WARD 86 LONG-ACTING ANTIRETROVIRAL TREATMENT (ART) GUIDELINES

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WARD 86 HIV CLINIC: Ward 86, established in January 1983, is a large HIV clinic based at San Francisco General Hospital at the University of California, San Francisco (UCSF). The approval of long-acting injectable antiretroviral treatment (ART) with cabotegravir and rilpivirine in 2021 provided a novel treatment strategy for HIV. The approval of lenacapavir for highly treatment experienced patients with HIV in December 2022 has allowed Ward 86 and other centers to use this third long-acting medication when indicated. This protocol describes procedures developed at Ward 86 to use long acting ART for the treatment of HIV infection in our Special Program on Long-Acting Antiretrovirals to Stop HIV (SPLASH) program. We have been providing long-acting ART for patients at Ward 86 since 2021, publishing our findings, and the below protocol describes our procedures in SPLASH

Ward 86
Special Program on Long-Acting Antiretrovirals to Stop HIV

PURPOSE OF THIS GUIDELINE

- Provide guidance to clinicians on long-acting injectable cabotegravir/rilpivirine (CAB/RPV LA) and lenacapavir (LEN) for their patients, even for those with adherence challenges and viremia
- Establish a workflow for referral, initiation, and management of patients starting CAB/RPV LA and LEN
- Provide guidance to clinicians on education to patients who will receive CAB/RPV LA and LEN LA
- Provide guidance on care coordination, including clinic appointments and follow ups, for patients on CAB/RPV LA and LEN

WARD 86 LONG-ACTING ART PROTOCOL

The following details Ward 86's protocol on initiating CAB/RPV LA for ART in patients with HIV

BACKGROUND

CAB/RPV LA is an injectable prescription medicine to treat HIV-1 infection in adults. CAB/RPV LA contains two different medications: *cabotegravir*, an integrase strand transfer inhibitor (INSTI) and *rilpivirine*, a non-nucleoside reverse transcriptase inhibitor (NNRTI). CAB/RPV LA is administered as intramuscular (IM) gluteal injection only and must be administered by a licensed health care

professional. On March 24, 2022, the FDA changed the CAB/RPV LA injection, labeling to take out the need for oral lead-in dosing with cabotegravir 30mg daily and rilpivirine 25mg daily. Ward 86 does not recommend the oral lead-in for CAB/RPV LA and uses the direct-to-inject approach.

Although LA CAB/RPV was originally studied in trials enrolling participants with virologic suppression (Orkin NEJM 2020; Swindells NEJM 2020; Overton Lancet 2021), demonstration projects such as ours at Ward 86 have shown great benefits to starting LA CAB/RPV among those with viremia. Therefore, patients who have detectable HIV viral loads should not be excluded from CAB/RPV LA therapy considerations per data from Ward 86 and other centers (Gandhi Annals of Internal Medicine July 2023; Hickey CID 2024; Spinelli JAMA 2025; Colasanti CID 2025; Hsu IAS 2025; Brock CID 2024; Mehtani JAIDS 2024). Moreover, CAB/RPV LA therapy should be considered for patients with adherence challenges, even without viremia (Rana NEJM 2025; Creswell IAS 2025)

Given accumulating data on the use of LA CAB/RPV among people with HIV with viremia in demonstration projects, including the one at Ward 86, the major U.S. guidelines to treat HIV now support the use of LA CAB/RPV in PWH with viremia (DHHS Panel on Antiretroviral Guidelines for Adults and Adolescents 2024; Sax PE. Updated Treatment Recommendation on Use of Cabotegravir and Rilpivirine for People With HIV. JAMA 2024). Indeed, our data contributed to modeling that LA ART among those with viremia will enhance virologic suppression rates and decrease mortality (Chen OFID 2023; Pei CID 2025)

WARD 86 CAB/RPV LONG-ACTING PROTOCOLS

The following are Ward 86 recommendations for clinicians initiating CAB/RPV LA in patients with HIV infection. Ward 86 recommends:

- Starting all adult and adolescent patients with HIV viral suppression on every 8-week (Q 8-week) injection dosing schedule).
- For adult and adolescent patients with HIV VL >200 copies/mL, Ward 86 recommends starting an every 4-week (Q 4-week) injection dosing schedule of CAB/RPV LA. This should continue until viral suppression is achieved for at least two injection cycles at Q 4-weeks prior to considering a switch to an every 8-week (Q 8-week) injection dosing schedule.

CLINICAL CONSIDERATIONS AND RECOMMENDATIONS FOR STARTING PATIENTS ON CAB/RPV LA THERAPY

GENERAL CONSIDERATIONS AND RECOMMENDATIONS PRIOR TO INITIATING LA ART

- Patient expresses willingness and demonstrates ability to attend regularly scheduled appointments to receive CAB/RPV LA injections.
- Patient demonstrates understanding of CAB/RPV LA administration and expresses willingness to receive two injections in the gluteal muscles each administration visit according to schedule.
- Patient understands and agrees to take a fully suppressive oral antiretroviral regimen if CAB/RPV LA therapy is interrupted.
- Patient has a reliable phone number(s), and/or other consistent means of communication, and provides additional method of contact, such as family member(s), friend(s), or case manager.

- Patients who have detectable HIV viral loads should be started on CAB/RPV LA therapy
- Patients who have chronic hepatitis B (HBV) infection should not be considered for CAB/RPV LA therapy except in select cases where patients who have a detectable HIV viral load and HBV co-infection are unable to attain HIV viral suppression due to adherence challenges to oral antiretroviral therapy (ART). For these patients, however, additional HBV treatment will be required.
- Provider should ensure current Hepatitis B status is updated by sending HepBsAb, HepBsAg, HepBcAb within the last 6 months if not performed.
    - If isolated Hep B core Ab (+) and Hep B surface Ab (-), patient should receive hepatitis B vaccination.
    - If Hep B core Ab (-) and Hep B surface Ab (-), patient should receive hepatitis B vaccination
    - Long-acting ART programs can be a forum in which to enhance Hepatitis B vaccination (Ochieng OFID 2025)

Ward 86 Recommendations for Hepatitis B screening with LA CAB/RPV, vaccination

HbS Ag (+) or HBV DNA (+): Treat with HBV-active ART (Tenofovir or add on Entecavir)

	HBsAb (-)	HBsAb (+)
HB Core Ab (+) RISK OF REACTIVATION	- HBV DNA (+): Don't switch (if possible) & offer oral HBV active ART if feasible - HBV DNA (-): Shared decision-making regarding possible risk - Consider risk of flare when *withdrawing* TAF/TDF, 3/FTC - Vaccinate	Risk of reactivation low, shared decision-making re possible reactivation risk
HB Core Ab (-)	- Vaccinate with full HBV series (Heplisav x2, may need 3^{d} shot) - Ok to start dual therapy at time of vax initiation - PCP to check s Ab response	Proceed to switch

*If **core Ab (+)** & no HBV-active ART,* follow LFTs regularly & low threshold to check HBV DNA if LFTs↑

Ward 86 Recommendations for Determining Whether Clinically Significant RPV or CAB Mutations are Present to Preclude Use of CAB-LA or RPV-LA

