Policy Number	**RX501.145**
Policy Effective Date	**10/15/2025**

Long-Acting Injectable Antiretroviral Agents for Treatment of HIV

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Disclaimer

Medical policies are a set of written guidelines that support current standards of practice. They are based on current generally accepted standards of and developed by nonprofit professional association(s) for the relevant clinical specialty, third-party entities that develop treatment criteria, or other federal or state governmental agencies. A requested therapy must be proven effective for the relevant diagnosis or procedure. For drug therapy, the proposed dose, frequency and duration of therapy must be consistent with recommendations in at least one authoritative source. This medical policy is supported by FDA-approved labeling and/or nationally recognized authoritative references to major drug compendia, peer reviewed scientific literature and generally accepted standards of medical care. These references include, but are not limited to: MCG care guidelines, DrugDex (IIa level of evidence or higher), NCCN Guidelines (IIb level of evidence or higher), NCCN Compendia (IIb level of evidence or higher), professional society guidelines, and CMS coverage policy.

Carefully check state regulations and/or the member contract.

Each benefit plan, summary plan description or contract defines which services are covered, which services are excluded, and which services are subject to dollar caps or other limitations, conditions or exclusions. Members and their providers have the responsibility for consulting the member's benefit plan, summary plan description or contract to determine if there are any exclusions or other benefit limitations applicable to this service or supply. **If there is a discrepancy between a Medical Policy and a member's benefit plan, summary plan description or contract, the benefit plan, summary plan description or contract will govern.**

Legislative Mandates

EXCEPTION: For members residing in the state of Ohio, § 3923.60 requires any group or individual policy (Small, Mid-Market, Large Groups, Municipalities/Counties/Schools, State Employees, Fully-Insured, PPO, HMO, POS, EPO) that covers prescription drugs to provide for the coverage of any drug approved by the U. S. Food and Drug Administration (FDA) when it is prescribed for a use recognized as safe and effective for the treatment of a given indication in one or more of the standard medical reference compendia adopted by the United States Department of Health and Human Services or in medical literature even if the FDA has not approved the drug for that indication. Medical literature support is only satisfied when safety and efficacy has been confirmed in two articles from major peer-reviewed professional medical journals that present data supporting the proposed off-label use or uses as

generally safe and effective. Examples of accepted journals include, but are not limited to, Journal of American Medical Association (JAMA), New England Journal of Medicine (NEJM), and Lancet. Accepted study designs may include, but are not limited to, randomized, double blind, placebo controlled clinical trials. Evidence limited to case studies or case series is not sufficient to meet the standard of this criterion. Coverage is never required where the FDA has recognized a use to be contraindicated, and coverage is not required for non-formulary drugs.

EXCEPTION: For members residing in the state of Maine, 24-A s 2837-G and 24-A s 4234-E (for HMOs) requires all group insurance policies and all health maintenance organization group contracts that provide coverage for prescription drugs must provide coverage for off-label use in accordance with the following: A) Group policies that provide coverage for prescription drugs may not exclude coverage of any such drug used for the treatment of HIV or AIDS on the grounds that the drug has not been approved by the federal Food and Drug Administration for that indication, as long as that drug is recognized for the treatment of that indication in one of the standard reference compendia or in peer-reviewed medical literature. B) Coverage of a drug required by this subsection also includes medically necessary services associated with the administration of the drug. C) This subsection may not be construed to require coverage for a drug when the federal Food and Drug Administration has determined its use to be contraindicated for treatment of the current indication. D) A drug use that is covered pursuant to paragraph A may not be denied coverage based on a "medical necessity" requirement except for a reason that is unrelated to the legal status of the drug use. E) A contract that provides coverage of a drug as required by this subsection may contain provisions for maximum benefits and coinsurance and reasonable limitations, deductibles and exclusions to the same extent that these provisions are applicable to coverage of all prescription drugs and are not inconsistent with the requirements of this subsection. For this provision: “Off-label use" means the prescription and use of drugs for indications other than those stated in the labeling approved by the federal Food and Drug Administration. "Peer-reviewed medical literature" means scientific studies published in at least 2 articles from major peer-reviewed medical journals that present data that supports the proposed off-label use as generally safe and effective. "Standard reference compendia" means: a. The United States Pharmacopeia Drug Information or information published by its successor organization; or b. The American Hospital Formulary Service Drug Information or information published by its successor organization. This applies to Fully Insured Small Group, Mid-Market, Large Group, Student PPO, HMO, POS, EPO.

