection between the groups with measurable and non-measurable TFV concentrations, but not compared to placebo. When the pharmacometrics reviewer analyzed the data, subjects in the TDF/FTC group with always measurable TFV concentrations had a 93.9% relative risk reduction of acquiring HIV-1 infection compared with subjects receiving placebo.

Conclusions

Once daily TDF/FTC or TDF greatly reduced the risk of acquiring HIV-1 infection compared to placebo. Both active drugs exceeded the prevention threshold of 30%. TDF/FTC (75%) had a numerically greater relative risk reduction than TDF (67%); however, this difference was not statistically significant. Subjects who always had measurable TFV plasma concentrations during the trial had a higher relative risk reduction (93.9%) compared to placebo, in contrast to the relative risk reductions for subjects who sometimes had measurable TFV concentrations (58.9%) and subjects who never had measurable TFV plasma concentrations (-6.5%). These results suggest that medication adherence greatly contributed to the efficacy outcome of this trial.

4.2 Consult Pharmacometrics review

OFFICE OF CLINICAL PHARMACOLOGY:

PHARMACOMETRIC REVIEW

Application Number	NDA 21752 S030
Submission Number (Date)	14 Dec 2011
Drug Name	Emtricitabine[FTC]-Tenofovir disoproxil fumarate[TDF] - Truvada
Proposed Indication	Pre-exposure prophylaxis (PrEP) to reduce the risk of sexually acquired HIV-1 in adults
Clinical Division	DAVP
Primary CP Reviewer	Ruben Ayala, Pharm.D.
Primary PM Reviewer	Jiang Liu, Ph.D.
Secondary CP Reviewer	Shirley Seo, Ph.D.
Secondary PM Reviewer	Yaning Wang, Ph.D.
Applicant	Gilead

1 SUMMARY OF FINDINGS

1.1 Key Review Questions

The main purpose of this review is to assess emtricitabine/ tenofovir (FTC/TDF) effectiveness based on exposure-response analyses.

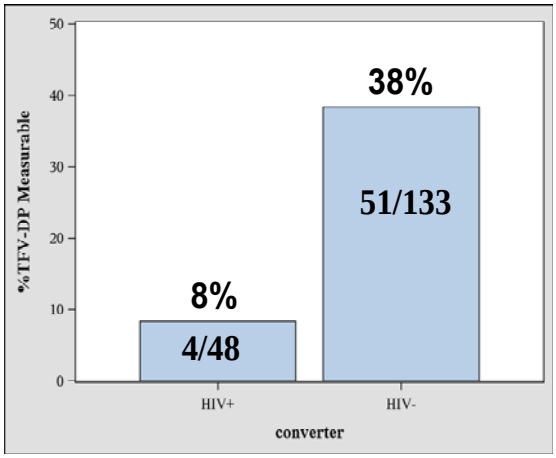
1.1.1 What is exposure-relative risk reduction relationship for FTC/TDF in men who have sex with men (MSM) in iPrEX study?

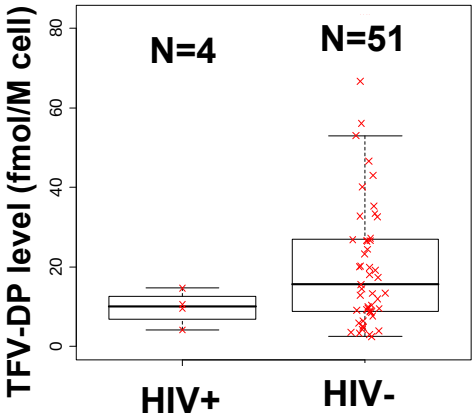
The case-control sub-study within the iPrEx was designed to evaluate FTC/TDF exposure on protection from HIV-1 infection. When a study participant was deemed a seroconverter, the PK samples closest to the date of seroconversion were evaluated for tenofovir and emtricitabine concentrations in plasma and 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 study week, while the third control subject was selected to be matched on site and study week and to have reported unprotected receptive anal intercourse (URAI) at time of drug level specimen.

Submitted data contained plasma and intracellular concentrations of tenofovir and emtricitabine closest to the date of seroconversion from 48 HIV seroconverters with FTC/TDF treatment. The PK data from 144 matched HIV- controls (among them 5 later became HIV+ and 11 subjects served as controls twice) were also presented. As shown in Figure 1 (left), only 8% of HIV seroconverters had measurable levels (above 2.5 fmol/M cell) of intracellular TFV-DP at the time of seroconversion compared to 38% in the matched HIV- controls (replicated subjects were excluded, P-value < 0.0001 from

Fisher's exact two-sided test). The measurable intracellular TFV-DP levels were also higher in the non-seroconverter (HIV-) group compared to those in the seroconverter (HIV+) group (Figure 1, right),

Figure 1: The intracellular TFV-DP levels were higher in the non-seroconverter (HIV-) group compared to those in the seroconverter (HIV+) group (iPrEx).





Non-measurable intracellular concentrations indicate poor drug adherence. In order to assess the impact of drug adherence on efficacy, the distribution of TFV-DP measurable status within the 133 HIV-uninfected subjects (i.e., 62% non-measurable vs. 38% measurable) was extrapolated to the entire HIV-uninfected subjects treated with FTC/TDF in iPrEx (n=1176). This method is referred as simple distribution method. After extrapolation, about 451 HIV- subjects treated with FTC/TDF were likely to have measurable TFV-DP levels, and 725 were likely to have non-measurable levels. Considering the 48 HIV seroconverters together, we can calculate the event rate per subject: for example 4/(451+4) for subjects with measurable TFV-DP and 44/(725+44) for subjects with non-measurable TFV-DP. Transforming to the conversion rate per patient year as shown in Figure 2, the point estimate of the seroconversion rate in the FTC/TDF group with non-measurable TFV-DP is 3.6% which is not significantly different from the observed 4.2% event rate in the placebo group (see Table 11 for 95% CI). For subjects with measurable intracellular drug levels, the HIV seroconversion event rate was 0.5% which is substantially lower than event rates in the placebo group, or the non-measurable drug concentration group. Translating these absolute conversion rates to the risk reduction relative to the placebo group, the FTC/TDF group with non-measurable TFV-DP has limited additional protection from HIV infection compared to placebo. However, the risk reduction in subjects with measurable intracellular drug levels is 87.5% (Figure 3). These results demonstrate that increased medication adherence based on detectable intracellular TFV-DP concentrations reduced the risk of acquiring HIV infection while poor adherence has limited protection.

Figure 2: Event rates in all subjects - placebo and FTC/TDF groups (iPrEx).

