Long Acting ART

WHAT YOU NEED TO KNOW

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Objectives

- Understand what long - acting antiretroviral therapy is.
- Know who is eligible for long - acting therapy
- What will be different for patients switching to long - acting ARV.
- Know dosing recommendations and appropriate schedules of long-acting antiretroviral therapy.
- Understand the appropriate steps if your patient misses a dose.

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Long-Acting ART Definition

A long-acting antiretroviral (ARV) refers to IM injections used in the treatment of HIV infection that has an extended duration of action within the body. LA-ARV are designed to provide sustained therapeutic levels of antiretroviral drugs over an extended period, reducing the frequency of dosing and potentially improving adherence to treatment.

The primary goal of LA - ARVs is to simplify the treatment regimen for HIV-infected individuals, particularly those who may struggle with daily pill-taking or have challenges with treatment adherence. By offering a longer duration of action, these medications aim to reduce the frequency of dosing to weekly, monthly, or even longer intervals, compared to the standard daily regimens of oral ARVs.

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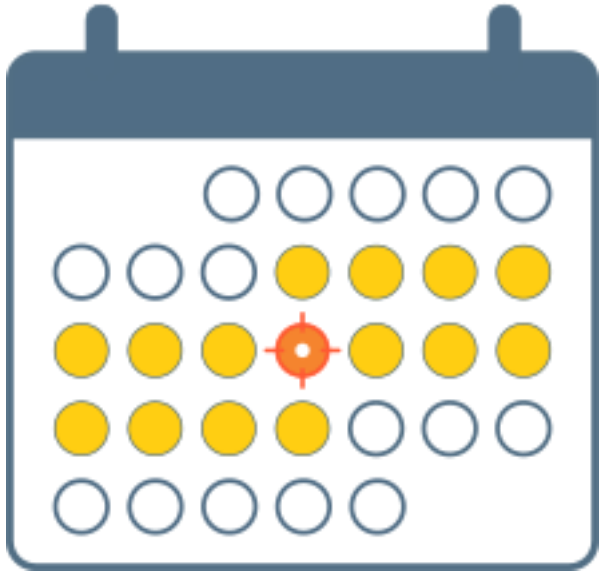
SCHEDULING CABENUVA (CABOTEGRAVIR/RILPIVERINE)TREATMENT



Target Treatment Date

You and your doctor will choose an ongoing date that works best for your injection appointments. This is called your Target Treatment Date.

You have a Flexible Treatment Window to schedule your appointment within—from 7 days before to 7 days after your Target Treatment Date.

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LONG-ACTING INJECTABLE CABOTEGRAVIR INDICATION FOR HIV PrEP

- **FDA Approval and Indication for HIV PrEP**: In December 2021, the FDA approved long-acting injectable cabotegravir as HIV PrEP for at-risk adults and adolescents (weighing at least 35 kg) who are at risk of sexual acquisition of HIV. Long-acting cabotegravir has not been studied as a prevention measure for people who are risk of acquiring HIV from injecting drugs.
- **Dosing**: Long-acting injectable cabotegravir is given as a 600 mg (3 mL) injection, which is repeated 1 month after the first injection, and then repeated every 2 months thereafter. An optional oral lead-in with cabotegravir 30 mg once daily may be used for approximately 1 month to assess the tolerability of cabotegravir. If the oral cabotegravir lead-in is used, the first injection of cabotegravir should be given on the last day of the oral lead-in (or within 3 days of completing the oral lead-in).
- **Formulation**: Cabotegravir is available as a 200 mg/mL solution and is administered as a 3 mL intramuscular injection in the gluteal region. Oral cabotegravir is a 30 mg tablet that is taken once daily.
- **Food Requirements**: Long-acting injectable cabotegravir has no food restrictions. Oral cabotegravir can be taken with or without food.
- **Use in Persons with Renal Impairment**: **For HIV PrEP, cabotegravir has no renal restrictions**. For persons who have a creatinine clearance less than 30 mL/min, increased monitoring for cabotegravir toxicity is recommended. The monitoring should consist of testing hepatic aminotransferease levels because of potential hepatotoxicity. Hemodialysis is not expected to impact cabotegravir levels.

