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Descovy for PrEP® (FTC/TAF) DISCOVER Study

This document is in response to your request for information regarding Descovy for PrEP® (emtricitabine/tenofovir alafenamide [FTC/TAF] for HIV-1 pre-exposure prophylaxis [PrEP]) and the DISCOVER study.

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Summary

DISCOVER: FTC/TAF vs FTC/TDF for HIV-1 PrEP in MSM and TGW

Once-daily FTC/TAF demonstrated non-inferiority to FTC/TDF for HIV-1 PrEP among adult MSM and TGW in the phase 3 DISCOVER study at both the primary and Week 96 analyses.[1-3] Results through the OL phase are presented below.

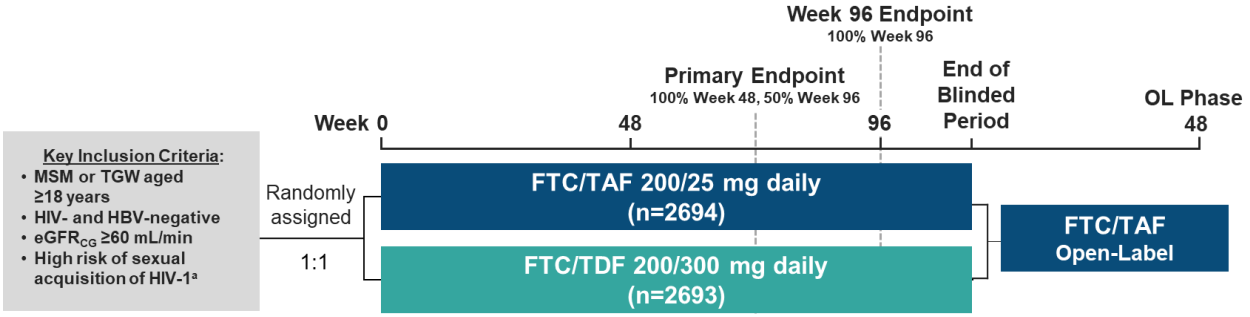
- FTC/TAF was non-inferior to FTC/TDF for HIV-1 PrEP at the primary analysis and at Week 96. At Week 96, participants in the FTC/TAF and FTC/TDF arms had HIV-1 incidence rates of 0.16 per 100 PY and 0.3 per 100 PY, respectively, and through Week 144, there were 27 participants who had a positive HIV-1 diagnosis (10 participants in the FTC/TAF arm and 17 in the FTC/TDF arm, including 1 participant who switched to FTC/TAF in the OL phase).[1-5] HIV-1 incidence rates remained low through Week 48 of the OL phase (FTC/TAF, 0.09 per 100 PY; FTC/TDF → FTC/TAF, 0.05 per 100 PY).[3]
- Four participants with suspected baseline HIV in the FTC/TDF arm had M184V/I RAMs at their HIV diagnosis study visit. Through Week 144 (OL Week 48), no participants randomly assigned to FTC/TAF and 1 participant randomly assigned to FTC/TDF developed resistance-associated mutations.[1,5,6]
- In an analysis of long-term outcomes of participants who were randomly assigned to and continued FTC/TAF in the OL phase until Week 144, 10 participants acquired HIV; 5 acquired HIV while on study drug and had suboptimal adherence, 4 discontinued study drug ≥30 days before being diagnosed with HIV, and 1 was suspected to have had HIV at baseline and had TFV-DP levels consistent with high adherence to study drug.[5]

DISCOVER: FTC/TAF vs FTC/TDF for HIV-1 PrEP in MSM and TGW

Study Design and Demographics

DISCOVER (NCT02842086) is a phase 3, double-blind, active-controlled multinational study in 5387 HIV-negative adult MSM and TGW that is evaluating the safety and efficacy of FTC/TAF vs FTC/TDF for HIV-1 PrEP. Figure 1 below includes the study design and key inclusion criteria. Prior use of FTC/TDF for HIV-1 PrEP was allowed.[1,2]

Figure 1. DISCOVER: Study Design[1,2]



[a]High risk was defined as ≥2 episodes of condomless anal intercourse with ≥2 unique male partners with HIV or with an unknown HIV status within the previous 12 weeks, or a documented history of syphilis, rectal gonorrhea, or rectal chlamydia in the previous 24 weeks.