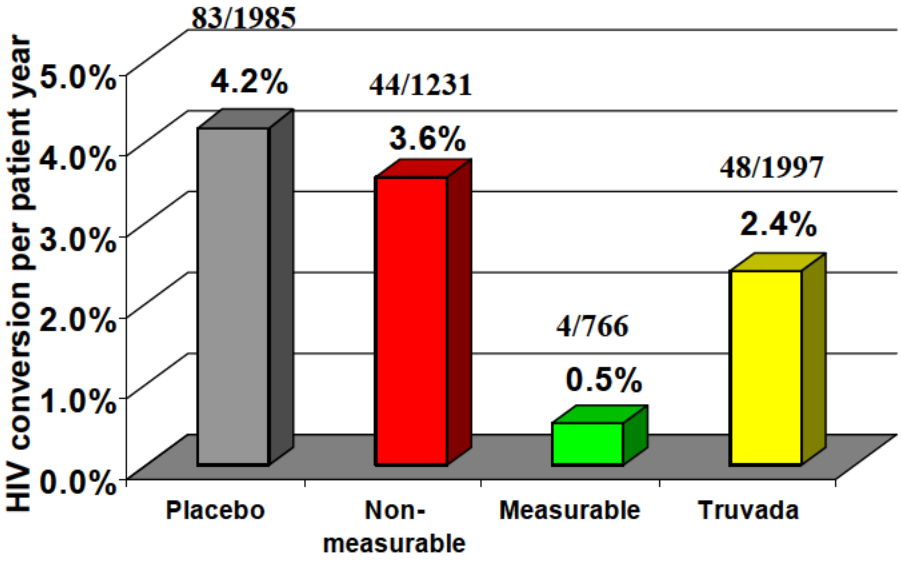
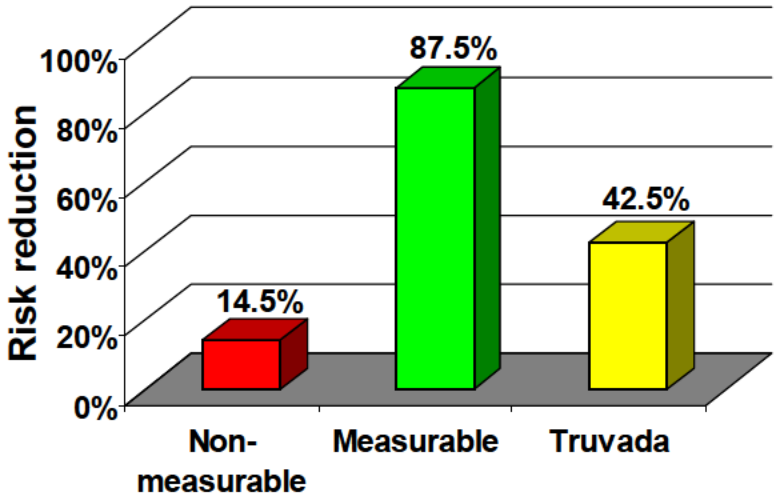


Figure 3: Relative risk reduction in acquiring HIV infection (compared with placebo) based on intracellular TFV-DP status (iPrEx).

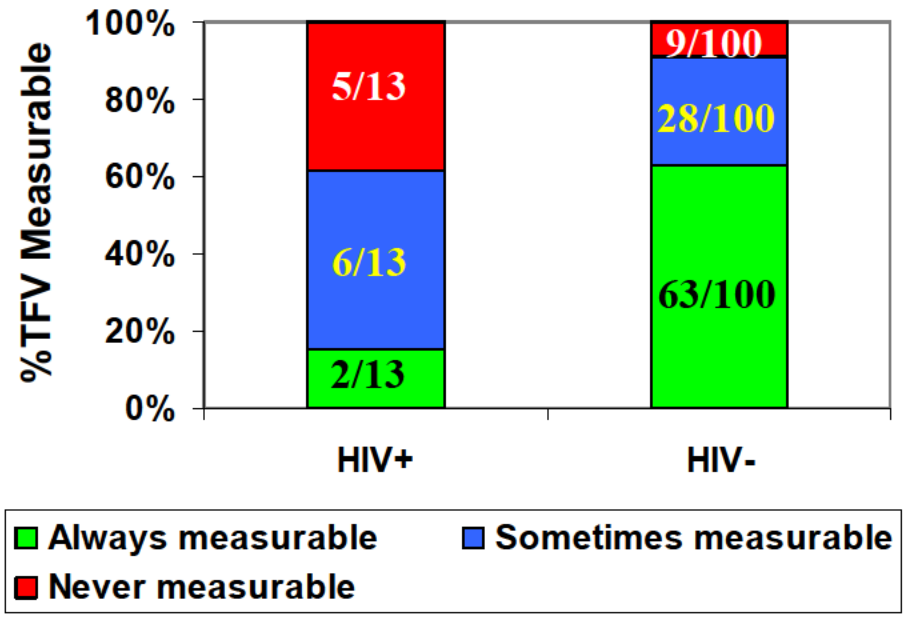


1.1.2 What is exposure-relative risk reduction relationship for FTC/TDF in HIV uninfected partners in serodiscordant couples in Partners PrEP study?

The case-cohort sub-study within the Parterns PrEP study was designed to evaluate tenofovir/ emtricitabine exposure on protection from HIV-1 infection. In this study, only plasma samples were collected at multiple visits (PK visits at Month 1, 3, 6, 12, 18, 24, 30, and 36) and at the conversion visit. Tenofovir plasma concentrations are available from all 17 and 13 (one subject in the FTC/TDF group did not have a sample available

and was imputed by the sponsor as not measurable; this subject was found to have seroconverted to HIV-1 at the Month 23 visit and had not attended any other study visits since enrollment) seroconverted cases receiving TDF and FTC/TDF respectively. 100 randomly selected cohorts of the HIV- subjects within each of the active treatment group also provided plasma samples. This case-cohort subgroup was classified into three categories: always measurable (for those whose samples are all measurable), never measurable (for those whose samples are never measurable), and sometimes measurable (those in between). As shown in Figure 4, HIV- subject had a much higher percentage of always measurable (63%) compared to the HIV-infected subjects (15%), indicating a better adherence in the HIV- subjects.

Figure 4: Percentage of subjects with plasma tenofovir concentrations that were always measurable, sometimes measurable, or never measurable, by seroconversion status (Partners PrEP, FTC/TDF treatment group only).



In order to assess the impact of drug adherence on efficacy in the Partners PrEP, the distribution of TFV measurable status within the 100 HIV-uninfected subjects (63% always measurable, 28% sometimes measurable, and 9% never measurable) was extrapolated to the entire 1566 HIV-uninfected subjects treated with FTC/TDF in Parterns PrEP. As demonstrated in Figure 5, the seroconversion rate in the FTC/TDF group with never measurable TFV level is 2.1% which is not significantly different from the observed 2% event rate in the placebo group. For subjects with sometimes measurable TFV level, the seroconversion rate was 0.8%. For subjects with always measurable TFV level, the seroconversion rate was 0.1%. These absolute conversion rates can be used to calculate the risk reduction relative to the placebo group. The FTC/TDF group with never measurable TFV level has no additional protection from HIV infection compared to placebo. The risk reduction in subjects with sometimes measurable TFV levels is 59%.

And the risk reduction in subjects with always measurable TFV level is 94% (Figure 6). This finding is consistent with what was shown for iPrEx trial.

Figure 5: Seroconversion event rates in placebo and FTC/TDF groups (Partners PrEP).

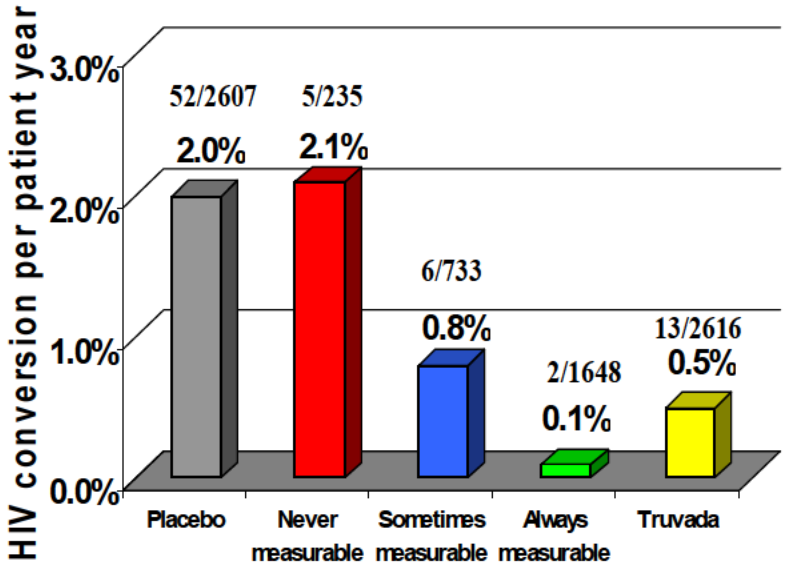
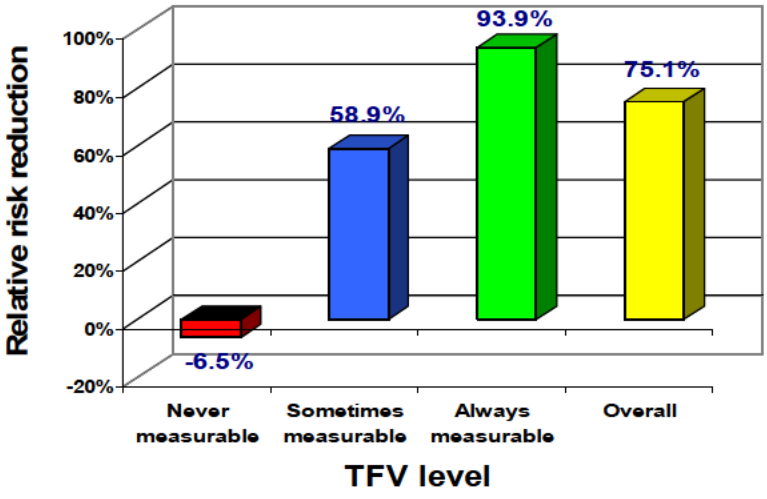


