AETC AIDS Education & Training Center Program Mountain West

State of the ART:
Update on Long-Acting Antiretrovirals for HIV Treatment

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Acknowledgment

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Disclosures

No conflicts of interest or relationships to disclose.

Objectives

- Discuss the latest updates and controversies on long-acting, injectable **cabotegravir/rilpivirine**
- Highlight data for **lenacapavir**, a capsid inhibitor likely coming soon as an option for heavily-treatment experienced PWH
- Review the latest changes and plans for the NRTTI **islatravir**

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Poll

- How many of your patients/clients are currently receiving long-acting, injectable cabotegravir/rilpivirine for HIV treatment?

A) 0

B) 1-10

C) 11-20

D) 21 or more

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Poll

- For patients/clients who express interest in long-acting, injectable cabotegravir/rilpivirine but never start it, the most frequent reason is:

A) Insurance coverage issues

B) Drug resistance mutations

C) Detectable viral load

D) Difficulty adhering to regular clinic visits

E) Choice (preference for daily oral ART)

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

- **For adults and adolescents (≥12 years who weigh ≥35 kg)**
  - Replace antiretroviral regimen in persons with HIV RNA <50 copies/mL
  - Taking stable oral antiretroviral regimen
  - No history of treatment failure
  - No known or suspected resistance to cabotegravir or rilpivirine

Source: Cabotegravir-Rilpivirine Prescribing Information

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Schedule for Every 1-Month Injectable Cabotegravir and Rilpivirine

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

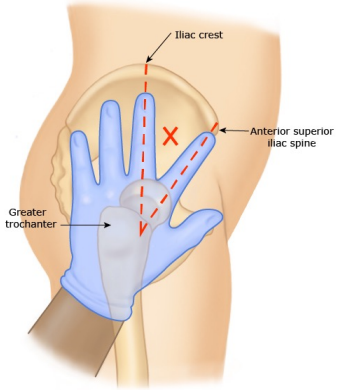
Cabotegravir 30 mg daily +
Rilpivirine 25 mg daily

***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



*Administer injections at opposite gluteal sites (or at least 2 cm apart). Give both during the same visit. Administer within 7 days of target date.
*Ventrolateral gluteal site (gluteus medius) recommended; dorsolateral (gluteus maximus) acceptable. Use longer needle if BMI >30 kg/m^2.

Sources: Cabotegravir-Rilpivirine Prescribing Information. National HIV Curriculum (https://www.hiv.uw.edu). Wood BR, UpToDate.

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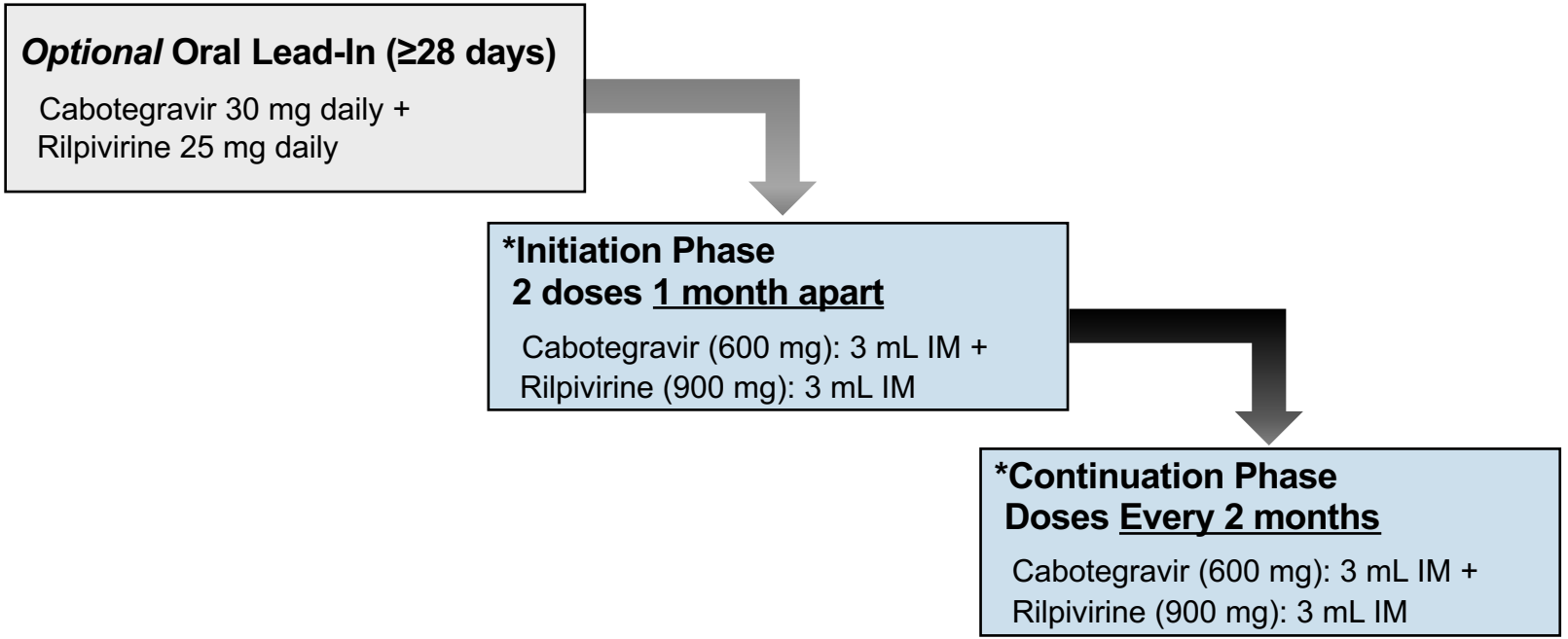
Schedule for Every 2-Month Injectable Cabotegravir and Rilpivirine