- Patients who have a history of known or suspected drug resistance that would compromise CAB/RPV LA therapy should not be considered for CAB/RPV LA therapy.
    - **Which mutations does Ward 86 consider significant in compromising CAB or RPV?** Mutations which emerge among virologic failures in studies examining CAB/RPV LA: Patients with virus with any NNRTI mutations or INSTI mutations that could compromise

either RPV or CAB in past genotypes should not be started on the long-acting regimen. Ward 86 has decided on the mutations which we will exclude based on which rilpivirine or cabotegravir resistance associated mutations were associated with virologic failures in multiple trials or observational studies of LA CAB/RPV, including FLAIR, ATLAS, ATLAS 2M (the registrational trials for CAB/RPV); the Ward 86 SPLASH program; the CARES trial in low-and-middle-income countries (96 week data); and the SOLAR study (switching from BIC/TAF/FTC to CAB/RPV LA). We also examined mutations which emerged among virologic failures on CAB/RPV in Canavesi HIV Glasgow 2024; D'Amico HIV Medicine 2022; Gagliardini HIV Glasgow 2024; Colasanti CID 2025; and other smaller studies. The Table of all the mutations associated with emergent virologic failures on CAB/RPV is available from Ward 86 on request.
Other mutations considered for RPV: The Echo/Thrive trials studied rilpivirine versus efavirenz for first-line therapy in treatment naïve patients. We also examined those trials to consider mutations with virologic failures on RPV
Other mutations considered for CAB: The HPTN 083 study examined long-acting CAB every 8 weeks for HIV prevention and there was emergent CAB-associated mutations with virologic breakthroughs in this study. These CAB mutations were also considered in our list of clinically significant mutations in the Table below

- Putting all these mutations together, we have generated the list of mutations in the Table below that we consider clinically significant based on the definitions above. We will not start CAB/RPV LA alone if these clinically significant mutations were seen in a historical or current HIV RNA genotype
- Of note, Ward 86 does not consider mutations seen in Archive resistance testing or HIV DNA sequencing for the consideration of the use of CAB/RPV LA

List of mutations in HIV RNA genotype considered clinically significant for RPV or CAB to exclude from using CAB/RPV LA alone
RPV: L100I, K101E/P/Q, E138A/G/K/Q/R, Y181C/I, Y188L, H221Y, P225H, F227C, M230L
CAB: T97A, G118R, Q148H/K/R/S, E138A/K, G140A/R/S, N155H, R263K

- Patients who have a known hypersensitivity to *cabotegravir* or *rilpivirine* should not be considered for CAB/RPV LA therapy.
- Patients who are currently taking the following medications should not be considered for CAB/RPV LA therapy due to potential for decreased drug levels of *cabotegravir* or *rilpivirine*:
  - Anticonvulsants: *carbamazepine, oxcarbazepine, phenobarbital, phenytoin*
  - Antimycobacterials: *rifabutin, rifampin, rifapentine*
  - Systemic glucocorticoids: more than short-term use of *dexamethasone*
  - Herbal: *St John's Wort*
- Note: If patient has BMI >30 kg/m2, the injection should be administered with a longer needle (e.g., 2-inch IM needle).
- Finally, based on data from our and other centers showing that viral load blips to >50 copies/mL and <200 copies/mL are common and do not have consequences for the development of viral resistance, we now consider an HIV RNA level of <200 copies/mL as being suppressive on LA ART with intervention occurring if the HIV RNA level is ≥200 copies/mL.

INJECTION DOSING RECOMMENDATIONS AT INITIATION, MAINTENANCE, AND WITH INJECTION DELAYS

Injection Dosing Recommendations:

Table 1: Recommended Q 8-Weeks CAB/RPV LA IM Injection Dosing Schedule in Adults

Drug	**Intramuscular (Gluteal) Initiation Injection Dosing (Two doses 4-weeks apart)**	**Intramuscular (Gluteal) Maintenance Injection Dosing (Every 8 weeks) (Start 8 weeks after initiation doses)**
Cabotegravir	600 mg (3 mL)	600 mg (3 mL)
Rilpivirine	900 mg (3 mL)	900 mg (3 mL)

Table 2: Recommended Q 4-Weeks CAB/RPV LA IM Injection Dosing Schedule in Adults

Drug	**Intramuscular (Gluteal) Initiation Injection Dosing (Q 4-Weeks Initiation Dosing)**	**Intramuscular (Gluteal) Maintenance Injection Dosing (Q 4-Weeks Maintenance Dosing)**
Cabotegravir	600 mg (3 mL)	400 mg (2 mL)
Rilpivirine	900 mg (3 mL)	600 mg (2 mL)

Table 3: Dosing Recommendation When Switching from Q 4-Weeks to Q 8-Weeks CAB/RPV LA IM Injection Dosing Schedule in Adults

Drug	**Initial Injection Dosing at Switch to Q 8-Weeks Dosing (Q 8-Weeks Initiation Dosing)**	**Maintenance Injection Dosing (Q 8-Weeks Maintenance Dosing)**
Cabotegravir	600 mg (3 mL)	600 mg (3 mL)
Rilpivirine	900 mg (3 mL)	900 mg (3 mL)

Recommended Response to Missed CAB/RPV LA Doses:

Recommended Responses to Unplanned Missed CAB/RPV LA Doses
If a patient misses a scheduled CAB/RPV LA dose, a local response, such as an active outreach to patient, should be initiated immediately. If patient is not reachable directly, patient's listed contacts should be contacted. If patient and contacts are not reachable, prescribing medical provider should be alerted and a care plan for patient's return to care is recommended.

If CAB/RPV LA Q 4-weeks injection is missed or delayed by more than seven days from scheduled dosing, and oral therapy has not been taken in the interim, prescribing medical provider should clinically

reassess the patient to determine if resumption of CAB/RPV LA injection dosing remains appropriate. The patient should be started on a fully suppressive oral antiretroviral regimen as soon as possible.

Table 4: Recommended Response to Late or Missed Doses for Adults on Q 4-Weeks CAB/RPV LA IM Injection Dosing Schedule

Time Since Scheduled Dosing	**Recommended Actions**
8-14 days after scheduled injection	• **Administer Q 4-Weeks Maintenance CAB/RPV LA dose (400mg/600mg) IM** • Obtain HIV VL (rapid resulting preferred) • Schedule patient to return to clinic/practice next day ▪ If HIV VL is detectable, obtain HIV genotype and start patient on DRV/c/FTC/TAF until genotype results become available
15-30 days or longer after scheduled injection	• **Administer Q 4-Weeks Initiation CAB/RPV LA dose (600mg/900mg) IM** (followed by same dose 4 weeks later for re-induction) • Obtain HIV VL (rapid resulting preferred) • Schedule patient to return to clinic/practice next day ▪ If HIV VL is detectable, obtain HIV genotype and start patient on DRV/c/FTC/TAF until genotype results become available

Table 5: Recommended Response to Late or Missed Doses for Adults on Q 8-Weeks CAB/RPV LA IM Injection Dosing Schedule and are late for q28day initiation schedule

Note: The following recommendation applies when a patient misses second q28day initiation scheduled dose.	
Time Since Scheduled Dosing	**Recommended Actions**
8-14 days after scheduled injection	• **Administer Q 8-Weeks Initiation CAB/RPV LA dose (600mg/900mg) IM** • Obtain HIV VL (rapid resulting preferred) • Continue to follow Q 8-weeks injection dosing schedule (*see* Table 2)

