Yeztugo® (lenacapavir) Resistance

This document is in response to your request for information regarding Yeztugo® (lenacapavir [LEN]) and resistance data.

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;
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Summary

Product Labeling: Boxed Warning and Section 5.2[1]

There is a boxed warning for potential risk of drug resistance with use of LEN for PrEP in individuals with undiagnosed HIV-1, either before or when receiving LEN, or following discontinuation of LEN. Individuals must be tested for HIV-1 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, because LEN alone does not constitute a complete regimen for HIV-1 treatment.

To minimize this risk, it is essential to 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

PURPOSE 1 Results

In the ongoing phase 3 PURPOSE 1 study in cisgender women, at the time of primary analysis (when 50% of participants had completed ≥52 weeks of follow-up), 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 LEN resistance-associated capsid mutations detected in 3 of these participants, 2 with N74D and 1 with T107A, likely as a result of LEN monotherapy and delay of antiretroviral therapy (ART) initiation.[3]

PURPOSE 2 Results

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 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.[4] Emergence of LEN resistance–associated mutations in the 2 participants receiving LEN was likely due to functional monotherapy after acquisition of HIV-1.[3] There were also 4 cases of HIV at baseline identified after starting LEN, and LEN resistance-associated capsid mutations were detected in 2 of these participants, both N74D.

Product Labeling: Post-Primary Analysis Data[1]

After the time of primary analysis in PURPOSE 1, there were 2 incident cases of HIV acquisition among participants in the LEN group.

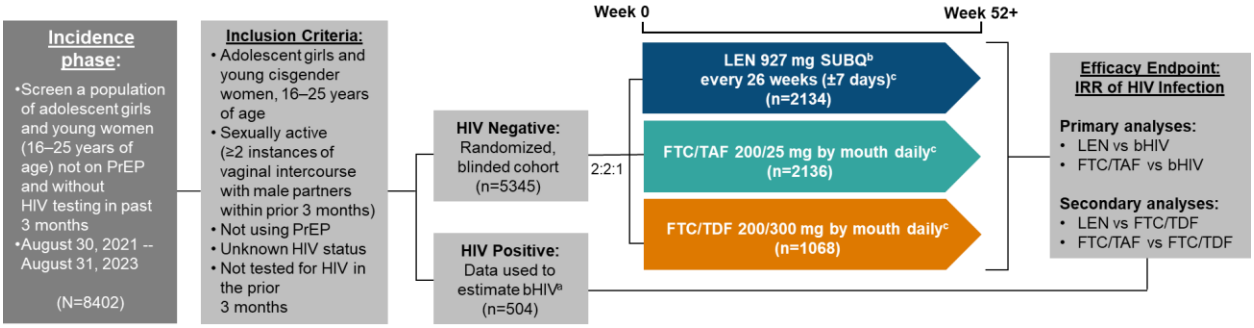
After the time of primary analysis in PURPOSE 2, 1 participant in the LEN arm had acquired HIV and had the Q67H/K70R resistance mutation.

Clinical Data on LEN Resistance

PURPOSE 1 Study

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 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]



[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.

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: 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)

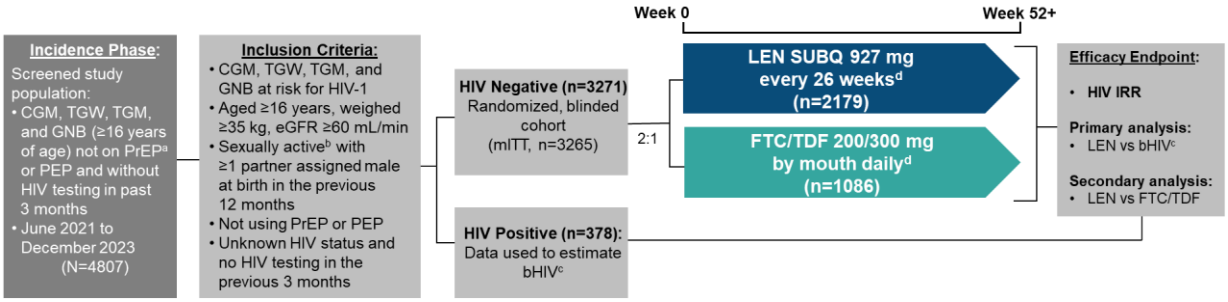
At the time of primary analysis (when 50% of participants had completed ≥52 weeks of follow-up), there were no cases of HIV acquisition reported among the 2134 participants in the LEN group. There were 4 cases of HIV at baseline identified after starting LEN, and LEN resistance-associated capsid mutations were detected in 3 of these participants, 2 with N74D and 1 with T107A. None of these participants had resistance substitutions detected on Day 1. However, the development of resistance may have resulted from the use of LEN as monotherapy and delay of ART initiation.[3]