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*Ventrolateral gluteal site recommended; dorsolateral acceptable. Use longer needle if BMI >30 kg/m^2.

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

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LAI Cabotegravir/Rilpivirine (CAB/RPV)
Factors Associated with Virologic Failure (VF) in phase 3 RCTs

- n = 13/1,039 (1.25%) cases of VF at 48 weeks
- Factors associated with VF per multivariate regression analysis:*
  - **1) Proviral RPV resistance mutation(s)** [OR 40.36, 8.81-99]
  - **2) Subtype A1/A6 virus** [OR 5.92, 62-22.89]
  - **3) BMI ≥30 kg/m^2** [OR 1.13, 1.02-1.24]
  - **4) Lower RPV trough concentration** [OR 5.00, 1.79-16.67]

*Not associated: L74I INSTI polymorphism, other INSTI mutations, non-RPV NNRTI mutations, female sex at birth, every 4-week vs every 8-week dosing

Source: Cutrell AG et al. AIDS. 2021;35:1333-1342.

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LAI Cabotegravir/Rilpivirine (CAB/RPV)
Factors Associated with Virologic Failure (VF) in Phase 3 RCTs

3 factors that can be clinically determined before starting (proviral RPV mutations, HIV subtype, BMI)	Confirmed VF, n (%) (of total 13 cases)
None of the 3 factors	**3/732 (0.41)**
1 of the 3 factors	**1/272 (0.37)**
HIV-1 subtype A6/A1 alone	1/95 (1.1)
BMI $\geq$30 kg/m^2 alone	0/153 (0)
RPV RAM(s) alone	0/24 (0)
2 of the 3 factors	**8/34 (23.5)**
RPV RAM(s) + HIV-1 subtype A6/A1	1/3 (33.3)
RPV RAM(s) + BMI $\geq$30 kg/m^2	3/10 (30.0)
HIV-1 subtype A6/A1 + BMI $\geq$30 kg/m^2	4/21 (19.0)
All 3 of the factors	**1/1 (100)**
Limitations: industry-sponsored, small # clinical endpoints, unclear how many received injection correctly	

Source: Cutrell AG et al. AIDS. 2021;35:1333-1342.

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Poll

- What is your comfort level prescribing or recommending LAI CAB/RPV for an individual who doesn't meet FDA eligibility criteria (e.g., has a detectable viral load or missed oral ART doses or missed clinic visits)?

A) Very comfortable

B) Comfortable

C) Uncomfortable

D) Very uncomfortable

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

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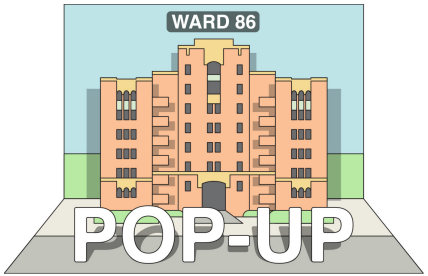
Demo Project of LAI CAB/RPV With or Without Detectable Viremia
Study Setting

- Safety net clinic for San Francisco city and county
- Serves >2,400 adults with HIV who have government insurance
- 21% Black, 27% Hispanic/Latinx
- 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



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

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Demo Project of LAI CAB/RPV With or Without Detectable Viremia
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

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

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Demo Project of LAI CAB/RPV With or Without Detectable Viremia
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 required; transition to every 8-week dosing only if sustained viral suppression for ≥6 months

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

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Demo Project of LAI CAB/RPV With or Without Detectable Viremia
Protocol

- Pharmacist eligibility review, visit, drug authorization/procurement
  - Bilingual team member calls within 1 week of first injection
  - Also 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 missed by >10 days, HIV RNA and genotypes
- Unplanned missed injection: attempts to contact, in-person outreach, repeat loading dose if missed by >42 days

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

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Demo Project of LAI CAB/RPV With or Without Detectable Viremia
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/Latinx, 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 (%)	24 (62)
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)

