GILEAD | Medical Information

Yeztugo® (lenacapavir) Resistance

This document is in response to your request for information regarding Yeztugo® (lenacapavir [LEN]) for HIV-1 pre-exposure prophylaxis (PrEP) and 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 warning(s) are available at:
www.gilead.com/-/media/files/pdfs/medicines/hiv/yeztugo/yeztugo_pi;
www.gilead.com/-/media/files/pdfs/medicines/hiv/descovy/descovy_pi;
www.gilead.com/-/media/files/pdfs/medicines/hiv/truvada/truvada_pi.

Summary

Product Labeling[1]

Individuals must be tested for HIV-1 infection prior to initiating LEN, and with each subsequent injection of LEN, using a test approved or cleared by the FDA for the diagnosis of acute or primary HIV-1 infection. Drug-resistant HIV-1 variants have been identified with use of LEN by individuals with undiagnosed HIV-1 infection. Do not initiate LEN unless negative infection status is confirmed. Individuals who acquire HIV-1 while receiving LEN must transition to a complete HIV-1 treatment regimen.

In addition, due to the long-acting properties of LEN, alternative forms of PrEP should be considered following discontinuation of LEN for those individuals with HIV-1 negative status who are at continuing risk of HIV-1 acquisition and initiated within 28 weeks of the last LEN injection.

Clinical Data on Resistance to LEN for HIV-1 PrEP

In the ongoing phase 3 PURPOSE 1 study in cisgender women, at the time of the primary analysis, no cases of HIV acquisition were reported among the 2134 participants in the LEN group.[2]

- Four participants in the LEN group had unidentified HIV-1 at baseline, with the N74D LEN resistance-associated capsid mutation detected in 2 of these participants and the capsid polymorphism T107T/A in 1 participant, likely as a result of LEN monotherapy and delay of ART initiation.[3]
- Through the end of the RBP, 2 participants in the LEN group acquired HIV-1; 1 of these participants had the N74D resistance-associated capsid mutation.[4]

In the ongoing phase 3 PURPOSE 2 study in men and gender-diverse persons, 2 of 2179 participants in the LEN group had acquired HIV at the time of the primary analysis.

Both participants had the N74D capsid resistance mutation found at their HIV diagnosis visit. Retrospective standard HIV-1 RNA viral load testing of samples obtained at previous visits did not reveal delayed diagnosis for either participant.[5]

- Four participants in the LEN group had unidentified HIV-1 at baseline, with the N74D LEN resistance-associated capsid mutations in 2 of these participants.[3]
- Through the end of the RBP, 1 additional LEN participant acquired HIV-1 and had Q67H and K70R resistance mutations.[4]

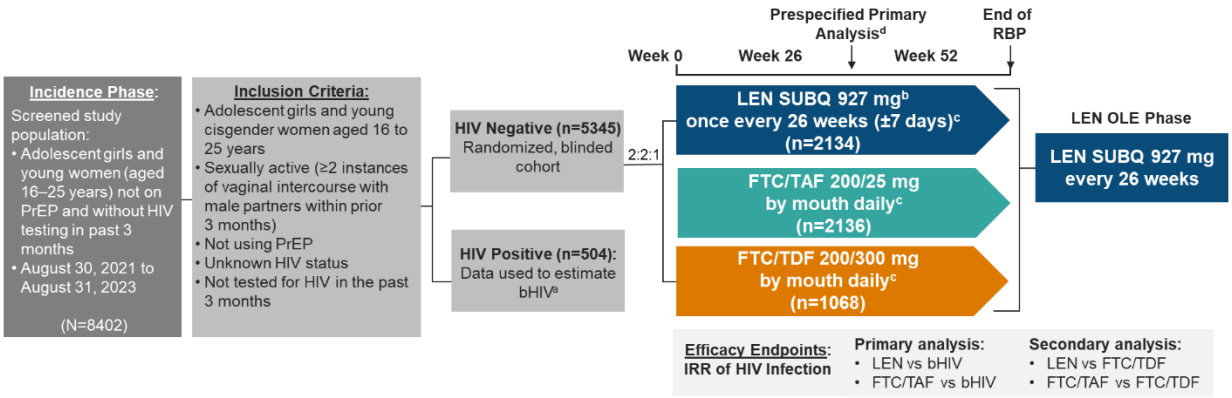
Clinical Data on Resistance to LEN for HIV-1 PrEP

