Long-acting Injectable Cabotegravir/Rilpivirine for Individuals Who Do Not Fulfill the FDA Eligibility Criteria

Brian R. Wood, MD
Medical Director, MWAETC Project ECHO
Associate Professor of Medicine, University of Washington

Last Updated: October 20, 2022

Disclosures

No conflicts of interest or relationships to disclose.

Disclaimer

Funding for this presentation was made possible by U1OHA29296 from the Human Resources and Services Administration HIV/AIDS Bureau. The views expressed do not necessarily reflect the official policies of the Department of Health and Human Services nor does mention of trade names, commercial practices, or organizations imply endorsement by the U.S. Government. *Any trade/brand names for products mentioned during this presentation are for training and identification purposes only.*

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HHS Adult and Adolescent HIV Treatment Guidelines
New Recommendation

- The Panel **recommends against** the use of the long-acting ART regimen of 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).**

Guidelines for the Use of Antiretroviral Agents in Adults and Adolescents with HIV. September 21, 2022 Update. http://clinicalinfo.hiv.gov

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Background
FDA Indication for Long-Acting Injectable (LAI) Cabotegravir/Rilpivirine (CAB/RPV)

- **Complete regimen for adults and adolescents (≥12 years who weigh ≥35 kg)**
  - Replace antiretroviral regimen in persons with HIV RNA <50 copies/mL
  - Taking stable antiretroviral regimen
  - No history of treatment failure
  - No known or suspected resistance to cabotegravir or rilpivirine
- **Oral lead in**
  - Optional
- **Initiation & continuation phase injections**
  - Initiation: initial dose and dosing interval depends on planned continuation schedule
  - Continuation: approved for every 1-month and every 2-month injections (doses differ)

Sources: Cabotegravir-Rilpivirine Prescribing Information. National HIV Curriculum (http://www.hiv.uw.edu)

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Background
Clinical Question and Controversy

- ***Should LAI CAB/RPV be considered an option for individuals who have significant challenges with oral ART adherence, detectable viral loads, or otherwise don't meet FDA eligibility criteria?***
- Consider: CAB time from last injection to concentration below limit of quantification: 44 weeks males (20-152), 67 weeks females (18-226)*

*Source: Landovitz RJ et al. Lancet HIV 2020; 7(7): e472–e481. HPTN 077.

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Study #1: Demonstration Project of LAI CAB/RPV for PWH with and without detectable viremia at UCSF Ward 86 Clinic

Background
Study Setting

- Safety net clinic for San Francisco city and county
- Serves >2,400 adults with HIV who have government insurance
- 21% Black, 27% Hispanic
- Estimated 15% viremic (10% chronic viremia); higher rates of mental illness, stimulant use, unstable housing
- POP-UP: established 2019; comprehensive multidisciplinary primary care with drop-in visits

Christopoulos KA, et al. Clin Infect Dis. 2022 Aug 1. Online ahead of print.
https://hividgm.ucsf.edu/pop-up

Background
LAI CAB/RPV Protocol

- Individuals **with or without undetectable viral load** can enroll
- Willing to attend injection visits, receive 2 gluteal injections each visit, resume oral ART if injections interrupted, give 2 contact methods
- Any RPV resistance excluded; ≤1 INSTI mutation allowed
- HBV allowed if willing to continue or start HBV therapy
- Favor direct-to-inject (no oral lead in), regardless of viral load

Christopoulos KA, et al. Clin Infect Dis. 2022 Aug 1. Online ahead of print.

Background
LAI CAB/RPV Protocol

- If viremia at baseline: **individualized plan for adherence support**
  - Case managers, home & street-based nursing services, community injection sites (including harm-reduction sites), financial incentive for visits/labs
  - Monthly HIV RNA recheck; resistance test at 2nd injection visit if viremic
- Regular multidisciplinary review of patients
- Every 4-week dosing; every 8-week only after suppression ≥6 months

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Background
LAI CAB/RPV Protocol

- Pharmacist eligibility review, visit, drug authorization/procurement
  - Bilingual team member calls within 1 week of first injection
  - Calls/texts for appointment reminders, missed visits
- Patients keep one month of oral ART on hand in case of missed injection by >7 days; if miss by >10 days, HIV RNA + genotypes
- Unplanned missed injection: attempts to contact, in-person outreach, repeat loading dose if missed by >42 days

Christopoulos KA, et al. Clin Infect Dis. 2022 Aug 1. Online ahead of print.

LAI CAB/RPV Demonstration Project at Ward 86
Results (132 referred, 51 started injections, 39 received ≥2 injections)

Participant Characteristic	Result (Total n = 39)
Age, median (range)	46 (31-68)
Cisgender men, n (%)	35 (90)
Black, n (%)	8 (21)
Hispanic, n (%)	10 (26)
Unstable housing, n (%)	13 (33)
Homeless, n (%)	3 (8)
Stimulant use (meth, cocaine), n (%)	20 (54)
HIV RNA ≥30 copies/mL proximal to first injection, n (%)	15 (38)
HIV RNA of those with ≥30 copies/mL at first injection, mean, $\log_{10}$ (SD)	4.67 (1.16)
CD4 count for those with HIV RNA ≥30 copies/mL, median (IQR)	99 (51, 299)
CD4 count for those with HIV RNA <30 copies/mL, median (IQR)	732 (364, 883)
5 patients were receiving other long-acting injections (4 antipsychotics, 1 naltrexone)	

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LAI CAB/RPV Demonstration Project at Ward 86
Results (participants who received ≥2 injections)

