Policy Number	**RX501.145**
Policy Effective Date	**5/7/2026**

Long-Acting Injectable Antiretroviral Agents for Treatment of HIV

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Related Policies (if applicable)
None

Disclaimer

Medical policies are a set of written guidelines that support current standards of practice. They are based on current generally accepted standards of care 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 of 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 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, New England Journal of Medicine, 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

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

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 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 [ribonucleic acid] 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.**

Policy Guidelines

None.

Description

Human Immunodeficiency Virus (HIV)
HIV 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 cure for HIV; and once a person has the virus, they have it for life. Individuals with HIV can get effective treatment, live long, healthy lives and protect their partners. (3)

There are an estimated 1.2 million individuals in the United States 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%; male-to-male sexual contact and injection drug use is responsible for about 4% of the reported cases. (4)

Antiretroviral Treatment/Therapy
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-ribonucleic acid (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 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. 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 naive- 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)

Cabotegravir extended-release injectable suspension; rilpivirine extended-release injectable suspension (Cabenuva) is a 2-drug copackaged 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.

Lenacapavir (Sunlenca) 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 first approved cabotegravir extended-release injectable suspension; rilpivirine extended-release injectable suspension (Cabenuva) 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 lenacapavir (Sunlenca) on December 22, 2022, as the first capsid inhibitor-based HIV treatment option. Lenacapavir (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 labels for cabotegravir extended-release injectable suspension; rilpivirine extended-release injectable suspension (Cabenuva) and lenacapavir (Sunlenca).

Cabotegravir extended-release injectable suspension; rilpivirine extended-release injectable suspension (Cabenuva) (1)

Clinical Trials in Adults

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-naive participants with human immunodeficiency virus type-1 received a dolutegravir integrase strand transfer inhibitor-containing regimen for 20 weeks (either dolutegravir/abacavir/lamivudine or dolutegravir plus 2 other non-nucleoside reverse transcriptase inhibitors if participants were human leukocyte antigen B*5701 positive). Participants who were virologically suppressed (HIV-1 ribonucleic acid 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 <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, respectively. In both studies, 7% had cluster of differentiation 4 (CD4)+ cell count <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 ≥50 copies/mL at Week 48.

The primary endpoint and other Week 48 outcomes, including outcomes by key baseline factors, for FLAIR and ATLAS are shown in Tables 1 and 2.

Table 1. Virologic Outcomes of Randomized Treatment in FLAIR and ATLAS Trials at Week 48

Virologic Outcomes	**FLAIR Monthly Dosing**		**ATLAS Monthly Dosing**	
	CAB plus RPV (n=283)	**CAR (n=283)**	**CAB plus RPV (n=308)**	**CAR (n=308)**
HIV-1 RNA ≥50 copies/mL[a]	2%	2%	2%	1%
Treatment difference	-0.4% (95% CI: -2.8%, 2.1%)		0.7% (95% CI: -1.2%, 2.5%)	
HIV-1 RNA <50 copies/mL	94%	93%	93%	95%
No virologic data at Week 48 window	4%	4%	6%	4%
• Discontinued due to adverse event or death	3%	<1%	4%	2%
• Discontinued for other reasons	1%	4%	2%	2%
• Missing data during window but on study	0	0	0	0

CAB: cabotegravir; CAR: current antiretroviral regimen; CI: confidence interval; HIV-1: human immunodeficiency virus type-1; n: number of participants in each treatment group; RNA: ribonucleic acid; RPV: rilpivirine.

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

Adjusted for study and randomization stratification factors, treatment difference of HIV-1 RNA ≥50 copies/mL for the pooled data was 0.2% with 95% confidence interval (CI) (-1.4%, 1.7%).