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

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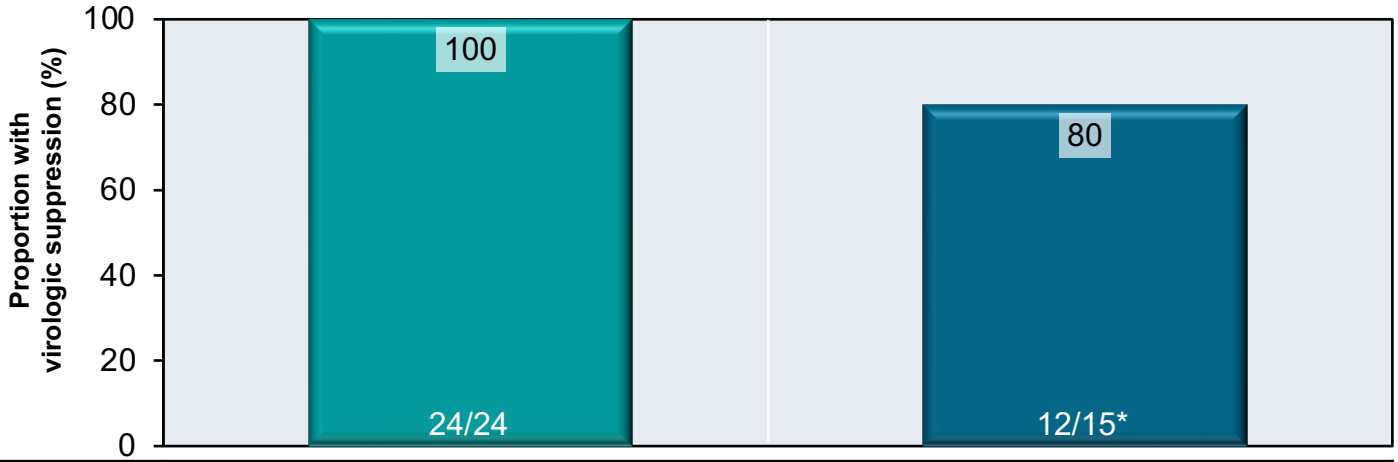
Demo Project of LAI CAB/RPV With or Without Detectable Viremia
Results (patients who received ≥2 injections)



	Baseline HIV RNA <30 copies/mL	Baseline HIV RNA ≥30 copies/mL
Direct-to-inject, n (%)	19 (79)	15 (100)
Median # injections (range)	6 (2-8)	6 (3-11)

*3 participants had not yet achieved suppression, but had 2-log decline in HIV RNA by median 22 days.
2 patients achieved suppressed VL for first time in >10 years (including 1 who had baseline INSTI mutation N155H).

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

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Demo Project of LAI CAB/RPV With or Without Detectable Viremia
Results (patients who received ≥2 injections)

- **Adherence:**
  - Overall high; 87% with only on-time injections (28 +/- 7 days)
  - Small # late injections; 2 required outreach & re-induction
  - 2 patients experiencing homelessness 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

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

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Demo Project of LAI CAB/RPV With or Without Detectable Viremia
Conclusions, Limitations, Questions

- **Conclusions**:
  - "Preliminary short-term effectiveness" of every 4-week LAI CAB/RPV 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?

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

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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
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

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

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)
Baseline HIV RNA <50 copies/mL, n (%)	7 (20)
Baseline HIV RNA ≥50 copies/mL, n (%)	28 (80)
HIV RNA >100,0000 copies/mL, n (%)	11 (31)
HIV RNA for those with ≥50 copies/mL, median (range)	60,300 (86 to >10,000,000)
CD4 count, cells/mm^3, median (range)	100 (3-918)
Direct-to-inject (no oral lead in)	12 (34)
All received every 4-week dosing; median follow up 10 months (range 1-47)	

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

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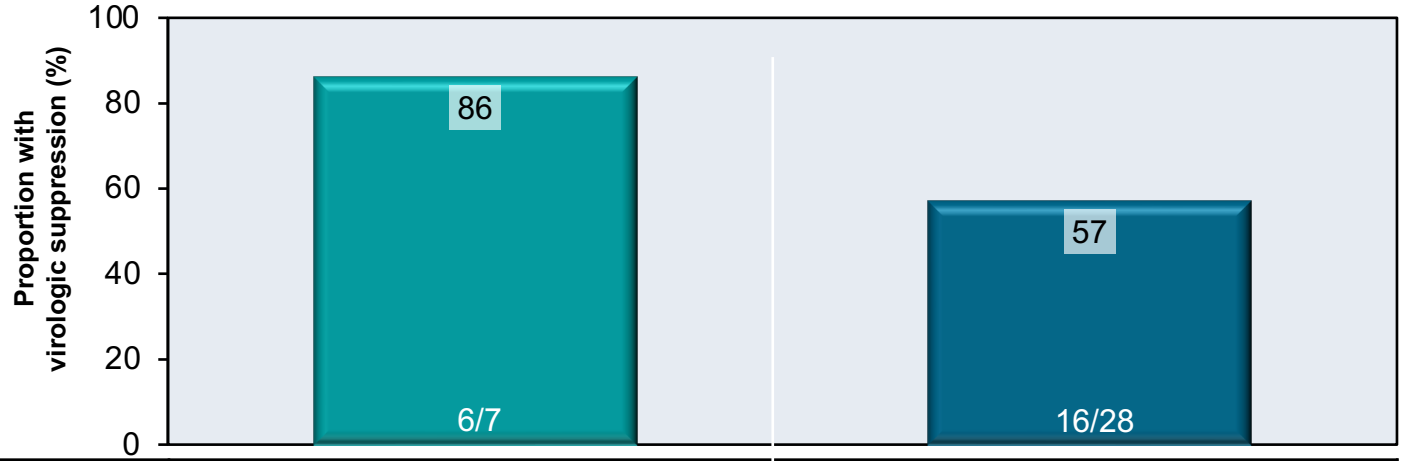
Compassionate Use of LAI CAB/RPV
Virologic Efficacy & Resistance Results



