GILEAD | Medical Information

Descovy for PrEP® (FTC/TAF) Drug Concentration in Rectal Tissue

This document is in response to your inquiry regarding Descovy for PrEP® (emtricitabine/tenofovir alafenamide [FTC/TAF] for HIV-1 pre-exposure prophylaxis) and drug concentrations in rectal tissue.

Some data may be outside of the US FDA-approved prescribing information. In providing this data, Gilead Sciences, Inc. is not making any representation as to its clinical relevance or to the use of any Gilead product(s). For information about the approved conditions of use of any Gilead drug product, please consult the FDA-approved prescribing information.

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

Summary

Product Labeling[1]

FTC/TAF is indicated in at-risk adults and adolescents weighing ≥35 kg for PrEP to reduce the risk of HIV-1 infection from sexual acquisition, excluding individuals at risk from receptive vaginal sex. Individuals must have a negative HIV-1 test immediately prior to initiating FTC/TAF for HIV-1 PrEP.

Limitations of Use: The indication does not include the use of FTC/TAF in individuals at risk of HIV-1 from receptive vaginal sex because effectiveness in this population has not been evaluated.

PK of Once-Daily FTC/TAF in HIV-Uninfected Women

CONRAD 137 was a phase 1, prospective, randomized study that evaluated local and systematic PK, pharmacodynamics, and safety of once-daily oral FTC/TAF vs FTC/TDF in 75 non-pregnant, HIV-uninfected, adult women randomly assigned 1:1:1 to receive FTC/TAF 200/10 mg (n=26), FTC/TAF 200/25 mg (n=24), or FTC/TDF 200/300 mg (n=25) oral tablets once daily for 14 days.[2]

- Rectal tissue levels of TFV-DP at 4 hours postdose were 16.8-fold lower with FTC/TAF vs FTC/TDF.[3]

TFV & TFV-DP Concentrations after a Single Dose of TAF

A single-center, open-label, dose-ranging, phase 1, PK study conducted in 24 healthy, premenopausal women who were given a single 5-, 10-, or 25-mg dose of TAF (n=8 per arm) evaluated the mucosal tissue distribution of TAF.[4]

- Compared with TDF, TFV exposures ($AUC_{0–48h}$) in rectal tissue were 10-fold lower with a single dose of TAF, while TFV-DP exposures were 13-fold lower in rectal tissue.[4]
- Please note, the clinical relevance of this PK data and the correlate of HIV protection is unknown.

Pharmacokinetics

The PK properties of the components of FTC/TAF are provided below (**Table 1**).

Table 1. PK Properties of the Components of FTC/TAF

	FTC	TAF
Absorption		
T_{max}	3 hours	1 hours
Effect of high-fat meal (relative to fasting)[a]	AUC ratio: 0.91 (90% CI: 0.89–0.93) C_{max} ratio: 0.74 (90% CI: 0.69–0.78)	AUC ratio: 1.75 (90% CI: 1.64–1.88) C_{max} ratio: 0.85 (90% CI: 0.75–0.95)
Distribution		
% bound to human plasma proteins	<4	~80
Source of protein binding data	*In vitro*	*Ex vivo*
Blood-to-plasma ratio	0.6	1.0
Metabolism		
Metabolism	Not significantly metabolized	Cathepsin A[b] (PBMCs) CES1 (hepatocytes) CYP3A (minimal)
Elimination		
Major route of elimination	Glomerular filtration and active tubular secretion	Metabolism (>80% of oral dose)
$t_{½}$[c]	10 hours	0.51 hours
% of dose excreted in urine[d]	70	<1
% of dose excreted in feces[d]	13.7	31.7

Abbreviations: CES1=carboxylesterase 1; $t_{½}$=median terminal plasma half-life

[a] Values refer to geometric mean ratio [high-fat meal / fasting] in PK parameters. High-calorie/high-fat meal = ~800 kcal, 50% fat.