Figure 6: Relative risk reduction in acquiring HIV infection (compared with placebo) based on plasma TFV status (Partners PrEP).



1.2 Recommendations

Medication adherence is critical for the proposed indication of pre-exposure chemoprophylaxis for HIV. Subjects should adhere to the proposed once-a-day regimen as much as possible to achieve the optimal risk reduction for HIV-1 infection.

2 PERTINENT REGULATORY BACKGROUND

Truvada is the brand name for the fixed-dose combination tablet that contains the active substances emtricitabine (FTC; Emtriva®, 200 mg), an HIV-1 nucleoside reverse transcriptase inhibitor (NRTI), and tenofovir disoproxil fumarate (TDF; Viread®, 300 mg), a nucleotide analog reverse transcriptase inhibitor (NtRTI). Truvada was granted marketing approval in 2004 for the treatment of HIV-1-infected adults, and it now is the most commonly prescribed NRTI/NtRTI backbone for treatment of HIV-1 infection in the US.

The currently submission, NDA 21752 Supplement 030, is for use of Truvada® in the setting of HIV-1 pre-exposure prophylaxis (PrEP). Two pivotal efficacy studies (Study #CO-US-104-0288 [known as the Pre-exposure Prophylaxis Initiative or "iPrEx Study"] and Study CO-US-104-0380 [known as the "Partners PrEP Study"]) provided the principal data sources for the sNDA.

The iPrEx Study is a large (n = 2499), randomized, placebo-controlled, double-blind, Phase 3 efficacy study designed to determine if daily oral FTC/TDF reduced HIV-1 seroincidence compared with placebo among HIV-1 uninfected MSM. The study is sponsored by the US National Institutes of Health (NIH), with cofunding provided by the Bill and Melinda Gates Foundation. Protocol oversight is provided by the Gladstone Institute of Virology and Immunology, an independent, non-profit biomedical research foundation affiliated with the University of California, San Francisco (UCSF) in San Francisco, California, United States, and Investigaciones Medicas en Salud in Lima, Peru.

The Partners PrEP Study is a large (n = 4747 couples), multinational (Kenya and Uganda), randomized, placebo-controlled, double-blind, Phase 3 efficacy study designed to evaluate the efficacy of daily PrEP with Viread or Truvada, compared with placebo, in preventing HIV-1 acquisition among the HIV-1 uninfected partner within stable, heterosexually active, serodiscordant couples and to assess the safety of daily PrEP using Viread or Truvada versus placebo by comparing rates of AEs among HIV-1-uninfected individuals. The study is sponsored by the Bill and Melinda Gates Foundation. The University of Washington assumed sponsor oversight responsibilities for the study.

3 RESULTS OF SPONSOR'S ANALYSIS

In the primary mITT efficacy analysis for iPrEx, emergent HIV-1 infections were observed postbaseline in 48 subjects in the FTC/TDF group and 83 subjects in the placebo group, representing a relative reduction in HIV-1 infection of 42% (95% CI: 18% to 60%) (Table 1). For Partners PrEP study, 17, 13 and 52 HIV-1 seroconversions occurred in TDF, FTC/TDF, and placebo treatment groups, respectively. The HRs for

TDF relative to placebo indicated a 67% reduction (95% CI: 44%–81%) in risk of HIV-1 acquisition, and the HRs for FTC/TDF relative to placebo indicated a 75% reduction (95% CI: 55%–87%) in risk of HIV-1 acquisition (Table 2).

Table 1. CO-US-104-0288: Relative Risk Reduction through the End of Treatment and through the End of Treatment Plus 8 Weeks, (iPrEx mITT and ITT Analyses)

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

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

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

b P-values by logrank test.

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

Source: Sponsor's CO-US-104-0288 Addendum report, Table 4-1, page 17

Table 2. CO-US-104-0380: HIV-1 Seroincidence and Relative Risk Reduction through the End of Treatment, (Partner Study mITT Analyses)

	TDF (N=1579)	FTC/TDF (N=1576)	Placebo (N=1578)	Total (N=4733)
Seroconversions, n	**17**	**13**	**52**	**82**
Person-years of follow-up	**2604**	**2616**	**2607**	**7827**
Incidence per 100 person-years (95%CI)	**0.65 (0.38, 1.05)**	**0.5 (0.27, 0.85)**	**1.99 (1.49, 2.62)**	**1.05 (0.83, 1.30)**
Relative Risk Reduction (%) (95%CI)	**67 (44, 81)**	**75 (55, 87)**		

Source: Sponsor's CO-US-104-0380 report, Table 9-1 and 9-2, page 66

In the iPrEx case-control study, greater efficacy was observed in subjects who were known to have taken study drugs as determined by objective drug concentration testing. Drug is considered detected at a time point if a quantifiable value is found in the plasma (TFV or FTC) or in the peripheral blood (TFV-DP or FTC-TP). As shown in Table 3, drug was detected in 63 of 144 HIV-negative subjects (44%) and in 5 (PTID: 92-1263-7 was counted as having detectable drug at the time of his infection) of 48 HIV-infected subjects (10%) (P<0.001). Conditional logistic regression mimicking a Cox proportional hazards model among participants on the active arm demonstrated that quantifiable drug level reduced the risk for HIV-1 seroconversion by 90% (95% CI, 71 to 98; P<0.001).

After adjustment for potential confounders (i.e., URAI at screening, URAI at the time of the specimen, total number of sex partners at screening, age, secondary education and body mass index), the relative risk reduction was 87% (95% CI, 59% to 97%; P<0.001) (Table 4). Case 92-1263-7 had detected drug level at Ab+ visit, however he had plasma on drawn on the date he was RNA positive but antibody negative and no drug was detected. Counting 92-1263-7 as not having drug detected demonstrated that quantifiable drug level reduced the risk for HIV-1 seroconversion by 94% (or 92% after adjustment for potential confounders).

Similarly, in the Partners PrEP case-cohort study, 35.3% of those in the TDF group (6 of the 17 subjects) and 25.0% of those in the FTC/TDF group (3 of 12 subjects) had detectable plasma tenofovir at the seroconversion visit. By comparison, 83.1% of the samples tested from uninfected partner subjects in the TDF group (363 of 437 samples) and 80.6% of the samples tested from uninfected partner subjects in the FTC/TDF group (375 of 465 samples) had detectable plasma tenofovir (Table 5). Overall, for partner subjects in the TDF group, having a detectable level of tenofovir, as compared with an undetectable level, was associated with an 86% reduction in HIV-1 risk (95% CI 67%–95%; p < 0.001). For the partner subjects in the TDF/FTC group, having a detectable level of tenofovir, as compared with an undetectable level, was associated with a 90% reduction in HIV-1 risk (95% CI 56%–98%; p = 0.002).

