

# Long-Acting Injectable Antiretroviral Agents for HIV

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[Instructions for Use](#)

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Commercial Policy
• <a href="#">Long-Acting Injectable Antiretroviral Agents for HIV</a>

## Application

This Medical Benefit Drug Policy does not apply to the states listed below; refer to the state-specific policy/guideline, if noted:

State	Policy/Guideline
Florida	None
Indiana	<a href="#">Long-Acting Injectable Antiretroviral Agents for HIV (for Indiana Only)</a>
North Carolina	None
Pennsylvania	Refer to the state’s Medicaid clinical policy
Washington	Refer to the state’s Medicaid clinical policy

## Coverage Rationale

This policy refers to the following long-acting injectable antiretroviral products:

- Apretude (cabotegravir)
- Cabenuva (cabotegravir/rilpivirine)

Apretude (cabotegravir) is proven to reduce the risk of sexually acquired HIV-1 infection in at-risk adults and adolescents weighing at least 35kg. Apretude is medically necessary when the following additional criteria are met:<sup>5-6</sup>

- For initial therapy, all of the following:
  - Used for HIV-1 pre-exposure prophylaxis (PrEP); and
  - Patient has a negative HIV-1 test; and
  - Provider confirms that the patient will be tested for 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); and
  - Provider attests that patient demonstrates treatment readiness by both of the following:
    - Patient understands the risks of missed doses of Apretude
    - Patient has the ability to adhere to the required every 2 months injection and testing appointments;

- and
- Dosing is in accordance with the United States Food and Drug Administration approved labeling; and
- Initial authorization is for no more than 12 months.
- For continuation therapy, all of the following:
  - Patient has previously received treatment with Apretude; and
  - Patient has a negative HIV-1 test; and
  - Provider confirms that the patient will be tested for HIV-1 infection with each subsequent injection; and
  - Dosing is in accordance with the United States Food and Drug Administration approved labeling; and
  - Authorization is for no more than 12 months.

Apretude is unproven and not medically necessary for the treatment of human immunodeficiency virus type-1 (HIV-1).

Cabenuva (cabotegravir/rilpivirine) is proven for the treatment of a human immunodeficiency virus type-1 (HIV-1) in patients who are virologically suppressed (HIV-1 RNA less than 50 copies per mL). Cabenuva is medically necessary when the following additional criteria are met:<sup>1-3</sup>

- For initial therapy, all of the following:
  - Diagnosis of HIV-1 infection; and
  - Patient has no prior virologic failures or baseline resistance to either cabotegravir or rilpivirine; 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) for at least 6 months prior to initiation of Cabenuva; and
  - Provider attests that patient demonstrates treatment readiness by both of the following:
    - Patient understands the risks of missed doses of Cabenuva
    - Patient has the ability to adhere to the required monthly or every 2 months injection appointments
  - Dosing is in accordance with the United States Food and Drug Administration approved labeling; and
  - Initial authorization is for no more than 12 months
- For continuation therapy, all of the following:
  - Patient has previously received treatment with Cabenuva; and
  - Provider confirms that the patient has achieved and maintained viral suppression (HIV-1 RNA less than 50 copies per mL) while on Cabenuva therapy; and
  - Dosing is in accordance with the United States Food and Drug Administration approved labeling; and
  - Authorization is for no more than 12 months

Cabenuva is unproven and not medically necessary for the treatment of Human immunodeficiency virus type-1 (HIV-1) in patients who are not currently virally suppressed (HIV-1 RNA less than 50 copies per mL)

## Documentation Requirements

Benefit coverage for health services is determined by the member specific benefit plan document and applicable laws that may require coverage for a specific service. The documentation requirements outlined below are used to assess whether the member meets the clinical criteria for coverage, but do not guarantee coverage of the service requested.

HCPCS Code*	Required Clinical Information
<b>Cabenuva</b>	
J0741	For initial therapy requests, medical notes or laboratory results documenting the following: <ul style="list-style-type: none"> <li>● Viral suppression (HIV-1 RNA less than 50 copies per mL) for at least 6 months prior to initiation of Cabenuva</li> </ul>

\*For code description, refer to the [Applicable Codes](#) section.

## Applicable Codes

The following list(s) of procedure and/or diagnosis codes is provided for reference purposes only and may not be all inclusive. Listing of a code in this policy does not imply that the service described by the code is a covered or non-covered health service. Benefit coverage for health services is determined by federal, state, or contractual requirements and applicable laws that may require coverage for a specific service. The inclusion of a code does not imply any right to reimbursement or guarantee claim payment. Other Policies and Guidelines may apply.

