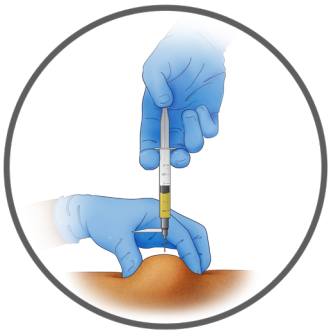

CLINICIAN'S INFORMATION GUIDE

Lenacapavir for HIV PrEP

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TABLE OF CONTENTS

ABOUT THIS INFORMATION GUIDE

This information guide from the *National HIV PrEP Curriculum* is intended for health care professionals involved in the care of persons interested in or receiving HIV preexposure prophylaxis (PrEP). The information in this guide emphasizes the dosing and administration of long-acting injectable lenacapavir (LEN) for HIV PrEP. This guide is produced by the University of Washington Infectious Diseases Education and Assessment Program (IDEA) as part of the federally-funded *National HIV PrEP Curriculum* project.

PERMISSION TO USE THIS GUIDE

LAST UPDATED

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GENERAL INFORMATION

What is Lenacapavir

Lenacapavir is a capsid inhibitor. It binds to HIV capsid proteins (the proteins that make up the conical core that houses the viral genome). Lenacapavir blocks HIV replication at multiple steps in the HIV life cycle, and it is used both for prevention and treatment of HIV. Lenacapavir (*Yeztugo*) is for HIV prevention and lenacapavir (*Sunlenca*) is a component of HIV antiretroviral treatment. This guide will address lenacapavir (*Yeztugo*) for HIV prevention.

Who May Benefit

Lenacapavir (*Yeztugo*) is indicated for HIV preexposure prophylaxis (PrEP) to reduce the risk of sexually acquired HIV in adults and adolescents weighing at least 35 kg and who are at risk for HIV acquisition. Studies have shown that lenacapavir, when administered as twice yearly subcutaneous injections, is extremely effective for preventing sexual acquisition of HIV. Individuals must have a negative HIV test prior to initiation.

Dosage Forms

Dosage forms and strength

- Oral tablets: 300 mg (used for initiation phase and if needed as oral bridge for missed injections) taken with or without food
- Injection: 463.5 mg/1.5 mL (309 mg/mL) in single-dose vials

Dosing and Administration Schedule

Initiation dosing

- Lenacapavir 927 mg (3 mL) subcutaneous injection dose (2 x 1.5 mL injections, each containing 463.5 mg of lenacapavir) + lenacapavir 600 mg orally (2 x 300 mg tablets) on day 1, followed by 600 mg orally (2 x 300 mg tablets) on day 2

Continuation dosing

- Lenacapavir 927 mg (3 mL) subcutaneous injection dose (2 x 1.5 mL injections, each containing 463.5 mg of lenacapavir) every 26 weeks (6 months) from the date of last injection, +/- 2 weeks

Missed Injections

Planned missed injections

- If a scheduled injection will be missed by more than 2 weeks, a 300 mg dose of oral lenacapavir may be taken as a bridge every 7 days (weekly) for up to 6 months, until injections resume. When resuming maintenance lenacapavir injections, administer the injection dose within 7 days of the last oral lenacapavir dose.

Unplanned missed injections

- If more than 28 weeks has passed since last injection and oral tablets have not been taken as a bridge, restart initiation phase from day 1, if clinically appropriate to resume lenacapavir.

When Not to Use

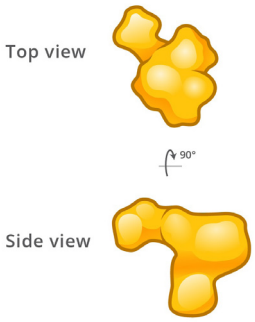
Contraindications: Use of lenacapavir for HIV PrEP is contraindicated in persons with positive (or unknown) HIV status and in persons who weigh less than 35 kg (77 lbs). Lenacapavir should not be used in a person who has a history of an allergic or hypersensitivity reaction to lenacapavir. In addition, lenacapavir should not be used if there is a prohibitive drug interaction with another medication the patient is taking or planning to take.

Adverse Reactions

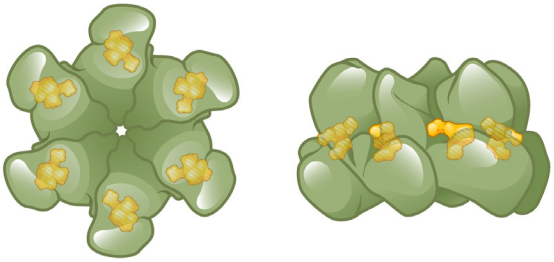
Adverse reactions: The most common adverse reactions are injection site reactions, nausea, and headache. The injection site reactions are common and include immediate-onset reactions (onset within hours to 1-2 days and typically resolve within days) and delayed or prolonged reactions (onset after 1-2 days and may persist for months).

LENACAPAVIR STRUCTURE AND BINDING TO HIV CAPSID PROTEINS

Lenacapavir Structure

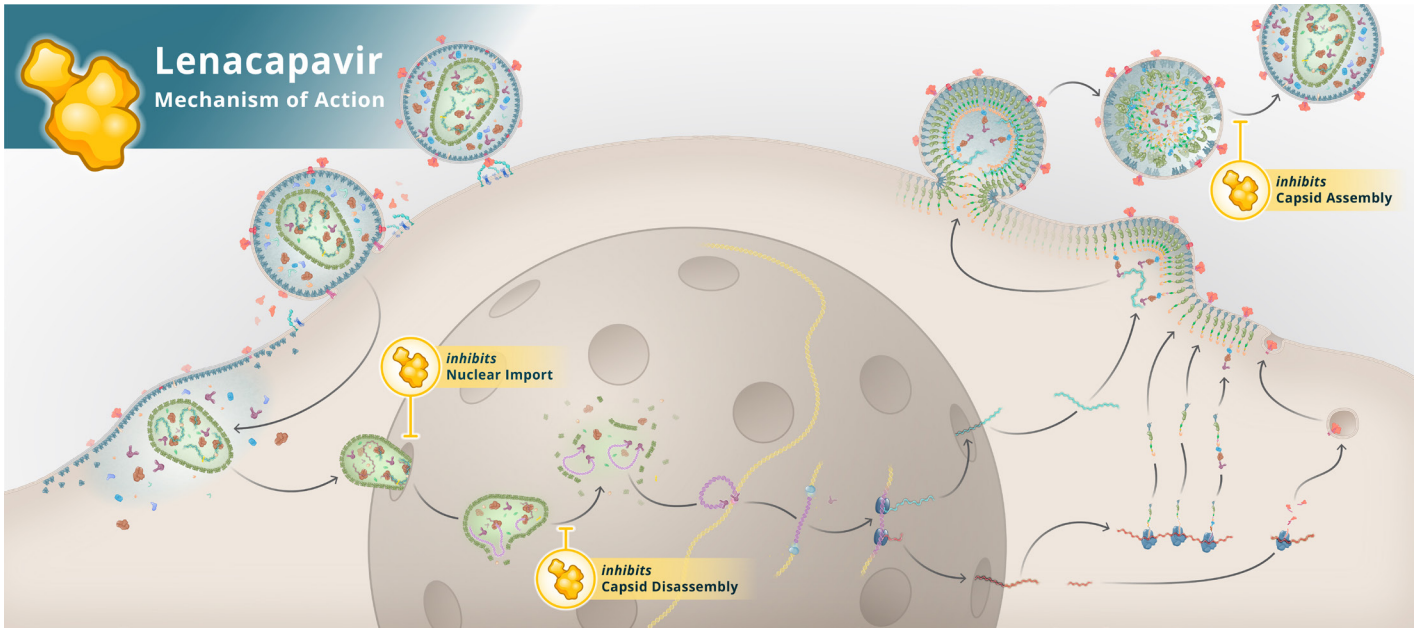


Lenacapavir bound to capsid (p24) hexamer



The illustration on the left shows a top view and side view of the small molecule lenacapavir. The illustration on the right shows 6 lenacapavir molecules binding to an HIV capsid hexamer (top and side views), which has the effect of locking adjoining hexamer proteins tightly together. This extensive intra-hexamer binding of lenacapavir causes an abnormal increase in the stability and stiffness of each hexamer.

LENACAPAVIR MECHANISM OF ACTION



Lenacapavir inhibits HIV replication at three different stages in the HIV life cycle. First, as shown on the left, lenacapvir, via complex mechanisms, inhibits the nuclear import of the HIV capsid (core) through the nuclear pore. Second, as shown in the middle and bottom, lenacapavir prevents the normal disassembly of the HIV capsid shell. The disassembly is required to release the contents inside the viral capsid (core) into the nucleus. Third, as shown on the top right, lenacapavir prevents the normal assembly of the HIV capsid shell, a process that occurs very late in the HIV life cycle.