Table 2. Proportion of Participants in FLAIR and ATLAS Trials with Plasma HIV-1 RNA ≥50 copies/mL at Week 48 for Key Baseline Factors

Baseline Factors	FLAIR Monthly Dosing		ATLAS Monthly Dosing	
	CAB plus RPV (N=283) n/N (%)	CAR (N=283) n/N (%)	CAB plus RPV (N=308) n/N (%)	CAR (N=308) n/N (%)
Baseline CD4+ (cells/mm^3)				
<350	0/19	1/27 (4%)	0/23	1/27 (4%)
≥350 to <500	3/64 (5%)	0/60	2/56 (4%)	0/60
≥500	3/200 (2%)	6/196 (3%)	3/299 (1%)	2/224 (<1%)
Gender				
Male	3/220 (1%)	6/219 (3%)	3/209 (1%)	3/204 (1%)
Female	3/63 (5%)	1/64 (2%)	2/99 (2%)	0/104
Race				
White	6/216 (3%)	5/201 (2%)	3/214 (1%)	2/207 (<1%)
African American/African Heritage	0/47	2/56 (4%)	2/62 (3%)	1/77 (1%)
Asian/Other	0/20	0/24	0/32	0/24
Body mass index				
<30 kg/m^2	3/243 (1%)	7/246 (3%)	3/248 (1%)	1/242 (<1%)
≥30 kg/m^2	3/40 (8%)	0/37	2/60 (3%)	2/66 (3%)
Age (years)				
<50	5/250 (2%)	6/254 (2%)	4/242 (2%)	2/212 (<1%)
≥50	1/33 (3%)	1/29 (3%)	1/66 (2%)	1/96 (1%)
Baseline antiviral therapy at randomization	0	0	1/51 (2%)	0/54
• Protease inhibitor-containing regimen	6/283 (2%)	7/283 (2%)	0/102	2/99 (2%)
• Integrase inhibitor-containing regimen	0	0	4/155 (3%)	1/155 (<1%)
• Non-nucleoside reverse transcriptase inhibitor-containing regimen				

CAB: cabotegravir; CAR: current antiretroviral regimen; HIV-1: human immunodeficiency virus type-1; n: number of participants in each treatment group; RNA: ribonucleic acid; RPV: rilpivirine.

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

Virologic Outcomes	**Cabotegravir plus Rilpivirine**	
	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.

Table 4. Proportion of Participants in ATLAS 2-M Trial with Plasma HIV-1 RNA ≥50 copies/mL at Week 48 for Key Baseline Factors

Baseline Factors	**Cabotegravir plus Rilpivirine**	
	Every-2-Month Dosing (N=522) n/N (%)	**Monthly Dosing (N=523) n/N (%)**
Baseline CD4+ (cells/mm^3)		
<350	1/35 (3%)	1/27 (4%)
≥350 to <500	1/96 (1%)	0/89
≥500	7/391 (2%)	4/407 (1%)
Gender		
Male	4/385 (1%)	5/380 (1%)
Female	5/137 (4%)	0/143
Race		
White	5/370 (1%)	5/393 (1%)
Black/African American	4/101 (4%)	0/90
Asian/Other	0/51	0/40

Body mass index		
<30 kg/m^2	3/409 (1%)	3/425 (1%)
≥30 kg/m^2	6/113 (5%)	2/98 (2%)
Age (years)		
<35	4/137 (3%)	1/145 (1%)
35 to <50	3/242 (1%)	2/239 (1%)
≥50	2/143 (1%)	2/139 (1%)
Prior exposure to cabotegravir plus rilpivirine		
None	5/327 (2%)	5/327 (2%)
1 to 24 Weeks	3/69 (4%)	0/68
>24 Weeks	1/126 (1%)	0/128
Baseline third-agent class		
Protease inhibitor-containing regimen	1/40 (3%)	1/30 (3%)
Integrase inhibitor-containing regimen	3/136 (2%)	2/141 (1%)
NNRTI-containing regimen	1/151 (1%)	2/156 (1%)
Cabotegravir plus rilpivirine	4/195 (2%)	0/196

CD4: cluster of differentiation 4; HIV-1: human immunodeficiency virus type-1; NNRTI: non-nucleoside reverse transcriptase inhibitor; RNA: ribonucleic acid.

