CLINICAL GUIDELINES PROGRAM
NEW YORK STATE DEPARTMENT OF HEALTH AIDS INSTITUTE | HIV • HCV • STIs • SUBSTANCE USE • LGBTQ+ HEALTH

Use of Injectable CAB/RPV LA as Replacement ART in Virally Suppressed Adults

Updates, Authorship, and Related Resources

Date of current publication	February 12, 2026
Highlights of changes, additions, and updates in the February 12, 2026 edition	• Efficacy of CAB/RPV LA section: Text added on CAB/RPV LA use in virally unsuppressed individuals. • Benefits, Potential Risks, and Limitations of CAB/RPV LA section: – Added recommendation: Clinicians should offer CAB/RPV LA as replacement ART for adults (aged ≥18 years) with HIV who are virally suppressed (HIV RNA level <50 copies/mL) and prefer an alternative to daily oral therapy. (A1) – Added recommendation: For patients who are not virally suppressed and have ongoing adherence challenges with oral ART (even with support) or are mechanically unable to ingest oral ART, the clinician should engage the patient in shared decision-making and offer monthly CAB/RPV LA, if susceptible, coupled with intensified follow-up support. (A2) Once viral suppression is achieved and maintained, consider transition to every-8-weeks dosing. (A3) – Added text in discussion and Box 1 indicating that CAB/RPV LA is safe and efficacious in patients with chronic renal disease or on intermittent hemodialysis.
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Author and writing group conflict of interest disclosures	There are no author or writing group conflict of interest disclosures.
Date of original publication	April 7, 2022
Committee	Medical Care Criteria Committee
Developer and funder	New York State Department of Health AIDS Institute (NYSDOH AI)
Development process	See Supplement: Guideline Development and Recommendation Ratings
Related NYSDOH AI resources	**Guidelines** • Laboratory Monitoring for Adverse Effects of ART • Rapid ART Initiation • Second-Line ART After Treatment Failure or for Regimen Simplification • Selecting an Initial ART Regimen • Virologic and Immunologic Monitoring in HIV Care **Guidance** • Drug-Drug Interaction Guide: From HIV Prevention to Treatment **Podcast** • Viremic—Cases in HIV

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Committee: Medical Care Criteria Committee
Date of original publication: April 7, 2022

Contents

Purpose of This Guideline

Purpose: This guideline was developed by the New York State Department of Health AIDS Institute (NYSDOH AI) to provide clinicians with evidence-based recommendations and information on the use of long-acting injectable cabotegravir/rilpivirine (CAB/RPV LA) as replacement antiretroviral therapy (ART) for adults (aged ≥18 years) with HIV who are virally suppressed (HIV RNA level <50 copies/mL) [FDA 2022]. The goal is to provide clinicians with the information necessary to:

- Weigh the risks and benefits of switching from an oral to an injectable ART regimen
- Engage patients in shared decision-making regarding a switch to injectable ART
- Choose, initiate, and maintain a monthly (every 4 weeks) or bimonthly (every 8 weeks) dosing schedule, respond to missed doses, and manage discontinuation of injectable ART when indicated
- Develop medical practice protocols and procedures for implementing injectable ART

Rationale for injectable ART: Daily adherence to oral ART is challenging for some individuals for a variety of complex and intersecting reasons, including pill counts and sizes, disclosure and privacy concerns, HIV-related stigma, neurocognitive disorders and mental health conditions, active substance use, psychological trauma, personal belief systems, travel requirements, occupation, and health literacy. Interventions to improve medication adherence include the use of pillbox organizers, motivational interviewing, peer-based education and counseling, directly administered ART, text messaging, and alarms [Babudieri, et al. 2011; Hardy, et al. 2011; Lester, et al. 2010; Altice, et al. 2007; Johnson, et al. 2007; Petersen, et al. 2007; Purcell, et al. 2007; Golin, et al. 2006; Mannheimer, et al. 2006; Remien, et al. 2005]. The availability of simplified, single-tablet oral regimens has improved medication adherence significantly [Sutton, et al. 2016; Hanna, et al. 2014; Nachega,

et al. 2014]. However, real-world clinician and patient experiences have demonstrated that barriers to ART adherence remain [Cohen, et al. 2020].

Phase 3 clinical trial results suggest that CAB/RPV LA may be a suitable option for patients engaged in care who would prefer an alternative to daily oral therapy [Overton, et al. 2021; Orkin, et al. 2020; Swindells, et al. 2020]. In the FLAIR and ATLAS trials, participants whose virus was suppressed with oral ART regimens were randomly assigned to receive monthly CAB/RPV LA or standard of care oral therapy. CAB/RPV LA was determined to be noninferior to oral therapy after 48 weeks of treatment [Orkin, et al. 2020; Swindells, et al. 2020].

Note on "experienced" HIV care providers: The NYSDOH AI Clinical Guidelines Program defines an "experienced HIV care provider" as a practitioner who has been accorded HIV Specialist status by the American Academy of HIV Medicine. Nurse practitioners (NPs) and licensed midwives who provide clinical care to individuals with HIV in collaboration with a physician may be considered experienced HIV care providers if all other practice agreements are met; NPs with more than 3,600 hours of qualifying experience do not require collaboration with a physician (8 NYCRR 79-5:1; 10 NYCRR 85.36; 8 NYCRR 139-6900). Physician assistants who provide clinical care to individuals with HIV under the supervision of an HIV Specialist physician may also be considered experienced HIV care providers (10 NYCRR 94.2).

Efficacy of CAB/RPV LA

CAB/RPV LA in Virally Suppressed Individuals

Based on safety and efficacy data from randomized clinical trials, the U.S. Food and Drug Administration (FDA) has approved the long-acting injectable combination of the integrase strand transfer inhibitor (INSTI) cabotegravir and the nonnucleoside reverse transcriptase inhibitor (NNRTI) rilpivirine (CAB/RPV LA)—administered as a monthly (every 4 weeks) or bimonthly (every 8 weeks) intramuscular injection—as replacement antiretroviral therapy (ART) for adults (aged ≥18 years) with HIV who are virally suppressed (HIV RNA level <50 copies/mL) [FDA 2022; ViiV Healthcare 2022]. See the NYSDOH AI guideline Second-Line ART After Treatment Failure or for Regimen Simplification for use of CAB/RPV LA in patients who are not virally suppressed.

FLAIR trial: In the randomized, open-label FLAIR trial, 566 participants who initiated ART with 20 weeks of fixed-dose dolutegravir/abacavir/lamivudine (DTG/ABC/3TC) were subsequently randomly assigned to either 4 weeks of oral lead-in therapy with CAB 30 mg and RPV 25 mg daily followed by monthly injections of CAB/RPV LA (n = 283) or to continue oral therapy with DTG/ABC/3TC (n = 283). Participants were aged 18 years or older, ART naive, and had a plasma HIV RNA level ≥1,000 copies/mL at screening. Key exclusion criteria included pregnancy, breast/chestfeeding, coinfection with hepatitis B virus (HBV), severe liver disease, and known resistance to INSTIs or NNRTIs, excluding the K103N mutation in isolation. The primary endpoint was the percentage of participants with an HIV RNA level ≥50 copies/mL at week 48 of the maintenance phase; a secondary endpoint was the percentage of participants with an HIV RNA level <50 copies/mL at week 48. At week 48, 6 of 283 (2.1%) participants in the injectable therapy arm had an HIV RNA level ≥50 copies/mL compared with 7 of 283 participants (2.5%) in the oral therapy arm, meeting criteria for noninferiority, and 93.6% of those in the injectable therapy arm achieved an HIV RNA level <50 copies/mL at week 48, compared with 93.3% of those in the oral therapy arm (see Table 1, below) [Orkin, et al. 2020].

ATLAS trial: The randomized, open-label ATLAS trial compared CAB/RPV LA with standard of care oral therapy in participants who were virally suppressed for a minimum of 6 months before enrollment. The trial included 616 adults aged 18 years or older on uninterrupted ART without medication changes in the last 6 months and without virologic failure for 6 months before screening with HIV RNA levels of <50 copies/mL at screening and within 6 and 12 months before screening. A single regimen switch was allowed ≥6 months before screening for reasons of tolerability, simplification, or access to medications but not for virologic failure. Participants taking DTG/ABC/3TC were excluded because prior treatment with that regimen was adequately represented in the FLAIR trial. Other exclusion criteria were active HBV infection, pregnancy, and the presence of INSTI or NNRTI resistance-associated mutations, except the K103N mutation in isolation. Participants were randomly assigned to continue oral therapy (n = 308) or switch to monthly injections of CAB/RPV LA (n = 308). The primary endpoint was the percentage of participants with an HIV RNA level ≥50 copies/mL at week 48 of the maintenance phase, and a secondary endpoint was the percentage of participants with an HIV RNA level <50 copies/mL at week 48. At week 48, 5 (1.6%) participants in the injectable therapy arm and 3 (1%) in the oral therapy arm had an HIV RNA level ≥50 copies/mL, meeting criteria for noninferiority, and 92.5% of those in the injectable therapy arm achieved an HIV RNA level <50 copies/mL at week 48, compared with 95.5% of those in the oral therapy arm (see Table 1, below) [Swindells, et al. 2020].