Table 3. A simple tabulation of drug detection among cases (iPrEx Case-Control)

	Drug Detected in Plasma and/or PBMC	
	Yes	No
Cases	5 (10%)	43 (90%)
Controls	63 (44%)	81 (56%)

p-value by two-sided Fisher exact test = 0.000019 (1.9×10^{-5})

Source: Sponsor's case-control report, Analysis 5.1, page 12

Table 4. Conditional logistic regressions indicate drug detection correlated with efficacy (iPrEx Case-Control)

Analysis	% Risk Reduct.	95% Conf Interval**	p-value***
5.2	90%	71% to 98%	1.4×10^{-6}
5.3	90%	67% to 98%	1.7×10^{-5}
5.4	87%	59% to 97%	1.3×10^{-4}

* % Reduction in HIV Risk = 100*(1-exp(-β)) comparing those randomized to FTC/TDF with a detected drug level to those without a detected drug level using a conditional logistic regression model

** Likelihood ratio based confidence interval for % risk reduction for analyses 5.2 and 5.4. Exact confidence interval for % risk reduction for analysis 5.3.

*** p-value for likelihood ratio test of H_0: β=0 for analyses 5.2 and 5.4. Exact score test for analysis 5.3.

Note: 5.2 – a conditional logistic regression

5.3 – an exact conditional logistic regression

5.4 – a conditional logistic regression with adjustment for potential confounders

Source: Sponsor's case-control report, Analysis 5.2 to 5.4, page 12

Table 5. Detection of Tenofovir in Plasma and HIV-1 Prophylactic Effects (Partners PrEP Case-Cohort)

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

Source: Sponsor's CO-US-104-0380 report, Table 10-1, page 72

Reviewer's Comments: The sponsor's analyses demonstrated greater efficacy in subjects who had better adherence as determined by measurable drug concentration compared to those without measurable drug concentration. We were able to reproduce the point estimates of risk reduction, but the 95% confidence intervals are slightly different. We did a modified version of the conditional logistic regression for iPrEx only using intracellular TFV-DP above limit of quantification to define measurable because of its long half life (87-150 hours) as a better marker for long-term adherence. As a result, we

got 83-86% relative risk reduction. Our results are slightly lowers numbers but overall consistent with the application's results. However, those analyses cannot provide the absolute event rate for either the non- measurable or the measurable group and cannot use the placebo group as a reference to derive the risk reduction relative to placebo.

4 REVIEWER'S ANALYSIS

4.1 Introduction

This is first submission for the indication of pre-exposure chemoprophylaxis for HIV prevention in populations at high risk of acquiring HIV infection. The daily fixed-dose combination of emtricitabine (FTC, 200 mg) and tenofovir (TDF, 300 mg) for the proposed indication is same as the approved regimen for the treatment of HIV-1-infected adults. A thorough review of the exposure-response relationships focusing on efficacy was performed.

4.2 Objectives

- Provide evidence of drug effectiveness based on exposure-response analyses
- Demonstrate the consequence of poor-compliance
- Explore baseline factors that may affect drug compliance

4.3 Methods

4.3.1 Data Sets

Data sets used are summarized in Table 6.

Table 6. Analysis Data Sets

Study Number	Name	Link to EDR
iPrEx Case-Control	druglev.xpt	\\Cdsesub1\evsprod\NDA021752\0396\m5\datasets\co-us-104-0288-addendum\analysis\datasets\data-feb2012\
iPrEx Time-to-Event	update.xpt	\\Cdsesub1\evsprod\NDA021752\0396\m5\datasets\co-us-104-0288-addendum\analysis\datasets\data-feb2012\
iPrEx Risk Behavior	behrisk.xpt	\\Cdsesub1\evsprod\NDA021752\0396\m5\datasets\co-us-104-0288-addendum\tabulations\legacy\data-feb2012\
Partners PrEP Case-Cohort	adconc.xpt	\\Cdsesub1\evsprod\NDA021752\0396\m5\datasets\co-us-104-0380\analysis\datasets\
Partners PrEP Time-to-Event	keyvars.xpt	\\Cdsesub1\evsprod\NDA021752\0396\m5\datasets\co-us-104-0380\analysis\datasets\

4.3.2 Software

SAS and R were used for the reviewer's analyses.

4.3.3 Models and Results

4.3.3.1 Exposure- relative risk reduction analyses

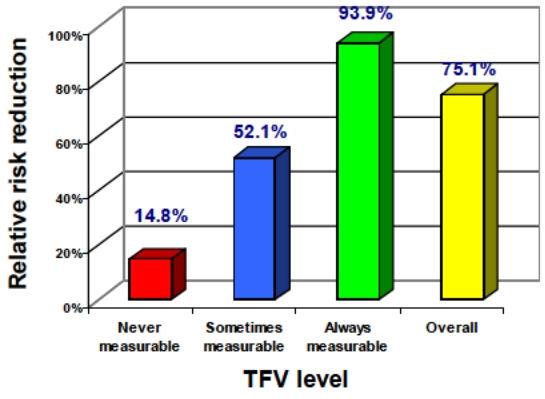
As shown in Figure 1-Figure 3, exposure-response analyses based on the simple distribution method provide strong evidence of drug effectiveness:

- Poor drug compliance (TFV-DP not measurable in iPrEx or TFV never measurable in Partners PrEP) provided very limited risk reduction;
- Better drug compliance (Measurable TFV-DP in iPrEx or TFV always measurable in Partners PrEP) was associated with ~90% relative risk reduction relative to placebo.

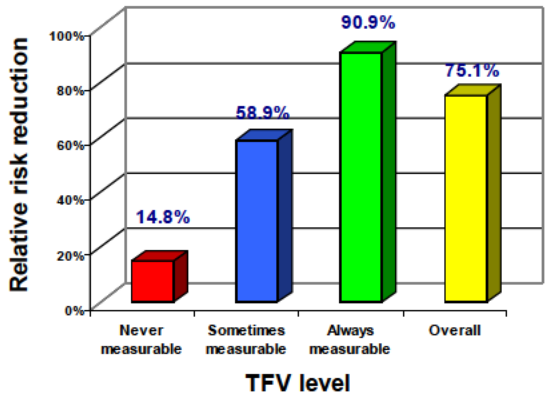
As mentioned in the summary section, one seroconversion with FTC/TDF in Partners PrEP (PTID: 5017613) did not have a sample available and was imputed by the sponsor as not measurable. We also performed sensitivity analyses by imputing its PK status as sometime measurable or always measurable. As shown in Figure 7, the relative risk reduction is reasonable consistent for different imputation methods, except that the never measurable cohort may also provide limit risk reduction (14.8% vs. -6.5% as previously estimated) which is quite similar to the risk reduction from the non-measurable cohort in iPrEx (14.5%).

Figure 7. Relative risk reduction in acquiring HIV infection (Partners PrEP) based on plasma TFV status (sensitivity analyses)

Impute 5017613 as Sometimes measurable



Impute 5017613 as Always measurable



We also conducted exploratory analyses to identify baseline factors that may affect adherence based on the intracellular TFV-DP concentrations. Age, education, URAI

status at screening, number of sex partners were found be numerically (more than 10% difference) associated with adherence; baseline HSV-2 status was suggested by the medical reviewers (Figure 8). Since these relationships were identified from the 133 HIV- subjects, we tried to confirm whether these relationships were consistent in the overall population from a risk reduction perspective. As shown in Table 7, the subgroups with higher adherence show greater risk reduction. For the combination of three factors (older than 25, higher education, and reported URAI at screening) representing a better adherence subgroup, the risk reduction is 85.4% relative to the corresponding placebo subgroup.