	Baseline HIV RNA <50 copies/mL	Baseline HIV RNA ≥50 copies/mL
Follow up HIV RNA >50*	1	6
Emergent RPV RAM(s)	0	6
Emergent CAB RAM(s)	1	2

*All 7 participants with HIV RNA >50 copies/mL at follow up required boosted darunavir-based ART (2/7 achieved HIV RNA <50 copies/mL)

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

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Compassionate Use of LAI CAB/RPV

- **Conclusions**:
  - "Valuable treatment option" for individuals with advanced HIV, limited treatment options, and issues preventing enteral administration of ART
- **Limitations**:
  - Small n, no comparator group, short follow up, no adherence data, more oral lead in

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

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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)"**

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

- Clinical considerations:
  - Adherence support, insurance coverage, # of clinic visits per year
  - Risks of missed doses (resistance, need for boosted darunavir)

Source: Guidelines for the Use of Antiretroviral Agents in Adults and Adolescents with HIV (http://clinicalinfo.hiv.gov)

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Poll

- What is your comfort level prescribing or recommending LAI CAB/RPV for an individual who doesn't meet FDA eligibility criteria (e.g., has a detectable viral load or missed oral ART doses or missed clinic visits)?

A) Very comfortable

B) Comfortable

C) Uncomfortable

D) Very uncomfortable

Future LAI CAB/RPV Innovations
Potential Alternate Site of Administration, Self-Administration

- **IM lateral thigh (vastus lateralis)**:
  - n = 15 persons without HIV; 6 cisgender women, 9 cisgender men
  - Monthly for 1 year, after oral lead in
  - PK (max, trough, AUC) comparable to gluteal injections; mild side effects only
  - Potential alternate site for administration, or self-administration (maybe)

Source: Han K et al. International AIDS Conference, Montreal, 2022. Abstract EPB176/9906.

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Lenacapavir (Capsid Inhibitor)

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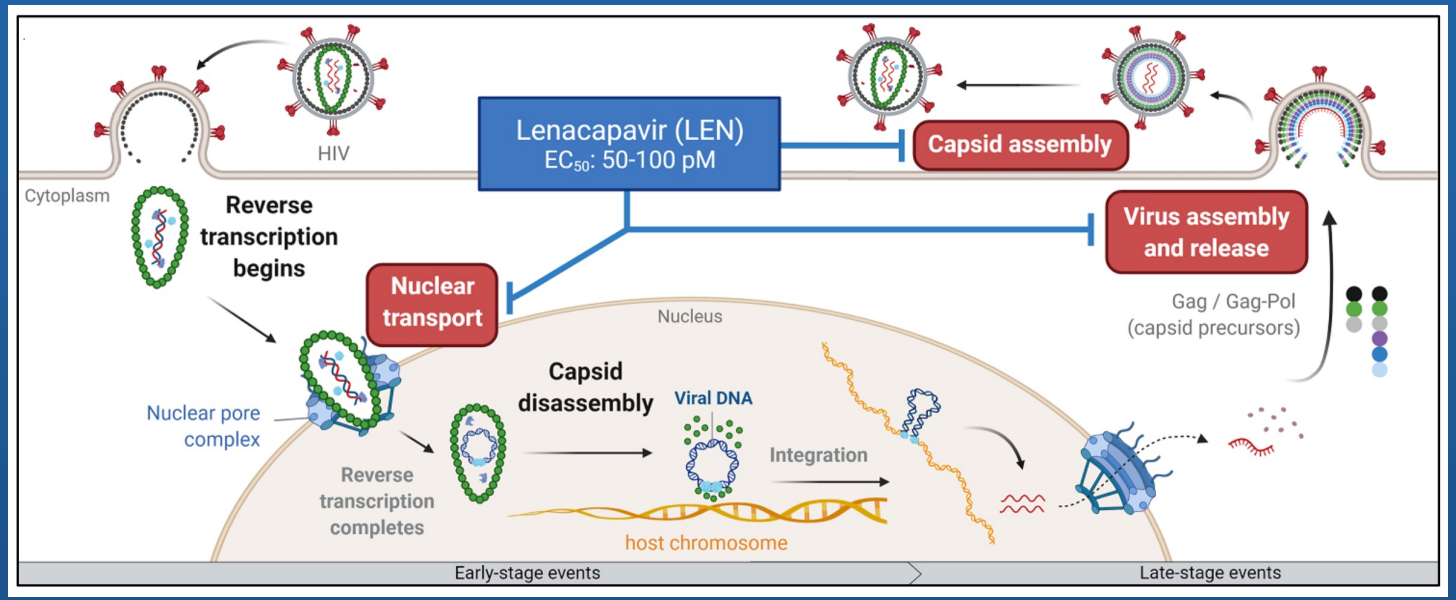
Lenacapavir (LEN)
Capsid Inhibitor: Mechanism