PURPOSE 2 Study

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.[4]

Figure 2. PURPOSE 2: Study Design[4,5]



[a] Included oral PrEP use within the last 12 weeks or any prior use of long-acting injectable forms of PrEP.
[b] Condomless receptive anal sex 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; 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 expected without PrEP that would be anticipated in a placebo group. A total of 45 participants (11.9%) were classified as recently acquiring HIV.
[d] All participants received an oral initiation dose of LEN (600 mg) or matching oral placebo on Days 1 and 2. Participants randomly assigned to the SUBQ LEN group received oral placebo FTC/TDF, and participants in the FTC/TDF group received SUBQ LEN placebo.

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).[4]

Table 2. PURPOSE 2: Select Baseline Demographics and Disease Characteristics[4]

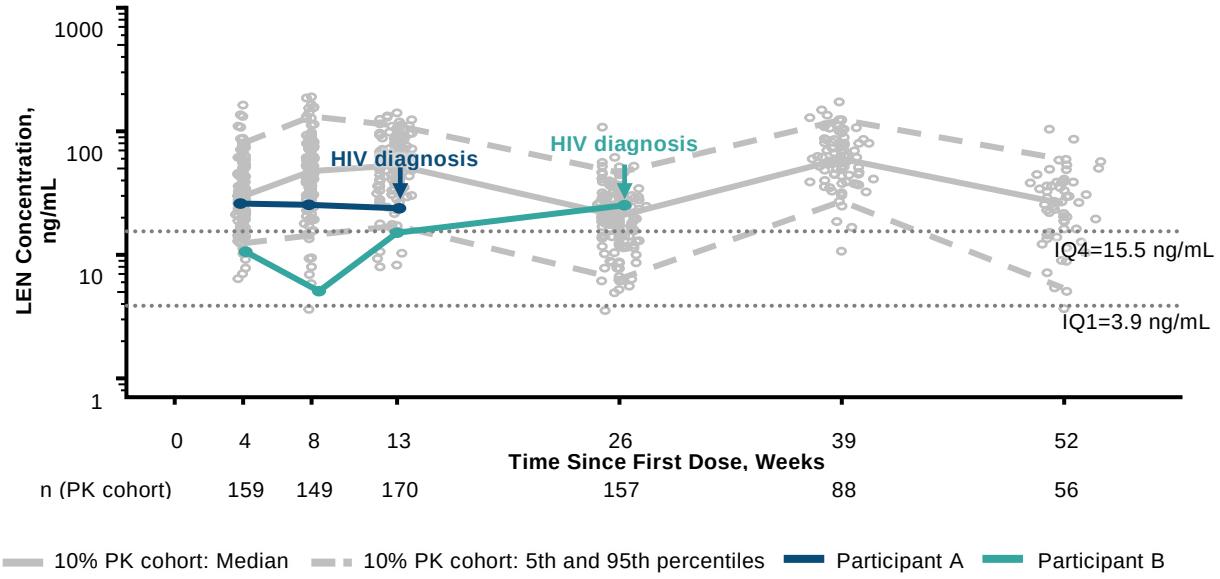
Key Demographics and Characteristics		LEN (n=2183)	FTC/TDF (n=1088)
Age	Median (range), years	28 (17–74)	29 (17–73)
	16 to ≤25 years, n (%)	752 (34.4)	344 (31.6)
Country, n (%)	Brazil	769 (35.2)	396 (36.4)
	United States	440 (20.2)	235 (21.6)
	Peru	309 (14.2)	138 (12.7)
	Thailand	250 (11.5)	139 (12.8)
	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)
Gender identity, n (%)	Cisgender man	1697 (77.7)	846 (77.8)
	Transgender woman	315 (14.4)	161 (14.8)
	Gender nonbinary[d]	136 (6.2)	63 (5.8)
	Transgender man	29 (1.3)	14 (1.3)
	Other[e]	6 (0.3)	4 (0.4)