Adverse effects in FLAIR and ATLAS trials: Pooled adverse effects of CAB/RPV LA in both the FLAIR and ATLAS trials included injection site reactions that rarely led to medication discontinuation, musculoskeletal pain, nausea, sleep disorders, dizziness, depression, and rash [FDA 2022]. Laboratory abnormalities in aspartate aminotransferase, alanine aminotransferase, total bilirubin, creatine phosphokinase, and lipase were also noted [FDA 2022] (for more details, see guideline section Benefits, Limitations, and Risks of CAB/RPV LA as ART > Adverse effects).

Noninferiority of bimonthly dosing—the ATLAS-2M trial: The randomized, open-label, phase 3b ATLAS-2M trial demonstrated similar efficacy between 4-week (n = 523) and 8-week (n = 522) maintenance dosing schemes of CAB/RPV LA. This study included 391 prior ATLAS study participants from both arms (injectable therapy and oral therapy). Newly recruited participants had received a first or second oral ART regimen for at least 6 months, had no history of virologic failure, had an HIV RNA level <50 copies/mL twice in the prior year, and no known INSTI or NNRTI resistance, excluding the K103N mutation in isolation. Participants were randomly assigned to receive CAB 400 mg/RPV 600 mg LA every 4 weeks or CAB 600 mg/RPV 900 mg LA every 8 weeks (those new to injectable therapy received the standard 4-week oral lead-in with CAB and RPV, similar to FLAIR and ATLAS). The primary endpoint was the percentage of participants with an HIV RNA level ≥50 copies/mL at week 48; a secondary endpoint was the percentage of participants with an HIV RNA level <50 copies/mL at week 48. Of participants in the 8-week treatment arm, 9 (2%) had an HIV RNA level ≥50 copies/mL at week 48, compared with 5 (1%) in the 4-week treatment arm, meeting criteria for noninferiority, and 94% of participants in the 8-week arm achieved an HIV RNA level <50 copies/mL at week 48, compared with 93% of those in the 4-week arm [Overton, et al. 2021].

At 96 weeks, 11 (2.1%) participants in the 8-week treatment arm and 6 (1.1%) in the 4-week treatment arm had an HIV RNA level ≥50 copies/mL, and 91% of those in the 8-week arm versus 90% in the 4-week arm achieved an HIV RNA level <50 copies/mL (see Table 1, below) [Jaeger, et al. 2021]. CAB/RPV LA was initially FDA-approved for monthly (every 4 weeks) maintenance dosing. Based on demonstrated safety and efficacy at 96 weeks, the FDA subsequently approved CAB/RPV LA for bimonthly (every 8 weeks) dosing and made the oral medication lead-in optional [FDA 2022].

Follow-up data from week 152 show that dosing every 8 weeks remains noninferior to dosing every 4 weeks, with 87% and 86% of participants, respectively, maintaining an HIV RNA level <50 copies/mL [Overton, et al. 2023].

Table 1: Viral Load at Weeks 48 and 96 of Maintenance Phase in the ATLAS, FLAIR, and ATLAS-2M Trials

	ATLAS (n = 308/308) [a]		**FLAIR** (n = 283/283) [b]		**ATLAS-2M** (n = 523/522) [c]	
HIV Viral Load	**CAB/RPV LA**	**Oral ART [d]**	**CAB/RPV LA**	**Oral ART [e]**	**CAB/RPV LA monthly**	**CAB/RPV LA bimonthly**
Week 48 HIV RNA <50 copies/mL	92.5%	95.5%	93.6%	93.3%	93%	94%
Week 48 HIV RNA ≥50 copies/mL	1.6%	1.0%	2.1%	2.5%	1.0%	2.0%
Week 96 HIV RNA <50 copies/mL	100% [f]	97% [f]	87%	89%	90.0%	91.0%
Week 96 HIV RNA ≥50 copies/mL	0% [g]	3%	3% [g]	3% [g]	1.0%	2.0%

Abbreviations: ART, antiretroviral therapy; CAB/RPV LA, long-acting injectable cabotegravir/rilpivirine; INSTI, integrase strand transfer inhibitor; NNRTI, nonnucleoside reverse transcriptase inhibitor; PI, protease inhibitor.

Notes:

a. Participants in ATLAS were aged 18 years or older, had received uninterrupted and unchanged ART with no virologic failure for 6 months before screening, and had an HIV RNA level of <50 copies/mL at screening and within 6 and 12 months before screening [Orkin, et al. 2020].
b. Participants in FLAIR were aged 18 years or older, ART naive, and had a plasma HIV RNA level of ≥1,000 copies/mL at screening [Swindells, et al. 2020].
c. [Jaeger, et al. 2021].
d. Participants continued their current daily PI-, NNRTI-, or INSTI-based oral regimens.
e. Daily oral dolutegravir/abacavir/lamivudine.
f. Extension phase of ATLAS study (n = 52) after discontinuations or roll-over to ATLAS-2M [Swindells, et al. 2022].
g. [Orkin, et al. 2021].

CAB/RPV LA in Virally Unsuppressed Individuals

→ KEY POINT

- Clinical recommendations to guide a change to long-acting injectable ART in patients who are not virally suppressed are available in the NYSDOH AI guideline Second-Line ART After Treatment Failure or for Regimen Simplification.

An off-label, nonrandomized study examined CAB/RPV LA use among patients with medication adherence challenges in a single safety-net clinic [Gandhi, et al. 2023]. The study population had high rates of unstable housing, substance use, and mental illness, and many participants had an unsuppressed HIV viral load when initiating or switching to CAB/RPV LA. The study enrolled 133 people with HIV who initiated CAB/RPV LA over an 18-month period. Participants were not required to have viral suppression at entry, had to commit to return every 4 weeks for injections, and had no RPV or INSTI RAMs (last criteria added after 2 emergent treatment failures); 38% of participants were Latinx, 16% were Black, and 14% were multiracial. Additionally, 8% were homeless and 58% were unstably housed, 100% were on government insurance, 38% had major mental illness, 43% were not virally suppressed (HIV RNA >30 copies/mL; median $\log_{10}$ HIV RNA 4.21), and 74% received on-time injections. After the switch to CAB/RPV LA, all of the 57% (n=76) of participants with viral suppression at initiation maintained it, and 96% of participants (55 of 57) who were not virally suppressed at initiation achieved viral suppression. At 48 weeks, 93% of participants who were initially unsuppressed had HIV viral loads <50 copies/mL [Hickey, et al. 2024]. Within the first 24 weeks, 2 virologic failures with resistance occurred before baseline resistance criteria were strengthened [Gandhi, et al. 2023]. The overall treatment failure rate was 1.5%, similar to those reported in the ATLAS and FLAIR studies. Per-protocol injections were delivered every 4 weeks, with the option to transition to every 8 weeks if viral suppression was achieved and maintained for 3 to 6 months [Hickey, et al. 2024]. Individuals with previously unsuppressed virus transitioning to every-8-week dosing of CAB/RPV LA may benefit from enhanced reminder calls and closer adherence support. This study addresses the minority population of people with HIV who have not achieved viral suppression with oral therapy but are the majority of those diagnosed with viremic HIV. Of note, CAB/RPV LA use in this study was accompanied by extensive case management, incentivization ($10 grocery vouchers for every-4-week dosing), social support, and outreach services with access to mental health and substance use wraparound services. The success of CAB/RPV LA in this population in the absence of comprehensive support services is unknown.

The results above were replicated in a small case series of 12 patients in Mississippi, all of whom were Black or Native American and 58% of whom were cisgender women. Mean viral load was 152,657 copies/mL, mean CD4 count was 233 cells/mm^3, 1 participant had a primary INSTI RAM (N155H), and all achieved viral suppression on CAB/RPV LA by month 3 with no viral rebound to >200 copies/mL on follow-up (1 to 17 months); 77 of 82 injection visits occurred within the dosing window [Brock, et al. 2024]. Similarly, in a study of 325 individuals with HIV initiating CAB/RPV LA in the New York City municipal health system, 17 with unsuppressed HIV (median baseline viral load of 21,045 copies/mL, range 390–152,997 copies/mL) achieved high rates of viral suppression (76% achieved viral load <200 copies/mL) despite a high prevalence of social barriers including housing instability, unemployment, financial needs, and lack of insurance [Gerber, et al. 2025].