15-30 days after scheduled injection	• **Administer Q 8-Weeks Initiation CAB/RPV LA dose (600mg/900mg) IM**
	• Obtain HIV VL (rapid resulting preferred)
	• Schedule patient to return to clinic/practice next day
	  ▪ If HIV VL is detectable, obtain HIV genotype and start patient on DRV/c/FTC/TAF until genotype results become available
	  ▪ If HIV VL is undetectable, administer Q-8 Weeks Initiation CAB/RPV LA dose (600mg/900mg) IM 4 weeks

	later and continue to follow Q 8-week injection dosing schedule (*see* Table 2)

Table 6: Recommended Response to Late or Missed Doses for Adults on Q 8-Weeks CAB/RPV LA IM Injection Dosing Schedule

Note: The following recommendations applies when a patient misses third, or subsequent, scheduled Q 8-weeks doses.	
Time Since Scheduled Dosing	**Recommended Actions**
10-14 days after scheduled injection*	• **Administer Q 8-Weeks Initiation CAB/RPV LA dose (600mg/900mg) IM** • Obtain HIV VL (rapid resulting preferred) • Continue to follow Q 8-weeks injection dosing schedule (*see* Table 2)
15-30 days or later after scheduled injection°	• **Administer Q 8-Weeks Initiation CAB/RPV LA dose (600mg/900mg) IM** • Obtain HIV VL (rapid resulting preferred) ▪ If HIV VL is undetectable, administer Q-8 Weeks Initiation CAB/RPV LA dose (600mg/900mg) IM 4 weeks later and continue to follow Q 8-week injection dosing schedule (*see* Table 1)

*Modelling data of missed cabotegravir and rilpivirine injections suggests that an interval of 30 days past scheduled injection is sufficient. However, to be conservative, Ward 86 allows an interval that is shorter by 14 days

Recommended Responses to Planned Missed CAB/RPV LA Doses

If a patient plans to miss a scheduled CAB/RPV LA dose by more than seven days, the patient should be given a fully suppressive oral antiretroviral regimen to replace injection. The following recommendations should be considered:

1. The first dose of a fully suppressive oral antiretroviral regimen should be started on planned next injection visit date. Oral antiretroviral regimen should be continued until the patient resumes scheduled CAB/RPV LA dosing.
2. Follow recommended actions in Tables 4-6 above for resuming treatment with CAB/RPV LA.

Recommendations Regarding Discontinuation of CAB/RPV LA Therapy

When CAB/RPV LA therapy is to be discontinued, the patient should be transitioned to a fully suppressive oral antiretroviral regimen. Oral regimen should be initiated the day they are due for the next injection.

Example Process for Internal Referral Workflow, CAB/RPV LA Therapy Initiation, Documentation, CAB/RPV LA Storage and Handling at Ward 86 (which has the EPIC medical record system):

See Appendix A

Manufacturer's Instructions for Handling and Management of CAB/RPV LA Therapy

See Appendix B

CLINICAL CONSIDERATIONS AND RECOMMENDATIONS FOR USING LENACAPAVIR (LEN) IN COMBINATION WITH CAB-LA ± RPV-LA

Cumulative experience and studies have reinforced that, for the majority of people with HIV, maintaining two fully active drugs can control active virus and maintain suppression. CAB-LA/RPV is the only combination regimen that has received FDA approval the treatment of HIV. However, ongoing concerns remain regarding the prevalence of underlying NNRTI resistance associated mutations (RAMs) in the general population of people with HIV given that efavirenz-based regimens were first-line for a number of years. Retrospective analyses of data from participants with virologic failure in the ATLAS, ATLAS-2M, and FLAIR trials found that underlying RPV RAMS were associated with a 30.23 (95% CI: 6.25->99) hazard ratio (HR) of failure [Cutrell AIDS 2021].

Lenacapavir is the only alternative FDA approved LA ART agent (excluding ibalizumab, which requires intravenous administration and more frequent administration at twice monthly) indicated for patients with multi-drug resistant (MDR) HIV-1 when combined with an optimized regimen. LEN-LA is the only approved long-acting agent that could be combined with CAB-LA ± RPV-LA for a potentially effective LA ART regimen for individuals with—or concerns for—NNRTI resistance and challenges to adherence to oral ART. This combination has yet to be studied, but providers in the U.S. have begun to obtain LA LEN through insurance programs and combine it with LA CAB (+/- RPV) off-label for select patients with adherence challenges if clinically indicated

In a case series compiled from four US academic medical centers, 34 participants with adherence challenges were prescribed LA LEN subcutaneously every 26 weeks with CAB-LA (+/- LA RPV) every 4-8 weeks (Gandhi OFID 2024). Twenty-one participants had documented or suspected NNRTI mutations and 18/34 (53%) were not suppressed at baseline. After starting LA LEN therapy, 32/34 (94%) achieved virologic suppression at a median of 8 (4-16) weeks. All 21 participants with documented or suspected NNRTI mutations (10 without viral suppression at baseline) maintained or achieved viral suppression (Gandhi 2024). The demonstration from this case series suggests that the combination of LA LEN+CAB seems to have preliminary effectiveness and supports further trials of this regimen, which are being planned in the Advancing Clinical Therapeutics Globally (ACTG) clinical trials network.

Based on this accumulating data, Ward 86 has been using a combination of LEN and CAB LA in patients with NNRTI resistance at Ward 86. Moreover, if there is a minor RPV-associated mutation, a minor CAB-associated mutation, interest in rapidly suppressing viral load (e.g. in the context of pregnancy), or persistent low-level viremia, we will use LEN + CAB/RPV LA together.

Ward 86 recently compiled data from the first 50 patients started on LEN in our center. Overall, 50 participants starting LA LEN from March 2023-May 2025 were included in the analyses: 92% were on LA

ART (31 on LEN/CAB and 15 on LEN + CAB/RPV) and 8% (4/50) were on LEN with an oral backbone. For the 62% on LEN/CAB only, the CAB was administered every 8 weeks. Documented baseline NNRTI resistance was high (70%), and baseline INSTI resistance low (10%). Beyond resistance, reasons for initiating LEN included slow viral decay (8%), persistent low-level viremia (6%) or injection site reactions on CAB/RPV (2%). Roughly half (44%) of the PWH in this series had virologic suppression when initiating LEN. Among those with a viral load >50 copies/mL prior to initiating LEN (56%), all (100%) achieved virologic suppression with a median time to virologic suppression of 29 days.

RECOMMENDED INITIATION AND MAINTENANCE DOSING FOR LENACAPAVIR

Dosing Schedule

Initiation	
Day 1	927 mg subcutaneous injection (2 x 1.5 mL injections) AND 600 mg orally (2 x 300 mg tablets)
Day 2	600 mg orally (2 x 300 mg tablets)
Continuation	
927 mg subcutaneous injection (2 x 1.5 mL injections) every 26 weeks +/- 2 weeks (can give every 24 weeks to synchronize with CAB dosing since CAB is given every 8 weeks)	

Missed Oral Dose

If Day 2 initiation dose of LEN (600mg) is missed, it should be taken as soon as possible.

