AETC AIDS Education & Training Center Program Mountain West

PrEP for HIV Prevention
Lenacapavir

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Project ECHO®

Disclosures

As of October 2025, the following medications are approved by the U.S. Food and Drug Administration (FDA) for use as HIV pre-exposure prophylaxis (though may not be approved for all populations):

2012: FTC/TDF (Truvada)
2019: FTC/TAF (Descovy)
2021: Long Acting Cabotegravir (CAB-LA, Apretude)
2025: Lenacapavir (as Yeztugo)

This talk may include discussion of non-FDA approved strategies for HIV prevention.

I have no conflicts of interest or relationships to disclose.

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Disclaimer

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CDC Clinical Recommendations

U.S. Centers for Disease Control and Prevention
MMWR
Morbidity and Mortality Weekly Report
Weekly / Vol. 74 / No. 35
September 18, 2025

Clinical Recommendation for the Use of Injectable Lenacapavir as HIV Preexposure Prophylaxis — United States, 2025

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Abstract

In 2023, approximately 39,000 persons received a diagnosis of HIV in the United States. Although HIV preexposure prophylaxis (PrEP) is highly effective in preventing HIV infection, acceptance of, adherence to, and persistence taking the available oral and injectable PrEP regimens have been suboptimal. CDC PrEP guidelines published in 2021 include two oral tenofovir-based regimens and cabotegravir, the only injectable PrEP regimen approved by the Food and Drug Administration (FDA) at that time. In June 2025

Introduction

In 2023, approximately 39,000 persons received a diagnosis of HIV in the United States (*1*). HIV preexposure prophylaxis (PrEP) is highly effective at preventing HIV infection (*2*,*3*); however, implementation has been challenged by low acceptance of, adherence to, and persistence taking currently available PrEP options in the United States: 1) daily oral tenofovir-based regimens and 2) injectable cabotegravir administered every 2 months (*4*–*8*). Multiple national assessments have found that approximately one half of oral

https://www.cdc.gov/mmwr/volumes/74/wr/pdfs/mm7435a1-H.pdf

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Lenacapavir updates

- June 18, 2025: FDA approved
  - https://www.gilead.com/-/media/files/pdfs/medicines/hiv/yeztugo/yeztugo_pi.pdf
- July 9: Global Fund secures agreement to obtain LEN for 2 million people at cost.
  - https://www.theglobalfund.org/en/news/2025/2025-07-09-global-fund-secures-access-breakthrough-hiv-prevention-drug-lenacapavir/
- July 14: WHO recommends LEN along with point-of-care HIV testing.
  - https://www.who.int/publications/i/item/9789240111608
- September 18: CDC issues clinical recommendations for use of LEN as PrEP
  - https://www.cdc.gov/mmwr/volumes/74/wr/pdfs/mm7435a1-H.pdf

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Clinical Recommendation for Use of Lenacapavir for HIV Prevention

"Lenacapavir, administered as subcutaneous injections every 6 months, is recommended as an HIV PrEP option in persons weighing ≥77 lbs (≥35 kg) who would benefit from PrEP. This is a strong recommendation, based on high certainty of evidence."

https://www.cdc.gov/mmwr/volumes/74/wr/pdfs/mm7435a1-H.pdf

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Clinical Recommendation for Use of Lenacapavir for HIV Prevention

Assessing LEN eligibility

1. Assess HIV acquisition risk.
2. Rule out acute HIV infection.
3. Identify any significant drug interactions or contraindications.

https://www.cdc.gov/mmwr/volumes/74/wr/pdfs/mm7435a1-H.pdf

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Clinical Recommendation for Use of Lenacapavir for HIV Prevention