LENACAPAVIR MEDICATION PREPARATIONS

Lenacapavir Vials

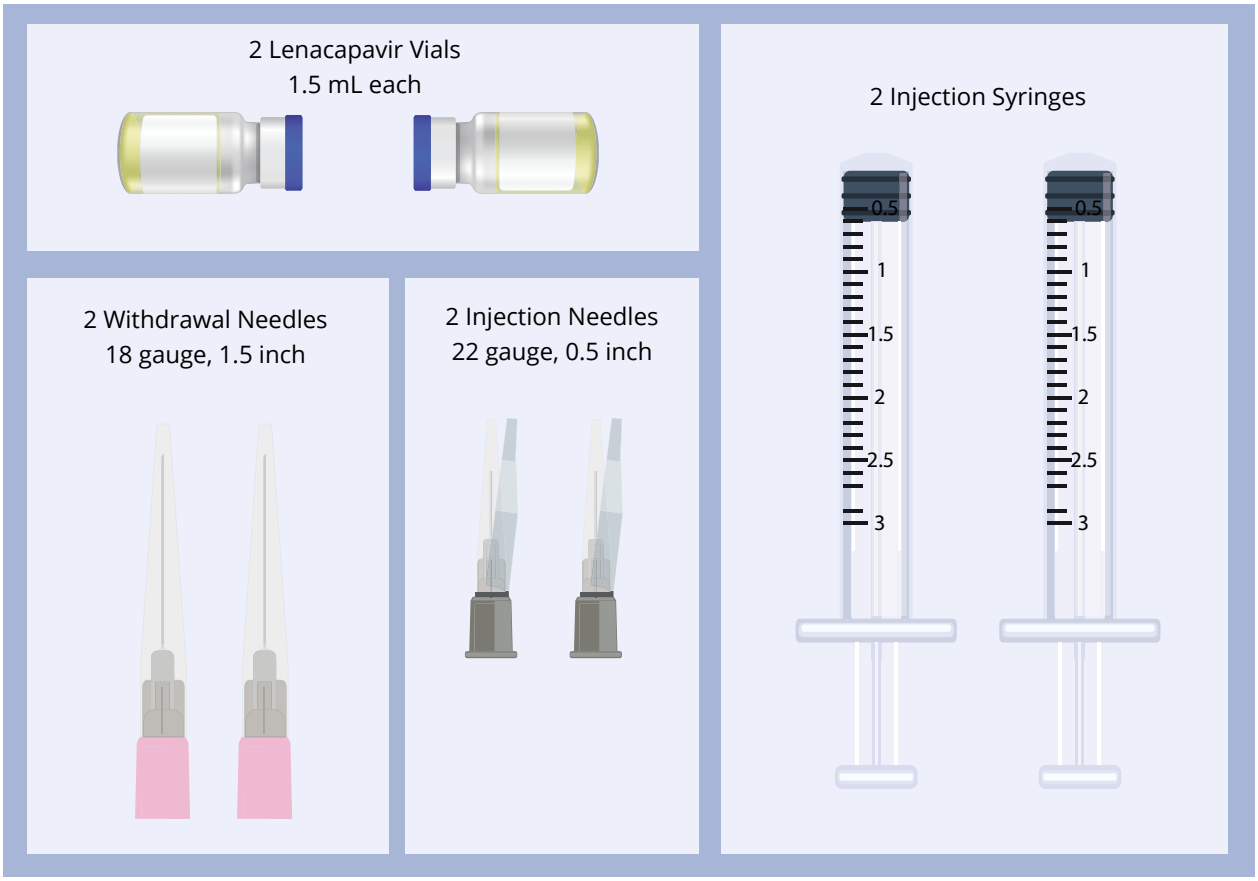
Each single-dose vial contains 463.5 mg/1.5 mL of lenacapavir. The recommended lenacapavir injection dose is 927 mg (administered as 2 x 1.5 mL subcutaneous injections) every 26 weeks. This requires use of two lenacapavir vials for each 927 mg dose. Separate syringes (and needles) should be used to withdraw and administer each 1.5 mL of lenacapavir. The injections must be given at distinct sites that are at least 4 inches apart.

Lenacapavir Tablets

Each tablet contains 300 mg of lenacapavir. For the lenacapavir initiation phase, the recommended oral lenacapavir dose is 600 mg (2 tablets) on days 1 and 2. The recommended oral lenacapavir dose when used for bridging is 300 mg (1 tablet) every 7 days. Oral lenacapavir can be taken with or without food.

MANUFACTURER'S ADMINISTRATION KIT

Kit Contents



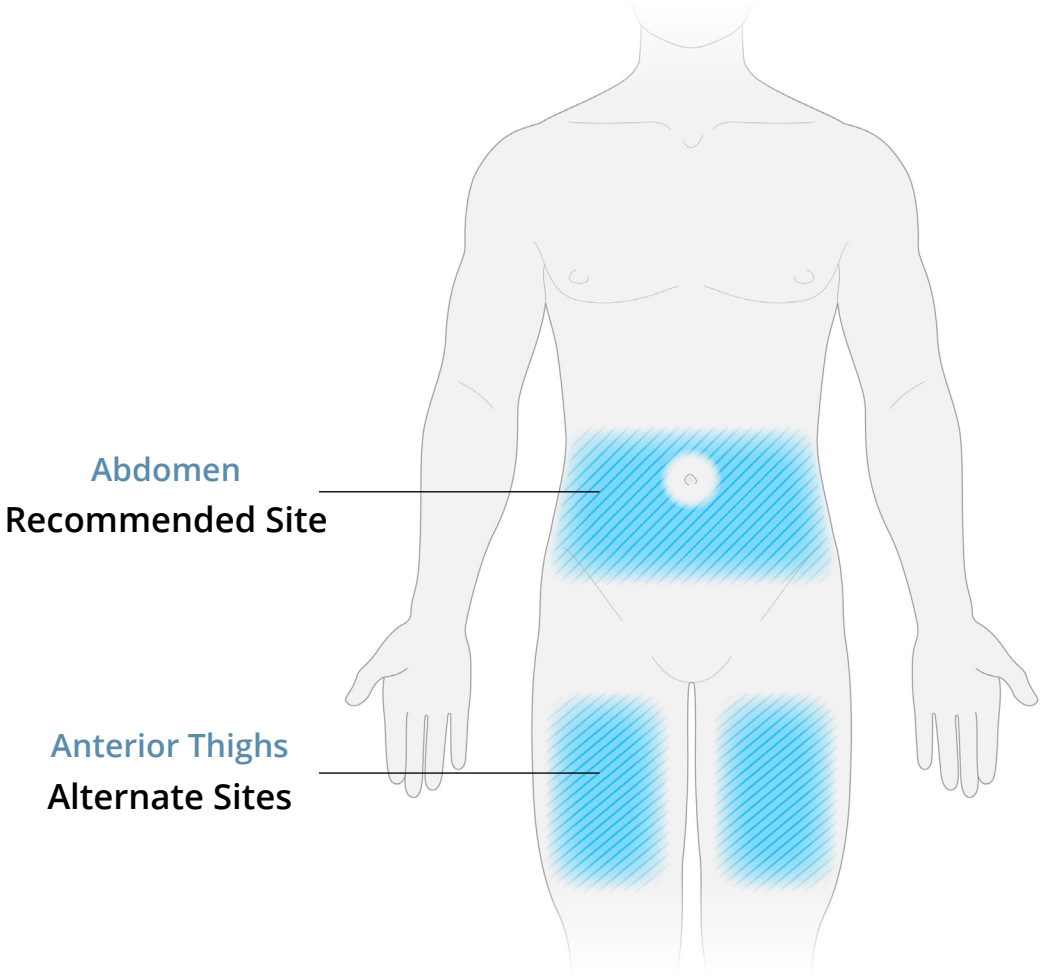
INSTRUCTIONS FOR LENACAPAVIR INJECTIONS

The following illustrations provide basic information on administering lenacapavir subcutaneous injections, including choosing an appropriate injection site, preparing the dose for administration, and the recommended injection technique. Lenacapavir injections should only be administered by a health care provider. Injections should be given subcutaneously; intradermal injections may cause severe injection site reactions. For detailed instructions for lenacapavir injections, see the lenacapavir (*Yeztugo*) prescribing information.

Choosing Sites for Lenacapavir Injections

At the beginning of the visit, discuss locations for the injection sites with the patient and choose the two injection sites. Allow adequate time for any techniques that will be used to prevent injection site pain (e.g., topical anesthetic applied 30-45 minutes before the injections and ice packs applied for 10-15 minutes).

The abdomen is the preferred site for the subcutaneous injections. Injections should be administered at least 2 inches from the umbilicus (navel). The thigh is an alternative injection site. Two injections are required for a complete dose of lenacapavir. Regardless of where the two injections are administered, they must be given at least 4 inches apart from each other.



EDITOR'S NOTE
There are limited, unpublished data that suggest the posterior upper arm or upper gluteus may be considered as injection sites for persons unable to receive subcutaneous lenacapavir in the abdomen or thigh regions.

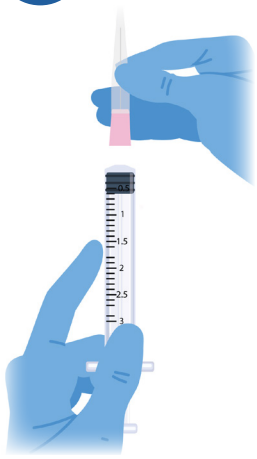
PREPARING THE LENACAPAVIR INJECTIONS

The lenacapavir dosing vials should be stored at room temperature. Keep the vials in the original carton until just before preparing the injections (to protect vials from light). Wait to draw up the injection until the patient is fully prepared and ready. Once the medication is drawn up into the syringe, the injection should be administered as soon as possible. The following summarizes the key sequential steps to follow when preparing lenacapavir for injection.

