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Truvada for PrEP® (FTC/TDF) Time to Protection for HIV-1 Pre-Exposure Prophylaxis

This document is in response to your request for information regarding Truvada for PrEP® (emtricitabine/tenofovir disoproxil fumarate [FTC/TDF] for HIV-1 pre-exposure prophylaxis [PrEP]) and time to protection.

This document includes content from, or references to, clinical practice guidelines, and inclusion should not be interpreted as a treatment recommendation or an endorsement of the guidelines by Gilead Sciences, Inc.

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The full indication, important safety information, and boxed warnings are available at: www.gilead.com/-/media/files/pdfs/medicines/hiv/truvada/truvada_pi.

Summary

Product Labeling[1]

The dosage of FTC/TDF for HIV-1 PrEP is one tablet (containing 200 mg of FTC and 300 mg of TDF) once daily taken orally with or without food in HIV-1 uninfected adults and adolescents weighing ≥35 kg.

Use FTC/TDF for HIV-1 PrEP to reduce the risk of HIV-1 infection as part of a comprehensive prevention strategy that includes other prevention measures, including adherence to daily administration and safer sex practices, including condoms, to reduce the risk of sexually transmitted infections. The time from initiation of FTC/TDF for HIV-1 PrEP to maximal protection against HIV-1 infection is unknown.

The effectiveness of FTC/TDF in reducing the risk of acquiring HIV-1 is strongly correlated with adherence, as demonstrated by measurable drug levels in clinical trials of FTC/TDF for HIV-1 PrEP.

PK and Modeling Data on Time to Protection of FTC/TDF for HIV-1 PrEP

In a PK substudy of participants in the ANRS PREVENIR study, testing of explants 2 hours after a double dose and one day after 7 days of single doses of FTC/TDF demonstrated risk reductions in ex vivo HIV acquisition of 80.9% and 92.2%, respectively. Reductions in p24 levels following FTC/TDF dosing were observed within each group and were similar between groups.[2]

Blood and tissue PK data and a PK model developed to predict the time required to achieve protective levels of TFV-DP and FTC-TP are described below.[3-5] The time from initiation of daily oral doses of FTC/TDF for HIV-1 PrEP to maximal protection against HIV infection is unknown.[4]

PK and Modeling Data on Time to Protection of FTC/TDF for HIV-1 PrEP

Several studies have established that the PKs of TDF and FTC vary by tissue type.[6-10]

PK Substudy of ANRS PREVENIR Study[2]

Study design

A PK substudy of participants from ANRS PREVENIR, a prospective cohort study, was conducted to assess time to protection from HIV-1 following oral FTC/TDF administration. Eligible participants (N=23) were aged ≥18 years, self-identified as MSM, and consented to a 14-day washout period from PrEP. Participants were assigned in a nonrandomized way based on arrival to receive either a single double dose (n=12) or 7 days of daily single doses (n=11) of FTC/TDF. Participants were sampled for blood, urine, and rectal tissue at each visit; tissue susceptibility to HIV in an ex vivo model was assessed at Visit 1, and the decrease in tissue susceptibility to HIV after exposure to FTC/TDF was assessed at Visit 2 (ie, either 2 hours after they received a double dose or the day after they took the seventh dose). The primary endpoint was the difference in the mean Day 14 cumulative p24 value between Visits 1 and 2.

Results

The median (IQR) washout period at Visit 1 was 48 (27–123) days. TFV was quantifiable in 3 participants (13%), and TFV-DP in DBS was quantifiable in 10 participants (48%). Neither FTC nor FTC-TP were detectable in plasma at Visit 1; however, TFV and FTC were detectable in urine at low levels in all participants. At Visit 2, the median of mean (IQR) Day 14 cumulative p24 reduction from V1 was -144 (-259 to -108) pg/mL/mg (*P*=0.0005) in the double-dose group and -179 (-253 to -86) pg/mL/mg (*P*=0.001) in the 7-day group; there was no statistically significant difference between groups (*P*=0.93). According to the moving average method at Visit 2, 10/65 explants (15.4%) in the double-dose group and 4/65 explants (6.2%) in the 7-day group were infected, representing risk reductions in ex vivo HIV acquisition of 80.9% and 92.2%, respectively (*P*=0.12).