Source: Cabotegravir Prescribing Information

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Pharmacologic Category

- Cabotegravir – Integrase Strand Transfer Inhibitor (INSTI's)

- Rilpiverine – Non Nucleoside Reverse Transcriptase Inhibitor (NNRTI)

Source: Cabotegravir-Rilpivirine Prescribing Information

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Pharmacokinetics

- **Metabolism -**Cabotegravir: UGT1A1, UGT1A9 (minor); Rilpivirine: CYP3A
- **Excretion-**Cabotegravir: Urine: 27% (0% as unchanged drug); Feces: 59% (47% as unchanged drug).Rilpivirine: Urine: 6% (<1% as unchanged drug); Feces: 85% (26% as unchanged drug).
- **Time to peak -** Cabotegravir: 7 days; Rilpivirine: 3 to 4 days.
- **Half-life elimination -**Cabotegravir: 5.6 to 11.5 weeks; Rilpivirine: 13 to 28 weeks.

Facts and Comparisons®: Drug Referential Resource

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Guidance on Use of LA CAB + RPV

Optimal Candidates

- Virologically suppressed on oral regimen for at least 3-6 mo
- Any renal function
- Engaged with their healthcare
- Agree to make frequent clinic visits

Contraindications

- Prior INSTI or NNRTI resistance (except K103N)
- Prior virologic failure
- Chronic HBV infection (active or occult)

DHHS Guidelines. Guidelines for the Use of Antiretroviral Agents in Adults and Adolescents Living with HIV.

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Starting patients on CABENUVA injections

- Before initiation of clinician-administered Cabotegravir/Rilpiverine, ensure patients agree to the required monthly dosing schedule they have agreed too and counsel patients about the importance of adherence to scheduled dosing visits.

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Long-Acting Cabotegravir-Rilpivirine (CAB-RPV) Considerations if Significant Adherence or Retention in Care Challenges

"The panel recommends **against** long-acting, intramuscular CAB and RPV in people who have detectable viral load due to suboptimal adherence to ART and who have ongoing challenges with retention in HIV care, except in a clinical trial." **(AIII)**

HHS Guidelines for Use of Antiretroviral Agents in Adults and Adolescents with HIV

Source: HHS Guidelines for Use of Antiretroviral Agents in Adults and Adolescents with HIV. Sept 21, 2022

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Cabotegravir and Rilpivirine
Oral and Injectable Preparations

Optional Lead-In Oral Components

Vocabria

Edurant

Cabotegravir + Rilpivirine

30 mg

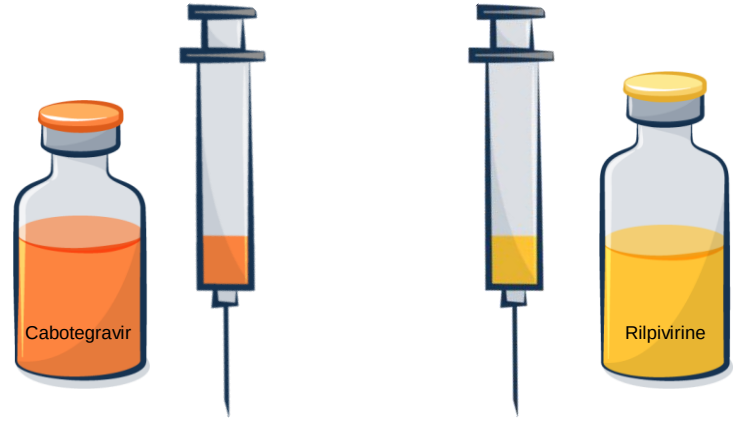
25 mg

INSTI

NNRTI

Intramuscular Injection Components

Brand name - Cabenuva



Cabotegravir + Rilpivirine

200 mg/mL

300 mg/mL

INSTI

NNRTI

Source: Cabotegravir-Rilpivirine Prescribing Information

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Cabotegravir and Rilpivirine Extended Release Injectable Suspension Indications

- **Complete regimen to treat HIV-1**
- **For adults and adolescents (≥12 years who weigh ≥35 kg)**
  - Replace antiretroviral regimen in persons with HIV RNA <50 copies/mL
  - On stable antiretroviral regimen
  - No history of treatment failure
  - No known or suspected resistance to cabotegravir or rilpivirine
- **Oral Lead-In**
  - Lead-in is optional
- **Continuation Phase Injections**
  - Approved for every 1-month and every 2-month injections
  - Doses are different with every 1-month and every 2-month injections
  - Injections may be given up to 7 days before or after the scheduled date
  - 23-gauge, 1.5-inch intramuscular needle recommended (use 2-inch needle if BMI ≥30 kg/m^2)
  - Give ventrogluteal IM injections on opposite sides when possible or ≥2 cm apart if given on same side.