The phase 3, randomized, multicenter, open-label ACTG A5359 study (LATITUDE), which included 434 people with HIV prescribed ART for at least 6 months who had viral loads >200 copies/mL at 2 time points at least 4 weeks apart or poor retention in care (2 missed appointments in 6 months or gap in medication of >7 days), compared CAB/RPV LA with continued standard of care (SOC) oral therapy [Rana, et al. 2024]. Participants received up to 24 weeks of incentive payments to promote achievement of viral suppression. Those who achieved viral loads <200 copies/mL (n= 294) after 4 weeks were randomized 1:1 to CAB/RPV (oral lead in for 4 weeks followed by monthly intramuscular injection) or continued SOC for 52 weeks. The incentives were not continued after randomization. The primary endpoint of regimen failure occurred in 28 participants (24.1%) in the CAB/RPV LA arm and 47 (38.5%) in the SOC arm, and the study was stopped by the Data and Safety Monitoring Board (DSMB) based on the finding of superiority of the CAB/RPV LA arm. Adverse effects were similar in both arms. Future studies to determine the need for viral suppression before initiating CAB/RPV LA in individuals facing adherence challenges with oral ART may be difficult to perform given the DSMB's assessment of the superiority of CAB/RPV LA in the LATITUDE study.

An off-label use of the 2-drug injectable combination of the capsid inhibitor lenacapavir (LEN) plus CAB with or without RPV has been described in a case series of 34 people with HIV who had challenges in maintaining adherence to oral ART [Gandhi, et al. 2024]. LEN was used with CAB/RPV in 68%, in individuals with INSTI-resistant virus, high body mass index, or high viral load. LEN was used with CAB alone in 32%, in individuals with documented or suspected NNRTI-resistant virus. At 8 weeks, HIV viral suppression <75 copies/mL had increased from 47% to 94% of participants. All participants with NNRTI-resistant virus were virally suppressed on LEN/CAB. The authors called for further investigation in a clinical trial. In a retrospective

review, 75 of 81 (93%) highly treatment-experienced individuals with HIV with viremia (9 with perinatally acquired HIV) achieved viral suppression after 1 to 2 injections of CAB/RPV alone (n = 56), CAB/RPV plus LEN (n = 23), or CAB/RPV plus LEN plus ibalizumab (n = 2) despite high rates of social needs [Colasanti, et al. 2025].

Modeling studies have shown that off-label use of long-acting injectable ART in the setting of unsuppressed viremia may be most beneficial to individuals with HIV who have low CD4 counts, especially those facing unremitting challenges to adherence, such as cognitive impairment, substance use, homelessness, mental illness, and lack of social support [Chen, et al. 2023]. Shared decision-making might include discussions focused on success, removing obstacles to treatment, and achievement of viral suppression rather than the burden of daily adherence to oral therapy.

Benefits, Potential Risks, and Limitations of CAB/RPV LA

☑ RECOMMENDATIONS

Patients for Whom CAB/RPV LA Is Not Recommended

- Clinicians should offer CAB/RPV LA as replacement ART for adults (aged ≥18 years) with HIV who are virally suppressed (HIV RNA level <50 copies/mL) and prefer an alternative to daily oral therapy. (A1)
- For patients who are not virally suppressed and have ongoing adherence challenges with oral ART (even with support) or are mechanically unable to ingest oral ART, the clinician should engage the patient in shared decision-making and offer monthly CAB/RPV LA, if susceptible, coupled with intensified follow-up support. (A2)
  - Once viral suppression is achieved and maintained, consider transition to every-8-weeks dosing. (A3)
- Before recommending a switch to CAB/RPV LA, clinicians should determine patients' HBV status (hepatitis B surface antigen, core antibody, and surface antibody tests, and HBV DNA test if indicated); CAB/RPV LA should not be recommended for patients with active HBV coinfection [a] without concurrent oral therapy for HBV. (A*)
- Clinicians should not recommend CAB/RPV LA in patients with known or suspected INSTI or NNRTI RAMs, excluding the K103N mutation in isolation, at baseline. (A1)
- Before recommending CAB/RPV LA, clinicians should review results of prior resistance testing and ART history, including all reasons for ART modification. (A3)
- Clinicians should obtain proviral DNA genotypic resistance testing that includes both the reverse transcriptase and integrase genes before switching to CAB/RPV LA in any patient for whom historical resistance test results are not available or if sustained viral suppression is not documented. (A2)
- Clinicians should not recommend treatment with CAB/RPV LA for patients who are pregnant or breast/chestfeeding, because of limited safety and efficacy data. (A*)

Abbreviations: ART, antiretroviral therapy; CAB, cabotegravir; CAB/RPV LA, long-acting injectable cabotegravir/rilpivirine; HBV, hepatitis B virus; INSTI, integrase strand transfer inhibitor; NNRTI, nonnucleoside reverse transcriptase inhibitor; RAM, resistance-associated mutation; RPV, rilpivirine.

Note:

a. Active HBV infection is defined as having a positive hepatitis B surface antigen or HBV DNA test result.

Benefits: Study participants have expressed high levels of satisfaction with injectable therapy in phase 2 and 3 trials. In the FLAIR trial, 257 of 283 (91%) participants who received CAB/RPV LA preferred it to their previous oral therapy [Orkin, et al. 2020]. In the ATLAS trial, 266 of 308 (86%) participants in the intention-to-treat exposed population preferred injectable therapy to daily oral therapy [Swindells, et al. 2020]. These data are consistent with participant preferences in the earlier LATTE-2 trial [Kerrigan, et al. 2018]. In the ATLAS-2M trial, 92% of participants preferred bimonthly injections of CAB/RPV LA over the oral regimen and the monthly dosing schedule [Chounta, et al. 2021]. Injectable therapy eliminates the need to take daily oral medications, may reduce any stigma associated with daily dosing, and may help patients maintain privacy regarding their HIV status. As both drugs are not renally cleared, they may be used in individuals with chronic renal disease (stage 4/5, creatinine clearance <30 mL/min) or on intermittent (3 times weekly) hemodialysis [Shon, et al. 2025].

Potential risks and limitations: Initiating injectable instead of oral antiretroviral medications requires shared decision-making and discussion of the benefits, limitations, and risks of injectable therapy (see Box 1, below).

Box 1: Summary of Benefits, Potential Risks, and Limitations of Long-Acting Injectable Cabotegravir and Rilpivirine [a]

Benefits:

- Improved patient satisfaction
- Monthly (every 4 weeks) or bimonthly (every 8 weeks) administration
- Directly observed
- Low rates of virologic failure (resistance can develop despite optimal adherence, but this is rare)
- Noninferior to oral antiretroviral therapy (ART)
- Potential option for patients who have ongoing substance use, mental health concerns, neurocognitive disorders, disclosure concerns, or other challenges associated with adherence to oral ART, including difficulty swallowing pills
- Removes the daily reminder of HIV status that is associated with taking pills
- Safe and efficacious in patients with chronic renal disease or on intermittent hemodialysis

Potential Risks:

- Injection site reactions and other adverse effects, including pyrexia
- Development of resistance if doses are missed outside the 7-day window period, given the long half-life ("tail") of CAB and RPV

Limitations:

- Cannot be used if a patient has prior resistance to integrase strand transfer inhibitors or nonnucleoside reverse transcriptase inhibitors, excluding the K103N mutation in isolation
- Limited data on use during pregnancy or breast/chestfeeding, in individuals with prior virologic failure, and in individuals with gluteal implants or soft tissue fillers
- Does not treat hepatitis B virus coinfection
- A 4-week oral lead-in of cabotegravir (CAB) and rilpivirine (RPV) may be used before the first injection to assess for unexpected reactions or allergies to CAB or RPV
- Requires oral medications as bridging therapy when injections are missed
- Medication storage requirements (2° C to 8° C [36° F to 46° F])
- Requires 6 to 12 in-person visits with a healthcare provider per year

Note:

a. [Orkin, et al. 2020; Swindells, et al. 2020; Margolis, et al. 2017; Margolis, et al. 2015]

Drug resistance: Existing NNRTI- and INSTI-associated drug resistance mutations may limit a patient's eligibility for CAB/RPV LA treatment. INSTI- and NNRTI-associated RAMs, except the K103N mutation in isolation, were exclusionary criteria in the ATLAS, FLAIR, and ATLAS-2M trials. In the FLAIR and ATLAS trials, 5 of the 7 participants who experienced virologic failure had HIV-1 subtype A1 and the integrase substitution L74I detected at baseline and upon failure [Orkin, et al. 2020; Swindells, et al. 2020]. The L74I mutation in other HIV subtypes, such as B, which is commonly seen in the United States, was not associated with virologic failure [Orkin, et al. 2020; Swindells, et al. 2020]. See the CAB/RPV LA package insert for other mutations commonly associated with CAB and RPV resistance [FDA 2022].

