

HHS Adults and Adolescents Antiretroviral Guidelines Panel Recommendation for the Long-Acting Injectable Antiretroviral Regimen of Cabotegravir and Rilpivirine

On January 21, 2021, the U.S. Food and Drug Administration (FDA) approved the first complete long-acting injectable antiretroviral (ARV) regimen, cabotegravir (CAB) and rilpivirine (RPV), as an option to replace the current ARV regimen in adults with HIV who are on stable ARV therapy (ART), with HIV RNA levels <50 copies/mL, have no history of treatment failure, and have no known or suspected resistance to these agents.¹

CAB is a novel integrase strand transfer inhibitor (INSTI) and structural analogue of dolutegravir. RPV is a non-nucleoside reverse transcriptase inhibitor (NNRTI), which was first approved in an oral tablet formulation in 2011.² A tablet formulation of CAB was concurrently approved by the FDA to be used with RPV tablets as a 4-week oral lead-in therapy prior to initiation of the long-acting injectable regimen and as oral bridging in the event of pre-planned missed injections.

The Panel's Recommendation

CAB and RPV intramuscular (IM) injections can be used as an optimization strategy for people with HIV currently on oral antiretroviral therapy (ART) with documented viral suppression for at least 3 months (although optimal duration is not defined) (**AI**), who:

- have no baseline resistance to either medication,
- have no prior virologic failures,
- do not have active hepatitis B virus (HBV) infection (unless also receiving an oral HBV active regimen),
- are not pregnant and are not planning on becoming pregnant, *and*
- are not receiving medications with significant drug interactions with oral (during lead-in or bridging therapy) or injectable CAB or RPV.

Key Information Regarding Dosing and Administration

- Tolerability to CAB and RPV should be assessed using an oral lead-in of CAB 30 mg plus RPV 25 mg once daily with food for at least 28 days before beginning the IM injections.
- The first IM injections should be administered on the last day of oral therapy with a loading dose of CAB 600 mg (3 mL) and RPV 900 mg (3 mL), given as two separate injections in separate ventrogluteal sites.
- Continuation therapy with monthly CAB 400 mg (2 mL) and RPV 600 mg (2 mL), also given as two separate ventrogluteal IM injections, begins thereafter with a +/- 7-day administration window.
- Specific administration instructions, such as the needle length for ventrogluteal IM injection in non-obese (1½ inch) versus obese (2 inch) individuals, contraindication with gluteal fillers, proper storage and preparation techniques, and other specific details can be found in the full prescribing information.

Management of Missed Doses of IM CAB and RPV

Long-acting CAB and RPV have extended half-lives (5.6–11.5 weeks for CAB and 13–28 weeks for RPV), and detectable concentrations may be present for ≥12 months after the last doses.¹ Individuals who miss doses or self discontinue therapy are at increased risk of virologic failure with development of drug resistance. Patients should be fully informed of this risk. Clinicians should consult the prescribing information for IM CAB and RPV for guidance on how to manage missed doses. Oral bridging should be made available to the patients pre-planned missed doses are anticipated. Unplanned missed doses (beyond the 7-day window) should prompt re-evaluation of whether the person remains an appropriate candidate for this injectable therapy. If injections are missed by more than 2 months and the regimen is re-initiated,

resume administration with a loading dose followed by monthly maintenance dosing. When stopping therapy, transition to a suppressive oral regimen should be undertaken within 4 weeks of the last IM dose.