Source: Cabotegravir-Rilpivirine Prescribing Information

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Dosing Schedule for Every 1-Month Injectable Cabotegravir and Rilpivirine

Recommended Dosing Schedule in Adults for Every 1-Month Cabotegravir and Rilpivirine			
Drug	**Optional Oral Lead-In**	**Initiation Phase Injections** (One-Time Dosing)	**Continuation Phase Injections** (Once-Monthly Dosing)
	If used, administer for ≥28 days	Administer on the last day of current antiretroviral therapy or last day of oral lead-in (if used)	Administer Monthly
Cabotegravir	30 mg orally once daily with a meal	600 mg IM (3 mL)	400 mg IM (2 mL)
Rilpivirine	25 mg orally once daily with a meal	900 mg IM (3 mL)	600 mg IM (2 mL)

Source: Cabotegravir-Rilpivirine Prescribing Information

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Schedule for Every 1-Month Injectable Cabotegravir and Rilpivirine

***Optional* Oral Lead-In (≥28 days)**

Cabotegravir 30 mg daily +
Rilpivirine 25 mg daily

***Initiation Phase (1-time)**

Cabotegravir (600 mg): 3 mL IM +
Rilpivirine (900 mg): 3 mL IM

***Continuation Phase (Monthly)**

Cabotegravir (400 mg): 2 mL IM +
Rilpivirine (600 mg): 2 mL IM

Source: Cabotegravir-Rilpivirine Prescribing Information

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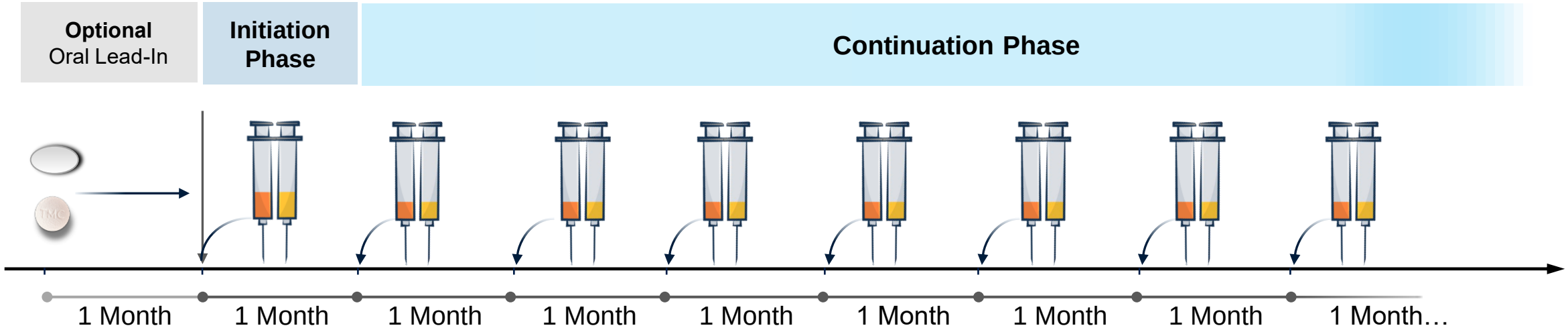
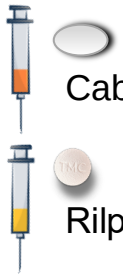
Schedule for Every 1-Month Injectable Cabotegravir and Rilpivirine

Schedule for Injections*: One-time initiation phase injections then monthly continuation phase injections thereafter

Administer first injections on the last day of current fully suppressive antiretroviral therapy or last day of oral lead-in (if used)





Optional Oral Lead-In Dosing: Cabotegravir 30 mg PO daily and Rilpivirine 25 mg PO daily

