GILEAD | Medical Information

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

This document is in response to your request for information regarding the hepatic safety profile of Descovy for PrEP® (emtricitabine/tenofovir alafenamide [FTC/TAF] for HIV-1 pre-exposure prophylaxis [PrEP]) in HIV-negative individuals.

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]

Severe acute exacerbations of HBV have been reported in HBV-infected individuals who have discontinued products containing FTC and/or TDF and may occur with discontinuation of FTC/TAF.

Hepatic function should be monitored closely with both clinical and laboratory follow-up for at least several months in individuals with HBV and discontinue FTC/TAF. If appropriate, anti-HBV therapy may be warranted.

Clinical Data on the Hepatic Safety Profile of FTC/TAF

Once-daily FTC/TAF was compared with FTC/TDF for HIV-1 PrEP among adult MSM and TGW in a phase 3 randomized, double-blind, active-controlled, multinational clinical trial.[2] AST elevations of Grade ≥3 occurred more frequently in participants randomly assigned to FTC/TAF than FTC/TDF (3% vs 2%), and ALT elevations of Grade ≥3 occurred at the same rate (2%) in both arms.[2,3]

Product Labeling[1]

Indications and Usage

HIV-1 PrEP

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.

Warnings and Precautions

Severe acute exacerbation of Hepatitis B in individuals with HBV infection

All individuals should be tested for the presence of HBV before or when initiating FTC/TAF.

Severe acute exacerbations of hepatitis B (eg, liver decompensation and liver failure) have been reported in HBV-infected individuals who have discontinued products containing FTC and/or TDF and may occur with discontinuation of FTC/TAF. Individuals with HBV who discontinue FTC/TAF should be closely monitored with both clinical and laboratory follow-up for at least several months after stopping treatment. If appropriate, anti-hepatitis B therapy may be warranted, especially in individuals with advanced liver disease or cirrhosis since post-treatment exacerbation of hepatitis may lead to hepatic decompensation and liver failure. HBV-uninfected individuals should be offered vaccination.

Lactic acidosis/severe hepatomegaly with steatosis

Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported with the use of nucleoside analogs, including FTC, a component of FTC/TAF, and TDF, another prodrug of TFV, alone or in combination with other antiretrovirals. Treatment with FTC/TAF should be suspended in any individual who develops clinical or laboratory findings suggestive of lactic acidosis or pronounced hepatotoxicity (which may include hepatomegaly and steatosis even in the absence of marked transaminase elevations).

Use in Specific Populations

Hepatic impairment

No dosage adjustment of FTC/TAF is recommended in individuals with mild (Child-Pugh Class A) or moderate (Child-Pugh Class B) hepatic impairment. FTC/TAF has not been studied in individuals with severe hepatic impairment (Child-Pugh Class C).

Clinical Pharmacology

PK

Patients with hepatic impairment

The PK of FTC has not been studied in subjects with hepatic impairment; however, FTC is not significantly metabolized by liver enzymes, so the impact of hepatic impairment should be limited.

Clinically relevant changes in TFV PK in subjects with hepatic impairment were not observed in subjects with mild to moderate (Child-Pugh Class A and B) hepatic impairment.

HBV and/or HCV infection

The PK of FTC and TAF have not been fully evaluated in subjects infected with HBV and/or HCV.

Clinical Data on the Hepatic Safety Profile of FTC/TAF

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

Study design and demographics

DISCOVER (NCT02842086) is a phase 3, randomized, double-blind, active-controlled, multinational study in 5387 HIV-negative adult MSM and TGW that is evaluating the safety and efficacy of once-daily FTC/TAF (n=2694) vs FTC/TDF (n=2693), both of which are fixed-dose combination products administered once daily for HIV-1 PrEP. Key inclusion criteria were individuals aged ≥18 years, HIV- and HBV-negative, with eGFR ≥60 mL/min, and at high risk of sexual acquisition of HIV (defined as ≥2 episodes of condomless anal intercourse with ≥2 unique male partners of HIV-positive or unknown HIV status within the previous 12 weeks, or a documented history of syphilis, rectal gonorrhea, or rectal chlamydia in the previous 24 weeks). Prior use of FTC/TDF for HIV-1 PrEP was allowed.[2,3] Participants had adequate hepatic function, defined as AST and ALT ≤2.5 × the upper limit of normal and total bilirubin ≤1.5 mg/dL, or normal direct bilirubin.[4]

