GILEAD | Medical Information

# Descovy for PrEP® (FTC/TAF) Development of Resistance

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 development of resistance.

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 use of FTC/TAF for prevention of HIV-1 in individuals at risk of HIV-1 from receptive vaginal sex is investigational and has not been approved by any regulatory authority. The full indication, important safety information, and boxed warnings are available at:**
**www.gilead.com/-/media/files/pdfs/medicines/hiv/descovy/descovy_pi;**
**www.gilead.com/-/media/files/pdfs/medicines/hiv/truvada/truvada_pi;**
**www.gilead.com/-/media/files/pdfs/medicines/hiv/yeztugo/yeztugo_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.

### Clinical Data on FTC/TAF for PrEP and Development of Resistance

A subanalysis of resistance outcomes through Week 144 in participants from the DISCOVER study showed overall low rates of resistance in the FTC/TAF group. Most HIV cases occurred in participants with low adherence (<2 tablets/week) or suspected baseline HIV.[2]

In the PURPOSE 1 study, most participants in the FTC/TAF group had low adherence (<2 tablets/week) or a decrease in adherence over time.[3] Two participants in the FTC/TAF group developed RAMs: 1 participant with low adherence at the time of HIV diagnosis had M184I at Week 26, and 1 participant had high adherence at HIV diagnosis at Week 8 with multiple RAMs (M184I, K65R, Y188L).[4] There were no significant delays in HIV diagnosis among participants who acquired HIV.[3,5]

# Clinical Data on FTC/TAF for PrEP and Development of Resistance

## DISCOVER Study

### Study design and demographics

DISCOVER was a phase 3, multinational study in 5387 HIV-negative adult MSM and TGW that evaluated the safety and efficacy of FTC/TAF vs FTC/TDF for HIV-1 PrEP. Prior use of FTC/TDF for HIV-1 PrEP was allowed.[6,7]

The primary measured 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.[6] Efficacy was evaluated by a rate ratio with the 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 (Table 1).[7]

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

| Key Demographics and Characteristics | | 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) |
| | Black[a] | 240 (9) | 234 (9) |
| | Asian | 113 (4) | 120 (5) |
| | Hispanic or Latinx | 635 (24) | 683 (25) |
| TGW, n (%) | | 45 (2) | 29 (1) |
| HIV risk factors, % | ≥2 instances of receptive condomless anal sex in the past 12 weeks | 62 | 60 |
| | Syphilis in the past 24 weeks | 9 | 10 |
| | Received FTC/TDF for HIV-1 PrEP at baseline | 17 | 16 |

[a]Included mixed Black race.

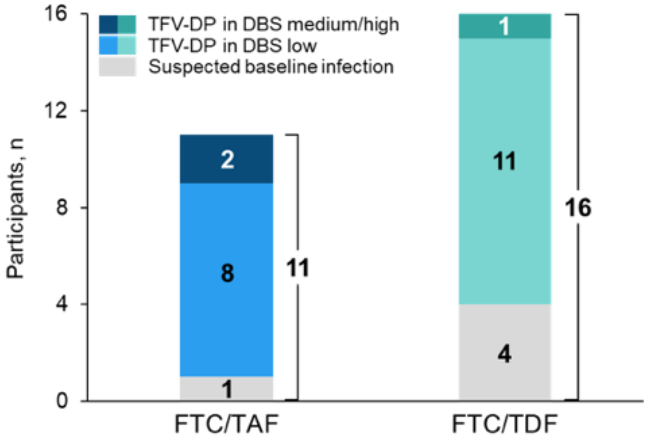
### Results

The primary endpoint had a total follow-up of 8756 PY (FTC/TAF, 4370 PY; FTC/TDF, 4386 PY) and included data from all participants with ≥48 weeks of follow-up and ≥50% of participants with 96 weeks of follow-up. There were a total of 22 HIV diagnoses (FTC/TAF, n=7; FTC/TDF, n=15), for an HIV incidence rate of 0.16 per 100 PY and 0.34 per 100 PY, respectively. The incidence rate ratio between the FTC/TAF and FTC/TDF arms was 0.47 (95% CI: 0.19–1.15), establishing non-inferiority of FTC/TAF to FTC/TDF.[6]