*__Dosing for 1-time Initiation Phase Injections__ = LA Cabotegravir (600 mg): 3 mL IM and Rilpivirine (900 mg): 3 mL IM

*__Dosing for Continuation Phase Injections__ = LA Cabotegravir (400 mg): 2 mL IM and Rilpivirine (600 mg): 2 mL IM

Injections of rilpivirine and cabotegravir given as 2 separate IM injections at separate gluteal sites (opposite sites or 2 cm apart on same site)
Injections may be given up to 7 days before or after the scheduled date

Source: Cabotegravir-Rilpivirine Prescribing Information; Illustration: David H. Spach, MD

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Management of Missed Injections in Persons on Every 1-Month Dosing

Management for Planned and Unplanned Missed Injections in Patients on Every 1-Month Dosing	
Time Since Last Injection	**Recommendation for Oral Bridging**
Planned Missed Injection • Time to miss a scheduled injection >7 days	• **Two oral options are are available**: - Take daily oral therapy with cabotegravir 30 mg plus rilpivirine 25 mg for up to 2 months to replace missed injection visits. - Take any fully suppressive antiretroviral regimen until injections resume • Start oral therapy with either option above approximately 1 month (+/- 7 days) after the last injection dose of cabotegravir and rilpivirine. • Continue oral therapy until the day injection dosing is restarted.
Unplanned Missed Injection • Time from last injections is >1 month + 7 days	• If oral therapy has not been taken, reassess patients clinically to ensure resumption of injections remains appropriate.

Source: Cabotegravir-Rilpivirine Prescribing Information

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Recommendations for Restarting Injection Doses after Missed Injections with Every 1-Month Dosing Schedule

Injection Dosing Recommendations after Missed Injections with Every-1-Month Dosing Schedule	
Time Since Last Injection	**Recommendation**
Less than or equal to 2 months	Resume with cabotegravir 400 mg (2 mL) and rilpivirine 600 mg (2 mL) monthly injections as soon as possible.
Greater than 2 months	Reinitiate with with cabotegravir 600 mg (3 mL) and rilpivirine 900 mg (3 mL) then continue to follow the monthly cabotegravir 400 mg (2 mL) and rilpivirine 600 mg (2 mL) monthly injection dosing schedule.

Source: Cabotegravir-Rilpivirine Prescribing Information

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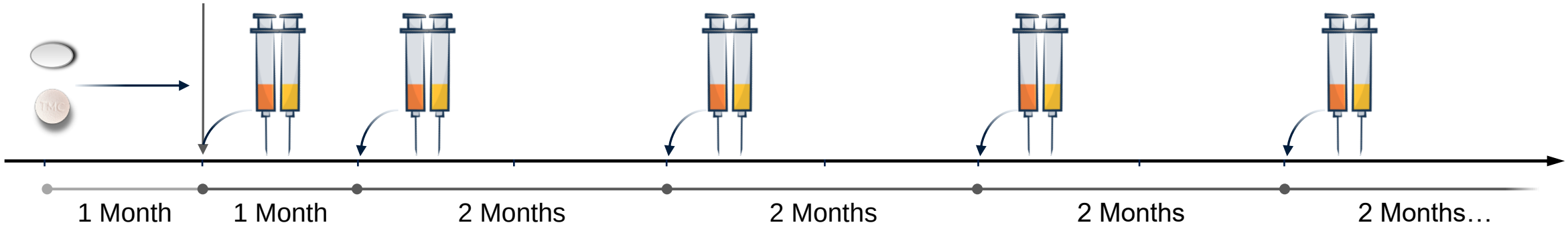
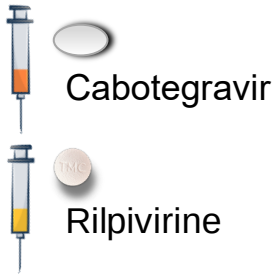
Schedule for Every 2-Month Injectable Cabotegravir and Rilpivirine

Schedule for Injections*: First two injections given 1 month apart then every 2 months thereafter

Administer first injections on the last day of current antiretroviral therapy or last day of oral lead-in (if used)

Optional Oral Lead-In	**Initiation Phase**	**Continuation Phase**





Optional Oral Lead-In Dosing: Cabotegravir 30 mg PO daily and Rilpivirine 25 mg PO daily

