Truvada for PrEP® (FTC/TDF) Non-Daily Dosing

This document is in response to your request for information regarding Truvada for PrEP® (emtricitabine/tenofovir disoproxil fumarate [FTC/TDF]) and non-daily dosing. This response was developed according to principles of evidence-based medicine and includes peer-reviewed clinical trial data and selected conference presentations reporting primary outcomes.

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]

FTC/TDF is indicated in at-risk adults and adolescents weighing at least 35 kg for PrEP to reduce the risk of sexually acquired HIV-1 infection. Individuals must have a negative HIV-1 test immediately prior to initiating FTC/TDF for HIV-1 PrEP.

The recommended 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.

Clinical Data

- In the IPERGAY trial, FTC/TDF on-demand dosing demonstrated an 86% relative reduction in HIV-1 infections (*P*=0.002) compared to placebo. FTC/TDF continued to be effective in the OLE phase and in a subgroup of 269 adult participants with less frequent sexual intercourse. Rates of serious AEs were similar between the two study groups.[2-5]
- In the HPTN 067 study, daily use resulted in higher sex act coverage and adherence than time- or event-driven use.[6,7]

Clinical Practice Guidelines

The “2-1-1” regimen (also called event-driven, intermittent, or on-demand) is a non-daily PrEP regimen that times oral FTC/TDF doses in relation to sexual intercourse events. While not an FDA-approved regimen, two clinical trials, IPERGAY and the subsequent Prévenir open-label study in Paris, have demonstrated the HIV prevention efficacy of 2-1-1 dosing only with FTC/TDF and only for MSM. These trials were conducted with European and Canadian adult MSM.[2-4]

The CDC, WHO, and IAS-USA recommend daily dosing of FTC/TDF for HIV-1 PrEP, as efficacy is highly correlated to adherence and studies suggest that adherence improves with

daily dosing.[2,8] The IAS-USA suggests that daily dosing is the optimal regimen, and non-daily dosing may be considered as an alternative limited to certain populations.[9]

Clinical Data

ANRS IPERGAY Trial

The IPERGAY trial studied on-demand use of FTC/TDF in adult men or TGW who have sex with men at high risk for HIV. This randomized, double-blind, placebo-controlled study assigned 199 participants in the treatment arm and 201 participants in the placebo arm to take 2 tablets (either FTC/TDF or placebo) 2 to 24 hours before sex, 1 tablet 24 hours after sex, and 1 tablet 48 hours after sex. The primary study objective was to show a reduction in HIV incidence with on-demand FTC/TDF for HIV-1 PrEP. In October 2014, the DSMB recommended the discontinuation of the placebo arm and that the on-demand FTC/TDF regimen be offered to all participants.[3-5]

Two participants in the FTC/TDF arm and 14 participants in the placebo arm acquired HIV, which resulted in an 86% relative reduction in the incidence of HIV-1 (95% CI: 40%–98%; *P*=0.002). The 2 participants who acquired HIV-1 in the FTC/TDF arm had no detectable levels of FTC/TDF at HIV acquisition or during prior clinical monitoring visits. No resistance was reported. Participants took a median of 15 tablets of either FTC/TDF or placebo per month (*P*=0.57). There were no significant differences in sexual behavior or STIs reported between the FTC/TDF and placebo arms.[3-5]

The rates of serious AEs were similar in the two study groups. Drug-related GI AEs (nausea, vomiting, diarrhea, abdominal pain, and other GI disorders) were reported more commonly in the FTC/TDF arm than in the placebo arm (14% vs 5%; *P*=0.002). Elevations in SCr levels were observed in 35 participants (18%) in the FTC/TDF arm compared to 20 participants (10%) in the placebo arm (*P*=0.03). All but one of these events were Grade 1, and none led to study drug discontinuation. Two participants (1%) had a transient decrease in CrCl to <60 mL/min; both were in the FTC/TDF arm.[3-5]

IPERGAY OLE phase[4]

The IPERGAY OLE phase began after the DSMB recommended the discontinuation of the placebo arm. This phase included 361 participants, with a median follow-up of 18.4 months. The overall HIV incidence during the OLE phase was 0.19/100 PY of follow-up (95% CI:0.01–1.08). On-demand FTC/TDF for HIV-1 PrEP remained highly effective in MSM at high risk of acquiring HIV, with an overall relative reduction in HIV-1 incidence of 97% (95% CI: 81–100) when compared to a counterfactual estimate based on the placebo group during the randomized phase of the study. In the single participant who acquired HIV during the OLE, low adherence was suspected based on pill count and undetectable levels of tenofovir in plasma. Participants used a median of 18 tablets per month (IQR: 11−25).

