National HIV Curriculum

Long Acting Injectables for Treatment of HIV

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Disclosures

Dr. Budak has no financial disclosures.

Objectives

- Describe long-acting injectable treatment options for people with HIV, including options for individuals not virally suppressed on oral medications
  - Cabotegravir-rilpivirine
  - Lenacapavir

- Incorporate data on long-acting injectable treatment options in decision making regarding use

Cabotegravir-Rilpivirine

Outline

- Background Data
- Virologic Failure
- Clinical Review Considerations
- Use in Persons with Viremia or Adherence Difficulties
- Implementation and Logistics

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FDA-Approved Antiretroviral 2-Drug Regimens

- **Initial Therapy**
  - Dolutegravir-lamivudine
- **Maintenance Therapy**
  - Dolutegravir-lamivudine
  - Dolutegravir-rilpivirine
  - *Cabotegravir-rilpivirine (long-acting injectable)*

Slide from David Spach, MD.

FDA-Approved Antiretroviral 2-Drug Regimens

- **DTG-3TC**
  - Dolutegravir + Lamivudine

INSTI + NRTI

- **DTG-RPV**
  - Dolutegravir + Rilpivirine

INSTI + NNRTI

- **IM CAB-RPV**
  - Cabotegravir + Rilpivirine

INSTI + NNRTI

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Background Studies

- **ATLAS, FLAIR,** and **ATLAS-2M** studies demonstrated efficacy of LAI CAB-RPV and led to FDA approval for virally suppressed (VS) PWH[1,2]

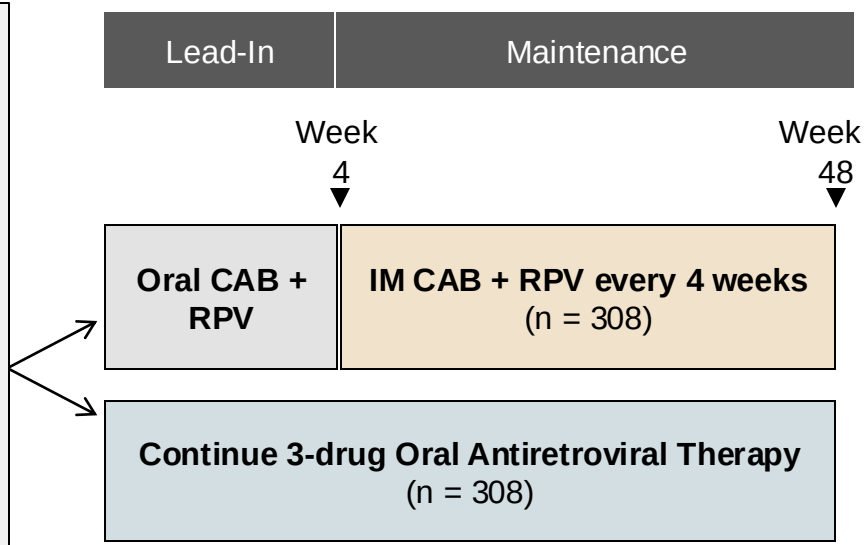
- In **LATITUDE**, in persons with adherence difficulties, injectable CAB-RPV q4w was superior to oral standard of care - the Drug and Safety Monitoring Board halted randomization and offered switch to CAB-RPV to all patients[3]

- The **CARES** Study of injectable CAB-RPV q8w administered in public health settings in sub-Saharan Africa was non-inferior in virologic efficacy to oral standard of care and was well tolerated[4]

1-Orkin C et al, NEJM, 2020. 2-Overton ET et al, CID, 2023. 3-Rana AI et al, CROI 2024 #212. 4-Kityo CM et al, CROI 2025 #202.

Long-Acting IM Cabotegravir and IM Rilpivirine for HIV Maintenance
ATLAS Study: Design

- **Background**: Phase 3, randomized, open-label trial assessing IM cabotegravir plus IM rilpivirine after oral induction for adults taking a 3-drug oral antiretroviral therapy regimen
- **Inclusion Criteria**
  - Age ≥18 years
  - Taking 2 NRTIs + INSTI, NNRTI, or PI
  - Stable ARV regimen ≥6 months
  - HIV RNA <50 copies/mL ≥6 months
  - No history of virologic failure
  - No INSTI or NNRTI resistance mutations allowed, except for K103N
  - No chronic hepatitis B



Abbreviations: CAB = cabotegravir; RPV = rilpivirine

Slide from Dr. Brian Wood. Source: Swindells S, et al. N Engl J Med. 2020;382:1112-23.

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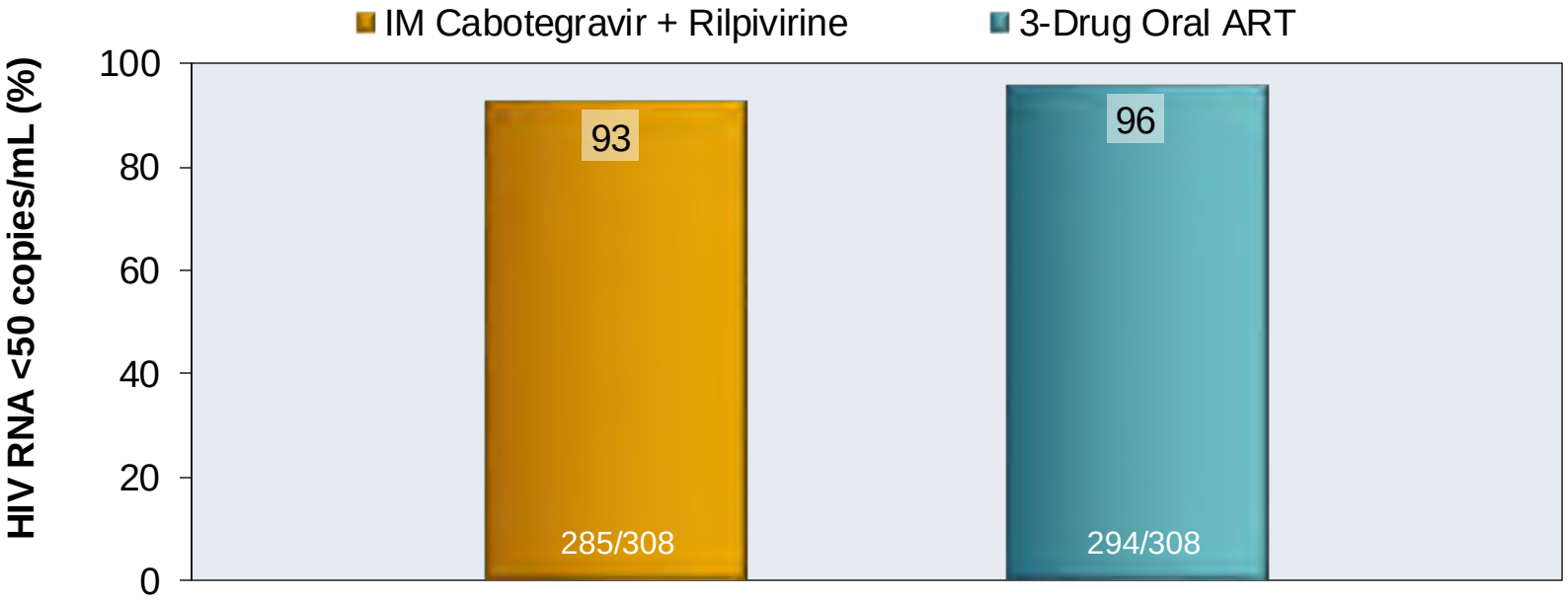
Long-Acting IM Cabotegravir and IM Rilpivirine for HIV Maintenance
ATLAS Study: Results

Weeks 48: Virologic Response by FDA Snapshot Analysis



HIV RNA ≥50 copies/mL at 48 weeks: 2 % CAB + RPV, 1% 3-drug oral ART

Slide from Dr. Brian Wood. Source: Swindells S, et al. N Engl J Med. 2020;382:1112-23.

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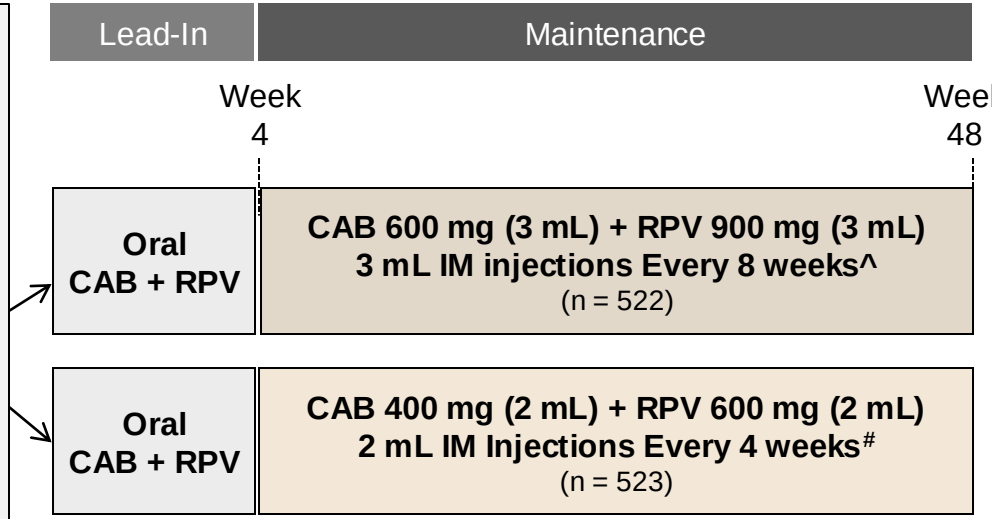
IM Cabotegravir and IM Rilpivirine Every 2 Months for HIV Maintenance

ATLAS-2M Study: Design

- **Background**: Phase 3, randomized, open-label trial assessing IM CAB plus IM RPV maintenance ART administered every 8 weeks versus every 4 weeks
- **Inclusion Criteria**
  - Age ≥18 years
  - Taking an uninterrupted first or second oral standard of care ART regimen for ≥6 months
  - HIV RNA <50 copies/mL ≥6 months at screening and >2x in prior year
  - No history of virologic failure
  - No INSTI or NNRTI resistance, except that K103N mutation allowed



*Some individuals enrolled from ATLAS trial; those already receiving IM CAB + RPV through ATLAS did not require oral lead-in for ATLAS-2M

^Participants first received loading doses of CAB 600 mg (3 mL) + RPV 900 mg (3 mL) 3 mL IM injections given at study weeks 4 and 8

#Participants first received loading dose of CAB 600 mg (3 mL) + RPV 900 mg (3 mL) 3 mL IM injections given at study week 4

Slide from Dr. Brian Wood. Source: Overton ET, et al. Lancet. 2020:396:1994-2005.