In a post-hoc multivariable analysis, baseline factors associated with confirmed virologic failure (CVF)—defined as 2 consecutive plasma HIV-1 RNA measurements ≥200 copies/mL—were investigated using pooled data from the ATLAS, FLAIR, and ATLAS-2M trials from 1,039 participants naive to CAB/RPV LA treatment [Cutrell, et al. 2021]. Virologic failure was confirmed in 13 participants. Proviral RPV RAMs, body mass index (BMI) ≥30 kg/m^2, and HIV-1 subtype A6/A1 were significantly associated with CVF; the presence of 2 of these factors concurrently was rare but was found in 9 of the 13 participants with CVF, and 1 participant had all 3. The L74I integrase polymorphism was commonly found among participants with CVF: 7 of these cases were associated with the A6/A1 HIV-1 subtype and 1 was associated with the HIV-1 C subtype. There were no cases of CVF among participants with both the L74I integrase polymorphism and HIV-1 B subtype, which was the most common subtype among participants, and 4 of the 13 participants with CVF had the HIV-1 B subtype alone, without the L74I integrase polymorphism [Cutrell, et al. 2021]. Further multivariable analysis through week 152 that included predicted CAB and RPV troughs confirmed that the strongest predictor of treatment failure for CAB/RPV LA was the presence of baseline RPV RAMs (adjusted incidence rate ratio [IRR], 25.7), followed by having HIV subtype A6/A1 (IRR, 15.5). The

analysis also found that having 2 or more factors (including BMI ≥30 kg/m^2) enhanced predictive sensitivity and specificity for risk of failure [Orkin, et al. 2023].

Similar findings were found in week 152 data from the ATLAS-2M trial itself [Overton, et al. 2023]. Among 13 participants with CVF (11 from the 8-week dosing arm and 2 from the 4-week dosing arm):

- CVF occurred in 10 participants by week 48, 6 of whom had at least 2 baseline factors (proviral RPV RAMs, HIV-1 subtype A6/A1, BMI ≥30 kg/m^2) associated with increased risk of virologic failure, and in the remaining 2 participants between weeks 96 and 152.
- There were no injection delays longer than 7 days.
- CAB and/or RPV RAMs were identified in 11 participants.
- Viral suppression was restored with oral ART in 12 participants; nonadherence to a protease inhibitor–based regimen was reported in the remaining 1 participant.

In the SOLAR study, in which 447 participants were randomized to switch from bictegravir/tenofovir alafenamide/emtricitabine (BIC/TAF/FTC) to CAB/RPV LA or continue BIC/TAF/FTC, 1 of 3 participants experiencing virologic failure had an INSTI RAM identified at baseline via proviral DNA sequencing [Rampgopal, et al. 2023].

In the CARES study, conducted in Africa, only 1 of 10 and 1 of 15 participants with RPV or CAB RAMS, respectively, identified on previral DNA genotypic testing developed confirmed virologic failure; however, virologic failure rates were higher than in participants without these RAMs, and the high rate of non-B HIV subtype virus in this population may have affected response [Kityo, et al. 2024]. These data are an outlier and require further confirmation before recommendations can be modified.

If oral bridging therapy is not taken when an injection of CAB/RPV LA is missed, the differing half-lives of CAB and RPV may result in the equivalent of HIV monotherapy and resistance may develop. After discontinuation of injectable therapy among participants in the LATTE-2 and ATLAS trials, the median half-lives of CAB and RPV were 6.4 weeks and 29.6 weeks, respectively, and measurable plasma levels of CAB or RPV were detected in participants for ≥1 year after final injections [Ford, et al. 2020]. Other prevention studies reported similar results. RPV persisted in plasma for up to 112 days in male and female participants in phase 1 trials and was detectable at 168 days after a 1,200 or 600 mg initial dose in female participants [McGowan, et al. 2016]. In a secondary analysis of CAB pharmacokinetic data from the HPTN 077 trial, 23% of male participants had detectable plasma CAB concentrations at 52 to 60 weeks after the final injection, and 13% had detectable CAB concentrations at week 76, compared with 63% and 42% of female participants, respectively. Median time from the last injection to CAB concentrations below the lower limit of quantification was 43.7 weeks for male participants and 67.3 weeks for female participants [Landovitz, et al. 2020].

Participants in the phase 3 ATLAS and FLAIR trials were required to take oral bridging therapy when ART injections occurred outside the recommended window period [Orkin, et al. 2020; Swindells, et al. 2020]. However, resistance to CAB/RPV has developed even in patients with optimal adherence (no missed injections). Among ATLAS participants who received CAB/RPV LA, virologic failure was confirmed in 3, the E138A RAM was found in 1, the E138K and V108I RAMs were found in 1, and the E138E/K and N155H RAMs were found in 1. None of these participants missed an injection or received injections outside the permitted window [Swindells, et al. 2020].

Adverse effects: Of participants receiving CAB/RPV LA in the ATLAS trial, 83% experienced injection site reactions [Swindells, et al. 2020]; however, 99% of these reactions were of mild or moderate severity. The most common reaction was pain, followed by nodules, induration, and swelling, generally beginning 1 day after injection and lasting 3 to 4 days. These reactions declined in incidence with subsequent injections. Similarly, in the FLAIR trial, the incidence of injection site reactions declined from 71% to 20% during the trial, and 4 of 238 participants receiving CAB/RPV LA withdrew because of injection site reactions [Orkin, et al. 2020]. The bimonthly (every 8 weeks) dose of CAB/RPV LA is higher than the monthly (every 4 weeks) dose. Through week 152 in the ATLAS-2M trial, 16% of participants in the 8-week dosing arm reported injection site reactions, with 2% discontinuing treatment as a result, compared with 11% in the 4-week arm, with 3% discontinuing treatment as a result [Overton, et al. 2023]. The number of injection site reactions declined through week 48 and remained stable thereafter. Counsel patients about possible discomfort from CAB/RPV LA injections, particularly with the initial doses, and discuss strategies to ameliorate these reactions if they occur.

Other possible adverse effects associated with CAB/RPV LA include pyrexia and elevations in liver function test results (aspartate aminotransferase, alanine aminotransferase, total bilirubin), creatine phosphokinase (8%, ≥10 × upper limit of normal [ULN]), and lipase (5%, ≥3 × ULN). Musculoskeletal pain and discomfort, nausea, sleep disorders, dizziness, and rash have also been reported [FDA 2022].

Weight gain has been associated with the use of INSTIs to treat HIV infection [Kanters, et al. 2022]. The SOLAR trial assessed weight gain at 12 months among participants on a suppressive oral regimen of BIC/TAF/FTC for at least 6 months who were randomized 2:1 to switch to CAB/RPV LA received every 2 months, with or without an oral lead-in, or to continue on BIC/FTC/TAF [Tan, et al. 2023]. There was no difference in weight gain, proportion of patients changing BMI categories, change in waist or hip circumference, or incidence of metabolic syndrome or insulin resistance. Of note, all participants were being switched from an INSTI-based regimen and any weight changes associated with use of agents in this drug class may have already occurred.

→ KEY POINT

- When engaging patients in informed decision-making regarding initiation of CAB/RPV LA, discuss the following:
  - Adherence requirements for monthly (every 4 weeks) or bimonthly (every 8 weeks) injections
  - Importance of using bridging oral therapy if injections are missed
  - Small risk of developing resistance even if adherence is optimal
  - Potential adverse effects, including injection site reactions; pyrexia; elevations in liver function test results, creatine phosphokinase, and lipase; musculoskeletal pain and discomfort; nausea; sleep disorders; dizziness; rash, and weight gain

Drug-drug interactions: Drugs that are contraindicated with CAB/RPV LA include the anticonvulsants carbamazepine, oxcarbazepine, phenobarbital, and phenytoin; the rifamycins rifabutin, rifampin, and rifapentine; dexamethasone (more than a single treatment); and St. John's Wort (*Hypericum perforatum*). These medications lower CAB and/or RPV drug levels and can be used after CAB/RPV LA has been discontinued. Macrolides other than azithromycin should not be coadministered. Refer to prescribing information for oral CAB and oral RPV for other drug interactions. Special attention should also be paid to over-the-counter medications and other supplements patients may be taking.

For more information on CAB and RPV drug-drug interactions, see the following tables in the NYSDOH AI resource Drug-Drug Interaction Guide: From HIV Prevention to Treatment:

- Table 1: Mechanisms of Antiretroviral Drug-Drug Interactions
- Table 6: Cabotegravir Interactions
- Table 11: Rilpivirine Interactions

Free online resources available to check specific drug-drug interactions include the University of Liverpool HIV Drug Interaction Checker.