Coverage

Cabotegravir/Rilpivirine (Cabenuva)

Cabotegravir/Rilpivirine (Cabenuva) **may be considered medically necessary** for the treatment of individuals with a diagnosis of human immunodeficiency virus type-1 (HIV-1) when ALL the following criteria are met:

- Individual is currently on a stable antiretroviral regimen; AND
- Submission of medical records (e.g., chart notes, laboratory results) showing viral suppression (HIV-1 RNA less than 50 copies per mL) has been achieved; AND
- Individual has no prior virologic failures or baseline resistance to either cabotegravir or rilpivirine.

All other non-Food and Drug Administration approved uses of cabotegravir/rilpivirine (Cabenuva) **are considered experimental, investigational and/or unproven.**

Lenacapavir (Sunlenca®)
Lenacapavir (Sunlenca) **may be considered medically necessary** for treatment-experienced individuals with multidrug resistant HIV-1 infection failing their current antiretroviral regimen due to resistance, intolerance, or safety consideration.

All other non-Food and Drug Administration approved uses of lenacapavir (Sunlenca®) **are considered experimental, investigational and/or unproven.**

NOTE 1: This policy addresses the use of long-acting injectable antiretroviral agents for the treatment of HIV-1. Requests for pre-exposure prophylaxis (PReP) are not addressed by this policy.

Policy Guidelines

None.

Description

Human Immunodeficiency Virus (HIV)
HIV (human immunodeficiency virus) is a virus that attacks the body's immune system. If HIV is not treated, it can lead to AIDS (acquired immunodeficiency syndrome). There is currently no effective cure; and once a person has HIV, they have it for life. Individuals with HIV can get effective treatment and live long, healthy lives and protect their partners. (3)

There are an estimated 1.2 million individuals in the United States (U.S.) currently living with HIV. In 2022, there were an estimated 31,800 new diagnoses of HIV infection reported in the U.S., with 67% attributed to male-to-male sexual contact. Heterosexual contact accounted for 22% of all HIV diagnoses in the same year; injection drug use accounts for about 7% and male-to-male sexual contact and injection drug use is responsible for about 4% of the reported cases. (4)

Antiretroviral Treatment/Therapy (ART)
Antiretroviral therapy not only reduces morbidity and mortality for persons with HIV but has now been definitively shown to prevent sexual transmission of the virus when the plasma HIV-RNA (viral load) is consistently suppressed to <200 copies/mL, which includes any measurable viral load that is lower than this threshold value. Adherence to ART is paramount for persons who intend to prevent HIV transmission by achieving and maintaining a suppressed viral load. Viral rebound typically occurs within days to weeks after ART cessation and has been observed as early as 3 to 6 days after stopping treatment. The minimum level of adherence that is

required to prevent sexual transmission has not been determined and may vary depending on the ART regimen. (5)

Integrase strand transfer inhibitors
Integrase strand transfer inhibitors (INSTIs) are a class of antiretrovirals for treatment of HIV. Favorable pharmacokinetic and pharmacodynamic properties contribute to both their effectiveness and ease of use. INSTIs are generally well tolerated by those living with HIV compared to older classes of antiretrovirals, but some may contribute to weight gain. Due to their efficacy, safety and ease of use, HIV treatment guidelines recommend oral INSTIs as preferred components of antiretroviral therapy for individuals initiating therapy. The newest INSTI, cabotegravir, represents an alternative to oral administration of life-long antiretroviral therapy with the availability of a long-acting injectable formulation. (6)

INSTIs inhibit HIV by blocking the strand transfer step of viral DNA integration into the host genome. However, to date, resistance to all antiretrovirals has been documented. Whether clinical resistance emerges to an INSTI (or any antiretroviral) is dependent upon a variety of factors including the drug's inherent genetic barrier to resistance, the drug's structure, inhibitory quotient, therapeutic index, and pharmacokinetic forgiveness/adherence. The consequences of resistance are virologic failure and reduced options for future ART regimens. Current treatment guidelines therefore contain specific recommendations for resistance testing in both naïve- and treatment-experienced individuals living with HIV, and recommendations for the use of ART regimens to maximally and durably suppress plasma HIV-RNA to minimize the emergence of resistance. (6)