See Appendix C for manufacturer's instructions on LEN administration

RECOMMENDATIONS FOR MANAGEMENT OF MISSED LEN-LA DOSES

RECOMMENDED RESPONSES TO UNPLANNED MISSED LEN LA DOSES

If more than 28 weeks have elapsed since last injection, follow initiation dosing schedule

APPENDIX A: EXAMPLE PROCESS FOR INTERNAL REFERRAL WORKFLOW FOR CAB/RPV LA THERAPY INITIATION WITH DOCUMENTATION

Internal Referral Workflow and CAB/RPV LA Therapy Initiation

- Referral is placed to Ward 86 Pharmacy staff via email, staff message, or electronic health record (Epic) documentation (telephone encounter)
- Standardized questionnaire, including specific questions about current and past HIV antiretroviral regimen(s), HIV resistance history, and patient's HBV status, is sent to referring medical provider to complete
- Once standard questionnaire is completed by referring medical provider, Clinical Pharmacist reviews clinical criteria, including HIV treatment and resistance history.
- Outcome of referral is documented in Epic
  - If patient does not meet clinical criteria, referring medical provider is notified of outcome
  - If a patient meets criteria, Pharmacy Team initiates insurance coverage query
    - CAB/RPV LA to be billed as a pharmacy benefit
- Clinical Pharmacist reaches out to patient to review CAB/RPV LA
- If direct to inject, patient is scheduled for CAB/RPV LA initiation injection
- If patient is to receive oral lead-in, it is ordered from Theracom Pharmacy and sent to patient or clinic, based on patient preference

<u>CAB/RPV Oral Lead-in Follow Up (if performed)</u>

- Telephone visit with Clinical Pharmacist is scheduled within a week post start of oral lead-in to assess adherence and tolerability
  - If intolerant or non-adherent to oral lead-in treatment, referring medical provider will be alerted and CAB/RPV LA initiation injection will not be scheduled
  - If patient tolerates oral lead-in and demonstrates adherence to regimen CAB/RPV LA initiation dose is ordered by the Clinical Pharmacist

<u>Ordering CAB/RPV LA Initiation Injection</u>

- For Q 8-weeks injections, CAB/RPV LA 600-900mg x 1 dose initiation prescription is sent to pharmacy and ordered as clinic administered medication.
    - Clinic administered medication is ordered to be administered on planned injection visit date
  - Once the initial dose has been administered, and pharmacist has reviewed with patient that they tolerated the first injection, the clinic administered medication will be ordered as:
    - CAB/RPV LA 600-900mg inject every 8 weeks to start 28 days after first injection.
  - Pharmacy Team schedules CAB/RPV LA initiation injection appointment in Ward 86 Injection Clinic (INJECTION) template
    - Appointment will be scheduled as:
      - Visit type "INJECTION"
      - With "CAB/RPV LA 600-900 **Initiation** Inj" in appointment notes
    - The following labs will be obtained on day of CAB/RPV LA initiation injection:

- HIV VL,
- Pharmacy Team contacts patient by phone the day before injection appointments
- If patient has BMI >30 kg/m^2, the injection should be administered with a longer needle (e.g., 2-inch IM needle).

CAB/RPV Initiation Injection Follow Up

- Telephone visit is scheduled within seven days of patient receiving CAB/RPV initiation injection to assess for tolerability
- If patient tolerates treatment and patient is on Q 8-weeks injection dosing:
  - CAB/RPV LA 600-900mg maintenance prescription is sent to pharmacy and ordered as clinic administered medication on a Q 8-week cycle
  - Pharmacy staff schedules a future appointment on a 56-day cycle
  - Appointment is scheduled as
    - Visit type "INJECTION"
    - With "CAB/RPV LA 600-900mg **q8-week** Inj" in notes
  - Patient will have HIV VL testing repeated at each injection visit for the first year:
  - After the first year of LA CAB/RPV, HIV VL testing will be performed every other administration visit (e.g. every 4 months)
  - Patients may be given CAB/RPV LA up to seven days before or after the date the patient is scheduled to receive Q 8-weeks injections (i.e., subsequent dose is to be within 49-63 day window)
  - Primary care provider will assess patient one month after first injection and at minimum every three months for six months following initiation

Documentation and Tracking

- Documentation will be conducted in Epic using developed smartphrases
- A list of patients on active CAB/RPV LA therapy will be maintained in Epic for ongoing monitoring and management
- Once a month, the SPLASH team will clinically review patients on CAB/RPV LA therapy to monitor clinical status, including potential for virologic failures and adverse effects
- Pharmacy Team maintains a list of patients who are on CAB/RPV LA therapy, ensures that future appointments and labs are scheduled appropriately, and conducts reminder calls to patients for all CAB/RPV LA related appointments
- Pharmacy Team coordinates CAB/RPV LA inventory and ensures CAB/RPV LA is available prior to injection appointments

Storage, Handling, and Administration

- See below manufacturer instructions (Appendix B)
- Note: If patient has BMI >30 kg/m^2, the injection should be administered with a longer needle (e.g., 2-inch IM needle).

APPENDIX B: STORAGE, HANDLING AND ADMINISTRATION (MANUFACTURER INSTRUCTIONS FOR CAB/RPV LA)

INSTRUCTIONS FOR USE

CABENUVA
(kab' en ue vah)

Cabotegravir extended-release injectable suspension
400 mg/2 mL (200 mg/mL)

co-packaged with

Rilpivirine extended-release injectable suspension
600 mg/2 mL (300 mg/mL)

For gluteal intramuscular use only.

Healthcare Professional administration only.

Overview:

A complete dose of CABENUVA requires two injections: 400 mg (2 mL) of cabotegravir and 600 mg (2 mL) of rilpivirine.

Cabotegravir and rilpivirine are suspensions that do not need further dilution or reconstitution.

The preparation steps for both medicines are the same.

Cabotegravir and rilpivirine are for gluteal intramuscular use only. Each injection must be administered to separate gluteal intramuscular sites (on opposite sides or at least 2 cm apart). The administration order is not important.

Note: The ventrogluteal site is recommended.

Storage information

- Store in refrigerator at 2°C to 8°C (36°F to 46°F)

Do not freeze.

Prior to administration:

- Before preparing the injections, the vials may sit in the carton at room temperature (maximum temperature of 25°C [77°F]) for up to 6 hours. If not used within 6 hours, the medication must be discarded.
- Once the medicines have been drawn into the syringe, the medication can remain in the syringes for up to 2 hours before injecting. If 2 hours are exceeded, the medication, syringes, and needles must be discarded.
- It is recommended to label the syringe with the time that the medication has been drawn into the syringe if the medication is not administered immediately.

INSTRUCTIONS FOR USE

CABENUVA
(kab' en ue vah)

Cabotegravir extended-release injectable suspension
600 mg/3 mL (200 mg/mL)

co-packaged with

Rilpivirine extended-release injectable suspension
900 mg/3 mL (300 mg/mL)

For gluteal intramuscular use only.

Healthcare Professional administration only.

Overview:

A complete dose of CABENUVA requires two injections: 600 mg (3 mL) of cabotegravir and 900 mg (3 mL) of rilpivirine.

Cabotegravir and rilpivirine are suspensions that do not need further dilution or reconstitution.

The preparation steps for both medicines are the same.

Cabotegravir and rilpivirine are for gluteal intramuscular use only. Each injection must be administered to separate gluteal intramuscular sites (on opposite sides or at least 2 cm apart). The administration order is not important.