See David Spach's amazing talk:
https://www.youtube.com/c/MWAETCProjectECHO/



Mechanism: binds to capsid, interferes with transport via nuclear pores, stabilizes shell and inhibits disassembly, plus distorts the capsid lattice resulting in abnormal structure that prevents viral maturation.

Dosing: oral daily or weekly, or subcutaneous every 6 months.

Sources: Molina JM et al. IAS 2021. clinicalinfo.hiv.gov

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Subcutaneous (SC) or Oral Lenacapavir (LEN)
Phase 2/3 Treatment & PrEP Studies

- **Treatment Trials**
  - CAPELLA: SC LEN plus OBR for heavily treatment-experienced PWH
  - CALIBRATE: SC or oral LEN with oral ART for treatment-naïve
- **PrEP Trials**
  - PURPOSE 1: SC LEN vs oral TAF/FTC for cisgender young women
  - PURPOSE 2: SC LEN vs oral TDF/FTC for cisgender men, transgender women, transgender men, gender non-binary individuals

Dec. 2021: FDA hold, vial compatibility concerns

May 2022: Hold lifted for all LEN trials

July 2022: NDA resubmitted (FDA to review by Dec. 27)

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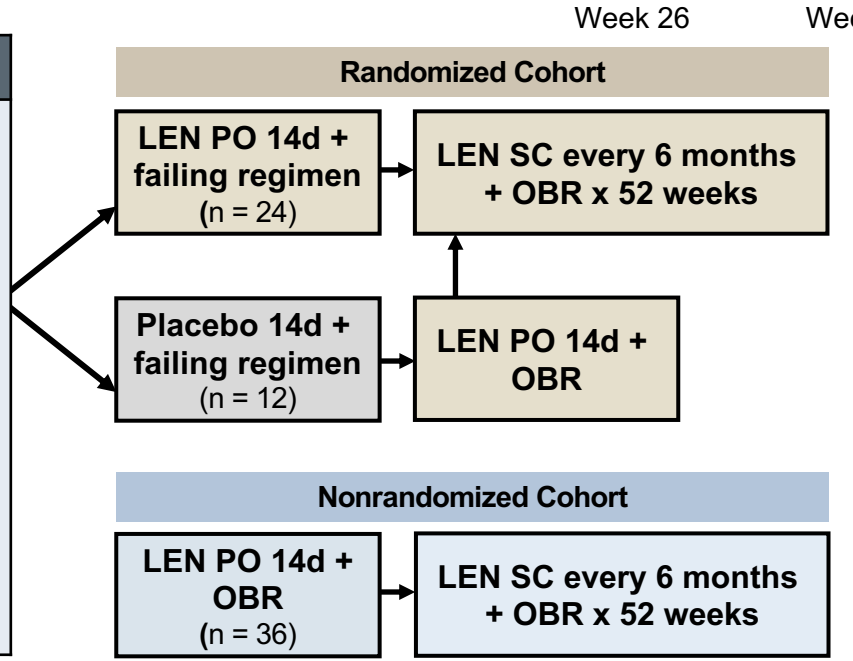
Lenacapavir (LEN)
CAPELLA Study: Background

Study Design: CAPELLA

- **Background**:
  - Phase 3, randomized controlled trial of lenacapavir plus OBR for heavily treatment-experienced PWH
- **Enrollment Criteria:**
  - Highly ART-experienced, age ≥12
  - Virologic failure on current ART
  - HIV RNA ≥400 copies/mL
  - Resistance to ≥2 agents from ≥3 of 4 main ARV classes
  - ≤2 predicted active agents



*Oral LEN for 14d = 600 mg day 1 & day 2 then 300 mg day 8; LEN SC = 927 mg (2 x 1.5 mL in abdomen)
*SC = subcutaneous; OBR = optimized background regimen

Source: Segal-Maurer S, et al. N Engl J Med. 2022;386(19):1793-1803.