PURPOSE 1 Study

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 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. 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 to 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]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.
[c]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.
[d]The prespecified primary analysis was when 50% of participants had completed ≥52 weeks of follow-up.
Note: Participants who chose to discontinue the blinded trial product were offered open-label FTC/TDF.

A total of 5345 participants were randomly assigned and received ≥1 dose of study drug. Of these, 7 were diagnosed with HIV at the time of randomization and were excluded from the efficacy analysis (mITT, n=5338). Baseline demographics were balanced between randomized groups (Table 1).

Table 1. PURPOSE 1: Select 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)
Sexually transmitted infections, n (%)	*Chlamydia trachomatis*	520 (24.3)	562 (26.3)	263 (24.6)
	Neisseria gonorrhoeae	197 (9.2)	178 (8.3)	90 (8.4)
	Trichomonas vaginalis	154 (7.2)	165 (7.7)	82 (7.7)
	Syphilis	57 (2.7)	63 (2.9)	29 (2.7)
Country, n (%)	South Africa	1809 (84.6)	1790 (83.8)	909 (85)
	Uganda	329 (15.4)	347 (16.2)	161 (15)

Resistance data

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). No resistance-associated mutations were detected in these participants at Day 1, and follow-up testing identified the N74D LEN resistance-associated capsid mutation in 2 of the 4 LEN participants and the capsid polymorphism T107T/A in 1 participant. The development of resistance may have resulted from the use of LEN as monotherapy and delay of ART initiation.[3]

Through the end of the RBP, an additional 24 participants acquired HIV-1 (FTC/TAF, n=13; FTC/TDF, n=9; LEN, n=2). Of the 2 LEN participants, 1 had good adherence to LEN, was diagnosed with HIV-1 at Week 52, and had the N74D resistance-associated capsid mutation. The other LEN participant missed LEN injections, had no resistance mutations, switched to open-label FTC/TDF after Week 80, and was diagnosed with HIV-1 at Week 95.[4]