***First Two Injections (Initiation Phase):** given 1 month apart, before transitioning to every 2-month dosing

***Dosing for All Injections** = LA Cabotegravir (600 mg): 3 mL IM and Rilpivirine (900 mg): 3 mL IM

Injections of rilpivirine and cabotegravir given as 2 separate IM injections at separate gluteal sites (opposite sites or 2 cm apart on same site)
Injections may be given up to 7 days before or after the scheduled date

Source: Cabotegravir-Rilpivirine Prescribing Information; Illustration: David H. Spach, MD

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Management of Missed Injections in Persons on Every 2-Month Dosing

Oral Bridge Therapy for Planned and Unplanned Missed Injections in Patients on 2-Month Dosing

Time Since Last Injection	Recommendation for Oral Bridging
Planned Missed Injection • Time to miss a scheduled injection >7 days	• **Two oral options are are available**: - Take daily oral therapy with cabotegravir 30 mg plus rilpivirine 25 mg for up to 2 months to replace missed injection visits. - Take any fully suppressive antiretroviral regimen until injections resume • Start oral therapy with either option above approximately 2 months (+/- 7 days) after the last injection doses. • Continue oral therapy until the day injection dosing is restarted.
Unplanned Missed Injection • Time for scheduled injection is missed or delayed by >7 days	• If oral therapy has not been taken, reassess patients clinically to ensure resumption of injections remains appropriate.

Source: Cabotegravir-Rilpivirine Prescribing Information

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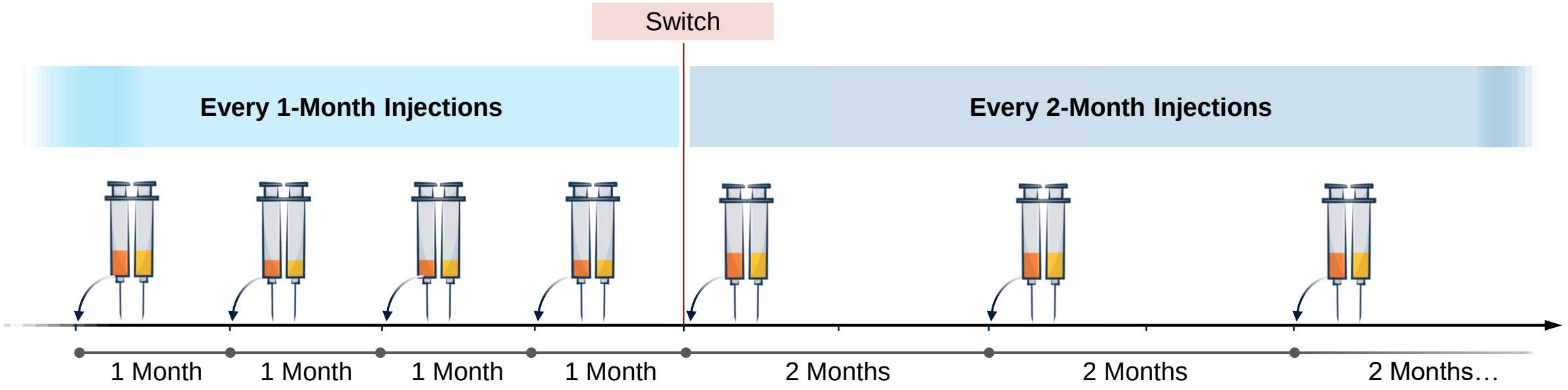
Recommendations for Restarting Injection Doses after Missed Injections with Every 2-Month Dosing Schedule

Injection Dosing Recommendations after Missed Injections with Every-2-Month Dosing Schedule

Missed Injection Visit	Recommendation
Injection 2	• **Time since last injection ≤2 months**: Resume with cabotegravir 600 mg (3 mL) and rilpivirine 900 mg (3 mL) as soon as possible, then continue to follow the every-2-month injection dosing schedule. • **Time since last injection >2 months**: Re-initiate the patient with cabotegravir 600 mg (3 mL) and rilpivirine 900 mg (3 mL) followed by the second initiation injection dose 1 month later. Then continue to follow the every-2-month injection dosing schedule thereafter.
Injection 3 or Later	• **Time since last injection ≤3 months**: Resume with cabotegravir 600 mg (3 mL) and rilpivirine 900 mg (3 mL) as soon as possible and continue with the every-2-month injection dosing schedule. • **Time since last injection >3 months**: Re-initiate the patient with cabotegravir 600 mg (3 mL) and rilpivirine 900 mg (3 mL) followed by the second initiation injection dose 1 month later. Then continue with the every-2-month injection dosing schedule thereafter.