Cabenuva (cabotegravir/rilpivirine) is a 2-drug co-packaged product of extended-release injectable suspension formulations of cabotegravir, a human immunodeficiency virus type-1 (HIV-1) INSTI, and rilpivirine, an HIV-1 non-nucleoside reverse transcriptase inhibitor (NNRTI). Cabotegravir inhibits HIV integrase by binding to the integrase active site and blocking the strand transfer step of retroviral DNA integration which is essential for the HIV replication cycle. Rilpivirine is a diarylpyrimidine NNRTI of HIV-1 and inhibits HIV-1 replication by non-competitive inhibition of HIV-1 reverse transcriptase (RT). (1)

Capsid Inhibitors
Capsid inhibitors are a class of drugs that interfere with HIV capsid, a protein shell that protects HIV's genetic material and enzymes needed for replication. Capsid inhibitors can disrupt HIV capsid during multiple stages of the viral life cycle.

Sunlenca® (lenacapavir) is a multistage, selective inhibitor of HIV-1 capsid function that directly binds to the interface between capsid protein (p24) subunits in hexamers. Surface plasmon resonance sensorgrams showed dose-dependent and saturable binding of lenacapavir to cross-linked wild-type capsid hexamer with an equilibrium binding constant (KD) of 1.4 nM. Lenacapavir inhibits HIV-1 replication by interfering with multiple essential steps of the viral lifecycle, including capsid-mediated nuclear uptake of HIV-1 proviral DNA (by blocking nuclear import proteins binding to capsid), virus assembly and release (by interfering with Gag/Gag-Pol

functioning, reducing production of capsid protein subunits), and capsid core formation (by disrupting the rate of capsid subunit association, leading to malformed capsids). (2)

Regulatory
The U.S. Food and Drug Administration (FDA) first approved Cabenuva (cabotegravir extended-release injectable suspension; rilpivirine extended-release injectable suspension) in 2021 as a complete regimen for the treatment of HIV-1 infection in adults to replace the current antiretroviral regimen in those who are virologically suppressed (HIV-1 RNA less than 50 copies per mL) on a stable antiretroviral regimen with no history of treatment failure and with no known or suspected resistance to either cabotegravir or rilpivirine. In March 2022, the FDA revised the indications for use to include the treatment adolescents 12 years of age and older and weighing at least 35 kg. (7)

The FDA approved Sunlenca® (lenacapavir) on December 22, 2022, as the first capsid inhibitor-based HIV treatment option. Sunlenca®, in combination with other antiretroviral(s), is indicated for the treatment of HIV-1 infection in heavily treatment-experienced adults with multidrug resistant HIV-1 infection failing their current antiretroviral regimen due to resistance, intolerance, or safety considerations. (8)

Rationale

This medical policy is based on the U.S. Food and Drug Administration (FDA) labels for Cabenuva (cabotegravir extended-release injectable suspension; rilpivirine extended-release injectable suspension) and Sunlenca® (lenacapavir)**.**

Cabenuva (cabotegravir extended-release injectable suspension; rilpivirine extended-release injectable suspension) (1)
Monthly Dosing Trials
The efficacy of Cabenuva has been evaluated in two Phase 3 randomized, multicenter, active controlled, parallel-arm, open-label, non-inferiority trials:

- Trial 201584 (FLAIR, [NCT02938520]), (n = 629): antiretroviral treatment (ART)-naive participants with human immunodeficiency virus type-1 (HIV-1) received a dolutegravir integrase strand transfer inhibitor (INSTI)-containing regimen for 20 weeks (either dolutegravir/abacavir/lamivudine or dolutegravir plus 2 other non-nucleoside reverse transcriptase inhibitors [NNRTIs] if participants were human leukocyte antigen [HLA] B*5701 positive). Participants who were virologically suppressed (HIV-1 RNA less than 50 copies/mL, n = 566) were then randomized (1:1) to receive either a cabotegravir plus rilpivirine regimen or remain on the current antiretroviral regimen. Participants randomized to receive cabotegravir plus rilpivirine initiated treatment with daily oral lead-in dosing with one 30-mg Vocabria (cabotegravir) tablet plus one 25-mg Edurant (rilpivirine) tablet for at least 4 weeks followed by monthly injections with Cabenuva for an additional 44 weeks.
- Trial 201585 (ATLAS, [NCT02951052]), (n = 616): ART-experienced, virologically-suppressed (for at least 6 months; median prior treatment duration was 4.3 years) participants (HIV-1