Consider PrEP in persons at risk for HIV

- People with STIs
- Men who have sex with men
- People w HIV+ sex partners without VL suppression
- People who engage in transactional sex
- People who are incarcerated
- People who share needles

https://www.cdc.gov/mmwr/volumes/74/wr/pdfs/mm7435a1-H.pdf

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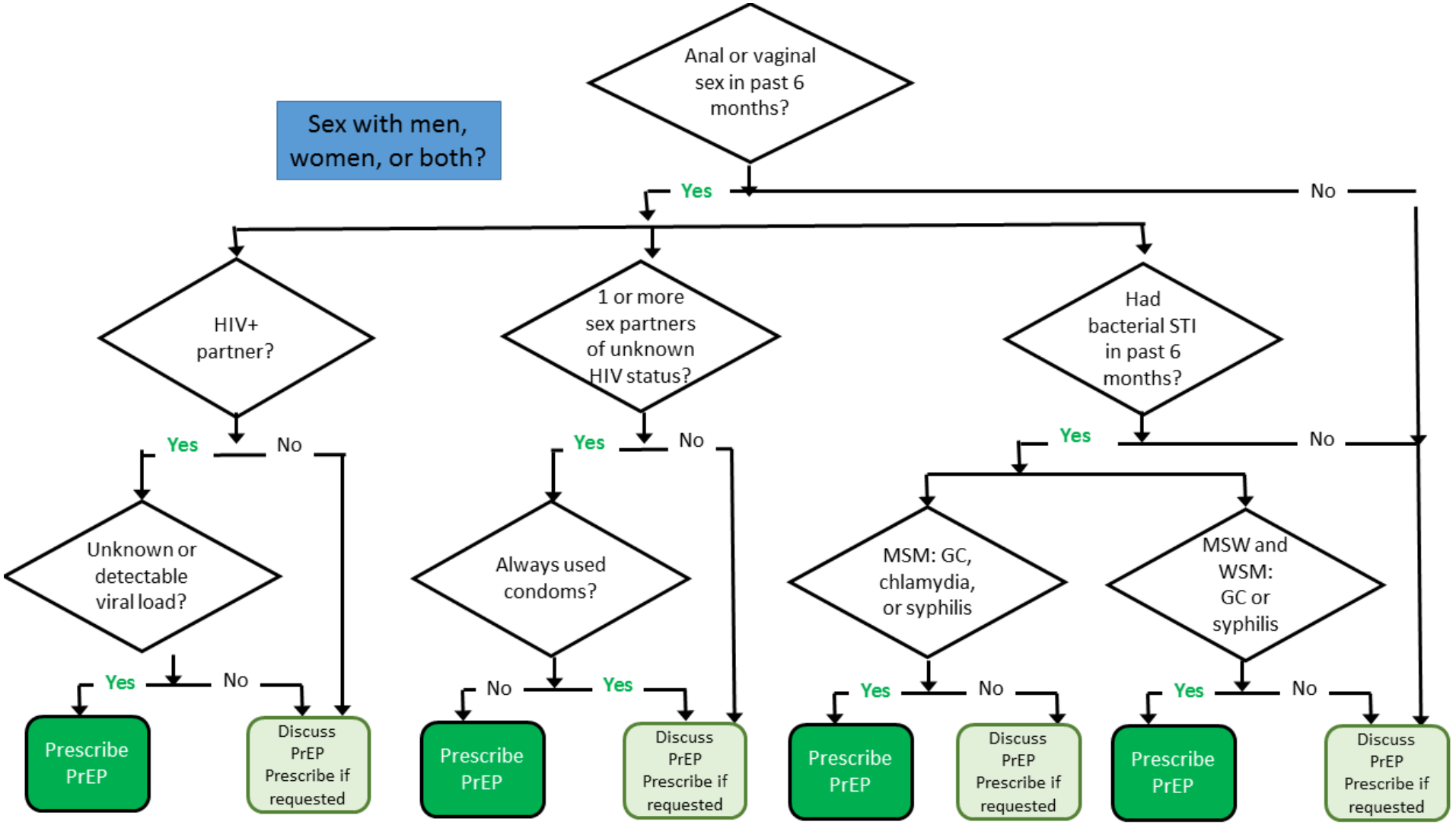
Assessing risk of sexual HIV acquisition (2021 CDC guidelines)



https://stacks.cdc.gov/view/cdc/112360

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Rule out HIV infection before initiating.

- Same day POC testing ok, but do not use oral fluid.
- All: laboratory-based Ag/Ab test (w/i 7 days before).