Source: Cabotegravir-Rilpivirine Prescribing Information

Cabotegravir and Rilpivirine Extended-Release Injectable Suspension
Switching from Every 1-Month to Every 2-Month Cabotegravir and Rilpivirine



Cabotegravir

Rilpivirine

*__Dosing for Every 1-Month Injections__ = LA Cabotegravir (400 mg): 2 mL IM and Rilpivirine (600 mg): 2 mL IM

*__Dosing for Every 2-Month Injections__ = LA Cabotegravir (600 mg): 3 mL IM and Rilpivirine (900 mg): 3 mL IM

Injections of rilpivirine and cabotegravir given as 2 separate IM injections at separate gluteal sites (opposite sites or 2 cm apart on same site)

Source: Cabotegravir-Rilpivirine Prescribing Information; Illustration: David H. Spach, MD

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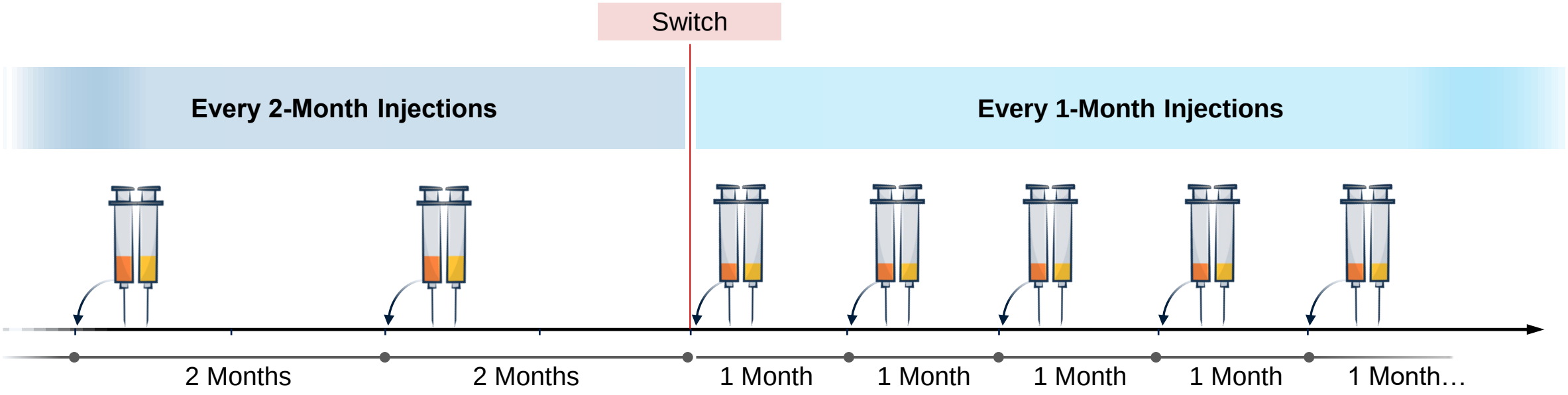
Cabotegravir and Rilpivirine Extended-Release Injectable Suspension
Switching from Every 2-Month to Every 1-Month Cabotegravir and Rilpivirine



Cabotegravir

Rilpivirine

*__Dosing for Every 2-Month Injections__ = LA Cabotegravir (600 mg): 3 mL IM + Rilpivirine (900 mg): 3 mL IM

*__Dosing for Every 1-Month Injections__ = LA Cabotegravir (400 mg): 2 mL IM + Rilpivirine (600 mg): 2 mL IM

Injections of rilpivirine and cabotegravir given as 2 separate IM injections at separate gluteal sites (opposite sites or 2 cm apart on same site)

Source: Cabotegravir-Rilpivirine Prescribing Information; Illustration: David H. Spach, MD

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Studies Show Safe and Effective