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Lenacapavir (LEN)
CAPELLA Study: Results

Participant Characteristic	Result (n = 72)
Age, median (range), years	52 (23-78)
Sex, % female at birth	25
Race, % Black	38
Ethnicity, % Hispanic/Latinx	21
HIV RNA, median (range), log_{10} copies/mL	4.5 (1.3-5.7)
HIV RNA >75,000 copies/mL, %	28
CD4 count, median (range), cells/mm^3	150 (3-1296)
CD4 count $\leq$200 cells/mm^3, %	64
# of fully active agents in OBR, %	
0	17
1	39
$\geq$2	44

Source: Segal-Maurer S, et al. N Engl J Med. 2022;386(19):1793-1803.

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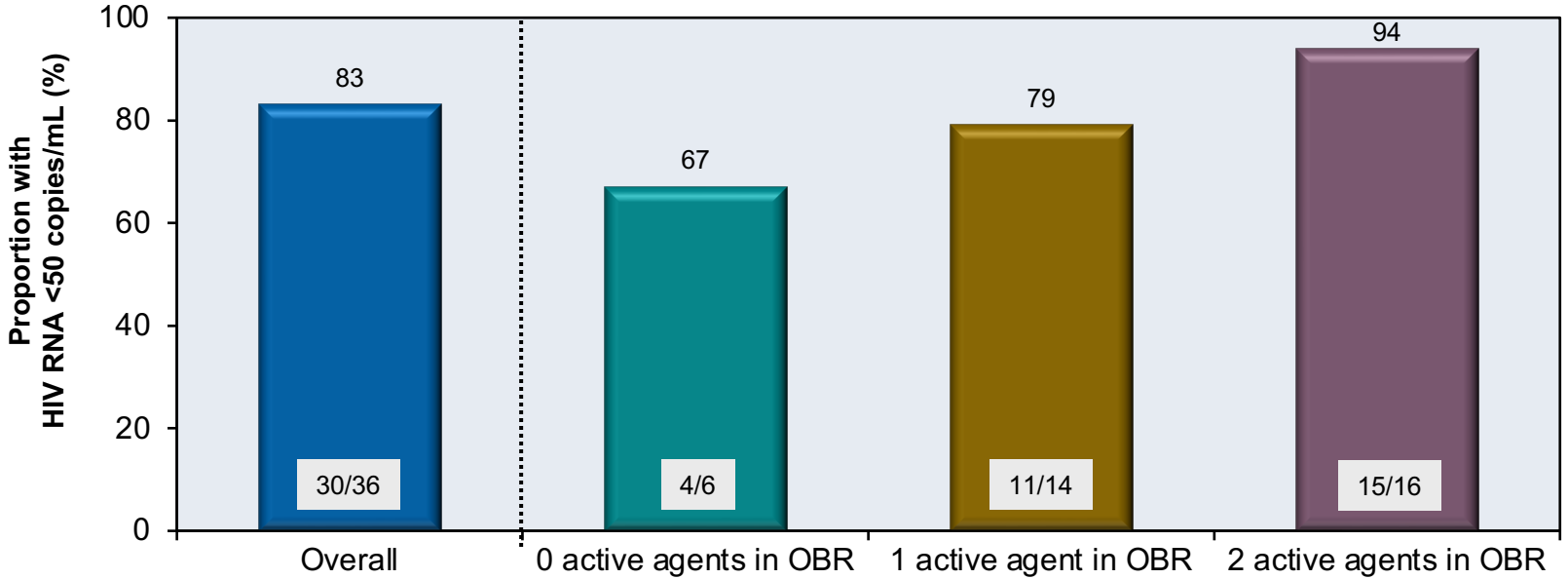
Lenacapavir (LEN)
CAPELLA Study: Results

Virologic efficacy results at 52 weeks (randomized cohort)



Source: Ogbuagu O, et al. CROI 2022. Abstract 491.

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Lenacapavir (LEN)
CAPELLA Study: Results

Virologic efficacy results

Virologic Result	Randomized Cohort (n=36) at 52 Weeks	Nonrandomized Cohort (n =36) at 26 Weeks
HIV RNA <50 copies/mL, %	83	81
HIV RNA <200 copies/mL, %	86	86
Met criteria for resistance testing, n (%)	11 (31)	10 (28)
Emergent LEN resistance, n (%)	4 (11)*	4 (11)*

*8 with emergent LEN resistance: 4 had 0 active drugs in OBR, 4 had inadequate adherence to OBR.
Most frequent capsid mutations: M66I, Q67H/K/N, K70H/N/R/S, N74D/H/S, A105S/T, T107A/C/N.

Source: Ogbuagu O, et al. CROI 2022. Abstract 491.