An increase in the proportion of participants reporting CAI was observed during the OLE phase (from 77% at baseline to 86%; *P*=0.0004).

AE were observed in most participants (98%), with serious AEs reported in 41 participants (11%). AEs that led to study drug discontinuation occurred in 4 participants (3 due to Grade 1–2 SCr elevations and 1 with Grade 2 transaminase elevations). The frequency of drug-related AEs was 20% (n=72). GI AEs (n=49; 14%) were the most common AEs reported and were similar to the proportion observed in the FTC/TDF group of the

double-blinded phase of the study. Of the 17% of participants (n=61) who experienced Grade 1 to 2 elevations in SCr, all but 3 of these events were Grade 1, and no cases of Fanconi syndrome were reported. Seven participants had Grade 3 or 4 ALT elevations associated with acute HCV infections acquired during the double-blind phase (n=2) or during the OLE phase (n=5).

HPTN 067: ADAPT Study[6,7]

The HPTN 067 study evaluated the coverage of sex events using 3 different FTC/TDF for HIV-1 PrEP dosing regimens and included adult MSM and TGW in Bangkok, Thailand, and Harlem/NYC, United States, as well as adult heterosexual women in Cape Town, South Africa. After 5 weeks of a directly observed therapy phase to estimate steady-state drug levels, participants were randomly assigned to 1 of 3 unblinded dosing regimens: FTC/TDF daily (1 tablet/day), time-driven use of FTC/TDF (1 tablet twice weekly with a post-intercourse dose), or event-driven use of FTC/TDF (1 tablet pre-intercourse and 1 tablet post-intercourse [≤2 tablets/day or 7 tablets/week]). Coverage was determined by comparing the date and time of a sex act to the date and time of tablet use (tablets were dispensed in an electronic dispensing Wisepill device that recorded each opening). A sex act was considered covered if ≥1 tablet was taken during the 96 hours before the sex act and 1 tablet was taken ≤24 hours after the sex act. Only vaginal and anal sex acts were considered; oral sex acts were not included.

MSM subanalysis[6]

A subanalysis of MSM participants at the Bangkok (n=178) and Harlem/NYC (n=179) sites was performed to compare daily vs non-daily dosing of FTC/TDF for HIV-1 PrEP, and the results are described below (Table 1). HIV infection was detected in 4 participants during the study. HIV was detected at Week 4 in 3 participants during the directly observed therapy phase, of which 2 participants had acute HIV at enrollment, including 1 participant who had an M184I mutation. HIV was detected at Week 18 in 1 participant who was randomly assigned to the FTC/TDF daily arm and identified as having low adherence.

Details regarding adherence and coverage of sexual events are presented in Table 1.

Table 1. Coverage of and Adherence to Daily vs Time-Driven vs Event-Driven Regimens of FTC/TDF for HIV-1 PrEP in Bangkok and NYC MSM[6]

Location	Adherence/ Covered Sexual Events	Regimens			*P*-value
		D	T	E	
Bangkok	Adherence	85%	79%	65%	D/T: *P*<0.42 D/E: *P*<0.001 T/E: *P*<0.001 Global (for all arms): *P*<0.001
	Complete coverage of sex events	85%	84%	74%	D/T: *P*=0.79 D/E: *P*=0.02 T/E: *P*=0.04 Global (for all arms): *P*=0.19
	Pre-sex dose only	11%	12%	19%	–
	Post-sex dose only	1%	3%	5%	–
	No coverage	3%	1%	3%	–

Location	Adherence/ Covered Sexual Events	Regimens			*P*-value
		D	T	E	
Harlem	Adherence	65%	47%	41%	D/T: *P*<0.0001 D/E: *P*<0.0001 T/E: *P*=0.17 Global (for all arms): *P*<0.0001
	Complete coverage of sex events	66%	47%	52%	D/T: *P*=0.01 D/E: *P*=0.01 T/E: *P*=0.47 Global (for all arms): *P*=0.03
	Pre-sex dose only	24%	30%	29%	–
	Post-sex dose only	2%	8%	6%	–
	No coverage	8%	15%	13%	–

Abbreviations: D=daily; E=event-driven; T=time-driven.