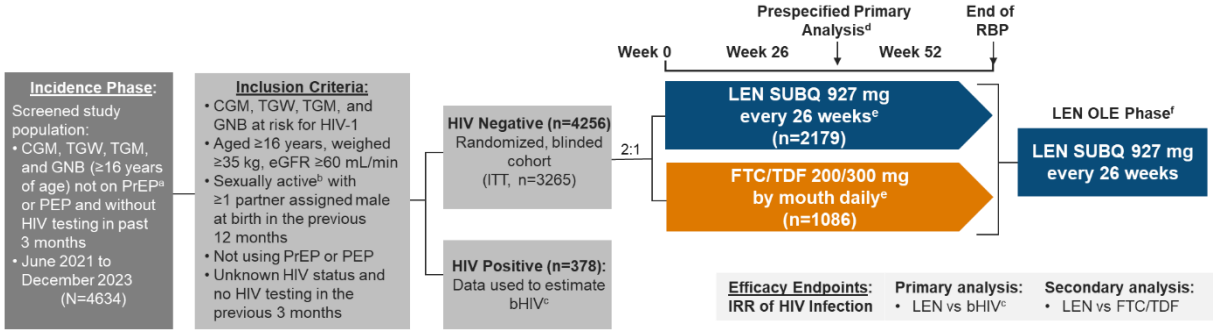
PURPOSE 2 Study

Study design and demographics

PURPOSE 2 (NCT04925752) is an ongoing, phase 3, double-blind, randomized study evaluating the efficacy and safety of twice-yearly SUBQ LEN and once-daily oral FTC/TDF for HIV-1 PrEP in cisgender gay, bisexual, and other men, TGW, TGM, and GNB individuals aged ≥16 years in Argentina, Brazil, Mexico, Peru, South Africa, Thailand, and the US who have condomless receptive anal sex with partners assigned male at birth (N=3265). Eligible participants were tested for HIV at screening, and those who tested negative were randomly assigned in a 2:1 ratio to SUBQ LEN every 26 weeks plus daily oral FTC/TDF placebo (n=2179) or SUBQ LEN placebo every 26 weeks plus daily oral FTC/TDF (n=1086;

Figure 2). Additional testing was performed with samples from participants who tested positive for HIV at screening to determine the recency of the HIV infection, and these data were used to estimate the bHIV that would be expected without PrEP.[5]

Figure 2. PURPOSE 2: Study Design[5-7]



[a]Included oral PrEP use within the last 12 weeks or any prior use of long-acting injectable forms of PrEP.
[b]Sexually active with ≥1 partner in the previous 12 months and met ≥1 of the following criteria: condomless receptive anal sex with ≥2 partners in the previous 12 weeks; a history of syphilis, rectal gonorrhea, or rectal chlamydia in the previous 24 weeks; self-reported use of stimulants with sex in the previous 12 weeks.
[c]The bHIV was the incidence of HIV that would be anticipated in a placebo group.
[d]Performed when 50% of participants reached RBP Week 52.
[e]All participants received a loading oral dose of LEN (600 mg) or matching placebo on Days 1 and 2. Participants in the LEN group received placebo FTC/TDF and participants in the FTC/TDF group received placebo SUBQ LEN. These participants were included in the full analysis set for primary efficacy analysis, and additional participants were included in the safety analysis.
[f]Participants who chose not to enter the OLE were offered open-label FTC/TDF for up to 78 weeks if they were assigned to receive LEN SUBQ during the RBP. Those who received FTC/TDF during the RBP and continued to the OLE received oral LEN 600 mg on Days 1 and 2 of the OLE. All participants who enter the OLE phase will complete this phase once LEN became commercially available or if the sponsor decided to discontinue the study.

A total of 3271 participants were randomly assigned and received ≥1 dose of study drug; 6 participants were diagnosed with HIV on Day 1 and were excluded from the efficacy analysis (mITT, n=3265). Baseline demographics were balanced between randomized groups (Table 2).[5]

Table 2. PURPOSE 2: Select Baseline Demographics[5]

Key Demographics and Characteristics		LEN (n=2183)	FTC/TDF (n=1088)
Age	Median (range), years	28 (17–74)	29 (17–73)
	16 to ≤25 years, n (%)	752 (34.4)	344 (31.6)
Country, n (%)	Brazil	769 (35.2)	396 (36.4)
	United States	440 (20.2)	235 (21.6)
	Peru	309 (14.2)	138 (12.7)
	Thailand	250 (11.5)	139 (12.8)
	South Africa	246 (11.3)	112 (10.3)
	Argentina	161 (7.4)	64 (5.9)
	Mexico	8 (0.4)	4 (0.4)
Race or ethnicity, n/N (%)	Hispanic or Latine	1378/2182 (63.2)	675/1088 (62)
	Black[a]	811/2175 (37.3)	420/1086 (38.7)
	White	722/2175 (33.2)	344/1086 (31.7)
	Indigenous or Indigenous ancestry[b]	341/2175 (15.7)	156/1086 (14.4)
	Asian	269/2175 (12.4)	144/1086 (13.3)
	Other and other multiracial[c]	32/2175 (1.5)	22/1086 (2)

