GILEAD | Medical Information

Yeztugo® (lenacapavir) Use in Pregnancy and Lactation

This document is in response to your request for information regarding the use of Yeztugo® (lenacapavir [LEN]) during pregnancy and lactation.

This document includes content from, or references to, clinical practice guidelines, and inclusion should not be interpreted as a treatment recommendation or an endorsement of the guidelines by Gilead Sciences, Inc.

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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]

There is a pregnancy exposure registry that monitors pregnancy outcomes in individuals exposed to LEN during pregnancy. Healthcare providers are encouraged to register individuals by calling the Antiretroviral Pregnancy Registry (APR) at 1-800-258-4263.

Available data from a randomized, controlled trial (PURPOSE 1) with LEN use during pregnancy have not identified a drug-associated risk for miscarriage, or adverse maternal or fetal outcomes when compared to the active control. The rate of major birth defects in LEN-exposed pregnancies did not exceed the background prevalence rates.

LEN is present in human milk. LEN was detected at very low levels in infants who were breastfed by individuals who became pregnant while receiving LEN. No adverse effects of LEN in breastfed infants have been observed. It is not known if LEN affects milk production.

Clinical Data on LEN Use During Pregnancy

PURPOSE 1 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 or FTC/TDF (control) for HIV-1 PrEP in cisgender women and adolescent girls in South Africa and Uganda.[2]

- At the data cutoff of May 8, 2024, there were 509 pregnancies among 487 participants: 193 pregnancies in the LEN group, 218 in the FTC/TAF group, and 98 in the FTC/TDF group.[3]

- Overall, 10 congenital abnormalities were reported, and study authors determined that the incidence was within the expected background rate and was balanced across all three treatment groups.[3]
- HIV acquisition occurred in 4 pregnant participants in the FTC/TAF group and 1 pregnant participant in the FTC/TDF group. There were no HIV cases among pregnant participants randomized to the LEN group. No cases of vertical transmission were observed.[3]

Pregnancy outcomes from the PURPOSE 2 study have not been published.

Clinical Data on LEN Use During Lactation

In a nested PK substudy of participants in PURPOSE 1 who were randomly assigned to the LEN group and became pregnant during the study, LEN exposures were similar between pregnant and non-pregnant participants. LEN was found in breast milk, but LEN concentrations were very low in breastfed infants.[3]

Product Labeling[1]

Use in Specific Populations

Pregnancy

Pregnancy exposure registry

There is a pregnancy exposure registry that monitors pregnancy outcomes in individuals exposed to LEN during pregnancy. Healthcare providers are encouraged to register individuals by calling the APR at 1-800-258-4263.

Risk summary

Available data from a randomized, controlled trial (PURPOSE 1) with LEN use during pregnancy have not identified a drug-associated risk for miscarriage, or adverse maternal or fetal outcomes when compared to the active control. The rate of major birth defects in LEN-exposed pregnancies did not exceed the background prevalence rates. The risk estimates are imprecise due to small numbers of exposed pregnancies. There is an increased risk of HIV-1 transmission from the mother to the child during acute HIV-1 infection. In animal reproduction studies, no adverse developmental effects were observed when LEN was administered to rats and rabbits at exposures (AUC) ≥7 times the exposure in humans at the recommended human dose of LEN.

The APR has been established to monitor for birth defects following prenatal exposure to ARVs. The APR uses the MACDP as the US reference population for birth defects in the general population. The background rate for major birth defects is 2.72% in the MACDP. The rate of miscarriage for individual drugs is not reported in the APR. In the US general population, the estimated background risk of miscarriage in clinically recognized pregnancies is 15% to 20%. The MACDP evaluates mothers and infants from a limited geographic area and does not include outcomes for births that occurred at <20 weeks gestation.

Clinical considerations: disease-associated maternal and/or embryo/fetal risk

Published studies indicate an increased risk of HIV-1 infection during pregnancy and an increased risk of mother-to-child transmission during acute HIV-1 infection. In women at risk of acquiring HIV-1, consideration should be given to methods to prevent acquisition of HIV-1, including continuing or initiating LEN for HIV-1 PrEP, during pregnancy.