Figure 8. Factors affecting compliance (iPrEX)

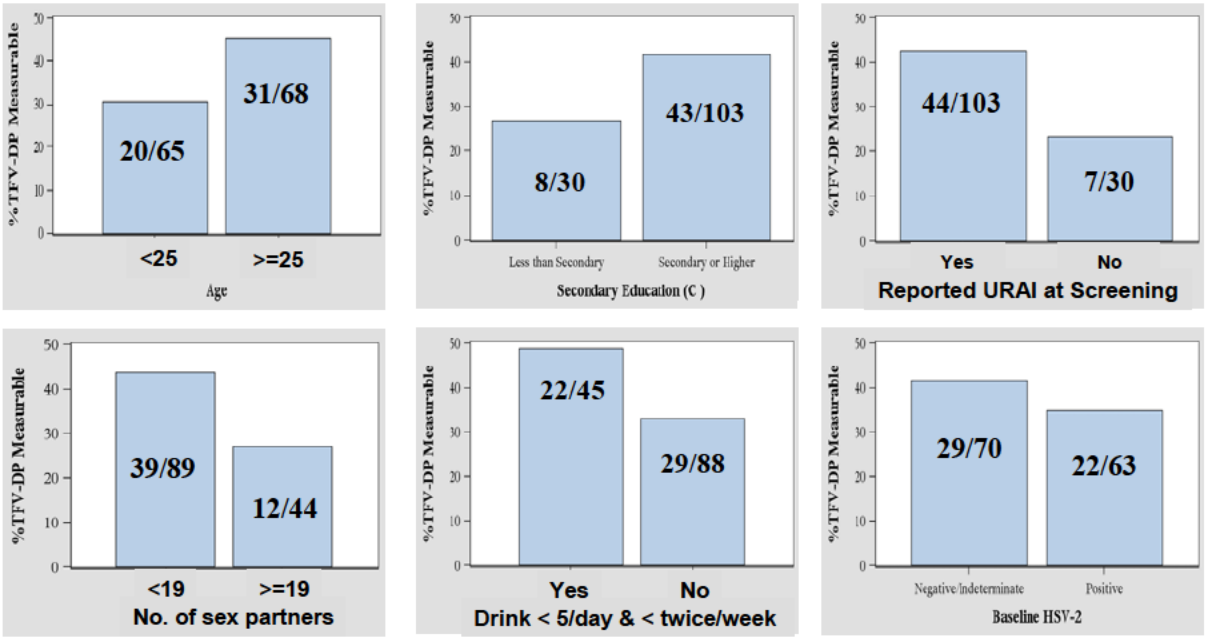


Table 7. Risk reduction appears greater in subgroups with higher adherence (iPrEx)

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

There are caveats of the exposure-efficacy analyses based on the inference of proportion of measurable or non-measurable TFV-DP from the case-control sub-study to the entire HIV-uninfected subjects treated with FTC/TDF in iPrEx given that the control subgroup was not randomly sampled but selected to match those cases:

- Do the controls in the case-control sub-study represent the entire HIV- FTC/TDF treatment group with respect to factors affecting the adherence?
  - As shown in Table 8, two factors affecting the adherence, URAI at screening and Number of sex partners. were not well balanced between the small control subgroup and the entire HIV- FTC/TDF treatment group. Therefore, the estimated event rate might be biased.
- Are the two subgroups (measurable and non-measurable) in the active arm comparable to the overall placebo group in terms of baseline risk factors for HIV-infection in order to estimate the risk reduction relative to placebo group?
  - Certain risk factors such as URAI at screening, number of sex partners and age (Table 9) are not well balanced between the two subgroups and the overall placebo group. There is a need to identify corresponding subgroups in placebo with balanced risk factors for seroconversion to match the distribution of risk factors in the two subgroups from the active arm.

Table 8. Comparison between the controls from the case-control sub-study and the entire HIV- FTC/TDF treatment group with respect to factors affecting the adherence (iPrEx)

Baseline Characteristic	Truvada PBMC Control group (n=133)	Truvada treatment HIV- group (n=1,176)	P-Value
Age: ≥25	68 (51%)	624 (53%)	0.7142
Education: ≥ Secondary	103 (77%)	904 (77%)	1
URAI at screening: Yes	103 (77%)	689 (59%)	<0.0001
No. of sex partner: <19	89 (67%)	938 (80%)	0.0012
Drink: ≤ 5/day and ≤2 times/week	45 (34%)	408 (35%)	0.9234
BLHSV: No	70 (53%)	743 (63%)	0.0186

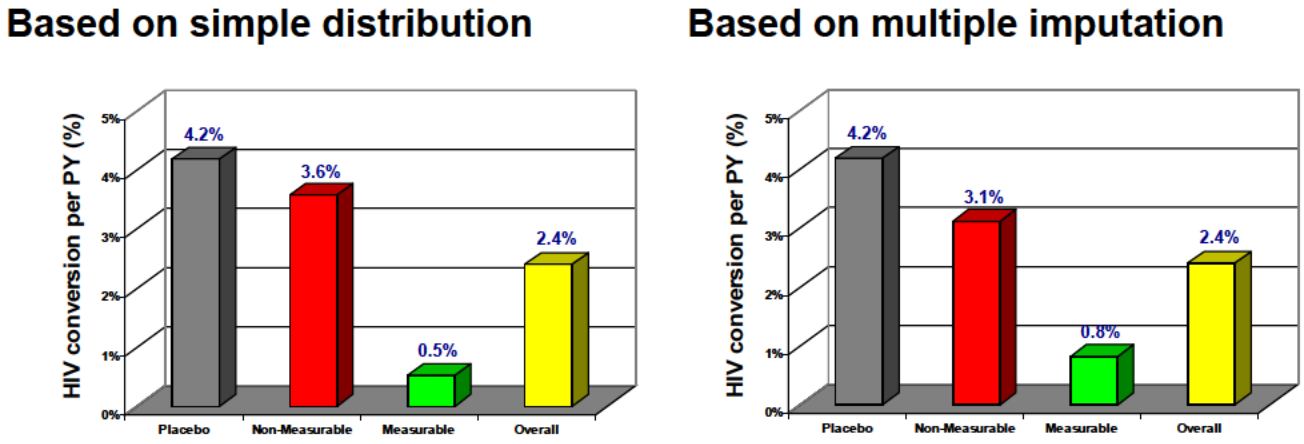
Note: P-value is from Fisher's exact test.

To evaluate the effect of imbalanced factors on the event rate estimation, sensitivity analyses using a multiple imputation approach were performed, i.e.:

1. Treat the TFV-DP status of the HIV- subjects treated with FTC/TDF who have no PK measurement as missing data
2. Impute the missing TFV-DP status according to their baseline factors based on a logistic model including all factors affecting compliance (i.e., age, education, URAI at screening, number of sex partners, drink, and baseline HSV-2 status). Procedure MI in SAS was used for this purpose
3. Calculate the event rate based on the observed TFV-DP status and imputed TFV-DP status
4. Repeat the above imputation 50 times and summarize the relevant statistics. Procedure MIANALYZE in SAS was used to derive the point estimates and their associated 95% confidence interval.

As shown in Figure 9, sensitivity analysis based on the multiple-imputation approach indicates the estimated conversion rates are 3.1% and 0.8% for TFV-DP non-measurable and measurable respectively, which is reasonably comparable to 3.6% and 0.5% from the simple distribution method presented previously.

Figure 9. Comparison of the sero-conversion rate estimated from the simple distribution method and the multiple imputation method



To address the second caveat, i.e., the relative risk reduction rate over a corresponding subgroup of placebo, sensitivity analyses based on the propensity score matching were performed. As shown in Figure 10, for subjects treated with placebo, URAI at screening, number of sex partners and age were risk factors for seroconversion. Comparing the TFV-DP measurable or non-measurable subgroup to the overall placebo group indicated some imbalanced distribution for the above risk factors (Table 9). After propensity score matching, the risk factors were well balanced between the TFV-DP measurable or non-measurable subgroup and their corresponding (matched) subgroup in placebo (Table 10). The placebo subgroup matching the non-measurable subgroup in the active arm showed a lower conversion rate (3.8%) than the placebo subgroup matching the measurable subgroup in the active arm (5%). The relative risk reduction over the corresponding (matched) placebo subgroup is 18.3% and 83.6% for TFV-DP non-measurable and measurable respectively, which is reasonably comparable to 14.5% and 87.5% presented previously based on the comparison against the overall placebo group (Figure 11).