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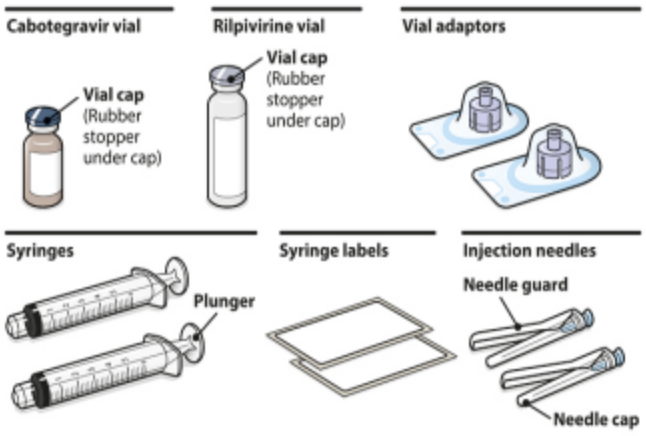
- Once the medicines have been drawn into the syringe, the medication can remain in the syringes for up to 2 hours before injecting. If 2 hours are exceeded, the medication, syringes, and needles must be discarded.
- It is recommended to label the syringe with the time that the medication has been drawn into the syringe if the medication is not administered immediately.



Your pack contains:

- 1 vial of Cabotegravir
- 1 vial of Rilpivirine
- 2 vial adaptors
- 2 syringes
- 2 syringe labels
- 2 injection needles (23 gauge, 1½ inch)

Consider the patient's build and use medical judgment to select an appropriate injection needle length.

You will also need:

- Non-sterile gloves
- 4 alcohol wipes
- 4 gauze pads
- A suitable sharps container

Preparation:

1. Inspect both vials.

Figure A

- Check that the expiration date has not passed. **See Figure A.**
- Inspect the vials immediately. If you can see foreign matter, do not use the product.

Note: The Cabotegravir vial has a brown tint to the glass.

Do not use if the expiration date has passed.

2. Wait 15 minutes.

Figure B

- Wait at least 15 minutes before you are ready to give the injection to allow the medication to come to room temperature. **See Figure B.**

3. Shake the vial vigorously.

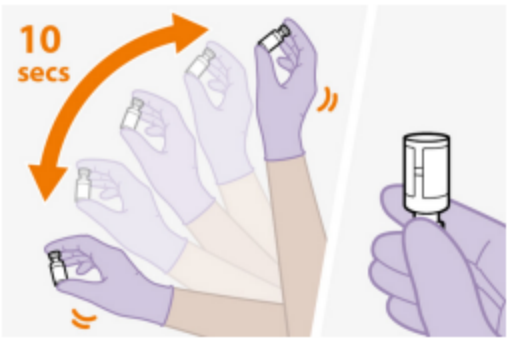


Figure C

- Hold the vial firmly, and vigorously shake for a full 10 seconds. **See Figure C.**
- Invert the vial and confirm the suspension is uniform.
- If the suspension is not uniform, shake the vial again.
- It is also normal to see small air bubbles.

4. Remove the vial cap.

Figure D

- Remove the cap from the vial. **See Figure D.**
- Wipe the rubber stopper with an alcohol wipe.

Do not allow anything to touch the rubber stopper after wiping it.

5. Peel open the vial adaptor.

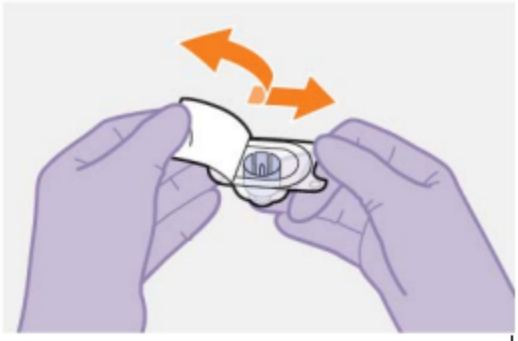


Figure E

- Peel off the paper backing from the vial adaptor packaging. **See Figure E.**

Note: Keep the adaptor in place in its packaging for the next step.

6. Attach the vial adaptor.

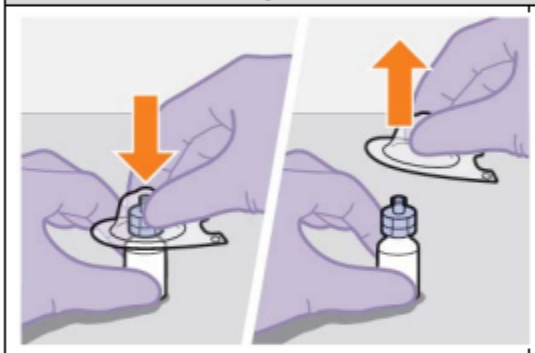


Figure F

- Press the vial adaptor straight down onto the vial using the packaging, as shown.
  The vial adaptor should snap securely into place.
- When you are ready, lift off the vial adaptor packaging as shown.

See Figure F.

7. Prepare the syringe.

Figure G

- Remove the syringe from its packaging.
- Draw 1 mL of air into the syringe. This will make it easier to draw up the medicine later. **See Figure G.**

8. Attach the syringe.

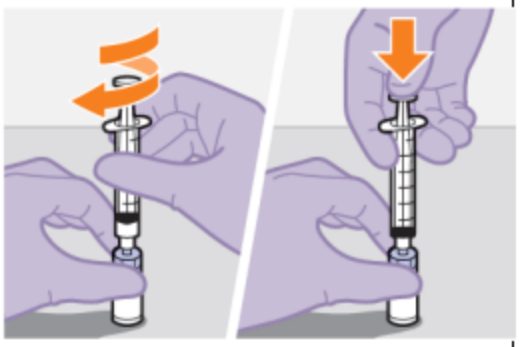


Figure H

- Hold the vial adaptor and vial firmly, as shown.
- Screw the syringe firmly onto the vial adaptor.
- Press the plunger all the way down to push the air into the vial.

See Figure H.

9. Slowly draw up the dose.

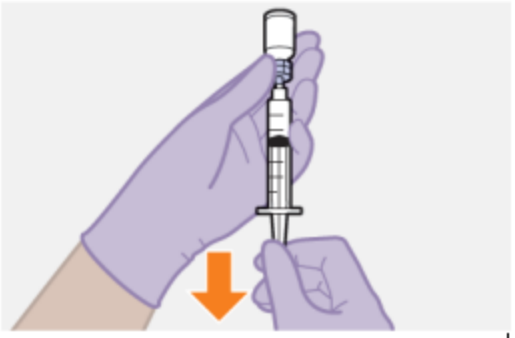


Figure I

- Invert the syringe and vial and slowly withdraw as much of the medicine as possible into the syringe. There may be more medicine than the dose amount. **See Figure I.**

10. Unscrew the syringe.

Figure J

- Unscrew the syringe from the vial adaptor, holding the vial adaptor as shown.

See Figure J.

Note: Keep the syringe upright to avoid leakage. Check that the suspension looks uniform and milky white.

11. Attach the needle and affix syringe label.

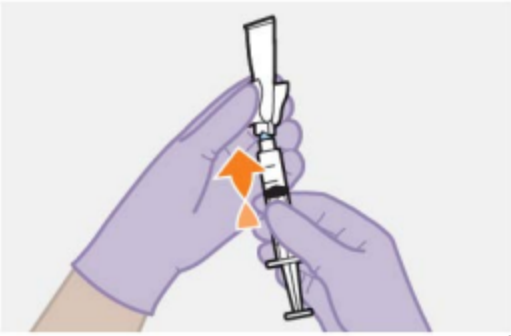


Figure K

- Peel open the needle packaging part way to expose the needle base.
- Keeping the syringe upright, firmly twist the syringe onto the needle.
- Remove the needle packaging from the needle.
- Write the name of the medicine on the syringe label. Affix the label to the syringe making sure the gradations remain visible.