Phase 3 Trials in Treatment Naïve

- FLAIR: IM CAB + IM RPV monthly versus oral DTG-ABC-3TC: 48 weeks
- FLAIR: IM CAB + IM RPV monthly versus oral DTG-ABC-3TC: 96 weeks
- FLAIR: IM CAB + IM RPV with or without oral lead in: 124-week extension

Phase 3 Trials in Treatment Experienced

- ATLAS: Switch to monthly IM CAB + IM RPV or continue 3-drug oral ART
- ATLAS-2M: switch to IM CAB + IM RPV taken every 1 or 2 months: 48 weeks
- ATLAS-2M: switch to IM CAB + IM RPV taken every 1 or 2 months: 96 weeks

Phase 2 Trials

- LATTE: oral CAB + oral RPV daily versus oral EFV plus 2 NRTIs
- LATTE-2: IM CAB + IM RPV every 1 or 2 months versus oral CAB + oral ABC-3TC
- POLAR: every 2-month IM CAB + IM RPV after 5 years or oral CAB + oral RPV

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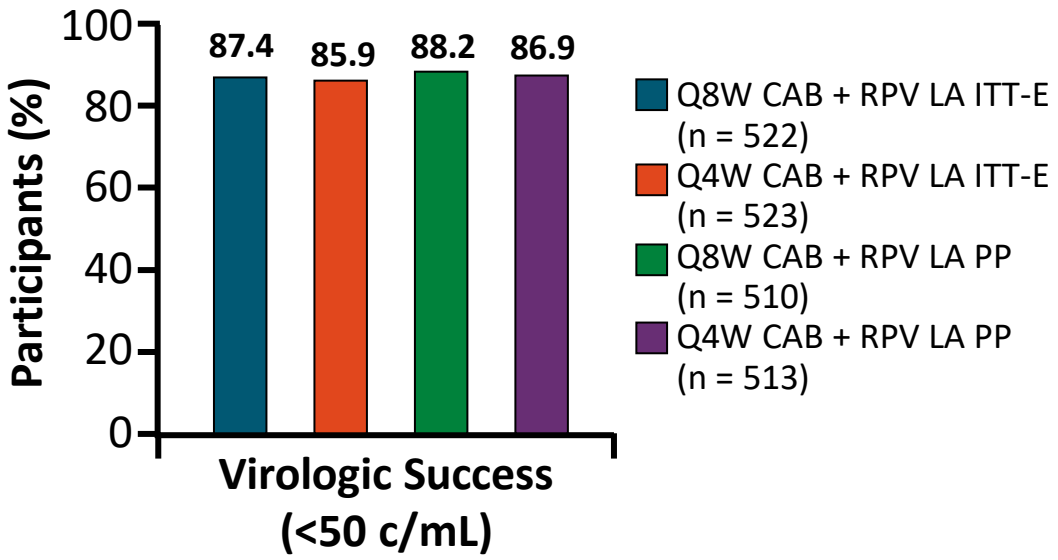
ATLAS-2M: Wk 152 Outcomes



Outcome	Q8W (n = 522)	Q4W (n = 523)
CVF, n (%)	11 (2)	2 (<1)
RPV RAMs, n/N	9/11	1/2
INSTI RAMs, n/N	8/11	2/2

- Multicenter, randomized, open-label phase IIIb noninferiority trial following ATLAS
- LA CAB + RPV well tolerated
  - 99% of ISRs were grade 1/2; median duration was 3 days
  - 8 (2%) Q8W and 13 (3%) Q4W withdrew due to ISRs
- Patient satisfaction scores significantly favored Q8W vs Q4W dosing at Wk 24, 48, and 152

Overton. Lancet. 2021;396:1994. Overton. CROI 2022. Abstr 479.