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Lenacapavir (LEN)
Lessons from the European Package Insert

- Indicated for treatment of adults with multidrug resistant HIV-1 infection for whom it is **not otherwise possible to construct a suppressive regimen**
- Each administration should be **administered by a healthcare professional**
- No dose adjustment for renal or hepatic impairment
- Few drug-drug interactions
- Emphasize importance of **adherence**

Treatment time	
	Dose of Sunlenca: initiation
Day 1	600 mg orally (2 x 300 mg tablets)
Day 2	600 mg orally (2 x 300 mg tablets)
Day 8	300 mg orally (1 x 300 mg tablet)
Day 15	927 mg subcutaneous injection (2 x 1.5 mL injections[a])
	Dose of Sunlenca: maintenance
Every 6 Months (26 weeks)[b] +/- 2 weeks	927 mg subcutaneous injection (2 x 1.5 mL injections[a])

a Two injections, each at a separate site in the abdomen.
b From the date of the last injection.

Source: https://www.ema.europa.eu/en/documents/product-information/sunlenca-epar-product-information_en.pdf

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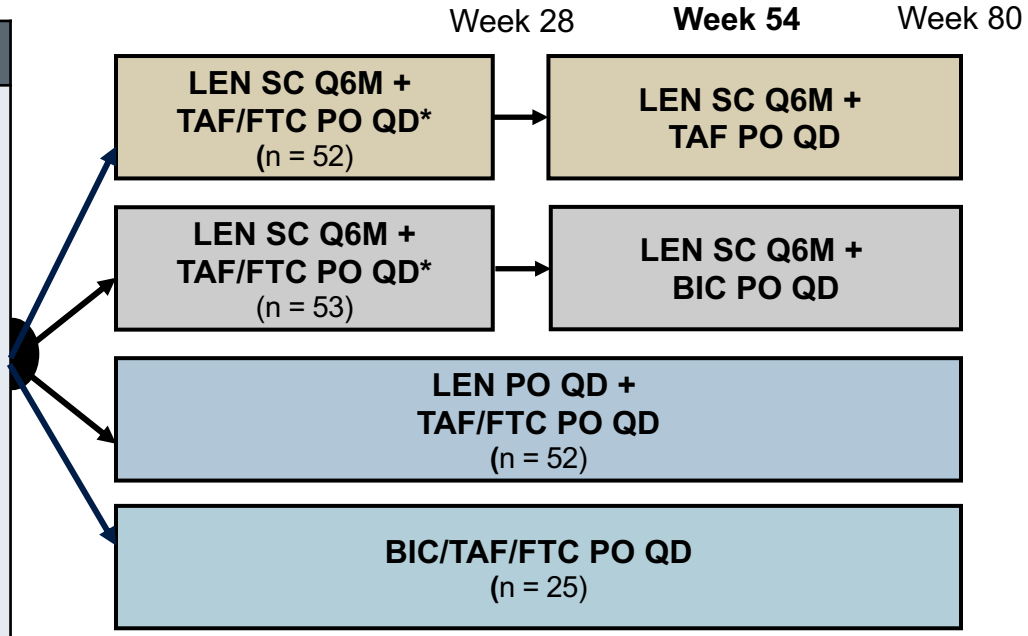
Lenacapavir (LEN)
CALIBRATE Study: Background

Study Design: CALIBRATE

- **Background**:
  - Phase 2, randomized, open-label trial of lenacapavir (LEN) plus NRTI(s) vs BIC/TAF/FTC for treatment-naïve PWH
- **Enrollment Criteria:**
  - ART-naïve adults
  - HIV RNA ≥200 copies/mL
  - CD4 ≥200 cells/mm^3
  - No active HCV or HBV
- **Primary Outcome:**
  - Proportion with HIV RNA <50 copies/mL at week 54



*Oral lead-in: oral LEN for 14d (600 mg day 1 & day 2 then 300 mg day 8)
*Transition to LEN SC if HIV RNA <50 copies/mL proximal to week 28
*LEN subcutaneous (SC) = 927 mg (2 x 1.5 mL in abdomen)

Source: Gupta S, et al. CROI, Feb 2022. Abstract 138.

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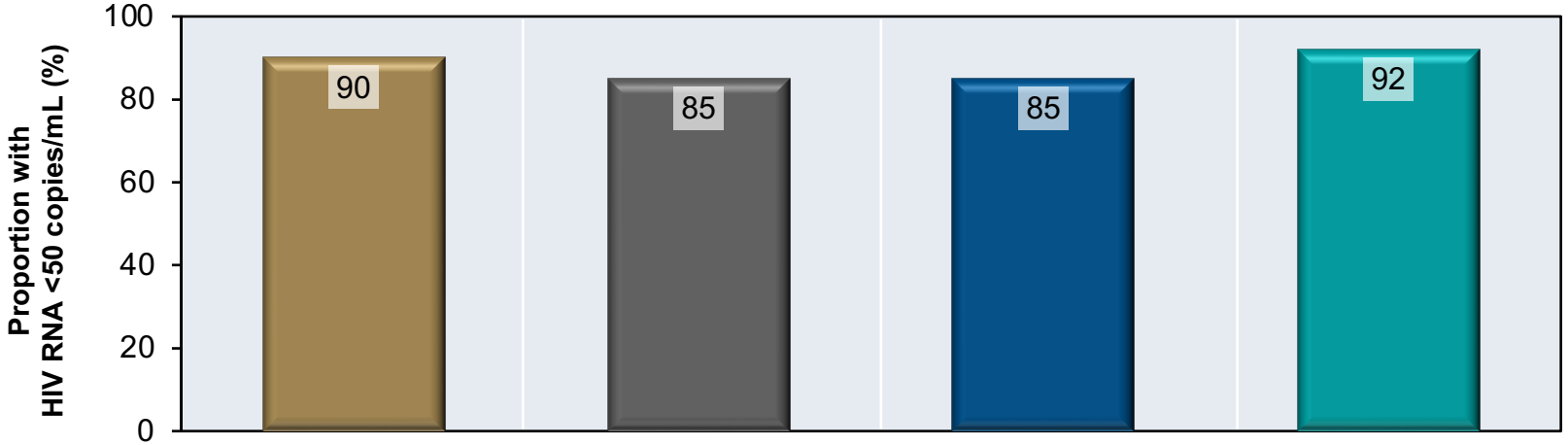
Lenacapavir (LEN)
CALIBRATE: Phase 2 Treatment-Naïve Trial (Week 54 Results)



