Yeztugo ® (lenacapavir) Coadministration With Gender-Affirming Hormone Therapy

This document is in response to your request for information regarding the coadministration of gender-affirming hormone therapy (GAHT) with Yeztugo® (lenacapavir [LEN]).

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/truvada/truvada_pi.

PK DDI Evaluation

Relevant LEN PK data are presented in Table 1 below. For more information on the specific hormone therapy of interest, please refer to its product labeling.

LEN PK

Table 1. LEN DDI Potential[1,2]

DDI Mechanism		LEN
Drug Transporters	OCT2	N/A
	MATE1	N/A
	P-gp	Substrate[a] and weak inhibitor
	BCRP	Weak inhibitor
	OATP1B1	N/A
	OATP1B3	N/A
Drug-Metabolizing Enzymes	CYP3A	Substrate[a,b] and moderate inhibitor
	UGT1A1	Substrate[a]

Abbreviations: BCRP=breast cancer resistance protein; MATE=multidrug and toxin extrusion protein; OATP=organic anion transporting polypeptide; OCT=organic cation transporter; UGT1A1=uridine 5'-diphospho-glucuronosyltransferase family 1 member A1.
[a]Combined P-gp, UGT1A1, and strong CYP3A inhibitors may significantly increase plasma concentrations of LEN. Concomitant administration of LEN with these inhibitors is not recommended.
[b]Drugs that are strong or moderate inducers of CYP3A may significantly decrease plasma concentrations of LEN, which may result in reduced effectiveness of LEN. Therefore, dosage modifications (supplemental doses) of LEN are recommended when initiating strong or moderate CYP3A inducers. Please refer to Section 2.5, *Dosage Modifications for Co-administration with Strong or Moderate CYP3A Inducers*, of the LEN US Prescribing Information for more information.

Relevant LEN Information[1]

There is no information in the LEN product labeling about the coadministration of LEN and GAHT.

Drug Interactions

Effect of LEN on other drugs: CYP3A and P-gp substrates

LEN is a moderate inhibitor of CYP3A and a P-gp inhibitor.

The coadministration of LEN with sensitive substrates of CYP3A or P-gp may increase the concentrations of these substrates and result in the increased risk of their adverse events. See the prescribing information for these sensitive substrates for dosing recommendations or appropriate monitoring of safety.

Due to the long half-life of LEN following SUBQ administration, LEN may increase the exposure of drugs primarily metabolized by CYP3A initiated within 9 months after the last SUBQ dose of LEN.

Clinical Data on Coadministration of LEN and GAHT

PURPOSE 2

PURPOSE 2 is an ongoing, phase 3, double-blind, randomized study evaluating the efficacy and safety of twice-yearly SUBQ LEN (n=2179) or once-daily oral FTC/TDF (n=1086) 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). The primary efficacy endpoint was the incidence of HIV among randomized participants.[3]

DDIs between LEN and masculinizing GAHT[4]

A PK analysis was performed in subsets of participants in this study to assess the effects of feminizing and masculinizing GAHT on LEN concentrations. Assessments of self-reported gender identity occurred at baseline, and GAHT use was reported at each study visit. Of the 2183 participants who received LEN, 486 participants (22.3%) self-identified as gender diverse, and GAHT use was reported in 253 participants (11.6%; Table 2).

In the subset of participants who received concomitant feminizing GAHT with estradiol (n=115), serum levels were measured at baseline pre-LEN dose and post-LEN dose visits from Week 4 up to Week 52; similarly, plasma testosterone and DHT levels were measured in participants who received masculinizing GAHT with testosterone (n=25).

Table 2. PURPOSE 2: Concomitant GAHT Among Participants in the SUBQ LEN Arm[4]

Self-Reported Gender Identity	SUBQ LEN, n	Concomitant GAHT, n (%)
Total	2183	253 (11.6)
Cisgender men	1697	23 (1.4)
TGW	315	190 (60.3)
GNB: assigned male at birth	122	7 (5.7)
TGM	29	22 (75.9)

Self-Reported Gender Identity	SUBQ LEN, n	Concomitant GAHT, n (%)
GNB: assigned female at birth	14	8 (57.1)
Other: assigned male at birth	6	3 (50)

Results

In participants who received concomitant GAHT, serum estradiol levels (feminizing GAHT) and plasma testosterone and DHT levels (masculinizing GAHT) at baseline were generally similar to levels observed from Weeks 4 to 52, regardless of dose, frequency, or changes in dose. These data support the concomitant use of feminizing or masculinizing GAHT with LEN without the need for dose adjustments. No safety data were reported.

Pooled Population PK Analysis[5]

In a population PK analysis of pooled data from participants across 13 phase 1 to phase 3 studies (N=1337 participants; N=14,648 samples), LEN exposures were characterized following a stepwise modeling approach of SUBQ, oral, and IV administration. Subgroups of interest that were modeled in graphical evaluations with PK parameters included participants in PURPOSE 1 who were receiving long-acting contraceptives and who became pregnant and participants in PURPOSE 2 who were receiving GAHT.

A total of 534 participants in PURPOSE 2 who were also receiving GAHT were evaluated. From the PK analysis, the use of GAHT did not have an impact on LEN exposures.

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. Lutz J. CLINICAL EVALUATION OF DRUG INTERACTIONS WITH ORAL LENACAPAVIR AND PROBE DRUGS [Presentation]. Paper presented at: Conference on Retroviruses and Opportunistic Infections (CROI); March 6-10, 2021; Virtual.
3. 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.* 2025;392(13):1261-1276.
4. Blumenthal J, Acevedo-Quiñones M, Phanuphak N, et al. No Clinically Significant Drug-Drug Interactions With Coadministration of Feminizing or Masculinizing Hormone Therapy and Twice-Yearly Lenacapavir PrEP in Gender-Diverse Persons [Poster #P-305]. Paper presented at: IDWeek; October 19–22, 2025; Atlanta, GA.
5. Imperial M, Hughes E, Panchia R, et al. Population Pharmacokinetic Analysis of Lenacapavir in People Who Want or Need Pre-Exposure Prophylaxisfor HIV [Poster I-109]. Paper presented at: Population Approach Group Europe (PAGE); 4–6 June, 2025; Thessaloniki, Greece.

Abbreviations

DDI=drug-drug interaction
DHT=dihydrotestosterone; active metabolite of testosterone
FTC=emtricitabine
GAHT=gender-affirming hormone therapy
GNB=gender non-binary
LEN=lenacapavir
P-gp=P-glycoprotein
PK=pharmacokinetic(s)
PrEP=pre-exposure prophylaxis
SUBQ=subcutaneous(ly)
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, please refer to the Yeztugo US Prescribing Information available at:
www.gilead.com/-/media/files/pdfs/medicines/hiv/yeztugo/yeztugo_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

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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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