

In It for the Long Haul: Perspectives on Long-Acting Injectable Treatment for HIV

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Disclosures

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AETC Program National Centers and HIV Curriculum

- **National Coordinating Resource Center** – serves as the central web –based repository for AETC Program training and capacity building resources; its website includes a free virtual library with training and technical assistance materials, a program directory, and a calendar of trainings and other events. Learn more: <https://aidsetc.org/>
- **National Clinician Consultation Center** – provides free, peer-to-peer, expert advice for health professionals on HIV prevention, care, and treatment and related topics. Learn more: <https://nccc/ucsf.edu>
- **National HIV Curriculum** – provides ongoing, up –to-date HIV training and information for health professionals through a free, web –based curriculum; also provides free CME credits, CNE contact hours, CE contact hours, and maintenance of certification credits. Learn more: www.hiv.uw.edu

Learning Outcomes

- By the end of this session, participants will be able to:
 - Summarize the pharmacologic action and effectiveness of long-acting injectable (LAI) cabotegravir/rilpivirine (CAB/RPV) for HIV treatment
 - List at least three important patient criteria to consider when assessing appropriateness of HIV treatment with LAI CAB/RPV
 - Explain the administration process, dosing schedule, and monitoring schedule for LAI CAB/RPV
 - List positive and negative patient experiences with using LAI CAB/RPV for HIV treatment

Who is Here Today?

- In what state are you located?
- Do you work in a clinical or non-clinical setting?
- If clinical, what is your role?
- On a scale of 1-10, how much do you already know about LAI CAB/RPV?

How Long is “Long-Acting”?

- Per US DHHS HIV treatment guidelines, the term LA (long-acting) refers to any ARV that is dosed once weekly or less frequently
- Achieving LA dosing requires:
 - unique longer pharmacokinetics (such as a long half-life) OR
 - altered formulations that last longer (such as nanoparticles) OR
 - a delivery method or device that achieves sustained delivery (such as vaginal rings or subcutaneous implants)

LAI Cabotegravir/rilpivirine (CAB/RPV) Approvals Timeline

- Jan 2021: FDA approved CAB/RPV, an INSTI/NNRTI combo, as a once-monthly IM injection with a *recommended* one month daily oral lead-in phase
 - 600mg CAB/900mg RPV initiation injection
 - 400mg CAB/600mg RPV continuation injections monthly
- Feb 2022: FDA approval updated to bimonthly dosing
 - Two 600mg CAB/900mg RPV initiation injections one month apart
 - 600mg CAB/900mg RPV continuation injections bimonthly