Key Demographics and Characteristics		LEN (n=2183)	FTC/TDF (n=1088)
Gender identity, n (%)	Cisgender man	1697 (77.7)	846 (77.8)
	Transgender woman	315 (14.4)	161 (14.8)
	GNB[d]	136 (6.2)	63 (5.8)
	Transgender man	29 (1.3)	14 (1.3)
	Other[e]	6 (0.3)	4 (0.4)
Sexually transmitted infections,[f] n (%)	*Chlamydia trachomatis*	253 (11.6)	126 (11.6)
	Neisseria gonorrhea	193 (8.8)	115 (10.6)
	Syphilis	84 (3.8)	43 (4)
No history of HIV test, n (%)		597 (27.3)	306 (28.1)
Any history of PrEP use, n (%)		515 (23.6)	249 (22.9)
Self-reported use of stimulants with sex in last 12 weeks, n (%)		491 (22.5)	271 (24.9)

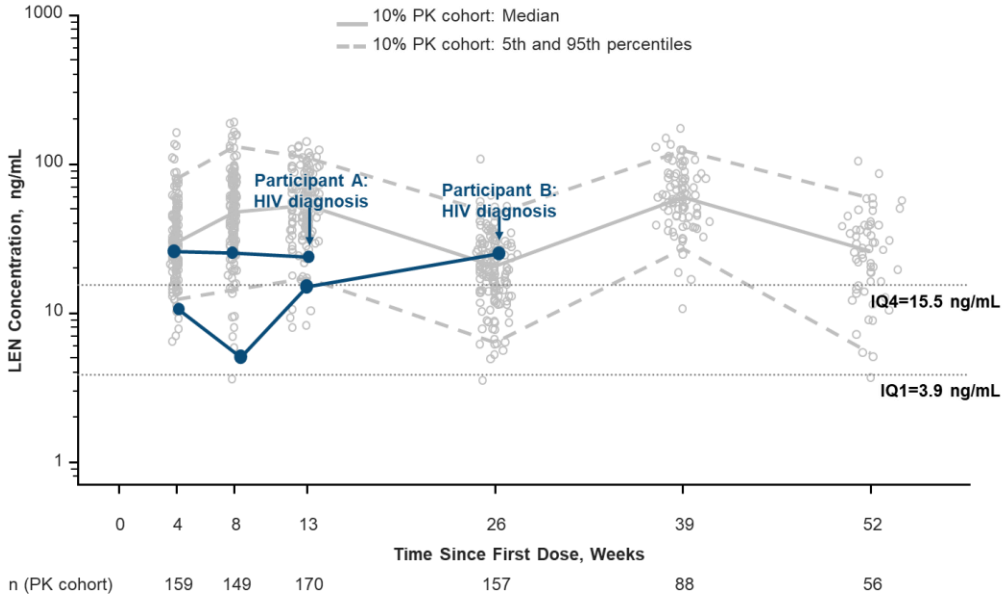
[a]Included all participants who identified as Black/of Black ancestry: Black, Black/White, Black/Pardo (a specific racial category in Brazil), Black/Brown (Brazil), Black/Colored (a specific racial category in South Africa), Black/American Indian or Alaskan Native, Black/Asian, and Black/Native Hawaiian or Pacific Islander.
[b]Included all participants who identified as American Indian or Alaskan Native, Native Hawaiian or Pacific Islander, Asian/Native Hawaiian or Pacific Islander, White/Native Hawaiian or Pacific Islander, and White/American Indian or Alaskan Native.
[c]Included all participants who identified as Asian/White, Colored (South Africa), Pardo (Brazil), White/Brown (Brazil), multiracial any other, and not multiracial other.
[d]Included 122 participants (89.7%) in the LEN group and 53 participants (84.1%) in the FTC/TDF group assigned male at birth.
[e]Included individuals who identified as travesti (LEN, n=3; FTC/TDF, n=3) or as an "other" gender (LEN, n=3; FTC/TDF, n=1).
[f]*Chlamydia trachomatis* and *Neisseria gonorrhea* were diagnosed based on testing pharyngeal, rectal, and urethral (urine) samples by central and local laboratories. Syphilis was diagnosed by testing blood and was performed locally by local testing protocols.

