CARECONTINUUM™

UTILIZATION MANAGEMENT MEDICAL POLICY

POLICY: Human Immunodeficiency Virus – Yeztugo Utilization Management Medical Policy
- Yeztugo® (lenacapavir subcutaneous injection – Gilead)

REVIEW DATE: 08/13/2025

OVERVIEW

Yeztugo, a human immunodeficiency virus-1 (HIV-1) capsid inhibitor, is indicated for **pre-exposure prophylaxis (PrEP)** to reduce the risk of sexually acquired HIV-1 in adults and adolescents (≥ 35 kg) who are at risk for HIV-1 acquisition.[1]

Yeztugo is contraindicated in individuals with an unknown or positive HIV-1 status.[1] There is a risk of drug resistance with the use of Yeztugo for HIV-1 PrEP in undiagnosed HIV-1 Infection (Boxed Warning). Individuals must be tested for HIV-1 infection prior to initiating Yeztugo, with each subsequent injection of Yeztugo, and as clinically appropriate using a test approved or cleared by the FDA for the diagnosis of acute or primary HIV-1 infection. If an antigen/antibody-specific test is used and provides negative results, then such negative results should be confirmed using an RNA-specific assay, even if the results of the RNA-assay are available after Yeztugo initiation. When screening for HIV-1 infection prior to continuing Yeztugo, negative results from a rapid, point-of-care antigen/antibody test should be confirmed using a more sensitive assay. Yeztugo should not be initiated unless negative HIV-1 infection status is confirmed. Individuals who acquire HIV-1 while receiving Yeztugo must transition to a complete HIV-1 treatment regimen. Yeztugo should also be used as part of a comprehensive prevention strategy including adherence to the administration schedule and safer sex practices, including condoms, to reduce the risk of sexually transmitted infections.

Dosing

Yeztugo injection is only for subcutaneous (SC) administration into the abdomen or thigh and is given by a healthcare provider.[1] Prior to starting Yeztugo, healthcare providers should carefully select individuals who agree to the required injection dosing and testing schedule and counsel individuals about the importance of adherence to scheduled dosing visits to help reduce the risk of acquiring HIV-1 infection and development of resistance.

Recommended Dosing: The Yeztugo dosing schedule consists of a required initiation dosing (SC injections and oral tablets) followed by once every 6 months (Q6M) continuation dosing (SC injection). Following initiation dosing (2 days), the recommended continuation dose is two 1.5 mL SC injections Q6M (Table 1).

Table 1. Yeztugo Dosing Schedule: Initiation and Continuation.[1]

Time	Dose of Yeztugo
Initiation†	
Day 1	927 mg by SC injection (2 x 1.5 mL injections) 600 mg orally (2 x 300 mg tablets)
Day 2	600 mg orally (2 x 300 mg tablets)
Continuation	
Once every 6 months (26 weeks)* ± 2 weeks	927 mg by SC injection (2 x 1.5 mL injections)

† The complete initiation dosing schedule, consisting of subcutaneous injections and oral tablets, is required. The efficacy of Yeztugo has only been established with this dosing schedule; SC – Subcutaneous; * From the date of the last injection.

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Dosing Schedule for Missed Doses. *Missed Oral Initiation Dose.* If the Day 2 oral initiation dose (2 x 300 mg tablets, see Table 1) is missed, it should be taken as soon as possible. However, Day 1 and Day 2 oral initiation doses should not be taken on the same day. *Anticipated Delayed Injections.* During continuation dosing, if the scheduled 6-month injection is anticipated to be delayed by > 2 weeks, Yeztugo tablets (300 mg once every 7 days) may be taken on an interim basis (for up to 6 months if needed), until injections resume (Table 2). *Missed Scheduled Injections.* Individuals who miss a scheduled injection visit should be clinically reassessed to ensure resumption of Yeztugo remains appropriate and that they remain HIV-1 negative. If > 28 days have elapsed since the last continuation dosing injection of Yeztugo, and Yeztugo tablets have not been taken, Yeztugo should be reinitiated with the initiation dosing schedule starting at Day 1 and then continue with the recommended continuation dosing outlined in Table 1.