1

Remove cap and clean vial stopper with alcohol wipe

2

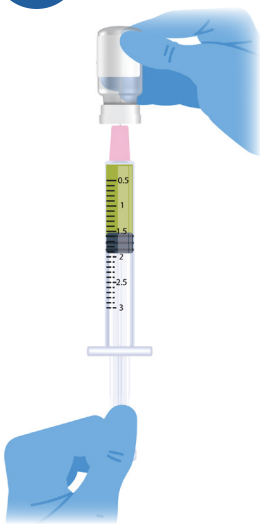


Attach 18G withdrawal needle to syringe

3

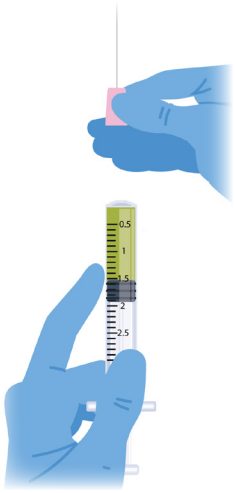
Pull plunger back to the 1.5 mL mark and inject 1.5 mL of air into vial

4



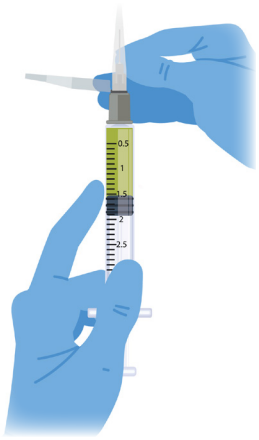
Withdraw all contents from vial

5



Remove 18G withdrawal needle from syringe

6

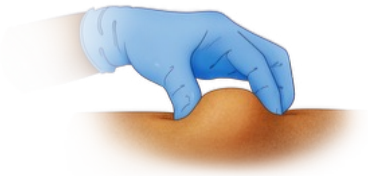


Attach 22G injection needle to syringe, expel air bubbles, and prime to 1.5 mL

INSTRUCTIONS FOR LENACAPAVIR INJECTIONS

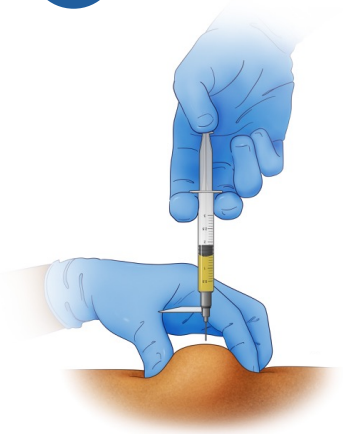
The following summarizes the key steps when administering lenacapavir injections. The goal for each injection is to administer the full 1.5 mL into the subcutaneous space.

1



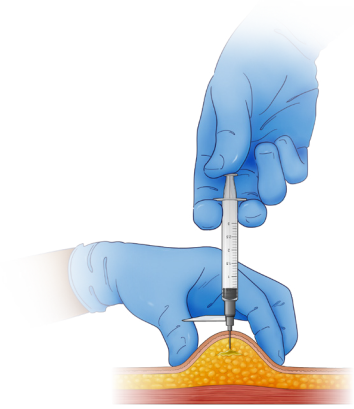
With one hand, gently pinch the skin at the injection site. This is typically done using the non-dominant hand so that the dominant hand remains free to administer the injection.

2



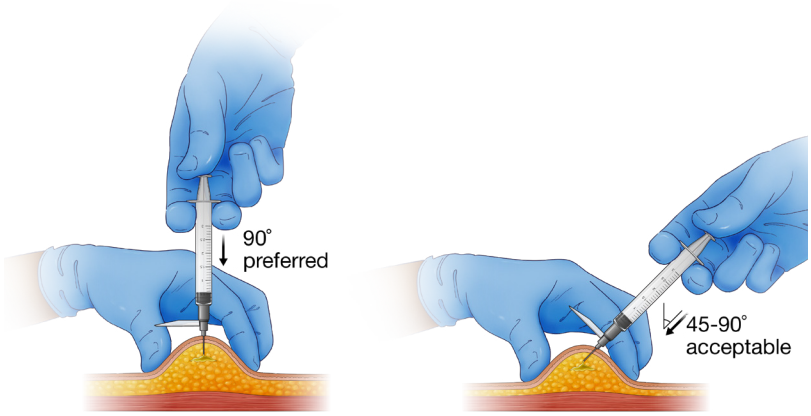
While the skin is pinched, prepare to administer the injection with other hand.

3



Keeping the skin pinched, slowly administer the full 1.5 mL dose of lenacapavir into the subcutaneous space.

4



The preferred angle for injecting is 90°. It is acceptable to inject at an angle between 45-90°. During the injection of lenacapavir, it is important to keep the skin pinched and keep the needle in the subcutaneous space. After the entire 1.5 mL has been injected into the subcutaneous tissue, pause for several seconds.

5

After injecting the entire dose, withdraw the needle at the same angle it was inserted. If this was the first injection, now administer the second dose, using the same injection technique. Note, the two injections must be administered at least 4 inches apart.

DOSING FORMS AND SCHEDULE

Dosing Forms

Each vial contains 463.5 mg of lenacapavir sodium per 1.5 mL. Therefore, the administration of 2 separate subcutaneous injections (each 1.5 mL) is required to achieve the recommended total dose of 927 mg each time. Each vial in the dosing kit is for single-use only; none of the dosing kit supplies should be reused.

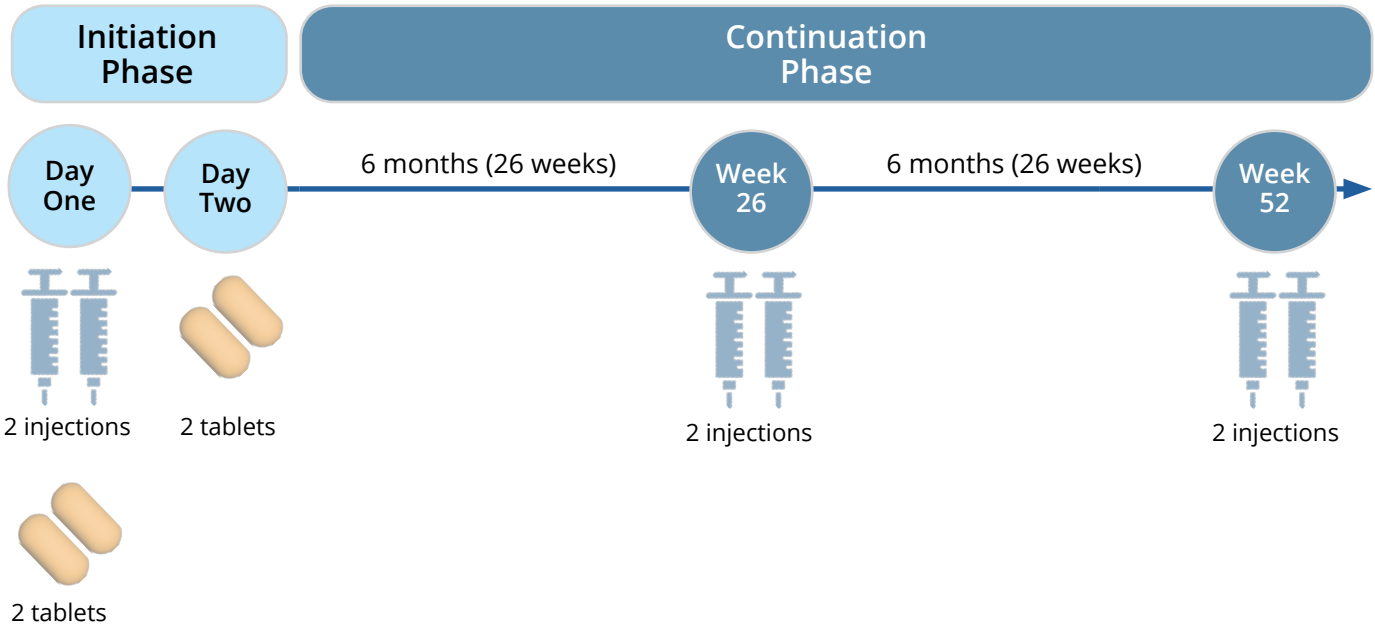
Lenacapavir is also available as a 300 mg oral tablet, used as part of the initiation phase of dosing and, if needed, as a bridge for planned missed injection doses.

Dosing Schedule

Dosing of lenacapavir includes an initiation phase and a continuation phase.

The initiation phase dosing occurs over 2 days. On day 1, two 1.5 mL subcutaneous injections are administered (total 927 mg) plus two 300 mg oral tablets (total 600 mg). On day 2, two 300 mg oral tablets (total 600 mg) are taken, typically at home. The purpose of this initiation phase is to achieve a protective level as soon as possible.

Following the initiation phase, the continuation phase requires two 1.5 mL subcutaneous injections (total 927 mg) every 6 months (target injection date should be 26 weeks after the previous injection). It is acceptable to administer each continuation dosage within 2 weeks before or after the target date.



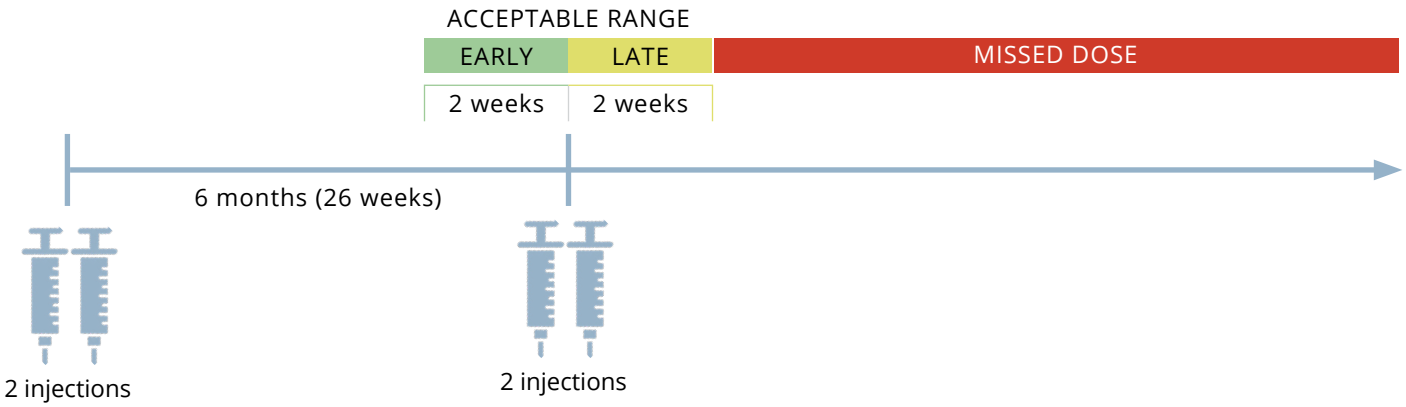
EDITOR'S NOTE

Day 1 requires injections and oral dosing and these should be administered in the clinic. Day 2 requires oral dosing only. The day-2 oral dose can be provided to the patient on day 1 so that the patient can self-administer the day-2 oral dose at home, without a visit to the clinic. A phone call or video appointment is recommended on day 2 to ensure that the oral doses are taken and to assess for any adverse reactions to the day-1 injections. A visit to the clinic on day 2 should be considered optional.