IM Cabotegravir and IM Rilpivirine Every 2 Months for HIV Maintenance
ATLAS-2M Study: Results

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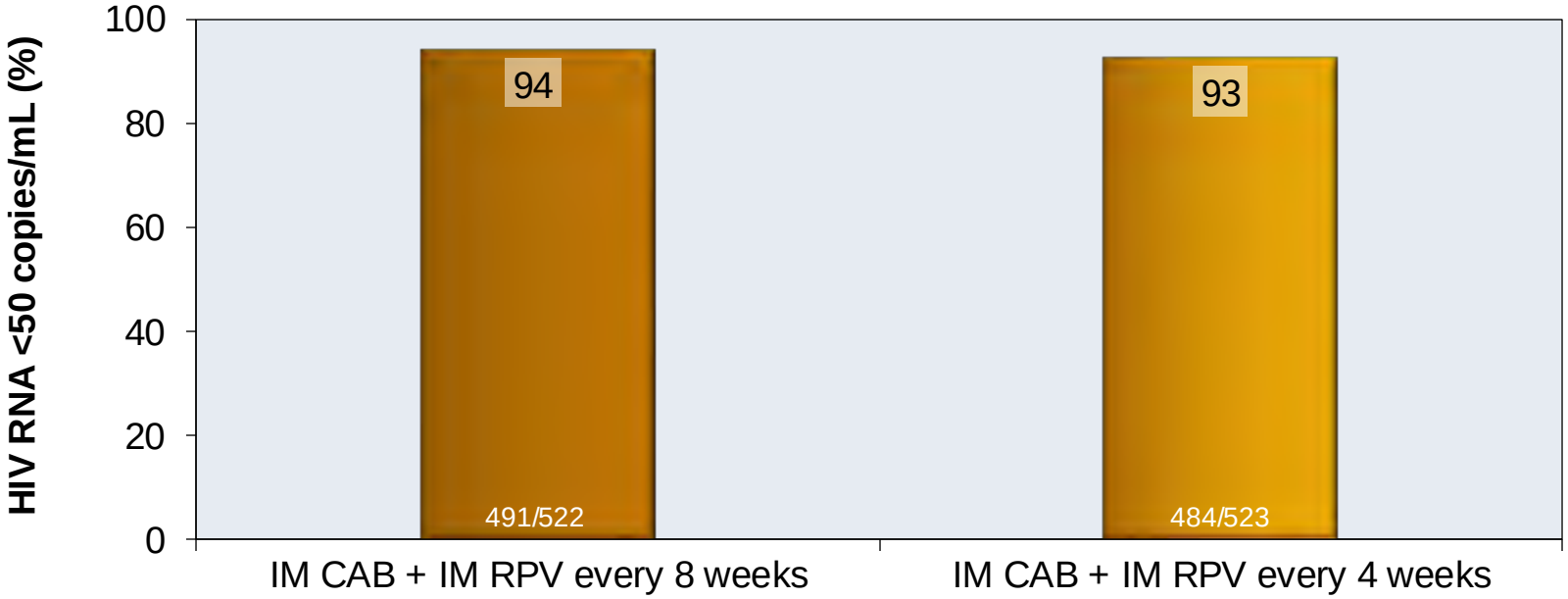

HIV RNA ≥50 copies/mL at 48 weeks: 9/522 (2%) in q8-week arm, 5/523 (1%) in q4-week arm

Slide from Dr. Brian Wood. Source: Overton ET, et al. Lancet. 2020:396:1994-2005.

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HHS Recommendations November 2023

- Monthly or every 2-month ventrogluteal IM injections of LA CAB and RPV can be used to replace an existing oral ARV regimen in PWH with sustained viral suppression for 3-6 months
- Criteria for use, with or without oral lead-in, included:
  - History of good adherence and engagement in care
  - No baseline resistance to either medication
  - No prior virologic failure (VF)
  - No active or occult HBV infection (unless already receiving HBV active meds)
  - No drug-drug interactions with oral or injectable CAB or RPV

Adapted from Landovitz R, ID Week 2024 referencing HHS Guidelines for Use of Antiretroviral Agents in Adults and Adolescents with HIV November 2023.

Outline

- Background Data
- **Virologic Failure**
- Clinical Review Considerations
- Use in Persons with Viremia or Adherence Difficulties
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Risk Factors for Virologic Failure (VF) with CAB-RPV

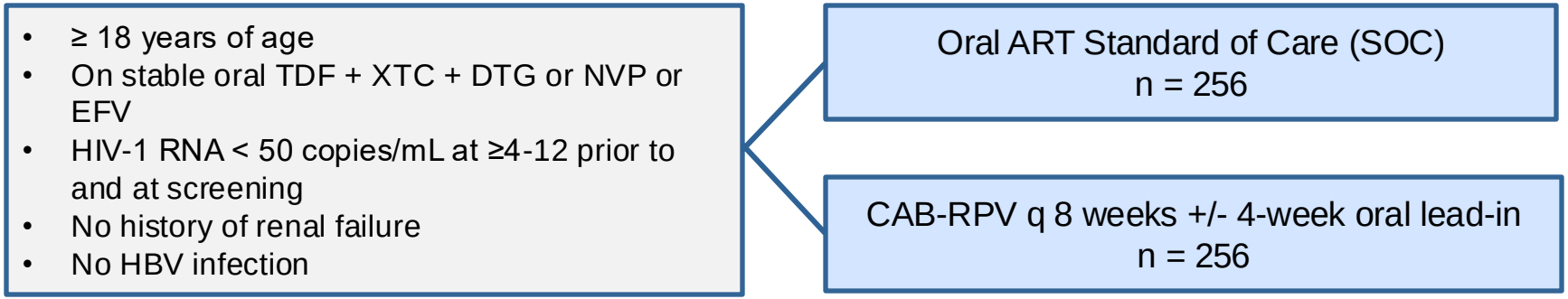
- Pooled data from 1651 participants in ATLAS, FLAIR, and ATLAS-2M
- Confirmed virologic failure seen in 23 PWH (1.4%), through 152 weeks
- Dosing, demographic, viral, pharmacokinetic (PK) covariates explored

- Having ≥ 2 of the below factors was associated with increased VF risk:
  1. Rilpivirine resistance-associated mutations
  2. A6/A1 subtype
  3. Body mass index ≥ 30 kg/m^2

Source: Orkin C et al, Clinical Infectious Diseases, 2023.

CARES: Study Design

- Phase 3b, Randomized, Open-Label, Active-Controlled, Non-Inferiority Study



- HIV-1 RNA checked every 24 weeks
- Due to a public health approach to enrollment, resistance analysis performed during therapy and proviral DNA was performed for archived resistance on stored PBMCs
- Study sites in Uganda, Kenya, and Tanzania

Source: Kityo CM et al, CROI 2025 #202.

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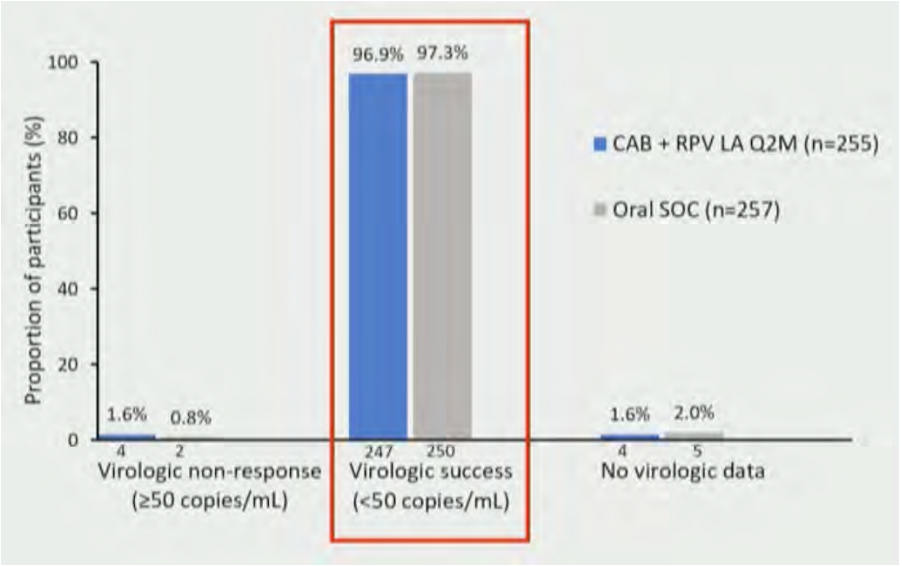
CARES: Week 96 Results

- LA CAB-RPV demonstrated noninferior virologic efficacy as compared to oral standard of care ART
- 77% had an injection site reaction (ISR)
- Over 99% on LA CAB-RPV preferred injectable to daily oral therapy
- 4 cases of virologic failure (1.6%)
- Of note, 55% of participants had subtype A1 virus



Source: Kityo CM et al, CROI 2025 #202.

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Modified from Source: Orkin C et al, Clinical Infectious Diseases, 2023.

What else is known about VF with LAI CAB-RPV?

- **VF typically occurs in the first year**
  - Median time to suspected VF (first of 2 consecutive measurements of HIV=1 RNA ≥ 200 copies/mL) was 24.9 (16.9-49.3) weeks[1]

- **Failure despite perfect adherence has been seen**
  - SOLAR Study: RCT of 670 stable PWH on BIC/TAF/FTC switched to CAB-RPV q8w vs continued BIC/TAF/FTC, VS was non-inferior at 12 months[2]
    - 3 individuals had confirmed VF (CVF) in the CAB-RPV arm despite on-time injections
    - No CVF in the BIC/TAF/FTC arm

1-Orkin C et al, CID, 2023. 2-Ramgopal MN et al, Lancet HIV, 2023.

Two Categories of Virologic Failure

1. Early failure despite on-time injections
2. Late failure due to late injections, personal choice not to resume oral ART, or loss-to-follow-up

> "…complexity of long-acting injectable treatment, in which the unique circumstances of a patient's care trajectory require nuanced decision making."

Source: Hickey MD et al, CID, 2025.

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A Case to Illustrate Eligibility Review

A 45-year-old man with HIV is suppressed on BIC-TAF-FTC. His last CD4 cell count was 476 cells/mm^3 and his last HIV-1 RNA was undetectable.

His viral load has been undetectable for several years, and generally, he has good adherence, but does shift work as a firefighter and has difficulty at times with taking his ART. This is stressful to him, and he does not like to bring his medication to his shift.

His PCP places a referral for injectable CAB-RPV.

Eligibility Review Considerations

- CD4/VL History
- ART History, including current ART
- Drug Resistance History, including subtype
- Clinic visit and ART prescription history
- Drug-drug interactions
- BMI
- Pregnancy
- Hepatitis B status

≥ 2 of the below factors are associated with increased VF risk[1]

- Rilpivirine RAMs
- A6 subtype
- BMI ≥ 30 kg/m^2

1- Orkin C et al, Clinical Infectious Diseases, 2023.

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Ward 86 Injectable Guidelines

Updated May 20, 2024

WARD 86 LONG-ACTING INJECTABLE ANTIRETROVIRAL GUIDELINES

PURPOSE OF THIS GUIDELINE

- Provide guidance to clinicians on long-acting injectable cabotegravir/rilpivirine (CAB/RPV LA) 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
- Provide guidance to clinicians on education to patients who will receive CAB/RPV LA
- Provide guidance on care coordination, including clinic appointments and follow ups, for patients on CAB/RPV LA

https://gettingtozerosf.org/wp-content/uploads/2024/05/Ward-86-LA-ART-protocol-5-20-2024.pdf

Polymorphism vs RAM?

- 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. We have decided on the mutations which we will exclude based on which rilpivirine or cabotegravir resistance associated mutations were associated with breakthrough infections in FLAIR, ATLAS, ATLAS 2M (the registrational trials for CAB/RPV); HPTN 083 (study examining every 8 weeks intramuscular CAB for HIV prevention) and the Echo/Thrive trials (studying rilpivirine versus efavirenz for first-line therapy in treatment naïve patients).
  - *Rilpivirine*: V90I, L100I, K101E, V106A, V108I, E138A/G/K/T, V179I, Y181C, Y188L, V189I, H221Y, P225H, F227C, M230L
  - *Cabotegravir*: T97A; G118R; Q148H/K/R; E138K; G140R; N155H; R263K

https://gettingtozerosf.org/wp-content/uploads/2024/05/Ward-86-LA-ART-protocol-5-20-2024.pdf

L74I is Now a Major Mutation in Subtype A6

- Of the 6 virologic failures from the ATLAS and FLAIR registrational trials, 5 had an L74I[1,2]
  - All 5 PWH with VF with an L74I had subtype A1 virus

- In March 2025, IAS-USA wrote that L74I, "a signature mutation in HIV-1 subtype A6 that may occur as a polymorphism in other HIV-1 subtypes…was associated with CVF in clinical trials of LA CAB and RPV."[3]

IAS–USA *Topics in Antiviral Medicine*

Table 1. Summary of mutation updates to the 2025 figure bars.

Drug	Figure bar changes (mutation type)
Doravirine	Added A98G (minor)
Dolutegravir	Added S147G (minor)
Cabotegravir	Added L74I (major)[a]
Lenacapavir	Added K70H (major) Updated K70N (major) Updated L56I (major) Updated N74D (major)
Raltegravir	Added G118R (major) Added G140C (minor)
Elvitegravir	Added G118R (major) Added E138A/K (minor) Added G140A/C/S (minor)

[a]Relevant for subtype A6 only.

1-Swindells S et al, NEJM, 2020. 2-Orkin C et al, NEJM, 2020. 3-Wensing AM et al, IAS-USA, 2025.

What about proviral DNA genotype resistance?

