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Descovy for PrEP® (FTC/TAF) Available Data in Cisgender Women

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 available data regarding its use in cisgender women (CGW). This response was developed according to principles of evidence-based medicine and contains data from Phase 3 studies.

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 warning(s) 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.[1]

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 of FTC/TAF for HIV-1 PrEP in CGW

PURPOSE 1 is an ongoing phase 3, double-blind, randomized study evaluating the efficacy and safety of twice-yearly SUBQ LEN (n=2138) and once-daily oral FTC/TAF (n=2137) or FTC/TDF (active control; n=1070) for HIV-1 PrEP in 5345 CGW and adolescent girls (16–25 years old) across South Africa and Uganda.[2]

- At the time of primary analysis, 39 participants acquired HIV in the FTC/TAF group (incidence rate: 2.02 per 100 PY), 16 cases occurred in the FTC/TDF group (incidence rate: 1.69 per 100 PY), and 0 cases occurred in the LEN group. The bHIV in the screened population was 2.41 per 100 PY.[2]
- The incidence rate of HIV in the FTC/TAF group was not different from the bHIV (IRR, 0.84; 95% CI: 0.55–1.28; *P*=0.21), and there was no evidence of a difference from the incidence rate in the FTC/TDF group (IRR, 1.2; 95% CI: 0.67–2.14). LEN significantly

reduced the incidence rate of HIV by 100% compared with FTC/TDF (IRR, 0; 95% CI: 0–0.1; *P*<0.001) and with bHIV (IRR, 0; 95% CI: 0–0.04; *P*<0.001).[2]

- At the end of the RBP, 52 participants acquired HIV in the FTC/TAF group (incidence rate, 1.98), 25 cases occurred in the FTC/TDF group (incidence rate, 1.94), and 2 cases occurred in the LEN group (incidence rate, 0.07).[3]
- FTC/TAF, LEN, and FTC/TDF were all generally well tolerated, with few discontinuations due to study drug-related AEs. The overall incidences of non-ISR AEs were generally similar across groups. Nausea and vomiting occurred at higher rates in the FTC/TAF and FTC/TDF groups than in the LEN group. ISRs were the most common AE in all groups and occurred at a higher rate with LEN than with the placebo injections that participants in the FTC/TAF and FTC/TDF groups received.[2]

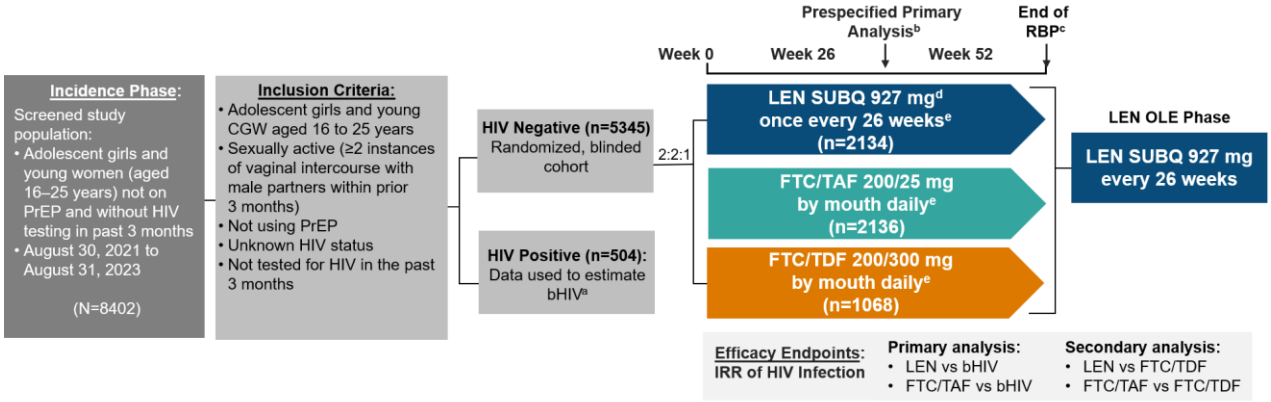
Clinical Data on FTC/TAF for HIV-1 PrEP in CGW