Storage and administration: CAB/RPV LA must be refrigerated at 2° C to 8° C (36° F to 46° F) until ready to use. Before injection, the medication must be brought to room temperature for a minimum of 15 minutes and no longer than 6 hours. Once the 2 separate syringes have been prepared, CAB/RPV LA must be administered within 2 hours [FDA 2022]. CAB/RPV LA must be administered in an office, hospital, or pharmacy setting by a licensed healthcare professional, given the volume of the injections (intragluteal 2 × 3 mL loading dose and 2 × 2 mL maintenance dose), refrigeration requirements, and need to administer within 2 hours of syringe preparation. Monitoring is required for 10 minutes after a patient receives the injection. Medical institutions and clinicians will need to develop internal protocols for appropriate patient scheduling, staff availability and training, storage of injectable ART medications, and dispensing of oral CAB and RPV for lead-in and bridging periods. Significant preparation is necessary, including revising hospital and clinic formularies to include injectable CAB and RPV; designating hospital and clinic personnel, such as nurses and medical providers, to administer the medication; and establishing appropriate billing protocols for monthly or bimonthly injections.

Initiation, Maintenance, and Discontinuation of CAB/RPV LA as ART

☑ RECOMMENDATIONS

Administration

- CAB/RPV LA should be administered by a licensed and trained healthcare professional. (A*)
- To prepare and administer CAB/RPV LA, clinicians should follow the protocols detailed in Box 2: Preparation and Administration of Initial and Maintenance Doses of Injectable CAB/RPV LA and in the medication package inserts. (A1)

Dosing Strategy

- If an oral lead-in is chosen to assess medication tolerability, the clinician should prescribe up to 4 weeks of oral CAB/RPV. (A3)
- Once a dosing schedule is decided upon, clinicians should administer CAB/RPV LA as detailed in Table 2: Optional Lead-in, Initiation, and Maintenance for Monthly CAB/RPV LA Dosing or Table 3: Optional Lead-in, Initiation, and Maintenance for Bimonthly CAB/RPV LA Dosing; a bimonthly (every 8 weeks) dosing schedule is preferred. (A1)

Managing Missed Injections

- If a patient plans to miss or delay a monthly CAB/RPV LA injection by >7 days, the clinician should arrange for oral medication (CAB 30 mg and RPV 25 mg daily, or other active regimen) to be available in advance in an adequate supply (up to 2 months/8 weeks) to cover the gap in injections.
- Clinicians should resume CAB/RPV LA in patients who miss injections as detailed in the guideline section Managing Missed or Delayed Injections. (A3)

Discontinuing CAB/RPV LA

- Clinicians should discontinue CAB/RPV LA in patients with confirmed virologic failure (defined as 2 consecutive plasma HIV-1 RNA measurements ≥200 copies/mL) or evidence of INSTI or NNRTI RAMs, excluding the K103N mutation in isolation, on subsequent genotype testing. (A1)
- Clinicians should discontinue CAB/RPV LA in patients with evidence of INSTI or NNRTI RAMs (excluding the K103N mutation in isolation) on subsequent proviral DNA-based genotype testing (which may be performed for another clinical indication or following a viral blip), regardless of viral load suppression status, including an undetectable viral load (defined as plasma HIV-1 RNA measurement <50 copies/mL). (B3)
- When extended or frequent gaps occur between injections, resulting in prolonged periods of subtherapeutic drug concentrations, the risk of drug resistance increases; to avoid this risk, clinicians should encourage patients to adhere to the injection schedule and should switch to oral therapy for patients who cannot maintain the injection schedule. (A3)
- If CAB/RPV LA is discontinued, the clinician should initiate a fully suppressive oral ART regimen no later than 1 month (4 weeks) following the final CAB/RPV LA monthly injection or 2 months (8 weeks) following final CAB/RPV LA bimonthly injection. (A2)

Abbreviations: ART, antiretroviral therapy; CAB, cabotegravir; CAB/RPV LA, long-acting injectable cabotegravir/rilpivirine; INSTI, integrase strand transfer inhibitor; NNRTI, nonnucleoside reverse transcriptase inhibitor; RAM, resistance-associated mutation; RPV, rilpivirine.

CAB/RPV LA given as an intramuscular (IM) injection in the gluteal muscle is currently the only regimen for injectable ART.

Clinicians may consider a lead-in of oral CAB and RPV for up to 4 weeks before initiation of CAB/RPV LA after discussing the need for adherence to daily oral medications, potential adverse effects, and the plan to initiate the injections at week 4, on the last day of the oral lead-in (see Tables 2 and 3, below). In the extension phase of the FLAIR study, no difference in adverse events was identified between participants who completed an oral lead-in before initiating CAB/RPV LA and those who did not, and 99% of participants who did not receive an oral lead-in maintained viral suppression, compared with 93% who did receive an oral lead-in [Orkin, et al. 2021]. Omitting the oral lead-in simplifies treatment initiation, allows earlier access to injectable treatment, and removes the barrier of maintaining adherence to an oral dosing regimen.

Dosing Strategies

Tables 2, 3, and 4, below, present the approved dosing strategies for CAB/RPV LA, each of which may be preceded by the same 4-week oral medication lead-in, and the advantages and limitations of each dosing strategy. A prospective cohort study demonstrated that omitting the oral lead-in dosing made no difference in viral suppression rate or CAB/RPV trough levels among 176 individuals followed for 9 months [Fernández-González, et al. 2025]. Monthly and bimonthly dosing schedules are initiated with an IM injection administered on the last day of the oral medication lead-in (if used) or the last dose of a prior suppressive ART regimen. For the monthly (every 4 weeks) schedule, the initial IM dose is higher than the maintenance dose that begins at month 3 (week 12) and is administered every month (every 4 weeks) thereafter.

Table 2: Lead-in, Initiation, and Maintenance for Monthly (every 4 weeks) CAB/RPV LA Dosing [a]

Timing	Dosing and Administration	Comments
Week 0 (month 0)	CAB 30 mg/RPV 25 mg once daily by mouth with a meal for 4 weeks	Optional oral medication lead-in
Week 4 (month 1)	CAB 600 mg (3 mL)/RPV 900 mg (3 mL) IM injection	**Initiation dose:** Administer on last day of oral lead-in or prior suppressive ART regimen
Week 8 (month 2) and every 4 weeks (every 1 month) thereafter	CAB 400 mg (2 mL)/RPV 600 mg (2 mL) IM injection	**Maintenance dose:** Administer within 7 days before or after scheduled date (see Managing Missed or Delayed Injections in this guideline)

Abbreviations: ART, antiretroviral therapy; CAB, cabotegravir (Vocabria); CAB/RPV LA, long-acting injectable cabotegravir/rilpivirine (Cabenuva); IM, intramuscular; RPV, rilpivirine (Edurant).

Note:

a. [FDA 2022]

For a bimonthly dosing schedule, the first 2 IM injections are administered 4 weeks apart, and then bimonthly maintenance injections begin 3 months (12 weeks) after the initial IM dose, at the same dose as the initial injection.

Table 3: Lead-in, Initiation, and Maintenance for Bimonthly (every 8 weeks) CAB/RPV LA Dosing [a,b]

Timing	Dosing and Administration	Comments
Week 0 (month 0)	CAB 30 mg/RPV 25 mg once daily by mouth with a meal for 4 weeks	Optional oral medication lead-in
Week 4 (month 1)	CAB 600 mg (3 mL)/RPV 900 mg (3 mL) IM injection	**Initiation dose:** Administer on last day of oral lead-in or prior suppressive ART regimen
Week 8 (month 2)	CAB 600 mg (3 mL)/RPV 900 mg (3 mL) IM injection	**Maintenance dose:** Administer within 7 days before or after scheduled date (see Managing Missed or Delayed Injections in this guideline)
Week 16 (month 4) and every 8 weeks (every 2 months) thereafter	CAB 600 mg (3 mL)/RPV 900 mg (3 mL) IM injection	**Maintenance dose:** Administer within 7 days before or after scheduled date (see Managing Missed or Delayed Injections in this guideline)

Abbreviations: ART, antiretroviral therapy; CAB, cabotegravir (Vocabria); CAB/RPV LA, long-acting injectable cabotegravir/rilpivirine (Cabenuva); IM, intramuscular; RPV, rilpivirine (Edurant)..

Notes:

a. [ViiV Healthcare 2022]
b. [FDA 2022]

Table 4: Advantages and Limitations of CAB/RPV LA Dosing Strategies		
Advantage or Lmitation	**Monthly (every 4 weeks) Dosing**	**Bimonthly (every 8 weeks) Dosing**
Required annual visits	12	6
Injection site pain [a]	Less	More
CVF despite on-time dosing [b]	Rare	Rare
Risk of CAB and/or RPV RAMs if CVF [c]	Common	Common
Patient satisfaction [c,d]	High	Preferred
Staffing, administration time, and cost	More	Less

Abbreviations: CAB, cabotegravir; CAB/RPV LA, long-acting injectable cabotegravir/rilpivirine; CVF, confirmed virologic failure; RAM, resistance-associated mutation; RPV, rilpivirine.