Risk Factors for Virologic Failure With LA CAB + RPV

- Post hoc analysis of **Wk 48 phase III data**[1]
  - ATLAS and FLAIR (Q4W dosing)
  - ATLAS-2M (Q4W and Q8W dosing)
- 13/1039 (1.25%) participants had CVF
- Among 96.7% with 0 or 1 risk factor for CVF, 0.4% had CVF
- Q8W dosing was not significant factor associated with CVF

Factors Associated With CVF	OR
RPV RAS(s) at baseline	40.36
Wk 8 RPV trough concentration	5.00
Baseline HIV-1 subtype A6/A1	5.92
BMI (kg/m^2) at baseline	1.13

No. of Baseline Factors Associated With CVF	CVF, %	HIV-1 RNA <50 c/mL, %
None	0.4	95
1	0.4	96
≥2	26	71
Total	**1.3**	**94**

- Expanded multivariate analysis of CVF from FLAIR through Wk 124, ATLAS through Wk 96, and ATLAS-2M through Wk 152[2]
  - Baseline RPV RAMs and HIV-1 subtype A6/A1 most significant predictive factors for CVF
  - Patients with 0/1 baseline factors had low risk of failure

1. Cutrell. AIDS. 2021;35:1333. 2. Orkin. HIV Glasgow 2022. Abstr O44.

Drug Interactions

Drugs that are strong inducers of UGT1A1 or UGT1A9 are expected to decrease the plasma concentrations of cabotegravir.

Drugs that induce or inhibit CYP3A may affect the plasma concentrations of rilpivirine.

- Carbamazepine
- Oxcarbazepine
- Phenobarbital, phenytoin
- Rifabutin, rifampin, rifapentine
- Systemic dexamethasone (>1 dose)
- St. Johns Wort

Source: Cabotegravir-Rilpivirine Prescribing Information

Drug Interactions

Concomitant drug class Drug name	**Effect on concentration**	**Recommendation**
Anticonvulsants: Carbamazepine Oxcarbazepine Phenobarbital Phenytoin	↓Rilpivirine	Coadministration with CABENUVA is contraindicated due to potential for loss of virologic response and development of resistance.
Antimycobacterials: Rifampin Rifapentine Rifabutin	↓Cabotegravir ↓Rilpivirine	
Glucocorticoid (systemic): Dexamethasone (more than a single-dose treatment)	↓Rilpivirine	
Herbal product: St John's wort (*Hypericum perforatum)*	↓Rilpivirine	
Macrolide or ketolide antibiotics: Azithromycin Clarithromycin Erythromycin	↔Cabotegravir ↑Rilpivirine	Macrolides are associated with risk of Torsade de Pointes. Where possible, consider alternatives such as azithromycin, which increases rilpivirine concentrations less.
Narcotic analgesic:	↔ Cabotegravir ↔ Rilpivirine	No dose adjustment required when starting coadministration with CABENUVA. Clinical monitoring is recommended as methadone maintenance therapy may need to be adjusted in some patients.

↑ = Increase, ↓ = Decrease, ↔ = No Change

Source: Cabotegravir-Rilpivirine Prescribing Information;

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Long-Acting Cabotegravir-Rilpivirine (CAB-RPV) and Virologic Failure

- Guidelines previously recommended checking resistance assay(s) within 4 weeks ART stoppage
- Injectable CAB and RPV have very long half-lives
- Resistance tests now recommended with virologic failure after CAB-RPV stoppage, regardless of time since last dose

Source: HHS Guidelines for Use of Antiretroviral Agents in Adults and Adolescents with HIV. Sept 21, 2022.

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Actual Acquisition Cost of LAR - (340B Pricing)

- Appretude -600mg -1 x 3 ml - SDV $2,883.37
- Cabenuva -400-600mg – 1 x 4 ml - SDV $3,234.25
- Cabenuva – 600 -900mg – 1 x 6ml – SDV $4,853.91

Cardinal Health Order Express. PHS340 contract pricing

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UNDERSTAND YOUR COSTS AND COVERAGE FOR CABENUVA

- Navigate the insurance process
- Check your coverage under pharmacy or medical insurance
- See if you're eligible for savings or assistance programs* that help pay for CABENUVA
- ViiVConnect.com - 1-844-588-3288 (toll-free), Monday-Friday, 8AM-11PM (ET) or visit ViiVConnect.com.

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Summary

- Intramuscular cabotegravir-rilpivirine (CAB-RPV) is the first approved long-acting antiretroviral treatment regimen
- Eligible patients are those taking a stable oral regimen with suppressed HIV RNA, no HBV, no CAB or RPV resistance
- Must attend visits every 1 or 2 months for injections administered by a healthcare professional
- Usage has been limited thus far due to clinical factors, insurance coverage, and logistical barriers

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