HCPCS Code	Description
J0739	Injection, cabotegravir, 1mg
J0741	Injection, cabotegravir and rilpivirine, 2 mg/3 mg

Diagnosis Code	Description
B20	Human immunodeficiency virus [HIV] disease
Z11.3	Encounter for screening for infections with a predominantly sexual mode of transmission
Z11.4	Encounter for screening for human immunodeficiency virus [HIV]
Z20	Contact with and (suspected) exposure to communicable diseases
Z20.2	Contact with and (suspected) exposure to infections with a predominantly sexual mode of transmission
Z20.6	Contact with and (suspected) exposure to human immunodeficiency virus (HIV)
Z21	Asymptomatic human immunodeficiency virus [HIV] infection status
Z72.5	High risk sexual behavior
Z72.51	High risk heterosexual behavior
Z72.52	High risk homosexual behavior
Z72.53	High risk bisexual behavior

## Background

Apretude (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. Blocking this key function within the HIV replication cycle plays a role in both treatment and prevention.

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) integrase strand transfer inhibitor (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 deoxyribonucleic acid (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).<sup>1</sup>

## Clinical Evidence

The efficacy of Apretude has been evaluated in two randomized, double-blind, controlled, multinational trials:<sup>5,7</sup>

- Trial 201738 [HPTN 083 (NCT02720094)], (n = 4,566): HPTN 083 was a non-inferiority study in cisgender men and transgender women who have sex with men who were randomized 1:1 and received either Apretude (n = 2,281) or Truvada (n = 2,285) as a blinded study up to Week 153. At baseline, the median age of participants was 26 years, 12% were transgender women, 72% were non-White, and 67% were younger than 30 years. The primary endpoint was the rate of incident HIV-1 infections among participants randomized to daily oral cabotegravir and intramuscular injections of Apretude every 2 months compared with daily oral Truvada (corrected for early stopping). The primary analysis demonstrated the superiority of Apretude compared with Truvada with a 66% reduction in the risk of acquiring HIV-1 infection, hazard ratio (95% CI) 0.34 (0.18, 0.62); further testing revealed 1 of the infections on Apretude to be prevalent then yielding a 69% reduction in the risk of HIV-1 incident infection relative to Truvada.

- Trial 201739 [HPTN 084 (NCT03164564)], (n = 3,224): HPTN 084 was a superiority study in cisgender women who were randomized 1:1 and received either Apretude (n = 1,614) or Truvada (n = 1,610) as blinded study medication up to Week 153. At baseline, the median age of participants was 25 years, > 99% were non-White, > 99% were cisgender women, and 49% were < 25 years of age. The primary endpoint was the rate of incident HIV-1 infections among participants randomized to oral cabotegravir and injections of Apretude compared with oral Truvada (corrected for early stopping). The primary analysis demonstrated the superiority of Apretude compared with Truvada with an 88% reduction in the risk of acquiring incident HIV-1 infection, hazard ratio (95% CI) 0.12 (0.05, 0.31); further testing revealed 1 of the infections on Apretude to be prevalent then yielding a 90% reduction in the risk of HIV-1 incident infection relative to Truvada.

In December 2021, the Centers for Disease Control and Prevention published the U.S. Public Health Service Pre-Exposure Prophylaxis for the Prevention of HIV Infection in the United States – 2021 Update – A Clinical Practice Guideline.<sup>6</sup> The updated included a new section about prescribing PrEP with intramuscular injections of cabotegravir in anticipation of likely FDA approval in early 2022. A recommendation was added that states PrEP with intramuscular cabotegravir injections (conditional on FDA approval) is recommended for HIV prevention in adults reporting sexual behaviors that place them at substantial ongoing risk of HIV exposure and acquisition. Regarding prescribing cabotegravir PrEP injections, the following information is included: “Patients considering PrEP should be informed of all FDA approved options. Cabotegravir injections may be especially appropriate for patients with significant renal disease, those who have had difficulty with adherent use of oral PrEP and those who prefer injections every 2 months to an oral PrEP dosing schedule.”

The efficacy of Cabenuva has been evaluated in three Phase 3 randomized, multicenter, active controlled, parallel-arm, open-label, non-inferiority trials:<sup>1-3</sup>

- Trial 201584 [FLAIR, (NCT02938520)], (n = 629): HIV-1–infected, antiretroviral treatment (ART)-naïve subjects received a dolutegravir INSTI-containing regimen for 20 weeks (either dolutegravir/abacavir/lamivudine or dolutegravir plus 2 other NRTIs if subjects were HLA-B\*5701 positive). Subjects 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. Subjects 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): HIV-1–infected, ART-experienced, virologically-suppressed (for at least 6 months; median prior treatment duration was 4.3 years) subjects (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. Subjects 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 207966 [ATLAS-2M, (NCT03299049)], (n = 1,045): HIV-1–infected, ART-experienced, virologically suppressed subjects, including 504 subjects from the ATLAS trial [randomized to CAB plus RPV (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. Subjects 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 endpoint of ATLAS-2M was the proportion of subjects with a plasma HIV-1 RNA  $\geq$  50 copies/mL at Week 48. The primary endpoint was met with 2% of subjects in the every 2-month dosing arm having an HIV-RNA  $\geq$  50 copies/mL compared to 1% in the monthly dosing arm.