Clinical Trial Data^{3,4}

- Two Phase 3 trials (ATLAS and FLAIR) that enrolled almost 1,200 participants with HIV evaluated the safety and efficacy of once-monthly IM injections of CAB and RPV. Individuals with active HBV infection or who were pregnant were excluded from both trials. In the ATLAS trial, participants had viral suppression for at least 6 months on standard oral ART prior to randomization and had no history of prior virologic failure or resistance to either CAB or RPV. In the FLAIR trial, ARV-naïve participants who had no baseline resistance to CAB or RPV were started on an oral regimen of dolutegravir/abacavir/lamivudine and needed to achieve HIV viral suppression at 16-20 weeks. Participants were then randomized to IM CAB and RPV once monthly or continued oral ART. Both studies used a one-month lead-in phase with oral CAB and RPV before the first IM injections. In the intention-to-treat exposed population, HIV-RNA >50 copies/mL at Week 48 was reported in 11 individuals (1.9%) in the IM CAB and RPV arm and 10 (1.7%) in the oral arm (combining data from both studies).⁵ This demonstrated non-inferiority of IM CAB and RPV compared to oral ART. Virologic failure was rare; however, when it occurred, resistance to INSTIs, NNRTIs, or both was common, and it was more likely to occur in persons with HIV-1 subtype A1 who had an L74I substitution at baseline. Subtype A1 is not common in the United States.
- The 48-week results of the ATLAS-2M trial in which participants were given every 8-week separate IM injections of CAB 600 mg (3 mL) with RPV 900 mg (3 mL) showed non-inferiority compared to every 4-week injections (doses described above),⁶ but this dosing schedule has not yet received FDA approval.

Safety and Tolerability

- Injection site reactions (ISRs) were the most common side effects with IM CAB and RPV, occurring in over 80% of participants at least once. ISRs were less commonly reported over time, occurring in about 10% to 30% at each monthly IM injection timepoint after the first year. ISRs were generally mild to moderate with 99% being grade 1 or 2 and the median duration of symptoms being 3 days.
- More than 90% of participants who received IM CAB and RPV in randomized clinical trials preferred monthly IM therapy over daily oral therapy.⁵
- Hypersensitivity reactions, post-injection reactions, hepatotoxicity, and depressive disorders have also been reported.

Additional Key Considerations

- Switching to long-acting injectable therapy can be advantageous in patients for a variety of reasons, including but not limited to reducing pill fatigue, disclosure concerns or stigma associated with taking daily oral medications, and to improve quality of life.
- To date, ARV-experienced participants enrolled in completed clinical trials for CAB with RPV were selected based on their history of good adherence and engagement in care, as documented by sustained viral suppression at baseline. These therapies are currently recommended for participants who are similarly engaged in care. A study of this regimen in populations with a history of non-adherence to oral ART is underway.⁷
- CAB and RPV do not have HBV activity. If CAB with RPV is used in patients with active HBV, they will need to be combined with appropriate oral HBV therapy (see [HBV-HIV Coinfection section](#)).

- Several drugs are contraindicated with CAB and RPV (oral and/or IM) due to significant drug interactions, including certain anticonvulsants and rifamycins. Please refer to the prescribing information for details.^{1,8}
- These regimens have not been studied in pregnancy. Management of patients who become pregnant while on therapy will need close oversight and should be reported to the [Antiretroviral Pregnancy Registry](#). In clinical trials, participants who became pregnant were switched from IM CAB and RPV to an alternative oral ARV regimen for the remainder of their pregnancies.⁹
- Practical considerations regarding the feasibility of monthly IM administration of CAB and RPV include:
 - Since IM CAB and RPV are only recommended to be administered by a health care provider, there is the potential for strain on clinical systems, pharmacies, and patients.
 - Clinic staff need to work closely with patients to avoid missed doses and ensure uninterrupted oral bridging of ART when missed doses are planned; if unexpected missed doses occur, healthcare providers should assess the appropriateness of continuing injectable therapy to minimize the risk of developing resistance.
 - Many patients with HIV are on oral therapies for medical and/or mental health comorbidities. Counseling to emphasize the importance of continued adherence to oral therapies for other indications is essential.

The Guidelines, including the section on Optimizing Antiretroviral Therapy in the Setting of Virologic Suppression, are currently under revision; an update will be available soon.

References

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