PLUS

- HIV RNA test obtained on day of initiation OR
- Follow-up laboratory-based Ag/Ab test in 4 weeks.

Limited data suggest protection after 2nd oral dose.

Follow up testing every 6 months.

https://www.cdc.gov/mmwr/volumes/74/wr/pdfs/mm7435a1-H.pdf

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Clinical Recommendation for Use of Lenacapavir for HIV Prevention

Rule out HIV infection (switching)

- Laboratory-based Ag/Ab test
- Confirm HBV status

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Ruling out HIV infection with Lenacapavir (Package Insert)

Initiation requires Ag/Ab testing + RNA

Follow-up testing requires a test approved for diagnosis of acute or primary HIV infection.

https://www.gilead.com/-/media/files/pdfs/medicines/hiv/yeztugo/yeztugo_pi.pdf

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Lenacapavir drug interactions

SUPPLEMENTARY TABLE. Lenacapavir drug interactions reported in association with selected commonly prescribed medications — Drug Prescribing Information*,†,§,¶

Drug Class	Drug Name	Comment	Effect on Concentration
Antimycobacterial	Rifampin (strong CYP3A inducer)	**Supplemental LEN doses required**	↓ LEN
Anticonvulsant	Carbamazepine, Phenytoin (strong CYP3A inducers)	**Supplemental LEN doses required**	↓ LEN
Benzodiazepine	Midazolam (Oral), Clonazepam	Use with caution. Consider alternative. Dose adjustment might be required.	↑ Midazolam (Oral), Clonazepam
Corticosteroid (systemic)	Dexamethasone, Hydrocortisone, Prednisone	Dose adjustment required. There is a risk for Cushing's syndrome and adrenal suppression.	↑ Dexamethasone, Hydrocortisone, Prednisone
Herbal Supplement	St John's Wort (strong CYP3A inducer)	**Supplemental LEN doses required**	↓ LEN
Hormonal Contraceptive (oral, injection)	Levonorgestrel, Ethinyl Estradiol, Depot MPA	No dose adjustment required	—
Hormones (other)	Estradiol, Testosterone	No dose adjustment required	—
Lipid Modifying	Lovastatin, Simvastatin	Dose adjustment required. Monitor for myopathy.	↑ Lovastatin, Simvastatin
Narcotic Analgesic	Fentanyl, Oxycodone, Tramadol	Careful monitoring of adverse reactions is recommended, including respiratory depression. Dose adjustment might be needed.	↑ Fentanyl, Oxycodone, Tramadol
Opioid Dependence Treatment	Buprenorphine, Methadone	Dose adjustment required	Unknown; possible ↑ Buprenorphine, Methadone
Phosphodiesterase-5 Inhibitor (Erectile Dysfunction)	Sildenafil, Tadalafil, Vardenafil	Dose adjustment required	↑ Sildenafil, Tadalafil, Vardenafil

https://stacks.cdc.gov/view/cdc/232180#tabs-3

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Lenacapavir drug interactions

- Strong CYP3A inducers should not be started for 2 days after LEN initiation.
  - supplemental full dose injection + 2 oral doses, Q6 months.
- Moderate CYP3A inducers may be started anytime.
  - half dose injection on day inducer started, Q6 months.
- No dosing recs for people already on inducers.

https://www.gilead.com/-/media/files/pdfs/medicines/hiv/yeztugo/yeztugo_pi.pdf

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Other dose adjustments

- No dose adjustment in renal impairment as low as 15mL/min.
- No dose adjustment with mild-mod (Child-Pugh Class A or B) hepatic impairment.
- Caution should be exercised in use of LEN in elderly (>65 yo) individuals due to greater frequency of concomitant illnesses or medications.

https://www.gilead.com/-/media/files/pdfs/medicines/hiv/yeztugo/yeztugo_pi.pdf

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Minimizing injection site reactions

- Use 90° angle (no less than 45°) to avoid interdermal injections.
- Ice packs, topical/oral analgesics may decrease reactions.

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Missed doses

- Window is +/- 2 weeks.
- If missed, prescribe one 300mg oral dose Qwk for up to 6 months.
- Resume maintenance injection within 7 days of oral.

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