Notes:

a. In the ATLAS-2M trial, 3% of participants in the monthly injection arm and 2% in the bimonthly injection arm discontinued treatment because of injection site pain [Overton, et al. 2023; Jaeger, et al. 2021].
b. In the ATLAS-2M trial, <1% of participants in the monthly injection arm and 2% in the bimonthly injection arm had CVF [Overton, et al. 2021].
c. [Overton, et al. 2021]
d. [Chounta, et al. 2021; Overton, et al. 2021]

Adherence requirement: Once the injection frequency is determined and a dosing schedule is planned, ensure the patient understands that to be adherent they must receive injections within 7 days of the scheduled date for each injection and the potential need to take oral CAB/RPV for up to 2 months (8 weeks) as bridging therapy if an injection is missed. It is reasonable to use the patient's previous suppressive oral ART regimen as a bridge if supplies are readily available and if it was well tolerated. Note the potential for drug-drug interactions if any of a patient's coadministered medications have been changed.

Injection preparation and administration: Box 2, below, provides guidance on preparing and administering the initial loading dose and ongoing maintenance doses of CAB/RPV LA. Administer maintenance doses of CAB/RPV LA within the recommended 7-day window period and with the same preparations outlined for the initial loading doses. Maintenance injections are administered at the same time at 2 different sites (i.e., gluteal injections on opposite sides or, if on the same side, 2 cm apart). Clinicians may choose to maintain laterality of medications throughout a patient's course of treatment by injecting CAB LA in the same gluteus medius muscle and RPV LA in the same contralateral gluteus medius muscle each time. Observe patients on site for at least 10 minutes after administering their initial loading dose in case of adverse reactions.

Box 2: Preparation and Administration of Initial and Maintenance Doses of Long-Acting Injectable Cabotegravir/Rilpivirine (CAB/RPV LA) [a]

1. Bring the vials [a] of CAB LA and RPV LA to room temperature for at least 15 minutes and for a maximum of 6 hours.
2. Prepare 2 syringes [a]. Once CAB/RPV LA has been drawn into the syringes, they must be used within 2 hours.
3. For aspiration, use a vial adaptor or general-use sterile 21 gauge × 1½ inch hypodermic needle [b]. Shake the vial vigorously for at least 10 seconds before aspiration.
4. For injection, use a general-use sterile 23 gauge × 1½ inch hypodermic needle [b]. Administer the injection within 2 hours of syringe preparation. A patient's build or body mass index may be considered when selecting an appropriate injection needle length.
5. Inject into the gluteus medius muscle [c] at a 90° angle, ventrogluteal (preferred) or dorsogluteal (upper-outer quadrant of the buttock), with care that the compound is not injected into a vein.

Notes:

a. The same preparation and administration are used for both initial and maintenance doses of CAB/RPV LA. Follow sterile technique at all points while preparing syringes and injecting compounds. Use 3 mL vials/syringes for the initial dose and 2 mL vials/syringes for maintenance doses.
b. The hypodermic needle must be long enough to inject the medication into the muscle mass without penetrating underlying nerves, blood vessels, or bone.
c. Inject CAB LA into the gluteus medius muscle and RPV LA into the contralateral gluteus medius muscle. Injections can be given on opposite sides or on the same side, 2 cm apart.

For more detail, see instructions for use in the CAB/RPV LA prescribing information [FDA 2022].

Managing Missed or Delayed Injections

Planned: If a patient plans to miss or delay a scheduled injection by >7 days, oral therapy (CAB 30 mg/RPV 25 mg, once daily with a meal) can be taken for up to 2 consecutive months (8 weeks). Alternatively, a patient's previous suppressive oral ART regimen may be considered as a bridge if it was well tolerated, with care to assess for potential drug-drug interactions with coadministered medications. Oral therapy should be started approximately 1 month (4 weeks) after the last injection of monthly CAB/RPV LA or 2 months (8 weeks) after the last bimonthly CAB/RPV LA injection and continued until the day on which injections are resumed [FDA 2022].

Unplanned, monthly (every 4 weeks) injection schedule: If a patient who is not taking oral bridging CAB/RPV misses a monthly injection by >7 days and will resume injectable therapy, restart injections as follows [FDA 2022]:

- If the patient's last injection was ≤2 months (≤8 weeks) prior, resume as soon as possible with a maintenance dose injection of CAB 400 mg (2 mL)/RPV 600 mg (2 mL) IM.
- If the patient's last injection was >2 months (>8 weeks) prior, resume as soon as possible with a high-dose injection of CAB 600 mg (3 mL)/RPV 900 mg (3 mL) IM once followed by monthly (every 4 weeks) maintenance dosing 400 mg (2 mL)/RPV 600 mg (2 mL) IM.

Unplanned, bimonthly (every 8 weeks) injection schedule: If a patient who is not taking oral bridging CAB/RPV misses an injection and will resume injectable therapy, restart injections as soon as possible: within 2 months (8 weeks) if the second initial injection was missed or within 3 months (12 weeks) if any other bimonthly maintenance injection was missed. If outside of those windows, a second dose should be administered 1 month (4 weeks) after reinitiation of injections, with subsequent return to bimonthly (every 8 weeks) dosing [FDA 2022; ViiV Healthcare 2022].

Discontinuing Injectable ART

Clinicians should recommend discontinuation of CAB/RPV LA when virologic failure (defined as confirmed plasma HIV viral load ≥200 copies/mL) occurs or if CAB- or RPV-associated RAMs are identified through current or historical genotypic or phenotypic resistance testing or proviral DNA genotypic resistance testing. In pooled data from the ATLAS, FLAIR, and ATLAS-2M trials, having at least 2 of the following factors was associated with virologic failure: HIV subtype A6/A1, a body mass index (BMI) ≥30 kg/m^2, low RPV trough levels at week 8, and the presence of RPV proviral genotypic RAMs [Cutrell, et al. 2021]. All but 1 of the participants with HIV subtype A6/A1 were from Russia; this subtype more commonly contains the L74I integrase gene polymorphism, which may facilitate treatment failure. The L74I polymorphism was not found in participants with HIV subtype B, which is the vastly predominant subtype in the United States. A separate analysis of baseline genotypic resistance testing of HIV-1 from 4,212 treatment-naive individuals from university clinics in Paris, France, found that 3.2% had virus with at least 1 CAB RAM (a rate that jumped to 16.2% if the L74I polymorphism was included) and 14.3% had RPV RAMs [Charpentier, et al. 2021]. Knowledge of these preexisting mutations may not be readily available when switching to CAB/RPV LA from a suppressive oral regimen. In post hoc analysis of data pooled from the FLAIR, ATLAS, ATLAS-2M, and SOLAR trials, participants who received CAB/RPV LA compared with oral therapy had similar rates of viral blips (single viral load measure between 50 and 199 copies/mL, 6% and 7%, respectively), low-level viremia (≥2 consecutive viral loads between 50 and 199 copies/mL, 1% each), single viral load >200 copies (<1% and 2%, respectively), and confirmed virologic failure (2 consecutive viral loads ≥200 copies/mL) after 1 year [Thornhill, et al. 2024]. Additional analyses of monthly and bimonthly dosing of CAB/RPV LA in the ATLAS-2M (week 152), FLAIR (week 96), and SOLAR (12 month) trials showed similar rates of viral blips and confirmed virologic failure across both dosing strategies compared with oral therapy [Latham, et al. 2024; Latham, et al. 2022]. These exploratory analyses support routine monitoring for virologic failure when CAB/RPV LA is initiated during virologic control in patients with no history of resistance.

Decreased drug exposure due to slower absorption rates of CAB LA and RPV LA has been associated with female sex and increased BMI [Ford, et al. 2014; Jackson, et al. 2014]; strict adherence to dosing schedules should be emphasized in these populations to prevent subtherapeutic drug levels. One study found lower CAB trough levels in individuals with higher BMIs and a trend toward lower levels in men and smokers, and lower RPV trough levels in smokers and younger individuals [Fernández-González, et al. 2025]. High interindividual variability and moderate intraindividual variability of CAB and RPV levels have been reported despite on-time dosing, which may account for unanticipated treatment failure, leading some investigators to advocate for therapeutic drug monitoring, although failure rates on CAB/RPV LA remain low [Sunagawa, et al. 2025].