The primary outcome was the incidence of HIV-1 per 100 PY after all participants had ≥48 weeks of follow-up and ≥50% of participants had 96 weeks of follow-up.[1] All participants were unblinded after 96 weeks, and participants in both arms were offered the opportunity to continue or switch to OL FTC/TAF for an additional 48 weeks. Participant baseline characteristics were similar between the FTC/TAF and FTC/TDF arms, including HIV risk factors.[2]

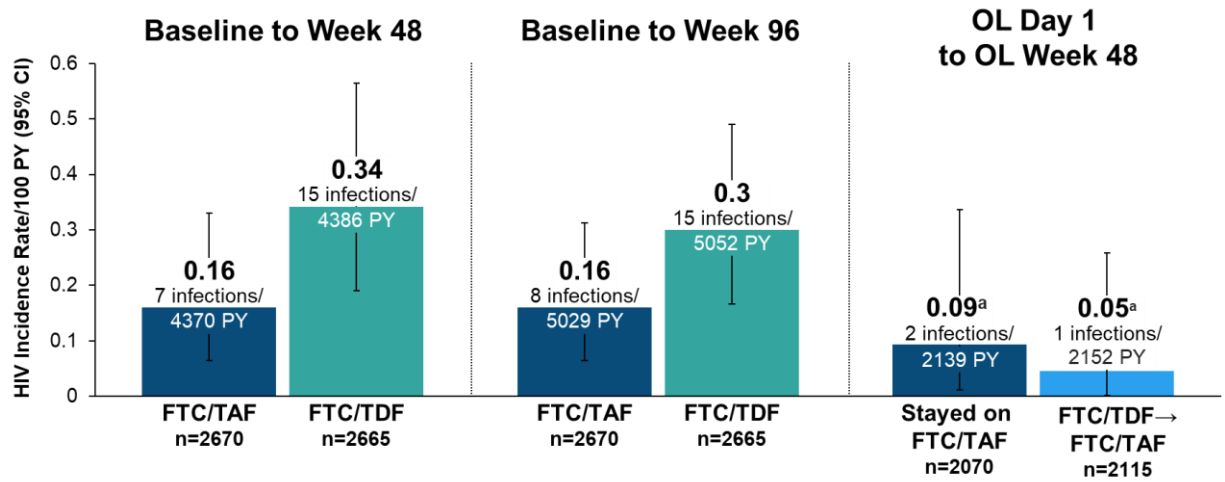
Table 1. DISCOVER: Baseline Demographics and HIV Risk Factors[2,7]

Select Demographics and Risk Factors		FTC/TAF (n=2694)	FTC/TDF (n=2693)
Age, median (IQR), years		34 (28–43)	34 (28–44)
Race or ethnicity, n (%)	White	2264 (84)	2247 (84)
	Hispanic or Latinx	635 (24)	683 (25)
	Black or mixed Black	240 (9)	234 (9)
	Asian	113 (4)	120 (5)
Cisgender MSM, n (%)		2649 (98)	2664 (99)
TGW, n (%)		45 (2)	29 (1)
HIV risk factors, n (%)	≥2 events of receptive condomless anal sex in the past 12 weeks	1660 (62)	1628 (60)
	Received FTC/TDF for HIV-1 PrEP at baseline	465 (17)	440 (16)
	Syphilis diagnosis in the past 24 weeks	230 (9)	263 (10)

Efficacy: Primary, Week 96, and OL Week 48 Analyses

At the primary analysis at Week 48, the IRR was 0.47 (95% CI: 0.19–1.15), meeting the prespecified non-inferiority margin of <1.62.[1] At Week 96, the IRR was 0.54 (95% CI: 0.23–1.26), thus maintaining non-inferiority.[2] From Day 1 to Week 48 of the OL phase, the HIV incidence rates were similar between the two study arms (Figure 2).[3]

Figure 2. DISCOVER: Incidence Rates of HIV From Baseline to Week 144[3]



[a]During the OL phase, 1 additional participant in each group had a positive quantitative HIV nucleic acid amplification test that was later confirmed to be a false positive.