Phase 3 Study: PURPOSE 1

Study design and demographics

PURPOSE 1 (NCT04994509) is an ongoing, phase 3, double-blind, randomized, active-controlled study evaluating the efficacy and safety of twice-yearly SUBQ LEN and once-daily oral FTC/TAF for HIV-1 PrEP in CGW 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. Eligible women and adolescent girls were tested for HIV at screening, and those who tested negative were randomly assigned in a 2:2:1 ratio to receive LEN 927 mg SUBQ every 26 weeks, FTC/TAF 200/25 mg orally daily, or FTC/TDF 200/300 mg orally daily (Figure 1). Those who tested positive for HIV at screening were referred for care at a local center, and their samples underwent additional testing to determine the recency of HIV; these data were used to estimate the bHIV that would be expected without PrEP. Participants who discontinued blinded study drug were given the option to take open-label FTC/TDF. Testing for HIV in the randomized cohort was conducted at Weeks 4, 8, and 13 and every 13 weeks thereafter.[2]

Figure 1. PURPOSE 1: Study Design[2-4]



[a]The bHIV was determined based on a cross-sectional incidence estimate derived from rates of recent HIV in 8094 screened participants; these participants were not followed longitudinally.
[b]The prespecified primary analysis was when 50% of participants had completed ≥52 weeks of follow-up.
[c]Participants who were on blinded LEN in the RBP and declined open-label LEN were offered up to 78 weeks of open-label FTC/TDF.

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[d]All participants randomly assigned to receive LEN received an initial loading dose of LEN, which consisted of 600 mg (two 300-mg tablets) administered on Days 1 and 2.
[e]Participants in the LEN SUBQ group also received placebo FTC/TAF or placebo FTC/TDF (2:1), and participants in the FTC/TAF and FTC/TDF groups also received placebo LEN oral loading doses and placebo LEN SUBQ.

A total of 5345 participants were randomly assigned and received ≥1 dose of study drug. Baseline characteristics at randomization among the three treatment groups were similar. Overall retention in the study was high and was similar across treatment groups, with 4855/5020 participants (96.7%) completing 26 weeks of follow-up, 2439/2612 participants (93.4%) completing 52 weeks, and 39/43 participants (91%) completing 104 weeks.[2]

An independent committee determined that the planned interim efficacy analysis (when 50% of participants had completed ≥52 weeks of follow-up; data cutoff for clinical data, May 28, 2024, and data cutoff for laboratory data, May 29, 2024) met the prespecified criteria for stopping the RBP portion of the trial and became the primary analysis. Starting July 8, 2024, all participants were offered open-label LEN.[2]

Table 1. PURPOSE 1: Baseline Demographics[2]

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)
	16 or 17 years of age, n (%)	56 (2.6)	45 (2.1)	23 (2.1)
Black race, n (%)		2135 (99.9)	2136 (>99.9)	1068 (99.8)
Living with primary partner, n/N (%)		148/2136 (6.9)	132/2134 (6.2)	73/1069 (6.8)
Previous use of PrEP, n (%)		143 (6.7)	121 (5.7)	71 (6.6)
Previously tested for HIV, n (%)		1713 (80.1)	1731 (81)	860 (80.4)
Time since last HIV test, median (IQR), months		6.8 (4.7–11.5)	6.6 (4.8–11)	6.5 (4.6–11)
Country, n (%)	South Africa	1809 (84.6)	1790 (83.8)	909 (85)
	Uganda	329 (15.4)	347 (16.2)	161 (15)

Primary and secondary efficacy analyses results[2]

