HIV/STI/HCV Program
Sexual Health Clinic
Ninth and Jefferson Building
908 Jefferson St, 11th Floor
Seattle, WA 98104
206-744-3590
www.kingcounty.gov/health

Public Health
Seattle & King County

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Use of Long-Acting Injectable Antiretroviral Therapy for HIV

Background

Long-acting injectable antiretroviral treatment (LAI-ART) is a promising intervention for increasing viral suppression among persons with HIV (PWH). LAI ART medications available in the US include cabotegravir/rilpivirine (CAB/RPV), lenacapavir (LEN), and ibalizumab. This guidance document primarily focuses on LAI CAB/RPV and implementation of LAI ART in healthcare settings. Injectable CAB/RPV is currently the only injectable, complete ART regimen approved by the US Food and Drug Administration (FDA) and is indicated for use among PWH who are virally suppressed on a stable regimen of oral ART with no history of treatment failure and no resistance mutations to CAB or RPV. However, a growing body of evidence supports the use of LAI-ART among persons who are not virally suppressed, and IAS-USA and US Department of Health and Human Services Guidelines were modified in 2024 to support the selective use of LAI-ART among viremic persons who have failed oral therapy and are at high risk for disease progression[1]. Modeling studies suggest that delayed implementation of LAI-ART among viremic patients will result in substantial HIV-associated mortality, highlighting the need to rapidly expand the use of this intervention among the patients who need it most[2].

While LAI-ART has the potential to benefit many PWH, administering these medications presents logistical challenges in busy clinics, and providing the medication requires well-developed procedures to assure adherence and, in some cases, requires hiring additional staff. Coupled with the high cost of long-acting medications – particularly when given monthly – these logistical and staffing issues can limit the availability of CAB/RPV. Moreover, while LAI-ART has the potential to benefit patients and the wider population, if provided without adequate follow-up, it can promote the emergence of resistant HIV, harming individual patients and potentially leading to transmission of resistant virus. PHSKC developed these local implementation guidelines to help medical providers and health care organizations prioritize the use of LAI-ART to maximize its benefit. The use of long-acting ART for HIV prevention is discussed separately in the 2026 PHSKC PrEP Implementation Guidelines[3].

Studies of LAI-ART for HIV treatment

Randomized controlled trials have demonstrated that cabotegravir/rilpivirine (CAB/RPV) given every 4 or 8 weeks is noninferior to oral ART regimens among virally suppressed persons[4-6]. These trials led to FDA approval of CAB/RPV for virally suppressed persons. However, subsequent studies suggest that CAB/RPV can also be used in PWH who are not virally suppressed. The Latitude Study investigated the use of CAB/RPV among PWH with suboptimal adherence to oral ART; the trial used cash incentives to promote viral suppression during an oral

therapy lead-in and required viral suppression prior to randomization, but 16% of participants randomized to receive CAB/RPV were viremic (HIV RNA >200 copies/ml) at the time of randomization. The trial was stopped early because virologic failure was lower among people treated with CAB/RPV than among persons on oral ART (6.8% vs. 28.2%, 98.4% for difference CI -31.6—6.9)[7]. More recently, a small, open-label randomized trial in Taiwan presented at the Conference on Retroviruses and Opportunistic Infections in 2026 reported that viral suppression was higher among viremic PWH (HIV RNA >200 copies/ml) randomly assigned to receive CAB/RPV than a control group receiving oral ART (88% vs. 55%, p=0.025)[8]. These findings align with a growing body of observational data supporting the efficacy of CAB/RPV among viremic persons, with most studies reporting that >90% of patients achieve viral suppression (Table 1). In a systemic review and meta-analysis of 8 studies including 244 persons who initiated CAB/RPV while viremic, 87% achieved viral suppression, with 11 patients developing RPV resistance mutations and 5 developing CAB resistance mutations[9]. Although CAB/RPV is currently the only ART regimen composed solely of LAI drugs, LEN and ibalizumab have been used for HIV with multidrug resistance in regimens that include oral drugs, CAB/RPV, and other injectable ART[10,11].