The slow clearance and prolonged exposure of both CAB LA and RPV LA, which are the key features that underlie the success of the combination for intermittent dosing, become an Achilles heel when doses are missed or irregularly administered. The

clearance half-life ($t_{1/2}$) of CAB LA is estimated to be as long as 40 days, and detectable levels in some individuals can be measured for 1 year after final dosing [Spreen, et al. 2014]; the $t_{1/2}$ of RPV LA is as long as 90 days [Wensing, et al. 2025; Verloes, et al. 2015]. Therefore, during prolonged lapses in administration, not only would plasma levels of both drugs be expected to slowly drop below the inhibitory threshold but would also remain there for prolonged periods and would do so differentially, with RPV persisting longer and further enhancing the risk for selection of RAMs. CAB LA and RPV LA have relatively low barriers to resistance, in that selection of 1 or a few mutations would be adequate to reduce antiviral activity [Oliveira, et al. 2018]. It is therefore important for clinicians to support patient adherence to the selected dosing interval within a 7-day window and to manage delays with either oral bridging therapy or resumption of injections as quickly as possible. As data are lacking on the forgiveness of CAB/RPV LA in the face of delayed or irregular dosing before resistance selection becomes more likely, seeking guidance from an experienced HIV care provider may assist in decision-making regarding when discontinuation of the injectable regimen would be advisable.

If CAB/RPV LA is discontinued, a fully suppressive oral ART regimen that addresses the reason for discontinuation and any identified RAMs should be initiated as soon as possible but no later than 1 month (4 weeks) after the final injection for a monthly (every 4 weeks) CAB/RPV LA dosing schedule or 2 months (8 weeks) for a bimonthly CAB/RPV LA dosing schedule [FDA 2022].

Laboratory Testing and Patient Follow-Up

☑ RECOMMENDATION

Laboratory Testing and Monitoring

- Clinicians should perform baseline and routine monitoring of patients receiving injectable antiretroviral therapy (ART) according to the recommendations in the following NYSDOH AI guidelines (A3): Virologic and Immunologic Monitoring in HIV Care and Laboratory Monitoring for Adverse Effects of ART.

Genotypic testing: Before initiating ART with long-acting injectable cabotegravir/rilpivirine (CAB/RPV LA) in patients with a history of virologic failure or if there is clinical suspicion for integrase strand transfer inhibitor (INSTI) or nonnucleoside reverse transcriptase inhibitor (NNRTI) resistance, clinicians should obtain or review a baseline HIV-1 genotype test that includes the reverse transcriptase and integrase genes to rule out underlying resistance-associated mutations (RAMs). Because CAB/RPV LA is recommended only for individuals already taking a fully suppressive oral ART regimen, proviral DNA genotype testing is preferred at baseline. Of note, K103 mutations alone (i.e., without additional NNRTI RAMs) are not considered exclusionary for the use of injectable RPV. Virologic failure is defined as 2 HIV-1 RNA measurements ≥200 copies/mL after an initial undetectable viral load or as HIV RNA ≥200 copies/mL after 24 weeks of adherent ART. All genotypic testing (baseline and while on treatment) should include the reverse transcriptase and integrase genes. Confirmed resistance to CAB or RPV at any time is grounds for discontinuing injectable ART and switching to an oral regimen that is compatible with the patient's resistance profile.

Abnormal laboratory test results were reported in phase 3 trials of CAB/RPV LA. Five participants in the long-acting therapy group of the ATLAS trial had elevations of alanine aminotransferase to a minimum of 3 times the upper limit of normal; however, hepatitis A virus infection was diagnosed in 3 of the 5 participants, hepatitis B virus infection in 1, and hepatitis C virus infection in 1 [Swindells, et al. 2020]. An elevated lipase level (grade 4) was reported in 1 participant in the FLAIR trial (for additional laboratory abnormalities, see guideline section Benefits, Potential Risks, and Limitations of CAB/RPV LA > Adverse effects) [Orkin, et al. 2020].

Monitoring for adverse effects: Of patients receiving CAB/RPV LA, 80% to 86% have reported injection site reactions involving pain, nodules, induration, swelling, or pruritus [Orkin, et al. 2020; Swindells, et al. 2020; Markowitz, et al. 2017]. Before initiation of CAB/RPV LA, education and counseling can prepare patients for adverse effects, which typically occur early in treatment, and reassure them that any ongoing adverse reactions are likely to diminish in frequency and intensity. Management of injection site reactions will depend on the severity but may include application of cold or warm packs, massage of the affected area, and application of a topical corticosteroid for pruritus. A severe adverse reaction may require clinical evaluation. A review of best practices to reduce injection site reactions included slowing the speed of the intramuscular push, having the medication come to room temperature before injection, asking the patient to relax the gluteus muscle before injection, checking landmarks to ensure proper injection location, using cold packs, using over the counter pain medications, and keeping activity light after injection [Teichner, et al. 2024].

Other reported adverse effects in the ATLAS and FLAIR phase 3 trials included pyrexia (7% and 8%, respectively), fatigue (7% in ATLAS), headache (11% and 14%, respectively), nausea (6% in FLAIR), and diarrhea (7% and 11%, respectively) [Orkin, et al. 2020; Swindells, et al. 2020].

→ GOOD PRACTICE

- Follow up by phone within 1 week after initiation of oral therapy lead-in, if used, and within 3 days after a patient receives the initial loading dose of injectable ART to assess the patient's tolerance.

Implementing CAB/RPV LA in Clinical Practice

Initiation of injectable antiretroviral therapy (ART) requires institutional, clinician, and patient preparation, as detailed in Box 3, below. Each institution or medical practice will have to address preparation and implementation in the context of their internal procedures and policies.

Box 3: Institutional, Clinician, and Patient Preparations for Implementation of Injectable Antiretroviral Therapy

Institutional and Clinician Preparations

- Assess pharmacy resources and on-site procedures for storage of oral and injectable medications.
- Train nurses and other medical care providers regarding proper syringe preparation and injection techniques.
- Establish billing protocols for the procurement and administration of injectable antiretroviral therapy (ART) medications.
- Implement a system to remind patients of appointments.
- Plan for treatment continuation in the event of shutdowns or other catastrophic events.
- Provide education on the use of oral bridging therapy.
- Educate patients about possible adverse effects associated with long-acting injectable cabotegravir/rilpivirine and how to manage them.
- Ensure that patients know how to reach a medical care provider if needed.
- Schedule administration appointments in advance.

Patient Preparations

- Obtain prior authorizations for insurance or third-party coverage of ART medications.
- Confirm ability to maintain required clinic visit schedule for injections, including transportation availability, adhere to the injection regimen, and tolerate 2 large-volume intramuscular injections regularly.

Storage requirements, including temperature regulation, security, and bookkeeping, may be a significant obstacle for some institutions. Billing protocols for longitudinal follow-up and injections will have to be established, including appropriate current procedural terminology codes, international classification of diseases (ICD)-10 diagnoses, and electronic medical record documentation. Patient scheduling and reminder systems will have to be developed before starting patients on an indefinite course of injectable ART to maximize staff time and resources. In addition, wait times should be minimized and attention given to individual patient needs regarding work schedules, available time off, parking, and transportation needs.

Along the same lines, contingency plans should be in place in case a clinic becomes unable to provide injections, with attention to resources for oral therapy to bridge periods when patients may miss injections. Patients will also need traditional counseling and education about HIV and ART adherence (see NYSDOH AI guidelines Selecting an Initial ART Regimen > Specific Factors to Consider and Discuss With Patients and Rapid ART Initiation > Counseling and Education Before Initiating ART). Specific concerns regarding travel to clinic appointments and accessing oral bridging therapy in the event of an emergency should be addressed as soon as possible.

Patients should also be advised about the potential for injection site reactions and other adverse effects described in earlier sections of the guideline.

All Recommendations

☑ ALL RECOMMENDATIONS: USE OF INJECTABLE CAB/RPV LA AS REPLACEMENT ART IN VIRALLY SUPPRESSED ADULTS

Patients for Whom CAB/RPV LA Is Not Recommended

- Clinicians should offer CAB/RPV LA as replacement ART for adults (aged ≥18 years) with HIV who are virally suppressed (HIV RNA level <50 copies/mL) and prefer an alternative to daily oral therapy. (A1)
- For patients who are not virally suppressed and have ongoing adherence challenges with oral ART (even with support) or are mechanically unable to ingest oral ART, the clinician should engage the patient in shared decision-making and offer monthly CAB/RPV LA, if susceptible, coupled with intensified follow-up support. (A2)
  - Once viral suppression is achieved and maintained, consider transition to every-8-weeks dosing. (A3)
- Before recommending a switch to CAB/RPV LA, clinicians should determine patients' HBV status (hepatitis B surface antigen, core antibody, and surface antibody tests, and HBV DNA test if indicated); CAB/RPV LA should not be recommended for patients with active HBV coinfection [a] without concurrent oral therapy for HBV. (A*)
- Clinicians should not recommend CAB/RPV LA in patients with known or suspected INSTI or NNRTI RAMs, excluding the K103N mutation in isolation, at baseline. (A1)
- Before recommending CAB/RPV LA, clinicians should review results of prior resistance testing and ART history, including all reasons for ART modification. (A3)
- Clinicians should obtain proviral DNA genotypic resistance testing that includes both the reverse transcriptase and integrase genes before switching to CAB/RPV LA in any patient for whom historical resistance test results are not available or if sustained viral suppression is not documented. (A2)
- Clinicians should not recommend treatment with CAB/RPV LA for patients who are pregnant or breast/chestfeeding, because of limited safety and efficacy data. (A*)