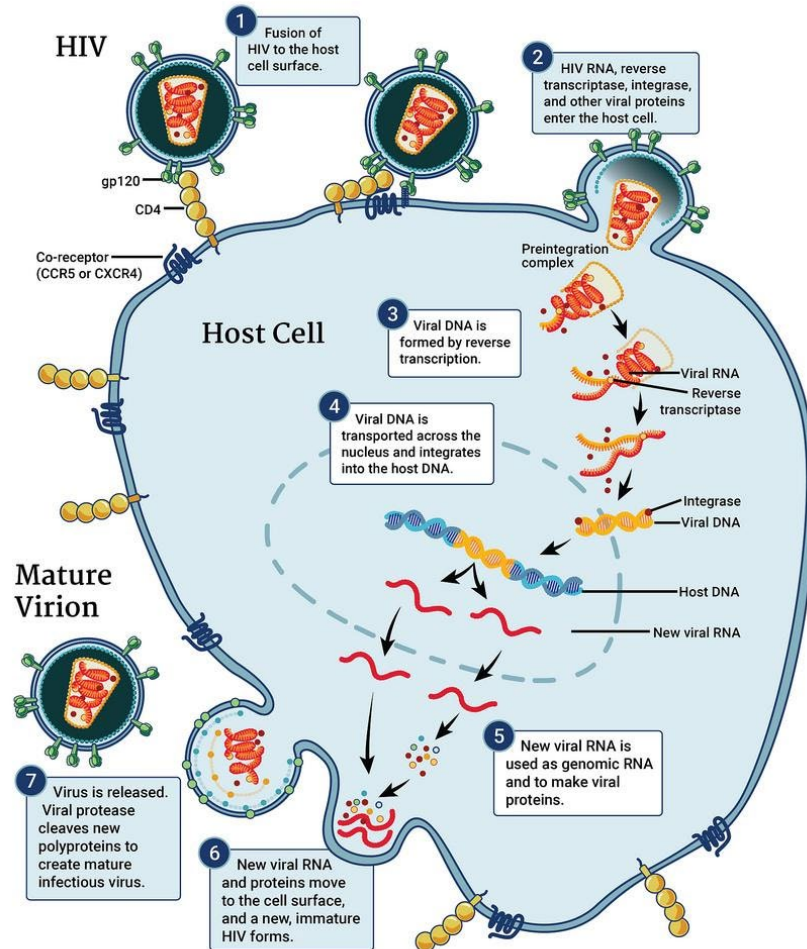
Quick Real-Life Check

- If you work in a clinical setting and have patients using LAI CAB/RPV, what percentage of patients at your clinic utilize the 30 day oral-lead in before starting injections?

Current DHHS Treatment Guidelines for CAB/RPV

- “A long-acting ARV regimen of injectable cabotegravir (CAB) and rilpivirine (RPV) given every 1 or 2 months is an optimization option for patients who are engaged with their health care, virologically suppressed on oral therapy for 3 to 6 months, and who agree to make the frequent clinic visits needed to receive the injectable drugs ” (AI)
- “Long-acting injectable CAB plus RPV is indicated in individuals with sustained (e.g., 3 to 6 months) virologic suppression (HIV-1 RNA <50 copies/mL) on a stable ARV regimen, with *no history of treatment failure*, and with *no known or suspected resistance to either CAB or RPV.*”

CAB/RPV Mechanisms



- Cabotegravir – integrase inhibitor (INSTI)
- Rilpivirine – non-nucleotide reverse transcriptase inhibitor (NNRTI)

FLAIR and ATLAS – Phase 3 Trials for LAI CAB/RPV

- FLAIR – **treatment-naïve** subjects were suppressed on a dolutegravir-based regimen for 20 weeks, then randomized to monthly LAI CAB/RPV or left on their original ART
- ATLAS – **ART-experienced**, virologically suppressed subjects were randomized to monthly LAI CAB/RPV or left on their current ART
- Both trials followed subjects for 48 weeks
- In both trials, the proportion of subjects with VL > 50 copies/mL was between 1-2%, with no significant difference between groups

Patient Criteria to Consider Ahead of LAI CAB/RPV

- Direct Clinical Factors
 - Pre-treatment genotype
 - History of ART adherence
 - Any known viral resistance
 - Recent VLs
 - Allergies to either CAB or RPV
 - Drug-drug interactions
 - Age (must be > 12 yo)
 - Weight (must be \geq 35 kg)
- Non-Clinical Factors
 - Patient preference for LAI
 - Patient's ability to come to clinic monthly/bimonthly
 - Acceptance of bilateral gluteal injections
 - Access to CAB/RPV - \$\$\$

This can be a long discussion and research process!

Viral Resistance

- Due diligence to gather all existing genotypes, an accurate ART history, and all available viral load results is needed
- Transmitted drug resistance (TDR) may be as high as 14%
- NNRTIs are the most common class for TDR
- Consider additional tools to confirm viral susceptibility to CAB/RPV past the initial genotype interpretation

Stanford's HIV Drug Resistance Database: <https://hivdb.stanford.edu/>

Stanford University
HIV DRUG RESISTANCE DATABASE
A curated public database to represent, store and analyze HIV drug resistance data.

HOME GENOTYPE-RX GENOTYPE-PHENO GENOTYPE-CLINICAL HIVDB PROGRAM ABOUT HIVDB SUPPORT HIVDB!