- Proviral DNA resistance testing has high specificity but **low sensitivity**[1]
- At UWMedicine, from 2015 to August 2024, 61% of proviral DNA testing were sent between 2023-2024[2]
- In a cohort of 383 PWH at UCSD referred for evaluation, proviral DNA resistance testing was sent in 35.2% of individuals; 18.5% had a RAM that led to a decision to defer CAB-RPV[3]
- Here, we sent proviral DNA sequencing on 15% of PWH being evaluated; 52% had treatment deferred due to results[4]
- **Thoughtful, judicious use of proviral DNA testing *may* have a role in evaluation for LAI CAB-RPV**

1-Wensing AM et al, CID, 2025. 2-Correspondence with Dr. Kate Crawford. 3-Hill LA et al, AIDS, 2023. 4-Unpublished data

Drug-Drug Interactions

- Rilpivirine may prolong QTc
- Drugs that induce UGT1A1 or CYP3A4 may decrease plasma concentrations of cabotegravir or rilpivirine, respectively
- Key classes with interactions, including contraindications in red:
  - Anticonvulsants: carbamezapine, oxcarbazepine, phenobarbital, phenytoin
  - Rifamycins
  - Systemic dexamethasone (more than a single-dose)
  - St. John's wort
  - Macrolides: may increase concentrations of rilpivirine
  - Methadone: may result in decreased concentrations of methadone

1-Cabenuva FDA Package Insert.

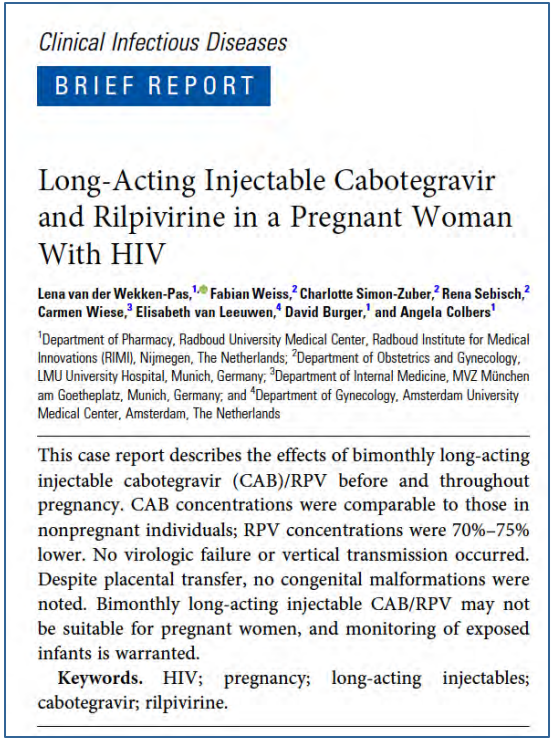
Body Mass Index and LAI CAB-RPV

- BMI ≥ 30 kg/m^2 is one of the three risk factors for VF[1]
- BMI is an extremely imperfect calculation
- There is variability in pharmacokinetic parameters with higher BMIs, among other factors[2]
- Little is known about the impact of class III obesity (BMI ≥ 40 kg/m^2) on CAB-RPV pharmacokinetics[2]
- **If BMI ≥ 30 kg/m^2, use of a longer (2-inch) needle is recommended**[3]

1-Orkin C et al, Clinical Infectious Diseases, 2023. 2-Maguire C et al, CID, 2024. 3-Cabenuva FDA Package Insert.

LAI CAB-RPV in Pregnancy

- Little is known about the safety, efficacy, and outcomes of CAB-RPV in pregnancy
- HHS Guidelines state, “Data are not available about the efficacy and safety of injectable cabotegravir (CAB) and rilpivirine (RPV) during pregnancy.”[1]
- Observational data suggests efficacy, safety for the fetus, and adequate concentrations, however, it use is not currently recommended[2,3]
- May submit to Antiretroviral Pregnancy Registry[4]



Clinical Infectious Diseases

BRIEF REPORT

Long-Acting Injectable Cabotegravir and Rilpivirine in a Pregnant Woman With HIV

Lena van der Wekken-Pas,[1] Fabian Weiss,[2] Charlotte Simon-Zuber,[2] Rena Sebisch,[2] Carmen Wiese,[3] Elisabeth van Leeuwen,[4] David Burger,[1] and Angela Colbers[1]

[1]Department of Pharmacy, Radboud University Medical Center, Radboud Institute for Medical Innovations (RIMI), Nijmegen, The Netherlands; [2]Department of Obstetrics and Gynecology, LMU University Hospital, Munich, Germany; [3]Department of Internal Medicine, MVZ München am Goetheplatz, Munich, Germany; and [4]Department of Gynecology, Amsterdam University Medical Center, Amsterdam, The Netherlands

This case report describes the effects of bimonthly long-acting injectable cabotegravir (CAB)/RPV before and throughout pregnancy. CAB concentrations were comparable to those in nonpregnant individuals; RPV concentrations were 70%–75% lower. No virologic failure or vertical transmission occurred. Despite placental transfer, no congenital malformations were noted. Bimonthly long-acting injectable CAB/RPV may not be suitable for pregnant women, and monitoring of exposed infants is warranted.

Keywords. HIV; pregnancy; long-acting injectables; cabotegravir; rilpivirine.

1-HHS Antiretroviral Therapy Guidelines. Clinical Info (clinicalinfo.hiv.gov). Sept 12, 2024. 2-Short WR et al, CROI 2025 #1015. 3-Patel P et al, HIV Medicine, 2022. 4-https://www.apregistry.com/

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Hepatitis B Status and LAI CAB-RPV

- Neither cabotegravir nor rilpivirine are active against hepatitis B
- HBV vaccination rates among PWH remain low[1]

- **Prevention:** Ideally, PWH would have HBV immunity prior to CAB-RPV initiation; can incorporate immunization into injectable ART workflows to facilitate immunization[2]

- **Treatment:** Can use CAB-RPV in chronic hepatitis B if paired with HBV active agent

1-Corcorran MA, Kim HN, Top Antivir Med, 2023. 2-Ochieng E et al, OFID, 2025.

To OLI or Not to OLI?

- Use of an oral lead-in is optional
- Participate in shared decision-making with the patient
- Recommend if a patient has many drug allergies or intolerances
- Use of the oral lead-in is logistically difficult as it requires acquisition of oral cabotegravir and oral rilpivirine from the pharmaceutical company

Dosing Frequency

- Most individuals are on every 8-week dosing

- Every 4-week dosing should be used for individuals with adherence difficulties or who are viremic
  - Based on the LATITUDE study, PWH with adherence difficulties should be receiving injections every 4 weeks[1]
  - The CROWN Study is recruiting individuals with adherence difficulties and viremia and will be administering injections every 8 weeks[2]

1- Rana AI et al, CROI 2024 #212. 2- https://www.viiv-studyregister.com/en/study/?id=221611

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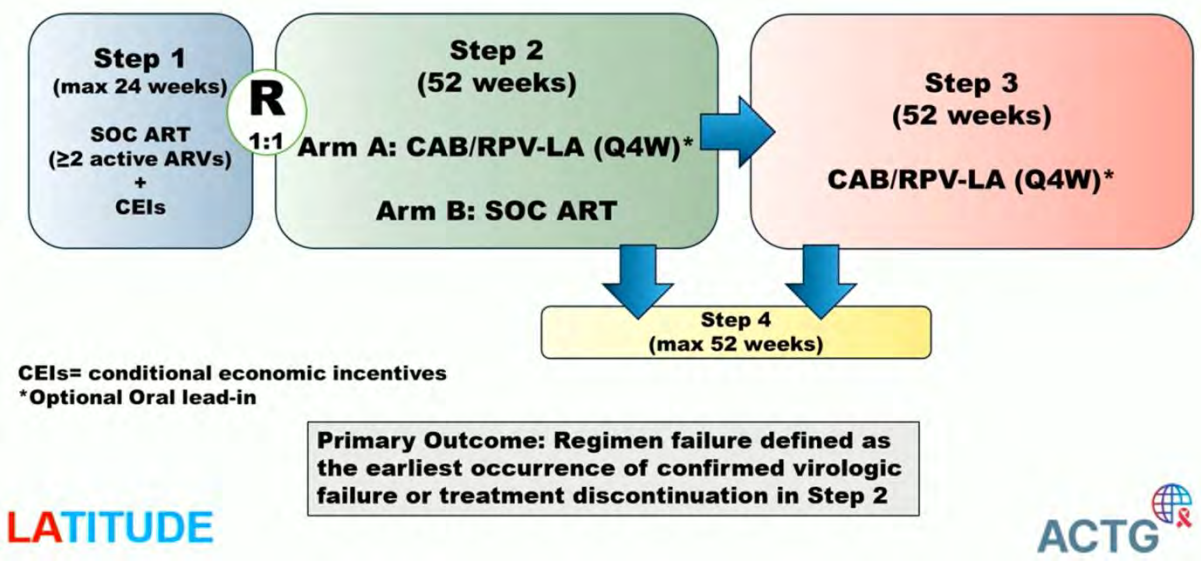
LATITUDE: Study Design

- Phase 3 prospective, randomized, open-label trial

- PWH who have barriers to adherence:
  - Poor viral response despite oral ART for ≥ 6m
  - Loss to follow up with ART non-adherence ≥ 6m
- No Hepatitis B
- No INSTI or RPV RAM historically or by screening



Source: Rana AI et al, CROI 2024 #212.

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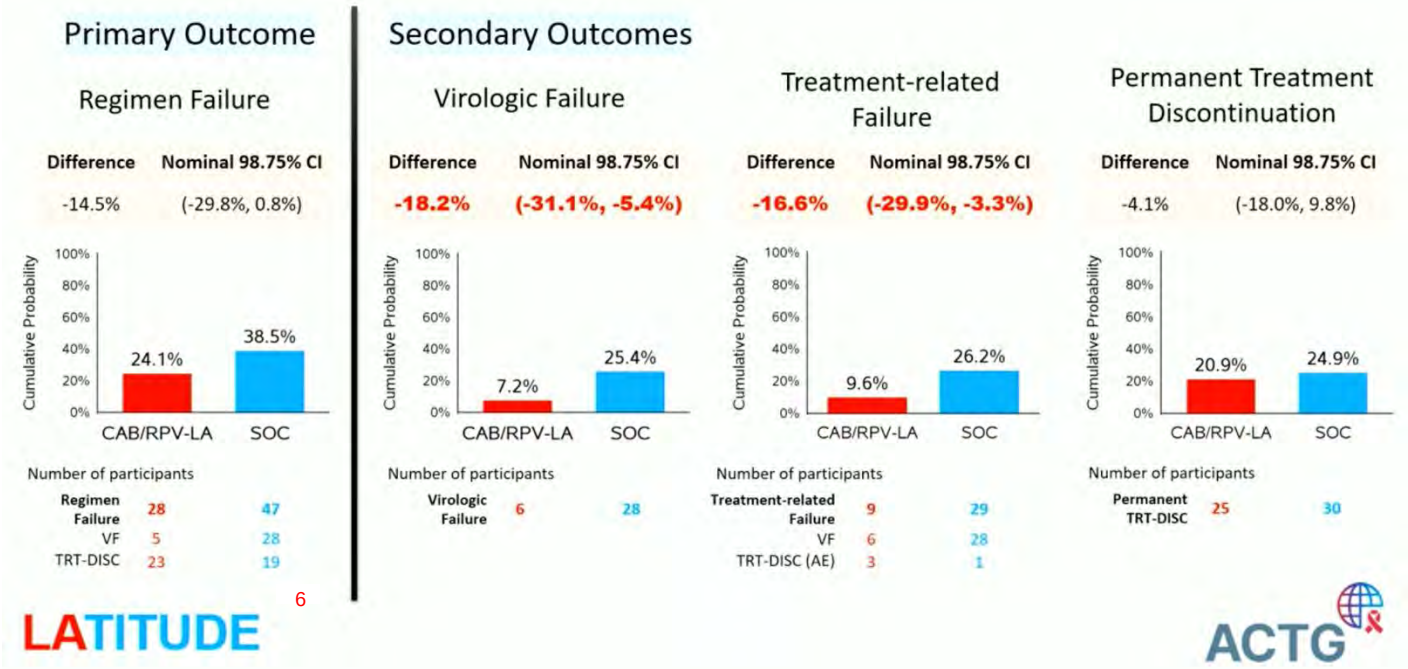
LATITUDE: Interim Data



LA CAB-RPV q4w was superior to oral SOC in secondary outcomes; there were fewer VFs and treatment-related failures

In 2/2024, DSMB recommended to stop randomization & offer all eligible participants switch to CAB/RPV

Source: Rana AI et al, CROI 2024 #212.