[b] *In vivo*, TAF is hydrolyzed within cells to form TFV (major metabolite), which is phosphorylated to the active metabolite, TFV-DP. *In vitro* studies have shown that TAF is metabolized to TFV by cathepsin A in PBMCs and macrophages; and by CES1 in hepatocytes. Upon coadministration with the moderate CYP3A inducer probe efavirenz, TAF exposure was unaffected.

[c] Note that the pharmacologically active metabolite, TFV-DP, has a half-life of 150–180 hours within PBMCs.

[d] Dosing in mass balance studies: FTC (single dose administration of [^{14}C] FTC after multiple dosing of FTC for 10 days); TAF (single dose administration of [^{14}C] TAF).

Clinical Data

PK of Once-Daily FTC/TAF in HIV-Uninfected Women

Study design and demographics

CONRAD 137 was a phase 1, prospective, randomized study that evaluated local and systematic PK, pharmacodynamics, and safety of once-daily oral FTC/TAF vs FTC/TDF in 75 non-pregnant, HIV-uninfected, adult women. Participants were randomly assigned 1:1:1 to receive FTC/TAF 200/10 mg (n=26), FTC/TAF 200/25 mg (n=24), or FTC/TDF

200/300 mg (n=25) oral tablets once daily for 14 days.[2] Please note, FTC/TAF 200/10 mg is not commercially available in the US.

Participants in the FTC/TAF 200/10 mg vs FTC/TAF 200/25 mg vs FTC/TDF 200/300 mg arms, respectively, had mean ages of 33.2 vs 34.6 vs 32.8 years, 58% vs 50% vs 52% were Black or African American, 31% vs 38% vs 40% were Hispanic, and 69% vs 83% vs 72% were White.[2]

PK results

In a subanalysis of drug levels in rectal tissue, participants in both the FTC/TAF 200/25 mg and FTC/TDF 200/300 mg arms (n=7 in both arms) each contributed four separate rectal samples at 4 hours postdose.[5] Rectal tissue levels of TFV-DP at 4 hours postdose were 16.8-fold lower with FTC/TAF vs FTC/TDF.[3] A greater proportion of rectal samples from participants randomized to FTC/TAF, compared with FTC/TDF, had median TFV-DP levels BLQ (29% vs 4%, respectively).[5]

More women reported ≥1 AE following F/TDF vs F/TAF dosing [80% vs 46.2% (TAF 10mg) and 66.7% (TAF 25mg)]. Women taking F/TDF reported a higher percentage of ≥1 gastrointestinal (GI) AE (44%) compared to women taking F/TAF (11% and 12.5% for TAF 10 and 25mg, respectively).[6]

No studies have evaluated the efficacy of FTC/TAF for PrEP in HIV-uninfected cisgender women, and the effectiveness of FTC/TAF in individuals at risk of HIV-1 from receptive vaginal sex has not been established.

TFV & TFV-DP Concentrations after a Single Dose of TAF

Study design

A single-center, open-label, dose-ranging, phase 1, PK study conducted in 24 healthy, premenopausal women who were given a single 5-, 10-, or 25-mg dose of TAF (n=8 per arm) evaluated the mucosal tissue distribution of TAF. Participants fasted for 8 hours prior to and 2 hours after being given TAF. Colorectal, cervicovaginal fluid, plasma, and PBMC samples were collected at regular intervals throughout the 14-day study and 2 biopsies of the cervix, vagina, and rectum were conducted. Participant median age was 27.5 years, 83% were White, and the median BMI was 24.4 kg/m^2.[4] Please note, TAF 5 mg and TAF 10 mg are not commercially available in the US.