LENACAPAVIR MAINTENANCE DOSING

Acceptable Dosing Range

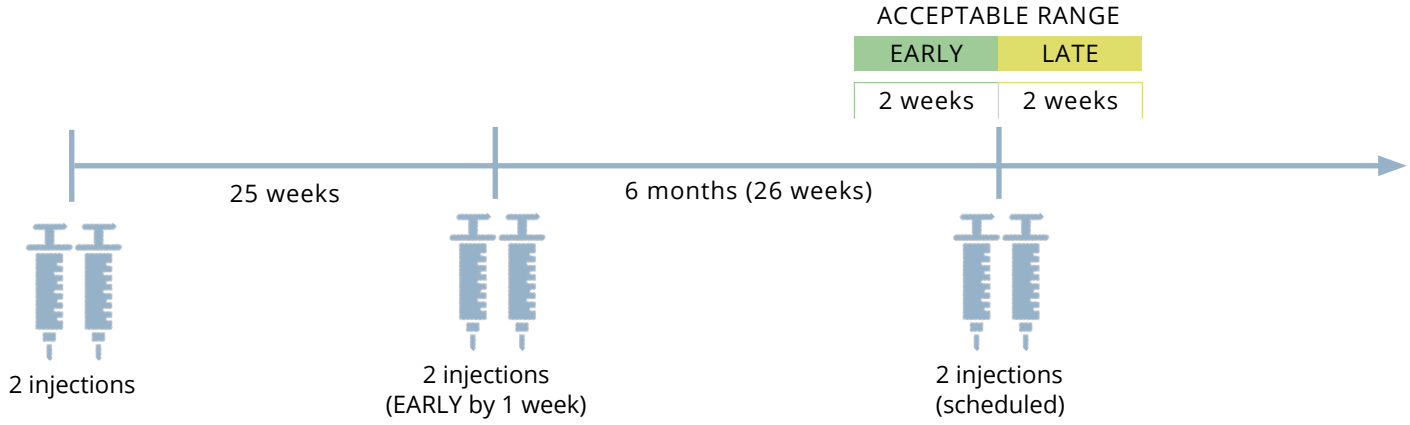
After the lenacapavir initiation dosing, the acceptable range for continuation doses is 26 weeks, +/- 2 weeks. If the maintenance dose has not been given by 28 weeks after the prior dose, it is considered a missed dose.



ADJUSTING DOSING SCHEDULE WITH EARLY OR LATE INJECTIONS

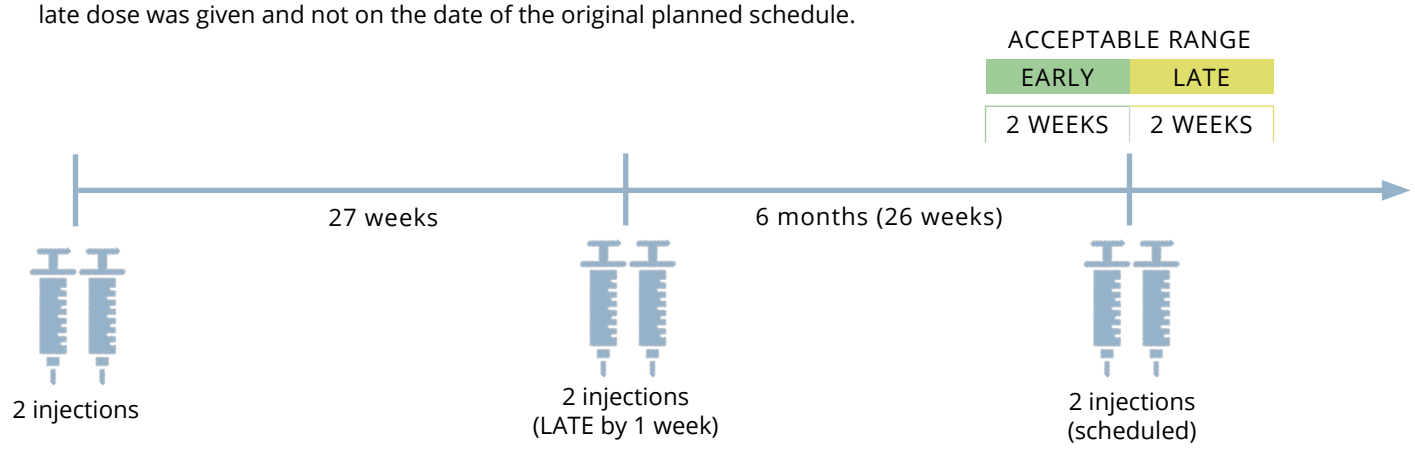
Example 1 - Early Injection

If a dose of injectable lenacapavir is given EARLY, the timing of the next dose should be adjusted based on the date when the early dose was given and not on the date of the originally planned scheduled dose.



Example 2 - Late Injection

If a dose of injectable lenacapavir is given LATE, the timing of the next dose should be based on the date when the late dose was given and not on the date of the original planned schedule.



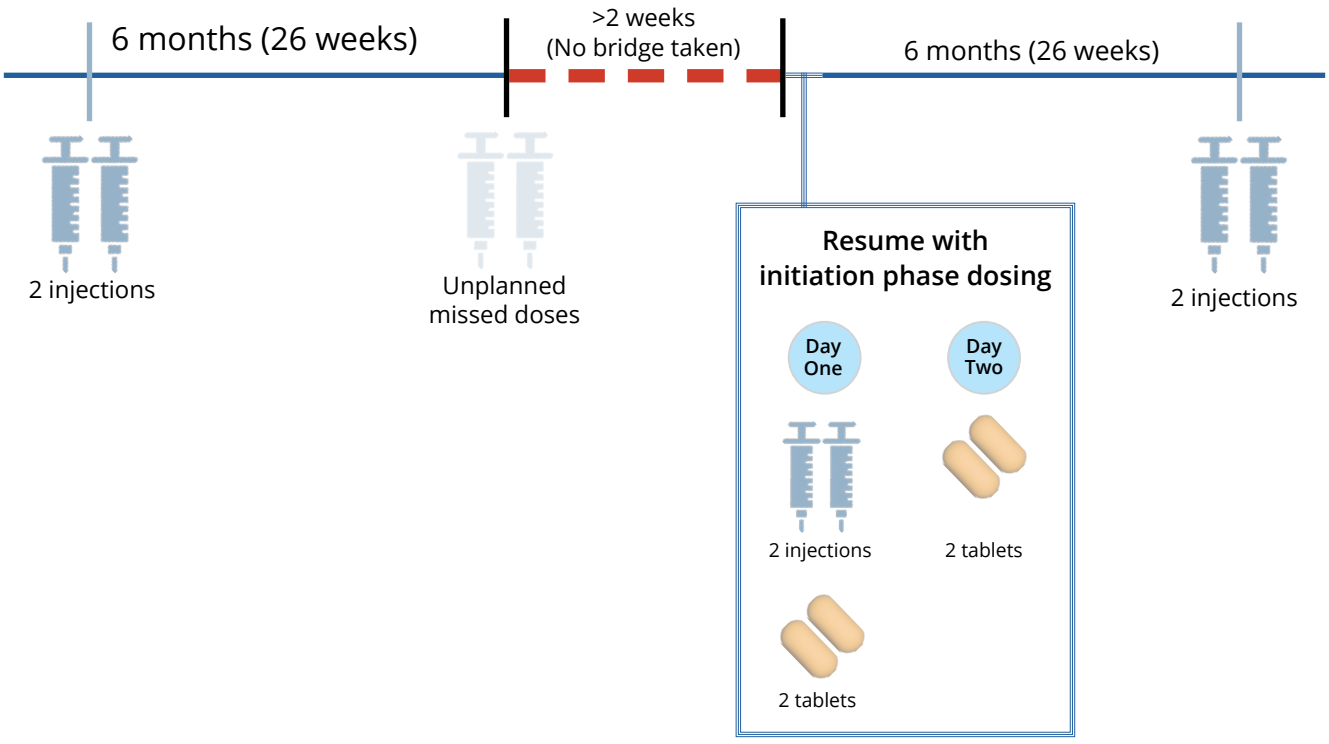
MISSED DOSES

Missed Oral Initiation Doses

- If the day-2 oral initiation dose (600 mg) is missed, it should be taken as soon as possible.
- Day-1 and day-2 oral initiation doses should not be taken on the same day.