Clinical Trial in Adolescents

Trial 208580 (MOCHA, [NCT03497676])

The safety, tolerability, and pharmacokinetics of oral and injectable cabotegravir and oral and injectable rilpivirine were assessed in an ongoing Phase 1/2 multicenter, open-label, non-comparative study, MOCHA (IMPAACT 2017).

Cohort 1:

Fifty-five virologically suppressed adolescents with HIV-1 aged 12 to younger than 18 years and weighing at least 35 kg were enrolled to 1 of 4 subgroups, 1C (Q4W): cabotegravir monthly dosing, 1C (Q8W): cabotegravir every-2-month dosing, 1R (Q4W): rilpivirine monthly dosing or 1R (Q8W): rilpivirine every-2-month dosing.

In cohort 1C, participants (n=30) received one 30-mg cabotegravir tablet daily for at least 4 weeks followed by monthly cabotegravir injections for 3 months (Month 1: 600-mg injection, Months 2 and 3: 400-mg injection), or every-2-month cabotegravir injections for 2 months (Months 1 and 2: 600-mg injection), while continuing background antiretroviral therapy. In cohort 1R, participants (n=25) received one 25-mg rilpivirine tablet daily for at least 4 weeks followed by monthly rilpivirine injections for 3 months (Month 1: 900-mg injection, Months 2 and 3: 600-mg injection), or every-2-month rilpivirine injections for 2 months (Months 1 and 2: 900-mg injection), while continuing background antiretroviral therapy.

At baseline, in cohort 1 (n=55), the median age of participants was 15.0 years, the median weight was 50.0 kg (range: 37.4, 98.5), 47% were female, 76% were Black/African American, 16% were Asian, 7% were White; and no participant had a CD4+ cell count <350 cells per mm^3. At baseline, median CD4+ cell count was 725 cells per mm^3 (range: 397 to 1808).

The primary objectives at Week 16, which were to confirm the use of the adult dose through the evaluation of safety and pharmacokinetics in virologically suppressed adolescents with HIV-1, were met enabling the progression of participants to cohort 2.

Cohort 2:
Cohort 2 enrolled eligible participants who had completed cohort 1 as well as eligible participants who had not been previously enrolled in the study. Cohort 2 participants (n=144) discontinued their background antiretroviral therapy and received one 30-mg cabotegravir tablet plus one 25-mg rilpivirine tablet daily for at least 4 weeks followed by every-2-month cabotegravir injections (Months 1 and 2: 600-mg injection, then 600-mg injection once every 2 months) and rilpivirine injections (Months 1 and 2: 900-mg injection, then 900-mg injection once every 2 months).

At baseline, in cohort 2, the median age of participants was 15.0 years, the median weight was 48.5 kg (range: 35.2, 100.9), 51% were female, 74% were Black/African American, 25% were Asian, 1% was White; and 4 participants had a CD4+ cell count less than 350 cells per mm^3. At baseline, median CD4+ cell count was 739.5 cells per mm^3 (range: 81 to 1925).

The primary objective at Week 24, which was to confirm the safety of injectable cabotegravir plus injectable rilpivirine in virologically suppressed adolescents with HIV-1, was met. Antiviral activity was assessed as a secondary objective: 139 of the 141 (98.6%) participants with available data remained virologically suppressed (HIV-1 RNA <50 copies/mL) at Week 24. The median change from baseline in CD4+ cell count at Week 24 was -36.0 cells per mm^3.

Lenacapavir (Sunlenca) (2)
The efficacy and safety of Sunlenca in heavily treatment-experienced participants with multidrug resistant HIV-1 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 (nucleoside reverse-transcriptase inhibitor, NNRTI, protease inhibitor 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.

In the 14-day functional monotherapy period, participants in cohort 1 were randomized in a 2:1 ratio in a blinded fashion to receive either Sunlenca or placebo, while continuing their failing regimen. This period was to establish the virologic activity of Sunlenca. After the functional monotherapy period, participants who had received Sunlenca continued on Sunlenca along with an optimized background regimen; participants who had received placebo during this period initiated Sunlenca along with an OBR.

