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Descovy for PrEP® (FTC/TAF) Lipid Safety Profile

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) and its lipid safety profile.

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

Summary

Phase 3 DISCOVER Study

Daily FTC/TAF was compared to FTC/TDF for HIV-1 PrEP in adult cisgender MSM and TGW in a phase 3, randomized, double-blind, active-controlled, clinical study.[1] The following median changes from baseline were seen at Week 96:

- Participants randomized to FTC/TAF experienced a smaller median decrease from baseline in TC, HDL, and LDL levels than those randomized to FTC/TDF (*P*<0.0001). Fasted TG levels increased in the FTC/TAF arm and decreased in the FTC/TDF arm.[2]
- TC:HDL ratio was similar with FTC/TAF and FTC/TDF (+0.1 vs 0 mmol/L, respectively; *P*=0.18).[2]
- A slightly greater proportion of participants in the FTC/TAF arm compared with the FTC/TDF arm initiated lipid-lowering agents during the study (1.6% vs 0.8%, respectively; *P*=0.008).[3]

At Week 144, a long-term analysis of participants randomized to the FTC/TDF arm at study enrollment and switched to FTC/TAF starting at Week 96 showed increases in TC, LDL, HDL, and TG (*P*<0.0001).[4-6]

Real-World Analysis

A retrospective cohort analysis was conducted using EHRs from Kaiser Permanente Southern California that evaluated outcomes including risk of statin initiation among health plan adults who started PS-matched FTC/TAF or FTC/TDF.

- Cumulative incidence of statin initiation was higher among those prescribed FTC/TAF vs matched FTC/TDF, although the incidence magnitude was small, differing by 2 cases per 100,000 PY of follow-up.[7]

Phase 3 DISCOVER Study

Study Design and Demographics

DISCOVER was a phase 3 study in 5387 HIV-negative adult MSM and TGW evaluating FTC/TAF vs FTC/TDF for HIV-1 PrEP. Prior use of FTC/TDF for HIV-1 PrEP was allowed.[1,2] The primary outcome was evaluated by 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] Efficacy was evaluated by a rate ratio with upper bound of the 95% CI below the prespecified non-inferiority margin of 1.62. All participants were unblinded after 96 weeks, and participants in both arms were offered the opportunity to continue on or switch to open-label, once-daily FTC/TAF for an additional 48 weeks. Participant baseline characteristics were similar between the FTC/TAF and FTC/TDF arms, including risk factors for HIV.[2]

Lipid Safety through Week 96

Median changes from baseline to Week 96 in TC, HDL, LDL, TG, fasting glucose, and TC:HDL ratio among participants in the DISCOVER study were evaluated (Table 1).[2]

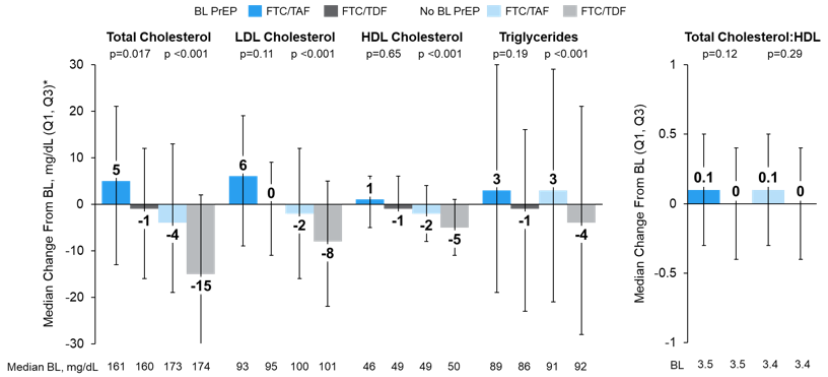
Table 1. Change from Baseline in Fasting Lipid Parameters at Week 96[2]

	FTC/TAF		FTC/TDF		*P*-value
	Median Baseline	Median Change from Baseline	Median Baseline	Median Change from Baseline	
TC (fasted), mmol/L	4.48	-0.08	4.48	-0.36	<0.0001
HDL (fasted), mmol/L	1.27	-0.03	1.3	-0.1	<0.0001
LDL (fasted), mmol/L	2.56	-0.05	2.59	-0.18	<0.0001
TG (fasted), mmol/L	1.05	0.02	1.05	-0.05	<0.0001
Glucose (fasted), mmol/L	5.11	0.11	5.11	0.11	0.63[a]
TC:HDL ratio	3.4	0.1	3.5	0	0.18[a]

[a]*P*-values from a two-sided Wilcoxon rank sum test to compare groups.