Women subanalysis[7]

In a subanalysis of 191 women at the Cape Town, South Africa site, 93% (n=178) of participants finished the directly observed therapy phase and were randomly assigned to 1 of 3 different FTC/TDF dosing arms: daily (n=59), time-driven (n=59), and event-driven (n=60). Eight participants acquired HIV during the study: 3 participants during the directly observed therapy phase, 2 participants in the time-driven arm, 2 participants in the event-driven arm, and 1 participant who had acute HIV at enrollment (excluded from the analysis). Among the 8 participants who acquired HIV, 2 resistance mutations were detected: the participant with HIV at enrollment had K65N, and 1 participant in the time-driven arm had K65N and M184I.

The total number of sex events was higher in participants who were randomly assigned to the daily arm than in those in one of the non-daily arms. FTC/TDF coverage of sex events was significantly higher in the daily arm than in the time-driven (*P*=0.0007) and event-driven (*P*<0.0001) arms. Adherence was higher in the daily arm than in the non-daily arms (Table 2).

Table 2. Coverage of and Adherence to Daily vs Time-Driven vs Event-Driven Regimens of FTC/TDF for HIV-1 PrEP in Women in Cape Town, South Africa[7]

Adherence/ Covered Sexual Events	Regimens			D vs T[a]	D vs E[a]	*P*-value[b]
	D	T	E			
Adherence[c]	75%	65%	53%	10% (3.8–16%)	22% (15.3–30%)	*P*<0.0001
Complete coverage of sex events	75%	56%	52%	2.35 (1.43–3.85)	2.76 (1.68–4.53)	*P*=0.0006
Pre-sex dose only	21%	30%	33%	0.64 (0.41–0.98)	0.55 (0.35–0.85)	*P*=0.035
Post-sex dose only	1%	9%	8%	0.1 (0.05–0.18)	0.11 (0.06–0.19)	*P*<0.0001
No coverage	3%	5%	7%	0.56 (0.21–1.54)	0.44 (0.17–1.13)	*P*=0.17

Abbreviations: D=daily; E=event-driven; T=time-driven.
[a]For coverage results, data are reported as odds ratio (95% CI); for sex event counts, data are reported as the

fold change in mean (95% CI).
[b]*P*-value is for the comparison between the 3 regimens
[c]Adherence was measured by adjusted electronic drug monitoring (with the Wisepill device) data. Adherence is defined as the proportion of doses taken as recommended for the specific assigned regimen, determined by the Wisepill device and the weekly interview.

AEs were uncommon, and most were mild or moderate. The number of Grade 3 or 4 AEs was ≤6 events/arm, with no difference among the arms. GI and neurological (headache, dizziness, and lightheadedness) AEs were reported in <13% of participants, with no differences by arm (*P*>0.05 for both events). No fractures related to trauma were reported, and no creatinine abnormalities were observed in any arms.

References

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Abbreviations

AE=adverse event
ANRS=National Agency of Research on AIDS & Viral Hepatitis CAI=condomless anal intercourse
CDC=Centers for Disease Control and Prevention
DSMB=Data and Safety Monitoring Board
FTC=emtricitabine
GI=gastrointestinal
IAS=International Antiviral Society
IQR=interquartile range
MSM=men who have sex with men
NYC=New York City
OLE=open-label extension
PrEP=pre-exposure prophylaxis
PY=person years
STI=sexually transmitted infection
TDF=tenofovir disoproxil fumarate
TGW=transgender women
WHO=World Health Organization

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

For any additional questions, please contact Gilead Medical Information at:

☎1-866-MEDI-GSI (1-866-633-4474) or 🖱 www.askgileadmedical.com

Adverse Event Reporting

Please report all adverse events to:

Gilead Global Patient Safety ☎ 1-800-445-3235, option 3 or
🖱 www.gilead.com/utility/contact/report-an-adverse-event

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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