Data: human data

In a randomized, controlled trial in Uganda and South Africa (PURPOSE 1), there were 208 pregnancies exposed to LEN with known outcomes and 132 deliveries (both live and non-live). In the active control arm of PURPOSE 1, there were 109 pregnancies exposed to FTC/TDF with known outcomes and 61 deliveries (both live and non-live). The adverse pregnancy outcomes of spontaneous abortion, stillbirth, preterm birth, and small for gestational age were similar across both treatment groups.

There were two major birth defects in the LEN arm. Both were ventricular septal defects. This resulted in a rate of major birth defects that fell within the background prevalence rate for major birth defects.

Concentrations of LEN during each trimester of pregnancy and postpartum were comparable to those in non-pregnant participants.

Lactation

Risk summary

LEN is present in human milk. LEN was detected at very low levels in infants who were breastfed by individuals who became pregnant while receiving LEN. No adverse effects of LEN in breastfed infants have been observed. It is not known if LEN affects milk production.

In women without HIV-1 infection, the developmental and health benefits of breastfeeding and the mother's clinical need for LEN for HIV-1 PrEP should be considered along with any potential adverse effects on the breastfed child from LEN and the risk of HIV-1 acquisition due to nonadherence and subsequent mother-to-child transmission.

Data: human data

The median LEN concentration in human breast milk to maternal plasma ratio in participants (n=8) who received LEN was 0.63 (range: 0.29–1.9). The median infant-to-mother plasma ratio for LEN in infants (n=10) who were breastfed by individuals receiving LEN from 0 to <13 weeks after delivery was 0.06 (range: 0.01–0.2).

Clinical Data on LEN Use During Pregnancy

PURPOSE 1

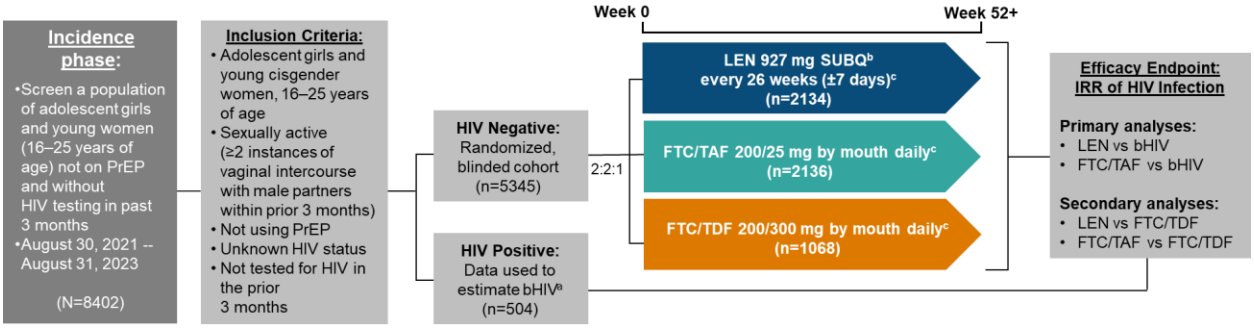
Study design

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 (Figure 1). Participants who discontinued blinded study drug were given the option to take open-label FTC/TDF. Randomized participants had body weight ≥35 kg and eGFR ≥60 mL/min.

Testing for HIV in the randomized cohort was conducted at Weeks 4, 8, and 13 and every 13 weeks thereafter.[2] Urine pregnancy testing was performed at every study visit. In the event of a positive urine pregnancy test, serum pregnancy testing was conducted for confirmation. Individuals were excluded if they were pregnant or lactating prior to administration of first dose of study drug.[4] Contraception was not required but was provided for participants. Participants could continue to receive the study drug if they became pregnant after a reconsent process on potential risks and benefits, and pregnant participants were permitted to receive the LEN SUBQ injection in the thigh.[2,4] If a participant gave birth while in the study, infant health follow-up was conducted for 1 year after birth or until the mother's participation in the study ended. Participants were allowed to breastfeed in the study.[4]

Figure 1. PURPOSE 1: Study Design[2]



Abbreviations: bHIV=background HIV; IRR=incidence rate ratio.
[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. Baseline (at randomization) characteristics among the three groups were similar (Table 1). Overall retention in the study was high and similar across 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 randomized, blinded portion of the trial. Starting July 8, 2024, all participants were offered open-label LEN.[2]

Table 1. PURPOSE 1: Baseline Demographics and Disease Characteristics[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)

Key Demographics and Characteristics		LEN (n=2138)	FTC/TAF (n=2137)	FTC/TDF (n=1070)
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)

Pregnancy outcomes[3]

At the data cutoff of May 8, 2024, there were 509 pregnancies among 487 participants: 193 pregnancies in the LEN group, 218 in the FTC/TAF group, and 98 in the FTC/TDF group (Table 2).