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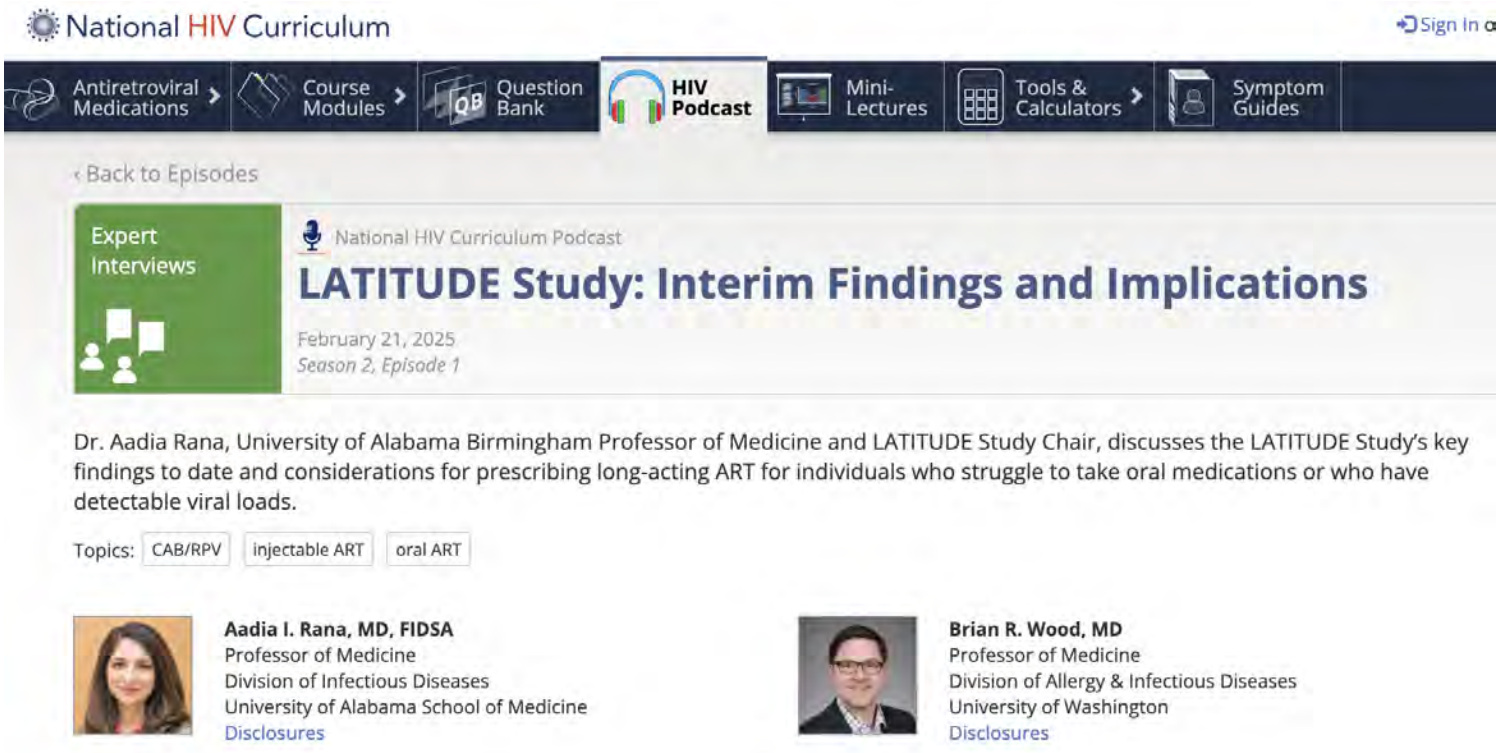
National HIV Curriculum Podcast



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CAB-RPV in PWH with Viremia

- [HHS] “Panel recommends the use of LA CAB/RPV on a case-by-case basis in select individuals with persistent virologic failure despite intensive adherence support on oral ART, who have no evidence of resistance to CAB or RPV, and with shared decision-making between providers and people with HIV (CIII).”[1]

- Real-world experience among PWH initiating CAB-RPV while viremic are encouraging, with >90% of individuals achieving viral suppression[2,3]

1-HHS Antiretroviral Therapy Guidelines. Clinical Info (clinicalinfo.hiv.gov). Sept 12, 2024. 2-Gistand NL et al, CROI 2025 #689. 3-Colasanti JA et al, CROI 2025 #690.

Benefits and Satisfaction of Injectable CAB-RPV

And also the psychological aspect of it. It's like being imprisoned in a space that you can't leave. You're locked in this room and you're pulling on the door, but you can't open it. That feeling of being imprisoned. There is no way escaping this daily routine of so many pills per day. There is no freedom from it.

66YO White gay man (VS), Chicago

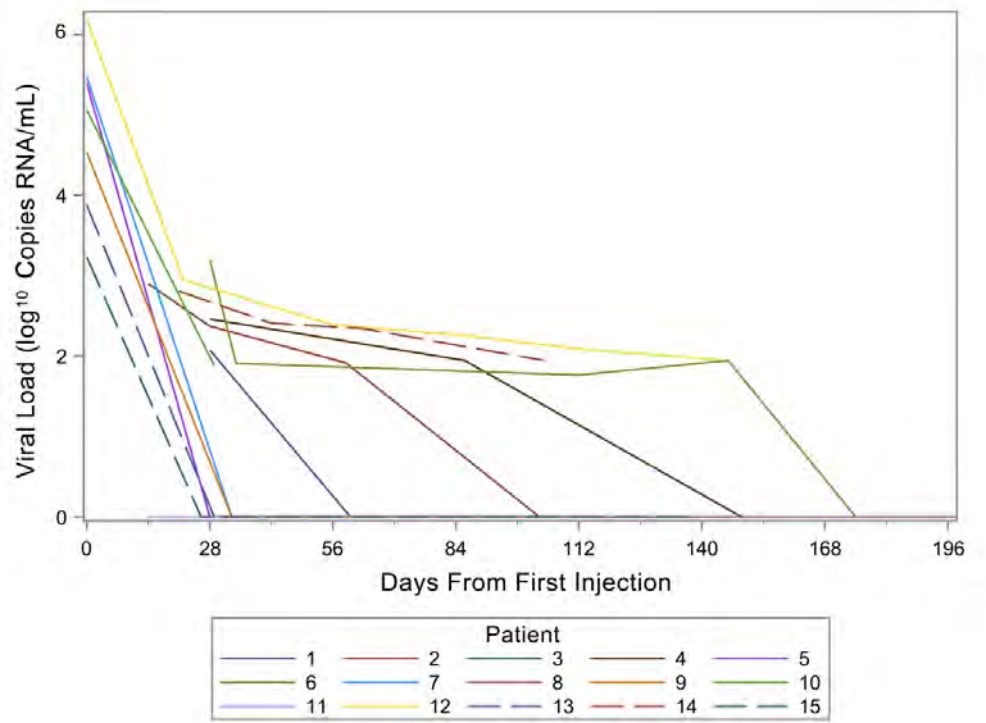
I would know that I wasn't going to be able to take the medication, so I would get high before. . . . Now that every-thing's better, everything's working, it's not so difficult to come here. It's so much easier because I know my health is right. . . . I'm happy to come in, and it's a better feeling. And I don't be high before I come here.

32YO Black gay man (NVS), San Francisco

Source: Christopoulos KA et al, JIAS 2024.

What do we know about viral decay with CAB-RPV?

HIV RNA levels of persons with viremia initiating injections

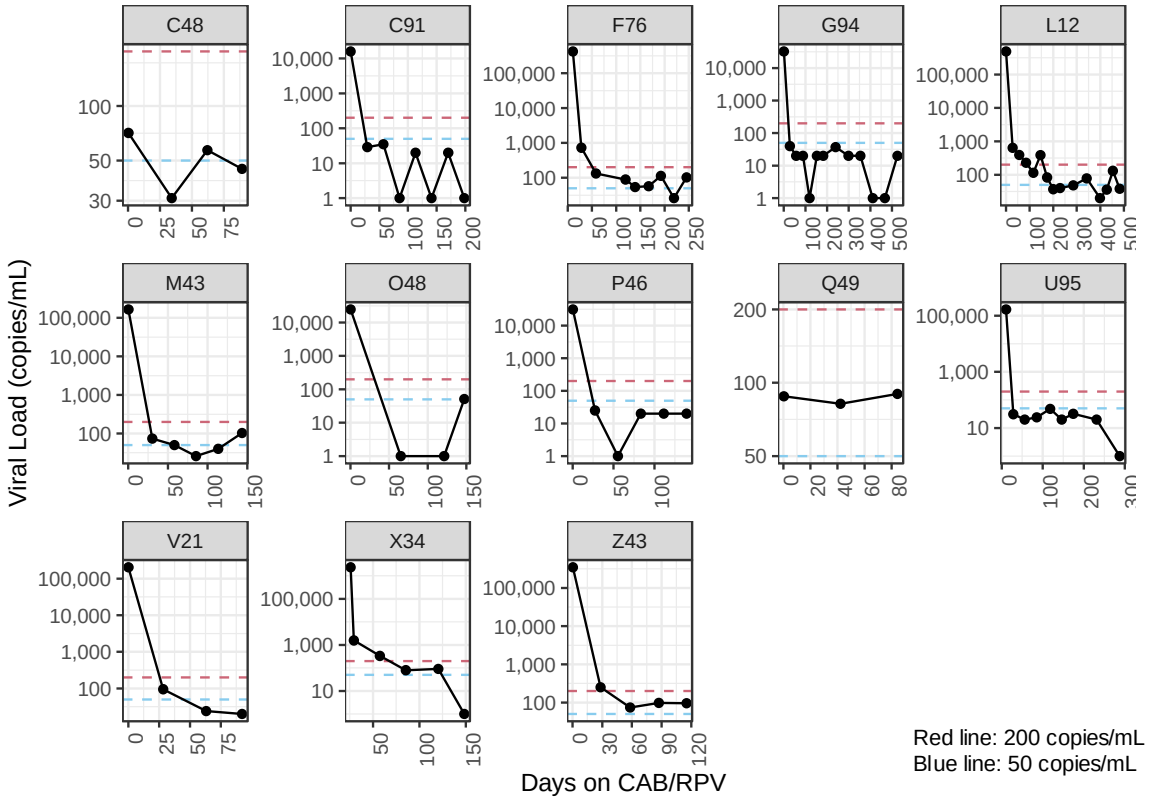


For 3 patients who had not yet achieved viral suppression, all had a 2-log decline by a median of 22 days

Source: Christopoulos KA et al, CID, 2023.

Viral Decay in PWH with Viremia Started on CAB-RPV

HIV RNA levels of PWH with viremia at UW initiating injections through 12/2024, data through 3/2025



Red line: 200 copies/mL
Blue line: 50 copies/mL

Graphs made by Kate Crawford, MD, PhD.