	SC LEN + TAF	SC LEN + BIC	PO LEN + FTC/TAF	BIC/FTC/TAF
Participants, n	52	53	52	25
Confirmed VF, n	1	1	3	1
New RAM(s), n	0	1, Capsid: Q67H, K70R RT: M184V/I	1, Capsid: Q67H	0

Source: Gupta S, et al. CROI, Feb 2022. Abstract 138.

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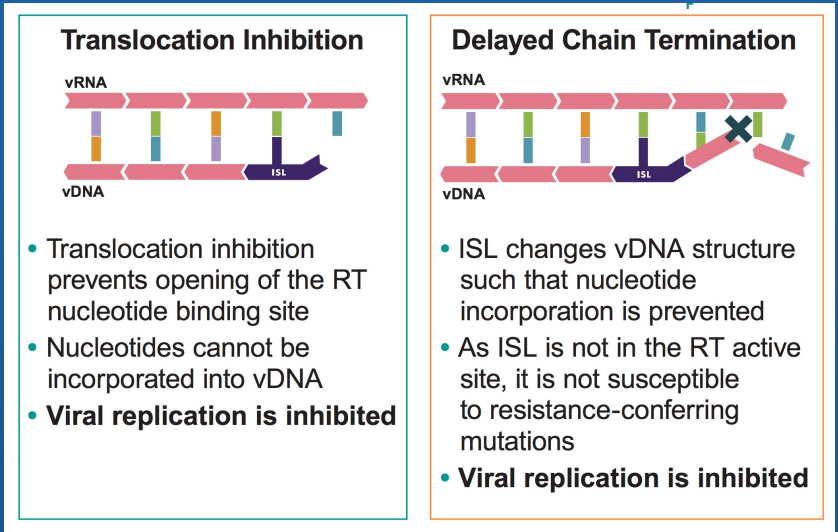
Islatravir (NRTTI)

Islatravir (ISL)
NRTTI: Mechanism, Advantages, & Lymphocyte Toxicity



- Active against isolates with pre-existing NRTI resistance
- Potent viral load reduction plus high barrier to resistance
- Potential daily, weekly, or monthly oral dosing; yearly implant
- Per early trial data, appears metabolically neutral

December 2021:
FDA hold due to decreases in total lymphocytes & CD4 T cells (high cellular levels of ISL-TP cause apoptosis)

September 2022:
Hold lifted for treatment trials with lower ISL dose

Sources: McComsey G. CROI 2020. Markowitz M, Sarafianos SG. Curr Opin HIV AIDS. 2018;13(4):294-299. Amblard F et al. Eur J Med Chem. 2022;240:114554.

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Islatravir (ISL) Lymphopenia

PrEP trials discontinued
(weekly or monthly oral & yearly implant)

011 Study: phase 2 RCT that compared DOR/ISL to DOR/TDF (with 3TC for first 24 weeks) for treatment-naïve PWH; change to laboratory parameters at 72 weeks

ARV	Total Lymph	CD4 T Cell	B Cell
TDF	+16%	+60%	+108%
ISL 0.25 mg	+20.5%	+80%	+90%
ISL 0.75 mg	-0.4%	+47%	+55.5%
ISL 2.25 mg	-16%	+24%	+7.5%

- Changes dose-dependent, reversible, not associated with increased infections
- Equal virologic efficacy at 96 weeks; 0.25 mg predicted active against M184V/I
- DOR/ISL 100 mg/0.25 mg daily for phase 3 trials (treatment-naïve and switch)

Sources: Correll TA, et al. HIV Drug Therapy, Glasgow, UK, 23-26 October 2022.
Vargo R, et al. HIV Drug Therapy, Glasgow, UK, 23-26 October 2022.
Molina J-M, et al. J Aquir Immune Defic Syndr. 2022 Sep 1;91(1):68-72.

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Questions or comments?
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