Overall, 10 congenital abnormalities were reported: LEN, n=6 (congenital hemangioma, umbilical hernia, left hand polydactyly, perimembranous ventricular septal defect, congenital ventricular septal defect, and congenital reducible umbilical hernia; each, n=1); FTC/TAF, n=4 (infant bilateral hydrocele; right inguinal hernia, umbilical hernia, and neonatal jaundice; Down syndrome; and clubfoot; each, n=1). The study authors determined that the incidence of congenital abnormalities was within the expected background rate and was balanced across all three treatment groups.

Table 2. PURPOSE 1: Pregnancy Outcomes[3]

Pregnancy Outcomes, n or n (%)		LEN (n=184)	FTC/TAF (n=208)	FTC/TDF (n=95)
Participants with confirmed pregnancies		184	208	95
Confirmed pregnancies		193	218	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)
Stillbirth[b]		5 (2.6)	6 (2.8)	3 (3.1)
Induced abortion		35 (18.1)	50 (22.9)	23 (23.5)
Spontaneous miscarriage[c]		20 (10.4)	33 (15.1)	15 (15.3)

[a]Included data from 3 pregnancies that had 2 outcomes due to twins.
[b]Defined as occurring at ≥20 weeks' gestation.
[c]Defined as occurring at <20 weeks' gestation.

Among pregnant participants, HIV acquisition occurred in 4 participants in the FTC/TAF group and 1 participant in the FTC/TDF group. There were no HIV cases among pregnant women randomly assigned to the LEN group. No cases of vertical transmission were observed.

Overall, 44/132 participants (33.3%) who received ≥1 dose of LEN SUBQ during pregnancy or postpartum reported an ISR. All reported ISRs were Grade 1 or 2 in severity, and the most frequently reported ISRs were nodules (n=35; 26.5%) and injection site pain (n=17; 12.9%). Additional safety outcomes during pregnancy and postpartum are presented in Table 3.

Table 3. PURPOSE 1: Safety Outcomes During Pregnancy and Postpartum[3]

AEs During Pregnancy and Postpartum,[a] n (%)		LEN (n=184)	FTC/TAF (n=208)	FTC/TDF (n=95)
Any AEs		135 (73.4)	142 (68.3)	68 (71.6)
Grade ≥2		112 (60.9)	112 (53.8)	55 (57.9)
Grade ≥3		36 (19.6)	39 (18.8)	22 (23.2)
SAEs		41 (22.3)	50 (24)	22 (23.2)
AEs that led to study drug discontinuation		1 (0.5)[b]	0	0
AEs in ≥10% of participants in any group[c]	Urinary tract infection	39 (21.2)	34 (16.3)	27 (28.4)
	Upper respiratory tract infection	20 (10.9)	16 (7.7)	6 (6.3)
	Vulvovaginal candidiasis	17 (9.2)	22 (10.6)	8 (8.4)

[a]Included AEs that occurred during the randomized blinded phase from the last menstrual period date to 6 weeks after the pregnancy outcome date. ISRs related to study drug injections were excluded.
[b]Study drug discontinuation was due to spontaneous miscarriage.
[c]Spontaneous miscarriages were excluded.
Note: AEs were coded according to Medical Dictionary for Regulatory Activities Version 27.1 and graded by the Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events, Version 2.1.

PURPOSE 2

Study design

PURPOSE 2 (NCT04925752) is an ongoing, phase 3, double-blind, randomized study evaluating the efficacy and safety of twice-yearly SUBQ LEN or once-daily oral FTC/TDF for HIV-1 PrEP in cisgender gay, bisexual, and other men; TGW; TGM; and GNB individuals 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).[5]

Participants of childbearing potential were required to have a negative pregnancy test at the screening visit and on Day 1 prior to receiving the study intervention. They must not have been breastfeeding at study entry. Participants were also required to use an acceptable form of contraception during trial participation.[6]

Pregnancy outcomes from PURPOSE 2 have not been published.

APR Data on LEN Use in Pregnancy[7]

Healthcare providers are encouraged to register individuals by calling the APR at 1-800-258-4263.