In participants on FTC/TDF for PrEP at baseline, there were no statistically significant changes from baseline in lipid parameters between the FTC/TAF and FTC/TDF arms. In participants without baseline FTC/TDF usage, there were significant differences in changes from baseline in TC, LDL, HDL, and TG between the two treatment groups (Figure 1).[8]

Figure 1. Week 96 Lipid Changes Among Baseline PrEP Users vs No Baseline PrEP[a8]

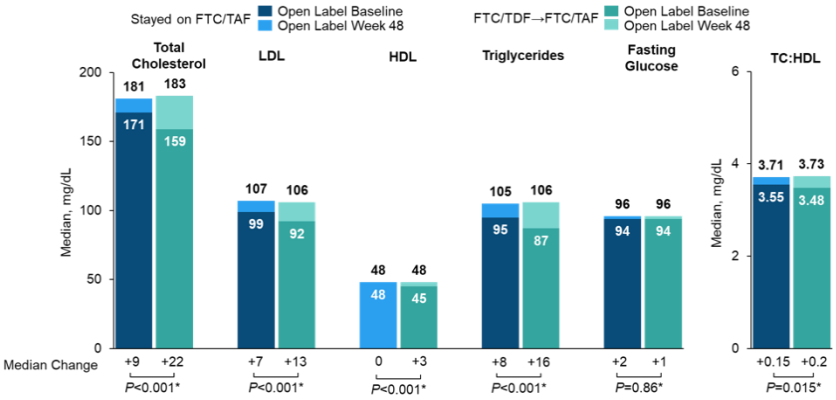


[a]*P*-values from a two-sided Wilcoxon rank sum test to compare groups.

A greater proportion of participants in the FTC/TAF arm compared with the FTC/TDF arm initiated LMAs during the study (1.6% vs 0.8%, respectively; *P*=0.008).[3] Among participants on FTC/TDF for PrEP at baseline, 3% of those who switched to FTC/TAF initiated a LMA, compared to 0.9% of participants who remained on FTC/TDF (*P*=0.03).[8]

At Week 48 of the open-label phase, median changes from baseline in TC, LDL, HDL, TG, and TC:HDL ratio were significantly greater in participants switching from FTC/TDF to FTC/TAF compared to those remaining on FTC/TAF (Figure 2).[9]

Figure 2. Median Absolute Values and Changes in Fasting Lipids at Week 48 of Open-Label Phase[a9]

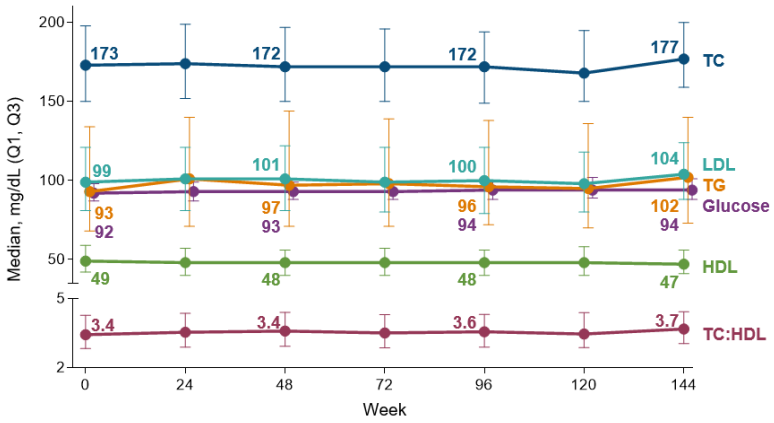


[a]*P*-values were calculated with a two-sided Wilcoxon rank sum test.

Long-Term FTC/TAF Lipid Profile through Week 144

Long-term FTC/TAF outcomes were assessed based on Week 144 results in participants who were randomized to FTC/TAF at study enrollment and continued on FTC/TAF through Week 144, including the open-label expansion (OLE). Glucose and lipid parameters were stable in participants randomized to FTC/TAF at baseline through Week 144.[4,5]

Figure 3. Fasting Lipids and Glucose Randomized to FTC/TAF at Baseline to Week 144[4]



Participants who switched to FTC/TAF from FTC/TDF in the OLE saw increases in LDL, HDL, TC and TG (*P*<0.0001) (Table 2).[5] Four percent (n=133) of participants in the FTC/TAF arm were taking LMAs upon study initiation, while 2% (n=61) initiated LMA's through Week 144.[4,5] The overall cholesterol concentrations at Week 144 of the participants who switched to FTC/TAF during OLE were similar to those who received FTC/TAF from the start of the study and throughout OLE.