Table 1: Studies of CAB/RPV in patients who are not virally suppressed

Author	Number Patients & Population	Baseline VL (copies/mL) and CD4 (cells/ µL)	Viral Suppression (copies/mL)	Length Follow-up	Regimen (every 4 or 8 weeks)	Resistance at Follow up
D'Amico[12]	28 Multiple Countries	Median VL=60,300 Median CD4=100	16/28 (57%) VL<50	Median 10 months (range 1-47)	4 weeks	6 RT 5 Integrase
Brock[13]	12 Mississippi	Mean VL= 152,657 Mean CD4=233	12/12 (100%) VL<200	1-17 months	6 patients – every 4 weeks for 3 months and every 8 weeks thereafter. 6 – 8 weeks	Not applicable
Hsu[14]	69 OPERA Cohort	VL>200 Median=35,000 Median CD4=319	62/69 (90%) VL <200 51/69 (74)% VL<50	Median 7.4 months	8 weeks	Not reported
Hickey[15]	59 Ward 86 (UCSF)	Median VL=42,900 CD4 - 49%<200	47/59 (80%) (92% on CAB/RPV or another regimen)	48 weeks	4 weeks – switch to 8 weeks 3-6 months after viral suppression	3 RT 2 Integrase + RT
Spinelli[16]	283 Ward 86 (SF) & Grady (Atlanta)	VL >1000 (21%)	93%	60% followed for >48 weeks		

PHSKC Recommendations

To maximize the benefits of LAI-ART and in acknowledgement of the healthcare system's limited capacity to provide these medications to all patients who might want them or benefit from them, PHSKC has established priority tiers to help medical providers and healthcare organizations define which patients should receive LAI-ART (Table 2). Medical providers should prioritize initiating LAI-ART in PWH with persistent viremia, particularly those who are pregnant or at high risk for disease progression.

Table 2: PHSKC Recommendations for Initiating LAI-ART

Tier 1: Highest priority for initiation of LAI-ART
- Persistent viremia despite best efforts to treat patient with oral ART AND - CD4 count <200 cells/µL OR current or past AIDS-defining illness OR - Pregnancy
Tier 2: Intermediate priority for initiation of LAI-ART
- Persistent viremia despite best efforts to treat patient with oral ART - CD4>200 cells/µL without a history of AIDS defining illness or pregnancy
Tier 3: Lowest priority for initiation of LAI-ART
- Virally suppressed on oral therapy

Experience using CAB/RPV in pregnant persons is limited, but current evidence suggests LAI CAB/RPV is safe during pregnancy[17,18]. The recommendation to use CAB/RPV in pregnant persons who have not achieved viral suppression on oral antiretrovirals with optimized adherence support reflects the critical importance of averting vertical transmission of HIV. PHSKC recommends that medical providers consult with a physician with expertise in HIV treatment in pregnancy and LAI-ART when considering the use of CAB/RPV in a pregnant patient. Consultations are available through the National Clinician Consultation Center (https://nccc.ucsf.edu/clinician-consultation/perinatal-hiv-aids/, 844-ASK-NCCC (275-6222)).

The decision to make LAI-ART available to other patients should be based on a health system's current and anticipated future capacity. PHSKC urges medical providers and healthcare organizations to define which tiers of patients they can provide with LAI-ART, carefully considering their ability to initiate and sustain patients on LAI-ART without exhausting their capacity to initiate long-acting treatment in new patients in the highest priority tiers.

Clinical considerations

The following brief guidance is adapted from the Ward 86 Long-Acting Antiretroviral Treatment (LA-ART) Guidelines, updated November 2025. Medical providers are advised to review these more detailed guidelines when initiating patients on LAI-ART (https://gettingtozerosf.org/ward-86-lai-prevention-treatment-guidelines/)

- Before initiating an LAI-ART-only regimen, medical providers should work with the patient to optimize oral ART adherence. This will help determine if the patient needs LAI-ART and will

lower the viral load before LAI-ART initiation, which may reduce the risk that the patient's virus develops resistance to a component of CAB/RPV. Some providers give patients with very high viral loads (e.g., >100,000 copies/mL) a one-time LEN injection at time of CAB/RPV initiation. However, some insurers will not cover LEN in the absence of known drug-resistance. Medical providers can also consider continuing an oral ART regimen for the first 2 weeks after LAI-ART initiation to lower the risk of resistance developing while the injectable medication reaches a therapeutic level.