HIVDB Algorithm Version 9.6
Mar 09, 2024

Sierra 3.5.0
[release notes](#) / [web service](#)
Mar 21, 2024

Open Postdoctoral Position
Collaborate on groundbreaking projects and contribute to the globally utilized Stanford HIV Drug Resistance Database (HIVDB)

HIV, HBV, HCV Genbank submission tool
HIV, HBV, HCV Genbank submission tool
May 7, 2024

HIV in vitro selection
HIV in vitro selected PR, RT, IN and CA mutations
May 13, 2024

Open Postdoctoral Position

Calibrated Population Resistance (CPR)

INTERACTIVE MAP

Surveillance Mutations

Reference Libraries

HIVDB released on May 22, 2024
[Query](#) / [Download](#)

Genotype-treatment
[ARV selection data](#) comprising 217,899 protease, 227,456 RT, 35,892 integrase and 23,816 capsid HIV-1 virus sequences from 257,726 persons; 1,075 protease, 838 RT and 340 integrase HIV-2 virus sequences from 1,139 persons. [In vitro selection data](#) includes 1,111 HIV-1 in vitro selection data of PR, RT and IN.

Genotype-phenotype
[Drug susceptibility data](#) comprising 30,312 PI, 23,814 NRTI, 14,125 NNRTI and 5,370 INI susceptibility results from HIV-1 virus isolates

Genotype-clinical
[Clinical outcome data](#) comprising genotype, treatments, plasma HIV-1 RNA levels and CD4 counts from 15 clinical trials and >1500 Treatment-Change Episodes

References
2,210 references of genotype-treatment and/or genotype-phenotype data [according to author-yr](#) or [according to year of addition](#) to HIVDB.
3,780 [Genbank submission sets](#) according to author-yr and submission title, including 17 new submissions from Genbank release on 2023-04-15.
1,245 [Genbank submission sets of capsid sequences](#) according to author-yr and submission title from Genbank release on 2021-10-15. capsid mutation profile according to subtype..

HIVdb Program

Drug resistance summaries (Download PDF)
[PIs](#) [NRTIs](#) [NNRTIs](#) [INSTIs](#) [CAIs](#)

Draft HIV Drug Resistance Tutorials
[NRTIs \(Apr 11, 2024\)](#)
[NNRTIs \(Apr 14, 2024\)](#)
[PIs \(Apr 15, 2024\)](#)
[INSTIs \(Apr 12, 2024\)](#)
[HIVDR Interpretation Program \(Apr 9, 2024\)](#)
Draft slides and transcripts of recently updated HIVDR tutorials, which will be updated further, recorded, and posted on this site. Questions or suggestion are welcomed: hivdbteam@lists.stanford.edu

SARS-CoV-2 Program



Mutations Analysis Tool



Stanford University
HIV DRUG RESISTANCE DATABASE
A curated public database to represent, store and analyze HIV drug resistance data.

- HOME
- GENOTYPE-RX
- GENOTYPE-PHENO
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HIVdb Program: Mutations Analysis

HIVdb accepts user-submitted protease, RT, and integrase sequences or mutations and returns inferred levels of resistance to the most commonly used protease, nucleoside, non-nucleoside, and integrase inhibitors. Its purpose is educational and as such it provides extensive comments and a highly transparent scoring system that is hyperlinked to data in the HIV Drug Resistance Database. A detailed description of the program as well as all updates is in the [Release Notes](#). A [web service](#) has been created to allow users to access HIVdb programmatically.

New: this program is now available for analyzing SARS-CoV-2 mutations, FASTA, and FASTQ (NGS) sequences.

Protease, RT, and integrase mutations can be entered using either the text box or auto-suggestion boxes. To use the text box, type each mutation separated by one or more spaces. The consensus wildtype and separating commas are optional. If there is a mixture of more than one amino acid at a position, write both amino acids (an intervening slash is optional). Insertions should be indicated by "Insertion" and deletions by "Deletion".