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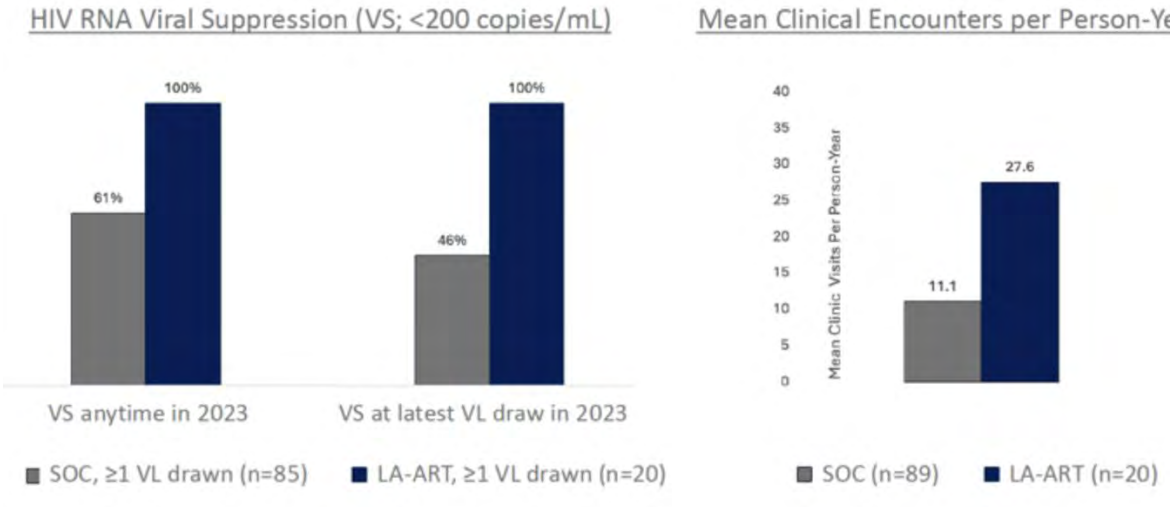
LAI in People Experiencing Homelessness

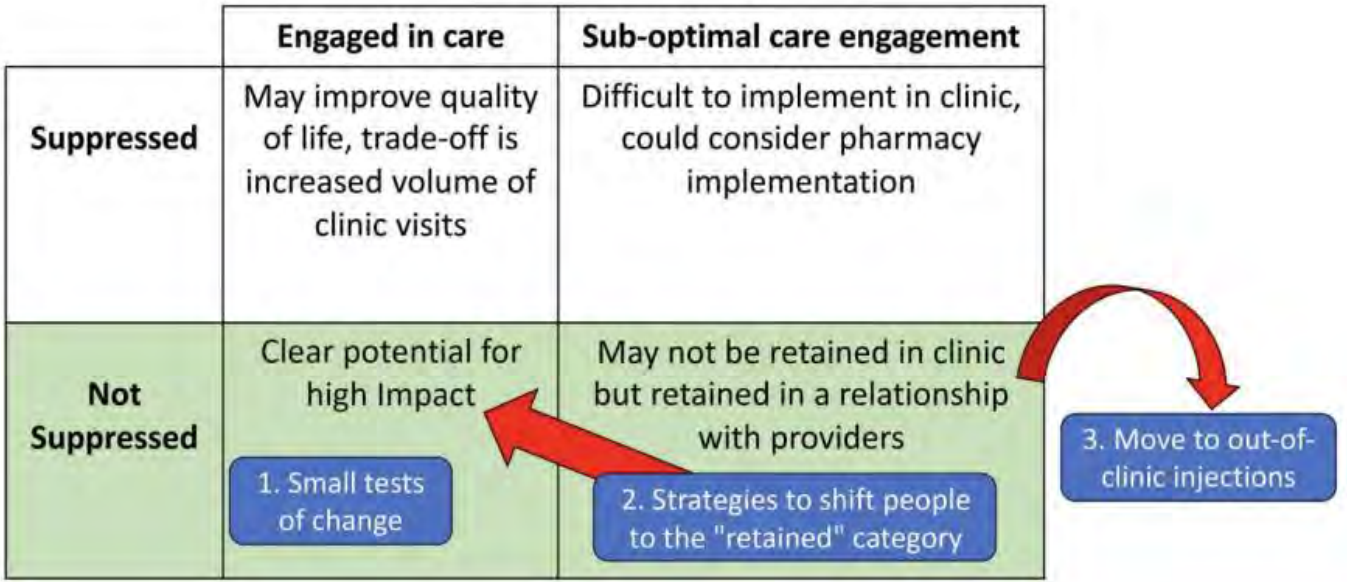
At an urban homeless healthcare center in SF, LA-ART was associated with improved viral suppression and twice as many clinical encounters, in a retrospective chart review of 94 PWH



Source: O'Connor KB et al, CROI 2025 #691.

Implementation Strategies Among PWH with Viremia

LA-CAB/RPV Strategies by Care Engagement and Viral Suppression Status



Source: Hickey MD et al, JAIDS, 2024.

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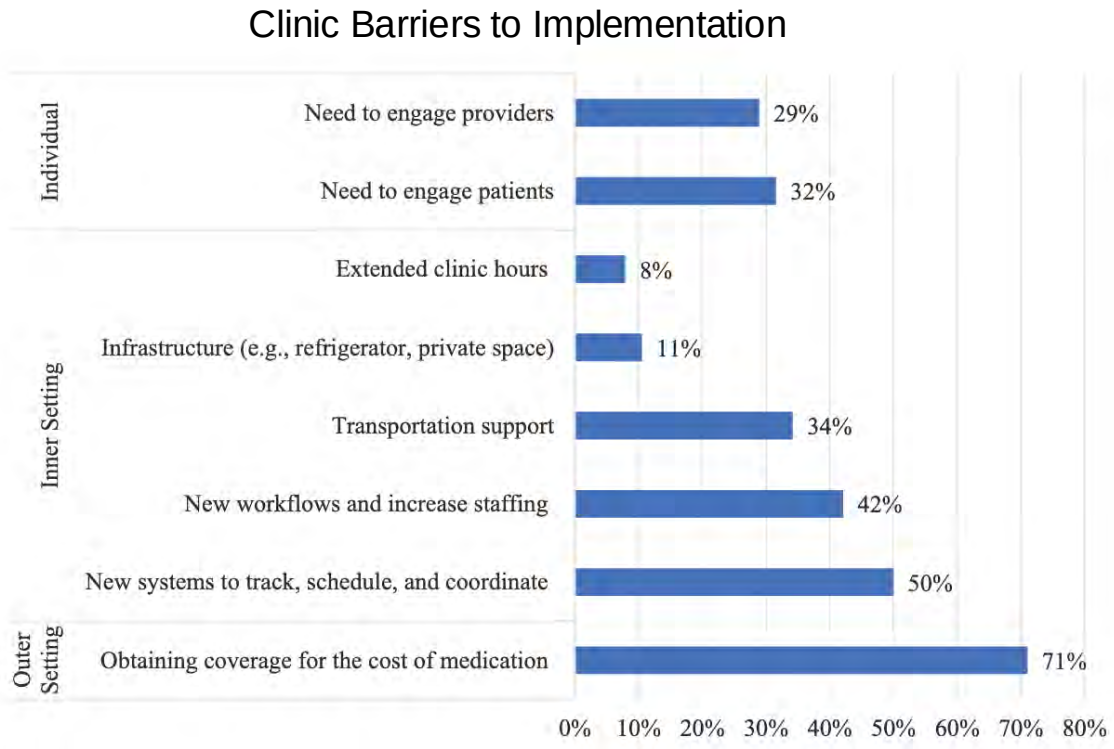
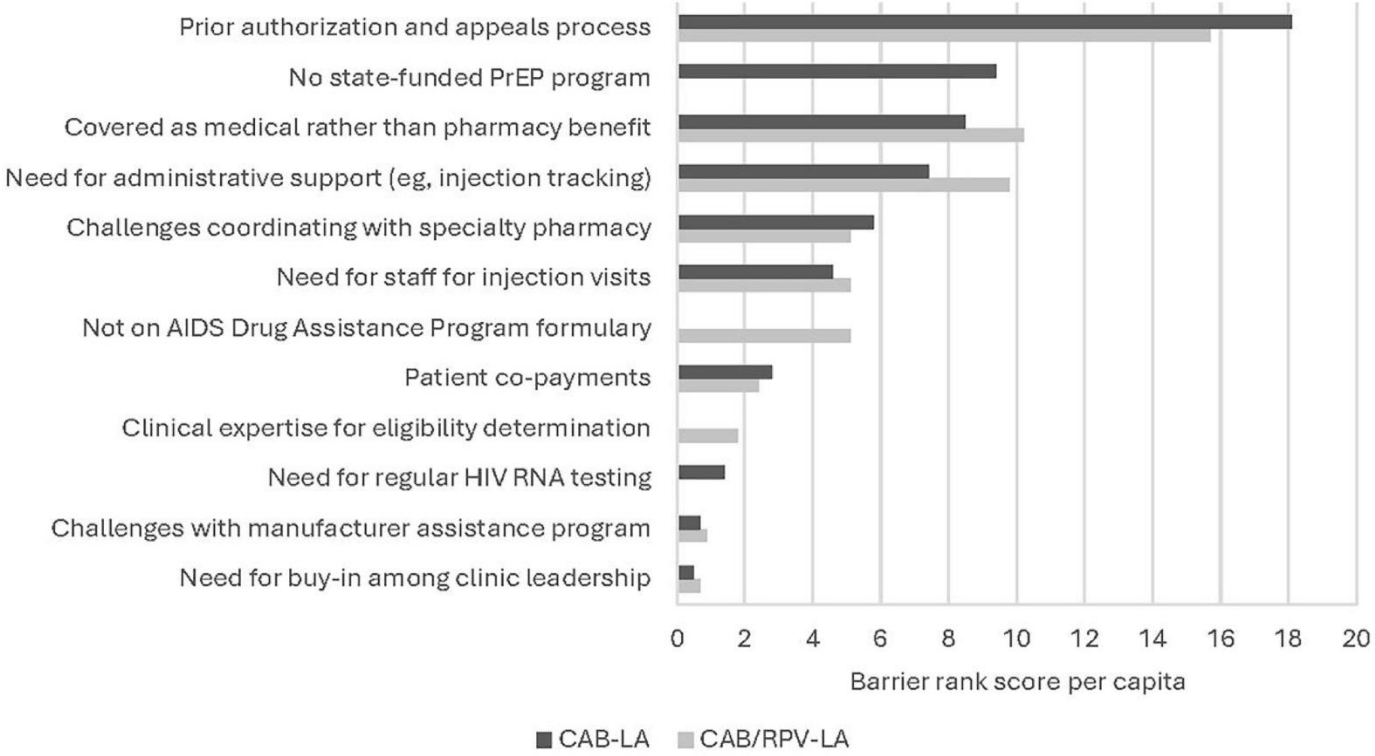
- **Implementation and Logistics**

Implementation Has Been Challenging



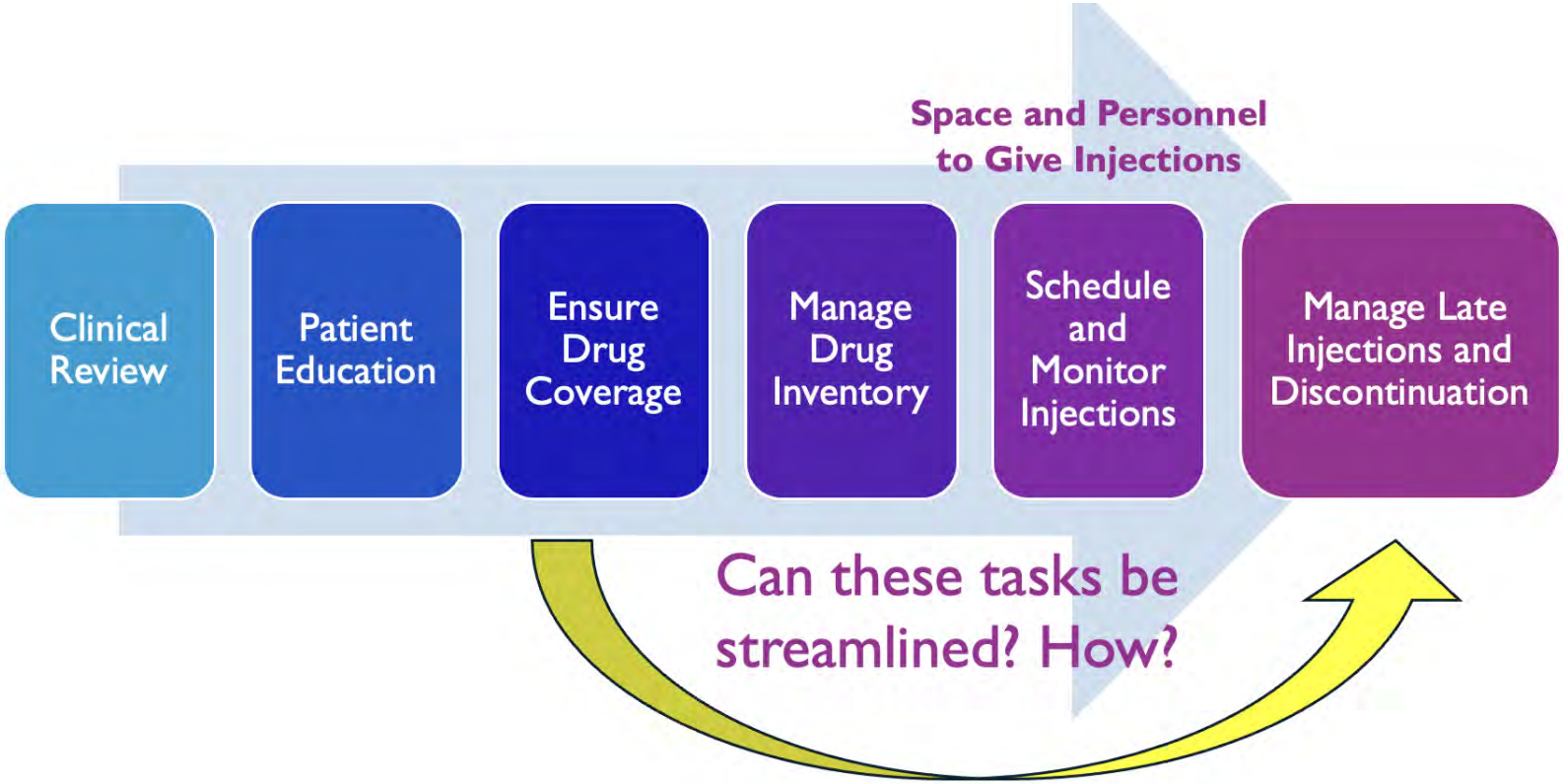
Source: Nguyen N et al, JIAS, 2024.