See Figure K.

Injection:

12. Prepare the injection site.

Figure L

Injections must be administered to the gluteal sites. **See Figure L.**

Select from the following areas for the injection:

- Ventrogluteal, as shown (recommended)
- Dorsogluteal (upper outer quadrant)

Note: For gluteal intramuscular use only. **Do not** inject intravenously.

13. Remove the cap.

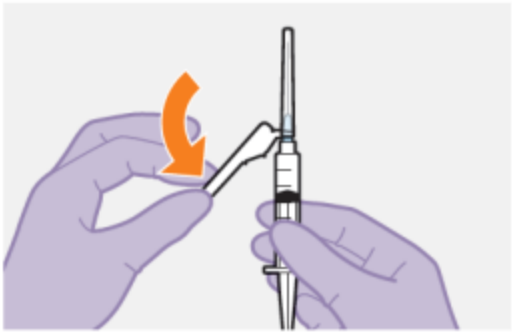


Figure M

- Fold the needle guard away from the needle. **See Figure M.**
- Pull off the injection needle cap.

14. Remove extra liquid from the syringe.

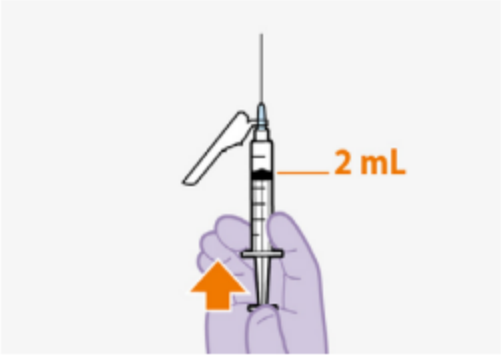


Figure N

- Hold the syringe with the needle pointing up. Press the plunger to the 2-mL dosing mark to remove extra liquid and any air bubbles. **See Figure N.**

Note: Clean the injection site with an alcohol wipe. Allow the skin to air dry before continuing.

15. Stretch the skin.

Figure O

Use the z-track injection technique to minimize medicine leakage from the injection site.

- Firmly drag the skin covering the injection site, displacing it by about an inch (2.5 cm). **See Figure O.**
- Keep it held in this position for the injection.

16. Insert the needle.

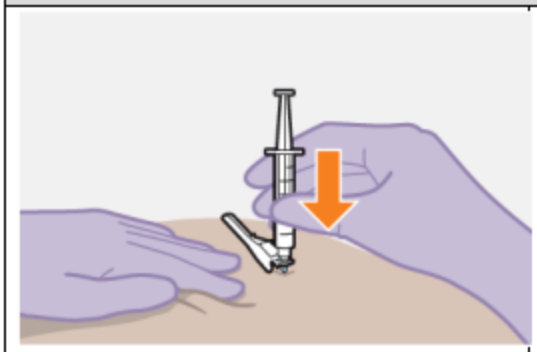


Figure P

- Insert the needle to its full depth, or deep enough to reach the muscle. **See Figure P.**

17. Inject the dose of medicine.

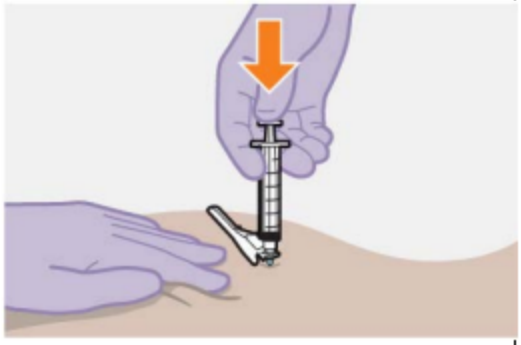


Figure Q

- Still holding the skin stretched – slowly press the plunger all the way down. **See Figure Q.**
- Ensure the syringe is empty.
- Withdraw the needle and release the stretched skin immediately.

18. Assess the injection site.

Figure R

- Apply pressure to the injection site using a gauze pad. **See Figure R.**
- A small bandage may be used if bleeding occurs.

Do not massage the area.

19. Make the needle safe.

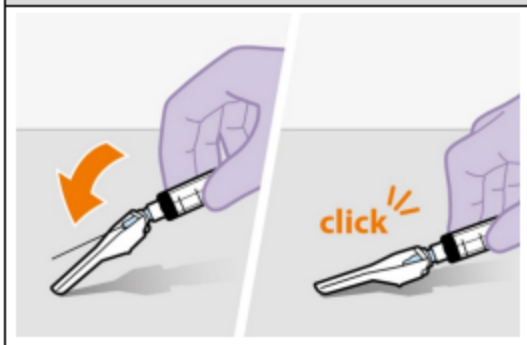


Figure S

- Fold the needle guard over the needle.
- Gently apply pressure using a hard surface to lock the needle guard in place.
- The needle guard will make a click when it locks.

See Figure S.

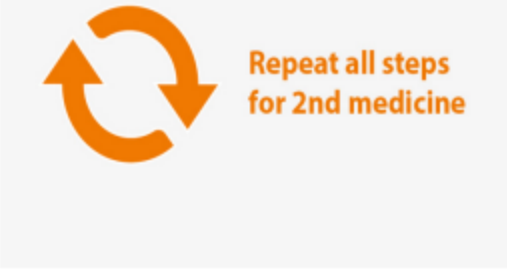
After injection:

20. Dispose safely.

Figure T

- Dispose of used needles, syringes, vials, and vial adaptors according to local health and safety laws. **See Figure T.**

Repeat for 2nd medicine.



- If you have not yet injected both medicines, use the same steps for preparation and injection of the other medicine.
- The second medicine must be injected into a separate gluteal intramuscular site (on opposite sides or at least 2 cm apart).

Questions and Answers

1. How long can the medicine be left out of the refrigerator?

It is best to inject the medicine as soon as it reaches room temperature. However, the vials may sit in the carton at room temperature (maximum temperature of 25°C [77°F]) for up to 6 hours. If not used within 6 hours, the medication must be discarded.

2. How long can the medicine be left in the syringe?

It is best to inject the (room temperature) medicine as soon as possible after drawing it up. However, the medication can remain in the syringe for up to 2 hours before injecting.

If 2 hours are exceeded, the medication, syringes, and needles must be discarded.

3. Why do I need to inject air into the vial?

Injecting 1 mL of air into the vial makes it easier to draw up the medicine into the syringe. Without the air, some liquid may flow back into the vial unintentionally, leaving less medicine than intended in the syringe.

4. Does the order in which I give the medicines matter?

No, the order is unimportant.

5. Is it safe to warm the vials up to room temperature more quickly?

It is best to let the vials come to room temperature naturally. However, you can use the warmth of your hands to speed up the warm-up time, but make sure the vials do not get above 25°C (77°F).

Do not use any other heating methods.