The APR is intended to provide an early signal of teratogenicity associated with prenatal use of ARV therapy for those drugs monitored in the registry. The APR contains analyses of voluntary, prospective reports of prenatal exposures to ARVs. The women included in this analysis were primarily HIV-1 monoinfected.

APR Advisory Committee Consensus for all ARVs

In reviewing all reported defects from the prospective registry, informed by clinical studies and retrospective reports of ARV exposure, the registry has found no apparent increases in the frequency of specific defects with first-trimester exposures and no pattern to suggest a common cause. While the registry population exposed and monitored to date is not sufficient to detect an increase in the risk of relatively rare defects, these findings should provide some assurance when counseling patients. However, potential limitations of registries such as this should be recognized. The registry is ongoing. Given the use of new

therapies about which data are still insufficient, health care providers are strongly encouraged to report eligible patients to the registry at SM_APR@APRegistry.com via the data forms available at www.APRegistry.com.

LEN data in the APR

The June 2025 interim report includes prospective reports of 24,443 pregnancies with follow-up data through January 31, 2025. The current APR reported 2 cases of LEN exposure during the first trimester. Currently, there are insufficient exposure data on LEN to detect a pattern of increase in risk of birth defects.

Clinical Data on LEN Use During Lactation

PURPOSE 1: PK Substudy[3]

A nested PK substudy of participants who were randomly assigned to the LEN group and became pregnant during the study was conducted to assess systemic LEN concentrations during pregnancy and postpartum and to assess LEN concentrations in breast milk and infants. Pregnant participants received LEN SUBQ injections in the thigh and/or abdomen. Maternal plasma PK samples were taken at regular intervals in the first through third trimesters, and maternal plasma, infant plasma, and breast milk samples were assessed at approximately 3 and 6 months postpartum.

At Weeks 26, 52, and 78, C_{trough} data were available from 107 first-trimester, 99 second-trimester, 59 third-trimester, and 65 postpartum visits. LEN exposures were similar in pregnant and non-pregnant participants. Furthermore, LEN PK were similar when LEN was injected in the thigh and the abdomen.

LEN was found in breast milk, but LEN concentrations were very low in breastfed infants. In 102 matched pairs, the median (IQR) breastmilk-to-maternal plasma ratio was 0.52 (0.38–0.77). In 98 matched pairs, the median (IQR) breastfed-infant-to-maternal plasma ratio was 0.02 (0.01–0.05).

Clinical Guidelines on PrEP Use in Pregnancy

Please see the US Department of Health and Human Services (DHHS) guidelines for recommendations regarding the use of PrEP to prevent HIV during periconception, antepartum, and postpartum periods: https://clinicalinfo.hiv.gov/en/guidelines/perinatal/pre-exposure-prophylaxis-prep-prevent-hiv. Please note, the guidelines are not specific to LEN.

References

1. YEZTUGO®, 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. Bekker L-G, Moodley D, Harkoo I, et al. Inclusion of Pregnant and Lactating People in the PURPOSE 1 Study: Efficacy, Safety, and Pharmacokinetics. [Presentation]. Paper presented at:

13th International AIDS Society (IAS) Conference on HIV Science; July 13–17, 2025; Kigali, Rwanda.
4. Bekker LG, Das M, Abdool Karim Q, et al. Twice-Yearly Lenacapavir or Daily F/TAF for HIV Prevention in Cisgender Women [Protocol]. *N Engl J Med.* 2024:1-672.
5. 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.
6. Kelley CF, Acevedo-Quinones M, Agwu AL, et al. Twice-Yearly Lenacapavir for HIV Prevention in Men and Gender-Diverse Persons [Protocol]. *N Engl J Med.* 2024.
7. Antiretroviral Pregnancy Registry Steering Committee. *The Antiretroviral Pregnancy Registry Interim Report: 01 January 1989 Through 31 January 2025. Morrisville, NC.* 2025.

Abbreviations

AE=adverse event
APR=Antiretroviral Pregnancy Registry
ARV=antiretroviral
AUC=area under the time-concentration curve
C_{trough}=trough concentration
FTC=emtricitabine
GNB=gender non-binary
ISR=injection site reaction
LEN=lenacapavir
MACDP=Metropolitan Atlanta Congenital Defects Program
PK=pharmacokinetic(s)
PrEP=pre-exposure prophylaxis
SAE=serious adverse event
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

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