Safety: Baseline Through Week 96

AEs[2]

Through Week 96, rates of STIs were similar between the two treatment arms (rectal gonorrhea, 21 cases per 100 PY; rectal chlamydia, 28 cases per 100 PY). Any-grade AEs were reported in 94% of participants in each arm, with study drug-related AEs reported in 21% of those who received FTC/TAF and 24% of those who received FTC/TDF. The most common AEs in both groups were STIs (Table 2). In the FTC/TAF and FTC/TDF arms, AEs led to study drug discontinuation in 1% and 2% of participants, respectively. Study drug-related renal AEs occurred in 1% of participants in each study arm. Through Week 96, there were 3 deaths in the FTC/TAF arm (traffic accident, amphetamine intoxication, and fatal drug overdose, n=1 each) and 2 deaths in the FTC/TDF arm (metastatic squamous cell carcinoma and unknown causes, n=1 each).

Table 2. DISCOVER: AEs in ≥10% of Participants in Either Arm at Week 96[2]

AEs, %	FTC/TAF (n=2694)	FTC/TDF (n=2693)
Rectal chlamydia	33	33
Oropharyngeal gonorrhea	32	31
Rectal gonorrhea	30	30
Exposure to communicable disease	21	20
Diarrhea	18	17
Nasopharyngitis	15	15
Syphilis	15	15

AEs, %	FTC/TAF (n=2694)	FTC/TDF (n=2693)
URTI	15	13
Urethral chlamydia	13	12
Urethral gonorrhea	10	9

Bone safety

In a BMD substudy, DEXA scans were conducted in 383 participants to assess bone safety through Week 96. The effects on spine and hip BMD significantly favored FTC/TAF (Table 3).[2,7] The long-term clinical significance of the BMD changes is not known.[8]

Table 3. DISCOVER: BMD Substudy of Bone Safety at Week 96[2,7]

	Spine BMD			Hip BMD		
	FTC/TAF (n=144)	FTC/TDF (n=140)	*P*-Value	FTC/TAF (n=140)	FTC/TDF (n=137)	*P*-Value
BMD change from baseline, mean, %	+1	-1.4	<0.0001[a]	+0.6	-1	<0.0001[a]
Participants with ≥3% increase in BMD from baseline, %	23	7	<0.001[b]	17	6	0.007[b]
Participants with ≥3% decrease in BMD from baseline, %	11	29	<0.001[b]	7	21	<0.001[b]

[a]*P*-values from analysis of variance model with baseline FTC/TDF for HIV-1 PrEP and treatment as fixed effects.
[b]*P*-values are based on a dichotomized response (ie, ≥3% vs <3%) with the Cochran-Mantel-Haenszel test for nominal data and adjusted for baseline FTC/TDF for HIV-1 PrEP use.

Renal safety

Through Week 96, the effects on $eGFR_{CG}$ significantly favored FTC/TAF over FTC/TDF. This same benefit was seen with the renal biomarkers RBP:Cr and β2M:Cr (Table 4).[2] The long-term clinical significance of these renal laboratory changes on adverse reaction frequencies between FTC/TAF and FTC/TDF is not known.[8]

Table 4. DISCOVER: Renal Safety for All Participants at Week 96[2]