Given the large proportion of missing data on TFV-DP status (90%), further sensitivity analyses were conducted to evaluate the impact of the number of imputations on the outcome. Up to 200 imputations were explored and the results are relatively stabilized after 50 imputations (Figure 12).

Figure 10: Risk factors for seroconversion (iPrEx).

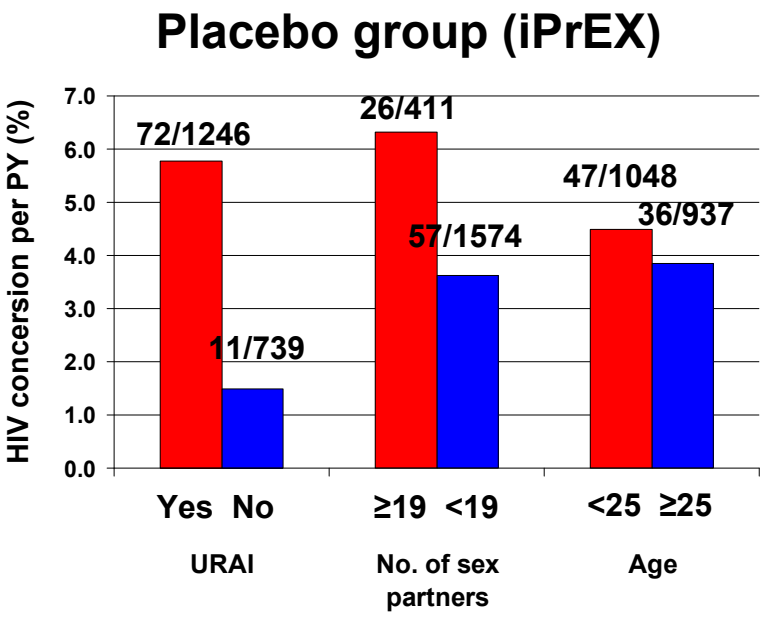


Table 9. Comparison between the TFV-DP measurable or non-measurable subgroup and the overall placebo group with respect to the risk factors of seroconversion (iPrEx)

Baseline Characteristic	TFVDP Measurable (n=319)	TFVDP Not Measurable (n=905)	Truvada (n=1224)	Placebo (n=1218)
URAI at screening: Yes	66.0%	57.0%	59.1%	60.0%
No. of sex partner: <19	84.6%	77.0%	79.0%	80.5%
Age: ≥25	58.9%	50.2%	52.5%	46.8%

Table 10. Comparison between the TFV-DP measurable or non-measurable subgroup and the corresponding placebo subgroup with respect to the risk factors of seroconversion after propensity score matching (iPrEx)

Baseline Characteristic	TFVDP Measurable (n=319)	Placebo Matching Measurable (n=319)	TFVDP Not Measurable (n=905)	Placebo Matching Not Measurable (n=899)
URAI at screening: Yes	66.0%	65.5%	57.0%	58.4%
No. of sex partner: <19	84.6%	84.6%	77.0%	79.1%
Age: ≥25	58.9%	58.9%	50.2%	42.5%

Figure 11. Sero-conversion rate (left) and relative risk reduction over the corresponding placebo subgroup (right) after multiple-imputation and propensity score matching sensitivity analyses

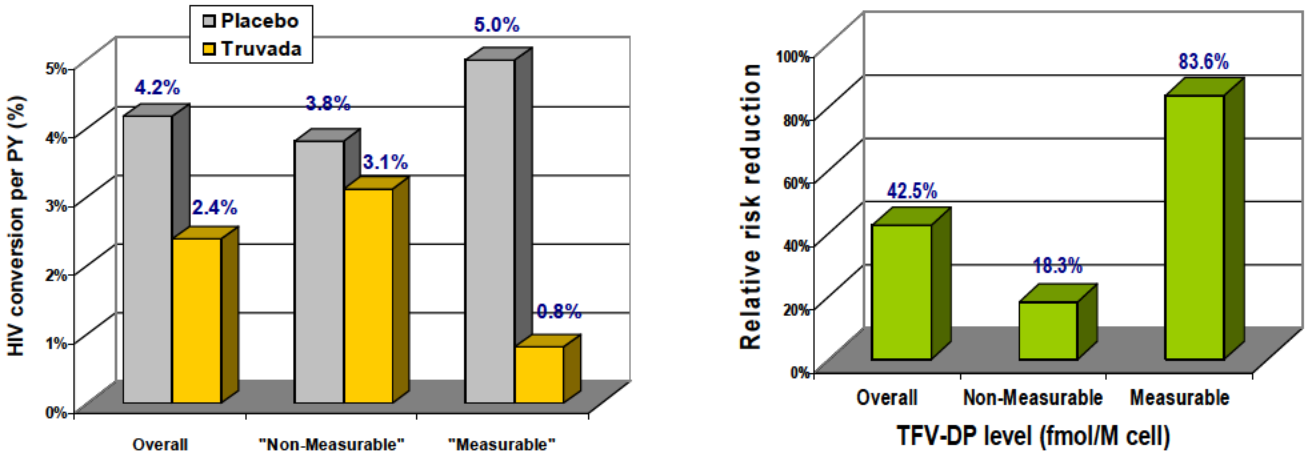
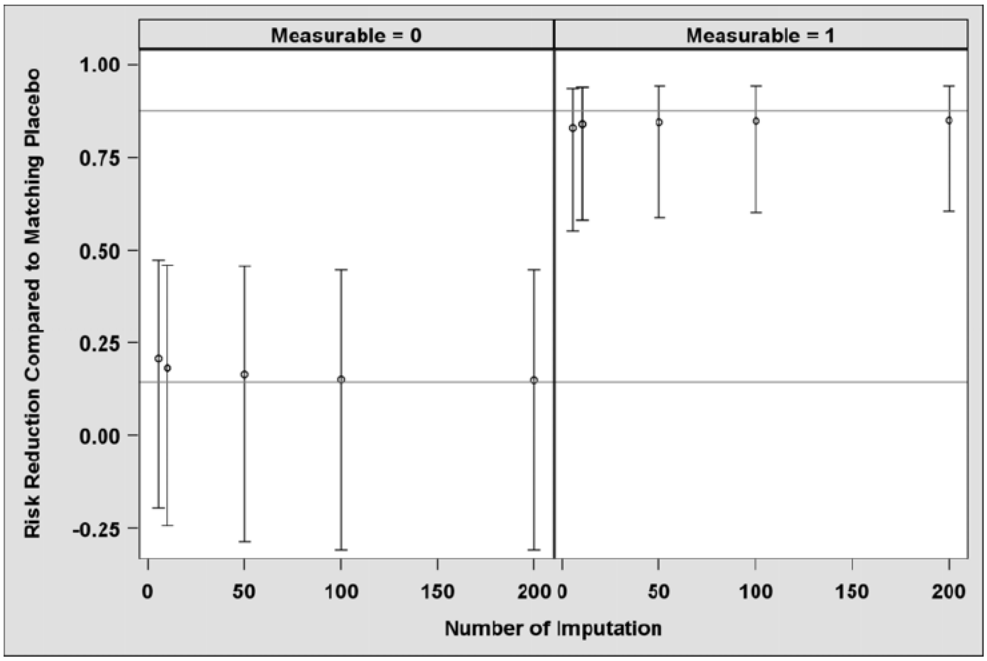


Figure 12. Impact of the number of imputations on the relative risk reduction estimation from the sensitivity analysis (iPrEx)



Even though only 133 HIV-uninfected subjects provided PK samples for the case-control sub-study, additional HIV-uninfected subjects provided PK samples for other purposes, such as for immunology sub-study. 238 additional HIV-uninfected subjects were identified from a data set that includes all subjects that provided PK samples in iPrEx. With these additional subjects with PK samples, the proportion of HIV-uninfected subjects with measurable TFV-DP was estimated to be 57-60% when all data from 371

HIV-uninfected subjects were used. Again, the additional data from 238 subjects confirmed that the initial estimate of 62% measurable TFV-DP based on the simple distribution method was reasonable.