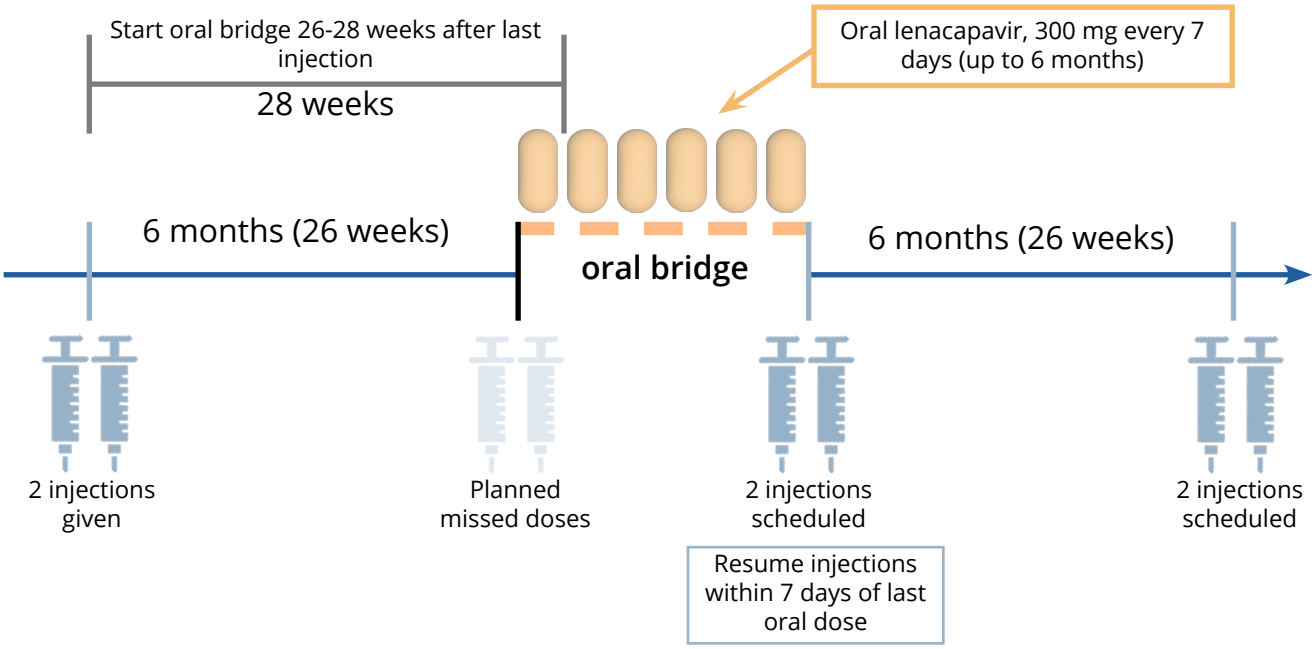
Unplanned Missed Injection Doses

If a scheduled lenacapavir injection has not been given within 28 weeks of the prior injection and weekly oral lenacapavir has not been taken as a bridge, injections should be re-initiated (injection on day 1 plus oral lenacapavir 600 mg, followed by another 600 mg oral lenacapavir on day 2). Then, the every 6-month injections should be continued. Individuals who miss a scheduled injection should be clinically re-assessed to ensure resumption of lenacapavir injections remains appropriate and that the individual has not acquired HIV.



Planned Missed Doses

During continuation injection dosing, if the scheduled 6-month injection is expected to be delayed by more than 2 weeks (e.g., if the time until the next injection is anticipated to be more than 28 weeks from the prior injection), oral lenacapavir tablets, administered 300 mg once every 7 days, may be taken on an interim basis until injections resume. Weekly oral lenacapavir tablets may be taken on an interim basis for up to 6 months, if needed. If oral lenacapavir is used as a bridge, then continuation injection doses can be restarted within 7 days after the last oral dose.



EDITOR'S NOTE

Using an oral lenacapavir bridge can be costly (and may be difficult to obtain), especially if used for a prolonged period. If oral lenacapavir is not available, daily oral tenofovir DF-emtricitabine (TDF-FTC) or tenofovir alafenamide-emtricitabine (TAF-FTC) may be used for the oral bridge, unless there is a contraindication.

- If TDF-FTC or TAF-FTC is used for the oral bridge, restarting lenacapavir injections requires repeating the initiation phase lenacapavir dosing (day-1 injections, day-1 oral doses, and day-2 oral doses). The oral HIV PrEP medications provide adequate tissue levels to prevent HIV acquisition for at least several days after discontination. Therefore, the oral TDF-FTC or TAF-FTC bridge should be discontinued on day 1 of the lenacapavir initiation phase dosing.
- If TDF-FTC or TAF-FTC is used as an oral bridge, it is important to check the patient's serum creatinine level and hepatitis B virus (HBV) status. Both of these medications have dosing limitations based on creatinine clearance and both have activity against HBV. In persons with active HBV who are receiving TDF-FTC or TAF-FTC, a hepatic flare may occur if these antiviral agents are abruptly stopped.

INJECTION SITE REACTIONS

Administration of lenacapavir requires 1.5 mL of a viscous fluid injected into the subcutaneous space, and injection site reactions are common. Most reactions, however, are mild-to-moderate, self-limited, and do not lead to stoppage of the medication. Reactions can occur immediately or can be delayed or prolonged.

Types of Injection Site Reactions

- Immediate-onset reactions (onset within hours to 1-2 days and typically resolve within days, though may last for 1-2 weeks): usually pain, tenderness, erythema, warmth, swelling, bruising, or itching of the injection site area.
- Delayed or prolonged reactions (onset after 1-2 days, may persist for months): nodules, feeling like there is a "mass" or "lump" under the skin, induration, hyperpigmentation or hypopigmentation of the skin, or persistent discomfort. Abscess or cellulitis at the injection site is also possible, though quite rare.

Strategies to Prevent Injection Site Reactions

1. Before the injection
    - Make sure the patient is in a comfortable position with abdomen relaxed (not flexed); recommend avoiding tight clothing in the area of the injections (to avoid additional irritation).
    - Apply an ice pack (or cold compress) for approximately 10 minutes to both of the planned injection sites.
    - If there is no contraindication, consider use of a topical analgesic, especially for patients with prior significant pain at an injection site. Apply lidocaine 2.5%-prilocaine 2.5% (*Emla*) cream to intact skin at both injection sites approximately 30-45 minutes before the injections, and wipe cream off with alcohol during final preparation for the injections.
2. Administering the injection
    - Use an appropriate size needle for the injection (22 gauge).
    - Avoid the 2-inch radius around the navel.
    - Administer the injection slowly (over 30-60 seconds) and at the recommended angle (90 degrees preferred, if possible).
    - Give the two injections at least 4 inches apart.
    - Ensure the medication is injected subcutaneously (not intradermally).
    - Avoid injecting into areas of irritated skin.
    - Avoid administering the injection at the exact same location as for a recent injection.
3. After the injection
    - Apply an ice pack (or cold compress) for approximately 10 minutes to both of the injection sites.

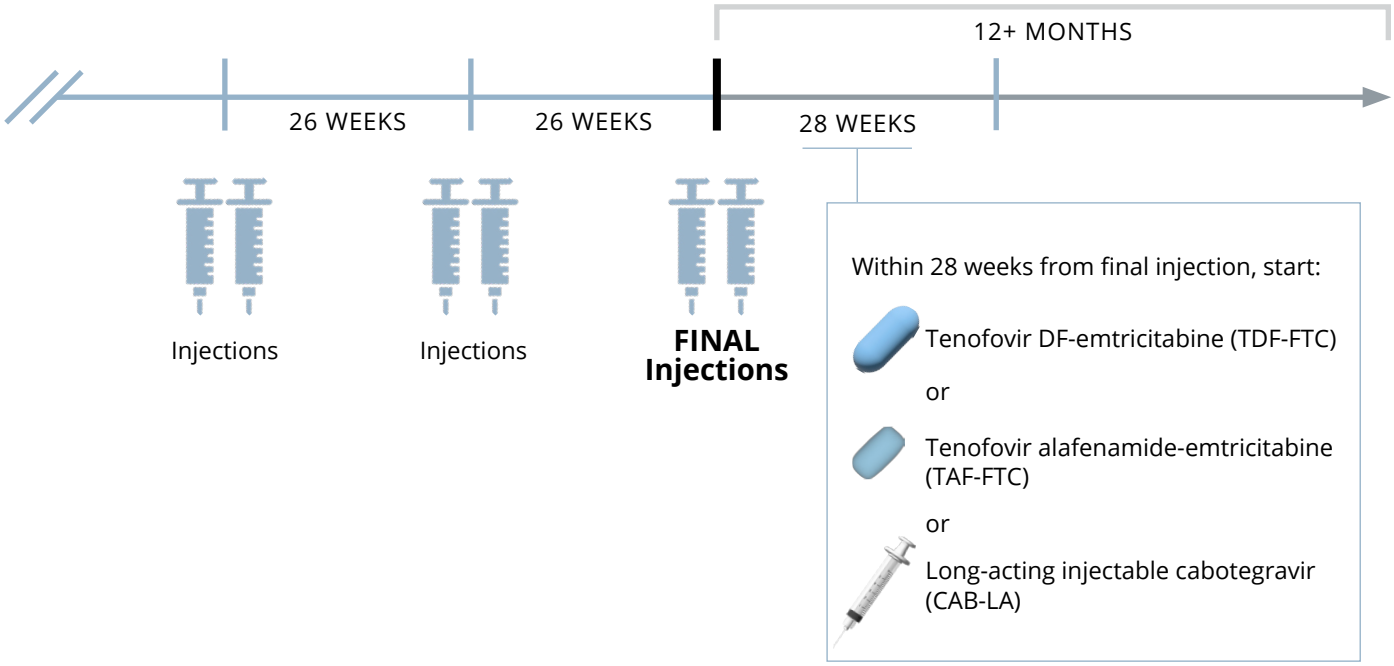
Management of Injection Site Reactions:

1. For immediate reactions (usually pain, redness, and/or swelling): Apply ice pack or cold compress for 10-15 minutes every few hours for the first 24 hours, topical steroid cream if pruritus is present, acetaminophen or NSAIDs for pain relief (if not contraindicated).
2. Persistent or delayed reactions (often nodules or induration): Apply warm compresses, and gently massage the affected area; if the injection site is tender, massage of the tissues around the injection site may be helpful.
3. Assess for cellulitis or abscess, though quite rare.