A total of 55 incident HIV acquisitions occurred in the randomized cohort: 39 HIV cases occurred in the FTC/TAF group (1932 PY; Figure 2), 16 HIV cases occurred in the FTC/TDF group (949 PY), and no participants in the LEN group acquired HIV (1939 PY). The bHIV in the screened population was 2.41 per 100 PY. The incidence rate of HIV in the FTC/TAF group did not significantly differ from the bHIV (IRR, 0.84; 95% CI: 0.55–1.28; *P*=0.21), and there was no evidence of difference from the incidence of HIV with FTC/TDF (IRR, 1.2; 95% CI: 0.67–2.14). LEN significantly reduced the incidence rate of HIV by 100% compared with both the bHIV (*P*<0.001) and the rate with FTC/TDF (*P*<0.001; Figure 3).

Figure 2. PURPOSE 1: Incidence of HIV (Modified ITT Population)[2]

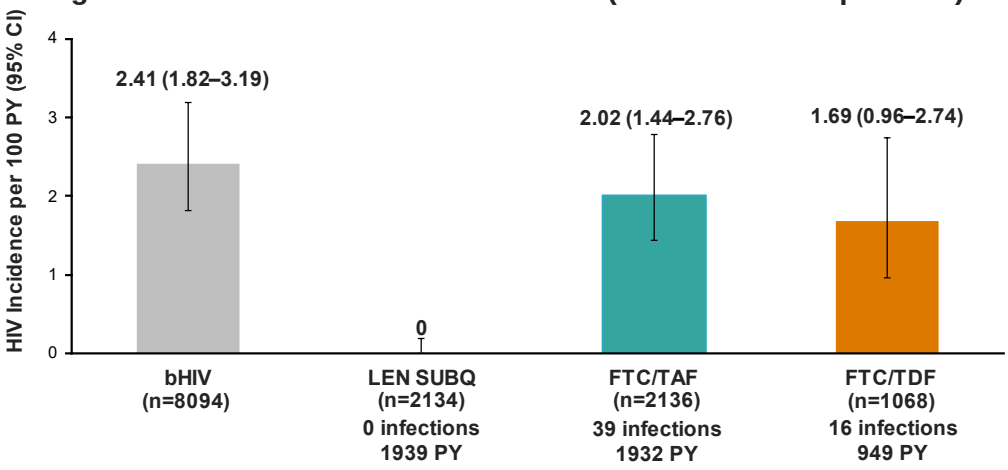
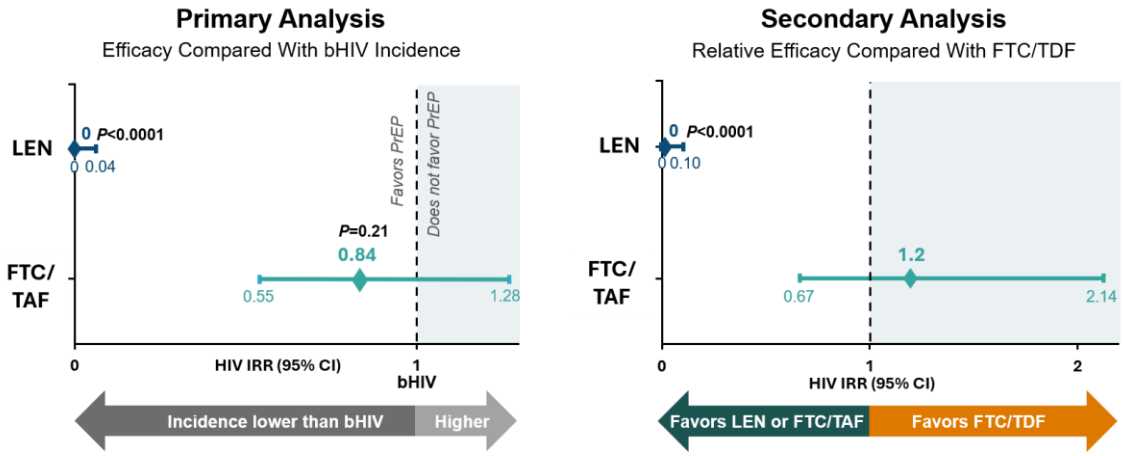


Figure 3. PURPOSE 1: Primary and Secondary Analyses[5,2]



End-of-RBP efficacy analysis[3]

The follow-up analysis conducted at the end of the RBP included all data from the RBP and from follow-up after the first dose of open-label oral PrEP was administered after early discontinuation of study drug during the RBP or after any PrEP was stopped during the study and on or before the first dose of open-label LEN was administered.