Table 2. Yeztugo Dosing Schedule for Anticipated Delayed Injections: Weekly Oral Dosage.[1]

Time Since Last Injection	Dose of Yeztugo
26 to 28 weeks	300 mg orally (1 x 300 mg tablet) Q7D[*] Resume the continuation injection dosage within 7 days after the last oral dose.

Q7D – Once every 7 days; [*] Use on an interim basis only (for up to 6 months if needed).

Dose Modification for Co-Administration with Strong or Moderate Cytochrome P450 (CYP)3A inducers. For all individuals, continue with scheduled dosing of Yeztugo SC injection Q6M; supplemental doses of Yeztugo are recommended for individuals initiating therapy with either strong or moderate CYP3A inducers (Tables 3 and 4). Strong CYP3A inducers may be started ≥ 2 days after Yeztugo is first initiated; moderate CYP3A inducers may be started any time after Yeztugo is first initiated. Dosing recommendations are not available for the initiation of Yeztugo in individuals already receiving strong or moderate CYP3A inducers. Additionally, there are no dosing recommendations for individuals receiving the weekly oral dose of Yeztugo (as outlined in Table 2 for anticipated delayed injections) in individuals already receiving strong or moderate CYP3A inducers.

Table 3. Yeztugo Dosing for Individuals Initiating Therapy with Strong CYP3A Inducers[*].[1]

Maintain Scheduled Continuation Injection Dosing	Schedule for Supplemental Doses of Yeztugo	
	Time	Yeztugo Dosage
Continue to administer Yeztugo SC Q6M scheduled continuation dosing (927 mg SC; see Table 1), PLUS administer supplemental doses of Yeztugo as shown in this Table.	Day strong CYP3A inducer is initiated (≥ 2 days after Yeztugo is first initiated)	Step 1 Supplemental dosage: 927 mg SC (2 x 1.5 mL injections) AND 600 mg orally (2 x 300 mg tablets)
	Day AFTER strong CYP3A inducer is initiated	Step 2 Supplemental dosage: 600 mg orally (2 x 300 mg tablets)
	If strong CYP3A inducer is co-administered for > 6 months	Subsequent supplemental dosage: Yeztugo SC Q6M[†] from initiation of strong CYP3A inducer, continue to administer supplemental doses of Yeztugo as described above in Steps 1 and 2.
	After stopping the strong CYP3A inducer, continue the Q6M scheduled continuation injection dosing of Yeztugo (refer to Table 1)	

CYP – Cytochrome P450; [*] Dosing recommendations are not available for the initiation of Yeztugo in individuals already receiving strong CYP3A inducers, nor in individuals receiving the weekly oral dosage of Yeztugo (refer to Table 2); SC – Subcutaneously; Q6M – Once every 6 months; [†] 26 weeks ± 2 weeks.

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Table 4. Yeztugo Dosing for Individuals Initiating Therapy with Moderate CYP3A Inducers*.[1]

Maintain Scheduled Continuation Injection Dosing	Schedule for Supplemental Doses of Yeztugo	
	Time	**Yeztugo Dosage**
Continue to administer Yeztugo SC Q6M scheduled continuation dosing (927 mg SC; see Table 1), PLUS administer supplemental doses of Yeztugo as shown in this Table.	Day moderate CYP3A inducer is initiated (any time after Yeztugo is first initiated)	Supplemental dosage: 463.5 mg SC (1 x 1.5 mL injections)
	If moderate CYP3A inducer is co-administered for > 6 months	Subsequent supplemental dosage: Yeztugo SC Q6M† from initiation of moderate CYP3A inducer, continue to administer supplemental doses of Yeztugo as described above.
	After stopping the moderate CYP3A inducer, continue the Q6M scheduled continuation injection dosing of Yeztugo (refer to Table 1).	

CYP – Cytochrome P450; * Dosing recommendations are not available for the initiation of Yeztugo in individuals already receiving moderate CYP3A inducers, nor in individuals receiving the weekly oral dosage of Yeztugo (refer to Table 2); SC – Subcutaneously; Q6M – Once every 6 months; † 26 weeks ± 2 weeks.