Resistance data

Overall, 11 of the 3265 participants in the primary analysis acquired HIV-1 after Day 1 (FTC/TDF, n=9; LEN, n=2). Of the 2 LEN participants, Participant A was a TGW who had undiagnosed syphilis that was detected and treated at the start of the study. She engaged in transactional sex and was diagnosed with HIV-1 at Week 13. Participant B was a cisgender gay man who had rectal chlamydia that was treated during the screening process. He was diagnosed with HIV-1 at Week 26.[5] Participant A had LEN concentrations above the IQ4 at all assessed time points, and Participant B had LEN concentrations at or below the IQ4 at three time points and above the IQ4 at the HIV diagnosis visit (Figure 3). Both participants had the N74D capsid resistance mutation, which was discovered at their HIV diagnosis visit. There was no evidence of delayed HIV seroconversion or delayed diagnosis with standard HIV-1 testing. The development of resistance may have resulted from the use of LEN as monotherapy and the delay of ART initiation. Additional HIV test results are presented below (Table 3).[5,8]

Central laboratory testing of samples collected on Day 1 identified 6 participants who had unrecognized HIV-1 at baseline (LEN, n=4; FTC/TDF, n=2); resistance testing was available for 3 of the 4 LEN participants. No resistance-associated mutations were detected at the earliest timepoint available for resistance testing (Day 1, n=2; Day 21, n=1), and follow-up testing identified the N74D LEN resistance-associated capsid mutation in 2 of the 3 LEN participants with unrecognized baseline HIV-1 and available resistance testing.[3]

Figure 3. PURPOSE 2: LEN Plasma Concentrations of the PK Cohort[a] and the Two Participants Who Acquired HIV-1[5]



[a]Randomly preselected, representative sample of 10% of participants. IQ was defined as the protein-adjusted 95% effective concentration in MT-4 cells, and IQ4 was 4 times the protein-adjusted 95% effective concentration in vitro.

Table 3. PURPOSE 2: Test Results of the Two LEN Participants Who Acquired HIV-1[8]

Participant A	Week 0	Week 4	Week 8	HIV Diagnosis at Week 13
Rapid Ag/Ab[a]	(-)	(-)	(-)	(+)
Central Ag/Ab[b]	(-)	(-)	(-)	(+)
HIV-1/2 Ab diff[c]				(HIV-1+ / HIV-2-)[d]
Qualitative RNA				(+)
VL,[e] c/mL	ND	ND[f]	ND[f]	934,000
SCA,[g] c/mL	ND[f]		ND[f]	4.8[f]

Participant B	Week 0	Week 4	Week 8	Week 13	HIV Diagnosis at Week 26
Rapid Ag/Ab[a]	(-)	(-)	(-)	(-)	(-)
Central Ag/Ab[b]	(-)	(-)	(-)	(-)	(+)
HIV-1/2 Ab diff[c]					(HIV-1+ / HIV-2-)[d]
Qualitative RNA					(+)
VL,[e] c/mL	ND			ND[f]	14,100
SCA,[g] c/mL	ND[f]	ND[f]	ND[f]	ND[f]	

Abbreviations: SCA=single-copy assay; VL=viral load.
[a]Local rapid HIV-1/2 Ag/Ab test.
[b]Central laboratory fourth-generation Ag/Ab test.
[c]HIV-1/2 Ab differentiation assay.
[d]Ab differentiation intermediate for HIV-1, negative for HIV-2. HIV-1 confirmed by qualitative RNA and quantitative RNA.
[e]HIV-1 RNA quantitative VL; blank denotes test not done.
[f]Tests run from archived samples after HIV diagnosis. ND denotes no HIV-1 RNA detected.
[g]HIV-1 RNA SCA.