WHEN STOPPING INJECTABLE LENACAPAVIR

Residual concentrations of lenacapavir may remain in the systemic circulation for prolonged periods (e.g., up to 12 months or longer after the last subcutaneous dose). Missed doses could lead to acquisition of HIV-1 and development of drug resistance. For individuals at continued risk of HIV acquisition, alternative forms of HIV PrEP should be considered after discontinuation of lenacapavir and should be started within 28 weeks of the last lenacapavir injection.

LENACAPAVIR INJECTIONS 927 mg (3 mL) SubQ	**TAIL PHASE**
	For persons with ongoing risk for HIV acquisition, all available HIV prevention strategies should be leveraged, including the use of oral HIV PrEP (started within 28 weeks of stopping lenacapavir). Continue follow-up visits quarterly for at least 12 months.



EDITOR'S NOTES

1. For a person discontinuing lenacapavir injections who has ongoing risk for HIV acquistion, the choice for the HIV PrEP medication should be chosen based on appropriate indications and recommendations. The duration of HIV PrEP will depend on the ongoing risk for HIV acquisition and the need for HIV PrEP.
2. Although it is unlikely that a person receiving lenacapavir injections every 6 months would switch to every 2 month injections with long-acting cabotegravir, this scenario is possible if the individual strongly prefers injection medications for HIV PrEP, and they needed to discontinue lenacapavir for HIV PrEP, either from intolerable side effects, prohibitive drug interactions, or reimbursement issues.
3. Persons who discontinue lenacapavir should have HIV testing every 3 months for at least 1 year.

ESTABLISHED AND POTENTIALLY SIGNIFICANT DRUG INTERACTIONS

Effect of Lenacapavir on Other Drugs

Lenacapavir is a moderate CYP3A inhibitor and a P-gp inhibitor. Due to its long half-life, lenacapavir may increase the exposure to drugs metabolized by CYP3A or P-gp initiated within 9 months after the last subcutaneous dose of lenacapavir.

Effect of Other Drugs on Lenacapavir

Medications that are strong or moderate inducers of CYP3A may significantly decrease plasma concentrations of lenacapavir. Dosage modifications (supplemental doses) of lenacapavir are recommended when initiating either a moderate or a strong inducer (see the manufacturer's prescribing information for more detailed information on drug interactions). Conversely, combined P-gp, UGT1A1, and strong CYP3A inhibitors may significantly increase plasma concentrations of lenacapavir. It is not recommended to use lenacapavir with combined P-gp, UGT1A1, and strong CYP3A inhibitors. This could occur through a single medication or a combination of medications that meet this criteria (combined P-gp, UGT1A1, and strong CYP3A inhibitors).

Effects of Other Drugs on Lenacapavir for HIV PrEP*

Concomitant Drug Class:	Effect on Concentration	Clinical Comment
Antimycobacterials Rifampin Rifabutin Rifapentine	All expected to decrease lenacapavir levels	Coadministration with lenacapavir is contraindicated.
Anticonvulsants Carbamazepine Eslicarbazepine Oxcarbazepine Phenobarbital Phenytoin Primidone	All expected to decrease lenacapavir levels	Coadministration of lenacapavir with either carbamazepine or phenytoin is contraindicated. Coadministration of lenacapavir with eslicarbazepine, oxcarbazepine, phenobarbital, or primidone is not recommended.
Corticosteroids Systemic betamethasone Systemic dexamethasone	Expected to decrease lenacapavir levels	Decreased lenacapavir concentrations expected if used with dexamethasone > 16 mg/day.
Herbal Products St. John's Wort	Expected to decrease lenacapavir levels	Coadministration with lenacapavir is contraindicated.

*For more detailed information about potential drug interactions with lenacapavir, see the University of Liverpool: HIV Drug Interaction Tracker

Laboratory Evaluation in Persons Starting or Receiving Lenacapavir for HIV PrEP

Test	Initial visit	Q 6 months	Q 12 months	When stopping
 HIV-1 Antigen/ Antibody*	ALL†	ALLΔ	ALLΔ	ALL
 HIV-1 RNA	ALL¶			
 Syphilis Serology	ALL	MSM‡	ALL	ALL
 Gonorrhea	ALL	MSM‡	ALL	ALL
 Chlamydia	ALL	MSM‡	ALL	ALL
 Hepatitis B Serology	ALL§			
 Hepatitis C Serology ^	ALL#		MSM	
 Pregnancy Test	ALL**	ALL**	ALL**	

LEGEND:

*Test should be FDA-approved or cleared for the diagnosis of acute HIV.

†Perform within 7 days prior to starting HIV PrEP. Confirm negative HIV status prior to giving the lenacapavir initiation dose. A laboratory-based HIV antigen-antibody test is recommended. A rapid (point-of-care) test is not recommended for HIV testing prior to the initiation dose.

ΔPerform within 7 days prior to giving the lenacapavir continuation dose. Confirm negative HIV status prior to giving the lenacapavir continuation dose. A blood-based rapid (point-of-care) HIV antigen-antibody test can be used for HIV testing prior to the continuation doses. Oral fluid HIV antibody testing should not be used. If a lenacapavir maintenance dose is administered on the basis of a negative rapid blood-based antigen-antibody test, then a laboratory-based HIV antigen-antibody test should also be obtained, with a plan for close follow-up of the results.

¶A blood sample for an HIV-1 RNA test should be drawn within 7 days prior to the initiation dose, but the lenacapavir initiation phase dosing can be given if the HIV-1 RNA test result is pending and the HIV antigen-antibody test is negative.

‡Testing for MSM is usually done every 3-6 months.

§One-time screening for hepatitis B virus (HBV) recommended for all adults in the United States. Screen with hepatitis B surface antigen (HBsAg), hepatitis B surface antibody (HBsAb), and hepatitis B core antibody (HBcAb).

^Screen with hepatitis C antibody test and, if reactive, reflex to hepatitis C virus (HCV) RNA test.

#One-time screening for HCV recommended for all adults in the United States.

**For women with childbearing potential; advised for counseling purposes.

Abbreviations: MSM = Men who have sex with men

EDITOR'S NOTES

1. Prior to giving any of the lenacapavir initiation phase injection or oral doses, a negative HIV antigen-antibody test should be confirmed and an HIV RNA test should be ordered. The lenacapavir initiation dose can be given if the results from the HIV RNA test are pending.
2. Prior to each continuation dose of lenacapavir, negative HIV status should be confirmed. If a point-of-care (rapid) blood HIV antigen-antibody test is used to confirm HIV negative status, a more sensitive laboratory-based HIV antigen-antibody test should also be ordered; the lenacapavir continuation dose can be given if the laboratory-based HIV test result is pending.
3. Some experts recommend HIV testing every 3 months for individuals at very high risk of HIV acquisition, particularly if they are already undergoing testing for bacterial sexually transmitted infections every 3 months.

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Note: The *National HIV PrEP Curriculum* does not provide clinical consultation or medical advice.

PURPOSE 1

Twice-Yearly Lenacapavir Versus TAF/FTC or TDF/FTC for HIV Prevention for Women

Summary

Lenacapavir demonstrated remarkable effectivess at preventing HIV in women; zero HIV infections occurred in trial participants receiving twice-yearly injectable lenacapavir.

Study Design

Phase 3, double-blind, randomized controlled trial conducted at sites in South Africa and Uganda

Participants

- 5,338 Adolescent girls and young women
- 16 - 25 Years of age
- Sexually active with male partners
- Not using PrEP at enrollment
- Unknown HIV status and no HIV testing within prior 3 months

Interventions

2:2:1 Randomization

Lenacapavir	TAF-FTC	TDF-FTC
Two 1.5 mL SQ injections every 26 weeks with a daily oral placebo	One tablet daily with placebo injections every 26 weeks	One tablet daily with placebo injections every 26 weeks
n = 2,134	n = 2,136	n = 1,068

Results

	Lenacapavir	TAF-FTC	TDF-FTC
New HIV Infections	0	39	16
HIV Incidence (per 100 person-years)	0 (95% CI 0.00 to 0.19)	2.02 (95% CI 1.44 to 2.76)	1.69 (95% CI 0.96 to 2.74)

Background Incidence

Estimated background HIV incidence in 8,094 participants screened for the study: 2.41 per 100 person-years (95% CI 1.82 to 3.19)

Notes

- Adherence with TAF/FTC and TDF/FTC was low
- Injection site reactions were common with lenacapavir but very few participants discontinued

Abbreviations
SQ = subcutaneous
TAF-FTC = tenofovir alafenamide-emtricitabine
TDF-FTC = tenofovir DF-emtricitabine

Source: Bekker LG, Das M, Karim QA, et al. N Engl J Med. 2024;391:1179-92. [PMID: 39046157]

PURPOSE 2

Twice-Yearly Lenacapavir or Daily TDF/FTC for HIV Prevention for Men who Have Sex with Men (and Other Populations*)

Summary

The incidence of HIV with twice-yearly injectable lenacapavir was significantly lower than the incidence with daily oral TDF/FTC and lower than the estimated background incidence, showing high efficacy for HIV prevention for men who have sex with men and other populations.*

Study Design

Phase 3, multinational, double-blind, randomized controlled trial conducted at 92 sites in geographic areas with evidence of substantial ongoing HIV transmission