Participant Characteristic	Result (Total n = 39)
Baseline HIV RNA <30 copies/mL, n (%)	24 (62)
Direct-to-inject (no oral lead in), n (%)	19 (79)
Median # of injections (range)	6 (2–8)
Maintained virologic suppression, n (%)	24 (100)
Baseline HIV RNA ≥30 copies/mL, n (%)*	15 (38)
Direct-to-inject (no oral lead in), n (%)	15 (100)
Median # of injections (range)	6 (3–11)
Achieved and maintained suppressed viral load, n (%)	12 (80)*

*3 participants have not yet achieved viral suppression but had 2-log decline in viral load by median of 22 days

*1 participant had N155H INSTI mutation at baseline and achieved a suppressed viral load

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LAI CAB/RPV Demonstration Project at Ward 86
Results (participants who received ≥2 injections)

- Adherence:
  - Overall high; 87% with only on-time injections
  - Small # late injections; 2 required outreach & re-induction
  - 2 received injections at community sites (harm reduction mobile van, community clinic) with street-based nursing services
- Tolerability:
  - No patients discontinued due to side effects
  - Injection site reactions frequent but mild to moderate
  - One instance of cellulitis at injection site

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LAI CAB/RPV Demonstration Project at Ward 86
Conclusions, Limitations, Questions

- **Conclusions**:
  - Data show “preliminary short-term effectiveness” of every 4-week LAI CAB/RPV in PWH with or without viral suppression in diverse urban clinic serving publicly-insured patients with frequent housing instability & stimulant use

- **Limitations**:
  - Small n, follow-up <1 year, unique setting (centralization of insurance authorization, extensive outreach, drop-in visits, injections in the field), 12 patients not included

- **Questions**:
  - Will results change with longer follow-up? Will findings be reproduced in larger studies or other settings? Will payers cover the meds?

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Study #2: Compassionate use of LAI CAB/RPV by persons with HIV in need of parenteral ART

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Background
LAI CAB/RPV compassionate use (early access) program

- Eligibility:
  - Adults with HIV-1 who need parenteral ART due to psychological or physical condition; or, prolonged oral ART non-adherence with progressive HIV disease
    - Psychological: difficulty swallowing, pill fatigue, stigma, chronic low oral ART adherence
    - Physical: dysphagia, malabsorption, chronic diarrhea, incarcerated ventral hernia, malnutrition, mucositis, dumping syndrome, intractable vomiting, pancreatic insufficiency
  - No resistance to CAB or RPV (K103N allowed)
  - Established relationship with provider, adherence to visits
  - Not eligible for phase 3 RCT

D'Amico R, et al. HIV Med. 2022 Aug 9. Online ahead of print.

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Compassionate Use LAI CAB/RPV
Participant Characteristics

Participant Characteristic	Result (Total n = 35)
Female at birth, n (%)	20 (57)
Acquired HIV perinatally, n (%)	11 (31)
Age, years, median (range)	36 (20-67)
Current AIDS diagnosis, n (%)	23 (66)
HIV RNA ≥50 copies/mL, n (%)	28 (80)
HIV RNA 50-10,000 copies/mL, n	9
HIV RNA 10,000-50,000 copies/mL, n	4
HIV RNA 50,000-100,000 copies/mL, n	4
HIV RNA >100,0000 copies/mL, n	11
HIV RNA for those with ≥50 copies/mL, median (range)	60,300 (86 to >10,000,000)
CD4 count, median (range), cells/mm^3	100 (3-918)
Direct-to-inject (no oral lead in)	12 (34)
All received q4-week dosing; median follow up 10 months (range 1-47)	

D'Amico R, et al. HIV Med. 2022 Aug 9. Online ahead of print.

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Compassionate Use of LAI CAB/RPV
Virologic Efficacy Results

Result	Proportion (Total N = 35)
Maintained or achieved suppressed HIV RNA (<50 copies/mL), n (%)	22 (63)
Maintained suppressed HIV RNA, n (%)	6/7 (86)
Achieved suppressed HIV RNA, n (%)	16/28 (57)
Stopped because of incomplete virologic suppression (HIV RNA >50), n (%)	7 (20)
1 had suppressed HIV RNA at entry; developed resistance to CAB not detected at entry (no NNRTI resistance)	
6 had detectable HIV RNA at entry; all 6 developed resistance to RPV not detected at entry (2 had E138G at entry) and 3 developed INSTI resistance not detected at entry (2 with CAB resistance)	

D'Amico R, et al. HIV Med. 2022 Aug 9. Online ahead of print.

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Conclusions, Limitations, and Questions

- **Conclusions**:
  - Moderate virologic success with LAI CAB/RPV in PWH with significant oral ART adherence challenges and advanced HIV
  - New RPV and/or CAB resistance occurred, especially if detectable viral load at entry
  - Most who didn't suppress on LAI CAB/RPV later suppressed with boosted darunavir
- **Limitations**:
  - Small n, no comparator group, short follow up, 2 entered with RPV resistance
- **Questions**:
  - How did use of oral lead in affect results? How will results change with longer follow up? Is 63% virologic success good news or bad news?

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- Clinical trial: ACTG 5359 (LATITUDE) https://actgnetwork.org/studies/a5359-the-latitude-study/

Acknowledgment

This Mountain West AIDS Education and Training (MWAETC) program is supported by the Health Resources and Services Administration (HRSA) of the U.S. Department of Health and Human Services (HHS) as part of an award totaling $3,098,654 with 0% financed with non-governmental sources.

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