4.3.3.2 The effect of adherence or dosing frequency on relative risk reduction

The exposure-risk reduction relationship in iPrEx was further explored by breaking the TFV-DP measurable group into low measurable and high measurable based on the median TFV-DP level of 15.6 fmol/M cell. As shown in Figure 13, the low measurable has 1% conversion rate while the high measurable group had 0% conversion rate. As a result, the risk reduction is 75.5% for the low measurable group and 100% (this is a point estimate with uncertainty, see Table 11) for the high measurable group, suggesting better adherence based on intracellular TFV-DP is associated with greater efficacy.

The effect of intermittent dosing on risk reduction was also explored. According to STRAND study provided by Dr. Peter L. Anderson, the median steady state TFV-DP levels are 11, 32 and 42 fmol/M Cell for 2 doses/week, 4 doses/week, and 7 doses/week respectively. Using the median level of 2 doses/week (11 fmol/M cell) as the cut-off, the low TFV-DP measurable (<11 fmol/M cell) has 1% conversion rate while the high measurable group (≥11 fmol/M cell) had 0.2% conversion rate. As a result, the risk reduction is 76.1% for the low measurable group (<11 fmol/M cell) and 94.9% for the high measurable group, suggesting dosing frequency higher than 2 times/week will provide greater efficacy than dosing frequency less than 2 times/week(Figure 14).

Figure 13. Better adherence by intracellular TFV-DP levels is associated with greater efficacy (iPrEx)

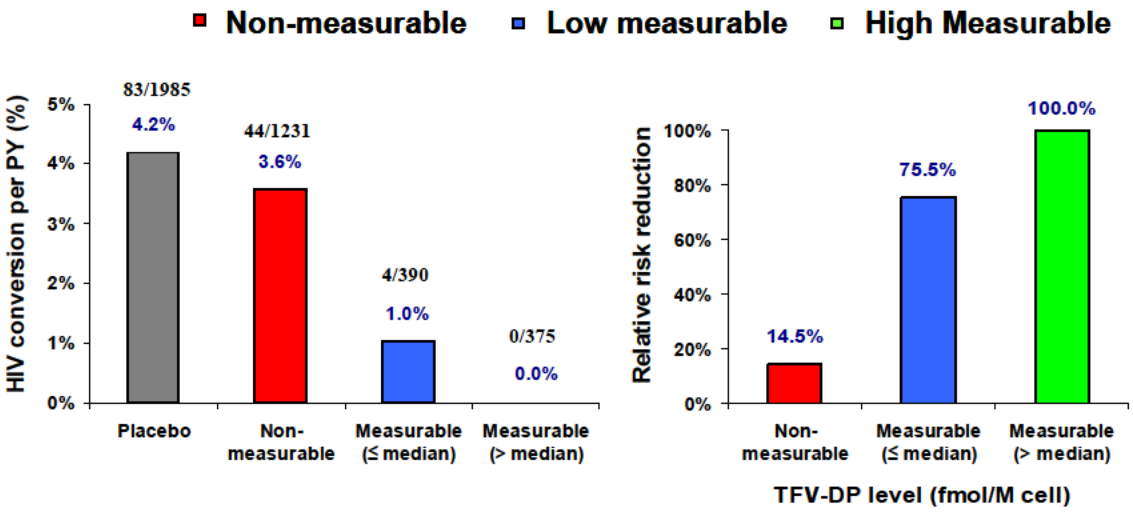


Figure 14. Dosing frequency higher than 2 time/week (by median TFV-DP level of 11 fmol/M cell) may provide greater efficacy (iPrEx)

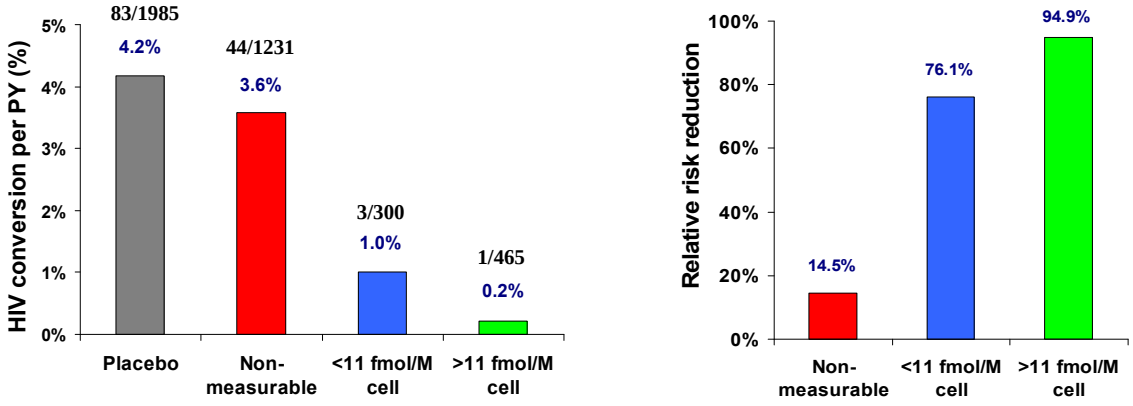


Table 11. Summary of the 95%CI of the conversion rate and risk reduction estimated from the simple distribution method and the sensitivity analysis method

Study	Group	Conversion rate	95%CI_Low	95%CI_High	Risk Reduction	95%CI_Low	95%CI_High
iPrEx	Non-Measurable	3.6%	2.5%	4.6%	14.5%	-22.3%	40.3%
iPrEx	Measurable	0.5%	0.0%	1.0%	87.5%	66.1%	95.4%
iPrEx	Measurable (≤median)	1.0%	0.0%	2.0%	75.5%	33.5%	91.0%
iPrEx	Measurable (>median)	0.0%	0.0%	0.6%*	100.0%	60.0%*	100.0%
Partners	Never measurable	2.1%	0.2%	4.0%	-6.5%	-164.5%	57.0%
Partners	Sometimes measurable	0.8%	0.2%	1.5%	58.9%	4.8%	82.3%
Partners	Always measurable	0.1%	0.0%	0.3%	93.9%	75.1%	98.5%
Sensitivity analyses:							
IPrEx_MI_PS	Non-Measurable	3.10%	2.1%	4.1%	18.3%	-26.1%	47.0%
IPrEx_MI_PS	Measurable	0.80%	0.2%	1.4%	83.8%	56.2%	94.0%

*CI was approximately estimated by adding one event to the group.