Participants

3,265
Participants

- Condomless receptive anal sex with male partners
- Not using PrEP in prior 3 months
- Participants at least 16 years of age
- Unknown HIV status and no HIV testing in prior 3 months

Interventions

2:1 Randomization

Lenacapavir
Two 1.5 mL SQ injections every 26 weeks with a daily oral placebo

n = 2,179

TDF-FTC
One tablet daily with placebo injections every 26 weeks

n = 1,086

Results

	Lenacapavir	TDF-FTC
New HIV Infections	2	9
HIV Incidence (per 100 person-years)	0.1 (95% CI 0.01 to 0.37)	0.93 (95% CI 0.43 to 0.77)
Background Incidence	Estimated background incidence of HIV in the screened population (4,634 participants) was 2.37 per 100 person-years (95% CI 1.65 to 3.42)	
Notes	• No safety concerns identified • Very few discontinuations on lenacapavir	

***See original publication for details of all populations included in study**

Abbreviations
TDF-FTC = Tenofovir DF-emtricitabine
SQ = Subcutaneous

Source: Kelley CF, Acevedo-Quiñones M, Agwu AL, et al. N Engl J Med. 2025;392:1261-76. [PMID: 39602624]

FREQUENTLY ASKED QUESTIONS

1. **What are the contraindications to starting lenacapavir as HIV PrEP?**
   There are three main contraindications for starting lenacapavir as HIV PrEP: (1) known HIV infection, (2) a prior history of hypersensitivity to lenacapavir or any of its components, and (3) body weight less than 35 kg (77 lbs). A confirmed negative HIV test is required prior to initiation of lenacapavir.

2. **If a laboratory-based HIV antigen-antibody test is negative but an HIV RNA test is not available for baseline testing (before initiating lenacapavir), what additional testing is needed?**
   The CDC guidance recommends that if a person starts lenacapavir HIV PrEP based on a negative laboratory-based HIV antigen-antibody assay result, and an HIV RNA assay cannot be obtained, clinicians should repeat the laboratory-based HIV antigen-antibody test 4 weeks after the lenacapavir initiation.

3. **Does a person need to come into clinic for both day-1 doses and day-2 doses of the initiation phase of lenacapavir?**
   The day-1 lenacapavir subcutaneous injections (2 injections) and oral lenacapavir dose (2 pills) must be given in the clinic. A visit to the clinic on day 2 should be considered optional, since it requires only the oral dose of lenacapavir (2 pills). One option is to provide the day-2 oral lenacapavir dose (2 pills) to the patient on day 1, with specific instructions to take the oral lenacapavir dose (2 pills) on day 2 at home 24 hours after they took the day-1 oral dose. If the patient will be taking the day-2 lenacapavir dose at home, it is ideal to have a phone call or video appointment on day 2 to ensure that the oral dose (2 pills) is taken and to assess for any adverse reactions to the day 1 doses. The other day-2 option is for the patient to return to the clinic and take the day 2 oral lenacapavir dose (2 pills) in the clinic.

4. **After initiating lenacapavir for HIV PrEP, how much time is required to reach protective levels?**
   In persons starting lenacapavir with initiation phase dosing, available pharmacokinetic data suggest that protective levels of lenacapavir are achieved approximately 2-4 hours after the day-2 oral lenacapavir dose. Oral dosing allows for initial drug accumulation prior to the long-acting injecton.

5. **Which alternative injection sites can be used if a patient wishes to avoid lenacapavir injections in the abdomen?**
   The abdomen is the recommended site for lenacapavir subcutaneous injection, and the anterior thighs are considered optional alternative sites. Upublished data suggest the posterior upper arms and upper gluteus may be acceptable injection sites if the abdomen or thigh regions cannot be used. The subcutaneous injection of lenacapavir in the posterior upper arms or upper gluteus regions should be considered off-label and should be approached with caution. Regardless of where the injection is given, it is important to ensure it is administered in the subcutaneous tissues. For more details, see Choosing sites for lenacapavir injection on page 4.

6. **What additional considerations should be considered if the thigh is used as an alternative injection site?**
   On the legs, if possible, choose an area with good fat coverage and avoid injecting in an area with visible veins, bruises, or scars. To minimize post-injection soreness and inflammation, counsel the patient to avoid strenuous leg workout the day before the lenacapavir injections and use a cold pack or numbing cream at the planned injection sites prior to injection (as outlined with abdominal injections). When administering the lenacapavir injections, instruct the patient to sit in a relaxed position with the thigh supported (so that muscles are relaxed and not flexed). Also, counsel the patient not to wear tight-fitting pants to avoid friction on the injection site. Similar to abdominal injections, apply a cold pack gently to the area after the injection for a few minutes. Last, instruct the patient to avoid intensive leg workouts for 1-2 days after the injection, but it may help to do some walking or gentle exercises to increase blood flow to the area.

7. **Would a person be considered eligible for lenacapavir HIV PrEP if they are unable to swallow oral tablets?**

   Lenacapavir for HIV PrEP has only been studied with the oral tablets as part of the loading dose (two tablets and first injection on day 1 plus two tablets on day 2). With this strategy, it is estimated (based on limited data) that lenacapavir reaches a protective level by around 2 hours after taking the day-2 tablets. If a person does not take the oral tablets on day 1 and day 2 (and thus only receives an injection at initiation without the oral tablet loading doses) it is estimated that lenacapavir will not reach protective levels until around day 21 to day 28. Starting lenacapavir injections for HIV PrEP in the absence of the day-1 and day-2 loading dose tablets has not been studied, is not recommended, and should be undertaken only in unique circumstances. If this scenario occurs, the individual should be advised to use an alternate form of HIV prevention for at least 21 to 28 days after the initial lenacapavir injection. Similarly, if a person misses an injection dose of lenacapavir for HIV PrEP for any reason and cannot take oral tablets as a bridge to restarting lenacapavir injections, they should be advised to use an alternate form of HIV prevention until approximately 21 to 28 days after they resume lenacapavir injections.

8. **Can lenacapavir HIV PrEP be used during pregnancy, while breastfeeding, or while trying to conceive?**

   Preclinical studies and limited human data from clinical trials do not indicate harmful effects of lenacapavir, when used during pregnancy or breastfeeding, on fetal development or infant outcomes. Animal studies have not shown harm. The lenacapavir (*Yeztugo*) prescribing information states, "In women at risk of acquiring HIV-1, consideration should be given to methods to prevent acquisition of HIV-1, including continuing or initiating lenacapavir (*Yeztugo*) for HIV-1 PrEP, during pregnancy." Women trying to conceive or pregnant should have a risk-benefit discussion with their provider. The CDC recommendations state that lenacapavir for HIV PrEP "may be used in pregnant women or continued in women who become pregnant while receiving injections, considering the woman's risk for HIV without PrEP, after provider-client shared decision-making."

9. **Can lenacapavir for HIV PrEP be used in patients with end-stage renal disease or on dialysis?**

   There is no recommended dosage adjustment of lenacapavir for individuals with mild, moderate, or severe renal impairment (estimated creatinine clearance greater than or equal to 15 mL per minute). There are inadequate data for use of lenacapavir in persons with end-stage renal disease, including persons on hemodialysis. Because lenacapavir is highly protein-bound, it is not likely to be removed by hemodialysis.

10. **For HIV PrEP, can a person switch to lenacapavir from other HIV PrEP medications, such as long-acting injectable cabotegravir or oral PrEP?**

    Yes, switching is possible. It's important to ensure continuous HIV PrEP coverage during the transition and to confirm HIV-negative status (i.e., a confirmed negative HIV test result rather than collected and pending) before starting lenacapavir. Prior to the switch, HIV testing should be repeated, and the requirements for the initiation phase must be followed. When transitioning to lenacapavir from oral HIV PrEP or long-acting injectable cabotegravir, HIV-negative status should be confirmed with a negative laboratory-based HIV antigen-antibody test. With long-acting injectable cabotegravir, given the prolonged tail concentrations of cabotegravir, tailored transition plans and advanced planning should account for dosing schedules and pharmacokinetics.

11. **If an individual switches from oral HIV PrEP tablets or from intramuscular injectable cabotegravir HIV PrEP to lenacapavir HIV PrEP, which laboratory tests are recommended prior to the switch?**

When initiating lenacapavir, the CDC guidance recommends checking both a laboratory-based HIV antigen-antibody test and an HIV RNA test. However, when switching from tenofovir-based or cabotegravir HIV PrEP without any interruption in HIV PrEP coverage, only the laboratory-based HIV antigen-antibody test is recommended before the lenacapavir initiation doses; the HIV RNA assay is not recommended because the utility would be quite low in the setting of uninterrupted protective levels of HIV PrEP medications.

12. **If an individual switches from oral HIV PrEP tablets or from long-acting injectable cabotegravir HIV PrEP to lenacapavir HIV PrEP, what is the recommended interval between the last dose of the prior HIV PrEP medication and first dose of lenacapavir?**

Since oral HIV PrEP medications maintain adequate tissue levels to protect against HIV acquisition for at least several days after discontinuation, stopping oral HIV PrEP the day before the lenacapavir load begins ensures continuous protective drug coverage. On the other hand, if a person is switching from every 2-month long-acting cabotegravir HIV PrEP to lenacapavir HIV PrEP, the first lenacapavir dose should be given on the date that the next cabotegravir dose would be due (or a few days before the dose is due); in other words, no later than two months after the last dose of cabotegravir. Theoretically, the lenacapavir dose could be given any time before the cabotegravir target administration window, and that would ensure continuous HIV PrEP drug coverage. The principal goal is to avoid a gap between the cabotegravir target injection window and the start of lenacapavir; if that were to occur, the individual would need alternate HIV prevention methods in between the target date of their cabotegravir injection and the initiation of the lenacapavir.