Manufactured for:

ViiV Healthcare

ViiV Healthcare
Research Triangle Park, NC 27709

by:
GlaxoSmithKline
Research Triangle Park, NC 27709

CBN:1IFU2

This Instructions for Use has been approved by the U.S. Food and Drug Administration. Issued: 01/2021

APPENDIX C: STORAGE, HANDLING AND ADMINISTRATION (MANUFACTURER INSTRUCTIONS FOR LEN LA)

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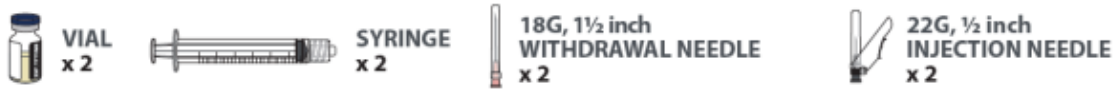
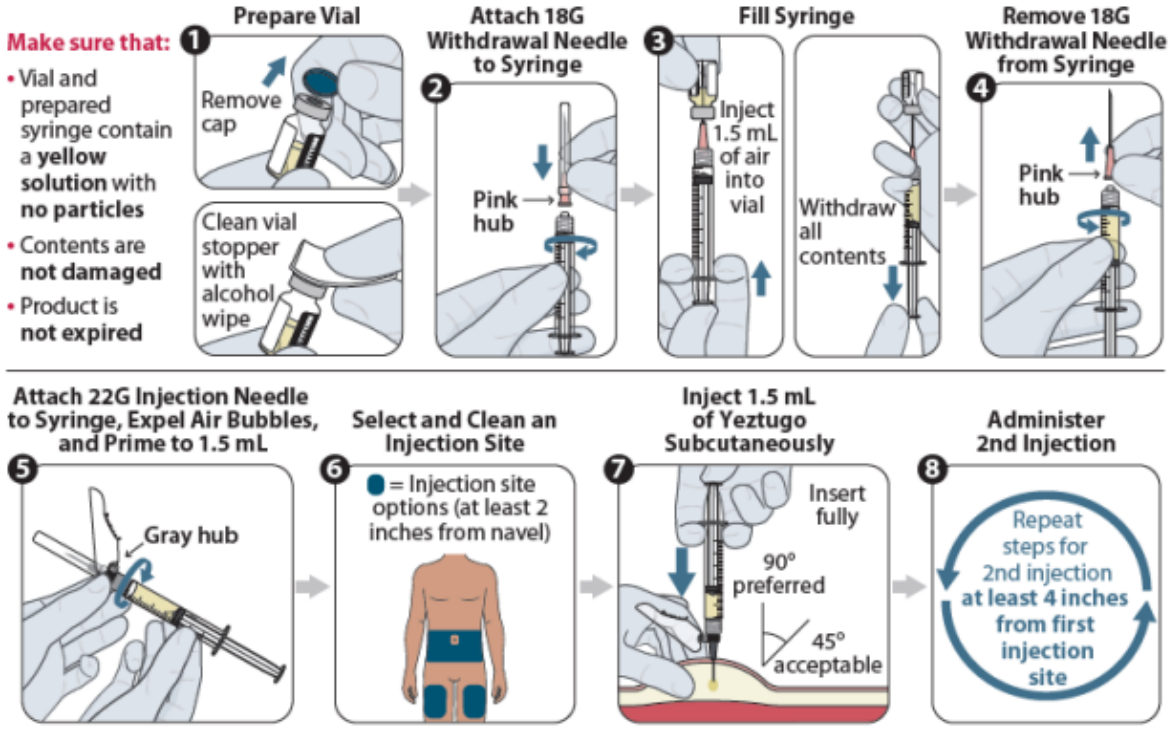
Figure 1 YEZTUGO Withdrawal Needle Injection Kit Components



NOTE: all components are for single use.

Figure 2 YEZTUGO Injection Steps for Withdrawal Needle Injection Kit



REFERENCES

1. Gandhi M, Hill L, Grochowski J, et al. Case Series of People With HIV on the Long-Acting Combination of Lenacapavir and Cabotegravir: Call for a Trial. *Open Forum Infect Dis.* 2024;11(4):ofae125. PMC11020301
2. Orkin C, Arasteh K, Gorgolas Hernandez-Mora M, et al. Long-Acting Cabotegravir and Rilpivirine after Oral Induction for HIV-1 Infection. *N Engl J Med.* 2020;382(12):1124-1135.
3. Orkin C, Oka S, Philibert P, et al. Long-acting cabotegravir plus rilpivirine for treatment in adults with HIV-1 infection: 96-week results of the randomised, open-label, phase 3 FLAIR study. *Lancet HIV.* 2021;8(4):e185-e196.
4. Swindells S, Andrade-Villanueva JF, Richmond GJ, et al. Long-Acting Cabotegravir and Rilpivirine for Maintenance of HIV-1 Suppression. *N Engl J Med.* 2020;382(12):1112-1123.
5. Jaeger H, Overton ET, Richmond G, et al. Long-acting cabotegravir and rilpivirine dosed every 2 months in adults with HIV-1 infection (ATLAS-2M), 96-week results: a randomised, multicentre, open-label, phase 3b, non-inferiority study. *Lancet HIV.* 2021;8(11):e679-e689.
6. Overton ET, Richmond G, Rizzardini G, et al. Long-acting cabotegravir and rilpivirine dosed every 2 months in adults with HIV-1 infection (ATLAS-2M), 48-week results: a randomised, multicentre, open-label, phase 3b, non-inferiority study. *Lancet.* 2021;396(10267):1994-2005.
7. Kityo C, Mambule IK, Musaazi J, et al. Switch to long-acting cabotegravir and rilpivirine in virologically suppressed adults with HIV in Africa (CARES): week 48 results from a randomised, multicentre, open-label, non-inferiority trial. *Lancet Infect Dis.* 2024;24(10):1083-1092.
8. Cresswell FV, Kafeero P, Norcross C et al.. Long-acting cabotegravir and rilpivirine in adults with suboptimal HIV control in sub-Saharan Africa: the IMPALA trial 48-week results. IAS 2025, 13-16 July 2025, Kigali, Rwanda. Oral late-breaker abstract OAS0105LBP. https://programme.ias2025.org/Abstract/Abstract/?abstractid=6781.
9. Centers for Disease Control and Prevention (CDC). National HIV Prevention and Care Objectives: 2025 Update. April 28, 2025. https://www.cdc.gov/hiv-data/nhss/national-hiv-prevention-and-care-objectives-2025.html (Accessed August 2, 2025).
10. Rana A. Bao Y, Zheng L. et al. Long-Acting Injectable CAB/RPV is Superior to Oral ART in PWH With Adherence Challenges: ACTG A5359). Conference on Retroviruses and Opportunistic Infections (CROI) 2024, March 3-6, Denver, CO; Abstract 212 (in press at NEJM 2025)
11. Spinelli MA, Heise MJ, Gistand N, et al. HIV Viral Suppression With Use of Long-Acting Antiretroviral Therapy in People With and Without Initial Viremia. *JAMA.* 2025;333(16):1451-1453. PMC11886863
12. Colasanti JA, Aldredge A, Niles-Carnes LV, et al. Long-acting cabotegravir/rilpivirine, lenacapavir, and ibalizumab use among persons with HIV-1 viremia at a Ryan White-funded clinic in the urban U.S. South. *Clin Infect Dis.* 2025.
13. Brock JB, Herrington P, Hickman M, Hickman A. Long-acting Injectable Cabotegravir/Rilpivirine Effective in a Small Patient Cohort With Virologic Failure on Oral Antiretroviral Therapy. *Clin Infect Dis.* 2024;78(1):122-124.
14. Hsu R, Sension M, Fusco JS, Brunet L, Levis B, Cochran Q, Sridhar G, Vannappagari V, van Wyck J. Wholfeiler M. Real-world effectiveness of CAB+RPV LA in individuals with HIV viremia at therapy initiation. International AIDS Society Conference (IAS 2025), 13-17 July, Kigali, RW, Abstract OAB0104.
15. Perez Navarro A, Nutt CT, Siedner MJ, McCluskey SM, Hill A. Virologic failure and emergent integrase strand transfer inhibitor drug resistance with long acting cabotegravir for HIV treatment: A meta-analysis. *Clin Infect Dis.* 2024;ciae631.