	FTC/TAF (n=2694)	FTC/TDF (n=2693)	*P*-Value
$eGFR_{CG}$ change from baseline,[a] median, mL/min	+3.7	-0.4	<0.0001[d]
RBP:Cr change from baseline,[b] mean, %	+0.2	+21.4	<0.0001[e]
β2M:Cr change from baseline,[c] mean, %	-14.6	+14.2	<0.0001[e]
Participants with treatment-emergent UPCR >22.6 mg/mmol, %	1	1.3	0.22
Renal AEs that led to study drug discontinuation, n	2	6	-
Fanconi syndrome, n	0	1	-

Abbreviation: UPCR=urine protein-creatinine ratio.
[a]FTC/TAF, n=2193; FTC/TDF, n=2217.
[b]FTC/TAF, n=2191; FTC/TDF, n=2216.
[c]FTC/TAF, n=2172; FTC/TDF, n=2200.
[d]*P*-values were from an ANOVA model with baseline FTC/TDF for PrEP and treatment as fixed effects.
[e]*P*-values were from the Van Elteren test stratified by baseline FTC/TDF for HIV-1 PrEP to compare the two treatment groups.

Long-Term Outcomes at Week 144

An analysis assessed the incidence of HIV-1 and long-term safety outcomes of participants who were randomly assigned to receive FTC/TAF (n=2694) and continued on FTC/TAF in the OL phase (n=2070) for a total follow-up duration of ≥144 weeks. The incidence of HIV-1 and safety outcomes of participants who were randomly assigned to receive FTC/TDF (n=2693) and switched to FTC/TAF in the OL phase (n=2115) were also assessed.[5]

Efficacy[5]

Overall, 27 participants acquired HIV: 17 participants (63%) randomly assigned to FTC/TDF and 10 participants (37%) randomly assigned to FTC/TAF (FTC/TAF group, n=2670; incidence of 0.13 per 100 PY; 95% CI: 0.061–0.23). Of the 10 participants in the FTC/TAF group, 5 acquired HIV while on study drug and had suboptimal adherence (as measured by TVF-DP levels in dried blood spots), 4 discontinued study drug ≥30 days before being diagnosed with HIV, and 1 was suspected to have had HIV at baseline and had TFV-DP levels consistent with high adherence to study drug. Of the 17 participants in the FTC/TDF group, 8 acquired HIV with either low/uncertain adherence to study drug or having discontinued ≤30 days of diagnosis, 4 discontinued study drug ≥30 days before being diagnosed with HIV, 4 were suspected to have had HIV at baseline, and 1 acquired HIV after switching to FTC/TAF in the OL phase and had low adherence.

Four participants with suspected baseline HIV in the FTC/TDF arm had M184V/I RAMs at their HIV diagnosis study visit. No participants randomly assigned to FTC/TAF and 1 participant randomly assigned to FTC/TDF developed resistance-associated mutations through Week 144.

Safety: baseline through Week 144

AEs[5]

Most AEs in participants who received ≥1 dose of FTC/TAF were Grade 1 or 2 in severity, and the most common AE was bacterial STI (Table 5).

Table 5. DISCOVER: Safety Summary of Participants Randomly Assigned to FTC/TAF Who Continued Up to Week 144[5]

Safety Parameter, n (%)		FTC/TAF (n=2694)
Any treatment-emergent AE		2544 (94)
Any Grade 3 or 4 treatment-emergent AE		67 (3)
Discontinuation of FTC/TAF due to AE		43 (2)
Any serious AE[a]		257 (10)
Related to FTC/TAF[b]		3 (<1)
Led to death[c]		7 (<1)
Common (≥10%) treatment-emergent AEs	Anal chlamydia infection	1030 (38)
	Oropharyngeal gonococcal infection	997 (37)
	Proctitis gonococcal	921 (34)
	Exposure to communicable disease	647 (24)
	Diarrhea	522 (19)
	Syphilis	494 (18)
	Nasopharyngitis	468 (17)
	URTI	456 (17)
	Urethritis chlamydial	394 (15)
	Urethritis gonococcal	295 (11)

Safety Parameter, n (%)		FTC/TAF (n=2694)
Any Grade 3 or 4 laboratory abnormality		385 (14)
Grade 3 or 4 laboratory abnormality in ≥2% of participants	Increased AST	83 (3)
	Increased LDL while fasting	70 (3)
	Increased ALT	54 (2)
	Increased amylase	49 (2)