- Review all prior genotypes - including subtype data - and any clinical history of resistance or regimen failure to identify resistance mutations to RPV or CAB. (HIV subtypes can sometimes affect the magnitude of the impact of specific mutations. For example, the L74I mutation in the presence of subtype A6 is a major mutation.) Viremic patients without recent resistance testing should have it done before initiating CAB/RPV. Medical providers should use the online Stanford HIV Drug Resistance Database to interpret genotypes (https://hivdb.stanford.edu/). Patients do not routinely require testing for archived resistance mutations before initiating LAI-ART[19].
- In patients with a Stanford HIV Drug Resistance Database penalty score ≥10 to either CAB or RPV on any genotype, consider adding LEN to CAB/RPV[10]. Those with penalty scores of <10 to CAB or RPV can typically be treated with CAB/RPV alone, though approaches to CAB/RPV dosing in viremic patients with resistance mutations vary.
- Check hepatitis B immune status (HBsAb, HBsAg, HBcAb) before initiating LAI-ART in patients who are not known to be immune and vaccinate patients who are not immune. Hepatitis B is not treated by LAI-ART drugs and patients with chronic active HBV (HBV DNA+ and/or HBsAg+) and, less commonly, people who are HBcAb+/HBsAb-, may experience flares of hepatitis when antiretrovirals that suppress HBV are discontinued. Active hepatitis B is not a contraindication to LAI-ART, but patients with chronic hepatitis B should also receive treatment for hepatitis B.
- Patients who are currently taking the following medications should not use LAI CAB/RPV due to potential for decreased drug levels of CAB or RPV:
    - Anticonvulsants: carbamazepine, oxcarbazepine, phenobarbital, phenytoin
    - Antimycobacterial drugs: rifabutin, rifampin, rifapentine
    - Systemic glucocorticoids: more than short-term use of glucocorticoids
    - Herbal: St John's Wort
- Use https://www.hiv-druginteractions.org/checker to check for other drug-drug interactions, which may require dose adjustments or additional caution.
- When starting an LAI-ART-only regimen, the patient should have an oral "backup" regimen designated in case they discontinue or have a gap in LAI-ART; this will most commonly be TDF/FTC or TAF/FTC + DTG or BIC-TAF-FTC. LAI-ART drugs have a long half-life, so there is a long "tail" of decreasing ART concentrations in the blood after discontinuation, which can

promote resistance. Providers may consider providing patients with a 1-month supply of oral ART to keep in case of LAI-ART treatment interruption. This oral backup regimen can also be used in patients discontinuing LAI-ART.

- The best approach to dosing CAB/RPV in viremic patients remains ill-defined. The Ward 86 recommendation is to prescribe CAB/RPV every 4 weeks until the patient has been virally suppressed (HIV RNA <200 copies/ml) for at least 6 months at which time medical providers can consider switching patients to every 8-week CAB/RPV dosing. Some providers continue every-4-week dosing indefinitely for patients with any CAB or RPV resistance, a history of late dosing, or other risks for virologic failure.

Guidance for developing clinic processes to provide LAI-ART and promote patient adherence

Medical practices seeking to provide LAI-ART should develop standard processes for identifying patients who are good candidates for LAI-ART and promoting their successful treatment[11]. This effort should include prioritizing LAI-ART for the patients who need it most and establishing support structures that help patients adhere to treatment. Providing LAI-ART for people who have persistent viremia despite best efforts to treat them with oral ART requires additional staff time and effort to navigate patients through the process of initiating LAI-ART and provide support for retention. This is crucial to reduce the risk of ART resistance developing if follow-up doses are delayed. Not all clinics will be able to establish these structures, and patients who cannot achieve viral suppression on oral therapy and who are interested in LAI-ART should be referred to clinics that can provide it. In addition, although virologic failure is rare, when individuals do experience virologic failure, it often occurs within the first year of CAB/RPV treatment. Persons with virologic failure on CAB/RPV typically have resistance to one or both components of the regimen, occurring in one-third to half of cases of virologic failure while on CAB/RPV, and with mutations that confer cross-resistance to other ART as well – including at least partial resistance to dolutegravir, bictegravir, and/or doravirine.[20-22]

Procedures for providing LAI-ART and promoting adherence include:

- Leadership and staffing
  - Identification of a point person to lead LAI-ART programs, including efforts to ensure adherence. Different aspects of the program may be led by different people.
  - Development of a staffing plan that identifies and trains people who will oversee, develop and carry out the procedures below, including backup staff to accommodate absences.
- Patient eligibility, data monitoring and tracking

- Approval processes for defining which patients are eligible to start LAI-ART, including review of medical and social factors which may affect the need for LAI-ART and the patient's ability to adhere to treatment.
- Procedures for ensuring that medications are paid for, including monitoring changes in insurance, use of drug assistance programs, identifying co-pays, etc.
- Procedures to monitor the clinic's capacity to provide LAI-ART, including the capacity to add additional patients.
- Development of a tracking system to monitor when patients are due for doses and laboratory monitoring. If applicable, this may include tracking the provision of incentives for timely receipt of LAI-ART injections.

- Outreach and retention
  - Collection and regular updating of comprehensive patient contact information (mobile phone, email, address, places the patient frequently goes, contacts in a patient's building). This should ideally include a way to contact patients through someone who can always reach them.
  - Development of a system for providing outreach to contact patients in need of LAI-ART follow up. Ideally, this should include staff who can go into the field to find patients who are late receiving doses.
- Pharmacy and drug administration
  - Pharmacy procedures for storing, handling, and dispensing medications.
  - Procedures and training of staff in the correct administration of LAI-ART (see prescribing information and Ward86 guideline).