Ranked Barriers to LAI Implementation – HIVMA Survey



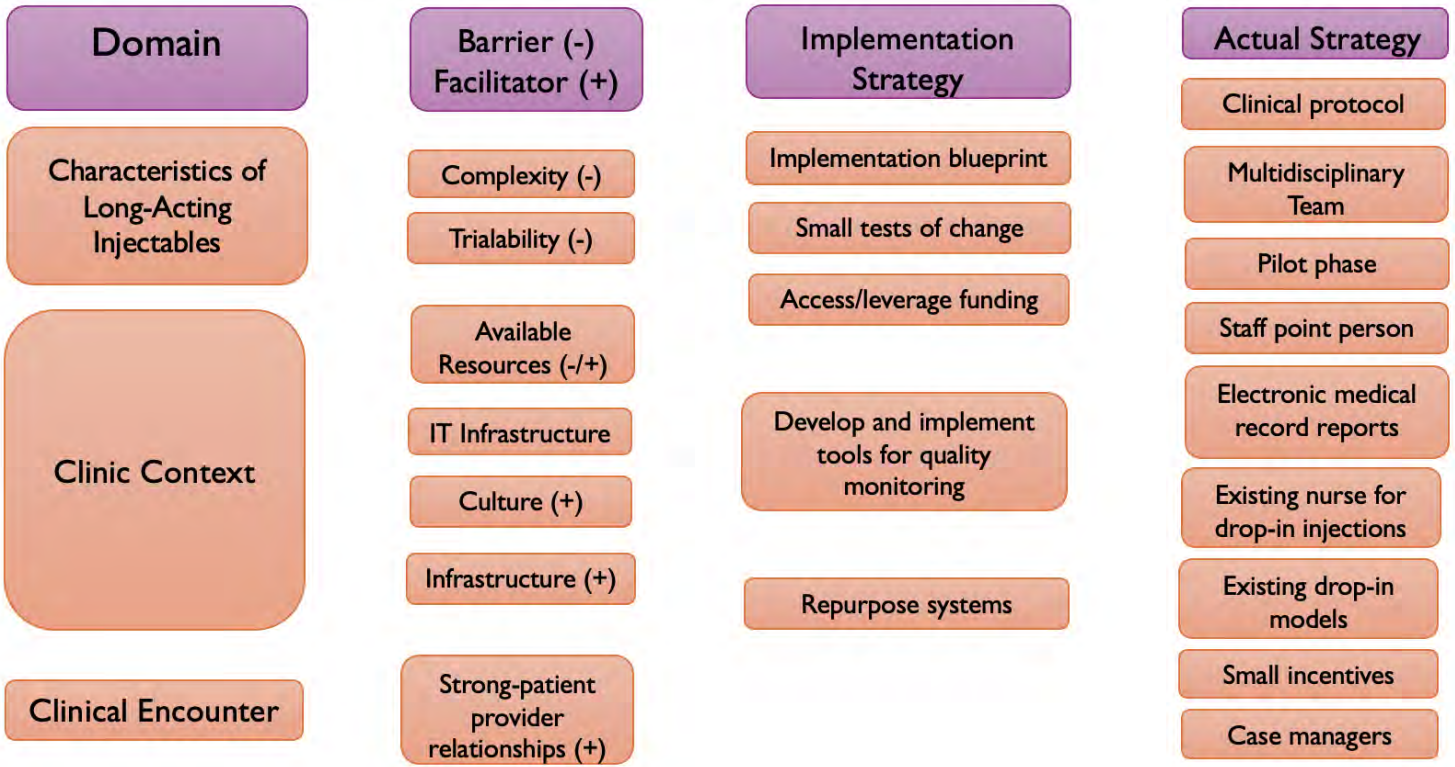
Source: Marcus JL et al, CID, 2025.

LAI Clinic Workflow: Common Threads



Slide from Christopolous K, Colasanti J. Optimizing LAI Patient Care and Program Features. ID Week 2024.

Mapping Barriers and Facilitators to Strategies



Slide from Christopolous K, Colasanti J. Optimizing LAI Patient Care and Program Features. ID Week 2024. Source: Hickey MD et al, JIAS 2024.

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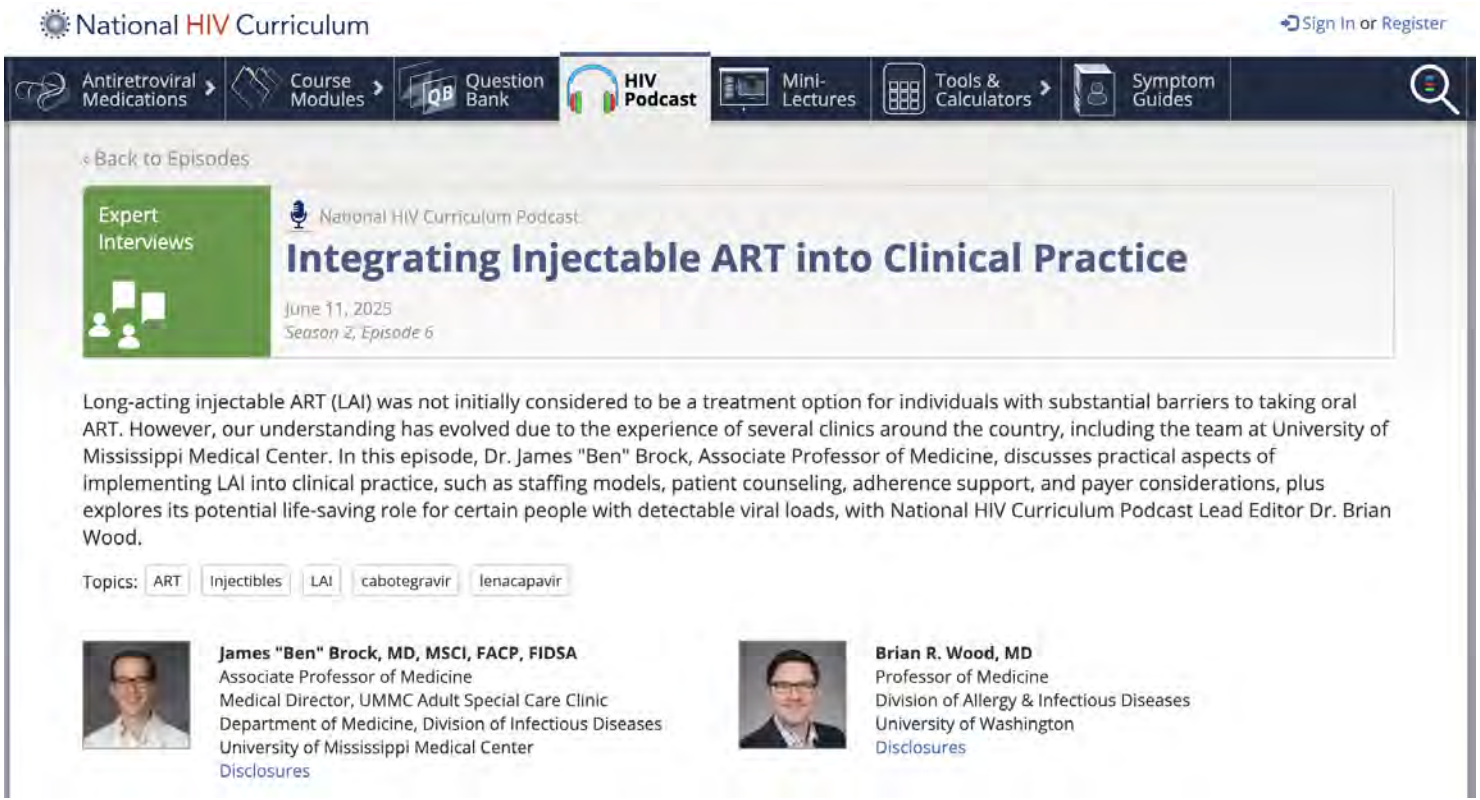
National HIV Curriculum Podcast



National HIV Curriculum

Cabotegravir and Rilpivirine Oral and Injectable Preparations

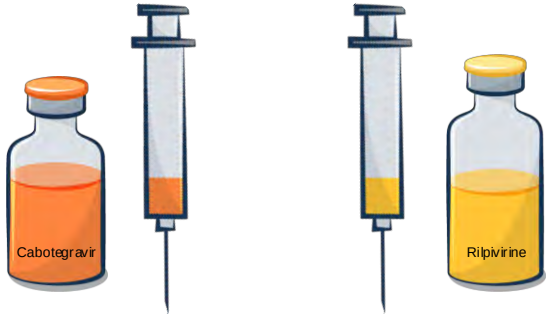
Optional Lead-In Oral Components

Cabotegravir + Rilpivirine

30 mg — 25 mg

INSTI — NNRTI

Intramuscular Injection Components



Cabotegravir + Rilpivirine

200 mg/mL — 300 mg/mL

INSTI — NNRTI

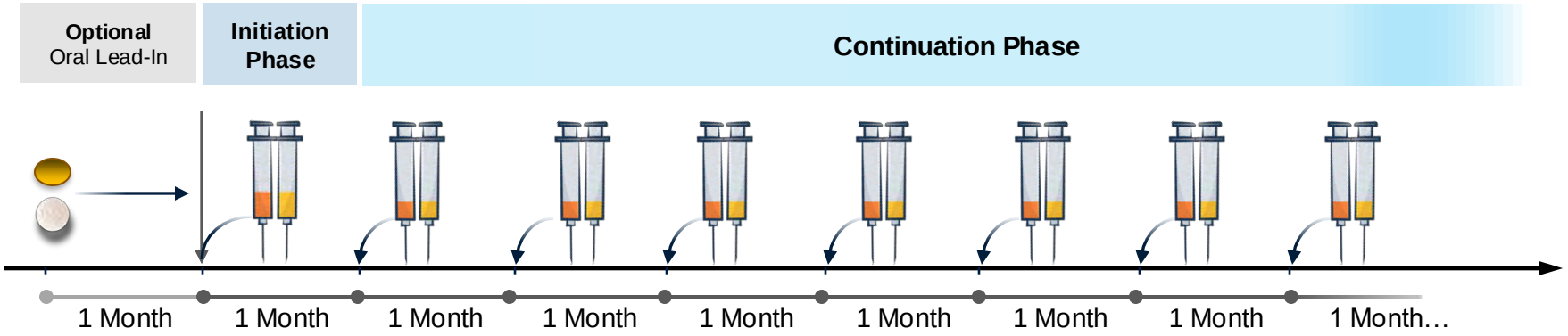
Slide from David Spach, MD. Source: Cabotegravir-Rilpivirine Prescribing Information

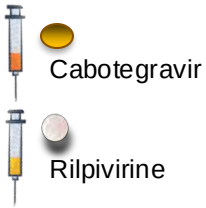
National HIV Curriculum

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

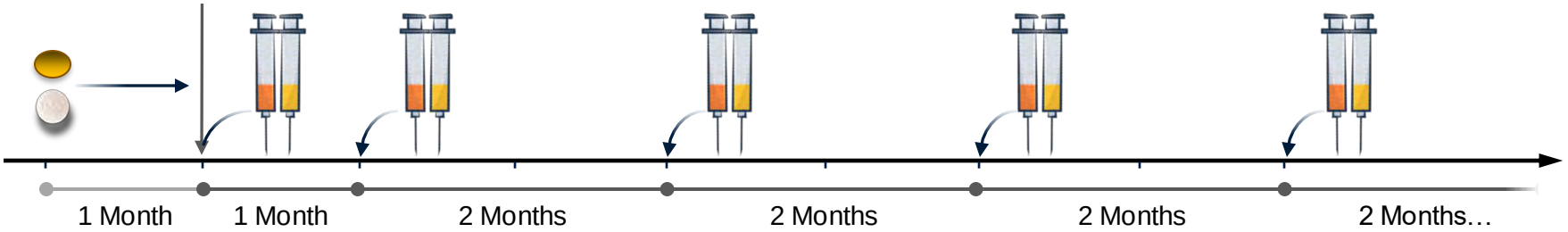
National HIV Curriculum

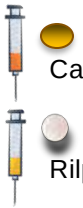
Schedule for Every 2-Month Injectable Cabotegravir and Rilpivirine