Table 2. Change from Baseline at OLE in Lipid Parameters at Week 144[6]

	Cohort	Median at OLE baseline	Median at Week 144	Median Change from OLE Baseline	*P*-value[a]
LDL, mg/dL	Stay on FTC/TAF	99	107	+7	<0.001
	FTC/TDF→FTC/TAF	92	106	+13	
HDL, mg/dL	Stay on FTC/TAF	48	48	0	<0.001
	FTC/TDF→FTC/TAF	45	48	+3	
TG, mg/dL	Stay on FTC/TAF	95	105	+8	<0.001
	FTC/TDF→FTC/TAF	87	106	+16	
TC, mg/dL	Stay on FTC/TAF	171	181	+9	<0.001
	FTC/TDF→FTC/TAF	159	183	+22	
Fasting glucose, mg/dL	Stay on FTC/TAF	94	96	+2	0.86
	FTC/TDF→FTC/TAF	94	96	+1	
TC:HDL ratio	Stay on FTC/TAF	3.55	3.71	+0.15	0.015
	FTC/TDF→FTC/TAF	3.48	3.73	+0.20	
Body weight, kg	Stay on FTC/TAF	82.3	83.7	+1.2	<0.001
	FTC/TDF→FTC/TAF	81	82.4	+2	

[a]Lipid and glucose p-values from 2-sided Wilcoxon rank sum test to compare 2 study arms, weight p-values from ANOVA including treatment as fixed effect.

Real-World Analysis

A retrospective cohort analysis conducted at Kaiser Permanente Southern California examined incident hypertension and risk of statin initiation using EHRs of health plan

members ≥18 years between October 2019 and May 2022. PS-matching was conducted to generate 1 FTC/TAF:4 FTC/TDF matched sets. 6149 individuals without a history of statin use at baseline were identified (382 FTC/TAF, 5767 FTC/TDF) to serve as a pool for matching. The PS model for the statin analysis adjusted for factors including baseline age, sex, race/ethnicity, insurance, clinical measures (BMI and lipids), ASCVD risk score, and cardiometabolic comorbidities (diabetes, dyslipidemia), as well as hypertension. Compared with unmatched individuals taking FTC/TDF, those taking FTC/TAF were older, more likely to be non-Hispanic White, and less likely to have hypertension at baseline; those taking FTC/TAF had higher ASCVD risk score and shorter follow-up. Cumulative incidence of statin initiation was higher in those prescribed FTC/TAF vs matched FTC/TDF, although the incidence magnitude was small, differing by 2 cases per 100,000 PY of follow-up. The increase was also observed in the sensitivity analyses for those aged >40 years; the analysis did not establish if the association was because of age or FTC/TAF use.[7]

Table 2. Risk of Statin Initiation in Adults Initiating FTC/TAF vs FTC/TDF[7]

Population	Cumulative incidence per 100 persons (%)		Incidence per 1,000 person-years		HR (95% CI)
	FTC/TAF	Matched FTC/TDF (95% CI)	FTC/TAF	Matched FTC/TDF (95% CI)	
Main cohort (n_{TAF}=382)	1.6	1 (0.7–1.3)	0.05	0.03 (0.02–0.04)	2.3 (0.8–6.7)
≥ 40 years at index (n_{TAF}=92)	6.5	3.6 (2.6–4.6)	0.18	0.1 (0.06–0.15)	2.7 (0.9–8.5)

References

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4. Ramgopal M, Ruane P, Shalit P, et al. Long-term Outcomes of Participants on F/TAF for Pre-Exposure Prophylaxis: Results for 144 Weeks of Follow-Up in the DISCOVER Trial [Poster 854]. 2021:
5. Wohl DA, Spinner CD, Flamm J, et al. HIV-1 infection kinetics, drug resistance, and long-term safety of pre-exposure prophylaxis with emtricitabine plus tenofovir alafenamide (DISCOVER): week 144 open-label extension of a randomised, controlled, phase 3 trial. *Lancet HIV*. 2024;11(8):508-521.

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Abbreviations

ASCVD=Atherosclerotic Cardiovascular Disease
EHRs=electronic health records
FTC=emtricitabine
HDL=high-density lipoprotein
LDL=low-density lipoprotein
LMA=lipid-modifying agent
MSM=men who have sex with men
OLE=open-label extension
PrEP=pre-exposure prophylaxis
PS=propensity score
PY=person-years
TAF=tenofovir alafenamide
TC=total cholesterol
TDF=tenofovir disoproxil fumarate
TG=triglyceride
TGW=transgender women

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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