16. Hastie E, Hill L, Bamford L, Karim A, Martin TCS. Long-acting injectable HIV therapy outcomes among persons with HIV who have adherence challenges to oral antiretroviral therapy. *Clin Infect Dis.* 2025.
17. Hill L, Kenney S, Patel N, et al. Predictors of Post-switch Viremia in People With HIV on Injectable Cabotegravir/Rilpivirine. *J Acquir Immune Defic Syndr.* 2024;95(1):90-96.
18. Hickey MD, Gistand N, Grochowski J, et al. Viral Suppression Rates at 48 Weeks in People With HIV Starting Long-Acting Cabotegravir/Rilpivirine With Initial Viremia. *Clin Infect Dis.* 2025;80(4):864-870. PMC12043055
19. Chen W, Gandhi M, Sax PE, et al. Projected Benefits of Long-Acting Antiretroviral Therapy in Nonsuppressed People With Human Immunodeficiency Virus Experiencing Adherence Barriers. *Open Forum Infect Dis.* 2023;10(8):ofad390. PMC10439527
20. Pei PP, Jones M, Hu R, et al. Clinical consequences of delaying implementation of long-acting antiretroviral therapy for people with HIV and persistent viremia in the US. *Clin Infect Dis.* 2025;ciaf428.
21. Elvstam O, Malmborn K, Elen S, et al. Virologic Failure Following Low-level Viremia and Viral Blips During Antiretroviral Therapy: Results From a European Multicenter Cohort. *Clin Infect Dis.* 2023;76(1):25-31. PMC9825828
22. Gandhi M, Hickey M, Imbert E, et al. Demonstration Project of Long-Acting Antiretroviral Therapy in a Population of People With HIV. *Ann Intern Med.* 2023;176(7):969-974. PMC10771861
23. Hickey MD, Grochowski J, Mayorga-Munoz F, et al. Identifying Implementation Determinants and Strategies for Long-Acting Injectable Cabotegravir-Rilpivirine in People With HIV Who Are Virally Unsuppressed. *J Acquir Immune Defic Syndr.* 2024;96(3):280-289. PMC11192618
24. Mehtani NJ, Strough A, Strieff S, et al. Feasibility of Implementing a Low-Barrier Long-Acting Injectable Antiretroviral Program for HIV Treatment and Prevention for People Experiencing Homelessness. *J Acquir Immune Defic Syndr.* 2024;96(1):61-67. PMC11009050
25. Collins LF, Christopoulos KA, McNulty MC, Colasanti JA. Comparing interest in thigh administration of long-acting cabotegravir/rilpivirine among hypothetical users, early adopters and trial participants with experience. *Clin Infect Dis.* 2025.
26. Gutierrez JI, Jr., Montgomery ET, Dilworth SE, et al. Identifying preferred program delivery attributes for long-acting injectable cabotegravir-rilpvirine in three U.S. HIV clinics: A discrete choice experiment. *J Acquir Immune Defic Syndr.* 2025.
27. Ochieng E, Robinson V, Anderson E, et al. Enhancing Hepatitis B Virus Vaccine Uptake and Immunity Through Long-Acting Antiretroviral Therapy Programmatic Synergy in the US South. *Open Forum Infect Dis.* 2025;12(3):ofaf096. PMC11879927
28. Christopoulos KA, Smith MB, Pareek P, et al. Learning from the first: a qualitative study of the psychosocial benefits and treatment burdens of long-acting cabotegravir/rilpivirine among early adopters in three U.S. clinics. *J Int AIDS Soc.* 2024;27(11):e26394. PMC11578930
29. Haser GC, Balter L, Gurley S, et al. Early Implementation and Outcomes Among People with HIV Who Accessed Long-Acting Injectable Cabotegravir/Rilpivirine at Two Ryan White Clinics in the U.S. South. *AIDS Res Hum Retroviruses.* 2024;40(12):690-700. PMC11807906
30. Collins LF, Koester KA, McNulty MC, et al. Patient Attitudes Toward Self- or Partner-, Friend-, or Family-Administered Long-acting Injectable Antiretroviral Therapy: A Mixed-Methods Study Across 3 Urban Human Immunodeficiency Virus Clinics. *Open Forum Infect Dis.* 2024;11(6):ofae265. PMC11161893
31. Erguera XA, Koester KA, Diaz Tsuzuki M, et al. Acceptability of Long-Acting Injectable Antiretroviral Therapy Among People with HIV Receiving Care at Three Ryan White Funded Clinics in the United States. *AIDS Behav.* 2024;28(7):2226-2238. PMC11199206

32. Koester KA, Colasanti JA, McNulty MC, et al. Assessing readiness to implement long-acting injectable HIV antiretroviral therapy: provider and staff perspectives. *Implement Sci Commun.* 2023;4(1):128. PMC10588099
33. Collins LF, Corbin-Johnson D, Asrat M, et al. Early Experience Implementing Long-Acting Injectable Cabotegravir/Rilpivirine for Human Immunodeficiency Virus-1 Treatment at a Ryan White-Funded Clinic in the US South. *Open Forum Infect Dis.* 2022;9(9):ofac455. PMC9487705
34. Christopoulos KA, Colasanti J, Johnson MO, et al. Are Patients and Their Providers Talking About Long-Acting Injectable Antiretroviral Therapy? Penetration into Clinical Encounters at Three U.S. Care Sites. *Open Forum Infect Dis.* 2022;9(7):ofac293. PMC9301580
35. Panel on Antiretroviral Guidelines for Adults and Adolescents. Guidelines for the Use of Antiretroviral Agents in Adults and Adolescents with HIV. Department of Health and Human Services. Year. Available at https://clinicalinfo.hiv.gov/en/guidelines/adult-and-adolescent-arv. Updated September 12, 2024.
36. Gandhi RT, Landovitz RJ, Sax PE, et al. Antiretroviral Drugs for Treatment and Prevention of HIV in Adults: 2024 Recommendations of the International Antiviral Society-USA Panel. *JAMA.* 2025;333(7):609-628.
37. Sax PE, Thompson MA, Saag MS, Panel I-UTG. Updated Treatment Recommendation on Use of Cabotegravir and Rilpivirine for People With HIV From the IAS-USA Guidelines Panel. *JAMA.* 2024;331(12):1060-1061.
38. Phillips A, Smith J, Bansi-Matharu L, et al. Potential impact and cost-effectiveness of long-acting injectable lenacapavir plus cabotegravir as HIV treatment in Africa. *Nat Commun.* 2025;16(1):5760. PMC12217318