[a]Serious AEs occurring in ≥5 participants were the following: appendicitis, n=17; suicidal ideation, n=9; cellulitis, n=8; suicide attempt, n=8; acute kidney injury, n=7; hepatitis A, n=6; pneumonia, n=5; and depression, n=5.
[b]Nephrotic syndrome, chest pain and loss of consciousness, and agranulocytosis and pyrexia in the same participant (each, n=1).
[c]Cardiac arrest, traffic accident, amphetamine intoxication, suspected suicide, homicide, fatal drug overdose, and progressive vasodilatory shock with metabolic acidosis and multisystem dysfunction after crystal methamphetamine injection (each, n=1).

Bone and renal safety

In a subgroup analysis of bone safety in participants randomly assigned to FTC/TAF who had DEXA scans (n=191), the median changes in hip and spine BMD from baseline to Week 144 were 0.54% (95% CI: -0.11 to 1.19) and 1.02% (95% CI: 0.4–1.63), respectively. Participants who switched from FTC/TDF to FTC/TAF in the OL phase had an increase in hip and spine BMD (Figure 3), a decrease in β2M and RBP:Cr ratio, and an increase in $eGFR_{CG}$ (Figure 4).[5] The long-term clinical significance of these bone and renal laboratory changes on adverse reaction frequencies between FTC/TAF and FTC/TDF is not known.[8]

Figure 3. DISCOVER: Changes in BMD From OL Baseline to OL Week 48[5,9]