Results

In rectal tissue, the TFV T_{max} was 72 hours for the TAF 25 mg dose. Dose proportionality was not evaluated in mucosal tissue, because a majority of TFV-DP concentrations were BLQ after 72 hours (**Table 3**). However, when looking at tissue samples, the median TFV-DP concentration was 2.6-fold higher in the 25 mg arm compared to the 10 mg arm.[4]

Table 2. TFV and TFV-DP Non-Compartmental Analysis[4]

PK Parameter	TAF 25 mg	TAF 10 mg	TAF 5 mg
TFV in rectal tissue			
C_{max}, ng/g	256	1402	122
$AUC_{0–24\ h}$, ng·h/g	877	8602	964
$AUC_{0–14\ days}$, ng·h/g	22,403	44,545	4752
TFV-DP in rectal tissue			
C_{max}, fmol/g	11,163	3456	BLQ

PK Parameter	TAF 25 mg	TAF 10 mg	TAF 5 mg
$AUC_{0–24\ h,}$ fmol·h/g	39,162	45,103	BLQ
$AUC_{0–14\ days,}$ fmol·h/g	1,041,352	315,145	BLQ

Table 3. Percentage Imputed BLQ Values for TAF Over 14 Days[4]

Tissue/Sample Location	TAF 25 mg		TAF 10 mg		TAF 5 mg	
	% with TFV BLQ	% with TFV-DP BLQ	% with TFV BLQ	% with TFV-DP BLQ	% with TFV BLQ	% with TFV-DP BLQ
Rectal tissue	0	75	0	69	25	100

Drug concentrations obtained from participants in the TAF 25 mg arm were compared with results from a separate PK analysis previously conducted with TDF 300 mg. Compared with TDF, TFV exposures ($AUC_{0–48h}$) in rectal tissue were 10-fold lower with a single dose of TAF, while TFV-DP exposures were 13-fold lower in rectal tissue. Additionally, 75% more rectal tissue samples with TAF had TFV-DP concentrations BLQ.[4]

Please note, the clinical relevance of these PK data and the correlate of HIV protection is unknown.

References

1. Descovy, Gilead Sciences Inc. DESCOVY® (emtricitabine and tenofovir alafenamide) tablets, for oral use. U.S. Prescribing Information. Foster City, CA. Revised January. 2022.
2. Schwartz JL, Cottrell M, Thurman AR, et al. HIV Prevention in Healthy Women: Safety and PK of a Potential New Tenofovir Alafenamide Fumarate (TAF)-based Oral PrEP Regimen (OA15.04) [Presentation]. Paper presented at: HIVR4P; 21-25 October, 2018; Madrid, Spain.
3. Gilead Sciences Inc. *DESCOVY® for HIV Pre-Exposure Prophylaxis. Antimicrobial Drugs Advisory Committee Meeting Briefing Document. NDA 208215/S-012. 04 July.* 2019.
4. Cottrell ML, Garrett KL, Prince HMA, et al. Single-Dose Pharmacokinetics of Tenofovir Alafenamide and Its Active Metabolite in the Mucosal Tissues. *J Antimicrob Chemother.* 2017;72:1731-1740. https://www.ncbi.nlm.nih.gov/pubmed/28369415
5. Brainard D. *Descovy® for PrEP. Antimicrobial Drugs Advisory Committee Meeting. 07 August.* 2019.
6. Schwartz JL, Thurman AR, Brache V, et al. HIV Prevention in Healthy Women: Safety and Pharmacokinetics of a Potential New Tenofovir Alafenamide Fumarate (TAF)-based Oral PrEP Regimen [Abstract OA15.04]. *HIV Research for Prevention 2018: AIDS Vaccine, Microbicide and ARV-based Prevention Science.* 2018;34(S1):58.

Abbreviations

AUC=area under the curve
BLQ=below the limit of quantification
C_{max}=maximum observed concentration of drug
FTC=emtricitabine
PBMC=peripheral blood mononuclear cells
PK=pharmacokinetic(s)
PrEP=pre-exposure prophylaxis
TAF=tenofovir alafenamide
TDF=tenofovir disoproxil fumarate
TFV=tenofovir
TFV-DP=tenofovir diphosphate
T_{max}=time that drug is at maximum concentration

Product Label

For the full indication, important safety information, and Boxed Warning(s), please refer to the Descovy US Prescribing Information available at:
www.gilead.com/-/media/files/pdfs/medicines/hiv/descovy/descovy_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

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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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