Participants in cohort 1 had a mean age of 52 years (range: 24 to 71), 72% were male, 46% were White, 46% were Black, and 9% were Asian. 29% percent of participants identified as Hispanic/ Latino. The mean baseline plasma HIV-1 RNA was 4.3 log_{10} copies/mL (range: 2.3 to 5.4). 19% of participants had baseline viral loads greater than 100,000 copies/mL. The mean baseline CD4+ cell count was 161 cells/mm^3 (range: 6 to 827). Seventy-five percent of participants had CD4+ cell counts below 200 cells/mm^3. The mean number of years since participants first started HIV treatment was 24 years (range: 7 to 33); the mean number of antiretroviral agents in failing regimens at baseline was 4 (range: 1 to 7). The percentage of participants in the randomized cohort with known resistance to at least 2 agents from the NRTI, NNRTI, PI and INSTI classes was 97%, 94%, 78% and 75%, respectively. In cohort 1, 53% of participants had no fully active agents, 31% had 1 fully active agent, and 17% had 2 or more fully active agents within their initial failing regimen, including 6% of participants were who were receiving fostemsavir, which was an investigational agent at the start of the CAPELLA trial.

Participants in cohort 2 initiated Sunlenca and an OBR on Day 1.

Participants in cohort 2 had a mean age of 48 years (range: 23 to 78), 78% were male, 36% were White, 31% were Black, 33% were Asian, and 14% of participants identified as Hispanic/Latino. The mean baseline plasma HIV-1 RNA was 4.1 log_{10} copies/mL (range: 1.3 to 5.7). 19% of participants had baseline viral loads greater than 100,000 copies/mL. The mean baseline CD4+ cell count was 258 cells/mm^3 (range: 3 to 1296). 53% of participants had CD4+ cell counts below 200 cells/mm^3. The mean number of years since participants first started HIV treatment was 19 years (range: 3 to 35); the mean number of antiretroviral agents in failing regimens at baseline was 4 (range: 2 to 7). The percentage of participants in the non-randomized cohort with known resistance to at least 2 agents from the NRTI, NNRTI, PI and INSTI classes was 100%, 100%, 83% and 64%, respectively. In cohort 2, 31% of participants had no fully active agents, 42% had 1 fully active agent, and 28% had 2 or more fully active agents within their initial failing regimen, including 6% of participants who

were receiving fostemsavir, which was an investigational agent at the start of the CAPELLA trial.

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 5.

Table 5. 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.

The results at Weeks 26 and 52 are provided in Table 6 and Table 7.

Table 6. Virologic Outcomes (HIV-1 RNA <50 copies/mL) at Weeks 26[a] and 52[b] with Sunlenca plus OBR in the CAPELLA Trial (Cohort 1)

	Sunlenca plus OBR (N=36)	
	Week 26	**Week 52**
HIV-1 RNA <50 copies/mL	81%	83%
HIV-1 RNA ≥50 copies/mL[c]	19%	14%
No virologic data in Week 26 or 52 Window	0	3%
Discontinued Study Drug Due to AE or Death[d]	0	0
Discontinued Study Drug Due to Other Reasons[e] and Last Available HIV-1 RNA <50 copies/mL	0	3%
Missing Data During Window but on Study Drug	0	0

AE: adverse event; HIV-1: human immunodeficiency virus type-1; OBR: optimized background regimen; RNA: ribonucleic acid.
[a] Week 26 window was between Days 184 and 232 (inclusive).
[b] Week 52 window was between Days 324 and 414 (inclusive).
[c] Includes participants who had ≥ 50 copies/mL in the Week 26 or 52 window; participant who discontinued early due to lack or loss of efficacy; participants who discontinued for reasons other than an adverse event, death or lack or loss of efficacy and at the time of discontinuation had a viral value of ≥ 50 copies/mL.
[d] Includes participants who discontinued due to AE or death at any time point from Day 1 through the time window if this resulted in no virologic data on treatment during the specified window.

[e] Includes participants who discontinued for reasons other than an AE, death or lack or loss of efficacy, e.g., withdrew consent, loss to follow-up, etc.