Guidelines

Recommendations and guidelines for PrEP align with the Yeztugo prescribing information regarding the provision of a negative HIV-1 test prior to initiating PrEP and prior to each dose. Ideally, testing should be performed and results provided on the same day PrEP is offered; however, tests taken within 7 days of initiation of PrEP may be utilized.[4]

World Health Organization (WHO)

The WHO Guidelines on Lenacapavir for HIV Prevention and Testing Strategies for Long-Acting Injectable PrEP (2025) provide recommendations regarding testing in the setting of long-acting injectable PrEP, including Yeztugo.[2] The WHO also published an implementation tool for PrEP (2024) that pre-dates the approval of Yeztugo, yet similarly emphasizes the importance of HIV testing with PrEP.[3] HIV testing is an important part of PrEP initiation and continuation.[2] Ideally, HIV testing should be performed and results provided on the same day that PrEP is offered to facilitate same-day initiation of PrEP.[3] There is no evidence supporting the prioritization of antigen/antibody rapid diagnostic tests over antibody-only rapid diagnostic tests.[2] Only individuals who have an HIV-negative test result should be started on PrEP.[3] It is practical for individuals taking PrEP to receive testing at their refill or injection visit. Depending on the PrEP option used, testing schedules may differ, for Yeztugo, testing should occur every 6 months.[2] However, it is important to provide individuals with the flexibility to support effective PrEP use. More, or less, frequent testing intervals may be considered where warranted and based on available resources. Self-tests can be a potential option where needed and considered beneficial by the individual or provider.

Individuals with a negative HIV test result should continue PrEP.[2] Anyone taking injectable PrEP who has a reactive HIV test result, including a self-test result, should receive further testing, to confirm an HIV diagnosis. Upon confirmation of a diagnosis, antiretroviral therapy should be initiated promptly. Individuals with an inconclusive HIV test status while taking injectable PrEP should be retested in 14 days to rule in or rule out seroconversion. If the serology profile remains inconclusive, the person receiving injectable is considered HIV-negative, and long-acting injectable PrEP can be continued. If the individual is diagnosed with HIV, they should be immediately referred for care and treatment.

Each suspected breakthrough infection should be evaluated individually.[2] Individuals should be encouraged to continue PrEP until more information and a final diagnosis are available, and they should consider taking precautions to prevent potential onwards transmission of HIV, such as the use of condoms during sex.

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International Antiviral Society (IAS)-USA
With the approval of Yeztugo, the IAS-USA issued a brief update (2025) to their 2024 recommendations for the prevention of HIV infection.[4] Laboratory-based HIV antigen/antibody testing is recommended prior to Yeztugo initiation; testing may be from samples acquired up to 7 days prior to initiation. For individuals with likely HIV exposures in the past 21 days, HIV RNA testing is recommended, if available. Yeztugo can be initiated if HIV test results are still pending, provided patient contact information is available for communication of positive test results. The same HIV testing algorithm used at Yeztugo initiation should be used before restarting delayed lenacapavir injections. For individuals taking Yeztugo, HIV testing, using a laboratory-based antigen/antibody assay, should be performed at in person visits every 6 months. HIV-1 RNA testing for routine monitoring for PrEP failure is not recommended.

US Preventative Services Task Force (USPTF)
The USPTF recommendations for PrEP to prevent acquisition of HIV (2023) pre-date the approval of Yeztugo.[5] However, general recommendations for testing are similar to those discussed above. All persons being considered for PrEP should have a recently documented negative HIV test. Prior to prescribing PrEP, clinicians should exclude individuals with acute or chronic HIV through medial history and HIV testing. Ongoing follow-up and monitoring, including HIV testing with the frequency determined by PrEP method, is recommended. Patients can continue PrEP for as long as the risk of acquisition continues. PrEP may be discontinued and re-initiated. Re-initiation should involve the same evaluation as initial therapy.