Two hours after participants received a double dose and 7 days after they received daily doses, TFV and FTC levels in plasma were >LLoQ in all participants. Median (IQR) TFV levels were 321 (236–405) ng/mL in the double-dose group and 173 (50–320) ng/mL in the 7-day group (*P*=0.046); median (IQR) FTC levels were 2508 (2306–2807) ng/mL and 849 (59–1591) ng/mL, respectively (*P*=0.0004). TFV-DP and FTC-TP levels in PBMCs were quantifiable in all participants except 1 in each group; 4/11 participants (36.4%) in the double-dose group and 9/9 participants in the 7-day group had TFV-DP concentrations in PBMCs ≥16 fmol/10^6 cells, which is the cutoff associated with a 90% reduction in HIV-1 acquisition.

In rectal explants, TFV-DP levels were <LLoQ in all participants in the double-dose group and were quantifiable in the 9/11 participants in the 7-day group; FTC-TP was detectable in all participants and in 9/11 participants, respectively (*P*=0.47).

CDC PK Study

The CDC guidelines reference PK studies conducted in adult men and women without HIV that explore the approximate time (expressed in days of oral FTC/TDF dosing) needed to achieve steady-state levels of TFV-DP in specific tissue types (Table 1). The correlation between reaching steady-state levels and protection is unknown.[4]

Table 1. Approximate Time to Achieve Maximum Intracellular TFV-DP Concentrations[4]

Tissue	Days of Oral Dosing
Blood (PBMCs)	7 days
Rectal tissue	7 days
Cervicovaginal tissues	20 days

Another modeling study concluded that, based on the ratio of active drug metabolite to competing endogenous nucleotide concentrations achieved with daily dosing, levels of TFV-DP:dATP and FTC-TP:dCTP ratios that may correlate with protection are achieved in rectal tissue after two doses and in the female genital tract after three doses of FTC/TDF.[5]

PK Modeling on Protective Levels of FTC/TDF in Adults[3]

A PK model was developed to predict the time needed to achieve protective levels of TFV-DP and FTC-TP in the female genital tract and colorectal tissues of 47 healthy adult women. TZM-bl (also known as JC53BL-13, a CXCR4-positive HeLa cell clone engineered to express CD4 and CCR5) and CD4+ T-cells were used to identify the EC_{90} ratios of TFV-DP and FTC-TP to their competing endogenous nucleotides dATP and dCTP, respectively, needed for protection against HIV. The colorectal TFV-DP concentration was 10 times higher than that in the lower female genital tract. The model predicted that ≥98% of the population achieved protective mucosal tissue exposure by the third daily dose of FTC/TDF. However, a minimum adherence to 6/7 doses per week was required to protect lower female genital tract tissue from HIV, while adherence to 2/7 doses per week was required to protect colorectal tissue.

References

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Abbreviations

CCR5=C-C chemokine receptor type 5
CD4=cluster of differentiation 4
CDC=Centers for Disease Control & Prevention
CXCR4=C-X-C chemokine receptor type 4
dATP=deoxyadenosine triphosphate
DBS=dried blood spots
dCTP=deoxycytidine triphosphate
EC_{90}=90% effective concentration
FTC=emtricitabine
FTC-TP=emtricitabine triphosphate
LLoQ=lower limit of quantification
MSM=men who have sex with men
p24=protein 24
PBMC=peripheral blood mononuclear cell
PK=pharmacokinetic
PrEP=pre-exposure prophylaxis
TDF=tenofovir disoproxil fumarate
TFV=tenofovir
TFV-DP=tenofovir diphosphate

Product Label

For the full indication, important safety information, and boxed warning, please refer to the Truvada US Prescribing Information available at: www.gilead.com/-/media/files/pdfs/medicines/hiv/truvada/truvada_pi.

Follow Up

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FDA MedWatch Program by ☎ 1-800-FDA-1088 or ✉MedWatch, FDA, 5600 Fishers Ln, Rockville, MD 20852 or 🖱 www.accessdata.fda.gov/scripts/medwatch

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