Through the end of the RBP, there were 79 incident HIV cases, comprising 52 cases in the FTC/TAF group (2630 PY; incidence rate, 1.98; 95% CI: 1.48–2.59), 25 in the FTC/TDF group (1291 PY; incidence rate, 1.94; 95% CI: 1.25–2.86), and 2 in the LEN group (2953 PY; incidence rate, 0.07; 95% CI: 0.01–0.25).

Adherence results at primary analysis[2]

Adherence to FTC/TAF and FTC/TDF was evaluated at study visits using DBS analysis of TDF levels in 10% of participants, who were randomly preselected from each group. Adherence in the 10% sample of participants in the FTC/TAF and FTC/TDF groups was low and decreased over time. At Week 8, in the FTC/TAF and FTC/TDF groups, adherence was low (<2 doses/week) in 34% and 50% of participants, respectively; at Week 52, adherence was low in 84% and 93%. Among participants who acquired HIV and had data available, 34/37 participants in the FTC/TAF group and 13/14 participants in the FTC/TDF group had

low or undetectable levels of TDF. In a matched case-control analysis to assess the association between adherence and efficacy in the FTC/TAF group, participants with medium (2 or 3 doses/week) or high (≥4 doses/week) adherence had lower odds of acquiring HIV than those with low adherence (odds ratio, 0.11; 95% CI: 0.01–0.49).

Adherence to LEN was defined as on-time injections (within 28 weeks after the last injection). Most participants received their injections (LEN and placebo LEN) on time at Weeks 26 (91.5%; 4545/4967) and 52 (92.8%; 2025/2181), and adherence to injections was similar across the groups.

Persistence results at primary analysis[6]

Persistence with daily oral FTC/TAF or FTC/TDF was assessed by TFV-DP concentration in DBS at Weeks 13, 26, 39, and 52. Compared with LEN injections, persistence to daily oral FTC/TAF or FTC/TDF was significantly lower, with 5.2% of participants (n=153) having DBS TFV-DP concentrations consistent with ≥4 doses/week through Week 52 (P<0.0001).

Persistence with LEN was defined as on-time injections (within 28 weeks after the last injection) at Week 26 and Week 52. Persistence was evaluated in 10% of participants, who were randomly preselected from each group and limited to those who had ≥1 year of study follow-up at time of interim analysis. Most participants demonstrated high persistence to LEN and placebo LEN, with 79.5% on LEN (n=112), 81.8% on FTC/TAF with placebo LEN (n=99), and 75.9% on FTC/TDF with placebo LEN (n=54) with on-time injections at Week 26 and Week 52.

Resistance data through end of RBP

Overall, 55 of the 5338 participants in the primary analysis acquired HIV-1 after Day 1 (FTC/TAF, n=39; FTC/TDF, n=16; LEN, n=0). Results of central laboratory testing of samples collected on Day 1 identified 7 participants who had unrecognized HIV-1 at baseline (LEN, n=4; FTC/TDF, n=2; FTC/TAF, n=1). Of the 39 participants in the FTC/TAF group who acquired HIV-1, 37 were analyzed for resistance, and reverse transcriptase genotypic data were available for 36 participants. Resistance-associated substitutions were detected in 2 of these participants. Participant A had the NRTI substitution M184M/I in RT at HIV-1 diagnosis at Week 26; adherence was low at Week 4, improved by Week 13, and declined around the time of HIV-1 diagnosis. Participant B had both NRTI substitutions M184M/I and K65K/R in RT and the NNRTI substitution Y188L; adherence was high through HIV-1 diagnosis at Week 8.[7]