RNA less than 50 copies/mL) were randomized and received either a cabotegravir plus rilpivirine regimen or remained on their current antiretroviral regimen. Participants randomized to receive cabotegravir plus rilpivirine initiated treatment with daily oral lead-in dosing with one 30-mg Vocabria (cabotegravir) tablet plus one 25-mg Edurant (rilpivirine) tablet for at least 4 weeks followed by monthly injections with Cabenuva for an additional 44 weeks.

The primary analysis was conducted after all participants completed their Week 48 visit or discontinued the trial prematurely.

At baseline, in FLAIR and ATLAS, respectively, the median age was 34 years and 40 years, 22% and 32% were female, and 24% and 31% were non-White. In both studies, 7% had CD4+ cell count less than 350 cells/mm^3; these characteristics were similar between treatment arms. In ATLAS, participants received an NNRTI (50%), integrase inhibitor (33%), or protease inhibitor (17%) as their baseline third-agent class prior to randomization; this was similar between treatment arms. Participants with hepatitis B co-infection were excluded from the trial.

The primary endpoint of FLAIR and ATLAS was the proportion of participants with plasma HIV-1 RNA greater than or equal to 50 copies/mL at Week 48. Adjusted for study and randomization stratification factors, treatment difference of HIV-1 RNA greater than or equal to 50 copies/mL for the pooled data was 0.2% with 95% confidence interval (CI) (-1.4%, 1.7%).

Participants in both the FLAIR and ATLAS trials were virologically suppressed prior to Day 1 or at study entry, respectively, and no clinically relevant change from baseline in CD4+ cell counts was observed.

In FLAIR at Week 96, the proportion of participants with HIV-1 RNA ≥50 copies/mL was 3.2 % for both the cabotegravir plus rilpivirine (n = 283) and current antiretroviral regimen (n = 283) treatment arms; adjusted treatment difference was 0.0% with 95% CI (-2.9%, 2.9%). The proportion of participants with HIV-1 RNA <50 copies/mL was 87% and 89% for the cabotegravir plus rilpivirine and the current antiretroviral regimen arms, respectively; adjusted treatment difference was -2.8% with 95% CI (-8.2%, 2.5%).

Optional Oral Lead-in: FLAIR Extension Phase

In the FLAIR study during the Extension Phase (Week 100 to Week 124), the efficacy of Cabenuva was evaluated in patients who switched (at Week 100) from their current antiretroviral regimen to Cabenuva, with and without an oral lead-in phase. A total of 121 participants chose to start the treatment with oral lead-in and 111 participants chose direct to injection. Participants were not randomized during the Extension Phase. At Week 124, the proportion of participants with HIV-1 RNA ≥50 copies/mL was 0.8% and 0.9% for the oral lead-in and direct to injection groups, respectively. The rates of virologic suppression (HIV-1 RNA <50 copies/mL) were similar in both the oral lead-in (93%) and direct to injection (99%) groups.

Every-2-Month Dosing Trial

The efficacy of Cabenuva dosed every 2 months has been evaluated in 1 Phase 3b randomized, multicenter, parallel-arm, open-label, non-inferiority trial:

- Trial 207966 (ATLAS-2M [NCT03299049]), (n = 1,045): ART-experienced, virologically suppressed participants with HIV-1, including 504 participants from the ATLAS trial (randomized to cabotegravir plus rilpivirine [n = 253] or current antiretroviral regimen (CAR) [n = 251]; prior exposure to cabotegravir plus rilpivirine [n = 391]), were randomized and received a cabotegravir plus rilpivirine regimen administered as injection doses of cabotegravir 400 mg plus rilpivirine 600 mg either monthly or cabotegravir 600 mg plus rilpivirine 900 mg every 2 months. Participants without prior exposure to cabotegravir plus rilpivirine initiated treatment with daily oral lead-in dosing with one 30-mg Vocabria (cabotegravir) tablet plus one 25-mg Edurant (rilpivirine) tablet for at least 4 weeks followed by monthly or every-2-month injections with Cabenuva for an additional 44 weeks.