Drug display options

By default, results will be shown for checked ARVs. Use checkboxes for additional ARVs. ([select all ARVs](#), [revert to default](#))

NRTI: ABC AZT FTC 3TC TDF D4T DDI

NNRTI: DOR EFV ETR NVP RPV

INSTI: BIC CAB DTG EVG RAL

PI: ATV/r DRV/r LPV/r FPV/r IDV/r NFV SQV/r TPV/r

- Input mutations
- Input sequences
- Input sequence reads

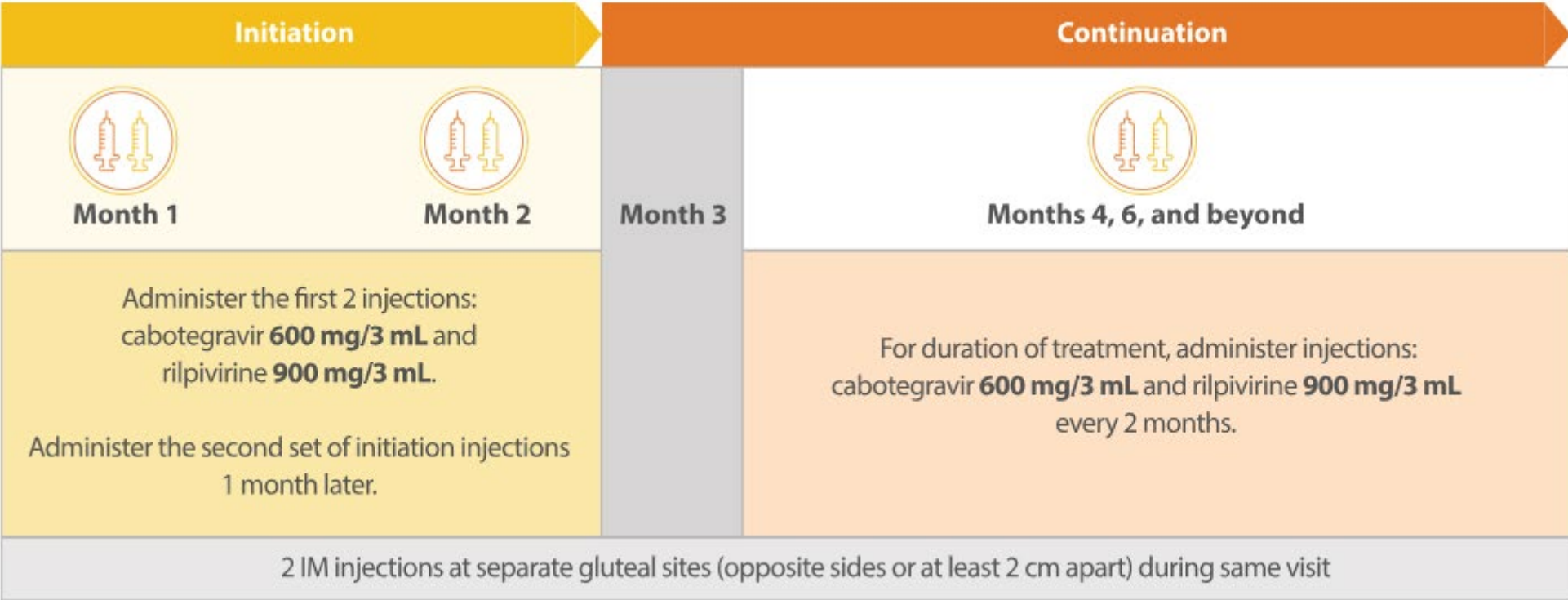
Reverse Transcriptase					Protease					Integrase				
Enter/paste mutations														
40	41	44	62	65	10	11	13	20	23	51	66	74	92	95
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67	68	69	70	74	24	30	32	33	35	97	114	118	121	128
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75	77	90	98	100	36	43	46	47	48	138	140	143	145	146
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101	103	106	108	115	50	53	54	58	63	147	148	149	151	153
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116	118	138	151	179	71	73	74	76	77	155	157	163	230	232
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181	184	188	190	210	82	83	84	85	88	263				



Obtaining LAI CAB/RPV for Patients

- Multiple options to obtain the medication, depending on insurance coverage
- LAI CAB/RPV may be covered under pharmacy or medical benefits
- Ordering through a specialty pharmacy for delivery to the clinic is common
 - Patients come to clinic for injections by clinic staff
- Alternative Sites for Administration (ASAs)
- Good resources exist for help with prior authorizations and copay support for patients

