OBSTACLE 1: INITIATING LAI CAB/RPV

Prior to initiating treatment with long-acting injectable (LAI) cabotegravir/rilpivirine (CAB/RPV), ensure that the patient:

- ✓ Does not have hepatitis B virus
- ✓ Does not have drug-drug interactions, or if any, that they are easily managed
- ✓ Does not have comorbidities that could be worsened by a change in regimen
- ✓ Is willing and able to adhere to regular clinic appointments for injections
- ✓ Is virally suppressed on an oral antiretroviral (ART) regimen

Please consult the Department of Health and Human Services guidelines for a full list of drug-drug interactions (https://clinicalinfo.hiv.gov/en/guidelines/hiv-clinical-guidelines-adult-and-adolescent-arv/drug-interactions-overview).

Clinicians should educate patients about the risks, benefits, and importance of adherence to injections:

- LAI ART is as effective as oral ART
- Patients must come to the clinic for injections
- Injection site reactions are possible, but usually lessen over time and are typically mild
- Adherence is important because of the risk of virologic failure and development of resistance

Although the US Food and Drug Administration has not authorized LAI CAB/RPV for use in people who are not virally suppressed (as of February 2025), there are compelling clinical trial and real-world data supporting its use in patients who are viremic when initiating treatment. This option may be explored according to clinic protocols, prior authorization requirements, and clinician comfort.

OBSTACLE 2: CLINIC PROTOCOLS FOR LAI ART

First and foremost, clinic protocols must be tailored to the clinic's staffing level, resources, and patient population. Some common steps or considerations for implementation are:

1. Assemble a multidisciplinary team, including treaters, pharmacists, support staff, and a pilot program director
2. In initial meetings, define patient eligibility, the referral process, and clinical decision-making metrics
3. Utilize a clinical database to monitor referred and enrolled patients, ideally incorporated into the clinic's electronic medical records
4. Develop protocols for insurance approval and drug procurement
5. Train clinicians on injection protocols and technique
6. Develop script regarding LAI ART for patient education
7. Assign staff roles based on availability and workload, including a pharmacist to obtain medication, store medication, and maintain drug inventory
8. Meet regularly to discuss patients receiving LAI ART and any recurring barriers to care

OBSTACLE 3: ADDRESSING MISSED DOSES

For planned missed injections, oral bridging using CAB (30 mg) and RPV (25 mg) may be done for 2 months for a planned missed injection, and injections should resume as soon as possible following the missed injection. Oral bridging should begin 1 month after the last injection and be continued until the next injection is received. Unplanned missed injections may require reinitiating injections using the loading dose if enough time has elapsed. Clinicians should emphasize the importance of adherence to LAI ART because of the risk of virologic failure and development of resistance. Though these are uncommon, they can have detrimental effects for subsequent oral ART regimens if the patient must discontinue LAI ART.

To resume injections, clinicians should follow these protocols:

Monthly Dosing	Every-2-Months Dosing
If missed injection ≤2 months ago • Resume with 400 mg (2 mL) CAB and 600 mg (2 mL) RPV gluteal intramuscular (IM) monthly injections as soon as possible	**If missed injection ≤2 months ago (injection 2 [month 2]) OR ≤3 months (injection 3 [month 4] or later)** • Resume with 600 mg (3 mL) CAB and 900 mg (3 mL) RPV IM injections as soon as possible, then continue to follow the every-2-months injection dosing schedule
If missed injection >2 months ago • Reinitiate the patient with 600 mg (3 mL) CAB and 900 mg (3 mL) RPV gluteal IM injections, then continue to follow the 400 mg CAB and 600 mg RPV monthly injection dosing schedule	**If missed injection >2 months ago (injection 2 [month 2]) OR >3 months (injection 3 [month 4] or later)** Reinitiate the patient with 600 mg (3 mL) CAB and 900 mg (3 mL) RPV IM injections, followed by the second initiation injection dose 1 month later • Continue to follow the every-2-months injection dosing schedule thereafter

OBSTACLE 4: DISCONTINUING LAI CAB/RPV

LAI ART can be discontinued based on patient preference, nonadherence (without virologic failure), or adverse events, and LAI CAB/RPV must be discontinued if 2 consecutive HIV RNA levels are ≥200 copies/mL or there is evidence of integrase strand transfer inhibitor or non-nucleoside reverse transcriptase inhibitor resistance-associated mutations (excluding K103N in isolation). Upon discontinuation or to inform a decision about discontinuation, **clinicians should**:

- ✓ Perform viral load testing
- ✓ If HIV RNA >500 copies/mL, perform genotype testing (including INSTI testing) regardless of time since last injection
  - Consider testing if HIV RNA >200 copies/mL but <500 copies/mL, though be aware results may be inconclusive
- ✓ Initiate an oral ART regimen within 1 month after the last injection for patients receiving monthly injections or within 2 months for those receiving every-2-months injections
  - Switch to a boosted protease inhibitor regimen if there is evidence of INSTI resistance
  - A new oral ART regimen should have 2 fully active drugs if ≥1 has a high barrier to resistance
- ✓ Retest viral load 4 to 8 weeks after switching