The primary analysis was conducted after all participants completed their Week 48 visit or discontinued the study prematurely.

At baseline, the median age was 42 years, 27% were female, 27% were non-White, and 6% had a CD4+ cell count <350 cells per mm^3; these characteristics were similar between the treatment arms. Participants received either an NNRTI (29%), an integrase inhibitor besides cabotegravir plus rilpivirine (26%), a protease inhibitor (7%), or cabotegravir plus rilpivirine (37%) as their baseline third-agent class prior to randomization.

The primary endpoint of ATLAS-2M was the proportion of participants with a plasma HIV-1 RNA ≥50 copies/mL at Week 48.

Table 1. Virologic Outcomes of Randomized Treatment in ATLAS 2-M Trial at Week 48

	Cabotegravir plus Rilpivirine	
Virologic Outcomes	**Every-2 Month Dosing n=522**	**Monthly Dosing n=523**
HIV-1 RNA ≥50 copies/mL[a]	2%	1%
Treatment difference	0.8 (95% CI: -0.6%, 2.2%)	
HIV-1 RNA <50 copies/mL	94%	94%
No virologic data at Week 48 window	4%	6%
Discontinued study due to adverse event or death	2%	3%
Discontinued for other reasons	2%	3%
Missing data during window but on study	0	0

[a] Includes participants who discontinued for lack of efficacy, discontinued while not suppressed.

n = Number of participants in each treatment group, CI = Confidence interval, HIV-1 = human immunodeficiency virus type-1, RNA = ribonucleic acid.

Sunlenca® (lenacapavir) (2)

The efficacy and safety of Sunlenca in HIV-1 infected, heavily treatment-experienced participants with multidrug resistance is based on 52-week data from CAPELLA, a randomized, placebo-controlled, double-blind, multicenter trial (NCT 04150068).

CAPELLA was conducted in 72 heavily treatment-experienced participants with multiclass resistant HIV-1. Participants were required to have a viral load ≥400 copies/mL, documented resistance to at least two antiretroviral medications from each of at least 3 of the 4 classes of antiretroviral medications (NRTI, NNRTI, PI and INSTI), and ≤ 2 fully active antiretroviral medications from the 4 classes of antiretroviral medications remaining at baseline due to resistance, intolerability, drug access, contraindication, or other safety concerns.

The trial was composed of two cohorts. Participants were enrolled into the randomized cohort (cohort 1, N=36) if they had a < 0.5 log_{10} HIV-1 RNA decline compared to the screening visit. Participants were enrolled into the non-randomized cohort (cohort 2, N=36) if they had a ≥ 0.5 log_{10} HIV-1 RNA decline compared to the screening visit or after cohort 1 reached its planned sample size.

The primary efficacy endpoint was the proportion of participants in cohort 1 achieving ≥ 0.5 log_{10} copies/mL reduction from baseline in HIV-1 RNA at the end of the functional monotherapy period. The results of the primary endpoint analysis are shown in Table 2.

Table 2. Proportion of Participants Achieving a ≥0.5 log_{10} Decrease in Viral Load at the End of the Functional Monotherapy Period in the CAPELLA Trial (Cohort 1)

	Sunlenca (N=24)	**Placebo (N=12)**
Proportion of Participants Achieving a ≥ 0.5 log_{10} Decrease in Viral Load	87.5%	16.7%
Treatment Difference (95% CI)	70.8% (34.9% to 90.0%)[a]	

[a] p < 0.0001.
CI=confidence interval.

In cohort 1, at Weeks 26 and 52, the mean change from baseline in CD4+ cell count was 81 cells/mm^3 (range: -101 to 522) and 82 cells/mm^3 (range: -194 to 467), respectively.

In cohort 2, at Week 26 and 52, 81% (29/36) and 72% (26/36) of patients achieved HIV1 RNA < 50 copies/mL, respectively, and the mean change from baseline in CD4+ cell count was 97 cells/mm^3 (range: -103 to 459) and 113 cells/mm^3 (range: -124 to 405), respectively.

Oral bridging

In CAPELLA across cohorts 1 and 2, 79% of participants (57/72) received Sunlenca 300 mg once every 7 days as oral bridging. A total of 13, 29, and 15 participants started oral bridging following Weeks 26, 52, and 78 injections, respectively. The median (Q1, Q3) duration of oral bridging was 19 weeks (11, 22), and 12% (7/57) received oral bridging for at least 28 weeks.