When all participants reached Week 96, there was a total follow-up of 10,081 PY (FTC/TAF, 5029 PY; FTC/TDF, 5052 PY) with 23 total HIV cases (FTC/TAF, n=8 and FTC/TDF, n=15), for an HIV incidence rate of 0.16 per 100 PY and 0.30 per 100 PY, respectively. The IRR was 0.54 (95% CI: 0.23–1.26), demonstrating the continued non-inferiority of FTC/TAF to FTC/TDF at 96 weeks.[7]

At Week 144, 27 total HIV diagnoses were reported (FTC/TAF, n=11; FTC/TDF, n=16). Five participants had suspected baseline infections, and low levels of TFV-DP were found in 19 participants on DBS analysis (Figure 1).[8,9]

**Figure 1. DISCOVER: Adherence and Resistance Analyses of HIV Diagnoses[8a]**




[a]Updated with data cut through Week 118. Adherence cutoffs per fmol/punches for FTC/TAF were as follows: low, <450; medium, ≥450 to <900; high, ≥900. Adherence cutoffs per fmol/punches for FTC/TDF were as follows: low, <350; medium ≥350 to <700; high ≥700.

Using standard sequencing, the development of FTC RAMs M184I and/or M184V was observed in 4 participants who seroconverted in the FTC/TDF group and were suspected to have had HIV at baseline. Ultrasensitive sequencing had similar resistance data, with the addition of an M184V mutation detected in 1 participant in the FTC/TAF arm who had low DBS TFV-DP levels at the time of diagnosis and 1 participant with possible low-level K65R mutation in the FTC/TDF arm.[10] Among 13 participants who seroconverted with drug resistance and initiated an ARV therapy regimen, 10 achieved virologic suppression, and 3 were lost to follow up.[8] In a sensitivity analysis that excluded 5 participants with suspected baseline HIV, FTC/TAF non-inferiority to FTC/TDF was maintained (IRR, 0.64; 95% CI: 0.25–1.65).[7]

# PURPOSE-1 Study

## Study design and demographics

PURPOSE 1 is a phase 3 ongoing, double-blind, randomized study evaluating the efficacy and safety of twice-yearly SUBQ LEN and once-daily oral FTC/TAF for HIV-1 PrEP in >5300 cisgender women and adolescent girls across South Africa and Uganda. Additionally, a third group was assigned once-daily oral FTC/TDF, which served as the active control. Study participants were randomly assigned in a 2:2:1 ratio to LEN, FTC/TAF, and FTC/TDF, respectively. Randomly assigned participants were seen for follow-up at Weeks 4, 8, and 13 and every 13 weeks thereafter. A planned interim analysis occurred when 50% of the randomly assigned participants had completed at least 52 weeks of follow-up.[3]

Key inclusion criteria in the randomized phase of the study included the following: negative fourth-generation HIV-1 Ab/Ag test confirmed with central HIV-1 testing, eGFR ≥60 mL/min at screening, and body weight ≥35 kg. Individuals were excluded if they had prior use of long-acting systemic HIV PrEP or HIV post-exposure prophylaxis in the past 12 weeks.[11]

**Table 2. PURPOSE 1: Baseline Demographics and HIV Risk Factors[3]**

| Key Demographics and Characteristics | | LEN (n=2138) | FTC/TAF (n=2137) | FTC/TDF (n=1070) |
|---|---|---|---|---|
| Age, median (range), years | | 21 (16–25) | 21 (16–26) | 21 (16–25) |
| Black race,[a] n (%) | | 2135 (99.9) | 2136 (>99.9) | 1068 (99.8) |
| Education, n/N (%) | No primary school | 17/2136 (0.8) | 19/2134 (0.9) | 3/1069 (0.3) |
| | Primary school | 235/2136 (11) | 223/2134 (10.4) | 106/1069 (9.9) |
| | Secondary school | 1701/2136 (79.6) | 1694/2134 (79.4) | 851/1069 (79.6) |
| | College or university | 183/2136 (8.6) | 198/2134 (9.3) | 109/1069 (10.2) |
| Living with primary partner, n/N (%) | | 148/2136 (6.9) | 132/2134 (6.2) | 73/1069 (6.8) |
| Any previous use of PrEP, n (%) | | 143 (6.7) | 121 (5.7) | 71 (6.6) |

[a]Race was reported by the participants. All non-Black participants were multiracial.