POLICY STATEMENT
Prior Authorization is recommended for medical benefit coverage of Yeztugo. Approval is recommended for those who meet the **Criteria** and **Dosing** for the listed indication. Extended approvals are allowed if the patient continues to meet the Criteria and Dosing. Requests for doses outside of the established dosing documented in this policy will be considered on a case-by-case basis by a clinician (i.e., Medical Director or Pharmacist). All approvals are provided for the duration noted below. In cases where the approval is authorized in months, 1 month is equal to 30 days. Because of the specialized skills required for evaluation and diagnosis of patients treated with Yeztugo as well as the monitoring required for adverse events and long-term efficacy, approval requires Yeztugo to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA
Coverage of Yeztugo is recommended in those who meet the following criteria:

FDA-Approved Indication

1. **Pre-exposure Prophylaxis (PrEP) of Human Immunodeficiency Virus-1 (HIV-1) Infection.** Approve for 7 months if the patient meets ALL of the following (A, B, C, and D):
   - **A)** Patient is ≥ 35 kg; AND
   - **B)** According to the prescriber, the medication will be administered only if the patient has a negative HIV-1 test result ≤ 7 days prior to each dose of Yeztugo; AND
   - **C)** The medication is prescribed as part of a comprehensive HIV-1 prevention strategy (i.e., adherence to administration schedule and safer sex practices, including condoms); AND

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D) The medication is prescribed by or in consultation with a physician who specializes in the management of HIV infection.

Dosing. Approve ONE of the following dosing regimens (A, B, or C):

A) Approve 927 mg by subcutaneous injection once every 6 months (26 weeks) ± 2 weeks; OR

B) If a strong cytochrome P450(CYP)3A inducer will be started in a patient who has been taking Yeztugo for ≥ 2 days: Approve 927 mg by subcutaneous injection for one dose to be administered on the day the strong CYP3A inducer is initiated, followed by 927 mg by subcutaneous injection once every 6 months (26 weeks) ± 2 weeks from the day the strong CYP3A inducer was initiated (while the patient is taking the strong CYP3A inducer). In addition, continue to approve 927 mg by subcutaneous injection once every 6 months (26 weeks) ± 2 weeks from the initial start date of Yeztugo; OR

C) If a moderate cytochrome P450(CYP)3A inducer will be started in a patient who has been taking Yeztugo for any amount of time: Approve 463.5 mg by subcutaneous injection for one dose to be administered on the day the moderate CYP3A inducer is initiated, followed by 463.5 mg by subcutaneous injection once every 6 months (26 weeks) ± 2 weeks from the day the moderate CYP3A inducer was initiated (while the patient is taking the moderate CYP3A inducer). In addition, continue to approve 927 mg by subcutaneous injection once every 6 months (26 weeks) ± 2 weeks from the initial start date of Yeztugo.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Yeztugo is not recommended in the following situations:

1. **Treatment of Human Immunodeficiency Virus (HIV).** Yeztugo is not indicated for the treatment of HIV.[1]

2. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

1. Yeztugo® tablets and subcutaneous injection [prescribing information]. Foster City, CA: Gilead; June 2025.
2. Guidelines on lenacapavir for HIV prevention and testing strategies for long-acting injectable pre-exposure prophylaxis (PrEP). Geneva: World Health Organization; 2025. License: CC-BY-NC-SA 3.0 IGO.
3. WHO implementation tool for pre-exposure prophylaxis (PrEP) of HIV infection: provider module for oral and long-acting PrEP. Geneva: World Health Organization; 2024. License: CC BY-NC-SA 3.0 IGO.
4. Landovitz RJ, Molina JM, and Buchinder SP for the International Antiviral Society-USA (IAS-USA) Panel. Preexposure prophylaxis for HIV: Updated recommendations from the 2024 International Antiviral Society-USA Panel. *JAMA*. 2025 June 27. [Online ahead of Print].
5. US Preventative Services Task Force. Preexposure prophylaxis to prevent acquisition of HIV. US Preventative Tast Force Recommendation Statement. *JAMA*. 2023;330(8):736-745.

HISTORY

Type of Revision	Summary of Changes	Review Date
New Policy	--	08/13/2025

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