13. **If a person who has chronic hepatitis B infection is taking tenofovir-based oral HIV PrEP and wishes to switch to injectable cabotegravir or lenacapavir for HIV PrEP, how should the hepatitis B infection be managed?**

It is important to be aware that tenofovir-based oral HIV PrEP (with tenofovir alafenamide or with tenofovir disoproxil fumarate) provides potent, active therapy for treating chronic hepatitis B infection. In contrast, cabotegravir and lenacapavir do not. Therefore, if a person has chronic hepatitis B infection and is switching to lenacapavir from a tenofovir-based oral HIV PrEP, clinicians need to plan for how to continue to manage and treat the hepatitis B infection; this may require alternate hepatitis B treatment options or co-management with a Hepatologist.

14. **Can rapid tests be used for HIV testing for lenacapavir PrEP follow-up visits?**

Yes, according to CDC guidance, if a clinician uses a rapid blood-based HIV antigen-antibody test to screen for HIV at a lenacapavir follow-up visit and the test is negative, the maintenance lenacapavir dose can be administered. In this situation, a confirmatory laboratory-based HIV antigen-antibody test should always be ordered at the visit, but it is acceptable to administer the lenacapavir injection prior to obtaining the laboratory-based HIV antigen-antibody test result. Clinicians should not use oral fluid-based point-of-care tests for HIV testing in persons receiving lenacapavir HIV PrEP (due to the relatively long window period with this test).

15. **Can you use oral tenofovir-DF-emtricitabine (TDF-FTC) or tenofovir alafenamide-emtricitabine (TAF-FTC) as a bridge instead of oral lenacapavir?**

Yes. Instead of using once-weekly oral lenacapavir, which may be costly and/or difficult to obtain, other oral HIV PrEP medications can be used, unless there is a contraindication to tenofovir-DF-emtricitabine (TDF-FTC) or tenofovir alafenamide-emtricitabine (TAF-FTC). If subcutaneous lenacapavir is to be restarted after use of a non-lenacapavir oral PrEP bridge, careful attention is required to ensure lenacapavir

reaches and maintains protective concentrations. If an alternative to once weekly oral lenacapavir was used as a bridge, lenacapavir levels will have waned during that interval time, and lenacapavir will need to be re-initiated with initiation phase dosing (oral plus injection loading doses). Similar to the initiation of lenacapavir, it is important to confirm HIV-negative status before restarting lenacapavir.

16. **Are there strategies or treatments for nodules that persist and/or may be bothersome days to weeks after lenacapavir subcutaneous injections?**

There are no known methods to prevent the development of these subcutaneous nodules after receiving lenacapavir subcutaneous injections. Warm compresses and gentle massage may provide symptomatic relief. It is important to counsel patients on the time course of the nodular injection site reactions, since nodules can appear in a delayed fashion and/or persist for even more than a year. In some circumstances, consultation with Dermatology may be helpful and may even warrant a biopsy. Biopsy results from lenacapavir nodules vary, but may include inflammation, fibrosis, and granulomatous foreign body reactions.

17. **What should you do if a person is receiving lenacapavir for HIV PrEP and needs to start a new medication that is a moderate or strong CYP3A enzyme inducer?**

Moderate or strong CYP3A inducers can significantly lower plasma levels of lenacapavir and thus potentially reduce the effectiveness of lenacapavir. If the situation arises in which a person is receiving lenacapavir and needs to start taking a moderate or strong inducer, the lenacapavir (*Yeztugo*) prescribing information recommends administering supplemental doses of lenacapavir and continuing the every 6-month lenacapavir injections. The supplemental lenacapavir doses are different depending on whether a strong or moderate inducer is started.

- Supplemental Dosing with Strong Inducer: On the day the new strong CYP3A inducer is started, also initiate lenacapavir supplemental dosing. The lenacapavir supplemental dosing consists of two subcutaneous injections (927 mg total) and two tables of oral lenacapavir doses (600 mg total) on the day the strong inducer is started (day 1), followed by 2 tablets of oral lenacapavir (600 mg total) on the day after the strong inducer is started (day 2). If the person stays on the strong CYP3A inducer for longer than 6 months, the same supplemental doses of lenacapavir should be administered every 6 months (from the time the first supplemental doses were given). In addition, the person should continue their regularly scheduled lenacapavir maintenance injection doses every 6 months.
- Supplemental Dosing with Moderate Inducer: On the day the new moderate inducer is started, administer one lenacapavir injection supplemental dose (463.5 mg); no supplemental oral lenacapavir should be administered. If the person stays on the moderate CYP3A inducer for longer than 6 months, the same supplemental lenacapavir injection dose (463.5 mg) should be administered every 6 months (from the time the first supplemental injection dose was given). In addition, the person should continue their regularly scheduled lenacapavir maintenance injection doses every 6 months.

For a list of strong and moderate CYP3A inducers, see the lenacapavir (*Yeztugo*) prescribing information. Note that using lenacapavir with a strong or moderate CYP3A inducer generates a considerable added cost burden and complexity to the management of lenacapavir for HIV PrEP. For this reason, HIV PrEP medications other than lenacapavir should strongly be considered in the situation in which a person taking HIV PrEP will require a medication that is a strong or moderate inducer.

18. **Can you start lenacapavir in a person who is already taking a medication that has significant drug interactions with lenacapavir?**

Lenacapavir should not be administered to a person who is taking a medication that is a combined P-gp, UGT1A1, and strong CYP3A inhibitor, since plasma levels of lenacapavir would be significantly increased in this situation. There are few medications used in clinical practice that are combined P-gp, UGT1A1, and strong CYP3A inhibitor. A much more common situation is the potential concomitant use of lenacapavir with a moderate or strong CYP3A inducer. Moderate or strong CYP3A inducers can significantly lower plasma levels of lenacapavir and thus potentially reduce the effectiveness of lenacapavir. At this time, there is no clear guidance on starting lenacapavir for a person who is already taking a strong or moderate CYP3A inducer. In the situation in which person is already taking a moderate or strong CYP3A inducer, we recommend starting an HIV PrEP medication other than lenacapavir. For a list of strong and moderate CYP3A inducers, see the lenacapavir (*Yeztugo*) prescribing information.

19. **If a person acquires HIV while receiving or after receiving lenacapavir for HIV PrEP, which antiretroviral therapy regimen would be recommended as initial HIV treatment?**

In this scenario, clinicians should check the recommended baseline tests for a person with a new diagnosis of HIV. There are no commercially available capsid inhibitor resistance tests, and this type of resistance testing would not be required. The appropriate initial antiretroviral regimen for a person who acquired HIV while receiving or after receiving lenacapavir would be a potent integrase inhibitor (bictegravir or dolutegravir) plus two nucleoside reverse transcriptase inhibitors (tenofovir alafenamide-emtricitabine [TAF-FTC] or tenofovir disoproxil fumarate-emtricitabine [TDF-FTC]).

20. **Can a patient self-administer lenacapavir injections?**

No. Lenacapavir is administered as a subcutaneous injection by a healthcare professional. Self-administration is not currently approved nor recommended due to the need for correct technique and injection depth.

21. **Is any special training needed to administer lenacapavir?**

Healthcare providers should be trained in the subcutaneous injection technique and familiar with the lenacapavir injection process, including handling, reconstitution, and patient counseling regarding side effects.

22. **Which health care professionals can administer lenacapavir injections?**

Any licensed healthcare professional trained in subcutaneous injection—including nurses, pharmacists (where scope allows), and physicians—can administer lenacapavir.

23. **Is a longer needle needed for lenacapavir injections if a person has elevated an BMI, like with injectable cabotegravir?**

No. Unlike intramuscular cabotegravir, lenacapavir is given subcutaneously, and a longer needle is generally not required regardless of BMI. However, proper technique to ensure subcutaneous delivery is essential.

24. **What are the storage requirements for lenacapavir?**

Store lenacapavir at room temperature (68°F to 77°F or 20°C to 25°C). Protect from excessive heat and moisture. Injection kits should remain sealed in original packaging until use.

25. **Can lenacapavir injection kit supplies be reused?**

    No. All components of the injection kit are single-use only. Re-use may lead to contamination or incorrect dosing.

26. **Are there any cost or patient assistance programs to help pay for lenacapavir PrEP?**

    Yes. Gilead offers a patient assistance program (Gilead Advancing Access®), which may help cover the cost for uninsured or underinsured patients. Co-pay support programs may also be available for those with private insurance.

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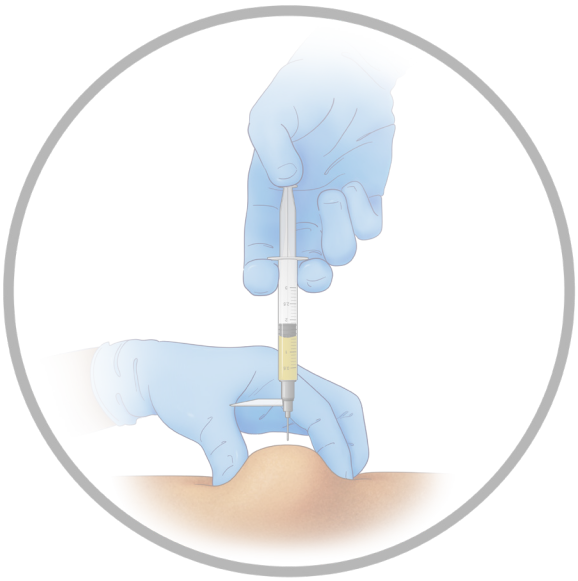

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