Key Demographics and Characteristics		LEN (n=2183)	FTC/TDF (n=1088)
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, Back/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.

Among 2179 participants in the LEN group, 2 acquired HIV by the time of the primary analysis. There was no evidence of delay of HIV seroconversion or delayed diagnosis with standard HIV-1 testing. Both participants had the N74D capsid resistance mutation found at their HIV diagnosis visit. LEN concentrations for these 2 participants and the pharmacokinetics cohort (10% random subset of participants) were measured (Figure 3) in addition to HIV test results (Table 3).[4,6]

Figure 3. LEN Plasma Concentrations in the 10% PK Cohort[a] and Preceding HIV Diagnosis[4]



[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 as 4 times the protein-adjusted 95% effective concentration *in vitro*.

Table 3. HIV Test Results in Participants Receiving LEN Who Were Diagnosed with HIV-1[6]

Participant A

HIV diagnosis

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

Participant B

HIV diagnosis

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

[a] Antibody differentiation intermediate for HIV-1, negative for HIV-2. HIV-1 confirmed by Qualitative RNA and Quantitative RNA.
[b] Tests run from archived samples after HIV diagnosis. ND denotes no HIV-1 RNA detected.
[c] Rapid Ag/Ab denotes local rapid HIV-1/2 antibody/antigen test.
[d] Central Ag/Ab denotes central laboratory fourth-generation antigen/antibody test.
[e] HIV-1/2 Ab diff denotes HIV-1/2 antibody differentiation assay.
[g] VL denotes HIV-1 RNA quantitative viral load; blank denotes test not done.
[h] SCA denotes HIV-1 RNA single-copy assay.

Participant A was a transgender woman 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 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 at Week 26. For both Participant A and Participant B, their LEN concentration levels were within the normal range observed in the pharmacokinetic cohort of the study.[4] Emergence of LEN resistance–associated mutations in Participant A and B was likely due to functional monotherapy after acquisition of HIV-1.[3]

Product Labeling[1]

Post-Primary Analysis Data

After the time of primary analysis in PURPOSE 1, there were 2 incident cases of HIV acquisition among participants in the LEN arm, one occurring after LEN exposures fell below the target concentration following discontinuation without detected LEN resistance-associated capsid mutations, and one where viral loads were too low for genotyping.

After the time of primary analysis in PURPOSE 2, 1 participant in the LEN arm had acquired HIV and had the Q67H/K70R resistance mutation. There were also 4 cases of HIV at baseline identified after starting LEN, and LEN resistance-associated capsid mutations were detected in 2 of these participants, both N74D.

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):1179-1192.
3. Cox S, Andreatta K, Hendricks MR, et al. Resistance Analyses of F/TAF, F/TDF, and Lenacapavir in the PURPOSE 1 and 2 Studies. [Poster #10]. Paper presented at: European Meeting on HIV & Hepatitis (EMHH); June 4–6, 2025; Barcelona, Spain.
4. Kelley CF, Acevedo-Quinones M, Agwu AL, et al. Twice-Yearly Lenacapavir for HIV Prevention in Men and Gender-Diverse Persons. *N Engl J Med.* 2024.
5. 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. Accessed: 22 December. Last Updated: 21 December. 2022.
6. 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 non-binary
IQ4=inhibitory quotient 4
LEN=lenacapavir
mITT=modified intent-to-treat
PK=pharmacokinetic
PrEP=pre-exposure prophylaxis
SUBQ=subcutaneous
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:

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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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