In a post-hoc analysis, rates of virologic suppression and change from baseline in CD4+ cell counts in the subset of patients who received oral bridging were consistent before and during the oral bridging period.

Summary of Evidence
Based on the studies provided to the U.S. Food and Drug Administration (FDA), cabotegravir/ rilpivirine (Cabenuva) may be considered medically necessary for the treatment of a human immunodeficiency virus type-1 (HIV-1) in individuals when all the criteria noted in Coverage are met. All other non-FDA approved uses of cabotegravir/rilpivirine (Cabenuva) are considered experimental, investigational and/or unproven.

Based on the studies provided to the FDA, lenacapavir (Sunlenca®) may be considered medically necessary for treatment-experienced individuals with multidrug resistant HIV-1 infection when all the criteria noted in Coverage are met. All other non-FDA approved uses of lenacapavir (Sunlenca®) are considered experimental, investigational and/or unproven.

Practice Guidelines and Position Statements
Department of Health and Human Services (HHS) Panel on Antiretroviral Guidelines for Adults and Adolescents – A Working Group of the Office of AIDS Research Advisory Council (OARAC)
The 2024 guidelines recommend that monthly or every 2-month long-acting (LA) cabotegravir/ rilpivirine (CAB/RPV), can be used to replace an existing oral antiretroviral (ARV) regimen in people with HIV who fulfill all of the following criteria:

- Sustained viral suppression for at least 3 months;
- No history of documented or suspected resistance to either CAB or RPV;
- No active hepatitis B virus (HBV) infection (unless also receiving tenofovir alafenamide [TAF], tenofovir disoproxil fumarate [TDF], or entecavir);
- Not pregnant or planning on becoming pregnant;
- Not receiving medications with significant drug interactions with oral (during lead-in or bridging therapy) or injectable CAB or RPV. (AI–strong recommendation; one or more randomized trials with clinical outcomes and/or validated laboratory endpoints). (5)

The guidelines also indicate that patients with ongoing detectable viremia who lack sufficient treatment options to construct a fully suppressive regimen with common ARVs may be candidates for the long-acting capsid inhibitor lenacapavir. (5)

The development of LA injectable ART provides additional options for treatment. The combination of injectable cabotegravir CAB and RPV is an optimization option for people with HIV who demonstrate retention in HIV care and who are virologically suppressed on oral therapy. (5)

These guidelines also provide the following reasons to consider regimen optimization in the setting of viral suppression:

- “To simplify a regimen by reducing pill burden and/or dosing frequency.

- To enhance tolerability and/or decrease short- or long-term toxicity.
- To prevent or mitigate drug-drug interactions.
- To eliminate food or fluid requirements.
- To switch to a long-acting injectable regimen to relive pill fatigue or to decrease potential stigma or disclosure concerns with taking daily oral medications.
- To allow optimal use of ART during pregnancy or when pregnancy is desired or may occur.
- To reduce costs." (5)

Coding

Procedure codes on Medical Policy documents are included **only** as a general reference tool for each policy. **They may not be all-inclusive.**

The presence or absence of procedure, service, supply, or device codes in a Medical Policy document has no relevance for determination of benefit coverage for members or reimbursement for providers. **Only the written coverage position in a Medical Policy should be used for such determinations.**

Benefit coverage determinations based on written Medical Policy coverage positions must include review of the member's benefit contract or Summary Plan Description (SPD) for defined coverage vs. non-coverage, benefit exclusions, and benefit limitations such as dollar or duration caps.

CPT Codes	None
HCPCS Codes	C9399, J0741, J1961, J3490

*Current Procedural Terminology (CPT®) ©2024 American Medical Association: Chicago, IL.

References

U.S. Food and Drug Administration Labels:

1. FDA. Cabenuva. Highlights of Prescribing Information. U.S. Food and Drug Administration. (4/2025) Available at: <https://www.accessdata.fda.gov> (accessed August 15, 2025).
2. FDA. Sunlenca®. Highlights of Prescribing Information. U.S. Food and Drug Administration. (11/2024) Available at: <https://www.accessdata.fda.gov> (accessed August 18, 2025).