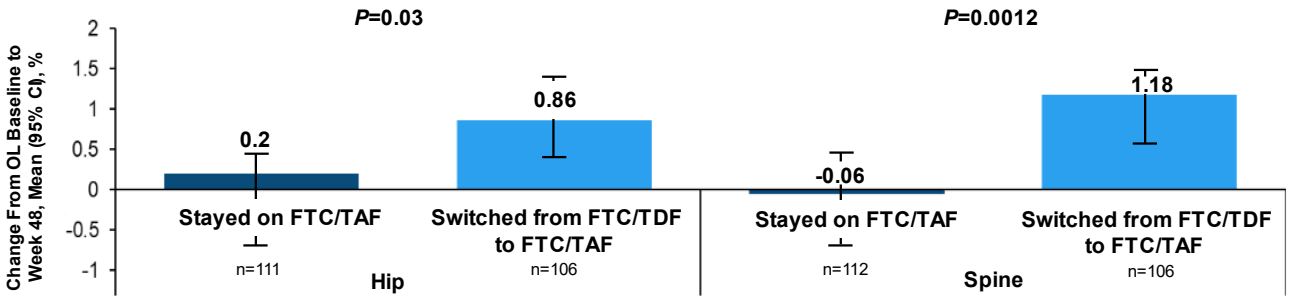
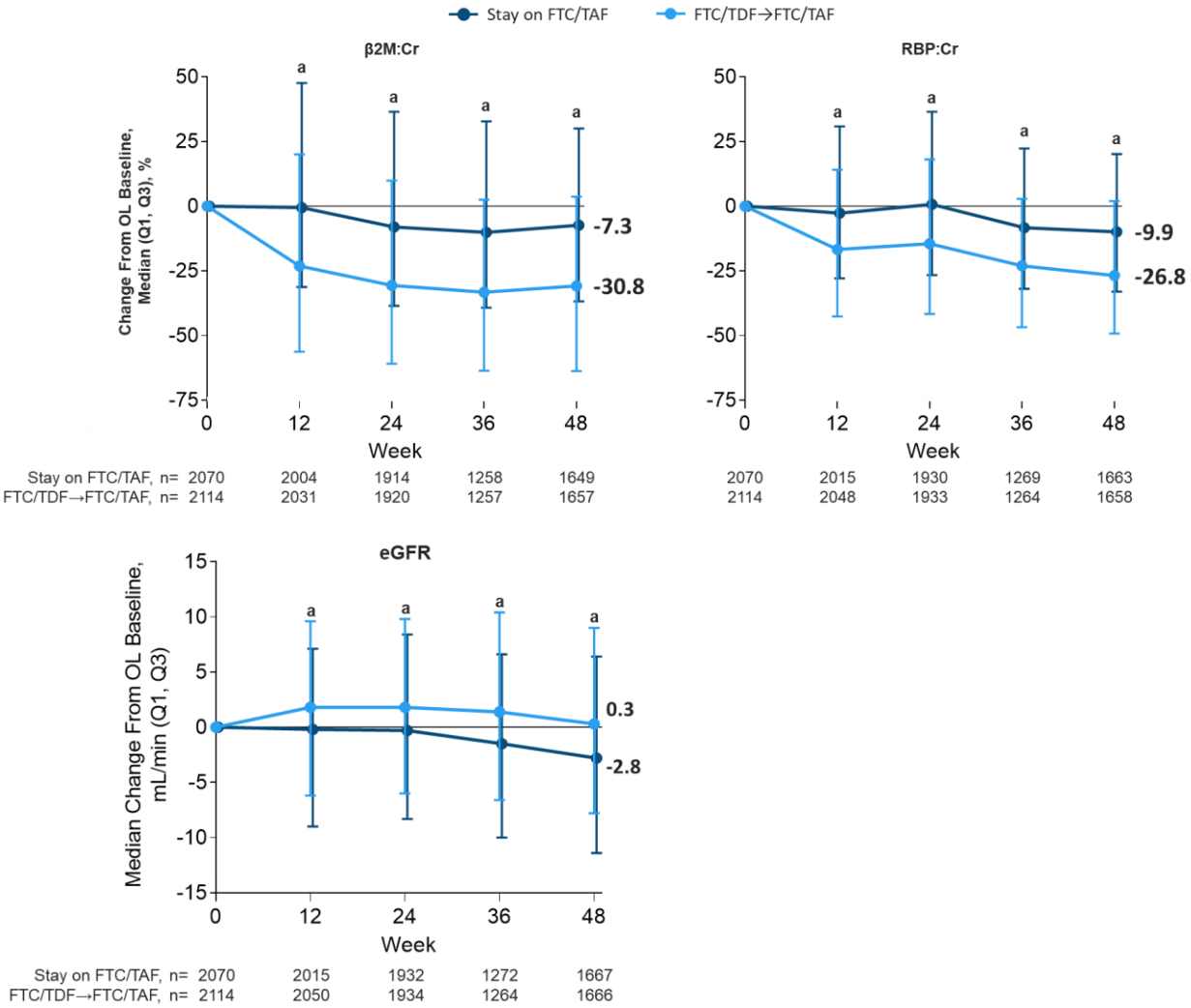


Figure 4. DISCOVER: Changes in Renal Parameters From OL Baseline to OL Week 48[5,9]



[a]*P*<0.0001.

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8. Enclosed. Gilead Sciences Inc, DESCOVY® (emtricitabine and tenofovir alafenamide) tablets, for oral use. U. S. Prescribing Information. Foster City, CA.
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Abbreviations

AE=adverse event
β2M=beta-2-microglobulin
BMD=bone mineral density
DEXA=dual-energy X-ray absorptiometry
$eGFR_{CG}$=eGFR estimated using the Cockcroft-Gault formula
FTC=emtricitabine
IRR=incidence rate ratio
MSM=men who have sex with men
OL=open-label
PrEP=pre-exposure prophylaxis
PY=person-years
Q=quartile
RAM=resistance-associated mutation
RBP=retinol-binding protein
STI=sexually transmitted infection
TAF=tenofovir alafenamide
TDF=tenofovir disoproxil fumarate
TFV=tenofovir
TFV-DP=tenofovir diphosphate
TGW=transgender women
URTI=upper respiratory tract infection

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

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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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