Eligible participants were randomly assigned 1:1 to receive either FTC/TAF 200/25 mg or FTC/TDF 200/300 mg with a corresponding placebo once daily. Follow-up visits occurred at baseline and every 12 weeks.[2,3] The primary measured outcome was the incidence of HIV-1 per 100 person years after all participants had ≥48 weeks of follow-up and ≥50% of participants had 96 weeks of follow-up, with a pre-specified non-inferiority margin of 1.62, representing the upper bound of the 95% CI for the measured incidence rate ratio of FTC/TAF over FTC/TDF.[2] All participants were unblinded after 96 weeks, and participants in both arms were offered the opportunity to continue on or switch to an ongoing open-label, once-daily FTC/TAF for an additional 48 weeks.[2,3]

Participant baseline characteristics were similar between the FTC/TAF and FTC/TDF arms, including risk factors for HIV acquisition.[2]

Hepatic safety results

Treatment-emergent hepatic laboratory abnormalities of Grade ≥3 occurred at similar rates in both treatment groups at primary analysis (Table 1).[2]

Table 1. DISCOVER: Hepatic Laboratory Abnormalities (Grade 3–4) Reported in ≥1% of Participants at Primary Analysis[2a]

Grade 3 or 4 Laboratory Abnormality, n (%)	FTC/TAF (n=2694)	FTC/TDF (n=2693)
ALT increase	39 (1)	40 (2)
AST increase	63 (2)	51 (2)

[a]Participants were counted once for the maximum postbaseline severity for each laboratory test.

In the secondary analysis at 96 weeks, hepatic laboratory abnormalities of Grade ≥3 also occurred at similar rates in both treatment groups (Table 2).[2]

Table 2. DISCOVER: Hepatic Laboratory Abnormalities (Grade 3–4) Reported in ≥1% of Participants at 96 Weeks[3a]

Grade 3 or 4 Laboratory Abnormality, n (%)	FTC/TAF (n=2694)	FTC/TDF (n=2693)
ALT increase	47 (2)	44 (2)
AST increase	73 (3)	60 (2)

[a]Participants were counted once for the maximum postbaseline severity for each laboratory test.

Clinical Guidelines

No clinical guidelines have been established that address the frequency of LFTs during the use of FTC/TAF for HIV-1 PrEP. Providers should use their clinical judgment to determine the appropriate schedule for LFTs.

References

1. Enclosed. Gilead Sciences Inc, DESCOVY® (emtricitabine and tenofovir alafenamide) tablets, for oral use. U. S. Prescribing Information. Foster City, CA.
2. Mayer KH, Molina JM, Thompson MA, et al. Emtricitabine and tenofovir alafenamide vs emtricitabine and tenofovir disoproxil fumarate for HIV pre-exposure prophylaxis (DISCOVER): primary results from a randomised, double-blind, multicentre, active-controlled, phase 3, non-inferiority trial. *Lancet.* 2020;396(10246):239-254.
3. Ogbuagu O, Ruane PJ, Podzamczer D, et al. Long-term safety and efficacy of emtricitabine and tenofovir alafenamide vs emtricitabine and tenofovir disoproxil fumarate for HIV-1 pre-exposure prophylaxis: week 96 results from a randomised, double-blind, placebo-controlled, phase 3 trial. *The lancet. HIV.* 2021;8:e397-e407.
4. Ogbuagu O, Ruane PJ, Podzamczer D, et al. Supplementary appendix Long-term safety and efficacy of emtricitabine and tenofovir alafenamide vs emtricitabine and tenofovir disoproxil fumarate for HIV-1 pre-exposure prophylaxis: week 96 results from a randomised, double-blind, placebo-controlled, phase 3 trial. *The lancet. HIV.* 2021;8(7):1-21.

Abbreviations

FTC=emtricitabine
LFT=liver function test
MSM=men who have sex with men
PK=pharmacokinetic(s)
PrEP=pre-exposure prophylaxis
TAF=tenofovir alafenamide
TDF=tenofovir disoproxil fumarate
TFV=tenofovir
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

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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