The primary analysis was conducted after all subjects completed their Week 48 visit or discontinued the trial prematurely. The primary endpoint of FLAIR and ATLAS was the proportion of subjects with plasma HIV-1 RNA greater than or equal to 50 copies/mL at Week 48. In both FLAIR and ATLAS 2% of subjects met the primary endpoint as compared to 2% and 1% in the comparator arms respectively. Subjects 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.<sup>1</sup>

In February 2021, the United States Department of Health and Human Services updated their guidelines for the use of antiretroviral agents in adults and adolescents with HIV with specific recommendations for use of Cabenuva. The guidelines panel made the following recommendation: “Cabenuva can be used as an optimization strategy for people with HIV currently on oral ART with documented viral suppression for at least 3 months (although optimal duration is not defined)”<sup>4</sup>. In the ATLAS

trial, participants had viral suppression for at least 6 months on standard oral ART prior to randomization. A key consideration noted by the guidelines panel includes “experienced participants enrolled in completed clinical trials for Cabenuva were selected based on their history of good adherence and engagement in care, as documented by sustained viral suppression at baseline. Therefore, these therapies are currently recommended for participants who are similarly engaged in care.” The Panel does not recommend Cabenuva as initial therapy for people with HIV at this time.

## U.S. Food and Drug Administration (FDA)

This section is to be used for informational purposes only. FDA approval alone is not a basis for coverage.

Apretude (cabotegravir) is an HIV-1 integrase strand transfer inhibitor (INSTI) indicated in at-risk adults and adolescents weighing at least 35 kg for HIV-1 Pre-Exposure Prophylaxis (PrEP) to reduce the risk of sexually acquired HIV-1 infection. Individuals must have a negative HIV-1 test prior to initiating Apretude (with or without an oral lead-in with oral cabotegravir) for HIV-1 PrEP.<sup>5</sup>

Cabenuva, a 2-drug co-packaged product of cabotegravir, a human immunodeficiency virus type-1 (HIV-1) integrase strand transfer inhibitor (INSTI), and rilpivirine, an HIV-1 non-nucleoside reverse transcriptase inhibitor (NNRTI), is indicated 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.

## References

1. Cabenuva [package insert]. Research Triangle Park, NC: ViiV Healthcare. March 2022.
2. Swindells S, et al. Long-Acting Cabotegravir and Rilpivirine for Maintenance of HIV-1 Suppression (ATLAS). N Engl J Med. 2020 March 382:1112-1123.
3. Orkin C, et al. Long-Acting Cabotegravir and Rilpivirine after Oral Induction for HIV-1 Infection (FLAIR). N Engl J Med. 2020 March 382:1124-1135.
4. U.S. Department of Health and Human Services. Guidelines for the Use of Antiretroviral Agents in Adults and Adolescents with HIV. Updated January 20, 2022. Available at: [Guidelines for the Use of Antiretroviral Agents in Adults and Adolescents with HIV](#). Accessed February 13, 2022.
5. Apretude [package insert]. Research Triangle Park, NC: ViiV Healthcare. December 2021.
6. Centers for Disease Control and Prevention: US Public Health Service: Preexposure prophylaxis for the prevention of HIV infection in the United States—2021 Update: a clinical practice guideline. <https://www.cdc.gov/hiv/pdf/risk/prep/cdc-hiv-prep-guidelines-2021.pdf>. Published December 2021.
7. Landovitz R.J., et al. Cabotegravir for HIV Prevention in Cisgender Men and Transgender Women (HPTN 083). N Engl J Med. 2021 August 385:595-608.

## Policy History/Revision Information

Date	Summary of Changes
11/01/2022	<p><b>Application</b> <i>Florida</i></p> <ul style="list-style-type: none"> <li>Removed instruction to refer to the state’s Medicaid clinical policy</li> </ul> <p><b>Supporting Information</b></p> <ul style="list-style-type: none"> <li>Archived previous policy version CS2022D0103H</li> </ul>

## Instructions for Use

This Medical Benefit Drug Policy provides assistance in interpreting UnitedHealthcare standard benefit plans. When deciding coverage, the federal, state or contractual requirements for benefit plan coverage must be referenced as the terms of the federal, state or contractual requirements for benefit plan coverage may differ from the standard benefit plan. In the event of a conflict, the federal, state or contractual requirements for benefit plan coverage govern. Before using this policy, please check the federal, state or contractual requirements for benefit plan coverage. UnitedHealthcare reserves the right to modify its Policies and Guidelines as necessary. This Medical Benefit Drug Policy is provided for informational purposes. It does not constitute medical advice.

UnitedHealthcare may also use tools developed by third parties, such as the InterQual<sup>®</sup> criteria, to assist us in administering health benefits. The UnitedHealthcare Medical Benefit Drug Policies are intended to be used in connection with the independent professional medical judgment of a qualified health care provider and do not constitute the practice of medicine or medical advice.