Other:

3. CDC. About HIV. Centers for Disease Control and Prevention. January 14, 2025. Available at: <https://www.cdc.gov> (accessed August 18, 2025).
4. CDC. Fast Facts: HIV in the United States. Centers for Disease Control and Prevention. April 22, 2024. Available at: <https://www.cdc.gov> (accessed August 18, 2025).
5. U.S. Department of Health and Human Services Panel on Antiretroviral Guidelines for Adults and Adolescents. Guidelines for the Use of Antiretroviral Agents in Adults and Adolescents with HIV. Updated September 12, 2024. Available at: <https://www.ncbi.nlm.nih.gov> (accessed August 18, 2025).
6. Scarsi KK, Havens JP, Podany AT, et al. HIV-1 Integrase Inhibitors: A Comparative Review of Efficacy and Safety. Drugs. Nov 2020; 80(16):1649-1676. PMID 32860583
7. Cabenuva Approval History. Available at: <https://www.drugs.com> (accessed August 18, 2025).

8. Sunlenca® Approval History. Available at: <https://www.drugs.com> (accessed August 18, 2025).

Centers for Medicare and Medicaid Services (CMS)

The information contained in this section is for informational purposes only. HCSC makes no representation as to the accuracy of this information. It is not to be used for claims adjudication for HCSC Plans.

The Centers for Medicare and Medicaid Services (CMS) does not have a national Medicare coverage position. Coverage may be subject to local carrier discretion.

A national coverage position for Medicare may have been developed since this medical policy document was written. See Medicare's National Coverage at <https://www.cms.hhs.gov>.

Policy History/Revision

Date	Description of Change
10/15/2025	Document updated with literature review. The following changes were made to Coverage: 1) Revised existing experimental, investigational and/or unproven statement for each medication by removing "not specified above" and adding "non-Food and Drug Administration approved"; and 2) Added NOTE 1: This policy addresses the use of long-acting injectable antiretroviral agents for the treatment of HIV-1. Requests for pre-exposure prophylaxis (PReP) are not addressed by this policy. Added reference 4; others updated.
07/01/2024	Document updated with literature review. The following change was made to coverage: Removed “and maintained for at least 6 months prior to initiation” from this statement for Cabotegravir/Rilpivirine (Cabenuva) – “Submission of medical records (e.g., chart notes, laboratory results) showing viral suppression (HIV-1 RNA less than 50 copies per mL) has been achieved.” References revised.
10/01/2023	Document updated with literature review. The following changes were made to Coverage: 1) Removed criteria specific to cabotegravir (Apretude), as it is now addressed on medical policy RX501.154; and 2) Added conditional criteria specific to lenacapavir (Sunlenca). Added/updated the following references: 2 and 4-7. Title changed from: Long-Acting Injectable Antiretroviral Agents for HIV.
02/15/2023	New medical document. Cabotegravir (Apretude) may be considered medically necessary to reduce the risk of sexually acquired human immunodeficiency virus type-1 (HIV-1) infection in at-risk adults and adolescents when ALL the following criteria are met: patient weighs at least 35kg; AND utilized for HIV-1 pre-exposure prophylaxis (PrEP); AND patient has a negative human immunodeficiency virus type-1 (HIV-1) test; AND provider confirms that the patient will be tested for human

	immunodeficiency virus type-1 (HIV-1) infection with each subsequent injection; AND patient is not an appropriate candidate for oral PrEP (e.g., difficulty with adherence to prior oral PrEP, significant renal disease). All other uses of cabotegravir (Apretude) not specified above are considered experimental, investigational and/or unproven, including but not limited to the treatment of human immunodeficiency virus type-1 (HIV-1). Cabotegravir/Rilpivirine (Cabenuva) may be considered medically necessary for the treatment of a human immunodeficiency virus type-1 (HIV-1) in patients when ALL the following criteria are met: patient has a diagnosis of human immunodeficiency virus type-1 (HIV-1) infection; AND patient is currently on a stable antiretroviral regimen; AND submission of medical records (e.g., chart notes, laboratory results) showing viral suppression (HIV-1 RNA less than 50 copies per mL) has been achieved and maintained for at least 6 months prior to initiation; AND patient has no prior virologic failures or baseline resistance to either cabotegravir or rilpivirine. All other uses of cabotegravir/rilpivirine (Cabenuva) not specified above are considered experimental, investigational and/or unproven.