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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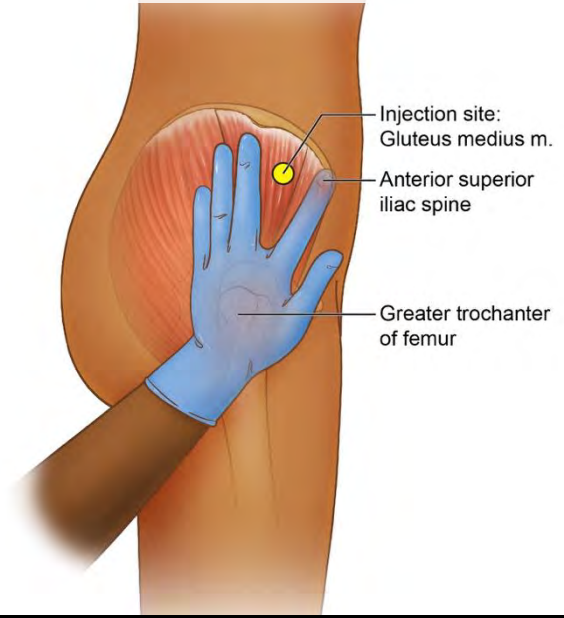
Cabotegravir plus Rilpivirine Long-Acting Injections

Preferred Injection Site (Ventrogluteal)

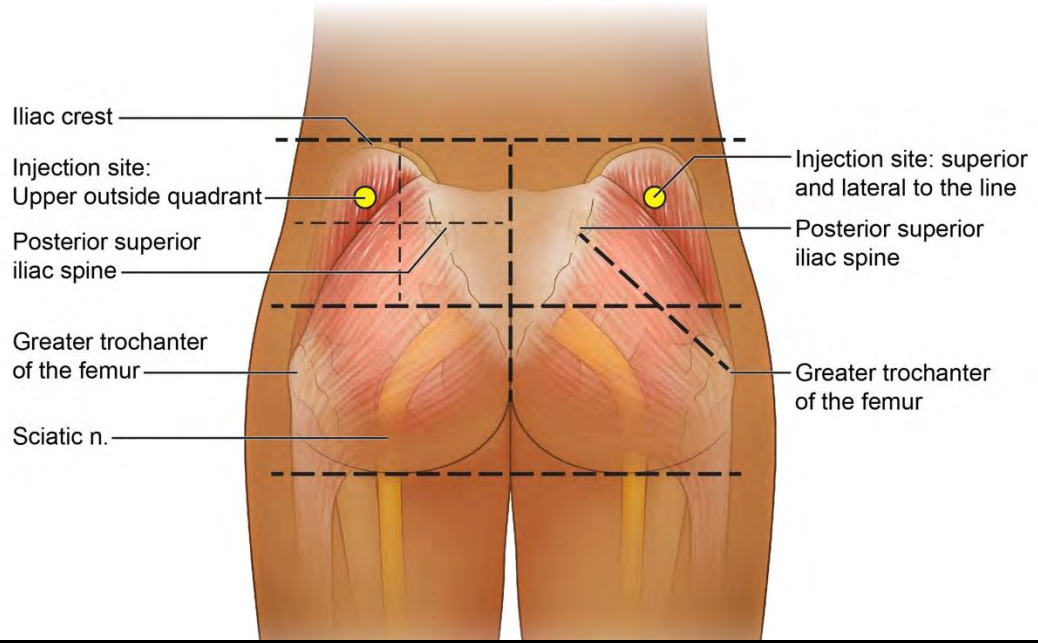


Longer needle (not included in the dosing kit) may be required for people with higher BMI (example: >30 kg/m ^{2})

Slide from David Spach, MD. Illustration: Cognition Studio, Inc. and David H. Spach, MD

Cabotegravir plus Rilpivirine Long-Acting Injections

Alternative Injection Site (Dorsogluteal)



Longer needle (not included in the dosing kit) may be required for people with higher BMI (example: >30 kg/m^2)

Slide from David Spach, MD. Illustration: Cognition Studio, Inc. and David H. Spach, MD

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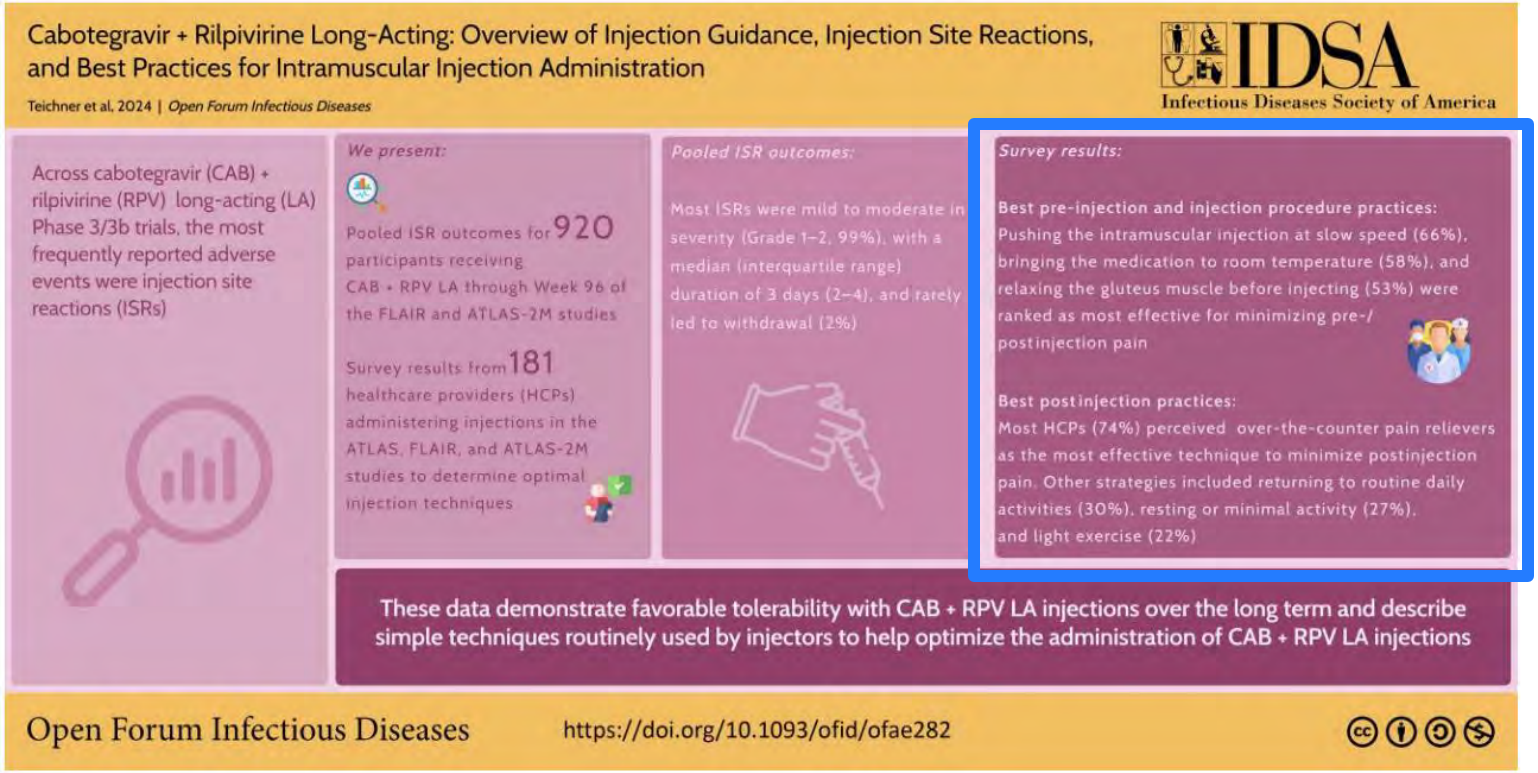
Management of Injection Site Reactions



Alternate Site Injections

- Data regarding non-gluteal IM injections are limited
- **What about the thigh?** Early thigh PK data, in persons on gluteal IM injections at steady-state who were temporarily switched to thigh IM injections for 16 weeks, are promising, but not recommended[1]
- **What if the patient has fillers and/or implants?** Make a clinical assessment to see if the gluteal muscle can be accessed[2]
- **What about subcutaneous injections?** Though PK data appears similar to IM, patients had more side effects (eg. pain, nodules) with subcutaneous injections, so it is not being pursued[3]

1-Felizarta F et al, CROI 2023, #519. 2-ViiV Package Insert. 3-D'Amico R et al, AIDS 2024.

Most individuals are receiving LAI CAB-RPV in clinic

- Infusion centers
  - Of 44 PWH receiving CAB-RPV at infusion centers, none had CVF[1]
  - At a Chicago HIV clinic, 2 of 3 CVFs (out of 75 PWH) occurred in PWH receiving injections at an infusion center[2]
- The “field”
  - At Ward 86, of 9 patients who received out-of-clinic injections, none had VF[3]
- Home?
  - Among 33 PWH in South Carolina, at-home injections by a healthcare professional were efficacious[4]

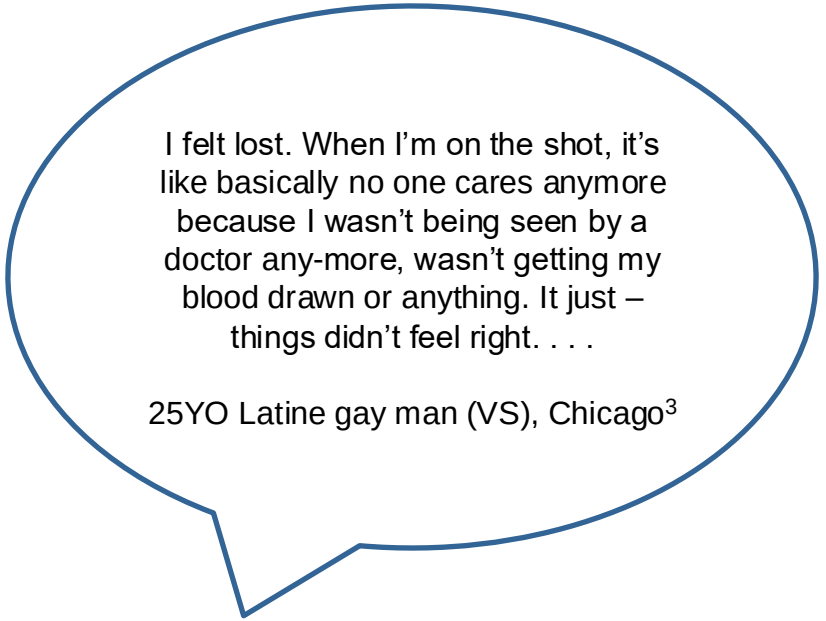
Table S2. Out of Clinic Injections

Patient	Location
1	Home health nursing (planned)
2	Other clinic while travelling (unplanned) Supportive housing onsite nurse (planned)
3	Skilled nursing facility (unplanned)
4	Inpatient (unplanned)
5	Inpatient (unplanned) Supportive housing onsite nurse (planned)
6	Inpatient (unplanned)
7	Inpatient (unplanned) Emergency department (unplanned)
8	Street medicine nurse (planned)
9	Street medicine nurse (planned)

1-Gutner CA et al, ID Week 2024 #P-545. 2-Shankaran S et al, CROI 2024 #686. 3-Hickey MD et al, CID, 2025. 4-Kirk SE et al, CID, 2025.