Table 7. Virologic Outcomes (HIV-1 RNA <50 copies/mL) by Baseline Covariates at Weeks 26[a] and 52[b] with Sunlenca plus OBR in the CAPELLA trial (Cohort 1)

	Sunlenca plus OBR (N=36)	
	Week 26	**Week 52**
Age (Years)		
<50	100% (9/9)	89% (8/9)
≥50	74% (20/27)	81% (22/27)
Gender		
Male	77% (20/26)	77% (20/26)
Female	90% (9/10)	100% (10/10)
Race		
Black	81% (13/16)	75% (12/16)
Non-Black	84% (16/19)	89% (17/19)
Baseline plasma viral load (copies/mL)		
≤100,000	86% (25/29)	86% (25/29)
>100,000	57% (4/7)	71% (5/7)
Baseline CD4+ (cells/mm^3)		
<200	78% (21/27)	78% (21/27)
≥200	89% (8/9)	100% (9/9)
Baseline INSTI resistance profile		
With INSTI resistance	85% (23/27)	81% (22/27)
Without INSTI resistance	63% (5/8)	88% (7/8)
Number of fully active ARV agents in the OBR		
0	67% (4/6)	67% (4/6)
1	86% (12/14)	79% (11/14)
≥ 2	81% (13/16)	94% (15/16)
Use of DTG and/or DRV in the OBR		
With DTG and DRV	83% (10/12)	83% (10/12)
With DTG, without DRV	83% (5/6)	83% (5/6)
Without DTG, with DRV	78% (7/9)	89% (8/9)
Without DTG or DRV	78% (7/9)	78% (7/9)

ARV: antiretroviral; CD4: cluster of differentiation 4; DRV: darunavir; DTG: dolutegravir; HIV-1: human immunodeficiency virus type-1; INSTI: integrase strand-transfer inhibitor; OBR: optimized background regimen; OBR: optimized background regimen; RNA: ribonucleic acid.

[a] Week 26 window was between Days 184 and 232 (inclusive).

[b] Week 52 window was between Days 324 and 414 (inclusive).

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 Weeks 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.

The safety and effectiveness of Sunlenca have not been established in pediatric patients.

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 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

*Current Procedural Terminology (CPT®) ©2025 American Medical Association: Chicago, IL.

References

U.S. Food and Drug Administration Labels:

1. Prescribing Label: Cabenuva (cabotegravir extended-release injectable suspension; rilpivirine extended-release injectable suspension). (November 2025). Available at accessdata.fda.gov (accessed Jan. 12, 2026).
2. Prescribing Label: Sunlenca (lenacapavir) injection, for subcutaneous use. (November 2024). Available at accessdata.fda.gov (accessed Jan. 12, 2026).

Other:

3. CDC. About HIV. Centers for Disease Control and Prevention. Jan. 14, 2025. Available at cdc.gov (accessed January 12, 2026).
4. CDC. Fast Facts: HIV in the United States. Centers for Disease Control and Prevention. April 22, 2024. Available at cdc.gov (accessed Jan. 12, 2026).
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 Sept. 25, 2025. Available at ncbi.nlm.nih.gov (accessed Jan. 12, 2026).
6. Scarsi KK, Havens JP, Podany AT, et al. HIV-1 Integrase Inhibitors: A Comparative Review of Efficacy and Safety. Drugs. November 2020; 80(16):1649-1676. PMID 32860583
7. Cabenuva Approval History. Available at drugs.com (accessed Jan. 12, 2026).
8. Sunlenca Approval History. Available at drugs.com (accessed Jan. 12, 2026).

Centers for Medicare and Medicaid Services

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 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 cms.hhs.gov.

Policy History/Revision

Date	Description of Change
5/7/2026	New medical document. NOTE 1: This policy addresses the use of long-acting injectable antiretroviral agents for the treatment of HIV-1. Requests for pre-exposure prophylaxis are not addressed by this policy. Cabotegravir/Rilpivirine (Cabenuva) may be considered medically necessary for the treatment of individuals with a diagnosis of human

	immunodeficiency virus type-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) 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.