Through the end of the RBP, an additional 24 participants acquired HIV-1 (FTC/TAF, n=13; FTC/TDF, n=9; LEN, n=2). Among these participants, 1 participant in the FTC/TAF group developed the NRTI resistance mutation M184M/V/I; adherence was medium to high through Week 13 and was low through HIV-1 diagnosis at around Week 65.[4]

Safety results at primary analysis

FTC/TAF, LEN, and FTC/TDF were generally well tolerated, with higher rates of nausea and vomiting AEs in the FTC/TAF and FTC/TDF groups than in the LEN group (Table 2). LEN ISRs were relatively common, and most were Grade 1 or 2. Six deaths occurred, all in the FTC/TAF group; none of these were considered by the investigator to be related to study drug.[2]

The most common AEs were ISRs.[2] A total of 25,329 injections were administered, with 10,154 administered to 2138 participants in the LEN group and 15,175 administered to

3206 participants receiving placebo injection in the FTC/TAF and FTC/TDF groups. SUBQ nodules, injection site pain, and swelling were the most common ISRs; these events occurred in 63.8%, 31.2%, and 4.4% of participants, respectively, who received LEN injections and in 16.6%, 23.7%, and 5.4% of participants, respectively, who received placebo injections.[8] No Grade 4 ISRs occurred, and the frequency of ISRs decreased over time. No keloid scars were reported in any group.

Table 2. PURPOSE 1: Safety Summary at Primary Analysis[2]

AE, n (%)		Primary Analysis		
		LEN (n=2138)	FTC/TAF (n=2137)	FTC/TDF (n=1070)
Any AE (excluding ISRs)		1631 (76.3)	1665 (77.9)	830 (77.6)
Grade ≥3 AE		88 (4.1)	95 (4.4)	50 (4.7)
SAE		59 (2.8)	85 (4)	35 (3.3)
AEs that led to discontinuation of study drug[a]		5 (0.2)	2 (<0.1)	0
Common AEs in ≥5% of participants in any group (excluding ISRs)	UTI	307 (14.4)	305 (14.3)	163 (15.2)
	Genitourinary tract chlamydia infection	300 (14)	317 (14.8)	129 (12.1)
	Headache	285 (13.3)	352 (16.5)	155 (14.5)
	URTI	271 (12.7)	274 (12.8)	121 (11.3)
	Vaginal discharge	166 (7.8)	191 (8.9)	87 (8.1)
	Vulvovaginal candidiasis	146 (6.8)	172 (8)	67 (6.3)
	Nausea	144 (6.7)	234 (10.9)	142 (13.3)
	Genitourinary tract gonococcal infection	141 (6.6)	157 (7.3)	66 (6.2)
	Diarrhea	133 (6.2)	161 (7.5)	67 (6.3)
	Vomiting	125 (5.8)	235 (11)	107 (10)
	Dizziness	120 (5.6)	141 (6.6)	79 (7.4)
Laboratory abnormalities[b]	Any	1929 (90.7)	1904 (90.1)	959 (91)
	Grade 3	92 (4.3)	81 (3.8)	50 (4.7)
	Grade 4	20 (0.9)	22 (1)	11 (1)
ISRs[c]	Any related to LEN, placebo LEN, or trial procedures	1470 (68.8)	755 (35.3)	363 (33.9)
	Led to discontinuation of study drug	4 (0.2)	0	0
	Grade 3[d]	4 (0.2)	2 (<0.1)	2 (0.2)

Abbreviations: MedDRA=Medical Dictionary for Regulatory Activities; SAE=serious adverse event, URTI=upper respiratory tract infection; UTI=urinary tract infection.