Through the end of the RBP, an additional 4 participants acquired HIV-1 (FTC/TDF, n=3; LEN, n=1). The LEN participant had good adherence, was diagnosed with HIV-1 at Week 52, and had Q67H and K70R resistance mutations.[4]

References

1. Enclosed, Gilead Sciences Inc. YEZTUGO® (lenacapavir) tablets, for oral use. YEZTUGO® (lenacapavir) injection, for subcutaneous use. U.S. Prescribing Information. Foster City, CA.
2. Bekker LG, Das M, Abdool Karim Q, et al. Twice-Yearly Lenacapavir or Daily F/TAF for HIV Prevention in Cisgender Women. *N Engl J Med*. 2024;391(13):1179-92.
3. Cox S, Andreatta K, Hendricks MR, et al. Resistance Analyses of Lenacapavir, Emtricitabine/Tenofovir Alafenamide and Emtricitabine/Tenofovir Disoproxil Fumarate in the PURPOSE 1 and 2 Studies. *J Infect Dis*. 2025;
4. Cox J, Andreatta K, Hendricks MR, et al. Resistance Analyses of the PURPOSE Studies Through the end of the Randomized Blinded Phase [Presentation]. 2026:
5. Kelley CF, Acevedo-Quinones M, et al. Use Endnote No. 76142. Twice-Yearly Lenacapavir for HIV Prevention in Men and Gender-Diverse Persons. *N Engl J Med*. 2024.
6. ClinicalTrials.gov. Study to Assess the Effectiveness and Safety of Lenacapavir for Human Immunodeficiency Virus (HIV) Pre-Exposure Prophylaxis (PURPOSE 2). ClinicalTrials.gov Identifier: NCT04925752. Available at: https://clinicaltrials.gov/ct2/show/NCT04925752?term=purpose-2&draw=2&rank=1. Last Updated: 23 December. 2025.
7. Cantos VD, Mngadi K, Supparatpinyo K, et al. Lenacapavir for PrEP: HIV-1 Incidence and Safety from PURPORSE 2 at the End of Randomized Blinded Phase [Presentation]. 2026:
8. Kelley CF, Acevedo-Quinones M, Agwu AL, et al. Twice-Yearly Lenacapavir for HIV Prevention in Men and Gender-Diverse Persons [Supplementary Appendix]. *N Engl J Med*. 2024.

Abbreviations

Ab=antibody
Ag=antigen
ART=antiretroviral therapy
bHIV=background HIV incidence
CGM=cisgender men
FTC=emtricitabine
GNB=gender nonbinary
IQ=inhibitory quotient
LEN=lenacapavir
mITT=modified intent-to-treat
PK=pharmacokinetic(s)
PrEP=pre-exposure prophylaxis
RBP=randomized blinded period
SUBQ=subcutaneous
TAF=tenofovir alafenamide
TDF=tenofovir disoproxil fumarate
TGM=transgender men
TGW=transgender women

Product Label

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

Adverse Event Reporting

Please report all adverse events to:

Gilead Global Patient Safety ☎ 1-800-445-3235, option 3 or 🖱 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

Data Privacy

The Medical Information service at Gilead Sciences may collect, store, and use your personal information to provide a response to your medical request. We may share your information with other Gilead Sciences colleagues to ensure that your request is addressed appropriately. If you report an adverse event or concern about the quality of a Gilead or Kite product, we will need to use the information you have given us in order to meet our regulatory requirements in relation to the safety of our medicines.

It may be necessary for us to share your information with Gilead's affiliates, business partners, service providers, and regulatory authorities located in countries besides your own. Gilead Sciences has implemented measures to protect the personal information you provide. Please see the Gilead Privacy Statement (www.gilead.com/privacy-statements) for more information about how Gilead handles your personal information and your rights. If you have any further questions about the use of your personal information, please contact gilead.privacy@gilead.com.