LAI CAB/RPV Every Other Month Dosing Schedule



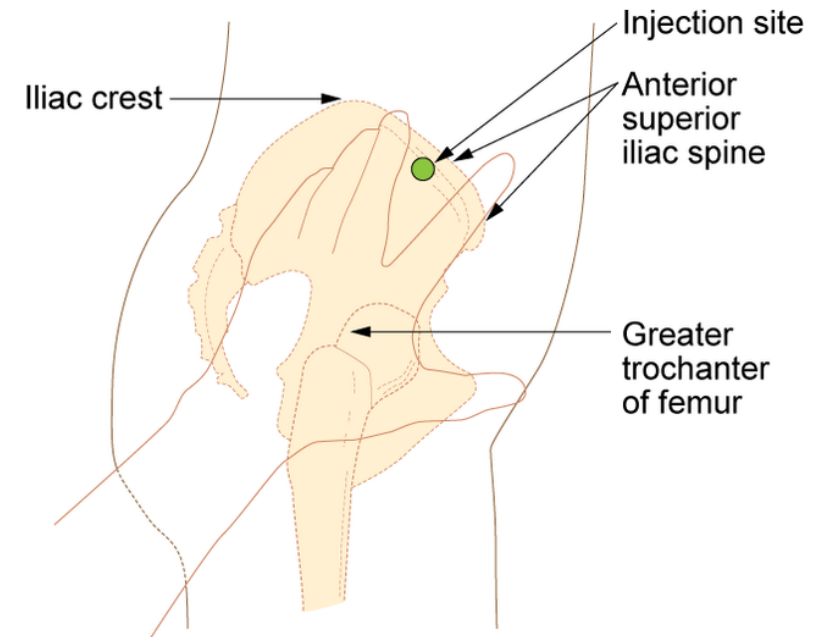
Initiate injections on the last day of current oral ART or the oral lead-in if used

What About Missed Injections?

- Ideally, injections will be given the same date every other month
- When necessary, a +/- 7 day window is acceptable – the “dosing window”
- After an adjusted injection within the dosing window, return to the target date
- For missed injections > 7 days but < 30 days, resume q2 month injections
- For missed injections > 30 days, restart with two injections one month apart, then resume q2 month injections

LAI CAB/RPV Administration

- The package labeling recommends two intramuscular ventrogluteal injections (on opposite sides or ≥ 2 cm apart) during the same visit.
- The ventrogluteal site is recommended and a longer needle length (not included in the dosing kit) may be required for patients with higher BMI.
- Kits are stored in the refrigerator
- Allow vials to sit at room temperature at least 15 minutes, for up to six hours
- Shake vials to create a uniform suspension
- Inject within two hours of pulling into syringes



<https://commons.wikimedia.org>

Monitoring Once Started on LAI CAB/RPV

- Because this is currently approved for switch therapy, no change in frequency of viral load monitoring is required
 - Some providers may prefer checking viral loads q3-4 months for a period of time, while patient is new to LAI CAB/RPV
- In patients with severe renal impairment, monitor more closely for adverse events
- Hepatotoxicity is possible – monitor LFTs periodically
- Injection site reactions (ISRs) are the most common adverse reaction

What Do Patients Think?

- Long-term studies and anecdotal evidence from clinicians demonstrate overall tolerability and satisfaction of LAI CAB/RPV
- Few cases of patients choosing to switch back to oral ART
- But let's hear from an expert on the patient experience!

On the Horizon...

Now, the IAS-USA guidelines panel has issued updated recommendations for use of LA CAB/RPV in PLWHIV **without virologic suppression** who meet the following additional criteria:

- Inability to take oral ART consistently despite optimal clinical support
- High risk for HIV disease progression (CD4 <200 cells/ μ L or history of AIDS-defining illness)
- No known resistance mutations to CAB or RPV
- Access to intensive clinical follow-up and case management

Sax PE et al. Updated treatment recommendation on use of cabotegravir and rilpivirine for people with HIV from the IAS-USA Guidelines Panel. *JAMA* 2024 Mar 1; [e-pub].
(<https://doi.org/10.1001/jama.2024.2985>.)

Thank You!