[a]AEs that led to discontinuation of LEN were nausea (n=1), decreased CrCl (n=1), increased liver enzyme levels (n=1), spontaneous abortion (n=1), and suicide attempt with major depression (n=1). In the FTC/TAF group, AEs that led to discontinuation were suicide attempt, depressive symptoms, and drug overdose (n=1, all in the same participant) and angioedema (n=1).

[b]Percentages shown are based on the number of participants who had ≥1 postbaseline laboratory result (LEN, n=2126; FTC/TAF, n=2113; FTC/TDF, n=1054).

[c]Reactions to trial-related injections only; percentages shown are based on the number of participants who received ≥1 placebo or LEN injection (LEN, n=2138; FTC/TAF, n=2136; FTC/TDF, n=1070).

[d]Grade 3 ISRs consisted of injection site ulcer (LEN, n=3; FTC/TAF, n=2; FTC/TDF, n=1), nodule (LEN, n=1), and pain (FTC/TDF, n=1).

Note: All AEs were coded according to MedDRA v27.0.

Pregnancy outcomes at primary analysis

Pregnancies occurred in 487 participants, with a total of 509 pregnancies (LEN, n=193; FTC/TAF, n=218; FTC/TDF, n=98). Five participants acquired HIV-1 during pregnancy (FTC/TAF, n=4; FTC/TDF, n=1); none of these cases occurred in the LEN group, and there were no cases of vertical transmission in any group. Pregnancy outcomes were balanced across arms (Table 3). Overall, there were 10 congenital abnormalities (LEN, n=6; FTC/TAF, n=4),[9] which was within the expected background incidence rate.[10,11] The

congenital abnormalities in the LEN group were congenital hemangioma, umbilical hernia, left hand polydactyly, perimembranous ventricular septal defect, congenital ventricular septal defect, and congenital reducible umbilical hernia (each, n=1). Among all participants who received ≥1 LEN injection during pregnancy or postpartum, 33.3% (44/132) reported ISRs; all ISRs were Grade 1 or 2 in severity. The most common ISRs were nodules (26.5%; n=35) and injection site pain (12.9%; n=17). One AE (0.5%) of spontaneous miscarriage led to LEN discontinuation.[9]

Table 3. PURPOSE 1: Pregnancy Outcomes[9]

Pregnancy Outcomes, n (%)		Primary Analysis		
		LEN (n=193)	FTC/TAF (n=218)	FTC/TDF (n=98)
Pregnancy status	Completed	186 (96.4)	207 (95)	97 (99)
	Unknown	7 (3.6)	11 (5)	1 (1)
Live births[a]		128 (66.3)	119 (54.6)	56 (57.1)
Pregnancy losses		60 (31.1)	89 (40.8)	41 (41.8)
Stillbirths[b]		5 (2.6)	6 (2.8)	3 (3.1)
Induced abortions		35 (18.1)	50 (22.9)	23 (23.5)
Spontaneous miscarriages[c]		20 (10.4)	33 (15.1)	15 (15.3)

[a]Data included 3 pregnancies that had 2 outcomes due to twins.
[b]Defined as fetal death that occurred at ≥20 weeks' gestation.
[c]Defined as fetal death that occurred at <20 weeks' gestation.

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Abbreviations

AE=adverse event
bHIV=background HIV incidence
CGW=cisgender women
DBS=dried blood spot
FTC=emtricitabine
IRR=incidence rate ratio
ISR=injection site reaction
LEN=lenacapavir
NRTI=nucleos(t)ide reverse transcriptase inhibitor
NNRTI=non-nucleos(t)ide reverse transcriptase inhibitor
PrEP=pre-exposure prophylaxis
PY=person-years
RBP=randomized blinded phase
SUBQ=subcutaneous(ly)
TAF=tenofovir alafenamide
TDF=tenofovir disoproxil fumarate
TFV-DP=tenofovir diphosphate

Product Label

For the full indication, important safety information, and boxed warning(s), 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.

Follow-Up

For any additional questions, please contact Gilead Medical Information at:

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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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