## Results

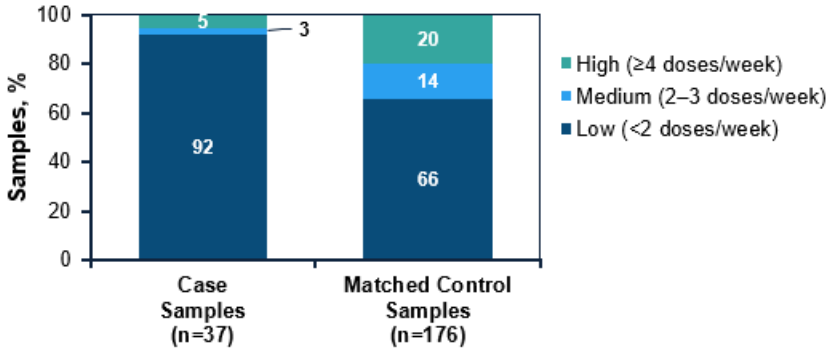
At the primary analysis, there were a total of 55 HIV infections (FTC/TAF, n=39 per 1932 PY; FTC/TDF, n=16 per 949 PY), with incidence rates of 2.02 and 1.69 per 100 PY in the FTC/TAF and FTC/TDF groups, respectively. The incidence of HIV in the FTC/TAF group was neither statistically significantly different from the background HIV incidence (IRR, 0.84; 95% CI: 0.55–1.28; *P*=0.21) nor the HIV incidence in the FTC/TDF group (IRR, 1.2; 95% CI: 0.67–2.14; *P*-value not provided).[5]

Adherence levels were defined as low (<2 tablets per week), medium (2 or 3 tablets per week), or high (≥4 tablets per week) based on TFV-DP concentration thresholds previously established for TAF and TDF. Among the preselected 10% sample of participants in the FTC/TAF group who had TFV-DP levels assessed, 34% at Week 8 and 84% at Week 52 had low adherence.[12]

The resistance analysis population included 53 participants (FTC/TAF, n=37; FTC/TDF, n=16) who acquired HIV during the randomized blinded phase and had HIV-1 RNA ≥200 c/mL.[4] Most participants in the FTC/TAF group had low adherence or a decrease in adherence over time. Emergence of ARV resistance was rare in participants in the FTC/TAF group. In an analysis of 2 participants with RAMs, 1 participant with M184I had low TFV-DP levels at HIV diagnosis at Week 26, and 1 participant had high TFV-DP levels at HIV diagnosis at Week 8 and RAMs consistent with transmitted drug resistance (ie, M184I, K65R, Y188L).[5] One participant had unrecognized HIV-1 at baseline; M184M/V was detected on Day 41, and the participant achieved virologic suppression (HIV-1 RNA <200 c/mL) on another regimen.[4] There were no significant delays in HIV diagnosis among participants who acquired HIV, suggesting that FTC/TAF did not cause a delay in diagnosis in individuals with low adherence.[5]

To assess the association between adherence and efficacy, a matched case-control analysis was conducted among participants in the FTC/TAF group who acquired HIV; up to 5 controls were selected and matched on the basis of trial site and VOICE risk score for HIV acquisition. TFV-DP levels in DBS were measured from the HIV diagnosis visit or from a time-matched visit for controls. Of the 39 participants in the FTC/TAF group with incident HIV acquisition, 2 participants had missing data, and 34 of the remaining 37 participants (92%) had low or no detection of TFV-DP (Figure 2). Participants with medium or high adherence had lower odds of acquiring HIV than participants with low adherence (OR, 0.11; 95% CI, 0.01–0.49).[3]

**Figure 2. PURPOSE 1: A Case-Control Analysis of FTC/TAF Adherence and Efficacy[3]**

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# Abbreviations

ARV=antiretroviral
DBS=dried blood spots
FTC=emtricitabine
IRR=incidence rate ratio
LEN=lenacapavir
MSM=men who have sex with men
PrEP=pre-exposure prophylaxis
PY=person-years
RAM=resistance-associated mutations
SUBQ=subcutaneous(ly)
TAF=tenofovir alafenamide
TDF=tenofovir disoproxil fumarate
TFV-DP=tenofovir diphosphate
TGW=transgender women
VOICE=Vaginal and Oral Interventions to Control the Epidemic

# Product Label

For the full indication, important safety information, and boxed warning(s), please refer to please refer to the Descovy, Truvada, and Yeztugo US Prescribing Information available at:
www.gilead.com/-/media/files/pdfs/medicines/hiv/descovy/descovy_pi;
www.gilead.com/-/media/files/pdfs/medicines/hiv/truvada/truvada_pi;
www.gilead.com/-/media/files/pdfs/medicines/hiv/yeztugo/yeztugo_pi.

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🖱 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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