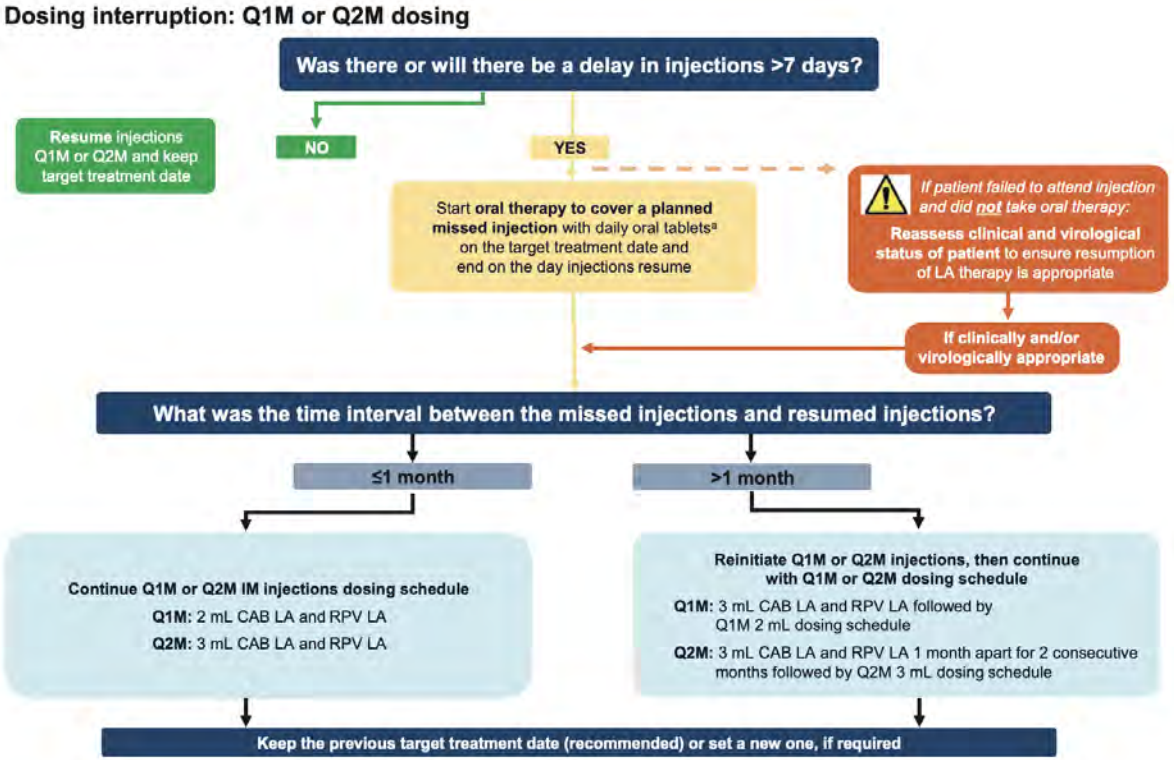
Stopping CAB-RPV

- In two clinics (Ward 86 in San Francisco and the Owen Clinic in San Diego), 16-20% of persons stopped injectables[1,2]
  - Reasons varied, but pain and injection site reactions and logistical difficulties were main drivers of discontinuation
- If stopping CAB-RPV, recall the long pharmacokinetic tail of CAB



1-Christopolous KA et al, CROI 2025 #683. 2-Faggiano T et al, CROI 2025 # 685. 3-Christopoulos KA et al, JIAS 2024.

Management of Dosing Interruptions



Source: Patel P et al, Ther Adv Infect Dis, 2023.

National HIV Curriculum

Lenacapavir

Lenacapavir: Background

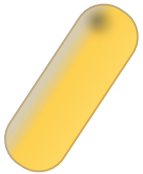
- Lenacapavir (LEN) is a capsid inhibitor administered subcutaneously every 6 months
- FDA approved in December 2022 for MDR HIV, informed by the CAPELLA Study[1]
- CAPELLA 156 Week Data: LEN, when combined with an optimized background regimen, led to high and sustained VS in heavily treatment experienced PWH[2]
- LEN has many drug-drug interactions, including with other ART

1-Segal-Maurer S et al, NEJM, 2022. 2-Ogbuagu O et al, ID Week 2024.

MWAETC

Lenacapavir

Oral Lenacapavir



300 mg tablets

Take with or without food

Subcutaneous Lenacapavir

1.5 mL vial = 463.5 mg

Administer as Subcutaneous Injection

Illustration: David H. Spach, MD

Lenacapavir

Dosing (Subcutaneous Injection)

- 2 x 1.5 mL single dose vials
- Inject 2 x 1.5 mL (927 mg total) every 6 months (26 weeks +/- 2 weeks)

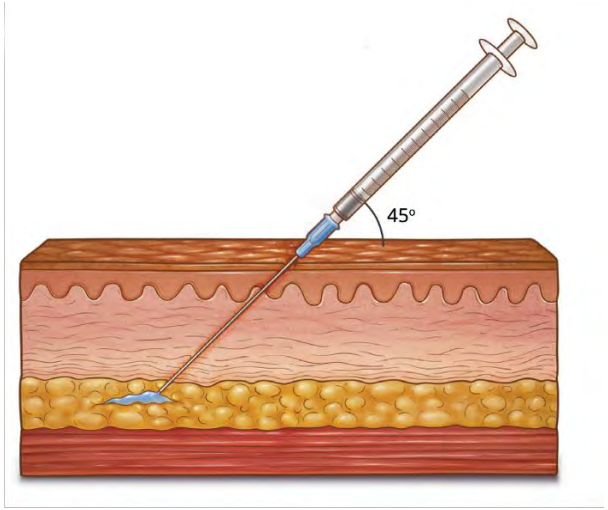


Illustration: David H. Spach, MD and *Cognition Studio, Inc.*

Lenacapavir Dosing for HIV Treatment: Initiation Option 1

Initiation Option 1

Day 1

600 mg

Day 2

600 mg

927 mg

Oral lenacapavir 300 mg

Subcutaneous lenacapavir 463.5 mg

Illustration: David H. Spach, MD

National HIV Curriculum

Lenacapavir Dosing for HIV Treatment: Initiation Option 1

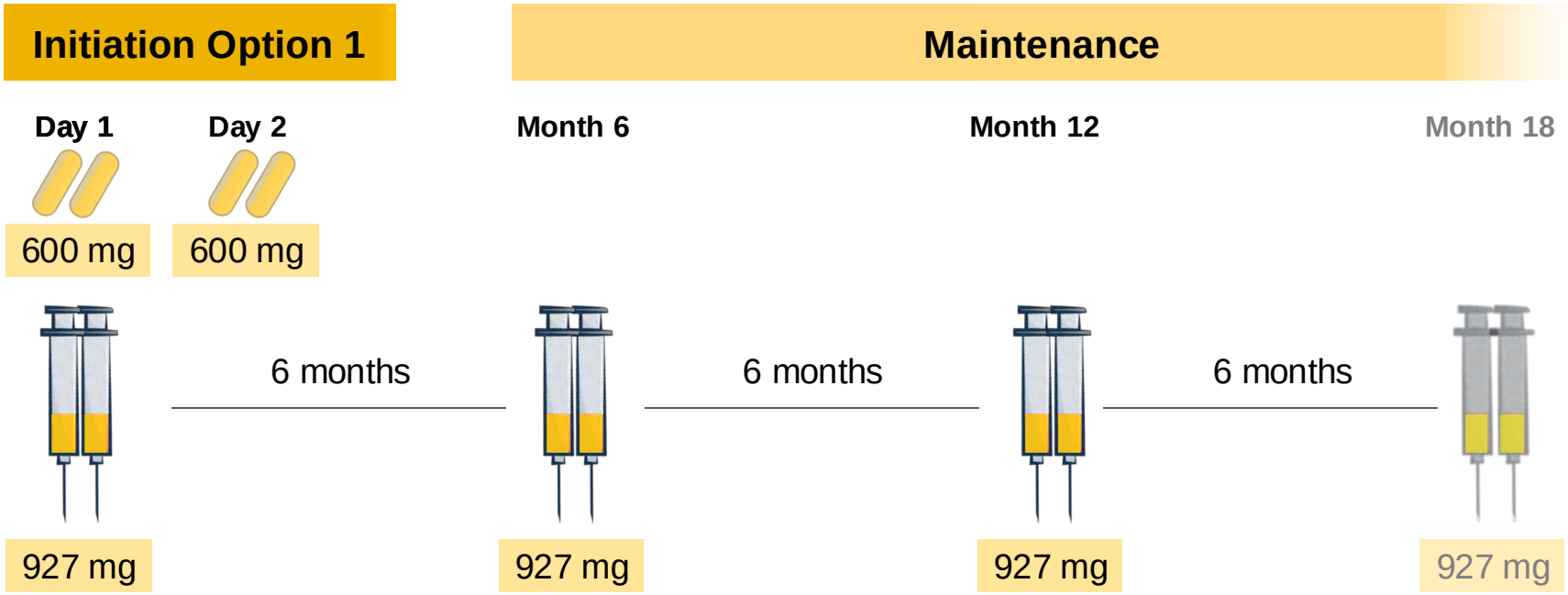


Illustration: David H. Spach, MD

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Lenacapavir Dosing for HIV Treatment: Initiation Option 2

Initiation Option 2

Day 1	Day 2	Day 8	Day 15
			
600 mg	600 mg	300 mg	927 mg

 Oral lenacapavir 300 mg

 Subcutaneous lenacapavir 463.5 mg

Illustration: David H. Spach, MD

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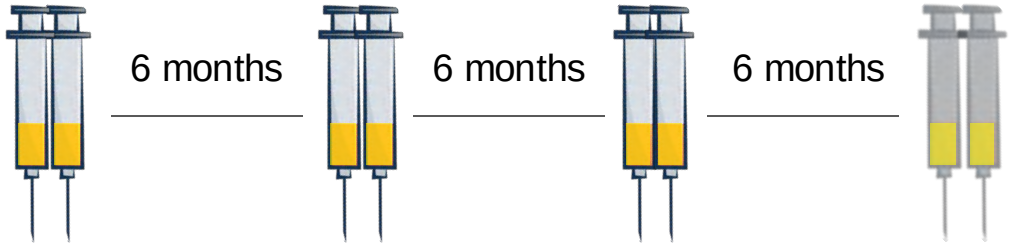
Lenacapavir Dosing for HIV Treatment: Initiation Option 2

Initiation Option 2

Maintenance

Day 1 **Day 2** **Day 8** **Day 15**

600 mg 600 mg 300 mg



927 mg 927 mg 927 mg 927 mg

Oral lenacapavir 300 mg

Subcutaneous lenacapavir 463.5 mg

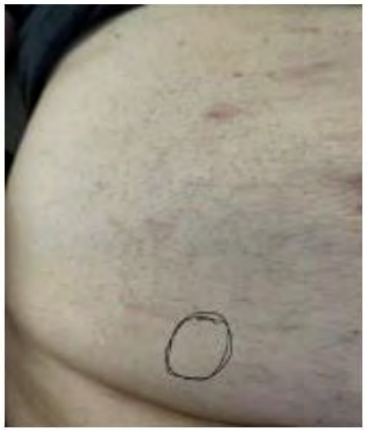
Illustration: David H. Spach, MD

National HIV Curriculum

Lenacapavir Side Effects and Nodules are Common

- ISRs ranged from 46-63% in CAPELLA and 42-52% in CALIBRATE

Median (IQR) duration, days	CAPELLA (n=72)	CALIBRATE (n=103)
Swelling	8 (4-15)	11 (6-15)
Erythema	5 (3-8)	5 (2-11)
Pain	3 (1-4)	2 (1-6)
Nodule	252 (113-524)	250 (100-369)
Induration	183 (63-498)	215 (144-415)



Source: Castagna A et al, EACS, 2023 #eP.A.104

CAB-RPV with Lenacapavir for MDR HIV

- A case series of 34 patients from 4 clinics using off-label LEN and CAB +/- RPV demonstrated 94% viral suppression[1]
- Nine patients in Mississippi were prescribed LEN and q8w CAB-RPV and all achieved viral suppression[2]

Patient	Y181C	K101E	E138K	G190A	A98G	E138K/Q/G	H221Y	RPV Mutation Score[a]
1	X			X				70
2					X			15
3		X		X		X		75
4		X	X		X			105
5						X		45
6	X			X				70
7							X	15
8	X							45
9		X				X		60

[a]Calculated by Stanford University HIV Drug Resistance Database (https://hivdb.stanford.edu/, access May 2, 2024)

1-Gandhi M et al, CROI 2024, #629. 2-Brock JB et al, ID Week 2024.

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- Dr. David Spach
- Dr. Brian Wood

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