5 LISTING OF ANALYSES CODES AND OUTPUT FILES

Table 12. Analysis Codes and Output Files

File Name	Description	Location in \\cdsnas\pharmacometrics\Reviews\Ongoing PM Reviews\
drugExp.sas	ER for iPrEx	TruvadaPrEP_NDA21752_JL \ER Analyses
boxplotScatterOverlay_TFVDPByConverter.r	Boxplot the TFV-DP level by HIV status	TruvadaPrEP_NDA21752_JL \ER Analyses
casecontrolsponsor.sas	Confirm conditional logistic analyses from the sponsor	TruvadaPrEP_NDA21752_JL \ER Analyses
Study380_measurable.sas	ER for Partners PrEP	TruvadaPrEP_NDA21752_JL \ER Analyses
Study380_safety.sas	safety analysis for Partners PrEP	Darunavir_NDA202895_JL\ER Analyses
CDFPlot_M.sas	SAS macro for cumulative distribution plots	TruvadaPrEP_NDA21752_JL \ER Analyses
RiskReductionCI_ProcFreq.sas	Calculating confidence interval of a risk reduction	Darunavir_NDA202895_JL\ER Analyses
MIcasecontrolFinalcorrect.sas	Multiple imputation codes for sensitivity analyses	TruvadaPrEP_NDA21752_JL \ER Analyses
MacroOneToManyMatch.sas	Matching codes for sensitivity analyses	TruvadaPrEP_NDA21752_JL \ER Analyses

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This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

RUBEN C AYALA
05/25/2012

JIANG LIU
05/27/2012

YANING WANG
05/27/2012
I am signing only for the Pharmacometric review.

SHIRLEY K SEO
05/29/2012

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

Office of Clinical Pharmacology

New Drug Application Filing and Review Form

General Information About the Submission

	Information		Information
NDA/BLA Number	NDA021752	**Brand Name**	Truvada
OCP Division (I, II, III, IV, V)	IV	**Generic Name**	Emtricitabine/Tenofovir DF
Medical Division	DAVP	**Drug Class**	Nucleos(t)ide reverse transcriptase inhibitors
OCP Reviewer	Ruben Ayala	**Indication(s)**	Prophylaxis of HIV-1 infection
Acting OCP Team Leader	Shirley Seo	**Dosage Form**	Tablet containing 200 mg emtricitabine + 300 mg tenofovir DF
Pharmacometrics Reviewer	None	**Dosing Regimen**	Once daily
Pharmacogenomics Reviewer	None	**Route of Administration**	Oral
Date of Submission	12/15/2011	**Sponsor**	Gilead Sciences
Estimated Due Date of OCP Review	05/21/2012	**Priority Classification**	Priority review
PDUFA Due Date	06/15/2012		

Clin. Pharm. and Biopharm. Information

	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	**X**	**2**		
Tabular Listing of All Human Studies	**X**	**2**		
HPK Summary				
Labeling	**X**	**1**		
Reference Bioanalytical and Analytical Methods				**We will request validation reports for two bioanalytical methods used in the Phase 3 studies to analyze drug levels in plasma and PBMCs.**
I. Clinical Pharmacology				
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose:				
multiple dose:				
Patients-				
single dose:				
multiple dose:	**X**	**2**		**Study populations consisted of non-HIV-infected subjects who are at high risk for acquiring HIV infection**
Dose proportionality -				
fasting / non-fasting single dose:				
fasting / non-fasting multiple dose:				

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS
FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

Drug-drug interaction studies -				
In-vivo effects on primary drug:				
In-vivo effects of primary drug:				
In-vitro:				
Subpopulation studies -				
ethnicity:				
gender:				
pediatrics:				
geriatrics:				
renal impairment:				
hepatic impairment:				
PD -				
Phase 2:				
Phase 3:				
PK/PD -				
Phase 1 and/or 2, proof of concept:				
Phase 3 clinical trial:				
Population Analyses -				
Data rich:				
Data sparse:				
II. Biopharmaceutics				
Absolute bioavailability				
Relative bioavailability -				
solution as reference:				
alternate formulation as reference:				
Bioequivalence studies -				
traditional design; single / multi dose:				
replicate design; single / multi dose:				
Food-drug interaction studies				
Bio-waiver request based on BCS				
BCS class				
Dissolution study to evaluate alcohol induced dose-dumping				
III. Other CPB Studies				
Genotype/phenotype studies				
Chronopharmacokinetics				
Pediatric development plan				
Literature References				
Total Number of Studies	**X**	**2**		

On **initial** review of the NDA/BLA application for filing:

	Content Parameter	Yes	No	N/A	Comment
Criteria for Refusal to File (RTF)					
1	Has the applicant submitted bioequivalence data comparing to-be-marketed product(s) and those used in the pivotal clinical trials?			X	Both Phase 3 studies used commercial formulations (Truvada and Viread)
2	Has the applicant provided metabolism and drug-drug interaction information?			X	
3	Has the sponsor submitted bioavailability data satisfying the CFR requirements?			X	
4	Did the sponsor submit data to allow the evaluation of the validity of the analytical assay?		X		We will request validation reports for two bioanalytical methods used in the Phase 3 studies to analyze drug levels in plasma and PBMCs.

File name: 5_Clinical Pharmacology and Biopharmaceutics Filing Form/Checklist for NDA_BLA or Supplement 090808

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

5	Has a rationale for dose selection been submitted?	X			
6	Is the clinical pharmacology and biopharmaceutics section of the NDA organized, indexed and paginated in a manner to allow substantive review to begin?	X			
7	Is the clinical pharmacology and biopharmaceutics section of the NDA legible so that a substantive review can begin?	X			
8	Is the electronic submission searchable, does it have appropriate hyperlinks and do the hyperlinks work?	X			
Criteria for Assessing Quality of an NDA (Preliminary Assessment of Quality)					
	Data				
9	Are the data sets, as requested during pre-submission discussions, submitted in the appropriate format (e.g., CDISC)?	X			PK datasets are available as SAS transport files.
10	If applicable, are the pharmacogenomic data sets submitted in the appropriate format?			X	
	Studies and Analyses				
11	Is the appropriate pharmacokinetic information submitted?		X		The PK datasets are missing the time when PK samples were collected relative to Truvada dosing during clinic visits. We will request the Sponsor to provide this information (if available).
12	Has the applicant made an appropriate attempt to determine reasonable dose individualization strategies for this product (i.e., appropriately designed and analyzed dose-ranging or pivotal studies)?			X	
13	Are the appropriate exposure-response (for desired and undesired effects) analyses conducted and submitted as described in the Exposure-Response guidance?		X		
14	Is there an adequate attempt by the applicant to use exposure-response relationships in order to assess the need for dose adjustments for intrinsic/extrinsic factors that might affect the pharmacokinetic or pharmacodynamics?		X		
15	Are the pediatric exclusivity studies adequately designed to demonstrate effectiveness, if the drug is indeed effective?			X	
16	Did the applicant submit all the pediatric exclusivity data, as described in the WR?			X	
17	Is there adequate information on the pharmacokinetics and exposure-response in the clinical pharmacology section of the label?	X			

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

	General				
18	Are the clinical pharmacology and biopharmaceutics studies of appropriate design and breadth of investigation to meet basic requirements for approvability of this product?	X			
19	Was the translation (of study reports or other study information) from another language needed and provided in this submission?			X	

IS THE CLINICAL PHARMACOLOGY SECTION OF THE APPLICATION FILEABLE?
Yes

If the NDA/BLA is not fileable from the clinical pharmacology perspective, state the reasons and provide comments to be sent to the Applicant.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

At this moment, we have not identified major review issues in the submission.

Please relay the following requests to the Sponsor:

Please submit all available method validation reports and bioanalytical study reports for both Phase 3 studies used in the analysis of tenofovir and emtricitabine concentrations in plasma and PBMCs.

If available, please provide the time of blood sampling (for analysis of plasma and PBMC drug concentrations) relative to the approximate time of the previous dose of study drug for all subjects (based on direct observation or self-reporting) from whom you collected samples in both Phase 3 studies. Please include this information as a separate data column in the DRUGORIG and DRUGLVL datasets. As an alternative, you may include this information in the consolidated PK and virology dataset(s) as requested by the Clinical Virology reviewer.

Ruben Ayala, Pharm.D. 01/09/2012

Reviewing Clinical Pharmacologist Date

Team Leader/Supervisor Date

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

RUBEN C AYALA
01/18/2012

SHIRLEY K SEO
01/18/2012