<u>King County clinics providing LAI ART that can take referrals</u>

Madison Clinic at Harborview Medical Center - Patients can be referred to the Madison Clinic by contacting the clinic coordinator at 206-744-5155.

MAX Clinic at Harborview Medical Center – MAX Clinic can only provide LAI-ART to persons in PHSKC priority tiers 1 and 2. The clinic only provides care to selected patients who have not been successful in achieving viral suppression through more conventionally organized medical care. Patients can be referred to MAX by contacting Sara Stewart at (206) 744-2284 and will be reviewed for eligibility to enroll in the clinic.

Resources:

Ward 86 LAI-ART Protocol
https://gettingtozerosf.org/ward-86-lai-prevention-treatment-guidelines

Advancing Long-Acting Injectables for Underserved Populations (ALAI Up) - Worksheets for a clinic to determine their policies and protocols:
Resource D Prescribing and Administering.docx

Resource C Procurement and Storage.docx

Resource E Supporting Retention.docx

References

1. 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.
2. 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 United States. *Clin Infect Dis.* 2026;81(6):e591-e599.
3. County PH-SK. Public Health - Seattle & King County Preexposure Prophylaxis (PrEP) Implementation Guidelines 2025. In. Seattle, WA2025.
4. 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.
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. Ramgopal MN, Castagna A, Cazanave C, et al. Efficacy, safety, and tolerability of switching to long-acting cabotegravir plus rilpivirine versus continuing fixed-dose bictegravir, emtricitabine, and tenofovir alafenamide in virologically suppressed adults with HIV, 12-month results (SOLAR): a randomised, open-label, phase 3b, non-inferiority trial. *Lancet HIV.* 2023;10(9):e566-e577.
7. Rana AI, Zheng L, Castillo-Mancilla J, et al. Cabotegravir plus Rilpivirine for Persons with HIV and Adherence Challenges. *N Engl J Med.* 2026;394(9):858-871.
8. Chen N, Chen C, Lin Y, et al. Week-24 Outcomes of Long-Acting Injectable ART in People With HIV and Suboptimal Viral Suppression. Conference on Retroviruses and Opportunistic Infections; 2026, 2026; Denver.
9. Barda B, Barilaro G, Bellini P, Turicchi G, Bernasconi E, Bongiovanni M. Efficacy of long-acting cabotegravir plus rilpivirine in viraemic people living with HIV: A systematic review and meta-analysis. *HIV Med.* 2025;26(7):993-1003.
10. 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.
11. 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 US South. *Clin Infect Dis.* 2026;82(4):564-574.
12. D'Amico R, Cenoz Gomis S, Moodley R, et al. Compassionate use of long-acting cabotegravir plus rilpivirine for people living with HIV-1 in need of parenteral antiretroviral therapy. *HIV Med.* 2023;24(2):202-211.
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 J. Real-world use of long-acting cabotegravir + rilpivirine in people with HIV with detectable viral loads at initiation: findings from the OPERA Cohort. *OFID.* 2023.

15. 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.
16. Spinelli M, Heise MJ, Glidden DV, et al. Virologic Outcomes After LA ART Initiation with and without Viremia in Two Large U.S. Clinic Cohorts. *Clin Infect Dis.* 2026.
17. McGuinty M, Giguere P, Angel JB. Cabotegravir/rilpivirine in pregnancy: early insights from clinical practice. *AIDS.* 2026.
18. Services USDoHaH. *Recommendations for the Use of Antiretroviral Drugs During Pregnancy and Interventions to Reduce Perinatal HIV Transmission in the United States.* 2026.
19. Crawford KHD, Kumbhakar RG, Lee J, et al. Letter: Limited Use of Proviral Sequencing in Adults with HIV Starting Long-Acting Injectable Cabotegravir-Rilpivirine. *AIDS Patient Care STDS.* 2026;40(8):283-287.
20. 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.* 2025;81(2):274-285.
21. Mazzitelli M, Parczewski M, Burger D, Wensing A. Virological Failure on Long-Acting Injectable Cabotegravir and Rilpivirine: An Analysis of Subtypes, Drug Levels, Resistance, and Therapeutic Implications. *Clin Infect Dis.* 2026;82(6):1023-1031.
22. Hill A, Orkin C. What Are the Causes and Consequences of Virological Failure on Long-acting Cabotegravir/Rilpivirine? *Clin Infect Dis.* 2026;82(6):1032-1034.