Administration

- CAB/RPV LA should be administered by a licensed and trained healthcare professional. (A*)
- To prepare and administer CAB/RPV LA, clinicians should follow the protocols detailed in Box 2: Preparation and Administration of Initial and Maintenance Doses of Injectable CAB/RPV LA and in the medication package inserts. (A1)

Dosing Strategy

- If an oral lead-in is chosen to assess medication tolerability, the clinician should prescribe up to 4 weeks of oral CAB/RPV. (A3)
- Once a dosing schedule is decided upon, clinicians should administer CAB/RPV LA as detailed in Table 2: Optional Lead-in, Initiation, and Maintenance for Monthly CAB/RPV LA Dosing or Table 3: Optional Lead-in, Initiation, and Maintenance for Bimonthly CAB/RPV LA Dosing; a bimonthly (every 8 weeks) dosing schedule is preferred. (A1)

Managing Missed Injections

- If a patient plans to miss or delay a monthly CAB/RPV LA injection by >7 days, the clinician should arrange for oral medication (CAB 30 mg and RPV 25 mg daily, or other active regimen) to be available in advance in an adequate supply (up to 2 months/8 weeks) to cover the gap in injections.
- Clinicians should resume CAB/RPV LA in patients who miss injections as detailed in the guideline section Managing Missed or Delayed Injections. (A3)

Discontinuing CAB/RPV LA

- Clinicians should discontinue CAB/RPV LA in patients with confirmed virologic failure (defined as 2 consecutive plasma HIV-1 RNA measurements ≥200 copies/mL) or evidence of INSTI or NNRTI RAMs, excluding the K103N mutation in isolation, on subsequent genotype testing. (A1)
- Clinicians should discontinue CAB/RPV LA in patients with evidence of INSTI or NNRTI RAMs (excluding the K103N mutation in isolation) on subsequent proviral DNA-based genotype testing (which may be performed for another clinical indication or following a viral blip), regardless of viral load suppression status, including an undetectable viral load (defined as plasma HIV-1 RNA measurement <50 copies/mL). (B3)

☑ ALL RECOMMENDATIONS: USE OF INJECTABLE CAB/RPV LA AS REPLACEMENT ART IN VIRALLY SUPPRESSED ADULTS

- When extended or frequent gaps occur between injections, resulting in prolonged periods of subtherapeutic drug concentrations, the risk of drug resistance increases; to avoid this risk, clinicians should encourage patients to adhere to the injection schedule and should switch to oral therapy for patients who cannot maintain the injection schedule. (A3)
- If CAB/RPV LA is discontinued, the clinician should initiate a fully suppressive oral ART regimen no later than 1 month (4 weeks) following the final CAB/RPV LA monthly injection or 2 months (8 weeks) following final CAB/RPV LA bimonthly injection. (A2)

Laboratory Testing and Monitoring

- Clinicians should perform baseline and routine monitoring of patients receiving injectable ART according to the recommendations in the following NYSDOH AI guidelines (A3): Virologic and Immunologic Monitoring in HIV Care and Laboratory Monitoring for Adverse Effects of ART.

Abbreviations: ART, antiretroviral therapy; CAB, cabotegravir; CAB/RPV LA, long-acting injectable cabotegravir/rilpivirine; HBV, hepatitis B virus; INSTI, integrase strand transfer inhibitor; NNRTI, nonnucleoside reverse transcriptase inhibitor; RAM, resistance-associated mutation; RPV, rilpivirine.

Note:

a. Active HBV infection is defined as having a positive hepatitis B surface antigen or HBV DNA test result.

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Supplement: Guideline Development and Recommendation Ratings

Table S1: Guideline Development: New York State Department of Health AIDS Institute Clinical Guidelines Program	
Developer	New York State Department of Health AIDS Institute (NYSDOH AI) Clinical Guidelines Program
Funding source	NYSDOH AI
Program manager	Clinical Guidelines Program, Johns Hopkins University School of Medicine, Division of Infectious Diseases. See Program Leadership and Staff.
Mission	To produce and disseminate evidence-based, state-of-the-art clinical practice guidelines that establish uniform standards of care for practitioners who provide prevention or treatment of HIV, viral hepatitis, other sexually transmitted infections, and substance use disorders for adults throughout New York State in the wide array of settings in which those services are delivered.
Expert committees	The NYSDOH AI Medical Director invites and appoints committees of clinical and public health experts from throughout New York State to ensure that the guidelines are practical, immediately applicable, and meet the needs of care providers and stakeholders in all major regions of New York State, all relevant clinical practice settings, key New York State agencies, and community service organizations.
Committee structure	• Leadership: AI-appointed chair, vice chair(s), chair emeritus, clinical specialist(s), JHU Guidelines Program Director, AI Medical Director, AI Clinical Consultant, AVAC community advisor • Contributing members • Guideline writing groups: Lead author, coauthors if applicable, and all committee leaders
Disclosure and management of conflicts of interest	• Annual disclosure of financial relationships with commercial entities for the 12 months prior and upcoming is required of all individuals who work with the guidelines program, and includes disclosure for partners or spouses and primary professional affiliation. • The NYSDOH AI assesses all reported financial relationships to determine the potential for undue influence on guideline recommendations and, when indicated, denies participation in the program or formulates a plan to manage potential conflicts. Disclosures are listed for each committee member.
Evidence collection and review	• Literature search and review strategy is defined by the guideline lead author based on the defined scope of a new guideline or update. • A comprehensive literature search and review is conducted for a new guideline or an extensive update using PubMed, other pertinent databases of peer-reviewed literature, and relevant conference abstracts to establish the evidence base for guideline recommendations. • A targeted search and review to identify recently published evidence is conducted for guidelines published within the previous 3 years. • Title, abstract, and article reviews are performed by the lead author. The JHU editorial team collates evidence and creates and maintains an evidence table for each guideline.
Recommendation development	• The lead author drafts recommendations to address the defined scope of the guideline based on available published data. • Writing group members review the draft recommendations and evidence and deliberate to revise, refine, and reach consensus on all recommendations. • When published data are not available, support for a recommendation may be based on the committee's expert opinion. • The writing group assigns a 2-part rating to each recommendation to indicate the strength of the recommendation and quality of the supporting evidence. The group reviews the evidence, deliberates, and may revise recommendations when required to reach consensus.

Table S1: Guideline Development: New York State Department of Health AIDS Institute Clinical Guidelines Program	
Review and approval process	• Following writing group approval, draft guidelines are reviewed by all contributors, program liaisons, and a volunteer reviewer from the AI Community Advisory Committee. • Recommendations must be approved by two-thirds of the full committee. If necessary to achieve consensus, the full committee is invited to deliberate, review the evidence, and revise recommendations. • Final approval by the committee chair and the NYSDOH AI Medical Director is required for publication.
External reviews	• External review of each guideline is invited at the developer's discretion. • External reviewers recognized for their experience and expertise review guidelines for accuracy, balance, clarity, and practicality and provide feedback.
Update process	• JHU editorial staff ensure that each guideline is reviewed and determined to be current upon the 3-year anniversary of publication; guidelines that provide clinical recommendations in rapidly changing areas of practice may be reviewed annually. Published literature is surveilled to identify new evidence that may prompt changes to existing recommendations or development of new recommendations. • If changes in the standard of care, newly published studies, new drug approval, new drug-related warning, or a public health emergency indicate the need for immediate change to published guidelines, committee leadership will make recommendations and immediate updates and will invite full committee review as indicated.

Table S2: Recommendation Ratings and Definitions		
Strength	**Quality of Evidence**	
A: Strong B: Moderate C: Optional	1	Based on published results of at least 1 randomized clinical trial with clinical outcomes or validated laboratory endpoints.
	*	Based on either a self-evident conclusion; conclusive, published, in vitro data; or well-established practice that cannot be tested because ethics would preclude a clinical trial.
	2	Based on published results of at least 1 well-designed, nonrandomized clinical trial or observational cohort study with long-term clinical outcomes.
	2†	Extrapolated from published results of well-designed studies (including nonrandomized clinical trials) conducted in populations other than those specifically addressed by a recommendation. The source(s) of the extrapolated evidence and the rationale for the extrapolation are provided in the guideline text. One example would be results of studies conducted predominantly in a subpopulation (e.g., one gender) that the committee determines to be generalizable to the population under consideration in the guideline.
	3	Based on committee expert opinion, with rationale provided in the guideline text.